The Counsyl Foresight™ Carrier Screen

Counsyl

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The Counsyl Foresight Carrier Screen - Disease Reference Book

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Test Methodologies

TRIPLET REPEAT DETECTION

PCR is used to size the CGG repeat in the 5' UTR of *FMR1* (NM_002024.4: c.1-131CGG[1_n]). PCR products generated from fluorescently labeled primers are detected by capillary electrophoresis. Reported sizes are accurate to +/- 1 repeat for up to 200 repeats. Alleles above 200 CGG repeats (full mutations), while identified, are not sized. Nearby mutations may interfere with detection of CGG repeat expansions. Deletion of the CGG repeat region and other similar *FMR1* mutations may not be detectable. Methylation is not analyzed. Small degrees of size mosaicism, including gonadal mosaicism, may not be detected as the test has been calibrated to yield results that are equivalent to the results from Southern blot.

SPINAL MUSCULAR ATROPHY

Targeted copy number analysis is used to determine the copy number of exon 7 of the *SMN1* gene relative to other genes. Other mutations may interfere with this analysis. Some individuals with two copies of *SMN1* are carriers with two *SMN1* genes on one chromosome and a *SMN1* deletion on the other chromosome. This is more likely in individuals who have 2 copies of the *SMN1* gene and are positive for the g.27134T>G SNP, which affects the reported residual risk; Ashkenazi Jewish or Asian patients with this genotype have a high post-test likelihood of being carriers for SMA and are reported as carriers. The g.27134T>G SNP is only reported in individuals who have 2 copies of *SMN1*.

ANALYSIS OF HOMOLOGOUS REGIONS

A combination of high-throughput sequencing, read depth-based copy number analysis, and targeted genotyping is used to determine the number of functional gene copies and/or the presence of selected loss of function mutations in certain genes that have homology to other regions. The precise breakpoints of large deletions in these genes cannot be determined, but are estimated from copy number analysis. High numbers of pseudogene copies may interfere with this analysis.

If *CYP21A2* is tested, patients who have one or more additional copies of the *CYP21A2* gene and a loss of function mutation may not actually be a carrier of 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH). Because the true incidence of non-classic CAH is unknown, the residual carrier and reproductive risk numbers on the report are only based on published incidences for classic CAH. However, the published prevalence of non-classic CAH is highest in individuals of Ashkenazi Jewish, Hispanic, Italian, and Yugoslav descent. Therefore, the residual and reproductive risks are likely an underestimate of overall chances for 21-hydroxylase-deficient CAH, especially in the aforementioned populations, as they do not account for non-classic CAH. If *HBA1*/*HBA2* are tested, some individuals with four alpha globin genes may be carriers, with three genes on one chromosome and a deletion on the other chromosome. This and similar, but rare, carrier states, where complementary changes exist in both the gene and a pseudogene, may not be detected by the assay.

SEQUENCING WITH COPY NUMBER ANALYSIS

High-throughput sequencing and read depth-based copy number analysis are used to analyze the listed exons, as well as selected intergenic and intronic regions, of the genes in the Conditions Tested section of the report. The region of interest (ROI) of the test comprises these regions, in addition to the 20 intronic bases flanking each exon. In a minority of cases where genomic features (e.g., long homopolymers) compromise calling fidelity, the affected intronic bases are not included in the ROI. The ROI is sequenced to high coverage and the sequences are compared to standards and references of normal variation. More than 99% of all bases in the ROI are sequenced at greater than the minimum read depth. Mutations may not be detected in areas of lower sequence coverage. Small insertions and deletions may not be as accurately determined as single nucleotide variants. Genes that have closely related pseudogenes may be addressed by a different method. *CFTR* and *DMD* testing includes analysis for both large (exon-level) deletions and duplications with an average sensitivity of 99%, while other genes are only analyzed for large deletions with a sensitivity of >75%. However, the sensitivity may be higher for selected founder deletions. If *GJB2* is tested, two large upstream deletions which overlap *GJB6* and affect the expression of *GJB2*, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854), are also analyzed. Mosaicism or somatic variants present at low levels may not be detected. If detected, these may not be reported.

Detection rates are determined by using literature to estimate the fraction of disease alleles, weighted by frequency, that the methodology is unable to detect. Detection rates only account for analytical sensitivity and certain variants that have been previously described in the literature may not be reported if there is insufficient evidence for pathogenicity. Detection rates do not account for the disease-specific rates of de novo mutations.

All variants that are a recognized cause of the disease will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, only variants classified as "likely" pathogenic are reported. Likely pathogenic variants are described elsewhere in the report as "likely to have a negative impact on gene function". Likely pathogenic variants are evaluated and classified by assessing the nature of the variant and reviewing reports of allele frequencies in cases and controls, functional studies, variant annotation and effect prediction, and segregation studies. Exon level duplications are assumed to be in tandem and are classified according to their predicted effect on the reading frame. Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported. Curation summaries of reported variants are available upon request.

TARGETED GENOTYPING

Targeted DNA mutation analysis is used to determine the genotypes of the listed variants in the Conditions Tested section of the report.

11-beta-hydroxylase-deficient Congenital Adrenal Hyperplasia

Available Methodology: sequencing with copy number analysis.
Gene: CYP11B1.
Exons Sequenced: NM_000497:1-9.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe

What is 11-Beta-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

Congenital adrenal hyperplasia (CAH) refers to a group of genetic disorders that affect the body's adrenal glands. The adrenal glands are located above each kidney and regulate essential functions in the body, including the production of several important hormones. CAH occurs when the adrenal glands are unable to produce these hormones properly, resulting in hormone imbalance.

CAH due to 11-beta-hydroxylase deficiency is the second most common type of CAH, and is thought to account for approximately 5-8% of cases in certain populations. When the 11-beta-hydroxylase enzyme is missing or present at low levels, the adrenal glands are unable to produce critical hormones leading to the excess production of male sex hormones, called androgens. Collectively, the excess androgen production and hormone deficiencies lead to a variety of medical problems, which vary in severity depending on the form of CAH.

There are two major forms of 11-beta-hydroxylase-deficient congenital adrenal hyperplasia (11b-OHD CAH): classic and non-classic.

CLASSIC

The classic form of 11b-OHD CAH is the most severe. The external genitals of female newborns typically do not clearly appear either male or female (ambiguous genitalia), though the internal reproductive organs develop normally. Signs of early puberty and virilization (exaggerated development of male characteristics) can occur in both males and females. These symptoms may include: rapid growth and development in early childhood, but shorter than average height in adulthood, abnormal menstruation cycles for females, excess facial hair for females, early facial hair growth for males, and severe acne. Infertility has been reported in men and women. In addition, approximately two-thirds of individuals with with classic type, will develop hypertension (high blood pressure) within the first few years of life, which can result in more significant medical problems if left uncontrolled.

NON-CLASSIC

The non-classic type is the the least severe form of 11b-OHD CAH. Individuals with this type may start experiencing symptoms related to excess androgen production in childhood, adolescence, or adulthood. Thus, both males and females with the non-classic type are born with normal-appearing genitals. Individuals may still exhibit rapid growth in childhood leading to shorter than average stature in adulthood. Additionally, girls may experience symptoms of masculinization, abnormal menstruation, and infertility. However, the only symptom males typically experience is short stature. Hypertension is also not a feature of the non-classic type. In general, some individuals may never know they are affected because the symptoms are so mild.

How common is 11-Beta-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

The worldwide incidence of 11b-OHD CAH has never been assessed. However, based on estimates that have been done in some populations, the classic form of 11b-OHD CAH is estimated to occur in approximately 1 in 100,000 to 1 in 200,000 births worldwide, though this number varies by region. For example, incidence in Moroccan Jews is estimated to be as high as 1 in 5,000 to 1 in 7,000, and may also be higher than the worldwide estimates in other individuals of Jewish descent from North Africa and the Middle East. The non-classic type is less common.

How is 11-Beta-Hydroxylase-Deficient Congenital Adrenal Hyperplasia treated?

Currently, there is no cure for CAH. However, treatments are available to address some of the associated symptoms. Patients benefit from taking hormone replacement medications, which work to increase levels of deficient hormones and suppress the overproduction of male hormones. Most people with the classic form will need to take hormone medications throughout their life. Those with the less severe forms of CAH are sometimes able to stop taking these medications in adulthood and are typically treated with lower doses. Some individuals with non-classic CAH do not require any treatment. A multidisciplinary team of physicians, including an endocrinologist, will need to monitor the medication dosage, medication side effects, growth, and sexual development of patients who continue to receive treatment. In addition, antihypertensive therapy may be required for patients diagnosed with high blood pressure to prevent the consequences of uncontrolled hypertension.

Newborn females with ambiguous genitalia may need surgery to correct the function and appearance of the external genitalia. Surgery, if needed, is most often performed during infancy, but can be performed later in life.

Treatments provided during pregnancy may reduce the degree of virilization in female fetuses. However, because the long term safety of prenatal treatment is unknown, these therapies are considered experimental and are not recommended by professional guidelines.

What is the prognosis for a person with 11-Beta-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

With early diagnosis and proper medication management, most individuals with 11b-OHD CAH will have a normal life expectancy. Early death has been reported due to uncontrolled hypertension, but is rare. Problems with growth and development, infertility, ambiguous genitalia, and virilization are monitored by physicians on an ongoing basis.

21-hydroxylase-deficient Congenital Adrenal Hyperplasia

Available Methodology: analysis of homologous regions.

Gene: CYP21A2.

Variants Genotyped (13): I173N, V282L, R357W, P31L, c.293-13C>G, G111VfsX21, Q319*, L308FfsX6, CYP21A2 deletion, CYP21A2 duplication, Q319*+CYP21A2dup, [I237N;V238E;M240K], CYP21A2 triplication.

Detection Rate	Population
92%	African American
>99%	Ashkenazi Jewish
88%	Eastern Asia
89%	Finland
96%	French Canadian or Cajun
95%	Hispanic
97%	Middle East
90%	Native American
96%	Northwestern Europe
96%	Oceania
88%	South Asia
88%	Southeast Asia
96%	Southern Europe

What is 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

Congenital adrenal hyperplasia (CAH) refers to a group of genetic disorders that affect the body's adrenal glands. The adrenal glands are located above each kidney and regulate essential functions in the body, including the production of several important hormones. CAH occurs when the adrenal glands are unable to produce these hormones properly, resulting in a hormone imbalance.

More than 90% of of CAH cases are caused by deficiency of the 21-hydroxylase enzyme. When this enzyme is missing or present at low levels, the adrenal glands are unable to produce two critical hormones, cortisol and aldosterone. The body responds to this deficiency by producing an excess of male sex hormones, called androgens. Collectively, the excess androgen production and hormone deficiencies can lead to a variety of medical problems, which vary in severity depending on the form of CAH.

There are two major forms of 21-hydroxylase-deficient CAH: classic CAH and non-classic CAH.

CLASSIC

The most severe form, referred to as classic CAH, can be divided into two different subtypes: the salt-wasting type and the simple virilizing type (non salt-wasting type). The classic salt-wasting type is associated with near to complete deficiency of the enzyme, 21-hydroxylase, resulting in the complete inability to produce the hormones, cortisol and aldosterone. In this type, the body cannot retain enough sodium (salt). When too much salt is lost in the urine, it may lead to dehydration, vomiting, diarrhea, failure to thrive, heart rhythm abnormalities (arrhythmias), and shock; if not properly treated, death may occur in some cases. In addition, female newborns often have external genitalia that do not clearly appear either male or female (ambiguous genitalia), whereas male newborns may present with enlarged genitalia. Signs of early puberty (virilization) occur in both males and females with CAH. These symptoms may include: rapid growth and development in early childhood, but shorter than average height in adulthood, abnormal menstruation cycles for females, excess facial hair for females, early facial hair growth for males, severe acne, and infertility in both men and women.

The simple virilizing type of CAH is associated with partial 21-hydroxylase deficiency. Unlike the salt-wasting type, these individuals typically do not experience severe and life-threatening sodium deficiency symptoms as newborns. However, the majority of female newborns with this type will have ambiguous genitalia, and both male and female children may show signs of early puberty.

NON-CLASSIC

The non-classic type (late-onset type) is the the least severe form of CAH and is caused by mild deficiency of the 21-hydroxylase enzyme. Individuals with this type may start experiencing symptoms related to excess androgen production in childhood, adolescence, or adulthood. Both males and females may exhibit rapid growth in childhood, shorter than average stature in adulthood, virilization, and infertility. Additionally, girls may experience symptoms of masculinization and abnormal menstruation. However, some individuals with non-classic CAH may never know they are affected because the symptoms are so mild.

How common is 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

The incidence of CAH varies by type and is more prevalent in certain ethnicities. Classic CAH occurs in approximately 1 in 15,000 births worldwide, while non-classic CAH is much more common, occurring in approximately 1 in 1,000 births. In some populations, namely individuals of Ashkenazi Jewish, Hispanic, Italian, and Yugoslav descent, the prevalence of the non-classic CAH can reach as high as 3-4 percent.

How is 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia treated?

Currently, there is no cure for CAH. However, treatments are available to address some of the associated symptoms. Patients benefit from taking hormone replacement medications, which work to increase levels of deficient hormones and suppress the overproduction of male hormones. Most people with classic CAH will need to take hormone medications for the rest of their life. Those with the less severe forms of CAH are sometimes able to stop taking these medications in adulthood and are typically treated with lower doses. Some individuals with non-classic CAH do not require any treatment. A multidisciplinary team of physicians, including an endocrinologist, will need to monitor the medication dosage, medication side effects, growth, and sexual development of patients who continue to receive treatment.

Newborn females with ambiguous genitalia may need surgery to correct the function and appearance of the external genitalia. Surgery, if needed, is most often performed during infancy, but can be performed later in life.

Treatments provided during pregnancy may reduce the degree of virilization in female fetuses. However, because the long term safety of prenatal treatment is unknown, these therapies are considered experimental and are not recommended by professional guidelines.

What is the prognosis for a person with 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia?

With early diagnosis and proper medication management, most individuals with CAH will have a normal life expectancy. Early death can occur during periods of significant sodium loss (salt crises) if medication dosage is not adequately adjusted, especially during times of illness or trauma. Problems with growth and development, infertility, ambiguous genitalia, and virilization are monitored by physicians on an ongoing basis.

6-pyruvoyl-tetrahydropterin Synthase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: PTS.
Exons Sequenced: NM_000317:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency is a rare disorder that results in the lack of a molecule called tetrahydrobiopterin (BH4). Lack of BH4 results in high levels of an amino acid called phenylalanine, a condition known as hyperphenylalaninemia. Phenylalanine and other amino acids are building blocks for proteins and are essential for proper growth and development. Additionally, BH4 deficiency results in very low levels of chemicals which transmit impulses from one nerve cell to another (neurotransmitters). Individuals with PTPS deficiency can have a variety of symptoms including neurological abnormalities (seizures and swallowing problems), low muscle tone (hypotonia) in the body, excess muscle tone (rigidity) in the arms and legs, loss of coordination or delayed motor development, delayed intellectual development, and temperature regulation problems. Infants with PTPS deficiency are often healthy at birth but quickly begin to show signs of failure to thrive. Additional symptoms generally appear within the first four to six months of life. A small head size (microcephaly) may also be identified in early infancy.

The symptoms of PTPS deficiency can vary widely and range from mild to severe. Twenty percent of individuals have the mild or atypical form. Individuals with the mild or atypical form of PTPS deficiency have moderate or transient alterations in phenylalanine levels and normal levels of neurotransmitters.

How common is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

PTPS deficiency is a rare disorder. In Caucasians, PTPS deficiency occurs in about 1 in 1,000,000 individuals, but is more frequent in East Asian populations.

How is 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency treated?

Treatment of PTPS deficiency will generally focus on reducing the high phenylalanine levels by dietary intervention and normalizing the neurotransmitter levels. Treatment may include synthetic BH4 and other medications which help restore neurotransmitter levels.

Patients with the severe form may need both synthetic BH4 supplementation and medications to restore neurotransmitters, while mild cases will need only BH4 supplementation.

What is the prognosis for a person with 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency?

Prompt diagnosis and early treatment of PTPS deficiency is critical for reducing or preventing potentially severe, irreversible neurologic damage. Without early diagnosis and treatment, this condition is potentially life-limiting.

ABCC8-related Hyperinsulinism

Available Methodology: sequencing with copy number analysis.
Gene: ABCC8.
Exons Sequenced: NM_000352:1-39.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is ABCC8-related Hyperinsulinism?

ABCC8-related hyperinsulinism, also called congenital hyperinsulinism, is an inherited condition in which the pancreas releases inappropriately large quantities of the hormone insulin, leading to low blood sugar (hypoglycemia). When blood sugar drops to dangerously low levels, seizures and permanent brain damage may occur. If untreated, the condition could ultimately be fatal.

ABCC8 refers to the name of the gene that causes this disease. Other genes have been identified which also cause hyperinsulinism.

The pancreas normally secretes insulin in response to rising blood sugar. In people with ABCC8-related hyperinsulinism, the pancreas secretes insulin even without sugar consumption, thereby removing too much sugar from the blood.

Infants with ABCC8-related hyperinsulinism tend to have significantly low blood sugar within the first few days of life. They often require immediate infusions of the sugar glucose to prevent seizures. These newborns are typically born larger than normal and may show difficulty feeding, poor muscle tone, and breathing problems.

In some people with ABCC8-related hyperinsulinism, symptoms do not appear until later in childhood. The low blood sugar associated with the condition can also range from mild to severe depending on the individual, and varies even among members of the same family. Early and aggressive treatment is important to avoid permanent brain damage.

How common is ABCC8-related Hyperinsulinism?

ABCC8-related hyperinsulinism affects roughly 1 in 50,000 Europeans. It is particularly common among people of Finnish and Saudi Arabian descent, where the disease may affect as many as 1 in 2,500. A certain genetic mutation is prevalent in people of Ashkenazi Jewish descent.

How is ABCC8-related Hyperinsulinism treated?

Treatments for ABCC8-related hyperinsulinism include dietary modification, medications, and surgical intervention. The aim of treatment is to keep the affected person's blood sugar level in the normal range to avoid brain damage.

If a child shows symptoms of ABCC8-related hyperinsulinism at birth, intravenous glucose is often given to raise and stabilize the blood sugar level. Babies may need frequent feedings with large amounts of carbohydrates, even overnight. A feeding tube may be helpful to ensure that a child gets sufficient quantities of carbohydrates and may facilitate automatic feedings overnight.

There are several types of medication to treat ABCC8-related hyperinsulinism. These are typically taken orally and/or injected several times daily.

When diet and medication do not sufficiently manage blood sugar levels, the person may require surgery to remove part of the pancreas.

After an extended period of successful treatment, many people with ABCC8-related hyperinsulinism find their symptoms lessen in severity or even go into remission.

People with ABCC8-related hyperinsulinism may find their symptoms aggravated by viral infections and should take particular precautions when they become ill, even if their symptoms have gone into remission. They should also avoid long periods of time without eating.

What is the prognosis for a person with ABCC8-related Hyperinsulinism?

The long-term outlook for someone with ABCC8-related hyperinsulinism depends upon the severity of the symptoms and the vigilance of the efforts to treat it. Permanent brain damage can occur from episodes of low blood sugar. Even with treatment, people with the disease can develop some degree of brain damage or have learning difficulties. They also may be at an elevated risk of diabetes. In the most serious cases, when the disease is not recognized and properly treated, it can be fatal. However with careful treatment, people with ABCC8-related hyperinsulinism can live normal lifespans.

Adenosine Deaminase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: ADA.
Exons Sequenced: NM_000022:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Adenosine Deaminase Deficiency?

Adenosine deaminase (ADA) deficiency is a metabolic disease that affects lymphocytes, which are components of, blood that play a significant role in the immune system. ADA is an enzyme produced by the body that breaks down a toxic substance called deoxyadenosine, which results from natural processes in the cells. When there is a deficiency of adenosine deaminase, deoxyadenosine builds up in the body and destroys lymphocytes. As a result, people with ADA can have higher risks for infections.

ADA deficiency is classified into different forms (as described below), because there can be variability in the age of onset and severity of a person's symptoms.

ADA-DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY DISEASE (ADA-SCID)

ADA-SCID is the most severe form of this condition and usually appears in the first six months. Infants may fall behind in growth (weight and height) and have a high chance of infection. Lung infections are common at this early age, and these and other infections can cause severe diarrhea, skin inflammation, or other severe symptoms. Some individuals with ADA deficiency have skeletal (abnormal rib shape), liver, and neurological problems (cognition, behavior, and/or deafness).

DELAYED/LATE-ONSET ADA DEFICIENCY

About 15% of people with ADA deficiency first develop symptoms after 6 months of age. Usually symptoms will present within the first few years of life, but a small number of people do not have symptoms until their teens or adulthood. Effects of infections on people with delayed/late-onset ADA deficiency are usually less severe compared to those observed in people with ADA-SCID. They often include ear, nose, and throat infections and the appearance of warts on the hands and feet. Eventually, many people develop chronic breathing problems and anemia.

PARTIAL ADA DEFICIENCY

Partial ADA deficiency does not typically result in symptoms, because the low levels of ADA enzymes that are present in this type function well enough to prevent symptoms. Thus, this form of the condition is generally recognized only by enzyme-based blood tests, though it may be predicted to some extent based on a person's genetic test results.

How common is Adenosine Deaminase Deficiency?

The worldwide frequency of ADA deficiency in the general population has not been established. Where estimates have been made, the number of people affected with the condition each year ranges from 1 in 450,000 to 1 in 1,500,000, and the number of people affected with the condition each year in the US is approximately 1 in 600,000.

How is Adenosine Deaminase Deficiency treated?

As soon as an ADA deficiency diagnosis known, taking steps to strengthen the immune system is the first goal. Patients receive medicine to prevent a common lung infection (pneumocystis) and intravenous infusion of IgG antibodies to help fight other infections. Long-term treatment is necessary via hematopoietic stem cell transplant (HSCT). If a transplant is not possible or if the risks are too high, a replacement ADA enzyme therapy is possible. This therapy consists of intramuscular injections once or twice a week. Researchers have also been experimenting with gene therapy for many years with some success. However, studies about long-term outcomes are still lacking.

What is the prognosis for a person with Adenosine Deaminase Deficiency?

Without treatment, a child with ADA-SCID can die in the first two years. When treated with a transplant from a matched sibling or family member, up to 90% will survive for at least one year with potentially higher success rates if done within the first few months of life. Some have been found to restore immune systems even 10 years after transplant. The survival rate for transplants from unrelated donors is lower (up to 70%). There appears to be a higher chance of cognitive and behavioral abnormalities, in addition to hearing loss, associated with HSCT. When treated with enzyme replacement therapy, the survival rates are similar to those who received transplants from an unrelated individual, but some have lived 8 to 10 years or more. Gene therapy, though still in the experimental stages, appears to be a promising option.

Alpha Thalassemia

Available Methodology: analysis of homologous regions.
Genes: HBA1, HBA2.
Variants Genotyped (13): Hb Constant Spring, -alpha4.2, anti4.2, -alpha3.7, anti3.7, --MEDII, --BRIT, -(alpha)20.5, --MEDI, --SEA, del HS-40, --THAI/--FIL, HBA1+HBA2 deletion.

What is Alpha Thalassemia?

Alpha thalassemia is a blood disorder that affects hemoglobin, a major component of red blood cells that carries oxygen in the body. Hemoglobin is a protein complex made up of two different chains. There are many forms of hemoglobin, but the primary type is made up of alpha chains and beta chains. Alpha thalassemia is caused by mutations involving the genes, *HBA1* and *HBA2*, that code for the alpha chains.

Most individuals have two functional pairs or four functional copies of the alpha globin genes (one copy each of *HBA1* and *HBA2* on both chromosomes).

Carriers generally have either two or three functional alpha globin genes and do not have any symptoms.

- **Three functional alpha globin genes, silent carrier:** These individuals are typically known as silent carriers, because they do not have any symptoms or abnormalities on a complete blood count. This status results from the presence of an alpha+ mutation (mutation that eliminates the function/presence of one copy of an alpha globin gene).

- **Two functional alpha globin genes, carrier:** These carriers generally have mild anemia characterized by hypochromic (pale) and microcytic (small) red blood cells, which can be measured on a complete blood count. However, they usually do not have any symptoms of the disease (note exception below). Carrier status may result from the presence of two alpha+ mutations (eliminates function/presence of one copy of an alpha globin gene on each chromosome) or an alpha0 mutation (eliminates function/presence of both copies of the alpha globin genes on one chromosome).

Exception: There have been reports of individuals with two copies of certain types of point mutations who have a diagnosis of hemoglobin H disease with variable symptoms. One example of this is when individuals have two copies of the hemoglobin Constant Spring mutation, which is common in the Southeast Asian population.

Disease symptoms most typically occur if an individual has one or zero functional alpha globin genes.

- **One functional alpha globin gene, hemoglobin H disease:** This form of alpha thalassemia is very variable. Disease severity ranges from asymptomatic to moderate microcytic/hypochromic anemia with the possibility of jaundice (yellowing of the skin or eyes), enlarged spleen, bone deformities, fatigue, and other minor complications.

- **Zero functional alpha globin genes, hemoglobin Bart syndrome:** Individuals who have no functional copies or are missing all four copies of the associated genes almost always have this fatal form of alpha thalassemia. Hb Bart syndrome is generally associated with death *in utero* due to the buildup of excess fluid in the body and tissues (hydrops fetalis). Signs and symptoms in the newborn period can include severe anemia, hepatosplenomegaly (enlarged liver and spleen), and birth defects of the heart, urinary system, and genitalia. Most babies with this condition are stillborn or die soon after birth.

How common is Alpha Thalassemia?

The carrier frequency and incidence of alpha thalassemia vary by the type and population. Carrier frequency of this condition is reported to be the highest in individuals of Southeast Asian, African, West Indian, and Mediterranean descent. In 2010, the estimated number of worldwide annual births of patients with Hb H disease was 9,568 and with Hb Bart syndrome was 5,183. Therefore, the

worldwide birth prevalence of Hb H disease and Hb Bart's hydrops is estimated at ~1/14500 and ~1/27000, respectively; however, for Hb Bart's hydrops, this is likely to be an underestimate because most at-risk couples are not currently identified.

How is Alpha Thalassemia treated?

Alpha thalassemia carrier status does not necessitate treatment. Treatment for hemoglobin H disease varies based on the severity of the symptoms. For many individuals, blood transfusions are given during crises, which are episodic and usually precipitated by environmental stressors, like oxidant medications or fever. Individuals with more severe symptoms may require regular blood transfusions, folic acid supplementation, prophylactic antibiotics, iron chelation therapy (removal of excess iron from the body), and possible hemoglobin F-enhancing agents and splenectomy.

Extremely rare cases of survivors with hemoglobin Bart syndrome have been reported when fetal blood transfusions were given, followed by regular treatments similar to those who have hemoglobin H disease. Treatments or surgical correction of potential birth defects may also be available. However, there is a high risk for intellectual and physical disability in these rare survivors. These individuals may be candidates for hematopoietic stem cell transplantation.

What is the prognosis for a person with Alpha Thalassemia?

Because hemoglobin H disease can be variable, prognosis ultimately depends on the severity of the disease. Mild disease may be manageable with little effect on daily life. However, more severe disease will necessitate frequent and regular therapy, and may be associated with a shortened lifespan. Untreated, the prognosis is poor with a shortened lifespan of up to age 5 years. However, when treated, individuals with hemoglobin H disease have a lifespan that approaches normal.

Hemoglobin Bart syndrome is the most severe clinical condition related to alpha thalassemia, and death may occur *in utero* or in the newborn period. Of note, there may also be maternal complications during pregnancy if the fetus has hemoglobin Bart syndrome. These complications include preeclampsia (high blood pressure, fluid build-up/swelling, protein in the urine), polyhydramnios (excessive amniotic fluid) or oligohydramnios (reduced amniotic fluid), hemorrhage, and premature delivery.

Alpha-mannosidosis

Available Methodology: sequencing with copy number analysis.
Gene: MAN2B1.
Exons Sequenced: NM_000528:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Alpha-Mannosidosis?

Alpha-mannosidosis is an inherited genetic disease that can cause many different health problems. These include mental retardation, skeletal abnormalities, hearing loss, muscle weakness, coarse facial features, and increased susceptibility to infection.

The severity of symptoms can vary widely among people with the disease. There are three main types of alpha-mannosidosis:

Type 1 - The mildest form, type 1, appears after the age of 10. People with type 1 typically do not have skeletal abnormalities, but do show muscle weakness. Their symptoms may be so mild as to be barely detectible. Symptoms tend to progress slowly.

Type 2 - In the moderate form known as type 2, symptoms appear before the patient reaches age 10. This form of the disease causes skeletal abnormalities and muscle weakness, but symptoms often progress slowly.

Type 3 - The severe form, type 3, the disease is usually fatal in childhood; some affected fetuses even die before birth. The symptoms appear early in infancy and progress rapidly.

While most of the people known to have alpha-mannosidosis fall into the moderate category, it may not be possible to predict which form of the disease a person will have based on their specific genetic mutation. Even siblings with the same genetic mutation may have symptoms that vary in severity.

All forms of alpha-mannosidosis involve some degree of intellectual disability, ranging from mild or moderate in type 1 to extreme in type 3. Combined with hearing loss, another symptom of the disease, this typically causes a delay in learning to speak, difficulties in pronouncing words, and a restricted vocabulary.

People with alpha-mannosidosis often experience an inability to coordinate their movements (ataxia) and general muscle weakness (myopathy). They often learn to walk later than other children and appear to be clumsy.

Many people with alpha-mannosidosis have immune deficiencies which leave them prone to frequent infection, particularly of the lungs, ears, and digestive system. Infections are most frequent in childhood.

Those with type 2 and 3 alpha-mannosidosis experience skeletal abnormalities that may include a reduction in bone density, deformed spine, bowed legs, and a deterioration of the bones and joints.

Some people with the disease experience hydrocephaly, a buildup of fluid around the brain. Some also have an enlarged livers and spleens, although these is not thought to cause health problems.

People with alpha-mannosidosis share certain facial characteristics, regardless of race. They have prominent foreheads, flattened nasal bridges, broad mouths, and protruding jaws.

Roughly 25% of people with the disease experience psychiatric problems distinct from their intellectual disabilities, often beginning in late puberty or early adolescence. These have included depression, confusion, anxiety, and hallucinations.

How common is Alpha-Mannosidosis?

Alpha-mannosidosis is extremely rare. It occurs in roughly 1 in 500,000 people worldwide. It can affect people from any race or ethnic group.

How is Alpha-Mannosidosis treated?

There is no treatment for the underlying cause of alpha-mannosidosis, however physicians can treat symptoms that arise in order to prevent complications and enhance the person's quality of life. Based on the person's symptoms, physicians often recommend a range of treatments such as antibiotics for viral infections; hearing aids; tubes to drain fluid from the middle ear; physical therapy to aid in movement; speech therapy; special education classes to facilitate learning; use of wheelchairs and other orthopedic aids; and/or an implanted shunt near the brain to help drain fluid buildup.

What is the prognosis for a person with Alpha-Mannosidosis?

People with milder forms of alpha-mannosidosis may live until their 50s. Those with the most severe forms, however, usually die before birth or in childhood.

People with alpha-mannosidosis tend to have more problems with infection during childhood. This often lessens by their 20s and 30s, when bone and muscle problems are more of a concern.

Alpha-sarcoglycanopathy

Available Methodology: sequencing with copy number analysis.
Gene: SGCA.
Exons Sequenced: NM_000023:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Alpha-Sarcoglycanopathy?

Alpha-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2D (LGMD2D), is an inherited genetic disease in which muscles of the hip, abdomen, and shoulder progressively weaken.

Symptoms of the disease vary greatly from person to person, even among people in the same family. They can range from mild complications that do not affect lifespan to severe symptoms that are fatal by the early 20s.

People with alpha-sarcoglycanopathy commonly develop symptoms before the age of 10, although in some cases, they do not appear until adulthood. Typically the later in life symptoms appear, the less rapidly they will progress. Muscles of the hip, shoulder, and abdomen progressively weaken, although the rate at which they weaken can vary greatly. The muscles may weaken to a point where a wheelchair becomes necessary.

Approximately 20% of people with alpha-sarcoglycanopathy experience a weakening of the heart muscles. Involvement of the heart muscles is less common in alpha-sarcoglycanopathy than in other forms of limb girdle muscular dystrophy.

Alpha-sarcoglycanopathy does not affect intelligence or mental function. The cause of alpha-sarcoglycanopathy is a deficiency in a protein called alpha-sarcoglycan. The function of this protein is not entirely understood. The degree of deficiency in alpha-sarcoglycan may correlate with the severity of disease symptoms.

How common is Alpha-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. The estimated prevalence of all types of limb-girdle muscular dystrophy is 1 in 15,000 individuals. Alpha-sarcoglycanopathy is rare, and its exact incidence is unknown. It is most common in Europe, the United States, and Brazil.

How is Alpha-Sarcoglycanopathy treated?

There is no cure for alpha-sarcoglycanopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. Those who develop heart problems should consult with a cardiologist for symptomatic treatments. As muscles deteriorate, a ventilator may be required to aid breathing.

What is the prognosis for a person with Alpha-Sarcoglycanopathy?

The outlook for a person with alpha-sarcoglycanopathy varies. Generally speaking, the earlier symptoms begin, the faster they progress. Some people with the disease experience only mild symptoms, and may have near-normal strength. Others with a mild course may remain able to walk for 30 years or more after symptoms appear. People with more severe symptoms can become wheelchair bound in their early teens and die in their early 20s. Death is often a result of respiratory failure.

Alstrom Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: ALMS1.
Exons Sequenced: NM_015120:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Alstrom Syndrome?

Alstrom syndrome is an inherited condition that affects fat cells and tiny hair-like parts of a cell called cilia. Although severity of symptoms can vary from person to person, even among those in the same family, most individuals develop vision and hearing loss, obesity, diabetes, and heart disease. The cause of vision loss is called cone-rod dystrophy, which leads to extreme sensitivity to light and and involuntary rapid eye movements. Vision loss begins in infancy and worsens over time, with most individuals eventually losing all ability to see. Eighty five percent of people with the disease will develop hearing loss in both ears that slowly becomes more severe. Nearly all people with the disease have high lipid levels, become obese in childhood, and have moderate to high weights as adults. Resistance to insulin begins in childhood and type 2 diabetes mellitus usually develops in adolescence. Two thirds of people with Alstrom syndrome develop a type of heart defect called dilated cardiomyopathy and congestive heart failure, which often happens during infancy, but can also occur in childhood or adolescence.

Some people with Alstrom syndrome develop liver disease or kidney disease. Chronic respiratory infections begin early in childhood and eventually cause various types of lung illnesses. Other common symptoms include short stature; scoliosis or kyphosis; extra, missing, or mislocated teeth and urinary problems. Most people with Alstrom syndrome have normal intelligence, but may have delayed developmental milestones.

Another common Alstrom syndrome symptom includes abnormal sexual development. About eighty percent of males with Alstrom syndrome do not produce enough testosterone and have small external genitalia and degeneration of the testes. Females with Alstrom syndrome may begin puberty early, and their periods may be abnormal or absent. Females also may have abnormal hair growth, hair that is completely absent in places, endometriosis, or polycystic ovaries. Most people with Alstrom syndrome cannot have biological children.

How common is Alstrom Syndrome?

Alstrom syndrome is considered a rare disorder. It is unknown exactly how often the condition occurs in the general population, though estimates range from 1 in 100,000 to less than 1 in 1,000,000. Only about 800 people have been diagnosed worldwide. The frequency is higher in isolated populations or those where marriage between blood relatives (consanguinity) is common.

How is Alstrom Syndrome treated?

There is no cure for Alstrom syndrome, but careful monitoring of vision, hearing, liver, heart, thyroid, and kidney function is important for detecting and treating symptoms early. Young children benefit from red tinted prescription glasses, development of non-visual language skills, and hearing aids. Cardiac function should be routinely monitored by echocardiography and patients who develop cardiomyopathy need to take angiotensin-converting enzyme (ACE) inhibitors. Physical exercise is important for weight management. Some patients require insulin, insulin-sensitizing agents, or thiazolidinediones. Patients may also need hormone replacement therapy. Intermittent self-catheterization can help with bladder control. Some patients may need specific medications and treatments to help with liver and kidney problems. Patients and their families benefit greatly from seeking social and emotional support to cope with the isolation that may come with living with a rare and complicated disorder.

What is the prognosis for a person with Alstrom Syndrome?

Prognosis is highly variable due to the range of disease presentations. Alstrom syndrome is associated with a number of chronic life-threatening issues, such as congestive heart failure and end-stage renal disease, the two major causes of death. Death typically occurs before age 40.

AMT-related Glycine Encephalopathy

Available Methodology: sequencing with copy number analysis.
Gene: AMT.
Exons Sequenced: NM_000481:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is AMT-related Glycine Encephalopathy?

AMT-related glycine encephalopathy (AMT-related GE) is a disease that impairs the body's ability to metabolize glycine, an amino acid found in proteins. Glycine accumulates in all body tissues, including the brain, and can lead to lethargy, seizures, low muscle tone, breathing difficulties, coma, and often death. Patients who survive with AMT-related GE have intellectual disability and seizures. The majority of patients with AMT-related encephalopathy present in the neonatal period, but there are multiple forms of the condition described.

The **neonatal form** of this disease presents in the first hours to days of life with rapid progression of symptoms. The **infantile onset form** is characterized by developmental delays and infantile-onset seizures at approximately 6 months of age. Other atypical types of AMT-related GE appear later in childhood or adulthood and cause a variety of medical problems that primarily affect the nervous system.

How common is AMT-related Glycine Encephalopathy?

Glycine encephalopathy affects approximately 1 in 250,000 live births in the United States. The incidence of glycine encephalopathy is higher in certain populations such as British Columbia (1 in 63,000) and in Finland (1 in 55,000). Approximately 15-20% of individuals with glycine encephalopathy have mutations in the *AMT* gene.

How is AMT-related Glycine Encephalopathy treated?

There is no cure for glycine encephalopathy. Disease management is aimed at trying to reduce the accumulation of glycine in the body. Glycine plasma concentrations can be reduced by sodium benzoate and low protein diet. Seizures are addressed with anticonvulsant medications, but may not be completely effective for all individuals.

What is the prognosis for a person with AMT-related Glycine Encephalopathy?

About 85% of those with neonatal onset and 50% of those with the infantile onset will have severe symptoms. These infants typically will have profound intellectual disability and will have seizures that are difficult to treat. Death in the first year is common in these individuals.

Approximately 20% of all children affected with glycine encephalopathy will have less severe symptoms. These individuals will have moderate intellectual disability. They are often able to communicate (most often non-verbally), and typically have seizures that respond to treatment. These children may develop movement disorders and behavioral problems.

Rarely, affected individuals present with late-onset glycine encephalopathy, in which symptoms appear usually after one year of age. These individuals typically have some intellectual disability, and seizures are uncommon.

Andermann Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: SLC12A6.
Exons Sequenced: NM_133647:1-25.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Andermann Syndrome?

Andermann syndrome, also called agenesis of corpus callosum with peripheral neuropathy, is an inherited disease causing progressive damage to the nervous system. Its symptoms appear early in life and include mental disability, a delay in motor skills, overall muscle weakness, curvature of the spine, and dysfunction in the nerves of the hands and feet resulting in numbness, pain, and muscle weakness. These symptoms will worsen over time.

The disease causes motor and sensory skills to be impaired from infancy. People with the disease also share certain physical traits including a small head, long asymmetric face, small upper jaw, large ears, and a large distance between the eyes.

Two-thirds of people with the disease are missing the corpus callosum, a structure which connects the right and left sides of the brain, while the remaining third have a partially-formed corpus callosum. People with the disease learn to walk later than normal, often around the age of 3, and progressively lose the ability to walk in their early teens. They may also experience seizures.

In their 20s, people with Andermann syndrome often develop hallucinations and psychosis. The disease is typically fatal before the age of 40.

The disease is seen almost exclusively in people from the Saguenay-Lac-St-Jean region of Québec, Canada.

How common is Andermann Syndrome?

According to one researcher, Andermann syndrome affects 1 in 2,117 births in the Saguenay-Lac-St-Jean region of Québec, Canada, making 1 in 23 people there a carrier of the disease. It is rarely seen in any other population.

How is Andermann Syndrome treated?

There is no cure for Andermann syndrome and few effective treatments for its symptoms. Physical therapy may be useful to maintain movement as long as possible. Surgery may also be recommended to straighten the spine.

What is the prognosis for a person with Andermann Syndrome?

Andermann syndrome is a progressive disease which impairs a person's motor functions and causes mental disability. All people with the disease will eventually be wheelchair bound. In their 20s, people with Andermann syndrome typically develop severe mental problems. The disease is usually fatal before the age of 40.

Argininemia

Available Methodology: sequencing with copy number analysis.
Gene: ARG1.
Exons Sequenced: NM_001244438:1-8.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Argininemia?

Argininemia belongs to a group of disorders called urea cycle disorders. Individuals with argininemia are missing an important enzyme called arginase. Lack of this enzyme leads to high levels of arginine in the blood.

Most affected individuals present with symptoms between the ages of 1 and 3 years, although cases of earlier onset have been reported. Symptoms typically include poor growth, stiff muscles (spasticity), seizures, and intellectual disability including loss of skills. Some individuals may also have microcephaly (small head size), liver cirrhosis, problems with balance and coordination, or episodes of hyperammonemia (high levels of ammonia in the blood). Hyperammonemia may cause additional complications like lethargy or vomiting.

How common is Argininemia?

Argininemia is a rare condition that occurs in about 1 in 350,000 to 1 in 1,000,000 births.

How is Argininemia treated?

People affected with argininemia will be monitored by a metabolic specialist. Appropriate treatment can lower the risk of hyperammonemic crises and may even reverse some of the neurological symptoms associated with argininemia. Treatment includes adherence to a protein-restricted diet, supplementation of necessary amino acids, and the use of medications to lower the levels of arginine in the blood. Seizures can be treated with medication, but valproic acid should be avoided. Liver transplantation may be considered if hyperammonemia cannot be otherwise controlled. During a severe hyperammonemic crisis, treatment is given to quickly reduce ammonia levels in the blood to prevent brain damage. Such treatment will likely take place in the hospital.

What is the prognosis for a person with Argininemia?

Without treatment, individuals will experience poor growth, stiff muscles, developmental delay, and intellectual disability. Lifespan is expected to be normal in most affected individuals, but some may die early from complications of a hyperammonemic crisis. With treatment, some neurological symptoms may be reversed and the risk of hyperammonemic crises may be reduced over the course of the individual's life, thereby improving outcomes.

Argininosuccinic Aciduria

Available Methodology: sequencing with copy number analysis.
Gene: ASL.
Exons Sequenced: NM_001024943:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Argininosuccinic Aciduria?

Argininosuccinic aciduria (ASL deficiency) is a urea cycle disorder that results from deficiency of the enzyme, argininosuccinate lyase. Defects in this enzyme cause increased levels of argininosuccinic acid and citrulline (amino acids) in the body, because the body cannot convert them into arginine. As a result, ammonia may build up in the body instead of being removed through the urea cycle, which contributes to disease symptoms. There are two forms of the disease:

NEONATAL-ONSET FORM

The neonatal-onset form is severe. It is noticed within the first few days of life by symptoms such as vomiting, lethargy, hypothermia, poor feeding, and tachypnea (rapid breathing). If left untreated, symptoms will progress and eventually lead to seizures, coma, and death. Other early symptoms may include brittle hair and an enlarged liver.

LATE-ONSET FORM

The late onset form can have a wide range of symptoms. Some symptoms include, but are not limited to, periodic increases in ammonia levels, developmental delay/intellectual disability, and behavioral abnormalities.

How common is Argininosuccinic Aciduria?

Argininosuccinic aciduria has an estimated incidence of 1 in 70,000, though this number may vary by region. For example, a founder effect has been described in Finland, Saudi Arabia, and the Druze community and thus, carrier risk and incidence of ASL deficiency may be higher in these areas.

How is Argininosuccinic Aciduria treated?

Argininosuccinic aciduria is primarily controlled by restricting protein from the diet and by taking arginine supplements. Other drugs called nitrogen-scavenging drugs may also help maintain lower amounts of ammonia in the body. In individuals where ammonia levels cannot be managed by the aforementioned therapies, or in those with liver cirrhosis, a liver transplant may be considered.

Acute hyperammonemic episodes are treated in a hospital. Though intravenous supplements and nitrogen-scavenging drugs can help lower the amount of ammonia in the body, hemodialysis may be necessary if these measures are ineffective.

What is the prognosis for a person with Argininosuccinic Aciduria?

There is no cure for argininosuccinic aciduria and the prognosis depends upon the severity of the symptoms. Individuals who have milder symptoms and who are provided with early dietary and therapeutic interventions will have a more favorable outcome, but they will still require long-term treatment to prevent additional neurologic and liver damage. Those who have more severe symptoms could experience seizures, coma, and early death. It is important to remember that treatments to reduce ammonia levels in the body do not prevent cognitive issues (for example, many individuals have mild to moderate intellectual disability), liver disease, brittle hair, and high blood pressure.

ARSACS

Available Methodology: sequencing with copy number analysis.
Gene: SACS.
Exons Sequenced: NM_014363:2-10.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe

What is ARSACS?

ARSACS is the common name for Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. It is a progressive disease that affects the body's ability to create a protein called sacsin, normally found in the brain, skin, and muscles.

The first symptom, unsteady gait, typically appears between 12 and 18 months of age as toddlers begin to walk. Children also develop speech problems due to weak neck and facial muscles. The condition becomes increasingly worse over time, with muscle tension and spasms, difficulty coordinating movements, involuntary eye movements, and muscle wasting. Some people with ARSACS also lose sensation in their arms and legs as the nerves degenerate.

Other symptoms include incontinence, deformities of the fingers and feet, and buildup of fatty tissue on the retina leading to vision problems. Occasionally, the disease also causes leaks in one of the valves that control blood flow through the heart.

Most people with the condition are usually of normal intelligence and are able to live independently well into adulthood, although they eventually lose the ability to walk.

How common is ARSACS?

The majority of people with ARSACS have ancestry in the Charlevoix-Saguenay region of Quebec, Canada, where the condition affects approximately 1 in 1,500 to 2,000 people. Elsewhere in the world, the condition is rare.

How is ARSACS treated?

Treatment for ARSACS focuses on easing the symptoms and postponing major functional disabilities. Physical therapy and anti-spasmodic oral medications can help control muscle spasms, prevent joint and tendon deformities, and preserve muscle function for

some time. Low doses of medication can control incontinence. Occupational therapy and adaptive tools such as leg braces can support people with ARSACS in daily tasks such as driving. As the disease progresses, however, people with ARSACS typically lose the ability to perform these tasks. Children with the condition may benefit from speech therapy and other forms of support in school.

What is the prognosis for a person with ARSACS?

People with ARSACS become wheelchair-bound at an average age of 41 and commonly die in their fifties.

Aspartylglycosaminuria

Available Methodology: sequencing with copy number analysis.
Gene: AGA.
Exons Sequenced: NM_000027:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Aspartylglycosaminuria?

Aspartylglycosaminuria (AGU) is an inherited condition in which an enzyme deficiency leads to variety of physical symptoms. It is most common among people of Finnish descent.

Symptoms typically appear within the first few years of life. Infants with AGU experience frequent diarrhea and infections. Other early signs include clumsiness, delayed speech, and hyperactivity.

People with the disease experience progressive mental disability, seizures, and behavioral problems. Between the ages of 13 and 16, they typically have the mental and motor development of a 5 or 6 year-old. By the mid-20s, they are severely mentally disabled.

People with AGU share certain physical features including sagging cheeks, eye deformities, a broad nose and face, a short neck, an asymmetrical head, and spinal deformities. Their facial features tend to coarsen over time, and connective tissue problems or osteoporosis may develop.

How common is Aspartylglycosaminuria?

Aspartylglycosaminuria is most common in Finland, where an estimated 1 in 26,000 babies are affected. In some regions of Finland, where carrier rates can be 1 in 40, as many as 1 in 3,600 babies will have the disease. AGU is the third most common cause of mental disability in Finland. Some studies have indicated that when the disease occurs in non-Finnish people, often the parents are close blood relatives.

How is Aspartylglycosaminuria treated?

There is no treatment for the cause of AGU. Medical professionals can only treat symptoms as they arise. These treatments may include, but are not limited to, special education, anti-seizure medication, and orthopedic aids to help in movement.

What is the prognosis for a person with Aspartylglycosaminuria?

The lifespan of a person with AGU has not been well-documented, perhaps due to the disease's rarity. In one Canadian family, three affected siblings died in their 30s and 40s. All people with the disease experience severe mental disability and impaired motor function.

Ataxia with Vitamin E Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: TTPA.
Exons Sequenced: NM_000370:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Ataxia With Vitamin E Deficiency?

Ataxia with vitamin E deficiency (AVED) is an inherited disease that causes the nervous system to degenerate, leading to a progressive inability to control one's voluntary movements (ataxia). If treated early and consistently with vitamin E, symptoms of the disease can be avoided.

If untreated with vitamin E, other symptoms of the disease can include difficulty speaking, loss of sensation in the arms and legs, and loss of some visual acuity. In some people, intellectual decline and mental problems can occur. Other people with AVED have experienced heart problems as well.

In people with the disease who remain untreated, movement problems often begin between the ages of 4 and 18 and worsen over time. Early symptoms often include clumsiness of the hands, problems with handwriting, and reduced awareness of how one's body is positioned. These people will lose tendon reflexes in the arms and legs.

The type and severity of symptoms will vary from person to person, even among those in the same family.

How common is Ataxia With Vitamin E Deficiency?

AVED is rare, but its exact prevalence is unknown. It may be more common in people of Mediterranean or North African descent.

How is Ataxia With Vitamin E Deficiency treated?

AVED is treatable with high doses of vitamin E taken regularly throughout life. If taken before symptoms begin, vitamin E can prevent symptoms from occurring at all. If symptoms have already begun, vitamin E may prevent them from worsening and in some people, symptoms have been reversed to some degree. Unsteadiness walking, however, often cannot be reversed.

People with AVED should not smoke, as this can reduce the amount of vitamin E in the body. They also should not undertake jobs that require quick responses or good balance. Before learning to drive a car, their abilities should be assessed to determine whether driving is safe.

What is the prognosis for a person with Ataxia With Vitamin E Deficiency?

If treated with vitamin E before symptoms start, people with AVED can lead normal lives. Without treatment, people with AVED will become wheelchair-reliant between the ages of 11 and 50, and may develop significant physical and mental problems.

Ataxia-telangiectasia

Available Methodology: sequencing with copy number analysis.
Gene: ATM.
Exons Sequenced: NM_000051:2-63.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
97%	Hispanic
>99%	Middle East
>99%	Native American
98%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
99%	Southern Europe

What is Ataxia-Telangiectasia?

Ataxia-telangiectasia (A-T) is an inherited disease which affects a person's ability to control movement. It also may weaken the immune system. People with A-T are at greatly increased risk for cancer, and the median age of death is around 22.

Shortly after children with A-T learn to walk, they will begin to wobble or stagger. Their motor skills will develop slower than normal and they will have poor balance and slurred speech. They lose the ability to follow objects with their eyes. This inability to control body movement, caused by damage to part of the brain, is called ataxia. By the age of seven or eight, children with the disease often lose the muscle control necessary to write, and most are confined to wheelchairs by the age of ten.

Teenagers and adults with the disease require help with everyday tasks, including dressing, eating, washing, and using the bathroom. Loss of muscle control often leads to drooling. While neurological problems may impair their ability to communicate, people with A-T are usually of average or above-average intelligence.

Another hallmark of the disease is the appearance of tiny red spider-like veins around the corners of the eyes and on the ears and cheeks. This is known as telangiectasia.

Between 60 and 80% of people with A-T have weakened immune systems, leaving them prone to infection, particularly in the lungs. They are also at an increased likelihood of developing cancer at an early age, particularly cancer of the blood (leukemia) and of the immune system (lymphoma). They are hypersensitive to the type of radiation found in X-rays and used in cancer treatment and typically must avoid it.

Other symptoms of the disease may include diabetes, premature graying of the hair, problems with swallowing, and delayed sexual development.

A-T is caused by mutations in a gene involved in the control of cell growth and division, and also in the repair of damaged DNA.

Carriers of A-T do not show symptoms of the disease, but studies have shown that they are at a greater than average risk of developing cancer, particularly breast cancer. Due to this increased risk, it is recommended that women who are carriers have an annual MRI and mammogram to screen for cancer.

How common is Ataxia-Telangiectasia?

A-T affects 1 in every 40,000 to 100,000 births worldwide. It is believed that around 1% of the U.S. population is a carrier of A-T.

How is Ataxia-Telangiectasia treated?

There is no cure for A-T, but symptoms of the disease can be addressed. Injections of gamma globulin may be prescribed to help boost the immune system. High-dose vitamins may also be suggested. Antibiotics are typically used for infections. Vaccines for influenza and pneumonia may be recommended, as these diseases can be devastating to people with A-T.

Physical and occupational therapy are recommended to aid in movement and flexibility. Speech therapy may also be useful.

What is the prognosis for a person with Ataxia-Telangiectasia?

Nearly all people with A-T are wheelchair-bound by the age of 10. Because intelligence remains normal, many people with the disease graduate high school and college. People with A-T have shortened lifespans, with the median age of death around 22 years. A small number of people have survived into their 40s and 50s. The most common causes of death from this disease are cancer, lung infection, or lung failure.

ATP7A-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: ATP7A.
Exons Sequenced: NM_000052:2-23.

Detection Rate	Population
92%	African American
92%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
96%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
96%	Southern Europe

What are ATP7A-related Disorders?

ATP7A-related disorders are a spectrum of diseases that result from improper regulation of copper in the body. They generally occur in males, as *ATP7A*, the gene associated with the disorders, is on the X-chromosome. Females are usually asymptomatic. The symptoms associated with each condition result from defective copper metabolism throughout the body which causes organ damage.

MENKES SYNDROME

Menkes syndrome, the most typical presentation of this condition, is associated with low or absent serum copper levels. Boys with Menkes syndrome usually start to show symptoms at a few months of age, and symptoms include delayed development or loss of milestones due to progressive neurodegeneration, low muscle tone, poor growth, seizures, and an out-pouching of the bladder. Changes in appearance may be noticeable around symptom onset, including hair with a specific coarse texture, twisting shape and lighter color, and sagging in the face.

OCCIPITAL HORN SYNDROME (OHS)

OHS is a milder copper transport disorder, with boys not displaying symptoms until they are several years old. Symptoms in OHS are related to the connective tissues, and typically include loose skin, unstable joints, differences in hair, and calcium deposits of a specific region of the skull that give the condition its name.

DISTAL MOTOR NEUROPATHY

In rare cases, *ATP7A* mutations can lead to a variable condition that causes weakness in the hands and feet, foot drop (front of foot drops and affects walking), and some absent reflexes. It has been reported in early childhood to late adulthood, but most individuals develop symptoms in adulthood (20s-30s).

CARRIERS

Females with an *ATP7A* mutation are usually asymptomatic, although about half express atypical hair findings.

How common are ATP7A-related Disorders?

ATP7A-related disorders are rare. Studies indicate that 1 in 300,000 babies in European populations have Menkes syndrome. The condition is less common in Japan with 1 in 360,000 individuals affected with the condition. Menkes syndrome may be more common in Australia, where some studies estimated that 1 in 50,000 to 1 in 100,000 were affected. The global incidence of occipital horn syndrome and distal motor neuropathy is unknown.

How are ATP7A-related Disorders treated?

These conditions are treated with copper supplementation, which must be given by injection. Early supplementation (within the first few weeks of life) may improve outcomes and increases life expectancy for some children with Menkes syndrome, though less is known about the effects for the other presentations.

In individuals where symptoms have already developed, treatment is symptomatic. For example, a feeding tube may be given to ensure proper nutrition. Early intervention may assist with developmental issues, and physical/occupational therapy and orthopedic aids may improve symptoms due to connective tissue problems.

What is the prognosis for a person with an ATP7A-related Disorder?

Without treatment, children with Menkes syndrome do not typically survive more than three years. Early treatment of Menkes syndrome with copper supplementation can improve outcomes and increase life expectancy. Individuals with OHS live into at least mid-adulthood. Little is known about the success of copper supplementation in OHS. Life expectancy is thought to be unaffected by distal motor neuropathy, but only a few cases of this presentation have been reported and long-term outcomes are unknown.

Autosomal Recessive Osteopetrosis Type 1

Available Methodology: sequencing with copy number analysis.
Gene: TCIRG1.
Exons Sequenced: NM_006019:2-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Autosomal Recessive Osteopetrosis Type 1?

Autosomal recessive osteopetrosis type 1 (ARO1) is an inherited condition characterized by abnormal bone formation. In most cases, symptoms of the condition first appear in infancy. Characteristic features include unusually dense bones, a high risk of bone fractures, a large head size with a prominent forehead, growth deficiency, and dental problems. The abnormal bone present in the skull may also lead to compression of nerves in the face and head, resulting in vision impairment or blindness, hearing loss, and paralysis of the facial muscles. In addition, breathing and feeding difficulties may result from narrowing of the passageways connecting the nose and throat.

The abnormal bone formation in ARO1 also affects the bone marrow, which is important for blood cell formation and immune system function. Consequently, children with ARO1 may have severe anemia, problems with immune system function that lead to an increased risk for infections, and enlargement of the liver and spleen. In addition, some affected individuals may have seizures due to low blood calcium levels. Intellectual disability (usually mild to moderate) may result from recurrent seizures and/or brain abnormalities that may occur in some individuals with ARO1.

How common is Autosomal Recessive Osteopetrosis Type 1?

It is currently unknown how often the condition occurs in the general population, although ARO1 is generally thought to be a rare disease worldwide. It is known, however, that ARO1 is more common in certain populations, including the Chuvash and Mari populations of Russia (1 in 3500 and 1 in 14,000, respectively), in the Middle East (~1 in 37,000), and in Costa Rica (~1 in 59,000).

How is Autosomal Recessive Osteopetrosis Type 1 treated?

The treatment for ARO1 is primarily supportive. Patients are monitored and symptoms are treated as they arise. Medical management typically includes blood transfusions and the treatment of fractures, infections, vision and hearing problems, and

seizures if they develop. In addition, certain medications have been shown to slow the progression of the disease in some individuals. The only known cure for ARO1 is a bone marrow transplant early in life, although this procedure is associated with a high mortality rate.

What is the prognosis for a person with Autosomal Recessive Osteopetrosis Type 1?

Generally, the prognosis for children with ARO1 is poor. Most children with the condition die within the first decade of life, although early bone marrow transplantation can be curative, if successful.

Bardet-Biedl Syndrome, BBS1-related

Available Methodology: sequencing with copy number analysis.
Gene: BBS1.
Exons Sequenced: NM_024649:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Bardet-Biedl Syndrome, BBS1-related?

Bardet-Biedl syndrome is an inherited disease that causes vision problems, kidney abnormalities, genital anomalies, extra fingers or toes, and mild obesity, among other symptoms. About half of people with the disease have developmental delay or mental disability.

One hallmark of the disease is a vision problem caused by degeneration of the retina. It begins as night blindness in childhood and progresses to a loss of peripheral vision. People with Bardet-Biedl syndrome can also lose central vision during childhood or adolescence. The mean age at which these adolescents become legally blind is 15.5 years. By early adulthood, they are severely visually impaired.

Kidney abnormalities are present in most people with Bardet-Biedl syndrome. The problems caused by these abnormalities can range from few functional problems to life-threatening kidney failure.

Around half of people with the disease have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to severe mental disability. In some cases these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Commonly, people with Bardet-Biedl syndrome have extra fingers and/or toes and mild obesity. Males with the disease often have small genitalia. Women with the disease typically have irregular menstrual cycles and may have structural deformities of the vagina. Some also have diabetes.

Bardet-Biedl syndrome is similar to Laurence-Moon syndrome, and they have been thought to be one and the same at times. The relationship between these two syndromes is still being studied.

How common is Bardet-Biedl Syndrome, BBS1-related?

Bardet-Biedl syndrome is rare, affecting about 1 in 100,000 in North America and 1 in 125,000 in Europe. It is more or less common in specific populations, such as Kuwaiti Bedouins (1 in 13,500), residents of Newfoundland, Canada (1 in 17,500), and the Swiss (1 in 160,000).

How is Bardet-Biedl Syndrome, BBS1-related treated?

There is no cure for Bardet-Biedl syndrome. Extra fingers and toes can often be surgically removed in childhood. The vision and kidney problems associated with the disease can be treated in the standard fashion by medical specialists. If kidney problems reach life-threatening levels, dialysis and/or kidney transplantation may be necessary. Diet and exercise can help control obesity. In women, vaginal malformations can be surgically corrected.

What is the prognosis for a person with Bardet-Biedl Syndrome, BBS1-related?

Kidney disease is a major cause of early death for people with Bardet-Biedl syndrome.

Bardet-Biedl Syndrome, BBS10-related

Available Methodology: sequencing with copy number analysis.
Gene: BBS10.
Exons Sequenced: NM_024685:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Bardet-Biedl Syndrome, BBS10-related?

Bardet-Biedl syndrome is an inherited disease that causes vision problems, kidney abnormalities, genital anomalies, extra fingers or toes, and mild obesity, among other symptoms. About half of people with the disease have developmental delay or mental disability.

One hallmark of the disease is a vision problem caused by degeneration of the retina. It begins as night blindness in childhood and progresses to a loss of peripheral vision. People with Bardet-Biedl syndrome can also lose central vision during childhood or adolescence. The mean age at which these adolescents become legally blind is 15.5 years. By early adulthood, they are severely visually impaired.

Kidney abnormalities are present in most people with Bardet-Biedl syndrome. The problems caused by these abnormalities can range from few functional problems to life-threatening kidney failure.

Around half of people with the disease have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to severe mental disability. In some cases these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Commonly, people with Bardet-Biedl syndrome have extra fingers and/or toes and mild obesity. Males with the disease often have small genitalia. Women with the disease typically have irregular menstrual cycles and may have structural deformities of the vagina. Some also have diabetes.

Bardet-Biedl syndrome is similar to Laurence-Moon syndrome, and they have been thought to be one and the same at times. The relationship between these two syndromes is still being studied.

How common is Bardet-Biedl Syndrome, BBS10-related?

Bardet-Biedl syndrome is rare, affecting about 1 in 100,000 in North America and 1 in 125,000 in Europe. It is more or less common in specific populations, such as Kuwaiti Bedouins (1 in 13,500), residents of Newfoundland, Canada (1 in 17,500), and the Swiss (1 in 160,000).

How is Bardet-Biedl Syndrome, BBS10-related treated?

There is no cure for Bardet-Biedl syndrome. Extra fingers and toes can often be surgically removed in childhood. The vision and kidney problems associated with the disease can be treated in the standard fashion by medical specialists. If kidney problems reach life-threatening levels, dialysis and/or kidney transplantation may be necessary. Diet and exercise can help control obesity. In women, vaginal malformations can be surgically corrected.

What is the prognosis for a person with Bardet-Biedl Syndrome, BBS10-related?

Kidney disease is a major cause of early death for people with Bardet-Biedl syndrome.

Bardet-Biedl Syndrome, BBS12-related

Available Methodology: sequencing with copy number analysis.
Gene: BBS12.
Exon Sequenced: NM_152618:2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Bardet-Biedl Syndrome, BBS12-related?

Bardet-Biedl syndrome (BBS) is an inherited disease that generally causes vision problems, mild obesity, extra fingers or toes, genital and kidney abnormalities, and learning difficulties.

One hallmark of the disease is a vision problem caused by degeneration of the retina. It begins as night blindness in childhood and progresses to a loss of peripheral vision. People with Bardet-Biedl syndrome can also lose central vision during childhood or adolescence. The mean age at which these adolescents become legally blind is 15.5 years. By early adulthood, they are severely visually impaired.

Kidney abnormalities are present in most people with Bardet-Biedl syndrome. The problems caused by these abnormalities can range from few functional problems to life-threatening kidney failure. Around half of people with the disease have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to more severe symptoms. In some cases these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Less common features include liver disease, diabetes, neurological issues (like poor balance and coordination), behavioral issues, characteristic physical features (facial features and dental irregularities), high blood pressure, defects in the heart or reproductive system, and hearing loss amongst others. These features tend to vary by the type.

There are at least 19 genes that are associated with Bardet-Biedl syndrome, and some of these genes have been associated with other syndromes (e.g. Laurence-Moon syndrome, retinitis pigmentosa, Meckel-Gruber syndrome). It is unclear if this represents a spectrum of disease or if BBS is a distinct condition from the other associated syndromes.

How common is Bardet-Biedl Syndrome, BBS12-related?

Bardet-Biedl syndrome is generally thought to be a rare disorder. A few studies, primarily in Caucasians, have suggested an overall frequency of cases from 1 in 100,000 individuals in North America to 1 in 150,000 in Europe. However, the global frequency of this

condition cannot be estimated from these numbers. One reason for this is that the disease frequency varies by population, being higher in populations where marriage between blood relatives (consanguinity) is common or the population was isolated. Examples of higher disease frequency for BBS include Kuwaiti Bedouins (1 in 6,900), Tunisians (1 in 87,000), and individuals from Newfoundland (1 in 18,000). *BBS12* only accounts for about 5% of all BBS cases, and to date, all cases of *BBS12* have been found in the Gypsy (Roma), Chinese, Kurdish, and Caucasian individuals.

How is Bardet-Biedl Syndrome, BBS12-related treated?

There is no cure for Bardet-Biedl syndrome, and symptoms of the condition are managed by a team of specialists. A geneticist is typically involved in the diagnosis and centralized management of an affected child. Management may include monitoring, provision of aids/therapies, or surgery.

Regular monitoring of vision, weight, blood pressure, thyroid/kidney/liver function, and development are recommended. Vision issues will be managed by an ophthalmologist and there may be aids that help improve quality of life. A dietician may help with weight regulation and medications may help with high blood pressure. An endocrinologist may be consulted for diabetes, thyroid disease, and proper pubertal development. Kidney issues are managed in a standard fashion, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood or heart/vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. Early intervention and therapies may assist with learning difficulties, and a pediatric neurologist may help monitor the progression of development, if necessary.

What is the prognosis for a person with Bardet-Biedl Syndrome, BBS12-related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition - even within families. One of the most consistent features is progressive vision loss, which frequently leads to blindness. Kidney disease is also frequent, with about a third of patients developing kidney failure and about 10% requiring dialysis or transplantation. Kidney disease is a major cause of early death for people with BBS, though complications of obesity, heart disease, and diabetes have also been reported as causes of death. A majority of individuals may have a normal or near-normal life expectancy though with various impairments.

Bardet-Biedl Syndrome, BBS2-related

Available Methodology: sequencing with copy number analysis.
Gene: BBS2.
Exons Sequenced: NM_031885:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Bardet-Biedl Syndrome, BBS2-related?

Bardet-Biedl syndrome (BBS) is an inherited disease that generally causes vision problems, mild obesity, extra fingers or toes, genital and kidney abnormalities, and learning difficulties.

One hallmark of the disease is a vision problem caused by degeneration of the retina. It begins as night blindness in childhood and progresses to a loss of peripheral vision. People with Bardet-Biedl syndrome can also lose central vision during childhood or adolescence. The mean age at which these adolescents become legally blind is 15.5 years. By early adulthood, they are severely visually impaired.

Kidney abnormalities are present in most people with Bardet-Biedl syndrome. The problems caused by these abnormalities can range from few functional problems to life-threatening kidney failure. Around half of people with the disease have developmental disabilities. This can range from mild learning disabilities or delayed emotional development to more severe symptoms. In some cases these delays are due in part to vision loss, while in other cases they are a direct result of the disease.

Less common features include liver disease, diabetes, neurological issues (like poor balance and coordination), behavioral issues, characteristic physical features (facial features and dental irregularities), high blood pressure, defects in the heart or reproductive system, and hearing loss amongst others. These features tend to vary by the type. Some secondary features reported in Bardet-Biedl syndrome, BBS2-related are characteristic facial features, heart defects, and short fingers that may be webbed or joined together.

There are at least 19 genes that are associated with Bardet-Biedl syndrome, and some of these genes have been associated with other syndromes (e.g., Laurence-Moon syndrome, retinitis pigmentosa, Meckel-Gruber syndrome). It is unclear if these represent a spectrum of disease or if BBS is a distinct condition from the other associated syndromes. Mutations in *BBS2* have been reported in a few individuals with retinitis pigmentosa (vision loss only) and Meckel-Gruber syndrome (typical features include kidney disease and extra fingers or toes with the addition of brain malformations).

How common is Bardet-Biedl Syndrome, BBS2-related?

Bardet-Biedl syndrome is generally thought to be a rare disorder. A few studies, primarily in Caucasians, have suggested an overall frequency of cases from 1 in 100,000 individuals in North America to 1 in 150,000 in Europe. However, the global frequency of this condition cannot be estimated from these numbers. One reason for this is that the disease frequency varies by population, being higher in populations where marriage between blood relatives (consanguinity) is common or the population was isolated. Examples of populations with a higher frequency of BBS include Kuwaiti Bedouins (1 in 6900), Tunisians (1 in 87,000), and individuals from Newfoundland (1 in 18,000). Populations with higher frequencies of *BBS2* have also been reported in Tunisia, a Hutterite population from South Dakota, and the Ashkenazi Jewish. *BBS2* only accounts for 7.5-17% of all BBS cases.

How is Bardet-Biedl Syndrome, BBS2-related treated?

There is no cure for Bardet-Biedl syndrome, and symptoms of the condition are managed by a team of specialists. A geneticist is typically involved in the diagnosis and centralized management of an affected child. Management may include monitoring, provision of aids/therapies, or surgery.

Regular monitoring of vision, weight, blood pressure, thyroid/kidney/liver function, and development are recommended. Vision issues will be managed by an ophthalmologist and there may be aids that help improve quality of life. A dietician may help with weight regulation and medications may help with high blood pressure. An endocrinologist may be consulted for diabetes, thyroid disease, and proper pubertal development. Kidney issues are managed in a standard fashion, but if they become life-threatening, dialysis or transplantation may be necessary. Surgery can correct some birth defects (extra digits may be removed in childhood or heart/vaginal malformation may be corrected), and an orthodontist may assist with correction of dental anomalies. Early intervention and therapies may assist with learning difficulties, and a pediatric neurologist may help monitor the progression of development, if necessary.

What is the prognosis for a person with Bardet-Biedl Syndrome, BBS2-related?

Predicting symptoms and the course of the disease for individuals with BBS can be difficult due to the variable nature of the condition - even within families. One of the most consistent features is progressive vision loss, which frequently leads to blindness. Kidney disease is also frequent, with about a third of patients developing kidney failure and about 10% requiring dialysis or transplantation. Kidney disease is a major cause of early death for people with BBS, though complications of obesity, heart disease, and diabetes have also been reported as causes of death. A majority of individuals may have a normal or near-normal life expectancy though with various impairments.

Beta-sarcoglycanopathy

Available Methodology: sequencing with copy number analysis.
Gene: SGCB.
Exons Sequenced: NM_000232:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Beta-Sarcoglycanopathy?

Beta-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2E (LGMD2E), typically causes muscle weakness as a result of a deficiency of the protein, beta-sarcoglycan, in the dystrophin-glycoprotein complex, a component of the muscle system. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal.

People with beta-sarcoglycanopathy develop symptoms at variable ages, though symptoms tend to first present in childhood. Beta-sarcoglycanopathy does not affect intelligence or mental function; the most common symptom is progressive muscle weakness of the hip, shoulder, and abdomen (proximal muscles). The rate at which the muscles weaken can vary, but many experience progressive weakness to a point where a wheelchair becomes necessary. Other possible features include enlarged calf muscles (calf hypertrophy), contractures, scapular winging (shoulder blade is prominent), and scoliosis. Respiratory complications (~10-30% of individuals) or heart complications (~60-70% of individuals) are also associated with the sarcoglycanopathies, and may be a cause of death.

How common is Beta-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. The estimated prevalence of all types of limb-girdle muscular dystrophy is 1 in 15,000 individuals. Beta-sarcoglycanopathy is rare and its exact incidence is unknown.

How is Beta-Sarcoglycanopathy treated?

There is no cure for beta-sarcoglycanopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a

ventilator may be required to aid breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with Beta-Sarcoglycanopathy?

The outlook for a person with beta-sarcoglycanopathy varies. Generally speaking, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. People with more severe symptoms can become wheelchair bound in their early teens and die in early adulthood with death usually being due to respiratory and/or cardiac complications.

Biotinidase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: BTD.
Exons Sequenced: NM_000060:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Biotinidase Deficiency?

Biotinidase deficiency is a highly-treatable inherited disease in which the body cannot process the vitamin biotin due to a deficiency in a particular enzyme. If left untreated, the disease can cause numerous life-threatening complications. By taking daily supplements of biotin before symptoms occur, however, all symptoms of the disease can be avoided. With early detection and treatment, a person with biotinidase deficiency can live a completely normal life.

PROFOUND BIOTINIDASE DEFICIENCY

People who have less than 10% of the normal amount of the enzyme biotinidase are said to have profound biotinidase deficiency. Without treatment, their symptoms tend to be significant. People with biotinidase deficiency can experience seizures, poor muscle tone, difficulty with movement and balance, vision and/or hearing loss, skin rashes, breathing problems, fungal infections, and intellectual and/or developmental delays. These symptoms often begin after the first few weeks or months of life and can be life-threatening if untreated.

If symptoms have already appeared, treatment with biotin can reverse damage to the body already done by the disease. Vision loss, hearing loss, and developmental delay are irreversible.

PARTIAL BIOTINIDASE DEFICIENCY

People who have between 10 and 30% of the normal amounts of biotinidase have a milder form of the disease known as partial biotinidase deficiency. They may experience less severe symptoms, or may be asymptomatic until periods of illness or stress.

How common is Biotinidase Deficiency?

Profound biotinidase deficiency occurs in about 1 in 137,000 births. Studies report that the milder partial biotinidase deficiency occurs in about 1 in 110,000 people. Counsyl's internal data suggests that partial biotinidase deficiency is more common.

How is Biotinidase Deficiency treated?

Biotinidase deficiency is treated with a biotin pill taken daily by mouth. A physician can determine the proper dosage and adjust that dosage over time if necessary. This treatment is lifelong and highly effective. Biotin is non-toxic, so it is recommended that people with partial biotinidase deficiency also take biotin supplements.

If treatment is begun after symptoms appear, some symptoms, such as skin problems and hair loss, will disappear. If the disease has already caused irreversible hearing or vision loss, low vision aids or hearing aids may be helpful. Learning specialists can assist with any irreversible developmental deficits.

What is the prognosis for a person with Biotinidase Deficiency?

With early diagnosis and treatment, people with biotinidase deficiency can live completely normal lives with no symptoms. Those in whom the disease is not detected early may experience permanent damage to their hearing, vision, or intellect. In cases where the disease is entirely unrecognized, it can be life-threatening.

Bloom Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: BLM.
Exons Sequenced: NM_000057:2-22.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What Is Bloom Syndrome?

Bloom syndrome is an inherited disease that causes a person's chromosomes to break and rearrange frequently. Bloom syndrome is caused by mutations in the *BLM* gene. The chromosome instability seen in patients with Bloom syndrome causes high rates of cancer beginning in childhood or early adulthood. People with Bloom syndrome are usually smaller in stature than their peers and have a high-pitched voice. They have distinct facial features including a long, narrow face, small lower jaw, prominent nose and ears, and red lesions on the cheeks and the bridge of the nose (often described as “butterfly-shaped” lesions) which appear and worsen with sun exposure. Most people with Bloom syndrome have a normal intellectual ability, however, some will have intellectual and developmental disabilities. They may also have diabetes, chronic lung problems, and suppressed immune systems. They tend to have high rates of pneumonia and ear infections. Men with Bloom syndrome are usually infertile. Women with Bloom syndrome are fertile but often experience early menopause.

How Common Is Bloom Syndrome?

The incidence of Bloom syndrome is unknown, and fewer than 300 affected individuals have been reported. Approximately one-third of people with the disease are of Ashkenazi Jewish descent, making it more common in this population than in others. Roughly 1 in 48,000 Ashkenazi Jews is affected by the disease.

How Is Bloom Syndrome Treated?

There is no cure for Bloom syndrome. Children with Bloom syndrome need nutritional monitoring to ensure maximum growth. People with the disease are advised to stay out of the sun and wear sunscreen to prevent skin lesions, particularly during childhood. They should also make an effort to avoid infection of all kinds. In school, they may require special education classes due to learning difficulties.

People with Bloom syndrome are prone to cancer, so they should be screened regularly starting in childhood and with increasing vigilance into adulthood. Because they are particularly sensitive to radiation and DNA-damaging chemicals, standard cancer treatments often need to be modified. If diabetes is present, this condition is typically treated with diet, blood-sugar monitoring, and insulin supplements.

What Is the Prognosis for a Person with Bloom Syndrome?

Despite dealing with numerous medical problems, people with Bloom syndrome can lead productive lives. They are most often of normal or near-normal intelligence. Typically, people with Bloom syndrome lead shortened lives, although lifespan can vary greatly from person to person. The cause of death is usually cancer, which can occur in childhood, but more commonly appears in the late teens or early to mid-twenties. Early detection of cancer and appropriate treatment can help extend the lifespan of these individuals.

Calpainopathy

Available Methodology: sequencing with copy number analysis.
Gene: CAPN3.
Exons Sequenced: NM_000070:1-24.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Calpainopathy?

Calpainopathy (also known as limb-girdle muscular dystrophy type 2A or LGMD2A) represents a spectrum of disorders that cause muscle weakness as a result of a deficiency of the protein, calpain-3. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal. Symptoms commonly begin in the early teens, although onset in childhood or adulthood is possible. Calpainopathy does not affect intelligence or mental function; the primary symptom is progressive muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary greatly, but many experience progressive weakness to a point where a wheelchair becomes necessary. Other occasional features include enlarged calf muscles, mild shortening and hardening of the muscles leading to rigid joints, and winging of the shoulder blade. Many individuals with calpainopathy live well into adulthood with rare cases of respiratory failure or heart complications being the most common causes of death. Three phenotypes have been identified: **pelvofemoral muscular dystrophy** (also known as Leyden-Moebius LGMD, where muscle weakness starts in the pelvic girdle), **scapulohumeral muscular dystrophy** (also known as Erb LGMD, where muscle weakness starts in the shoulder girdle), or **hyperCKemia** (elevated creatine kinase levels with no known symptoms).

How common is Calpainopathy?

There are numerous types of limb-girdle muscular dystrophy. Autosomal recessive LGMD has an estimated prevalence of 1 in 15,000 individuals. Calpainopathy is thought to account for 10% of all cases of LGMD, though this varies by region. Calpainopathy is more common in Eastern European, Japanese, and Indiana Amish populations, as well as several others.

How is Calpainopathy treated?

There is no cure for calpainopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for people with Calpainopathy?

The outlook for a person with calpainopathy varies. Generally, the earlier symptoms begin, the faster they progress. Some people with the disease experience only mild symptoms, and may have near-normal strength. Others with a mild course may remain able to walk for 30 years or more after symptoms appear. People with more severe disease typically become wheelchair-bound as early as 10 years after their diagnosis.

Canavan Disease

Available Methodology: sequencing with copy number analysis.
Gene: ASPA.
Exons Sequenced: NM_000049:1-6.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is Canavan Disease?

Canavan disease is an inherited disorder that destroys the myelin sheath, the white matter that insulates nerve cells in the brain. It causes overall muscle weakness and developmental delay leading to severe mental disability. Symptoms usually begin at 3 to 5 months of age with poor muscle tone (hypotonia), which causes problems turning over, controlling head movements, and sitting up. The infant's head also becomes rapidly larger. Over time, people with the condition become unable to swallow and develop sleep disturbances, seizures, and blindness. Most people with Canavan disease die in childhood, although some have lived into their teens and early twenties.

Canavan disease is caused by a deficiency in an enzyme called aspartoacylase. This enzyme breaks down a material called N-acetyl-L-aspartic acid (NAA) in the brain. Without enough enzyme, the NAA builds up in the brain and destroys its white matter.

How common is Canavan Disease?

The prevalence of Canavan disease in the general population is unknown. Among people of Ashkenazi Jewish descent, the disease affects approximately 1 in 6,400 to 13,500 people, making 1 in every 40 to 58 Ashkenazi Jews a carrier.

How is Canavan Disease treated?

At this time, there is no cure for Canavan disease. Treatment focuses on keeping the affected person comfortable with proper nutrition and hydration and controlling seizures with medication.

What is the prognosis for a person with Canavan Disease?

Most people with Canavan disease die in childhood, although some survive into their teens or early twenties. In childhood they become severely mentally disabled and lose muscle control.

Carbamoylphosphate Synthetase I Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: CPS1.
Exons Sequenced: NM_001875:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Carbamoylphosphate Synthetase I Deficiency?

Carbamoylphosphate synthetase I (CPS1) deficiency belongs to a group of disorders called urea cycle disorders. Individuals with CPS1 deficiency are missing an important liver enzyme. This leads to high ammonia levels in the blood (hyperammonemia), which can be harmful especially to the brain.

Most affected individuals will show symptoms within the first few days of life (**neonatal-onset form**), which may include unusual sleepiness, a poorly regulated breathing rate or body temperature, unwillingness to feed, vomiting after feeding, unusual body movements, seizures, or coma. Affected children who survive the newborn period may experience recurrence of these symptoms if diet is not carefully managed or if they experience infections or other stressors. They may also have delayed development and intellectual disability.

Less commonly, people with CPS1 deficiency, have moderate or mild severe symptoms that appear later during childhood or adulthood (**late-onset form**). Patients with the milder form of CPSI deficiency may still experience hyperammonemic coma and life-threatening complications.

How common is Carbamoylphosphate Synthetase I Deficiency?

The exact incidence of CPS1 deficiency is unknown, but is estimated to occur in approximately 1 in 1,300,000 infants born in the USA. Slightly higher incidences have been reported in less ethnically-diverse countries, such as Finland (1 in 539,000) and Japan (1 in 800,000).

How is Carbamoylphosphate Synthetase I Deficiency treated?

There currently is no cure for CPS1 deficiency. The treatment consists of dietary management to limit ammonia production along with medications and supplements that provide alternative pathways for the removal of ammonia from the bloodstream. Maintaining this special diet is needed to make sure that the individual gets enough calories and essential amino acids. Routine blood tests are needed to monitor the disorder and manage treatment. In some cases, transplants have been effective in reversing the symptoms.

What is the prognosis for a person with Carbamoylphosphate Synthetase I Deficiency?

CPS1 deficiency is the most severe of the urea cycle disorders. Outcomes vary, and depend on age at diagnosis and how closely the treatment plan and diet are followed. Some states screen all infants for this disease at birth. Infants who are diagnosed in the first week of life and are put on a diet immediately may reach normal brain function. Even with treatment, some individuals will experience hyperammonemic episodes leading to permanent intellectual disability and death. Without treatment, CPS1 deficiency results in death.

Carnitine Palmitoyltransferase IA Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: CPT1A.
Exons Sequenced: NM_001876:2-19.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Carnitine Palmitoyltransferase IA Deficiency?

Carnitine palmitoyltransferase IA deficiency (CPT1A deficiency) is an inherited disease in which the body cannot process long-chain fatty acids (a type of fat) and turn them into energy. Symptoms occur in severe episodes, often during long periods without eating and/or during times of fever or gastrointestinal illness.

A key symptom of the disease is low blood sugar (hypoglycemia) combined with low blood levels of ketones, a by-product of fat breakdown which is used for energy. Together, these symptoms are known as hypoketotic hypoglycemia. Prolonged periods of hypoketotic hypoglycemia can lead to loss of consciousness or seizures.

Other symptoms of CPT1A deficiency include an enlarged liver, muscle weakness, and damage to the liver, heart, and brain due to excess fatty-acid buildup. If untreated, the disease can be life-threatening.

Pregnant women whose fetus has CPT1A deficiency (and therefore is herself a carrier of CPT1A deficiency) are at risk of developing a complication called fatty liver of pregnancy. This can cause nausea, abdominal pain, fatigue, and frequent thirst and urination. It is potentially life-threatening and requires aggressive treatment.

Symptoms of CPT1A deficiency usually begin in infancy, but in some cases they appear later in life.

How common is Carnitine Palmitoyltransferase IA Deficiency?

CPT1A deficiency is extremely rare. Fewer than 50 cases have been identified worldwide. The disease is thought to be more common among Hutterite people in the northern United States and Canada as well as the Inuit people of northern Canada, Alaska, and Greenland.

How is Carnitine Palmitoyltransferase IA Deficiency treated?

A key goal of treatment is to combat low blood sugar (hypoglycemia). A physician will recommend a modified diet, typically with high-carbohydrate, low-fat foods. Infants will need to eat frequently during the day. A corn starch solution consumed regularly overnight will provide a slow release of energy that prevents blood sugar from dipping to dangerously low levels. People with CPT1A deficiency should never go long periods without eating.

When hypoglycemia does occur, it needs to be quickly treated with an intravenous sugar solution in order to prevent damage to the brain.

Women who are carriers of CPT1A deficiency and become pregnant should undergo testing for liver enzyme levels, especially during times of fasting or illness.

What is the prognosis for a person with Carnitine Palmitoyltransferase IA Deficiency?

After fasting or illness, people with CPT1A deficiency are at risk for life-threatening liver failure. These episodes can also cause permanent damage to the brain and liver. However when the disease is carefully managed, people with CPT1A deficiency can live fairly normal lives.

Carnitine Palmitoyltransferase II Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: CPT2.
Exons Sequenced: NM_000098:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Carnitine Palmitoyltransferase II Deficiency?

Carnitine palmitoyltransferase II deficiency (CPT II deficiency) is an inherited disease in which the body cannot process long-chain fatty acids and turn them into energy. This is due to a defective enzyme.

There are three versions of the disease, listed below, each with a very different profile.

LETHAL NEONATAL FORM

The lethal neonatal form of CPT II deficiency is the most severe form of the disease. Symptoms begin within days of birth and include liver failure, respiratory failure, a weakened and/or inflamed heart, irregular heartbeat leading to heart attack, kidney disease, and brain abnormalities. Usually these infants die within the first year of life.

SEVERE INFANTILE HEPATOCARDIOMUSCULAR FORM

Symptoms of the severe infantile hepatocardiomuscular form of CPT II deficiency usually begin between 6 months and 2 years of age. They include liver failure, a weakened and/or inflamed heart, seizures, low blood sugar, abdominal pain, headache, muscle weakness in the arms and legs, and irregular heartbeat which can result in sudden death during infancy. Severe episodes are often triggered by fasting, infection, or fever.

MYOPATHIC FORM

The myopathic form of CPT II deficiency is the most common and least severe form of the disease. Symptoms can begin at any time from childhood to one's 60s. People with the myopathic form of CPT II deficiency experience periodic attacks involving their muscles. These episodes are characterized by muscle pain and weakness. In many people with the disease, muscle tissue breaks down during these periods, causing brown or red-colored urine. Rarely, this can cause kidney problems. These attacks can be brought on by exercise, exposure to cold, stress, general anesthesia, sleep deprivation, or long periods of time without eating. Between attacks, people with the myopathic form of CPT II deficiency are typically normal.

The episodes of muscle pain are usually mild. Some people experience a limited number of severe attacks with long periods of normalcy. A smaller number of people experience frequent muscle pain that impairs their normal activity.

Most commonly, carriers of CPT II deficiency do not have any symptoms of the disease, however a small number of symptomatic carriers have been reported.

The myopathic form of CPT II deficiency is more often seen in men than women. Studies have shown the ratio of symptomatic men to women to be as high as 5-to-1. The reason for this gender differential is not well understood.

How common is Carnitine Palmitoyltransferase II Deficiency?

CPT II deficiency is rare. The lethal neonatal form has been documented in 13 families, while the severe infantile hepatocardiomuscular form has been studied in 20 families. There are more than 200 known cases of the myopathic form, however scientists believe this form often goes unrecognized, particularly in its mildest cases, and may be more common than studies have indicated.

How is Carnitine Palmitoyltransferase II Deficiency treated?

There is no cure for CPT II deficiency, and very little can be done to help infants and children with the more severe forms of the disease, other than to treat symptoms as they arise.

For people with the myopathic form, there are recommendations that can help prevent attacks. Frequent meals with a high-carbohydrate, low-fat diet can be helpful. Supplements of carnitine may also be recommended. During infection, a physician may recommend infusions of glucose. Circumstances to avoid include strenuous exercise, long periods of time without eating, and extreme cold.

During attacks, a person with the myopathic form of CPT II deficiency should drink plenty of fluids to avoid kidney problems.

People with the myopathic form of CPT II deficiency should avoid taking ibuprofen, valproic acid, and diazepam in high doses. They should also notify their physician before undergoing general anesthesia, as this can provoke an episode of muscle pain and weakness.

What is the prognosis for a person with Carnitine Palmitoyltransferase II Deficiency?

Infants with the lethal neonatal form of CPT II deficiency typically die within the first year of life. Infants and children with the severe infantile hepatocardiomuscular form are susceptible to life-threatening heart problems and typically have shortened lifespans with numerous medical problems.

People with the myopathic form of the disease typically live normal lifespans with periodic muscle problems. This form of the disease is usually manageable and allows for a good quality of life.

Cartilage-hair Hypoplasia

Available Methodology: sequencing with copy number analysis.
Gene: RMRP.
Exon Sequenced: NR_003051:1.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Cartilage-Hair Hypoplasia?

Cartilage-hair hypoplasia (CHH) is an inherited condition that causes an affected person to have an extremely small stature with short arms and legs. This is known as short-limbed dwarfism. People with CHH also tend to have fine, sparse hair and abnormal cartilage. Some people with CHH have an impaired immune system, leaving them more susceptible to infection, notably to a severe course of chicken pox. Some also have low levels of certain white blood cells. Anemia, a lowered number of red blood cells leading to fatigue and weakness, is common in children with CHH, though it usually disappears by adulthood. Some people with CHH are at a higher risk for certain cancers including non-Hodgkin's lymphoma and skin cancer. Symptoms and their severity vary widely among people with the disease.

How common is Cartilage-Hair Hypoplasia?

Cartilage-hair hypoplasia is rare. It is most common among the Amish population. One study indicated that 1 in 19 Amish were carriers of the disease and 1 in 1340 Amish babies were born with the disease. It is also more common in the Finnish population where 1 in 76 is a carrier and 1 in 23,000 babies has the disease.

How is Cartilage-Hair Hypoplasia treated?

There is no treatment for cartilage-hair hypoplasia. The drug Acyclovir can be useful to treat chicken pox. Infections, particularly those in childhood, should be given close medical attention. Growth hormones may be a possibility for some patients. Those with extreme immunodeficiency may want to consider bone marrow transplantation to ameliorate this symptom.

What is the prognosis for a person with Cartilage-Hair Hypoplasia?

People with cartilage-hair hypoplasia can live a normal lifespan. Those with severe immunodeficiency need to monitor their health more closely. Opportunistic infections can be fatal, particularly in childhood.

Cerebrotendinous Xanthomatosis

Available Methodology: sequencing with copy number analysis.
Gene: CYP27A1.
Exons Sequenced: NM_000784:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Cerebrotendinous Xanthomatosis?

Cerebrotendinous xanthomatosis (CTX) is a disease that leads to increased storage of fats, such as cholesterol, in the body. Common features of this disorder include diarrhea that starts in infancy, clouding of the eyes that affect vision (cataracts), deposits of fat under the skin (xanthomas), and neurologic problems that get worse over time.

For many affected individuals, chronic diarrhea beginning in infancy is the earliest manifestation. Development of cataracts during early childhood is typical for CTX. Xanthomas most commonly begin appearing in adolescence and early adulthood, often on the back of the heel (the Achilles) and other tendons, though they can occur throughout the body. Most individuals with CTX have no or mild neurologic problems before puberty. Beginning in the 20s, neurologic symptoms such as seizures and an inability to control movements can develop. These symptoms will often worsen over time. Additional neurological features may include intellectual disability and mental health problems such as depression or hallucinations. Some other reported features of CTX include weak and brittle bones and heart problems.

How common is Cerebrotendinous Xanthomatosis?

Cases have been reported in most regions of the world, but exact statistics are limited. At this time, there is no consensus on the global incidence of this disorder. the condition seems to be most common in the Druze population in Israel and in Sephardic Jews of Moroccan descent. The incidence in Caucasians is at least 1 in 50,000, and in those of Spanish descent it is estimated to be 1 in 1,800,000.

How is Cerebrotendinous Xanthomatosis treated?

There is no cure for CTX, but early diagnosis and treatment with chenodeoxycholic acid (CDCA) may prevent and can improve some symptoms. Other treatment focuses on the management of symptoms, such as medication for seizures and trouble controlling movements or calcium and vitamin D for weak and brittle bones. Eye surgery to remove cataracts is often required in adulthood.

What is the prognosis for a person with Cerebrotendinous Xanthomatosis?

If identified and treated early, clinical symptoms of the disorder may be prevented. While treatment may improve some symptoms, it may not be able to reverse all features once there has been disease progression. In addition, lifespan may be normal if treated early. Without treatment, the average lifespan is 50-60 years due to progressive deterioration.

Citrullinemia Type 1

Available Methodology: sequencing with copy number analysis.
Gene: ASS1.
Exons Sequenced: NM_000050:3-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
86%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Citrullinemia Type 1?

Citrullinemia type I is a disease in which ammonia and other toxic substances build up in the blood, causing life-threatening complications shortly after birth.

While infants with citrullinemia type I appear normal at birth, within the first week of life, most will become lethargic and display poor feeding, vomiting, and seizures that often lead to unconsciousness, stroke, increased pressure around the brain, and death if untreated.

While there are less severe and later-onset versions of citrullinemia type I, the mutations for which Counsyl screens are associated with the more severe form that affects infants shortly after birth. It is also known as "classic" citrullinemia.

Citrullinemia type I belongs to a group of diseases known as urea cycle disorders. When the body consumes protein, it also produces excess nitrogen. Under normal circumstances, the body converts that nitrogen to urea, which is then excreted in urine. People with citrullinemia type I are deficient in an enzyme known as argininosuccinate synthase which is needed for this vital process, leading to a buildup of ammonia and other urea cycle byproducts in the body. The excess of ammonia is harmful to the nervous system, causing many of the disease's symptoms.

How common is Citrullinemia Type 1?

Scientists estimate that 1 in 57,000 births are affected by Citrullinemia type I.

How is Citrullinemia Type 1 treated?

The goals of treatment for citrullinemia type I are to regulate the amount of ammonia in the blood. Physicians adhere to certain protocols to control the body's ammonia levels. These protocols utilize medication, dialysis, and a specifically prescribed diet. Children with citrullinemia will need to be monitored closely by a physician specializing in metabolic disorders. Physicians will also monitor and attempt to relieve any excess of pressure around the brain.

What is the prognosis for a person with Citrullinemia Type 1?

The prognosis for a child with citrullinemia type I has not been well established. Without treatment, the longest known survival was 17 days. With treatment, these children can survive for an unknown period of time, however they will have significant mental and neurological impairment.

CLN3-related Neuronal Ceroid Lipofuscinosis

Available Methodology: sequencing with copy number analysis.
Gene: CLN3.
Exons Sequenced: NM_001042432:2-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is CLN3-related Neuronal Ceroid Lipofuscinosis?

CLN3-related neuronal ceroid lipofuscinosis (also known as Batten disease) is an inherited disease that causes degeneration of the brain leading to a progressive loss of mental and motor skills. It typically causes blindness and leads to an early death.

Batten disease is the juvenile form of a disease known as neuronal ceroid lipofuscinosis (NCL). It is also known as Spielmeyer-Vogt-Sjogren-Batten disease. (Some physicians use the term "Batten disease" to describe any form of NCL, but here we use it to refer only to the juvenile form.)

Symptoms of Batten disease begin between the ages of 4 and 10, typically with a loss of vision. These children typically become completely blind within 2 to 4 years.

People with Batten disease often develop periodic seizures between the ages of 9 and 18. Between the ages of 8 and 14, mental functions typically decline. The child may have speech difficulty and behavioral problems. Some people with Batten disease also develop psychiatric problems including disturbed thoughts, attention problems, and aggression. They will eventually progress to dementia.

People with Batten disease also show a decline in motor function and may have difficulty controlling their own movement. Eventually people with Batten disease will be bedridden.

How common is CLN3-related Neuronal Ceroid Lipofuscinosis?

An estimated 2 to 4 in 100,000 births in the United States are affected by some form of NCL. Batten disease is most common in Finland, Sweden, and other parts of northern Europe, but has been seen worldwide.

How is CLN3-related Neuronal Ceroid Lipofuscinosis treated?

There is no treatment for the underlying cause of Batten disease. Treatments can only address the symptoms as they arise. Various medications can be useful for treating seizures, poor muscle tone, sleep disorders, mood disorders, excessive drooling, and digestion.

What is the prognosis for a person with CLN3-related Neuronal Ceroid Lipofuscinosis?

Batten disease causes blindness and a progressive loss of mental and motor function. Death usually occurs between the late teens and 20s. Some people with the disease have lived into their 30s.

CLN5-related Neuronal Ceroid Lipofuscinosis

Available Methodology: sequencing with copy number analysis.
Gene: CLN5.
Exons Sequenced: NM_006493:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is CLN5-related Neuronal Ceroid Lipofuscinosis?

CLN5-related neuronal ceroid lipofusciosis (NCL) is an inherited disease that causes degeneration of the brain leading to a progressive loss of mental and motor skills. It causes blindness and leads to an early death.

Mutations in the CLN5 gene cause a form of NCL that is often referred to as the Finnish variant of late-infantile neuronal ceroid lipofuscinosis (fLINCL).

Symptoms usually begin between the ages of 4 and 7. By the age of 10, children typically have lost their vision and develop seizures, mental disability, muscle twitching, and an inability to control muscle movements (ataxia). Between the ages of 8 and 11, they lose the ability to walk independently. They will gradually lose their ability to speak and move and will become profoundly mentally disabled.

How common is CLN5-related Neuronal Ceroid Lipofuscinosis?

CLN5-related NCL is most common in an area of western Finland known as Southern Ostrobothnia. There, 1 in 24 to 44 is a carrier of the disease. In other parts of Finland, studies have found that 1 in 385 are carriers in Eastern Finland and 1 in 1000 in the capital of Helsinki. To date, 29 cases of CLN5-related NCL have been diagnosed in Finland, one in Sweden, and one in the Netherlands.

How is CLN5-related Neuronal Ceroid Lipofuscinosis treated?

There is no treatment for the underlying cause of CLN5-related NCL. Treatments, such as anti-seizure medication, can only address the symptoms as they arise.

What is the prognosis for a person with CLN5-related Neuronal Ceroid Lipofuscinosis?

The prognosis for people with the disease is poor. They will be profoundly mentally disabled and unable to speak or move some time after the age of 10. The average life expectancy is about 20 years, though the lifespan of people with the disease has ranged from 14 to 39 years.

CLN6-related Neuronal Ceroid Lipofuscinosis

Available Methodology: sequencing with copy number analysis.
Gene: CLN6.
Exons Sequenced: NM_017882:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is CLN6-related Neuronal Ceroid Lipofuscinosis?

CLN6-related neuronal ceroid lipofuscinosis (NCL6) is an inherited disease that causes degeneration of the brain, leading to a progressive loss of mental and motor skills.

There are several forms of NCL, largely differentiated by the gene responsible and the age at which symptoms begin. Mutations in the CLN6 gene typically result in variant late-infantile neuronal ceroid-lipofuscinosis (vLINCL) or rarely, adult-onset NCL (Kufs disease type A).

Variant late-infantile neuronal ceroid-lipofuscinosis The symptoms of vLINCL typically begin between 3 and 8 years of age. Early symptoms often include seizures, vision loss and difficulty controlling movements. Other symptoms include jerking movements, mental decline, and speech problems. In general, most children with vLINCL will lose all motor skills and vision by 4-10 years of age. Death occurs around 20 years of age.

Adult-onset NCL The symptoms of adult-onset NCL typically begin around the age of 30 but range between 16-51 years. Individuals experience difficulty controling seizures, dementia and have difficulty balancing and controlling movements. Death usually occurs 10 years after the onset of symptoms. Vision is not affected in adult-onset NCL.

How common is CLN6-related Neuronal Ceroid Lipofuscinosis?

Approximately 1 in 25,000 people globally are affected by some form of NCL. The exact incidence and prevalence of CLN6-related neuronal ceroid lipofuscinosis is unknown.

How is CLN6-related Neuronal Ceroid Lipofuscinosis treated?

There is no cure for CLN6-related neuronal ceroid lipofuscinosis. Symptoms such as seizures and poor muscle tone can be treated as they arise with various medications. Some individuals may benefit from a feeding tube.

What is the prognosis for a person with CLN6-related Neuronal Ceroid Lipofuscinosis?

The prognosis for people with the disease is poor. Individuals with variant late-infantile neuronal ceroid-lipofuscinosis generally lose their vision and all motor skills by 4 to 10 years of age. Lifespan is around 20 years of age. Individuals with adult-onset NCL generally pass within 10 years of the onset of symptoms.

Cohen Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: VPS13B.
Exons Sequenced: NM_017890:2-62.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Cohen Syndrome?

Cohen syndrome, also known as Pepper syndrome, is a genetic disorder that affects motor skills, mental development, and behavior. Infants with the condition grow slowly and do not gain weight at the normal rate. They also have decreased muscle tone and unusually flexible joints. They feel floppy, like a rag doll, when lifted, and cannot control their heads. Over time, they have difficulty learning to roll over, sit up, crawl, and walk. Beginning in late childhood, people with the illness may begin to put on weight in the torso. Without intervention, they can become obese, although their arms and legs remain slender.

They show moderate to severe mental and motor retardation that remains constant and do not become progressively worse over time.

People with Cohen syndrome are prone to frequent and potentially severe infections because they have a lower than average level of certain infection-fighting white blood cells.

Cohen syndrome generally causes severe, progressive vision problems, notably extreme nearsightedness and degeneration of the retina. People with the condition often become functionally, if not entirely, blind.

People with Cohen syndrome tend to be unusually friendly and cheerful, even towards strangers they have no reason to trust. As a result, parents must be extra vigilant about their child's personal safety.

How common is Cohen Syndrome?

The exact prevalence of Cohen syndrome is unknown. It has been reported in fewer than 1000 people worldwide, although more cases likely exist. It is most common in a small Amish community in Ohio, where it affects an estimated 1 in 500 people. It is also more common in Finland.

How is Cohen Syndrome treated?

There is no cure for Cohen syndrome, but early intervention with physical, occupational, and speech therapy can address symptoms like joint overflexibility, clumsiness, and developmental delays. Children with nearsightedness need glasses, while those with retinal degeneration benefit from training for the visually impaired.

In order to prevent recurrent infections, people with Cohen syndrome should be monitored throughout their lives for low white blood cell count.

What is the prognosis for a person with Cohen Syndrome?

The exact effect of Cohen syndrome on one's lifespan is unclear. Some people with the disease are known to be alive in their 50s.

COL4A3-related Alport Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: COL4A3.
Exons Sequenced: NM_000091:1-52.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is COL4A3-related Alport Syndrome?

Alport syndrome is a genetic condition characterized by progressive kidney disease, hearing loss, and abnormalities affecting the eyes. Alport syndrome can be inherited in an X-linked or autosomal recessive manner. COL4A3-related Alport syndrome is inherited in an autosomal recessive manner. The presentation of autosomal recessive Alport syndrome is variable in severity; some individuals have a milder disease course, while others develop more severe disease with complications. Disease severity is similar amongst males and females with autosomal recessive Alport syndrome.

Blood in the urine is often the first sign of kidney disease and typically presents during childhood. This is usually not detectable by the naked eye, but may be visible during periods of illness such as a cold or flu. Individuals also develop protein in the urine during childhood. Kidney disease often progresses to kidney failure by early adulthood. Kidney failure is associated with a variety of symptoms including: high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Medications may delay the progression of kidney failure, but for the most part, either a kidney transplant and/or dialysis is eventually necessary.

Autosomal recessive Alport syndrome is also associated with varying degrees of progressive hearing loss. The onset and severity of hearing loss is variable, but it is not uncommon for some degree of hearing loss to develop by adolescence.

Individuals may also develop eye abnormalities. Specific problems with the lens, retina and cornea are the most common and may result in light sensitivity, cataract formation, and blurred vision. Glasses are sometimes required to correct vision.

How common is COL4A3-related Alport Syndrome?

Collectively, all forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. The two genes associated with autosomal recessive Alport syndrome, the *COL4A3* and the *COL4A4* genes, are responsible for about 15% of all cases of Alport syndrome, with an estimated incidence of 1 in 350,000 births. Among individuals of Ashkenazi Jewish descent, the incidence of COL4A3-related Alport syndrome is estimated to be 1 in 400,000.

How is COL4A3-related Alport Syndrome treated?

Currently, there is no cure for autosomal recessive Alport syndrome. However, treatments are available to address many of the associated symptoms. Medications are used to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will develop eventually in individuals with autosomal recessive Alport syndrome. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years, but most often is necessary by adulthood.

Hearing aids may be required to treat hearing loss. Additionally, ophthalmologic intervention, such as cataract surgery, may be required for some individuals.

A multidisciplinary team of physicians, including: nephrologists, audiologists, ophthalmologists and other healthcare professionals will need to be involved in the ongoing treatment and management of individuals with autosomal recessive Alport syndrome.

What is the prognosis for a person with COL4A3-related Alport Syndrome?

While the prognosis of autosomal recessive Alport syndrome is variable, the vast majority of individuals develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients are approaching kidney failure. Although, complications from kidney disease may still result in a shortened life span. Hearing loss develops in the vast majority of individuals by 40 years. Many times, the eye complications associated with autosomal recessive Alport syndrome do not cause any severe visual abnormalities; although, cataract surgery and/or corrective lenses may be required.

COL4A4-related Alport Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: COL4A4.
Exons Sequenced: NM_000092:2-48.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is COL4A4-related Alport Syndrome?

Alport syndrome is a genetic condition characterized by progressive kidney disease, hearing loss, and abnormalities affecting the eyes. Alport syndrome can be inherited in an X-linked or autosomal recessive manner. COL4A4-related Alport syndrome is inherited in an autosomal recessive manner. The presentation of autosomal recessive Alport syndrome is variable in severity; some individuals have a milder disease course, while others develop more severe disease with complications. Disease severity is similar amongst males and females with autosomal recessive Alport syndrome.

Blood in the urine is often the first sign of kidney disease and typically presents during childhood. This is usually not detectable by the naked eye, but may be visible during periods of illness such as a cold or flu. Individuals also develop protein in the urine during childhood. Kidney disease often progresses to kidney failure by early adulthood. Kidney failure is associated with a variety of symptoms including: high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Medications may delay the progression of kidney failure, but for the most part, either a kidney transplant and/or dialysis is eventually necessary.

Autosomal recessive Alport syndrome is also associated with varying degrees of progressive hearing loss. The onset and severity of hearing loss is variable, but it is not uncommon for some degree of hearing loss to develop by adolescence.

Individuals may also develop eye abnormalities. Specific problems with the lens, retina and cornea are the most common and may result in light sensitivity, cataract formation, and blurred vision. Glasses are sometimes required to correct vision.

How common is COL4A4-related Alport Syndrome?

Collectively, all forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. The two genes associated with autosomal recessive Alport syndrome, the *COL4A3* and the *COL4A4* genes, are responsible for about 15% of all cases of Alport syndrome, with an estimated incidence of 1 in 350,000 births. Autosomal recessive Alport syndrome occurs at a similar frequency amongst all ethnicities.

How is COL4A4-related Alport Syndrome treated?

Currently, there is no cure for autosomal recessive Alport syndrome. However, treatments are available to address many of the associated symptoms. Medications are used to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will develop eventually in individuals with autosomal recessive Alport syndrome. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years, but most often is necessary by adulthood.

Hearing aids may be required to treat hearing loss. Additionally, ophthalmologic intervention, such as cataract surgery, may be required for some individuals.

A multidisciplinary team of physicians, including: nephrologists, audiologists, ophthalmologists and other healthcare professionals will need to be involved in the ongoing treatment and management of individuals with autosomal recessive Alport syndrome.

What is the prognosis for a person with COL4A4-related Alport Syndrome?

While the prognosis of autosomal recessive Alport syndrome is variable, the vast majority of individuals develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients are approaching kidney failure. Although, complications from kidney disease may still result in a shortened life span. Hearing loss develops in the vast majority of individuals by 40 years. Many times, the eye complications associated with autosomal recessive Alport syndrome do not cause any severe visual abnormalities; although, cataract surgery and/or corrective lenses may be required.

Congenital Disorder of Glycosylation Type Ia

Available Methodology: sequencing with copy number analysis.
Gene: PMM2.
Exons Sequenced: NM_000303:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Congenital Disorder of Glycosylation Type Ia?

Congenital disorder of glycosylation type Ia (CDG-Ia) is an inherited metabolic disorder that impairs the production of glycoproteins, which are proteins that have attached carbohydrates. In CDG-Ia, there is a defect in an enzyme called phosphomannomutase.

CDG-Ia affects many systems of the body, notably the nervous system. The disease causes developmental delay that can lead to mental disability. It can also cause seizures and stroke-like episodes. It impairs both the ability to move physically and the ability coordinate that movement. Approximately 20% of infants with the disease die within the first year of life. Most people with CDG-Ia will be wheelchair bound.

A person with CDG-Ia may show some or all of the following symptoms: a failure to grow at the normal rate; a particular type of limited vision which leads to blindness (retinitis pigmentosa); an underactive thyroid (hypothyroidism); an enlarged liver and/or liver disease; heart and kidney problems; low blood sugar; a decreased ability for blood to clot following an injury; thickened, swollen, pitted skin (peau d'orange); and bone abnormalities. Some people have many of the above symptoms while others have few.

In people with CDG-Ia, certain distinct features are apparent at birth. These may include inverted nipples, poor muscle tone, almond shaped eyes which are crossed, a large forehead, an unusual distribution of body fat, and abnormal genitals. Part of the brain called the cerebellum is often partially wasted away. Females with the disease often do not reach sexual development.

How common is Congenital Disorder of Glycosylation Type Ia?

CDG-Ia accounts for 70% of the congenital disorders of glycosylation, which combined affect 1 in every 50,000 to 100,000 births. Cases of CDG-Ia have been reported worldwide, with about half coming from Scandinavian countries.

How is Congenital Disorder of Glycosylation Type Ia treated?

There is no cure for CDG-Ia, however some measures may be taken to improve the lives of people affected by the disease. Parents of a young child with CDG-Ia should ensure the child gets the best possible nutrition to help with growth. Some children will require a feeding tube. Early use of occupational, physical, and speech therapy may be helpful in improving the child's long-term abilities in these areas. Surgical or non-surgical measures may correct crossed eyes and ensure better vision. Infusion of blood plasma may be necessary before a surgery to help clotting. Medications may help to control seizures. Various hormones may be useful if the person has an underactive thyroid gland. Wheelchairs and other movement aids are often useful as well.

What is the prognosis for a person with Congenital Disorder of Glycosylation Type Ia?

Twenty percent of people with CDG-Ia die within the first year of life, often due to infection, liver problems, or heart disease. Others with CDG-Ia may live into adulthood. Most are wheelchair bound throughout their life. Some are able to speak and converse, albeit with some impairment. People with CDG-Ia are unable to live independently, but may accomplish certain tasks independently.

Congenital Disorder of Glycosylation Type Ib

Available Methodology: sequencing with copy number analysis.
Gene: MPI.
Exons Sequenced: NM_002435:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Congenital Disorder of Glycosylation Type Ib?

Congenital disorder of glycosylation type Ib (CDG-Ib) is an inherited metabolic disorder that impairs the production of glycoproteins, which are proteins that have attached carbohydrates. In type Ib, there is a defect in an enzyme called phosphomannose isomerase.

If left untreated, the disease can cause a wide array of problems including chronic diarrhea, a failure to grow at the expected rate, a loss of protein from the body, vomiting, low blood sugar, difficulty in forming blood clots, and liver disease.

CDG-Ib can be effectively treated by taking supplements of mannose, a sugar. With this supplement, life can be relatively normal. Without it, symptoms of the disease can be life-threatening. For this reason, early diagnosis and treatment is important.

CDG-Ib is distinct from other forms of CDG in that it does not affect the central nervous system. People with CDG-Ib are intellectually normal.

How common is Congenital Disorder of Glycosylation Type Ib?

CDG-Ib is extremely rare, although the exact frequency is unknown.

How is Congenital Disorder of Glycosylation Type Ib treated?

CDG-Ib is treated with oral supplements of mannose, a sugar. People with CDG-Ib who begin mannose treatment show improvement in most of the symptoms of the disease. Treatment with mannose must be lifelong.

What is the prognosis for a person with Congenital Disorder of Glycosylation Type Ib?

With early and regular treatment, a person with CDG-Ib can live a near-normal life. Without it, the disease can be fatal. Generally, the prognosis will vary depending on the severity of symptoms and their response to mannose treatment.

Congenital Disorder of Glycosylation Type Ic

Available Methodology: sequencing with copy number analysis.
Gene: ALG6.
Exons Sequenced: NM_013339:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Congenital Disorder of Glycosylation Type Ic?

Congenital disorders of glycosylation are a group of conditions that affect glycosylation, a process that is necessary to diversify the function of proteins in the body. The CDG-I disease types are a result of defects in various steps of the glycoslyation process. As a result of this impairment, a variety of symptoms may be seen in the CDG-I forms (a-z); CDG-Ic results from a defect in the glucosyltransferase I enzyme.

CDG-Ic affects many systems of the body, notably the nervous system, resulting in poor muscle tone, developmental delay, and intellectual disability in almost all cases. Brain malformations, impaired ability to coordinate movement, and seizures are also common. Many affected individuals have poor growth, autistic or behavioral problems, certain physical features, and skeletal abnormalities. Physical features include deep-set eyes, forehead narrowing, broad nasal bridge, shortened region above lip, and wide-spaced eyes. Skeletal abnormalities include shortening of fingers and toes, limited joint extension, short arms, and scoliosis. Other symptoms like deep vein thrombosis, enlarged liver and spleen, enlarged heart, protein loss in the intestines, or pubertal abnormalities, may occur but are less typical.

How common is Congenital Disorder of Glycosylation Type Ic?

CDG-Ic is a rare disorder, but may be the second most common form of congenital disorder of glycosylation. Though it has been reported in at least 89 individuals (most of Caucasian descent), the global incidence is unknown. Other presentations of CDG-Ic may not be recognized as of yet.

How is Congenital Disorder of Glycosylation Type Ic treated?

There is no cure for CDG-Ic; management of the condition involves treating symptoms of the disease. Early intervention and education planning may help improve cognition. Medications may help to control seizures. Parents of a young child with CDG-Ic

should ensure the child gets the best possible nutrition to help with growth; some children will require a feeding tube. Early use of occupational, physical, and speech therapy may be helpful in improving the child's long-term abilities in these areas. However, wheelchairs and other movement aids are often useful and become necessary. If non-surgical interventions do not work, surgical measures with proper management to minimize risk for blood clots may correct crossed eyes and scoliosis. Laboratory tests are often used for monitoring of other functions in the body.

What is the prognosis for a person with Congenital Disorder of Glycosylation Type Ic?

Up to 25% of people with CDG-Ic die in infancy or early childhood, often due to infection, seizures, or protein loss in the intestines. Most individuals that live into adulthood will require a wheelchair. Adults are unlikely to be able to live independently, but most will be able to speak, albeit with some impairment, and be able to accomplish certain tasks independently.

Congenital Finnish Nephrosis

Available Methodology: sequencing with copy number analysis.
Gene: NPHS1.
Exons Sequenced: NM_004646:1-29.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Congenital Finnish Nephrosis?

Congenital Finnish nephrosis is an inherited disease in which the kidneys are unable to properly filter protein from the urine due to an abnormality in a protein called nephrin. The disease occurs mainly in people of Finnish origin. It is often fatal by the age of five and many cases are fatal within the first year. If the child survives to the age of two or three, kidney transplantation may allow for a more normal lifespan.

Children with congenital Finnish nephrosis are often born prematurely with a low birth weight. High levels of protein in the blood, combined with kidney failure, cause the whole body to swell with excess fluids. These children have a poor appetite and urinate less frequently than chidren without the disease. Children with congenital Finnish nephrosis have difficulty getting needed nutrients and may not grow as large as they would otherwise.

People with congenital Finnish nephrosis cannot retain sufficient amounts of antibodies that help the body fight infection. As a result, they are more prone to infection. They are also prone to inappropriate and potentially harmful blood clots.

Symptoms of the disease begin in the first days or weeks after birth, but always before the age of three months.

How common is Congenital Finnish Nephrosis?

As indicated by its name, congenital Finnish nephrosis is fairly common in Finland, where it affects 1 in 8,000 births. In the United States, it is rare, but more common in people of Finnish ancestry. The disease is extremely common among Old Order Mennonites in Lancaster County, Pennsylvania. It is estimated that 1 in 500 children born in this population are affected by the disease.

How is Congenital Finnish Nephrosis treated?

Because congenital Finnish nephrosis is often fatal in infancy, early and vigilant treatment is necessary to allow the child to live until the age of two or three, at which time he or she may receive a kidney transplant. This is the only hope for a normal lifespan. The disease does not affect the new kidney.

If the disease is too severe, the child's kidneys may need to be removed before he or she is old enough for a transplant. Dialysis machines can be used as a stopgap measure to filter wastes from the child's blood until a transplant can be completed.

A physician may recommend infusions of protein for these children to help replace what is lost in the urine. Diuretic drugs may be prescribed to help eliminate excess water and thus eliminate some swelling. Antibiotics will be necessary to control infection.

Some children with the disease have abnormal thyroid activity and may require hormone replacement. Others have a tendency towards blood clots and may benefit from a blood thinner.

Good nutrition is key to growth. Those who cannot eat sufficient quantities may need a feeding tube.

What is the prognosis for a person with Congenital Finnish Nephrosis?

Many cases of congenital Finnish nephrosis are fatal within five years. If the child lives until the age of two or three, an early kidney transplant may help him or her to live a more normal lifespan.

Costeff Optic Atrophy Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: OPA3.
Exons Sequenced: NM_025136:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Costeff Optic Atrophy Syndrome?

People with Costeff optic atrophy syndrome, also called 3-methylglutaconic aciduria type 3 (3-MGCA 3), experience both visual problems as well as involuntary spastic physical movements. The symptoms tend to worsen through childhood.

A hallmark of the disease is optic atrophy, a progressive loss of visual acuity beginning in the first few years of life. In some, the eyes also show an involuntary horizontal back-and-forth movement.

The other defining symptom of Costeff optic atrophy syndrome is chorea, a tendency toward involuntary jerky movements that begin before the age of 10. Most will develop weakness and spasticity in the leg muscles along with a general lack of control of the body muscles. They may have trouble maintaining their posture. Many, though not all, will need to use a wheelchair from an early age.

Some people with the disease have mild cognitive problems, which often develop between the ages of 10 and 20. People develop most symptoms by the end of their 20s.

The severity of symptoms can vary from person to person, even among those in the same family.

How common is Costeff Optic Atrophy Syndrome?

This disease is most common in Iraqi Jews, in whom 1 in 10,000 newborns are affected by the disease. Only a few cases of the disease have been seen outside the Iraqi Jewish population. The mutation for which Counsyl screens has been found exclusively in Iraqi Jews and is responsible for all the known cases of Costeff optic atrophy syndrome in that population.

How is Costeff Optic Atrophy Syndrome treated?

There is no cure for Costeff optic atrophy syndrome; treatments can only address symptoms as they arise. Medical teams can attempt to maximize the person's vision and address the movement problems. In many cases, a wheelchair will be necessary. Often the medical team includes a neurologist, orthopedic surgeon, ophthalmologist, geneticist, and physical therapist.

What is the prognosis for a person with Costeff Optic Atrophy Syndrome?

People with the Costeff optic atrophy syndrome have been known to live into their 30s; life expectancy beyond that is unknown.

Cystic Fibrosis

Available Methodology: sequencing with copy number analysis.

Gene: CFTR.

Exons Sequenced: NM_000492:1-27.

IVS8-5T allele analysis is only reported in the presence of the R117H mutation.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Cystic Fibrosis?

Cystic fibrosis (CF) is a genetic condition characterized by the production of abnormally thick, sticky mucus, particularly in the lungs and digestive system. While it is normal to have mucus lining the organs of the respiratory, digestive, and reproductive systems in order to lubricate and protect them, in people with CF this mucus is thick and sticky. This abnormal mucus results in the clogging and obstructing of various systems in the body. CF is a chronic condition that worsens over time.

Most people with CF experience breathing problems and frequent lung infections that lead to permanent lung damage such as scarring (fibrosis) and sac-like growths (cysts). The pancreas, an organ that produces insulin and digestive enzymes, is often affected by CF. The sticky mucus caused by CF can block ducts which ferry enzymes from the pancreas to the rest of the body, resulting in problems such as diarrhea, malnutrition, and poor growth. Infertility, particularly in men, and delayed puberty are also common among people with cystic fibrosis.

The severity of symptoms varies from person to person, even among individuals with the same mutations. Most cases of CF are diagnosed in early childhood. However, in general, individuals with two classic mutations are more likely to have a severe form of the disease including problems with the pancreas, while individuals with one classic and one non-classic or individuals with two non-classic mutations are more likely to have a milder form of the condition and may avoid problems with the pancreas.

Mutations in the same gene that causes CF can result in a condition in males called congenital absence of the vas deferens (CAVD). In CAVD, the vas deferens (a reproductive organ involved in sperm transport) is improperly formed, leading to infertility.

How common is Cystic Fibrosis?

According to the National Institutes of Health, CF is the most common deadly inherited condition among Caucasians in the United States. Disease-causing mutations in the CFTR gene are more common in some ethnic populations than others.

Ethnic Group	Carrier Rate	Affected Rate
French Canadian	1 in 16	1 in 900
Caucasian	1 in 28	1 in 3,000
Ashkenazi Jewish	1 in 28	1 in 3,000
Hispanic	1 in 46	1 in 8,300
African American	1 in 66	1 in 17,000
Asian	1 in 87	1 in 30,000

How is Cystic Fibrosis treated?

There is no treatment that addresses the cause of CF, but there are many options to treat the symptoms it produces. Because thick mucus can build up in the respiratory system, it is important to keep the person's airways open in order to ease breathing and prevent infection. This can be accomplished with various prescription drugs as well as by physically loosening mucus by pounding on the person's back in a prescribed way. This treatment, known as "postural drainage and chest percussion" must be performed by someone other than the affected person, and is typically done at least once daily. As respiratory infections occur, physicians typically prescribe antibiotics.

Physicians will also monitor the digestive system to ensure that the person is getting proper nutrition. Enzymes or vitamin supplements may be prescribed. Both the respiratory and digestive systems of a person with CF must be monitored regularly by his or her medical team.

Surgery may be needed to correct certain problems caused by CF. Lung transplants are an option for some people.

What is the prognosis for a person with Cystic Fibrosis?

Thanks to improved treatments and a better understanding of the condition, the average life expectancy for people with CF who live to adulthood is 35 years. Children born with CF today who receive early treatment may live even longer.

Cystinosis

Available Methodology: sequencing with copy number analysis.
Gene: CTNS.
Exons Sequenced: NM_004937:3-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Cystinosis?

Cystinosis is an inherited disease that causes the amino acid cysteine to accumulate within body cells and form crystals which can damage the body's organs, particularly the kidneys and eyes. Without treatment, children with the condition will experience kidney failure around the age of 10.

There are three forms of cystinosis. The most severe form, nephropathic cystinosis, appears in infants. It causes poor growth and renal tubular Fanconi syndrome, a kidney disorder in which the organ eliminates certain essential nutrients and minerals. The loss of these nutrients inhibits normal body growth and may result in soft, bowed bones. Cysteine crystals also accumulate in the eyes, causing photophobia, an extreme sensitivity to light. Other symptoms may include muscle wasting, difficulty swallowing, diabetes, an underactive thyroid gland, and nervous system problems.

Less severe forms of the disease cause symptoms to begin later in life and may not affect the kidneys.

How common is Cystinosis?

Cystinosis affects approximately 1 in 200,000 people. The disease is most common in Brittany, France, where it affects 1 in 26,000.

How is Cystinosis treated?

Thanks to a drug called cysteamine, cystinosis has become easier to manage. Taken orally in capsules (brand name: Cystagon), it reduces the accumulation of cysteine crystals in the body. The drug has been shown to delay or prevent kidney failure and improve growth rates in children. Cysteamine eye drops have been successful in relieving photophobia in people with cystinosis, although they are not yet approved by the FDA for that purpose.

Nutritional monitoring is important in children with cystinosis. These children require a large amount of water to prevent dehydration. Supplements of several vitamins and minerals are also recommended for most people with the disease. Human growth hormone treatments have been shown to help people with cystinosis reach normal height.

Kidney transplants are an option for people with cystinosis. Cysteine crystals will not build up in the newly transplanted kidney, although they may still affect other organs of the body.

What is the prognosis for a person with Cystinosis?

Cystagon has extended the lifespan of people with cystinosis, but exact lifespan is not known. Some people with the disease have lived into their 50s.

D-bifunctional Protein Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: HSD17B4.
Exons Sequenced: NM_000414:1-24.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is D-Bifunctional Protein Deficiency?

D-bifunctional protein deficiency, also known as peroxisomal bifunctional enzyme deficiency, is an inherited disease causing severe biochemical abnormalities that are usually fatal within the first two years of life.

Infants with D-bifunctional protein deficiency are floppy at birth with poor muscle tone. Most experience seizures shortly after birth and almost all develop seizures within the first few months of life. The majority show visual and hearing impairment and have severe intellectual disability. Few infants with D-bifunctional protein deficiency reach any developmental milestones or develop motor skills. Brain scans of these infants typically find a range of physical abnormalities. Infants with D-bifunctional protein deficiency also tend to share characteristic facial features.

D-bifunctional protein deficiency is the most severe among a group of diseases known as peroxisomal fatty acid oxidation disorders. Peroxisomes are structures that help detoxify our cells.

How common is D-Bifunctional Protein Deficiency?

D-bifunctional protein deficiency is extremely rare, but is estimated to affect 1 in 100,000 newborns.

How is D-Bifunctional Protein Deficiency treated?

There is no successful treatment for D-bifunctional protein deficiency. Treatment can only serve to address seizures with medication and ensure proper nutrition.

What is the prognosis for a person with D-Bifunctional Protein Deficiency?

The prognosis is poor. Most children with D-bifunctional protein deficiency die within the first two years of life without developing any mental or motor skills.

Delta-sarcoglycanopathy

Available Methodology: sequencing with copy number analysis.
Gene: SGCD.
Exons Sequenced: NM_000337:2-9.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe

What is Delta-Sarcoglycanopathy?

Delta-sarcoglycanopathy represents a spectrum of disorders that typically cause muscle weakness as a result of a deficiency of the protein, delta-sarcoglycan, in the dystrophin-glycoprotein complex, a component of the muscle system. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal. Presentations of this condition are described below.

LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2F

People with limb-girdle muscular dystrophy type 2F (LGMD2F) develop symptoms at variable ages, though symptoms tend to first present in childhood. LGMD2F does not affect intelligence or mental function; the primary symptom is progressive muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary, but many experience progressive weakness to a point where a wheelchair becomes necessary. Other features include enlarged calf muscles, contractures, winging of the shoulder blade, and scoliosis. Respiratory complications are associated with the sarcoglycanopathies, and up to 20% of individuals will have heart complications (e.g. arrhythmia, cardiomyopathy) - both of which may be a cause of death.

DILATED CARDIOMYOPATHY TYPE 1L

Individuals have also been described with only dilated cardiomyopathy (weakening of the heart muscle).

How common is Delta-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. Autosomal recessive LGMD has an estimated prevalence of 1 in 15,000 individuals and LGMD2F accounts for a small subset of all cases of LGMD, though this varies by region. LGMD2F is more common in the Brazilian population.

How is Delta-Sarcoglycanopathy treated?

There is no cure for delta-sarcoglycanopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with Delta-Sarcoglycanopathy?

The outlook for a person with delta-sarcoglycanopathy varies. Generally speaking, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. People with more severe symptoms can become wheelchair bound in their early teens and die in early adulthood, and other causes of early death include respiratory and cardiac complications.

Dysferlinopathy

Available Methodology: sequencing with copy number analysis.
Gene: DYSF.
Exons Sequenced: NM_001130987:1-56.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is Dysferlinopathy?

Dysferlinopathy represents a spectrum of disorders that cause muscle weakness as a result of a deficiency of the protein, dysferlin. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course, while others may have severe symptoms that can be fatal. Common presentations of this condition are described below.

LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2B

People with limb-girdle muscular dystrophy type 2B (LGMD2B) develop symptoms at variable ages. Symptoms can present at as early as 14 years of age, although onset in adulthood is possible. LGMD2B does not affect intelligence or mental function; the primary symptom is progressive muscle weakness of the hip, shoulder, and abdomen (proximal muscles). The rate at which the muscles weaken can vary greatly, but many experience progressive weakness to a point where a wheelchair becomes necessary.

Many individuals with LGMD2B live well into adulthood with respiratory failure being the most common cause of death. However, a minority of people with LGMD2B experience respiratory complications (~20%) or heart complications (~10%). Involvement of the heart muscles is less common in type 2B than in other forms of limb girdle muscular dystrophy.

MIYOSHI MUSCULAR DYSTROPHY TYPE 1

Miyoshi muscular dystrophy type 1 (MMD1) is also associated with muscle weakness, but the muscles involved are those away from the center of the body (distal muscles), such as the legs and calves. Progression tends to be slower.

OTHER

Other presentations include distal myopathy with anterior tibial onset (initially distal muscle weakness that progressives to the proximal muscles) and scapuloperoneal syndrome (distal muscle weakness with weakness in the shoulder muscles). A few case reports of congenital muscular dystrophy (severe presentation with extremely poor prognosis) have also been reported.

How common is Dysferlinopathy?

There are numerous types of limb-girdle muscular dystrophy. LGMD has an estimated prevalence of 1 in 15,000 individuals. LGMD2B is thought to account for ~5% of all cases of LGMD, though this varies by region. For example, in Japan, LGMD2B accounts for ~19% of all cases of LGMD and 75% of all cases of Miyoshi muscular dystrophy. In addition, LGMD2B is most commonly found in individuals of Libyan and Caucasus Jewish descent.

How is Dysferlinopathy treated?

There is no cure for dysferlinopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with Dysferlinopathy?

The outlook for a person with dysferlinopathy varies. Generally, the earlier symptoms begin, the faster they progress. Some people with the disease experience only mild symptoms, and may have near-normal strength. Others with a mild course may remain able to walk for 30 years or more after symptoms appear. People with more severe disease typically become wheelchair-bound approximately 20 years after their diagnosis.

Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)

Available Methodology: sequencing with copy number analysis.

Gene: DMD.

Exons Sequenced: NM_004006:1-79.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)?

Dystrophinopathies are a group of conditions that generally cause muscle weakness. They are inherited in an X-linked manner, which means that females are far less likely to experience symptoms compared to males. However, up to 20% of females may also experience mild symptoms. Common presentations of dystrophinopathies are described below.

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is characterized by progressive muscle weakness and degeneration. Symptoms typically begin in early childhood with the first muscles affected being those of the hips, pelvic region, thighs, and shoulders. Muscle weakness of these areas results in general motor (sitting up, standing, walking) delays and an abnormal gait (way of walking). A small percentage of males also develop learning difficulties early in life, though the level of intellectual disability is variable. Because DMD is progressive, most individuals will need a wheelchair by 13 years of age. By the mid-teenage years the heart muscles will weaken (dilated cardiomyopathy), as will the respiratory muscles, which can lead to early death.

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy (BMD) is similarly characterized by muscle weakness and dilated cardiomyopathy. However, symptoms are much more variable in presentation, may be milder, and tend to develop later than DMD. In addition, a longer life expectancy is generally seen with BMD in comparison to DMD.

DMD-ASSOCIATED DILATED CARDIOMYOPATHY

DMD-associated dilated cardiomyopathy (DMD-associated DCM) may occur without any muscle disease, and both males and females are at risk to develop this condition. However, onset is generally earlier in males than in females, and progression of DCM tends to be more rapid in males than females.

How common is Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)?

Duchenne and Becker muscular dystrophies are seen in all ethnic groups and, at most, affect about 1 in 3500 males. However, approximately 1/3 of individuals affected by DMD/BMD do not inherit a mutation from a carrier mother (*de novo* mutation). Of note, because the condition is X-linked, estimates generally do not include females though they are affected at a much lower rate.

How is Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy) treated?

There is no cure for Duchenne muscular dystrophy and the related disorders. A combination of physical therapy, medication, and regular cardiac and respiratory screenings is the current standard practice for treating the disease.

Females who are carriers for the disease are at an increased risk for dilated cardiomyopathy, and should also be seen regularly by a cardiologist.

What is the prognosis for people with Dystrophinopathy (Including Duchenne/Becker Muscular Dystrophy)?

The prognosis for Duchenne muscular dystrophy is variable, but most males will be wheelchair-dependent by age 13 and die before 30 years of age due to heart or respiratory failure. Males who have Becker muscular dystrophy have a longer life expectancy reaching into their 40s or 50s. Prognosis in females is generally better, but lifespan may still be shortened in the presence of DCM.

ERCC6-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: ERCC6.
Exons Sequenced: NM_000124:2-21.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe

What are ERCC6-related Disorders?

ERCC6-related disorders are more commonly known as Cockayne syndrome type B, an inherited disorder characterized by severe growth delay, a small head size, developmental delays, and intellectual disabilities. Other common features of the condition include an increased sensitivity to sunlight (photosensitivity), significant tooth decay, vision problems, and hearing loss. In addition, affected individuals may have certain facial features such a small chin, large ears, and a slender nose, which may make them appear older than their actual age.

ERCC6-related disorders are sometimes divided into three forms called Cockayne syndrome type I, Cockayne syndrome type II, and Cockayne syndrome type III. These forms differ in the age at which symptoms first appear and how fast the symptoms progress. However, the three forms are not completely distinct, with some patients having features consistent with more than one type.

Cockayne syndrome type I is the most common type of ERCC6-related disorder. Newborns with this type generally appear normal. However, their growth slows considerably within the first two years of life. With time, their length, weight, and head size are all significantly less than expected for their age. Affected children also develop vision and hearing problems that worsen over time, as well as neurological problems such as increased muscle tone, difficulty walking, tremors, seizures, feeding difficulties, and behavioral issues. Other possible symptoms include (but are not limited to) cataracts, frequent cavities, dry skin and hair, bone problems, and changes in the brain that can be seen on brain imaging.

Cockayne syndrome type II (sometimes called cerebro-oculo-facio-skeletal [COFS] syndrome or Pena-Shokeir syndrome type II) is the most severe form of the disease, with signs and symptoms appearing at birth or in the newborn period. Infants are small at birth and often have cataracts or other eye abnormalities (such as small corneas). With time, they continue to have significant problems with growth and severe developmental delays. Affected children are typically unable to speak and cannot sit or walk independently.

Cockayne syndrome type III is the mildest form of the condition, with symptoms appearing later in childhood. While affected children with this type have some of the features associated with Cockayne syndrome types I and II, their growth deficiency and developmental delays are not as severe.

How common are ERCC6-related Disorders?

It has been estimated that Cockayne syndrome affects approximately 1 in 200,000 Europeans each year. *ERCC6* accounts for 65% of individuals affected with Cockayne syndrome. Studies have also suggested that the condition may be more common in certain populations (such as the Druze population in Northern Israel) and that certain recurring *ERCC6* gene changes may be more common in individuals from Reunion Island and in some individuals of French or British ancestry.

How are ERCC6-related Disorders treated?

There is no cure for ERCC6-related disorders. Treatment is focused on managing the symptoms of the condition. This may include medication for muscle stiffness, tremors, or seizures, physical therapy or assistive devices for mobility issues, educational programs for intellectual disabilities, feeding tubes for those with significant feeding difficulties, hearing aids for those with hearing loss, and standard therapies for the treatment of cataracts or other vision problems. In addition, aggressive dental care will help minimize the risk of cavities and sun protection is necessary for managing photosensitivity, although exposure to excessive sunlight should be avoided. Metronidazole (a type of antibiotic) should also be avoided, as use of this medication can cause liver failure in individuals with Cockayne syndrome.

What is the prognosis for a person with an ERCC6-related Disorder?

The prognosis for ERCC6-related disorders varies depending on the type of Cockayne syndrome. Most individuals with Cockayne syndrome type I die by the age of 20, with an average age at death of 12 years. However, survival past the age of 20 has been reported. For those with Cockayne syndrome type II, the most severe form of the condition, death by age 7 is typical. The average life expectancy for those with Cockayne syndrome type III is not currently known.

ERCC8-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: ERCC8.
Exons Sequenced: NM_000082:1-12.

Detection Rate	Population
95%	African American
95%	Ashkenazi Jewish
95%	Eastern Asia
95%	Finland
95%	French Canadian or Cajun
95%	Hispanic
95%	Middle East
95%	Native American
95%	Northwestern Europe
95%	Oceania
95%	South Asia
95%	Southeast Asia
95%	Southern Europe

What are ERCC8-related Disorders?

ERCC8-related disorders are more commonly known as Cockayne syndrome type A, an inherited disorder characterized by severe growth delay, a small head size, developmental delays, and intellectual disabilities. Other common features of the condition include an increased sensitivity to sunlight (photosensitivity), significant tooth decay, vision problems, and hearing loss. In addition, affected individuals may have certain facial features such a small chin, large ears, and a slender nose, which may make them appear older than their actual age.

ERCC8-related disorders are sometimes divided into three forms called Cockayne syndrome type I, Cockayne syndrome type II, and Cockayne syndrome type III. These forms differ in the age at which symptoms first appear and how fast the symptoms progress. However, the three forms are not completely distinct, with some patients having features consistent with more than one type.

Cockayne syndrome type I is the most common type of ERCC8-related disorder. Newborns with this type generally appear normal. However, their growth slows considerably within the first two years of life. With time, their length, weight, and head size are all significantly less than expected for their age. Affected children also develop vision and hearing problems that worsen over time, as well as neurological problems such as increased muscle tone, difficulty walking, tremors, seizures, feeding difficulties, and behavioral issues. Other possible symptoms include (but are not limited to) cataracts, frequent cavities, dry skin and hair, bone problems, and changes in the brain that can be seen on brain imaging.

Cockayne syndrome type II (sometimes called cerebro-oculo-facio-skeletal [COFS] syndrome or Pena-Shokeir syndrome type II) is the most severe form of the disease, with signs and symptoms appearing at birth or in the newborn period. Infants are small at birth and often have cataracts or other eye abnormalities (such as small corneas). With time, they continue to have significant problems with growth and severe developmental delays. Affected children are typically unable to speak and cannot sit or walk independently.

Cockayne syndrome type III is the mildest form of the condition, with symptoms appearing later in childhood. While affected children with this type have some of the features associated with Cockayne syndrome types I and II, their growth deficiency and developmental delays are not as severe.

How common are ERCC8-related Disorders?

It has been estimated that Cockayne syndrome affects approximately 1 in 200,000 Europeans each year. *ERCC8* accounts for 35% of individuals affected with Cockayne syndrome. Studies have also suggested that the condition may be more common in certain populations in Northern Israel.

How are ERCC8-related Disorders treated?

There is no cure for ERCC8-related disorders. Treatment is focused on managing the symptoms of the condition. This may include medication for muscle stiffness, tremors, or seizures, physical therapy and assistive devices for mobility issues, educational programs for intellectual disabilities, feeding tubes for those with significant feeding difficulties, hearing aids for those with hearing loss, and standard therapies for the treatment of cataracts or other vision problems. In addition, aggressive dental care will help minimize the risk of cavities and sun protection is necessary for managing photosensitivity, although exposure to excessive sunlight should be avoided. Metronidazole (a type of antibiotic) should also be avoided, as use of this medication can cause liver failure in individuals with Cockayne syndrome.

What is the prognosis for a person with an ERCC8-related Disorder?

The prognosis for ERCC8-related disorders varies depending on the type of Cockayne syndrome. Most individuals with Cockayne syndrome type I die by the age of 20, with an average age at death of 12 years. However, survival past the age of 20 has been reported. For those with Cockayne syndrome type II, the most severe form of the condition, death by the age of 7 is typical. The average life expectancy for those with Cockayne syndrome type III is not currently known.

EVC-related Ellis-van Creveld Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: EVC.
Exons Sequenced: NM_153717:1-21.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe

What is EVC-related Ellis-van Creveld Syndrome?

EVC-related Ellis-van Creveld syndrome is an inherited condition that impacts the formation of cartilage. Affected individuals typically have shortening of the arms and legs (dwarfism), a narrow chest due to shortened ribs, abnormally formed fingernails and toenails, dental abnormalities, and extra fingers (polydactyly). Approximately 60% of affected individuals are born with heart defects. Common dental problems include small teeth, missing teeth, abnormal tooth alignment or teeth that are present at birth.

Some features of EVC-related Ellis-van Creveld syndrome may be detected before birth via ultrasound, such as extra fingers, shortening of the bones or heart defects.

How common is EVC-related Ellis-van Creveld Syndrome?

Ellis-van Creveld syndrome is a rare disorder; therefore it is difficult to predict its frequency in the general population. An estimated 1 in 60,000 to 1 in 200,000 individuals of various ethnicities are affected worldwide. Mutations in the *EVC* gene and the *EVC2* gene are responsible for more than have of all reported cases Ellis-van Creveld syndrome. It is more commonly seen among individuals in the Amish community.

How is EVC-related Ellis-van Creveld Syndrome treated?

There is no cure for the underlying cause of this condition and treatment is based on symptoms. In the neonatal period, treatment is based on management of respiratory and cardiac symptoms. Individuals with heart defects will need to be treated by a cardiologist. Affected individuals typically require dental treatment and infants born with teeth may require removal if the teeth impact feeding.

What is the prognosis for a person with EVC-related Ellis-van Creveld Syndrome?

Prognosis of affected individuals may be impacted by whether the size of the chest restricts breathing after birth and the presence and severity of heart defects. Individuals who survive infancy will likely have a normal life expectancy.

EVC2-related Ellis-van Creveld Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: EVC2.
Exons Sequenced: NM_147127:1-22.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is EVC2-related Ellis-van Creveld Syndrome?

EVC2-related Ellis-van Creveld syndrome is an inherited condition that impacts the formation of cartilage. Affected individuals typically have shortening of the arms and legs (dwarfism), a narrow chest due to shortened ribs, abnormally formed fingernails and toenails, dental abnormalities, and extra fingers (polydactyly). Approximately 60% of affected individuals are born with heart defects. Common dental problems include small teeth, missing teeth, abnormal tooth alignment or teeth that are present at birth.

Some features of EVC2-related Ellis-van Creveld syndrome may be detected before birth via ultrasound, such as extra fingers, shortening of the bones or heart defects.

How common is EVC2-related Ellis-van Creveld Syndrome?

Ellis-van Creveld syndrome is a rare disorder; therefore it is difficult to predict its frequency in the general population. An estimated 1 in 60,000 to 1 in 200,000 individuals of various ethnicities are affected worldwide. Mutations in the *EVC* gene and the *EVC2* gene are responsible for more than have of all reported cases Ellis-van Creveld syndrome. It is more commonly seen among individuals in the Amish community.

How is EVC2-related Ellis-van Creveld Syndrome treated?

There is no cure for the underlying cause of this condition and treatment is based on symptoms. In the neonatal period, treatment is based on management of respiratory and cardiac symptoms. Individuals with heart defects will need to be treated by a cardiologist. Affected individuals typically require dental treatment and infants born with teeth may require removal if the teeth impact feeding.

What is the prognosis for a person with EVC2-related Ellis-van Creveld Syndrome?

Prognosis of affected individuals may be impacted by whether the size of the chest restricts breathing after birth and the presence and severity of heart defects. Individuals who survive infancy will likely have a normal life expectancy.

Fabry Disease

Available Methodology: sequencing with copy number analysis.
Gene: GLA.
Exons Sequenced: NM_000169:1-7.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is Fabry Disease?

Fabry disease is a lysosomal storage disorder caused by a deficiency of the alpha-galactosidase A enzyme. As this is an X-linked recessive disorder, generally males are affected with a classic form of the disease, but carrier females can exhibit milder symptoms with later age of onset than males. There is also an atypical form of this condition.

CLASSIC FORM

The classic form occurs in males with symptoms usually beginning in early childhood or adolescence. Patches of dark skin (angiokeratomas) are an early sign and most often appear on the lower half of the body. Other common symptoms include severe pain in the extremities (acroparesthesia), altered sweating (usually decreased sweating, hypohidrosis, but there are reports of increased sweating, hyperhidrosis), and characteristic eye changes such as cloudiness of the cornea and/or lens (vision is typically not affected). Less common symptoms include hearing loss and ringing in ears (tinnitus), gastrointestinal issues, obstructive pulmonary disease such as chronic bronchitis or wheezing, and swelling (edema) in the lower extremities in adulthood.

The symptoms that are a major cause of mortality are renal insufficiency, cardiac complications, and cerebrovascular disease. The kidney function slowly deteriorates over time with end-stage renal disease (ESRD) usually occurring in one's 30s-50s. Hypertension is the most frequent cardiac manifestation, this and other cardiac issues may lead to angina (chest pain), arrhythmia, heart attack, and heart failure. Cerebrovascular disease often presents as stroke or transient ischemic attacks (TIA).

ATYPICAL FORM

In the atypical forms, most of the classic symptoms do not manifest. Typically there is only involvement of the heart or kidneys later in life. This difference in presentation is attributed to higher activity levels of the alpha-galactosidase A as compared to those individuals with the classic form.

CARRIER FEMALES

Carrier females may be asymptomatic or may exhibit symptoms ranging from mild to severe. However, in most cases, symptoms tend to be milder with onset being later in life than in their affected male relatives.

How common is Fabry Disease?

Fabry disease has an estimated pan-ethnic incidence of approximately 1 in 40,000 males, though regional incidences may vary. Because atypical forms may be unrecognized or diagnosed late in life, this incidence is likely an underestimate and higher frequencies have been reported in both Taiwan and Italy.

How is Fabry Disease treated?

Pain may be treated with diphenylhydantoin, carbamazepine, or gabapentin. Renal insufficiency can initially be treated with ACE inhibitors or angiotension receptor blockers to reduce protein in the urine. Late stage renal involvement may necessitate dialysis or kidney transplantation.

There is evidence that enzyme replacement therapy (ERT) may prevent some primary manifestations of Fabry disease and it is typically recommended for all affected males (including children) and for some female carriers. However, because ERT may not improve symptoms of renal, cardiac, or cerebrovascular disease, other medications may be recommended to help manage kidney/heart disease and stroke.

What is the prognosis for a person with Fabry Disease?

The majority of affected males with Fabry disease live well into adulthood, with an average life expectancy of ~58 years. Renal and cardiac disease are the main causes of mortality. For carrier females, the prognosis is good and approaches a near-normal life span, though some may be more severely affected.

Familial Dysautonomia

Available Methodology: sequencing with copy number analysis.
Gene: IKBKAP.
Exons Sequenced: NM_003640:2-37.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Familial Dysautonomia?

Familial dysautonomia is an inherited condition that causes nerve cells to deteriorate. It affects the autonomic nervous system, which controls involuntary actions such as breathing, tear production, blood pressure, and body temperature. It also affects the sensory nervous system, which controls senses such as the abilities to perceive taste, pressure, pain, and temperature.

Early symptoms in infants include feeding problems, poor growth, lack of tears, poor muscle tone, frequent lung infections, and marked fluctuations in body temperature. Until about age 6, children with the condition may also hold their breath for long periods of time, which may cause fainting or make their lips or skin appear blue. They may learn to walk and talk later than average.

Starting around age 5 or 6, children with the condition may develop symptoms including bed-wetting, vomiting, reduced sensitivity to temperatures and pain, decreased ability to taste, poor balance, abnormal curvature of the spine, easily fractured bones, and kidney and heart problems. They commonly experience a sharp drop in blood pressure when they stand up, which can cause blurred vision, dizziness, or fainting. They may also have episodes of high blood pressure when nervous or excited.

By adulthood, people with familial dysautonomia may have balance problems that prevent them from walking unaided. Other common complications include sleep apnea, lung damage due to repeated infections, poor vision as optic nerves atrophy, and kidney disease. Intellect is not usually impaired.

How common is Familial Dysautonomia?

Familial dysautonomia is found almost exclusively in people of Ashkenazi Jewish descent, where it affects approximately 1 in 3,700 people. Roughly 1 in 31 Ashkenazi Jews is a carrier of the disease. It is extremely rare in the general population.

How is Familial Dysautonomia treated?

There is no cure for the cause of familial dysautonomia. Treatment focuses on relieving its symptoms.

Infants with the condition may need to be fed thickened formula to ensure adequate nutrition and prevent them from inhaling their food. Vomiting crises are treated with IV fluids and anti-nausea medication. Recurrent pneumonia caused by inhaling food or vomit requires daily chest physiotherapy. Older children who experience low blood pressure may require elastic stockings and leg exercises to improve muscle tone and prevent blood from pooling in leg veins. Corneal injuries caused by low tear production may be treated with regular eye drops, soft contact lenses, or in rare cases, surgery. Spinal fusion surgery may be necessary to correct scoliosis. Kidney disease may require dialysis. Sleep apnea is generally treated with a machine to support breathing. Many adults require walkers or wheelchairs.

What is the prognosis for a person with Familial Dysautonomia?

The average lifespan of a person with familial dysautonomia is significantly shortened. Only 60% of people with the disease survive to age 20.

Familial Mediterranean Fever

Available Methodology: sequencing with copy number analysis.
Gene: MEFV.
Exons Sequenced: NM_000243:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Familial Mediterranean Fever?

Familial Mediterranean fever (FMF) is an inherited condition which causes episodic attacks of fever and painful inflammation of the abdomen, chest, and joints. People with FMF may also develop a rash during these attacks. The attacks last for 1 to 3 days and can vary in severity. Between attacks, the person typically feels normal. These symptom-free periods can last for days or even years.

In 80-90% of people affected by FMF, the first attack occurs by the age of 20. Less commonly, symptoms begin later in life. Children who have FMF may experience periodic fever as their only symptom.

Some people with FMF develop a protein buildup in various parts of the body, notably the kidney. If left untreated, this can lead to life-threatening kidney failure. People who do not experience the characteristic attacks of FMF can still develop this particular form of kidney failure. This symptom is most common among people of Turkish and North African Jewish heritage, affecting 60% and 75% respectively.

Other symptoms that can occur during an attack of FMF include headache and inflammation of the heart and/or testicles. Affected people may also develop an inflammation of the membrane that surrounds the brain and spinal cord, though this is not usually serious or damaging. People with FMF who go untreated may experience decreased fertility.

About half of people with FMF have mild symptoms preceding an attack. These may include a mild, unpleasant sensation in parts of the body that will soon be affected or may consist of other physical and emotional symptoms.

How common is Familial Mediterranean Fever?

FMF is most common among ethnic groups from the Mediterranean region, notably people of Armenian, Arab, Turkish, Iraqi Jewish, and North African Jewish ancestry. One in every 200 to 1,000 people in these groups is affected by the disease and carrier rates in some populations have been estimated as high as 1 in 5.

Cases of FMF have also been found in other populations, including Italians, Greeks, Spaniards, Cypriots, and less commonly, Northern Europeans and Japanese.

How is Familial Mediterranean Fever treated?

There is no cure for FMF, however the drug colchicine has been very effective in preventing the disease's characteristic attacks. With daily doses of colchicine, 75% of people with FMF can avoid attacks with an additional 15% showing an improvement in their symptoms. Colchicine also prevents the dangerous buildup of proteins in the kidneys which could otherwise lead to kidney failure.

Episodic attacks of fever and inflammation can be treated with non-steroidal anti-inflammatory drugs. Those who do develop serious kidney failure may be helped by kidney transplantation.

What is the prognosis for a person with Familial Mediterranean Fever?

With early and regular treatment, people with FMF can live a normal lifespan and may even be symptom-free. The disease has the potential to be life-threatening only if the person is untreated (or does not respond to treatment) and develops kidney failure.

Fanconi Anemia Complementation Group A

Available Methodology: sequencing with copy number analysis.
Gene: FANCA.
Exons Sequenced: NM_000135:1-43.

Detection Rate	Population
92%	African American
92%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
92%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
92%	Southern Europe

What is Fanconi Anemia Complementation Group A?

Fanconi anemia is a group of inherited disorders in which the body cannot properly produce a protein that protects DNA from damage. The defective protein results in an impaired ability of bone marrow to produce all types of blood cells. Without a sufficient number of red blood cells, the body does not receive enough oxygen, which can lead to abnormal bones and organs, as well as developmental delay. Similarly, a shortage of white blood cells makes the body more susceptible to infection and cancer, and a reduction in blood platelets make it difficult for the blood to clot when an injury arises.

Individuals with Fanconi anemia are typically born with some kind of physical abnormality with the most common being short stature, thumb or finger malformation, skin discoloration, kidney and eye anomalies, and skeletal irregularities. However, 25 to 40% of people with the condition do not have physical abnormalities. Thus, individuals may be first diagnosed in childhood with abnormally low levels of red blood cells, white blood cells, or platelets caused by bone marrow failure (because it is progressive most individuals will have some blood-related complication), hearing loss (10% of individuals), some degree of developmental delay (10% of individuals), and/or cancer.

The higher than average risk for cancer stems from the cells' inability to repair themselves when the DNA is damaged. Occasionally, the initial signs of leukemia appear in childhood as the first symptom of the disease. Other cancers may also appear at an unusually early age, particularly tumors of the head and neck, esophagus, cervix, vulva (external opening of the vagina), or liver.

How common is Fanconi Anemia Complementation Group A?

Fanconi anemia type A is the most common type of Fanconi anemia, making up between 60-70% of all cases and affecting approximately 1 in 200,000 people. However, incidence of the condition and the number of cases attributed to *FANCA* vary in certain ethnic groups due to founder effects (high frequency of disease because the group arose from a small, possibly isolated population). Founder effects have been noted in individuals of Sephardic Jewish descent (Moroccan and Indian), Tunisian descent, Afrikaners, Brazilians, Spanish Gypsies, and others.

How is Fanconi Anemia Complementation Group A treated?

There is currently no cure for Fanconi anemia type A. Treatment consists of monitoring for symptoms and treating them as they appear.

Roughly half of all people with the condition can improve their blood cell counts with medication. Over a period of years, however, people often develop resistance to the medication. Treatment with medication may also decrease the effectiveness of a later bone marrow transplant.

Bone marrow transplantation can cure leukemia associated with Fanconi anemia type A. However people with the condition are extremely sensitive to the chemotherapy and the radiation treatment necessary to prepare for transplantation, so they may not be good candidates for this surgery. A bone marrow transplant does not prevent solid tumors elsewhere in the body, which must be treated with chemotherapy and radiation.

People with Fanconi anemia type A must undergo regular blood cell count tests, bone marrow biopsies, liver scans, and gynecological, dental, and rectal exams to detect early-stage cancers so they can be removed as soon as possible.

What is the prognosis for a person with Fanconi Anemia Complementation Group A?

The prognosis for a person with the disease is dependent upon the severity of the symptoms, which will be variable from person to person.

Fanconi Anemia Type C

Available Methodology: sequencing with copy number analysis.
Gene: FANCC.
Exons Sequenced: NM_000136:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Fanconi Anemia Type C?

Fanconi anemia type C is an inherited disorder in which the body cannot properly produce a protein that protects DNA from damage. This defective protein results in an impaired ability of bone marrow to produce all types of blood cells. Without a sufficient number of red blood cells, the body does not receive enough oxygen, which can lead to abnormal bones and organs as well as developmental delay. A shortage of white blood cells makes the body more susceptible to infection and cancer. A reduction in blood platelets make it difficult for the blood to clot when an injury arises.

In many cases, the first symptoms of Fanconi anemia type C appear in infancy as frequent nosebleeds, a tendency to bruise, and physical abnormalities such as spotted skin or malformations of the thumbs, forearms, eyes, kidneys, gastrointestinal system, ears, or heart. Children with the disease may also show signs of hearing loss or developmental delay. However 25 to 40% of people with the condition do not have physical abnormalities. They may be first diagnosed in childhood with abnormally low levels of red blood cells, white blood cells, or platelets. Although their bone marrow may appear normal at first, it deteriorates progressively. Most people with the disease are diagnosed by age 12.

Because Fanconi anemia type C prevents cells from repairing themselves when the DNA is damaged, people with the condition are at higher than average risk of cancer. Occasionally, the initial signs of leukemia appear in childhood as the first symptom of the disease. Other cancers may also appear at an unusually early age, particularly tumors of the head and neck, esophagus, cervix, vulva, or liver. These cancers commonly develop in the early 20s.

Certain mutations are associated with more or less severe courses of Fanconi anemia type C. For example, one particular mutation is associated with less severe symptoms in people of Japanese ancestry.

How common is Fanconi Anemia Type C?

Fanconi anemia type C affects approximately 1 in 100,000 people. Fanconi anemia is most common in people of Ashkenazi Jewish descent, where 1 in 90 are carriers and 1 in 32,000 have the disease.

How is Fanconi Anemia Type C treated?

There is currently no cure for Fanconi anemia type C. Treatment consists of watching for symptoms and treating them as they appear.

About half of all people with the condition can improve their blood cell counts with medication. Over a period of years, however, people often develop resistance to the medication. Treatment with medication may also decrease the effectiveness of a later bone marrow transplant.

Bone marrow transplantation can cure the leukemia associated with Fanconi anemia type C. However people with the condition are extremely sensitive to the chemotherapy and the radiation treatment necessary to prepare for transplantation, so they may not be good candidates for this surgery. A bone marrow transplant does not prevent solid tumors elsewhere in the body, which must be treated with chemotherapy and radiation.

People with Fanconi anemia type C must undergo regular blood cell counts, bone marrow biopsies, liver scans, and gynecological, dental, and rectal exams to detect early-stage cancers so they can be removed as soon as possible.

What is the prognosis for a person with Fanconi Anemia Type C?

Most people with Fanconi anemia type C die before the age of 30. A bone marrow transplant can extend lifespan.

FKRP-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: FKRP.
Exon Sequenced: NM_024301:4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are FKRP-related Disorders?

Mutations in the *FKRP* gene may cause a wide spectrum of disorders known as limb-girdle muscular dystrophy-dystroglycanopathy, but has primarily been associated with limb-girdle muscular dystrophy type 2I (LGMD2I). LGMD2I causes muscle weakness as a result of a deficiency of the fukutin-related protein (FKRP) found in skeletal and cardiac muscle. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal.

LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2I

People with LGMD2I develop symptoms at variable ages, though symptoms tend to first present in adolescence. LGMD2I does not typically affect intelligence or mental function though some studies have shown rare brain abnormalities and cognitive dysfunction; the most common symptom is progressive muscle weakness of the hip, shoulder, and abdomen. The rate at which the muscles weaken can vary, but many experience progressive weakness to a point where a wheelchair becomes necessary. Other possible features include enlarged calf muscles, contractures, winging of the shoulder blade, and scoliosis. Respiratory complications (~30-50% of individuals) or heart complications (>50% of individuals) are also associated with these conditions, and may be a cause of death.

OTHER FKRP-RELATED DISORDERS

Mutations in the *FKRP* gene also cause other forms of muscular dystrophy including **merosin-deficient congenital muscular dystrophy type1C (MDC1C)**, **muscle-eye brain disease (MEB)** and **Walker-Warburg syndrome (WWS)**.

- Individuals with **MDC1C** have most often have an early age of onset (although it can vary), an inability to walk, enlarged calf muscles, intellectual disability, and often have brain abnormalities.

- Individuals with **MEB and WWS** are born with muscle weakness and structural abnormalities of the brain and eyes.

How common are FKRP-related Disorders?

Mutations in the *FKRP* gene are most often associated with LGMD2I. Autosomal recessive LGMD has an estimated prevalence of 1 in 15,000 individuals. The percentage of LGMD that is attributed to LGMD2I is approximately 10%. Rarely, mutations in the *FKRP* gene are associated with other disorders such as MDC1C, WWS, and MEB.

How are FKRP-related Disorders treated?

There is no cure for any of the FKRP-related disorders and there are few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with an FKRP-related Disorder?

The outlook for a person with LGMD2I varies. Generally speaking, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. People with more severe symptoms can become wheelchair bound in their early teens and die in early adulthood with death usually being due to respiratory and/or cardiac complications.

Individuals with MDC1C have a range of outcomes. Some are never able to walk and die as a result of respiratory complications in the second decade of life, while others have been reported to retain the ability to walk into their fifth decade of life.

The prognosis for individuals with WWS/MEB is poor. Some individuals with MEB may survive until their teens, whereas individuals with WWS usually do not survive past early childhood.

FKTN-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: FKTN.
Exons Sequenced: NM_001079802:3-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
10%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are FKTN-related Disorders?

FKTN-related Disorders includes a spectrum of conditions that cause muscle weakness because of a deficiency in the fukutin (FKTN) protein. Symptoms vary greatly from person to person, even among people in the same family. Some conditions can have a mild course, while others may have severe symptoms that can be fatal. The various conditions associated with mutations in the FKTN gene are described below in order of severity.

WALKER-WARBURG SYNDROME (WWS)

Walker-Warburg syndrome is the most severe presentation. Symptoms begin at birth and babies are born with severe abnormalities in the structure of the brain. Eye defects, such as cataracts at birth, unusually small eyes, or unusually large eyes, are common. Most patients only have control of their heads and do not develop the ability to move other body parts.

FUKUYAMA CONGENITAL MUSCULAR DYSTROPHY (FCMD)/MUSCLE-EYE-BRAIN DISEASE (MEB)

Fukuyama congenital muscular dystrophy and muscle-eye-brain disease have overlapping symptoms. Symptoms include muscle weakness and abnormalities in the structure of the brain that are less severe than in WWS. Less severe eye defects, such as glaucoma at birth, progressive nearsightedness, weakening of the retina, and cataracts in childhood, are common. Rarely, individuals with these conditions learn to walk at later stages in life and may speak a few words.

LIMB GIRDLE MUSCULAR DYSTROPHY TYPE 2M (LGMD2M)

Limb Girdle Muscular Dystrophy type 2M is the most mild presentation. Age of onset and severity of symptoms vary greatly among individuals. Typically, the only symptom is weakness in the muscles closest to the body, specifically the muscles of the shoulders, upper arms, pelvic area, and thighs. Rarely, individuals have a heart condition called dilated cardiomyopathy. The brain and eyes are not affected.

How common are FKTN-related Disorders?

WWS is rare and the exact incidence is unknown, though it is more common in individuals of Ashkenazi Jewish descent. FCMD is rarely seen outside of individuals of Japanese descent where approximately 1 in 140,000 live births have the condition. All forms of LGMD affect 1 in 14,5000 to 1 in 123,000 live births and this specific type, LGMD2M, is rare with unknown specific incidence.

How are FKTN-related Disorders treated?

There is no successful treatment or cure for WWS or FCMD/MEB. Medical specialists can help treat specific symptoms, such as using medication to control seizures, placement of a shunt to reduce fluid buildup around the brain, tube feeding and physical and occupational therapy to aid in movement.

Treatment for LGMD2M mainly involves physical and occupational therapy, assistive devices, and monitoring for heart and breathing complications.

What is the prognosis for a person with a FKTN-related Disorder?

The prognosis depends on the severity of the condition. Individuals with WWS typically pass away in infancy. Individuals with FCMD/MEB typically live until childhood or in their teens. Those with LGMD2M do not typically have an altered lifespan.

Fragile X Syndrome

Available Methodology: triplet repeat detection.
Gene: FMR1.
Variant (1): FMR1 CGG repeat number.

What is Fragile X Syndrome?

Fragile X syndrome is a condition that causes a spectrum of developmental and behavioral problems which tend to be more severe in males. The condition is also more common among men than women. It is the most common form of inherited intellectual disability.

Fragile X syndrome typically causes moderate intellectual disability in males, although the severity of intellectual impairment varies from person to person. A small number of males do not have intellectual disability, defined as an IQ below 70. About a third of women with fragile X syndrome have no cognitive impairment, while the remainder have some degree of cognitive, behavioral, or social difficulties. Some females with fragile X syndrome have mild intellectual disability.

As infants, children with fragile X syndrome may display poor muscle tone, gastric reflux, and frequent ear infections. Their motor and mental milestones, as well as their speech, tend to be delayed.

Children with fragile X syndrome often have behavioral problems such as anxiety, hyperactivity, hand-flapping, biting, and temper tantrums. About one-third of males with fragile X syndrome have autism or autism-like behavior.

In females, who often have milder symptoms, behavioral problems may appear as depression, shyness, and avoidance of social situations.

Some people with the condition have attention deficit disorder, with an inability to sustain focused attention on a specific task.

As they become adolescents and young adults, people with fragile X syndrome, particularly males, may lack impulse control, make poor eye contact, and/or be easily distracted. They often have unusual responses to being touched or to sights and sounds.

Males with fragile X syndrome often share characteristic physical features such as a long, narrow face with a prominent jaw and forehead, a large head, flexible joints, and large ears. These symptoms tend to be milder or absent in females with the condition. After puberty, males with fragile X syndrome typically have enlarged testicles. Roughly 15 percent of males and 5 percent of females with fragile X syndrome will experience seizures. While some experience heart murmurs from a condition called mitral valve prolapse, it is usually harmless and may not require treatment.

Effects of a Premutation

Men and women with a premutation (please see below for a description) do not have fragile X syndrome, but may experience certain physical symptoms. While they are intellectually normal, they are thought to be more vulnerable to anxiety and depression.

The key risks for carriers of a premutation are fragile X-associated tremor/ataxia syndrome (FXTAS) and premature ovarian failure (POF).

About 40% of men over the age of 50 with a fragile X premutation will develop FXTAS. (The percentage of women premutation carriers affected by FXTAS is unknown, but known to be lower.) FXTAS causes an inability to coordinate muscle movements (ataxia) that worsens over time, tremors, memory loss, dementia, a loss of feeling and weakness in the lower legs, and some mental and behavioral changes.

Often symptoms of FXTAS begin around age 60 with a tremor, followed several years later by ataxia. One study of 55 men with FXTAS found that from the time symptoms begin, additional life expectancy ranged from 5 to 25 years.

About 20 percent of women with a premutation experience premature ovarian failure (POF), in which their menstrual periods stop by age 40. Only 5 to 10 percent of women with POF will be able to have children. One study found that 21 percent of women with a premutation experienced POF, compared to 1 percent in the general population. In general, women with premutations larger than 80 repeats (see below for an explanation) were at lower risk for POF when compared to women with smaller premutations. Women with full mutations are not at increased risk for POF.

How is Fragile X Syndrome inherited?

Fragile X syndrome is inherited in a complex way that is different from many other genetic diseases. If you have any questions about fragile X syndrome, a healthcare professional can help explain this condition and your risk of transmitting it to the next generation.

Fragile X syndrome is inherited in an X-linked dominant pattern. The gene associated with the disease is located on the X chromosome. The X and Y chromosomes determine gender. Women have two X chromosomes (XX) while men have one X chromosome and one Y chromosome (XY). Girls receive one X chromosome from their mother and one from their father. Boys receive one X chromosome from their mother and a Y chromosome from their father. Typically, unaffected female full mutation carriers of fragile X syndrome are at risk of transmitting the condition to their children.

Fragile X syndrome is among a group of diseases called "trinucleotide repeat disorders." At its most basic level, these diseases are caused by a sequence of DNA that is repeated over and over in the same gene. While everyone has these repeats, it is the number of times that it is repeated which determines whether or not a person has the disease or can pass it on to future generations.

Fragile X syndrome is caused by a mutation in the FMR1 gene, which is located on the X chromosome. This gene contains a segment of DNA called the "CGG repeat," in which a particular section of DNA is repeated a certain number of times in a row. By counting the number of CGG repeats that each parent has, we can determine the likelihood that his or her child will have fragile X syndrome.

The CGG repeat in the FMR1 gene falls into one of four categories, each of which are explained below:

Category	FMR1 CGG repeat size
Normal	5 to 44 repeats
Intermediate	45-54 repeats
Premutation	55 to 200 repeats
Full mutation	More than 200 repeats

Normal

A FMR1 gene with 5 to 44 CGG repeats is considered normal. Someone with this size FMR1 CGG repeat is very unlikely to pass on fragile X syndrome to his or her children. You can think of these genes as "stable": they usually pass from parent to child with the same number of repeats. For example, if the parent's gene has 15 CGG repeats, his or her child is also very likely to have a gene with 15 CGG repeats.

Intermediate

Someone with 45 to 54 repeats is not at substantial risk for passing on fragile X syndrome to his or her child, however the number of repeats transmitted to the next generation may increase slightly. For example, a parent with 45 CGG repeats could have a child with 50 CGG repeats. If the number of repeats continues to increase in subsequent generations, future generations (i.e. grandchildren or great-grandchildren) may be at risk for inheriting fragile X.

Premutation

Those with 55 to 200 CGG repeats have a "premutation." They themselves do not have symptoms of fragile X syndrome, although they are at increased risk for FXTAS and POF (see above). However, depending which parent has the premutation, future children may be at risk.

You can think of premutations as "unstable." When passed from mother to child, premutations may expand into full mutations in the child. If the number of CGG repeats exceeds 200 in the child, that child will have fragile X syndrome.

Men who have a premutation will pass on that premutation unchanged to their daughters, who would then also have a premutation. While a daughter is not at risk for fragile X syndrome, her future children may be at risk. Also, daughters of men with a premutation will be at risk for POF. (Men pass Y chromosomes to their sons, so this disease is not transmitted from father to son.)

Mutation

Someone with more than 200 repeats has a full mutation, and likely has symptoms of fragile X syndrome.

Because symptoms of the disease are often milder in women, some women with a full mutation can have children. Those children each have a 50% chance of having fragile X syndrome. Men who have a full mutation generally do not reproduce.

Full mutations cause the FMR1 gene to malfunction, shutting down its ability to produce a protein called fragile X mental retardation 1 protein. The function of this protein is not well understood, but scientists believe that it plays a role in the proper functioning of the nervous system.

IF A PARENT HAS A MUTATION OR PREMUTATION, WHAT IS THE RISK THAT HIS OR HER CHILD WILL DEVELOP FRAGILE X SYNDROME?

If a mother has a full mutation, 50% of her children will have fragile X syndrome. Men who have full mutations typically do not reproduce.

Premutations are more complicated. When the parent has a premutation, the risk of a child developing fragile X syndrome depends on the answers to several questions, each of which are detailed below:

1. Which parent has the premutation?
2. Will the child inherit the gene containing the premutation?
3. Will the premutation expand to a full mutation?

WHICH PARENT HAS THE PREMUTATION?

If a women is a premutation carrier, then she is at risk of having children with fragile X syndrome. Premutations inherited from the mother are unstable and may expand to become full mutations in the child.

Premutations pass more or less identically from father to child; the CGG repeats do not expand in number. Therefore, men with premutations are not at risk of having children with fragile X syndrome.

WILL THE CHILD INHERIT THE PREMUTATION?

If the father has a premutation on his X chromosome, all of his daughters will have that same premutation. These daughters are generally not at risk of having fragile X syndrome themselves, but their future children (the grandchildren of the original premutation carrier) will be at risk. Fathers pass a Y chromosome to their sons instead of an X, so fragile X premutations cannot be passed from father to son.

If the mother has a premutation on one of her X chromosomes, 50% of her children will inherit that abnormal gene and 50% will inherit the normal gene. Only children who inherit the abnormal gene would be at risk for fragile X syndrome.

WILL THE PREMUTATION EXPAND TO A FULL MUTATION?

If a mother has a gene with a premutation and that abnormal gene gets passed to her children, there are two possibilities:

1. The premutation does not expand beyond 200 repeats and remains a premutation in the child. That child has no symptoms of fragile X syndrome, but may experience FXTAS (male) or POF (female) as adults.
2. The premutation expands into a full mutation, causing fragile X syndrome.

The greater the number of CGG repeats a woman has, the more unstable the gene is and the more likely it will expand to a full mutation in her children. The smallest allele yet observed to expand to a full mutation in a single generation is 56 repeats.

Number of Maternal Premutation CGG Repeats	Percentage (total women) which expanded to full mutations
55-59	<1% (0/66)
60-69	2% (1/63)
70-79	11% (2/18)
80-89	33% (4/12)
90-99	80% (89/111)
>100	100% (2/2)

Adapted from Nolin et al. (2003) and Nolin et al. (2011). These percentages typically exclude families with a family history of fragile X syndrome.

Nolin SL, Brown WT, Glicksman A, Houck GE Jr, Gargano AD, Sullivan A, et al. (2003). Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. American Journal of Human Genetics, 72(2):454-64.

Nolin SL, Glicksman A, Ding X, Ersalesi N, Brown WT, Sherman SL, Dobkin C. (2011). Fragile X analysis of 1112 prenatal samples from 1991 to 2010. Prenatal Diagnosis, 31(10):925-31.

How common is Fragile X Syndrome?

An estimated 1 in 4000 males and 1 in 8000 females is affected by fragile X.

Based on a review of the literature and Counsyl's internal data, approximately 1 in 225 women carries a premutation and 1 in 45 carries an intermediate allele.

How is Fragile X Syndrome treated?

There is no cure for fragile X syndrome, however children with the condition can be treated and supported in many ways, depending on their particular symptoms and the severity of those symptoms. They may benefit from educational support like early developmental intervention, special education classes in school, speech therapy, occupational therapy, and behavioral therapies. A physician may also prescribe medication for their behavioral issues such as aggression, anxiety, or hyperactivity.

A small number of these children experience seizures which can be controlled with medication. While some experience heart murmurs from a condition called mitral valve prolapse, it is usually harmless and may not require treatment.

What is the prognosis for a person with Fragile X Syndrome?

While many of the children with fragile X syndrome have learning and behavioral problems, they generally do not have major medical problems and can live a normal life span.

Galactokinase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: GALK1.
Exons Sequenced: NM_000154:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Galactokinase Deficiency?

Galactokinase deficiency, also called galactosemia type II, is a treatable inherited disease that reduces the body's ability to metabolize galactose, a simple sugar found in milk. The primary symptom is cataracts (clouding of the lens of the eye), which can cause vision impairment. Cataracts are due to the build up of a substance in the lens of the eye called galactitol. Cataracts in affected individuals are usually seen in both eyes and typically develop in infancy within the first few weeks or months. Galactokinase deficiency is anticipated to be milder with better outcomes than another more severe forms of galactosemia.

Other, less common symptoms have been reported in a few affected individuals, such as low blood sugar, intellectual disability, and problems with growth; however, it is unclear whether they were caused by galactokinase deficiency in these individuals.

How common is Galactokinase Deficiency?

Approximately 1/40,000 - 1/370,000 newborns are affected with galactokinase deficiency. It is seen more frequently in the Romani populations across Europe. The number of affected individuals may vary across populations.

How is Galactokinase Deficiency treated?

People with classic galactosemia must monitor their galactose-1-phosphate levels with regular blood tests and follow a lifelong diet free of milk, milk products, or other foods containing galactose. Infants should be fed with galactose-free formulas. As children learn to feed themselves, parents must teach them how to read product labels so they can avoid any food containing milk, dry milk, milk products, and other galactose-containing foods. Often they require calcium supplements to avoid calcium deficiency. Dietary restriction often resolves the cataracts in affected individuals.

What is the prognosis for a person with Galactokinase Deficiency?

The prognosis of galactokinase deficiency is excellent if affected individuals continue a galactose free diet. With treatment, cataracts can be prevented or at least partially resolved if they have started to form prior to treatment.

Galactosemia

Available Methodology: sequencing with copy number analysis.
Gene: GALT.
Exons Sequenced: NM_000155:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Galactosemia?

Galactosemia is a treatable inherited disease that reduces the body's ability to metabolize galactose, a simple sugar found in milk. The classic form of galactosemia can be fatal without prompt treatment and careful management. Because milk is a staple of an infant's diet, diagnosis and treatment within the first week of life is critical to avoiding mental retardation and life-threatening complications.

Classic galactosemia, the most severe form of the disease, is caused by a deficiency in an enzyme called galactose-1-phosphate uridyltransferase. People with classic galactosemia have less than 5% of the normal activity in this enzyme. After only a few days of drinking milk, including breast milk, an infant with classic galactosemia will show symptoms including loss of appetite, jaundice, vomiting, lethargy, and convulsions. Without immediate and vigilant lifelong treatment, children with the condition will experience life-threatening complications such as severe infections, cirrhosis of the liver, and mental retardation. Even with treatment, children can still develop cataracts, speech problems, stunted growth and motor function, and learning disabilities, and most females will eventually develop menstrual irregularities and go through premature menopause.

Duarte galactosemia is a much milder form of the disease in which a person has 25 to 50% of the normal amount of galactose-1-phosphate uridyltransferase. People with Duarte galactosemia generally do not suffer any of the symptoms of classic galactosemia.

Please note that galactosemia is not the same as lactose intolerance, a more common and less serious condition.

How common is Galactosemia?

Classic galactosemia affects approximately 1 in 30,000 newborns. It is thought that 6% of the U.S. population (6 in 100) is a carrier of Duarte galactosemia.

How is Galactosemia treated?

People with classic galactosemia must monitor their galactose-1-phosphate levels with regular blood tests follow a lifelong diet free of milk, milk products, or other foods containing lactose. Infants should be fed with galactose-free formulas such as soy formula or Nutramigen, a hypoallergenic formula with no galactose, lactose, or soy. As children learn to feed themselves, parents must teach them how to read product labels so they can avoid any food containing milk, dry milk, milk products, and other galactose-containing foods. Often they require calcium supplements to avoid calcium deficiency.

There is debate on whether people with Duarte galactosemia need to adhere to a galactose-free diet. Some medical professionals recommend modifying an affected person's diet while others do not. The decision whether or not to treat a person with Duarte galactosemia may depend upon his or her level of enzyme activity.

People with galactosemia should work with a nutritionist to determine the best course of treatment.

What is the prognosis for a person with Galactosemia?

Most people who are diagnosed early with classic galactosemia and carefully follow a galactose-free diet can have a normal lifespan. They are still at risk, however, for cataracts, speech defects, poor growth, poor intellectual function, neurologic deficits and ovarian failure (in women). If the treatment of classic galactosemia is not prompt and consistent, life-threatening complications and irreversible mental retardation can result.

Duarte galactosemia has not been associated with any long-term health problems.

Gamma-sarcoglycanopathy

Available Methodology: sequencing with copy number analysis.
Gene: SGCG.
Exons Sequenced: NM_000231:2-8.

Detection Rate	Population
88%	African American
88%	Ashkenazi Jewish
88%	Eastern Asia
88%	Finland
88%	French Canadian or Cajun
88%	Hispanic
88%	Middle East
88%	Native American
88%	Northwestern Europe
88%	Oceania
88%	South Asia
88%	Southeast Asia
88%	Southern Europe

What is Gamma-Sarcoglycanopathy?

Gamma-sarcoglycanopathy, also known as limb-girdle muscular dystrophy type 2C (LGMD2C), represents a spectrum of disorders that typically cause muscle weakness as a result of a deficiency of the gamma-sarcoglycan protein in the dystrophin-glycoprotein complex, a component of the muscle system. Symptoms of the disease vary greatly from person to person, even among people in the same family. Some people with the disease can have a mild course where they are nearly asymptomatic, while others may have severe symptoms that can be fatal.

People with limb-girdle muscular dystrophy type 2C (LGMD2C) develop symptoms at variable ages, though symptoms tend to first present in childhood. LGMD2C does not affect intelligence or mental function; the primary symptom is progressive muscle weakness of the hip, shoulder, and abdomen (proximal muscles). The rate at which the muscles weaken can vary, but many experience progressive weakness to a point where a wheelchair becomes necessary, often in adolescence, although in individuals with later onset, a wheelchair may not be needed until adulthood. Other possible features include enlarged calf muscles, contractures, winging of the shoulder blade, scoliosis, and mild heart complications, such as heart rhythm abnormalities and cardiomyopathy, which can lead to heart failure. Respiratory complications are also associated with the sarcoglycanopathies, and may be a cause of death.

There have also been reports of just **muscle pain with exercise**, **proximal muscle weakness** (muscles that are close to the center of the body are weak), or **hyperCKemia** (elevated creatine kinase levels with no known symptoms). These may not be distinct forms of the condition and represent the variable nature of the condition.

How common is Gamma-Sarcoglycanopathy?

There are numerous types of limb-girdle muscular dystrophy. Autosomal recessive LGMD has an estimated prevalence of 1 in 15,000 individuals. The percentage of LGMD cases attributed to LGMD2C is unknown, but it may be more common in certain populations, such as North Africans and Gypsies.

How is Gamma-Sarcoglycanopathy treated?

There is no cure for gamma-sarcoglycanopathy and few effective treatments. Physical therapy is often recommended to retain muscle strength and mobility for as long as possible. Stretching, mechanical aids, or surgery may aid in that goal. As muscles deteriorate, a ventilator may be required to aid breathing. Cardiac surveillance is recommended, and those who develop heart problems should consult with a cardiologist for symptomatic treatments.

What is the prognosis for a person with Gamma-Sarcoglycanopathy?

The outlook for a person with LGMD2C varies. LGMD2C is considered one of the more severe forms of autosomal recessive LGMD. Generally speaking, the earlier symptoms begin, the faster they progress. However, because symptoms and onset can be variable, prognosis can be variable. People with more severe symptoms can become wheelchair bound in their early teens and die in early adulthood, typically from respiratory complications.

Gaucher Disease

Available Methodology: analysis of homologous regions.

Gene: GBA.

Variants Genotyped (10): N409S, V433L, D448H, D448V, L483P, R502C, R502H, R535H, c.84dupG, c.115+1G>A.

Detection Rate	Population
60%	African American
95%	Ashkenazi Jewish
60%	Eastern Asia
60%	Finland
60%	French Canadian or Cajun
60%	Hispanic
60%	Middle East
60%	Native American
60%	Northwestern Europe
60%	Oceania
60%	South Asia
60%	Southeast Asia
60%	Southern Europe

What is Gaucher Disease?

Gaucher disease is an inherited condition in which the body fails to properly produce a particular enzyme needed to break down a fatty substance called glucocerebroside. Without this enzyme, glucocerebroside and several other associated substances will build up in the body causing a wide range of symptoms.

There are five main types of Gaucher disease, each with different manifestations. These types are described below.

TYPE 1

Type 1 is the most common form of the disease. It can affect people at any age and its symptoms vary widely from mild to severe.

Many people with type 1 Gaucher disease have symptoms related to their bones. Symptoms may include bone pain, low bone mineral density, and an increased risk for fractures. On the mild end of the spectrum, some people experience only a small drop in their bone mineral density. In more severe cases, blood supply to the bones is lost, leading to permanent damage. Bone problems are often the most debilitating aspect of the disease.

People with type 1 Gaucher disease often have an enlarged liver and spleen. They may also have a lowered number of red blood cells and platelets. With fewer red blood cells (anemia), a person with the disease will often be tired and weak. Fewer platelets in the blood will make him or her more prone to bruising and excessive bleeding. Lung disease is another possible symptom.

Type 1 is distinct from other forms of Gaucher disease in that it usually does not affect the individual's brain or spinal cord.

TYPE 2

Type 2 is known as the infantile or acute neuropathic form of Gaucher disease. Symptoms usually appear before age 2 and progress rapidly. Children with type 2 Gaucher disease have some of the symptoms of type 1. These may include enlarged liver and spleen, lowered number of red blood cells (anemia) leading to weakness and tiredness, lowered number of platelets leading to bleeding and bruising, and lung disease.

While type 2 is distinct from types 1 and 3 in that it does not cause bone problems, type 2 does cause neurological problems. Neurological symptoms often include limited cognitive and motor development, brainstem abnormalities that can cause breathing problems and difficulty swallowing, constant arching of the back and tilting back of the head, uncontrollable tightening and releasing of the muscles, and an inability to open the mouth. As the nervous system deteriorates, children with type 2 Gaucher may develop dementia and the inability to coordinate his or her own movement.

In severe cases, death may occur in utero or shortly before or after birth. In most cases, lifespan is shortened to 2 to 4 years.

TYPE 3

Type 3 Gaucher disease is known as the juvenile or chronic neuropathic form. Symptoms often begin before age 2, though this is variable. Usually the symptoms associated with type 3 progress more slowly than with type 2. While some people with type 3 Gaucher disease die in childhood, others can live into their 30s or 40s.

People with type 3 Gaucher disease have the symptoms of type 1. These may include enlarged liver and spleen, lowered number of red blood cells (anemia) leading to weakness and tiredness, lowered number of platelets leading to bleeding and bruising, lung disease, and bone problems including include pain, fractures, and arthritis.

As with type 2, type 3 Gaucher disease also causes neurological problems. These may include seizures which worsen over time, progressive cognitive problems, and difficulty controlling eye movement. Towards the end of their lives, people with type 3 may also develop dementia.

PERINATAL-LETHAL FORM

The perinatal-lethal form is a rare but severe form of Gaucher disease. This form usually leads to death in utero or shortly after birth. Infants with the disease have symptoms including enlarged liver and spleen, lowered number red blood cells and platelets, neurological problems, skin abnormalities, and often distinct facial features.

CARDIOVASCULAR FORM

As the name implies, the cardiovascular form of Gaucher disease causes symptoms involving the heart, notably a hardening of the mitral and aortic valves. If this symptom is severe, heart valve replacement may be required. In addition, the cardiovascular form causes symptoms including slightly enlarged liver and spleen, bone problems including pain, fractures, and arthritis, as well as difficulty controlling eye movement and a clouding of the eye's cornea, which can affect vision. The cardiovascular form of the disease is sometimes called type 3C.

How common is Gaucher Disease?

Type 1 Gaucher disease is the most common form of this disease. This type is particularly prevalent among people of Ashkenazi Jewish descent, of whom 1 in 855 is affected by the disease and 1 in 16 is a carrier. In the general population, researchers believe that about 1 in 50,000 will be affected.

Other forms of Gaucher disease are more rare. Type 2 occurs in roughly 1 in 100,000 births. A form of type 3 is most common among people in the Norrbottnian region of Sweden, where 1 in 50,000 are affected.

How is Gaucher Disease treated?

Enzyme replacement therapy (ERT) is one of the mainstays for treating Gaucher disease. ERT is given by infusion twice a month and helps eliminate the buildup of glucocerebrosides in the body. For many affected individuals, ERT is effective in treating disease symptoms and preventing complications, particularly bone and organ damage. ERT does not improve or prevent the neurological symptoms found in types 2 and 3.

Currently, FDA-approved enzyme replacement therapies in the U.S. include Cerezyme®, Elelyso® and VPRIV®. Zavesca® is an oral therapy for adult patients who cannot tolerate ERT. Newer therapies are also under investigation.

People with the cardiovascular form of Gaucher disease often need heart valve replacements, after which ERT can be helpful.

Additional treatments for the symptoms of Gaucher disease include blood transfusions for tiredness and excessive bleeding, joint replacement to relieve pain and restore movement, and medication to treat bone pain.

What is the prognosis for a person with Gaucher Disease?

Because symptoms of Gaucher disease vary widely in type and severity, both among the different types and among people with the same type, the outlook is similarly varied. The prognosis for an individual with Gaucher disease depends on the type of Gaucher, the severity in that particular individual, and the availability and effectiveness of treatment.

Those with a milder form of type 1 are expected to have a normal lifespan, particularly if ERT is administered when necessary. Some individuals with severe cases of type 1 Gaucher may have debilitating symptoms that are more difficult to manage.

Those with type 2 Gaucher disease often have significant developmental delays and die between the ages of 2 and 4. In the most severe type 2 cases, death may occur before or shortly after birth.

People with type 3 Gaucher disease usually develop symptoms in childhood which slowly worsen over time. While some have died in childhood, others have lived into their 30s and 40s.

For those with the cardiovascular form of the disease, the prognosis depends upon the success of valve replacement surgery.

With the perinatal-lethal form, death occurs before or shortly after birth.

Women with milder cases of Gaucher disease can have successful pregnancies.

GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness

Available Methodology: sequencing with copy number analysis.
Gene: GJB2.
Exons Sequenced: NM_004004:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness?

DFNB1 nonsyndromic hearing loss and deafness is an inherited condition in which a person has mild to severe hearing loss from birth. It is caused by mutations in GJB2 (which encodes the protein connexin 26) and GJB6 (which encodes connexin 30). The condition is not progressive, meaning that it does not worsen over time.

The word “nonsyndromic” refers to the fact that there are no other symptoms or systems of the body involved with the disease. Unlike some other forms of hearing loss, DFNB1 nonsyndromic hearing loss and deafness does not affect balance or movement.

The degree of hearing loss is difficult to predict based on which genetic mutation one has. Even if members of the same family are affected by DFNB1 nonsyndromic hearing loss and deafness, the degree of hearing loss may vary among them.

How common is GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness?

In the United States, the United Kingdom, France, Australia, and New Zealand, approximately 14 in 100,000 people have DFNB1 nonsyndromic hearing loss and deafness. Roughly 1 in 33 people are carriers of the mutation that causes the condition.

How is GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness treated?

People with DFNB1 nonsyndromic hearing loss and deafness may show improvement by using hearing aids. For people with profound deafness, cochlear implants may also be helpful. They may also want to consider enrolling in an educational program for the hearing impaired.

What is the prognosis for a person with GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness?

While a person with GJB2-related DFNB1 nonsyndromic hearing loss and deafness will have mild to severe hearing loss, it does not affect lifespan and does not affect any other part of the body.

GLB1-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: GLB1.
Exons Sequenced: NM_000404:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are GLB1-related Disorders?

GM1-gangliosidosis and mucopolysaccharidosis type IVB (MPSIVB) are two distinct, autosomal recessive lysosomal storage disorders caused by mutations the *GLB1* gene. GM1-gangliosidosis results from *GLB1* mutations which specifically cause a build up of GM1 gangliosides. This buildup leads to destruction of certain cells in many organs, particularly those in the brain. There is a wide range of severity for this disorder, however most individuals tend to be severely affected. MPSIVB is caused by *GLB1* mutations which affect the breakdown of keratan sulfate, a molecule which is found primarily in cartilage and bone. The resulting buildup of keratan sulfate in these tissues causes abnormal bone growth and development.

GM1-gangliosidosis can be broken down into three subtypes.

- **Type I (Infantile form)**: Type I is the most common form of GM1-gangliosidosis. Affected infants will have developmental delay followed by regression of milestones typically before six months of age. Another characteristic finding is a cherry-red spot on the macula of the eye. Skeletal dysplasia (short stature, curvature of the spine), hepatosplenomegaly (enlarged liver and spleen), and corneal clouding are also common findings. By one year of age, most infants will be blind and deaf. Some individuals may also have heart disease (cardiomyopathy), seizures and coarse facial features. Progression in Type I-gangliosidosis is rapid and most individuals with this type will pass away before the age of three.

- **Type II**

    - **Late-infantile form**: The age of onset of this form is between the one and three years of age. Individuals with the late-infantile form exhibit motor and cognitive delay. Similar to the infantile form, there is progressive brain atrophy, and the potential for cardiac disease and skeletal abnormalities. Individuals with this form will also have corneal clouding. Life expectancy is approximately 5 to 10 years.

    - **Juvenile form**: The age of onset of this form is between three and ten years of age. Progression of symptoms is slower than the late infantile form. These individuals do not typically have cherry-red spots, enlarged organs or coarse facial features. Life expectancy may be into early adulthood.

- **Type III (Adult form)**: This is the mildest subtype and early symptoms include dystonia (abnormal movement featuring sustained muscle contractions) and speech difficulty in the second or third decade of life. Other symptoms may include heart disease, mild brain atrophy, and skeletal abnormalities. Life span is variable and may be shortened.

Mucopolysaccharidosis type IVB is an autosomal recessive condition that causes short stature and skeletal dysplasia. In its severe form, the age of onset is between one to three years. Early signs include kyphoscoliosis (a type of abnormal spine curvature), pectus carinatum (a chest deformity in which the ribs and sternum protrude outwards) and "knocked-knees." Some individuals have an attenuated form with onset in late childhood or adolescence. Other features of MPS IVB include corneal clouding and cardiac disease. Intellectual ability is typically normal.

How common are GLB1-related Disorders?

GM1-gangliosidosis is rare occurring in approximately 1 in 100,000 to 300,000 individuals. The disease is more common in Brazil (1 in 17,000) and in those with Roma ancestry (1 in 10,000). The adult form of the disorder has been observed more frequently in the Japanese population. MPS IVB affects 1 in 250,000 to 1 in 1,000,000 individuals.

How are GLB1-related Disorders treated?

There is no cure for GLB1 related disorders and management focuses on improving quality of life for affected individuals. Physical, occupational, and speech therapies are often recommended. Individuals with GM1 gangliosidosis often need specialized strollers or wheelchairs. It is important to ensure that there is adequate hydration and caloric intake, which may necessitate a feeding tube. Other treatment focuses on managing seizure activity and heart disease. For MPS IVB, there is no treatment and management focuses on physical and occupational therapies. Individuals should also be monitored by pulmonologists, audiologists, ophthalmologists, and cardiologists.

What is the prognosis for people with GLB1-related Disorders?

For GM1-gangliosidosis, the prognosis is poor. The infantile form of this disorder is the most common, however there is a range of severity and some may be mildly affected. For MPSIVB, the prognosis is variable depending on the severity of symptoms. Some may live into adulthood, however life expectancy is shortened.

GLDC-related Glycine Encephalopathy

Available Methodology: sequencing with copy number analysis.
Gene: GLDC.
Exons Sequenced: NM_000170:1-25.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe

What is GLDC-related Glycine Encephalopathy?

GLDC-related glycine encephalopathy (GLDC-related GE) is a disease that impairs the body's ability to metabolize glycine, an amino acid found in proteins. Glycine accumulates in all body tissues, including the brain, and can lead to lethargy, seizures, low muscle tone, apnea, coma, and often death. Patients who survive with GLDC-related GE have intellectual disability and seizures. The majority of patients with GLDC-related encephalopathy present in the neonatal period, but there are multiple forms of the condition described.

The **neonatal form** of this disease presents in the first hours to days of life with rapid progression of symptoms. The **infantile onset form** is characterized by developmental delays and infantile-onset seizures at approximately 6 months of age. Other atypical types of GLDC-related GE appear later in childhood or adulthood and cause a variety of medical problems that primarily affect the nervous system.

How common is GLDC-related Glycine Encephalopathy?

Glycine encephalopathy affects approximately 1 in 250,000 live births in the United States. At least 50% of cases worldwide result from mutations in the *GLDC* gene (may vary by region). However, studies suggest that the incidence of glycine encephalopathy is higher in certain populations such as Finland (1 in 55,000, almost exclusively a result of *GLDC* mutations) and British Columbia (1 in 63,000, mainly a result of *GLDC* mutations).

How is GLDC-related Glycine Encephalopathy treated?

There is no treatment GLDC-related glycine encephalopathy. Disease management is aimed at trying to reduce the accumulation of glycine in the body. Glycine plasma concentrations can be reduced by sodium benzoate and low protein diet. Seizures are addressed with anticonvulsant medications, but may not be completely effective for all individuals.

What is the prognosis for a person with GLDC-related Glycine Encephalopathy?

About 85% of those with neonatal onset and 50% of those with the infantile onset will have severe symptoms. These infants typically will have profound intellectual disability and will have seizures that are difficult to treat. Death in the first year is common in these individuals.

Approximately 20% of all children affected with glycine encephalopathy will have less severe symptoms. These individuals will have moderate intellectual disability. They are often able to communicate (most often non-verbally), and typically have seizures that respond to treatment. These children may develop movement disorders and behavioral problems.

Rarely, affected individuals present with late-onset glycine encephalopathy, in which symptoms appear usually after one year of age. These individuals typically have some intellectual disability and seizures are uncommon.

Glutaric Acidemia Type 1

Available Methodology: sequencing with copy number analysis.
Gene: GCDH.
Exons Sequenced: NM_000159:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Glutaric Acidemia Type 1?

Glutaric acidemia type 1 (GA I) is an inherited metabolic disease in which the body lacks an enzyme to properly break down certain amino acids, the building blocks of protein. When these amino acids build up in the body, a person can develop brain damage that can impair their ability to move as well as their intellectual function.

The type and severity of symptoms in people with GA I can vary widely. A small number of people with genetic mutations that cause the disease have no symptoms at all, while others have severe movement problems and/or mental disability.

In most children, symptoms appear between two months and four years of age. A smaller number do not show symptoms until later, even as late as adulthood. Symptoms appear as a “metabolic crisis,” an episode marked by low blood sugar, vomiting, lack of energy, difficulty feeding, irritability, and poor muscle tone that causes the body to seem floppy. If unrecognized and untreated with a special diet, these episodes can progress to cause spastic and jerking muscle movements, seizures, swelling and bleeding of the brain, coma, and even death. They can often be triggered by illness, fever, or going too long without eating.

In children with GA I, the first metabolic crisis often results in permanent damage to a part of the brain known as the basal ganglia. This damage can result in a severe and permanent loss of motor skills, though often intellect remains normal.

Other children do not experience a metabolic crisis, but show a delay in motor and intellectual development. Children with these symptoms are more likely to have intellectual impairment later in life.

Early diagnosis and strict control of the child’s diet can avert a metabolic crisis and significantly reduce the risk of brain damage and impaired movement ability. Even with careful treatment, however, roughly 25 to 35% of people with GA I develop significant motor problems and other symptoms, even without a metabolic crisis.

Most children with the disease are born with large heads. Some develop bleeding in the brain that has been mistaken for child abuse.

How common is Glutaric Acidemia Type 1?

GA I affects 1 in 40,000 Caucasians. It is more common in certain ethnicities and communities. In Sweden, 1 in 30,000 people have the disease. Among Old Order Amish in Pennsylvania and the Ojibwa tribe in Canada, as many as 1 in 300 children are affected by GA I.

How is Glutaric Acidemia Type 1 treated?

A physician specializing in metabolism should help devise a treatment plan for any child with GA I. Often these plans include vitamins and supplements and frequent meals low in certain proteins. Diets will need to be carefully structured to both avoid problem foods and ensure proper nutrition. In some cases, meals may be necessary around the clock, even overnight. A specialist will also devise a “sick day plan” to use when a child shows signs of illness that could lead to a metabolic crisis. Often this involves frequent meals with carbohydrates and an increased fluid intake, even if the child isn't hungry or thirsty.

As children get older, the disease is often easier to manage and the risk of metabolic crises lessens. Many will still need lifelong dietary treatment, however.

It is believed that those who receive treatment before their first metabolic crisis do better in the long term.

Children who are having a metabolic crisis must be promptly treated, often with intravenous fluids, certain vitamins and supplements, and in some cases, dialysis.

What is the prognosis for a person with Glutaric Acidemia Type 1?

If treated early and carefully, many children with GA I can live healthy lives with normal or near-normal motor and intellectual development. It should be noted, however, that even with treatment, 25 to 35% of children with GA I develop some level of motor and intellectual impairment.

Children who have already had a metabolic crisis are likely to develop permanent brain damage that causes severe motor difficulties and involuntary spastic movement. In children who go untreated during a metabolic crisis, the disease can be fatal.

Glycogen Storage Disease Type Ia

Available Methodology: sequencing with copy number analysis.
Gene: G6PC.
Exons Sequenced: NM_000151:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Glycogen Storage Disease Type Ia?

Glycogen storage disease (GSD) type Ia, sometimes called von Gierke's disease, is an inherited disease that interferes with the way the body turns food into energy. Due to a missing or impaired enzyme, the body is unable to maintain normal blood sugar levels between meals, leading to low blood sugar (hypoglycemia). As a result, both children and adults with GSD type Ia will be chronically hungry, tired, and irritable unless they eat regularly—typically every 1 to 3 hours during the day and every 3 to 4 hours at night. If their blood sugar reaches a critically low level, some may experience seizures.

Children with GSD type Ia appear normal at birth, but will begin to show symptoms of enlarged liver, swollen abdomen, delayed or stunted growth, irritability, and seizures. They will have abnormal levels of certain metabolic substances in their blood and urine. If not properly diagnosed, these children will likely experience a medical crisis within the first few months of life. Children with GSD type Ia will typically be shorter than their family members and will experience delayed puberty. Mental function is not affected by GSD type Ia.

These symptoms occur due to the lack or improper functioning of an enzyme called glucose-6-phosphatase (G6Pase). Normally, glucose (a sugar) in the food we eat is converted into a substance called glycogen that is stored in the liver. When a person does not eat for 3 to 4 hours, this glycogen will be turned back into glucose and used to stabilize sugar levels in the body. People with GSD Ia lack a component of G6Pase so they cannot turn glycogen back into glucose, and therefore they suffer from hypoglycemia.

People with GSD type Ib lack a different component of G6Pase, and experience similar symptoms. For this reason, type Ia and Ib are often spoken about as one disease: GSD type I.

The buildup of glycogen in the liver and kidneys causes them to swell, although these organs are still able to perform the majority of their functions. Benign (non-cancerous) tumors in the liver are often seen around the time of puberty. Rarely, these can become cancerous. Changes in kidney function may occur as the person reaches his or her 20s, and may include kidney stones and a decreased ability to filter waste products. In advanced cases, dialysis and/or a kidney transplant may be needed.

How common is Glycogen Storage Disease Type Ia?

Roughly 1 in every 20,000 to 25,000 babies in the U.S. and Europe is born with some form of Glycogen Storage Disease. Of those, 25% have type I (either Ia or Ib).

How is Glycogen Storage Disease Type Ia treated?

The treatment of GSD type Ia involves a careful monitoring of the affected person's diet, both in frequency of meals and type of foods eaten. People with GSD type Ia should avoid foods with sucrose (table sugar), fructose (sugar from fruits), and lactose and galactose (sugars found in milk). They need to eat around the clock, typically every 1 to 3 hours during the day and every 3 to 4 hours at night, to maintain healthy blood sugar levels.

Infants and young children often need a feeding tube in order to tolerate frequent eating. They may also need to use a feeding pump at night and for emergency feedings should their blood sugar drop dangerously low. Because they must eat so frequently, children with GSD type Ia often have problems eating and swallowing food orally. They often need therapy to re-learn sucking, swallowing, and even speech.

Physicians often recommend people with GSD type Ia drink cornstarch mixed with water, soy formula, or soy milk. Cornstarch is digested slowly and therefore releases its glucose gradually, helping to safely extend the time between meals.

What is the prognosis for a person with Glycogen Storage Disease Type Ia?

With careful monitoring of diet and blood sugar levels, people with GSD can cope with their metabolic abnormalities and live into adulthood. Without close monitoring of the diet, extremely low blood sugar can be fatal. In adolescence and adulthood, people with the disease must be alert to kidney complications, high blood pressure, and/or cancerous liver tumors.

Glycogen Storage Disease Type Ib

Available Methodology: sequencing with copy number analysis.
Gene: SLC37A4.
Exons Sequenced: NM_001164277:3-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Glycogen Storage Disease Type Ib?

Glycogen storage disease (GSD) type Ib is an inherited disease that interferes with the way the body turns food into energy. Due to a missing or impaired enzyme, the body is unable to maintain normal blood sugar levels between meals, leading to low blood sugar (hypoglycemia). As a result, both children and adults with GSD type Ib will be chronically hungry, tired, and irritable unless they eat regularly—typically every 1 to 3 hours during the day and every 3 to 4 hours at night. If their blood sugar reaches a critically low level, some may experience seizures.

Children with GSD type Ib appear normal at birth, but will begin to show symptoms of enlarged liver, swollen abdomen, delayed or stunted growth, irritability, and seizures. They will have abnormal levels of certain metabolic substances in their blood and urine. If not properly diagnosed, these children will likely experience a medical crisis within the first few months of life. Children with GSD type Ib will typically be shorter than their family members and will experience delayed puberty. Mental function is not affected by GSD type Ib.

Individuals with GSD type Ib are also prone to frequent bacterial and fungal infections, due to abnormalities in and/or low levels of a type of white blood cell called neutrophils. They are also more likely to develop chronic inflammation of the pancreas, chronic inflammatory bowel disease, and Crohn's disease.

The symptoms of GSD type Ib occur due to the lack or improper functioning of an enzyme called glucose-6-phosphatase (G6Pase). Normally, glucose (a sugar) in the food we eat is converted into a substance called glycogen that is stored in the liver. When a person does not eat for 3 to 4 hours, this glycogen will be turned back into glucose and used to stabilize sugar levels in the body. People with GSD Ib lack a component of G6Pase so they cannot turn glycogen back into glucose, and therefore they suffer from hypoglycemia.

People with GSD type Ia lack a different component of G6Pase, and experience similar symptoms. For this reason, type Ia and Ib are often spoken about as one disease: GSD type I.

The buildup of glycogen in the liver and kidneys causes them to swell, although these organs are still able to perform the majority of their functions. Benign (non-cancerous) tumors in the liver are often seen around the time of puberty. Rarely, these can become

cancerous. Changes in kidney function may occur as the person reaches his or her 20s, and may include kidney stones and a decreased ability to filter waste products. In people with advanced cases, dialysis and/or a kidney transplant may be needed.

How common is Glycogen Storage Disease Type Ib?

Roughly 1 in every 20,000 to 25,000 babies in the U.S. and Europe is born with some form of Glycogen Storage Disease. Of those, 25% have type I (either Ia or Ib).

How is Glycogen Storage Disease Type Ib treated?

The treatment of GSD type Ib involves a careful monitoring of the affected person's diet, both in frequency of meals and type of foods eaten. People with GSD type Ib should avoid foods with sucrose (table sugar), fructose (sugar from fruits), and lactose and galactose (sugars found in milk). They need to eat around the clock, typically every 1 to 3 hours during the day and every 3 to 4 hours at night, to maintain healthy blood sugar levels.

Infants and young children often need a feeding tube in order to tolerate frequent eating. They may also need to use a feeding pump at night and for emergency feedings should their blood sugar drop dangerously low. Because they must eat so frequently, children with GSD type Ib often have problems eating and swallowing food orally. They often need therapy to re-learn sucking, swallowing, and even speech.

Physicians often recommend people with GSD type Ib drink cornstarch mixed with water, soy formula, or soy milk. Cornstarch is digested slowly and therefore releases its glucose gradually, helping to safely extend the time between meals.

People affected by GSD type Ib also frequently take medication to increase the number of neutrophils, a type of white blood cell that fights infection. They must also be vigilant to treat any infection in the body as it arises.

What is the prognosis for a person with Glycogen Storage Disease Type Ib?

With careful monitoring of diet and blood sugar levels, people with GSD type Ib can improve their metabolic abnormalities and live into adulthood. Without close monitoring of the diet however, extremely low blood sugar can be fatal. In adolescence and adulthood, people with GSD type Ib must be alert to infections, kidney complications, high blood pressure, and/or cancerous liver tumors. Long-term complications can include kidney damage, brittle bones (osteoporosis), benign cysts on the ovaries (in women), and benign tumors of the liver (adenomas).

Glycogen Storage Disease Type III

Available Methodology: sequencing with copy number analysis.
Gene: AGL.
Exons Sequenced: NM_000642:2-34.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Glycogen Storage Disease Type III?

Glycogen storage disease type III (GSD III)—also known as Cori disease or Forbes disease—is an inherited condition in which the deficiency of an enzyme called glycogen debranching enzyme results in various complications, notably involving the liver and muscles. The lack of this enzyme means the body cannot properly break down glycogen, a stored form of sugar. As a result, glycogen cannot properly be used to energize the body and glycogen molecules accumulate in the body.

Symptoms of GSD III often appear in infancy or childhood. The liver is enlarged, leading to a noticeably swollen abdomen. This enlargement usually subsides with puberty, although there may be long term liver damage.

Muscle weakness is a problem seen in 85% of people with GSD III. This weakness can at times be severe and may worsen in adulthood. Children with the disease may experience delayed growth, but usually reach normal adult height. A minority of people with the disease also have a mildly enlarged heart, though its function is usually normal.

Low blood sugar and feelings of tiredness may occur with GSD III, although they are less common and less severe than with another form of GSD, type I.

The onset of the disease may occur in adulthood, which typically corresponds with milder symptoms.

How common is Glycogen Storage Disease Type III?

About 1 in 100,000 U.S. births is affected by GSD III. This disease is much more common in Israeli Jews of North African descent, where 1 in 35 are carriers and 1 in 5,400 babies has the disease. The highest rate is found among people on the Faroe Islands of the North Atlantic, where 1 in 30 is a carrier and 1 in 3,600 babies is affected.

How is Glycogen Storage Disease Type III treated?

There is no treatment for the cause of GSD III. Physicians will monitor the liver, heart, and muscles in affected people and recommend physical therapy when necessary to promote better movement. Frequent small meals and a high-protein diet may also be beneficial. Physicians may recommend consuming corn starch, which breaks down slowly into simple sugars and may alleviate symptoms of low blood sugar between meals. Parents of infants should be particularly careful to monitor the child's diet to avoid hypoglycemic seizures.

What is the prognosis for a person with Glycogen Storage Disease Type III?

Among infants with GSD III, there is an increased rate of fatalities due to seizures caused by low blood sugar. While an exact lifespan is unknown, many people with GSD III live well into adulthood. Liver disease and muscle weakness may contribute to a cause of death long-term.

GNPTAB-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: GNPTAB.
Exons Sequenced: NM_024312:1-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
98%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are GNPTAB-related Disorders?

Mutations in *GNPTAB* cause mucolipidosis II and mucolipidosis III alpha/beta, which are inherited lysosomal storage disorders that slowly progress over time. People with these disorders lack an enzyme called GlcNAc-1-phosphotransferase which is important for the proper functioning of lysosomes, the digestive system of the cell. Mucolipidosis II is more severe because the enzyme is absent and mucolipidosis III alpha/beta is milder because very low levels of the enzyme are present.

Mucolipidosis II

Mucolipidosis II presents at birth with limited growth and skeletal abnormalities. Babies develop coarse facial features and thick gums in early infancy that become more prominent with age. Most affected children will have joint stiffening, hernias, malformed bones, microcephaly (small head and incomplete brain development), and severe learning difficulties. Heart abnormalities and respiratory insufficiency are the major causes of death. People with mucolipidosis II typically pass away in early childhood.

Mucolipidosis III alpha/beta

Mucolipidosis III alpha/beta presents around age 3 years when growth begins to slow. Individuals will usually be shorter than their unaffected family members. Affected children have coarse facial features that are less prominent and progress more slowly. Heart and respiratory complications are still the major cause of death. Individuals with mucolipidosis III alpha/beta are typically able to walk, though due to joint stiffening, may need to use a wheelchair by early adulthood. Intelligence and language development are typically normal, though many still require special education due to their physical limitations. Motor development is variable and may be normal to moderately delayed. People with mucolipidosis III alpha/beta usually live into early to mid adulthood.

How common are GNPTAB-related Disorders?

Mucolipidosis II and mucolipidosis III alpha/beta are rare. They affect less than 1 in 100,000 individuals worldwide and may be more common in individuals from Portugal.

How are GNPTAB-related Disorders treated?

There is no cure for mucolipidosis II or III alpha/beta. Management of symptoms may include occupational therapy, speech therapy and low-impact physical therapy. Dental and audiologic management may be beneficial, but surgeries should be avoided to prevent airway complications and adverse reactions to anesthesia. Hip replacement has been helpful for some individuals with a milder disease course. For patients with mucolipidosis III alpha/beta, intravenous pamidronate may provide relief from bone density loss, joint pain, and immobility, but it is not a cure.

What is the prognosis for a person with a GNPTAB-related Disorder?

The prognosis for an individual with mucolipidosis II is poor, with death typically occurring in early childhood. Mucolipidosis III alpha/beta is more variable and many survive to early adulthood.

GRACILE Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: BCS1L.
Exons Sequenced: NM_004328:3-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is GRACILE Syndrome?

GRACILE syndrome is a fatal inherited disorder caused by a mutation in a gene necessary for providing cells with energy. “GRACILE” is an acronym for symptoms caused by the disease:

Growth Retardation The baby is born significantly smaller than normal.

Aminoaciduria There are increased levels of amino acids in the child’s urine.

Cholestasis The flow of bile from the liver is blocked.

Iron overload The body does not metabolize iron properly, leading to excess levels, particularly in the liver.

Lactic acidosis Lactic acid builds up in the body, causing the blood to become too acidic.

Early death Half of babies with GRACILE syndrome die within 24 hours. Virtually none live beyond the age of four months.

How common is GRACILE Syndrome?

GRACILE syndrome has only been reported in Finland. Here, researchers estimate that 1 in 47,000 babies are affected, meaning that roughly 1 in 110 Finnish people are carriers of the genetic mutation. There have been reports of several infants in the United Kingdom and Turkey with similar but not identical symptoms. It is not known whether this represents the same disease.

How is GRACILE Syndrome treated?

There is no effective treatment for GRACILE syndrome. Experimental treatments to reduce acidity and/or iron levels in the infants' blood have not been shown to extend life beyond several months.

What is the prognosis for a person with GRACILE Syndrome?

About half of infants with GRACILE syndrome die within the first few days of life. Even with the best possible treatment, nearly all will die within four months.

HADHA-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: HADHA.
Exons Sequenced: NM_000182:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are HADHA-related Disorders?

HADHA-related disorders, including long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) and mitochondrial trifunctional protein deficiency (MTPD), are inherited conditions in which the body lacks sufficient amounts of the enzyme(s) needed to turn certain fatty acids from food and body fat into energy. This process, called fatty acid oxidation, normally breaks down fatty acids stepwise until they can be turned into usable energy. Enzyme deficiencies interrupt this process, allowing fatty acids to build up in the body and damage various organs and body tissues.

HADHA is responsible for three enzyme functions in the final steps of fatty acid oxidation. HADHA-related disorders can be divided into two main categories: LCHAD which results from deficiency in just one enzyme and MTPD which includes deficiencies of all three enzymes.

The symptoms of LCHAD and MTPD are overlapping and variable with some individuals severely affected and some more mild forms. Most often, the symptoms begin in infancy or early childhood when affected children may begin to display changes in behavior, poor appetite or feeding difficulties, lack of energy, muscle weakness and developmental delays.

Children with these disorders may experience acute episodes characterized by low blood sugar and increased amounts of harmful substances in the blood. If untreated, they are at high risk for life-threatening heart and breathing problems, comas, seizures, and sudden death. These episodes can be triggered by stresses on the body such as going a long time without eating, illness and infections, or strenuous exercise. Some children may not have symptoms between these episodes, however, repeated crisis events can lead to brain damage and intellectual and developmental disabilities.

Older children and adults may develop muscle pain, a breakdown in muscle tissue, and problems with the nerves in their arms and legs. Some people with LCHAD and MTPD do not have the classic symptoms and may only have the muscle pain and weakness.

Both LCHAD and MTPD have been shown to cause damage to the retina of the eye leading to progressive visual impairment over many years, though this is more commonly associated with LCHAD.

Women carrying a pregnancies that are affected with a HADHA-related disorder are at risk for certain pregnancy complications and should speak with their physician for recommendations.

How common are HADHA-related Disorders?

HADHA-related disorders are rare. Studies in Finland and the United States have shown that the E474Q mutation—which causes the majority of LCHAD deficiency cases—has a carrier rate of approximately 1 in 150 to 200. Based on a carrier rate estimation of 1 in 150, 1 in 90,000 people would be affected by the disease. A study in Estonia found a similar carrier frequency and inferred an incidence of 1 in 91,700.

A study of the results of newborn screening in Germany found 11 cases of LCHAD/MTPD in 1.2 million births. Another newborn screening study in Germany found just 1 case of LCHAD/MTPD in 250,000 babies screened.

The overall incidence in Poland is estimated to be 1 in 118,336, but in specific regions it is more common, up to 1 in 16,900.

How are HADHA-related Disorders treated?

The main method of management for LCHAD and MTPD is a special diet and avoidance of fasting. A physician or nutritionist will recommend a diet low in fats and high in carbohydrates, which are easier for an affected person to break down, and a feeding schedule with frequent meals. Often it is necessary to have an additional dietary protocol in place for illness or other stressful times. A physician may also prescribe medium chain triglyceride oil, L-carnitine, or other supplements for additional energy.

What is the prognosis for a person with a HADHA-related Disorder?

Often when symptoms appear in infancy, treatment is not effective because the disease causes irreparable damage to the heart. Untreated, both infant or early childhood onset disease is often fatal or leads to cognitive impairments.

For childhood onset forms, early detection and early treatment can prevent many of the severe complications and allow affected individuals to have typical growth and development. Even with careful treatment, there may still be some episodes of low blood sugar and the possibility of heart, liver, and muscle problems. Recurrent acute episodes of low blood sugar can lead to cognitive impairments over time.

Individuals with later onset disease and symptoms limited to muscle weakness and pain are typically healthy and do not have problems with the heart, liver, or changes in cognitive ability or intellect.

Hb Beta Chain-related Hemoglobinopathy

INCLUDING BETA THALASSEMIA AND SICKLE CELL DISEASE

Available Methodology: sequencing with copy number analysis.
Gene: HBB.
Exons Sequenced: NM_000518:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Hb Beta Chain-related Hemoglobinopathy?

Hb beta chain-related hemoglobinopathies are a group of inherited blood disorders that affect hemoglobin, the major component of red blood cells which carries oxygen throughout the body. Hemoglobin is made up of two different proteins, alpha and beta. Mutations of the HBB gene can result in reduced levels of beta proteins (thalassemias), or the formation of structurally abnormal beta proteins (sickle cell disease and other hemoglobinopathies).

People with Hb beta chain-related thalassemia do not produce enough beta protein—and in some cases do not produce it at all—resulting in a shortage of red blood cells (anemia). Without sufficient numbers of properly functioning red blood cells, the organs of the body do not receive enough oxygen. There are three main types of beta thalassemia. In the most severe form, thalassemia major (also called Cooley's Anemia), a child will begin to show symptoms of severe anemia late in the first year of life. The lack of oxygen can cause him or her to be pale, listless, tired, and irritable. The child's spleen, liver, and heart may be enlarged, which is made noticeable by a swollen abdomen and yellowed skin. The child's overall growth will be slowed and his or her bones may be thin, brittle, and/or deformed. Without frequent blood transfusions, the condition can be life-threatening at an early age.

Beta thalassemia intermedia, a less severe form of the condition, causes mild to moderate anemia and a wide spectrum of possible health problems. The types of symptoms are the same as with thalassemia major, including bone deformities and an enlarged spleen, though these are typically not as severe. Thalassemia intermedia may not be diagnosed until later in life. People with thalassemia intermedia require fewer blood transfusions and use them to improve the quality of their lives.

Sickle cell disease is a type of hemoglobinopathy caused by two Hb S mutations, or one copy of the Hb S mutation along with a beta thalassemia mutation. People with sickle cell disease produce an abnormal type of beta protein. This results in red blood cells having a stiff crescent shape resembling a sickle. The sickled blood cells die prematurely, causing a person to feel weak and tired, a condition known as anemia. People with sickle cell anemia develop symptoms including anemia, repeated infections, shortness of breath, fatigue, jaundice, and bone pain starting in early childhood. These sickled cells also get stuck in small blood vessels, blocking blood flow and causing serious medical complications such as blood-starved organs or tissue deterioration. The most recognizable symptom is episodes of acute back, chest, or abdominal pain called "crises."

There are other types of Hb beta chain-related hemoglobinopathies that can be considerably milder in presentation. These include mutations of hemoglobins C, E, D-Punjab and O-Arab. Interactions between beta globin proteins and these mutations can alleviate or exacerbate the effects of the individual variants. A consultation with a hematologist is useful in predicting phenotype.

How common is Hb Beta Chain-related Hemoglobinopathy?

Mutations of the HBB gene are considered common worldwide, with an estimated prevalence of 1/100,000 affected individuals. Thalassemias are most common in people of Mediterranean descent, especially in those from Sardinia and Cyprus. In Cyprus, 1 in 7 people are carriers of beta thalassemia, a rate which prompted a successful government-run disease prevention program. Beta thalassemia is also commonly found in the Middle East and Asia.

Sickle cell disease is common in people from Africa, the Mediterranean, the Arabian Peninsula, India, South America, and Central America. The large percentage of carriers in these regions is attributed to the sickle cell mutation's protective effect against malaria. In the African American population, approximately 1/10 people are carriers of sickle cell.

Ethnic Group	Carrier Rate	Affected Rate
Cypriot	1 in 7	1 in 170
Sardinian	1 in 8	1 in 240
Italian	1 in 31	1 in 3,700
Middle Eastern	1 in 34	1 in 4,500
Southeast Asian	1 in 35	1 in 4,800
East Asian	1 in 62	1 in 15,000
Indian	1 in 64	1 in 16,000

How is Hb Beta Chain-related Hemoglobinopathy treated?

The most common treatment for beta thalassemia is blood transfusions, which provide a temporary supply of healthy red blood cells to bring oxygen to the body. Among people with thalassemia major, transfusions may take place every two to three weeks. While these transfusions can be life-saving and life-enhancing, they result in a toxic buildup of iron in the blood. To counteract this side-effect, people with beta thalassemia require a procedure called chelation therapy in which a medication is taken to eliminate excess iron from the body. These individuals require frequent monitoring by a physician to assess the efficacy of transfusion/chelation therapy. In a small minority of people, a bone marrow transplant from a sibling or other suitable donor has been able to cure the disease. This procedure, however, is risky and could even be fatal.

The symptoms of sickle cell disease can vary in severity, depending upon the mutations that a person carries. The Hemoglobin S mutation (sickle cell disease) is associated with the most severe symptoms. Sickle cell anemia can be cured with bone marrow transplants, but the procedure is extremely risky, both because the drugs needed to make the transplant possible are highly toxic and because it can be difficult to find suitable donors. For patients who are not candidates for bone marrow transplantation, sickle cell anemia requires lifelong care to manage and control symptoms and limit the frequency of crises. Fortunately, a better understanding of how to manage the illness has extended patients' average lifespan by a decade or more.

People with sickle cell anemia, particularly children, should drink plenty of water, avoid demanding physical activity and too much sun exposure, and get all appropriate vaccines and immunizations. Preventing dehydration and avoiding infection can fend off crises and may prevent the sickling of red blood cells. Nutrional therapy and pain medications are also useful.

What is the prognosis for a person with Hb Beta Chain-related Hemoglobinopathy?

The prognosis is entirely dependent on the specific type of hemoglobin disorder, and an accurate diagnosis coupled with treatment. Lifespan can be shortened, but varies and may even be normal depending on disease severity.

Hereditary Fructose Intolerance

Available Methodology: sequencing with copy number analysis.
Gene: ALDOB.
Exons Sequenced: NM_000035:2-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Hereditary Fructose Intolerance?

Hereditary fructose intolerance (HFI) is a condition in which the body lacks a substance called aldolase B needed to process fructose, a common sugar found in fruit and many other foods. When a person with HFI consumes fructose, the result is low blood sugar (hypoglycemia) and a buildup of toxic substances in the liver.

Infants or children with the disease who consume the sugars fructose and sucrose or the sugar substitute sorbitol typically experience symptoms after eating, including vomiting, convulsions, irritability, and/or sleepiness. Many infant formulas are made with the sugar lactose, although some also contain fructose and sucrose, as do many baby foods. Infants or children with HFI may show a yellowing of the skin and whites of the eyes (jaundice) and have an enlarged liver and spleen. If unrecognized and untreated, these children will fail to grow at a normal rate.

If the disease is not detected and treated, HFI can lead to serious liver disease, hypoglycemic shock, seizures, gout, bleeding, and kidney or liver failure. In extreme cases, it can be fatal. For this reason, early detection is critical.

A strict diet free from fructose, sucrose, and sorbitol allows most people with HFI to live normal, symptom-free lives, although those with a severe course of the disease may develop serious liver disease later in life, even with a careful diet.

Symptoms of the disease can vary from mild to severe. People with HFI often show an aversion to sweets and fruit, and thus those with a mild case may be protected from some of the symptoms they would otherwise experience.

How common is Hereditary Fructose Intolerance?

The exact prevalence of HFI is unknown, but several studies have placed the number of affected people in the U.S. and Europe at 1 in 20,000. A recent U.K. study placed the figure at 1 in 12,000 to 58,000.

How is Hereditary Fructose Intolerance treated?

The key to treating people with HFI is to strictly control their diet, eliminating all fructose, sucrose, and sorbitol. On this careful diet, people with HFI can be symptom-free, though symptoms will quickly return upon consuming fructose, sucrose, or sorbitol.

In cases where liver disease has progressed to a life-threatening stage, liver transplantation is a possible treatment.

What is the prognosis for a person with Hereditary Fructose Intolerance?

Without a careful monitoring of the diet—elimination of all fructose, sucrose, and sorbitol—HFI can be life-threatening, causing serious liver disease, hypoglycemic shock, or liver or kidney failure.

With a careful diet, however, people with HFI may be symptom free and able to live normal lives. The earlier the condition is diagnosed and the diet corrected, the less damage is done to the liver and kidneys and the better the overall prognosis. Early detection and diet modification is also important so that children can grow to normal height. Within three to four weeks of adopting a fructose-free diet, people with HFI can be symptom-free.

In a minority of people who have a severe form of the disease, liver disease may still develop, despite a careful diet.

Herlitz Junctional Epidermolysis Bullosa, LAMA3-related

Available Methodology: sequencing with copy number analysis.
Gene: LAMA3.
Exons Sequenced: NM_000227:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Herlitz Junctional Epidermolysis Bullosa, LAMA3-related?

Herlitz junctional epidermolysis bullosa (H-JEB) is an inherited disease that causes severe blistering on the skin. Infants with H-JEB frequently also have internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes. These symptoms are present from birth. Occasionally people with the disease survive into their teens, however 87% die in the first year of life.

People with H-JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Skin chafes and wears away, leaving the person open to infection.

Granulation tissue, a kind of soft, pink, bumpy, moist skin, is often seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. This tissue bleeds easily and can be a site of fluid loss.

Infants and children with the disease often develop a hoarse cry, cough, and other breathing problems. They are prone to developing fevers, often lose their fingernails and toenails, and have poorly-formed tooth enamel. They may also have abnormalities in their urinary tract and bladder which can lead to urinary tract infections and kidney failure.

These infants do not grow at the expected rate and may also develop electrolyte imbalances, hair loss, osteoporosis, and skin cancer.

How common is Herlitz Junctional Epidermolysis Bullosa, LAMA3-related?

H-JEB is extremely rare. Estimates indicate that 0.37 people per million are affected by the disease and 1 in 781 Americans is a carrier.

How is Herlitz Junctional Epidermolysis Bullosa, LAMA3-related treated?

Even with the best of care, H-JEB is ultimately fatal. There are no successful treatments other than to protect the child as much as possible from skin damage and treat symptoms as they arise. A cesarean section may be recommended to protect the child from the skin trauma of birth.

Open wounds and blistered skin is often covered with multiple layers of non-adhesive bandages and anyone handling the child must use extreme care. The child must avoid any movement or clothing that could damage the skin.

Antibiotics are often prescribed for infection and antiseptics used to prevent infection. A dietitian should be consulted for an infant's proper nutrition. People with H-JEB should drink plenty of fluids to avoid dehydration.

To aid in breathing, an opening may be made in the neck to deliver air to the trachea, however this may be difficult on a person with fragile skin.

What is the prognosis for a person with Herlitz Junctional Epidermolysis Bullosa, LAMA3-related?

The prognosis for a person with H-JEB is poor. Roughly 87% will die within the first year of life, and all will die by the late teens. The disease is extremely painful. Causes of death often include infection, breathing problems, and loss of fluid leading to dehydration.

Herlitz Junctional Epidermolysis Bullosa, LAMB3-related

Available Methodology: sequencing with copy number analysis.
Gene: LAMB3.
Exons Sequenced: NM_000228:2-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Herlitz Junctional Epidermolysis Bullosa, LAMB3-related?

Herlitz junctional epidermolysis bullosa (H-JEB) is an inherited disease that causes severe blistering on the skin. Infants with H-JEB frequently also have internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes. These symptoms are present from birth. Occasionally people with the disease survive into their teens, however 87% die in the first year of life.

People with H-JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Skin chafes and wears away, leaving the person open to infection.

Granulation tissue, a kind of soft, pink, bumpy, moist skin, is often seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. This tissue bleeds easily and can be a site of fluid loss.

Infants and children with the disease often develop a hoarse cry, cough, and other breathing problems. They are prone to developing fevers, often lose their fingernails and toenails, and have poorly-formed tooth enamel. They may also have abnormalities in their urinary tract and bladder which can lead to urinary tract infections and kidney failure.

These infants do not grow at the expected rate and may also develop electrolyte imbalances, hair loss, osteoporosis, and skin cancer.

How common is Herlitz Junctional Epidermolysis Bullosa, LAMB3-related?

H-JEB is extremely rare. Estimates indicate that 0.37 people per million are affected by the disease and 1 in 781 Americans is a carrier.

How is Herlitz Junctional Epidermolysis Bullosa, LAMB3-related treated?

Even with the best of care, H-JEB is ultimately fatal. There are no successful treatments other than to protect the child as much as possible from skin damage and treat symptoms as they arise. A cesarean section may be recommended to protect the child from the skin trauma of birth.

Open wounds and blistered skin is often covered with multiple layers of non-adhesive bandages and anyone handling the child must use extreme care. The child must avoid any movement or clothing that could damage the skin.

Antibiotics are often prescribed for infection and antiseptics used to prevent infection. A dietitian should be consulted for an infant's proper nutrition. People with H-JEB should drink plenty of fluids to avoid dehydration.

To aid in breathing, an opening may be made in the neck to deliver air to the trachea, however this may be difficult on a person with fragile skin.

What is the prognosis for a person with Herlitz Junctional Epidermolysis Bullosa, LAMB3-related?

The prognosis for a person with H-JEB is poor. Roughly 87% will die within the first year of life, and all will die by the late teens. The disease is extremely painful. Causes of death often include infection, breathing problems, and loss of fluid leading to dehydration.

Herlitz Junctional Epidermolysis Bullosa, LAMC2-related

Available Methodology: sequencing with copy number analysis.
Gene: LAMC2.
Exons Sequenced: NM_005562:1-23.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Herlitz Junctional Epidermolysis Bullosa, LAMC2-related?

Herlitz junctional epidermolysis bullosa (H-JEB) is an inherited disease that causes severe blistering on the skin. Infants with H-JEB frequently also have internal blistering on the lining of the nose, mouth, esophagus, trachea, rectum, stomach, intestines, and eyes. These symptoms are present from birth. Occasionally people with the disease survive into their teens, however 87% die in the first year of life.

People with H-JEB lack anchors to hold the layers of their skin together. They develop large, fluid-filled blisters in response to any trauma, even something as minor as increased room temperature. Skin chafes and wears away, leaving the person open to infection.

Granulation tissue, a kind of soft, pink, bumpy, moist skin, is often seen around the nose, mouth, ears, fingers, and toes, as well as in areas that receive friction, such as the buttocks and back of the head. This tissue bleeds easily and can be a site of fluid loss.

Infants and children with the disease often develop a hoarse cry, cough, and other breathing problems. They are prone to developing fevers, often lose their fingernails and toenails, and have poorly-formed tooth enamel. They may also have abnormalities in their urinary tract and bladder which can lead to urinary tract infections and kidney failure.

These infants do not grow at the expected rate and may also develop electrolyte imbalances, hair loss, osteoporosis, and skin cancer.

How common is Herlitz Junctional Epidermolysis Bullosa, LAMC2-related?

H-JEB is extremely rare. Estimates indicate that 0.37 people per million are affected by the disease and 1 in 781 Americans is a carrier.

How is Herlitz Junctional Epidermolysis Bullosa, LAMC2-related treated?

Even with the best of care, H-JEB is ultimately fatal. There are no successful treatments other than to protect the child as much as possible from skin damage and treat symptoms as they arise. A cesarean section may be recommended to protect the child from the skin trauma of birth.

Open wounds and blistered skin is often covered with multiple layers of non-adhesive bandages and anyone handling the child must use extreme care. The child must avoid any movement or clothing that could damage the skin.

Antibiotics are often prescribed for infection and antiseptics used to prevent infection. A dietitian should be consulted for an infant's proper nutrition. People with H-JEB should drink plenty of fluids to avoid dehydration.

To aid in breathing, an opening may be made in the neck to deliver air to the trachea, however this may be difficult on a person with fragile skin.

What is the prognosis for a person with Herlitz Junctional Epidermolysis Bullosa, LAMC2-related?

The prognosis for a person with H-JEB is poor. Roughly 87% will die within the first year of life, and all will die by the late teens. The disease is extremely painful. Causes of death often include infection, breathing problems, and loss of fluid leading to dehydration.

Hexosaminidase A Deficiency

INCLUDING TAY-SACHS DISEASE

Available Methodology: sequencing with copy number analysis.
Gene: HEXA.
Exons Sequenced: NM_000520:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Hexosaminidase A Deficiency?

Hexosaminidase A deficiency is an enzyme deficiency that causes brain and other nerve cells to die, which can lead to severe neurological and mental problems.

Hexosaminidase A (HEX A) deficiency is caused by a deficiency in an enzyme called beta-hexosaminidase A. This enzyme helps break down a particular fatty acid called GM2 ganglioside. Without adequate amounts of functional enzymes, GM2 ganglioside will build up in nerve cells and cause them to die.

There are several forms of HEX A deficiency, including acute infantile (Tay-Sachs disease), juvenile, chronic, or adult-onset forms.

Acute infantile (Tay-Sachs disease) - Tay-Sachs disease is the most common and severe form of hexosaminidase A deficiency. Tay-Sachs disease is a progressive condition that results in the gradual loss of movement and mental function. It is typically fatal early in childhood.

The symptoms of Tay-Sachs disease usually appear in infants between three and six months of age. Initially, infants lose the ability to turn over, sit, or crawl. They also become less attentive and develop an exaggerated startle response to loud noise. As the disease progresses and nerve cells further degenerate, infants with Tay-Sachs develop seizures, vision and hearing loss, mental disabilities, and eventually become paralyzed. Death usually occurs by the age of four.

Juvenile - Those with juvenile onset HEX A deficiency typically begin to show symptoms between the ages of 2 and 10. Early signs can include a decline in verbal skills, the ability to accomplish life skills, and overall thought processes. These symptoms become progressively worse over time. The child will also develop spastic movement, seizures, and vision loss. Most children with HEX A deficiency will enter a vegetative state by the age of 10 to 15.

Chronic - Symptoms of the chronic form of the disease can begin any time from early childhood until the age of 10. While this form of HexA deficiency can cause a variety of movement problems, the decline of verbal skills and thought processes tends to happen later than in the juvenile form.

Adult-onset - Adult-onset HEX A deficiency is rare, but it is thought that symptoms often begin in one's 20s or 30s. This form of the disease has the greatest variation in symptoms from person to person, even among people in the same family. Often its symptoms appear identical to other more common diseases, leading to misdiagnoses. These symptoms can include some or all of the following: muscle weakness, involuntary muscle twitching, speech difficulties, altered thought, or severe mental disorders like psychosis or schizophrenia. Some people with adult-onset HEX A deficiency may develop movement disorders but be spared mental decline until their 60s or 70s. For some, adult-onset HEX A deficiency is not fatal.

How common is Hexosaminidase A Deficiency?

Acute infantile (Tay-Sachs disease) - Tay-Sachs disease is most common among specific ethnic populations, particularly Ashkenazi Jews from Central and Eastern Europe, certain French-Canadian communities in Quebec, Amish populations in Pennsylvania, and Louisiana Cajuns. Tay-Sachs disease is found in people of all ethnicities, though the risk outside of the ethnic groups mentioned above is much lower.

Roughly 1 in 30 Ashkenazi Jews is a carrier of Tay-Sachs, compared to 1 in 300 for the non-Jewish Caucasian population. Since 1970, an organized campaign in the Jewish community to educate potential parents about Tay-Sachs and test them for mutations causing this disease has dramatically lowered the number of children affected by the disease. Because of these successful screening programs, today the majority of children born in the U.S. with Tay-Sachs disease do not have an Ashkenazi Jewish background.

Juvenile/Chronic/Adult-onset - The other forms of HEX A deficiency are extremely rare. Their exact prevalence is unknown. Mutations that cause these later-onset forms have been found in multiple ethnic groups.

How is Hexosaminidase A Deficiency treated?

Acute infantile (Tay-Sachs disease) - At this time there is no cure for Tay-Sachs disease, and treatment largely focuses around ensuring the child’s proper nutrition and hydration, protecting his or her ability to breathe, managing any infections, and controlling seizures with medication.

Juvenile/Chronic/Adult-onset - There is also no cure for these later onset forms of hexosaminidase A deficiency. Treatment largely addresses symptoms as they arise, such as aiding mobility with mechanical aids or controlling seizures and mental disorders with medication. Because the symptoms of these forms of the disease vary widely, treatment is dependent upon the type of symptoms and their severity.

What is the prognosis for a person with Hexosaminidase A Deficiency?

Acute infantile (Tay-Sachs disease) - Even with the best care available, children affected by Tay-Sachs disease usually die by the age of four. They have worsening seizures and lapse into an unresponsive vegetative state.

Juvenile/Chronic/Adult-onset - The prognosis for a person with these forms of hexosaminidase deficiency A can vary widely, depending on when in life the symptoms begin and the severity of the individual's case.

Those with juvenile or chronic HEX A deficiency typically experience severe mental decline between the ages of 2 and 10 and often reach a vegetative state between the ages of 10 to 15, with death following several years later. In more severe cases, someone with juvenile HEX A deficiency can die in early childhood.

Those with the adult-onset form of the disease face more varied outcomes. Some may develop severe mental problems such as psychosis by age 20 while others may reach their 60s or 70s with movement difficulty, but without mental problems. The lifespan of people with adult-onset HEX A deficiency are not well understood and can be difficult to predict. In some cases, the disease has not impacted lifespan.

HMG-CoA Lyase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: HMGCL.
Exons Sequenced: NM_000191:1-9.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is HMG-CoA Lyase Deficiency?

HMG-CoA lyase deficiency is an inherited metabolic disease, in which the body lacks an enzyme required to properly break down the amino acid leucine, one of the protein building blocks. Individuals with HMG-CoA lyase deficiency are also unable to produce ketones, a key source of energy used by the body during times of fasting or illness.

In most children, symptoms of HMG-CoA lyase deficiency appear before one year of age. In approximately 30% of affected individuals symptoms begin between the second and fifth day of life. A few cases of late onset disease, during puberty or adulthood, have been reported. Symptoms appear as a “metabolic crisis,” an episode marked by low blood sugar, vomiting, lack of energy, difficulty feeding, irritability, and poor muscle tone that causes the body to seem floppy. These episodes, or crises, may be triggered by illness, infection, periods of fasting, or stress. Consumption of large amounts of protein may also serve as a catalyst for metabolic crisis. If unrecognized and untreated with a special diet, the episodes can rapidly progress to permanent neurological damage, coma, and even death. Even when appropriately treated, individuals with HMG-CoA lyase deficiency are at increased risk for infections and pancreatitis, which may be fatal.

How common is HMG-CoA Lyase Deficiency?

HMG-CoA lyase deficiency is a rare disorder. It has been reported in at least 93 individuals worldwide, but the global incidence is unknown. Note that other presentations of HMG-CoA lyase deficiency may not be recognized or undiagnosed as of yet. It is more common among individuals of certain ethnic groups, most notably those of Saudi Arabian, Portuguese, and Spanish ancestry. However, estimates of incidence in these populations have not been published.

How is HMG-CoA Lyase Deficiency treated?

A physician specializing in metabolism should help devise a treatment plan for any child with HMG-CoA lyase deficiency. Often these plans include avoidance of fasting, feeding with a low-leucine diet, medications, and prompt attention during metabolic crises. Diets will need to be carefully structured to both avoid problem foods and to ensure proper nutrition. In some cases, meals may be necessary around the clock, even overnight. A specialist will also devise a “sick day plan” to use when a child shows signs of illness that could lead to a metabolic crisis. This typically involves frequent meals with carbohydrates and increased fluid intake, even if the child is not hungry or thirsty. During times of illness, fats and proteins should be completely eliminated from the diet.

As children get older, the disease frequently becomes easier to manage and the risk of metabolic crisis decreases. However, many will still need lifelong dietary treatment. It is believed that those who receive treatment before their first metabolic crisis do better in the long term.

What is the prognosis for a person with HMG-CoA Lyase Deficiency?

With prompt and careful management of symptoms, children with HMG-CoA lyase deficiency are likely to live healthy lives with minimal effects of the disorder. However, this condition can be fatal in approximately 20 percent of cases. Among those that survive their first incident, repeated crises may result in brain damage and significant learning/intellectual disabilities. After childhood, symptoms are often milder, however, long-term effects may include heart damage, pancreatitis, vision loss, hearing loss, and intellectual disability.

Holocarboxylase Synthetase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: HLCS.
Exons Sequenced: NM_000411:4-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Holocarboxylase Synthetase Deficiency?

Holocarboxylase synthetase deficiency is a treatable inherited disease in which the body is unable to use the vitamin biotin effectively. If left untreated, the disease can cause numerous complications. The signs and symptoms of HCLSD typically appear within the first few months of life, although the age of onset can vary. Affected infants often have difficulty feeding, breathing problems, skin rash, hair loss, and a lack of energy. It can also lead to delayed development, seizures, and coma. These medical problems may be life-threatening in some cases.

How common is Holocarboxylase Synthetase Deficiency?

Holocarboxylase synthetase deficiency is estimated to affect between 1 in 87,000 to 1 in 100,000 people worldwide. The occurrence is higher for individuals of Scandinavian descent, with rates as high as 1 in 1,200 people from the Faroe Islands. Certain mutations are also believed to be relatively common among the Japanese population.

How is Holocarboxylase Synthetase Deficiency treated?

In most cases, biotin is the only required treatment for holocarboxylase synthetase deficiency, and affected individuals do not need to modify their diet or activity due to this condition. By taking daily supplements of biotin before symptoms occur, all symptoms of the disease can be avoided. If treatment begins after symptoms appear, some symptoms, such as skin problems and hair loss, will disappear; however, irreversible developmental deficits are possible and may require assistance from learning specialists.

Biotin supplements must be taken by mouth throughout life. This treatment is highly effective, provided a physician determines the proper dosage of biotin and adjusts that dosage over time if necessary.

What is the prognosis for a person with Holocarboxylase Synthetase Deficiency?

Early detection and treatment with biotin supplementation may prevent, manage, and possibly reverse symptoms. With treatment, most affected individuals are expected to have normal growth and development, although some individuals may have lifelong learning problems. Without treatment, holocarboxylase synthetase deficiency can be life-threatening.

Homocystinuria Caused by Cystathionine Beta-synthase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: CBS.
Exons Sequenced: NM_000071:3-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency?

Homocystinuria caused by cystathionine beta-synthase deficiency, or CBS deficiency, is an inherited metabolic disease in which affected people cannot process certain amino acids, the building blocks of proteins, due to the lack of a particular enzyme. The disease causes an array of symptoms including eye problems, skeletal abnormalities, an increased risk for dangerous blood clots, and in some people it causes developmental delay or intellectual disability.

Not all people with the disease exhibit all of the symptoms described below, and the severity of the symptoms varies widely from person to person. In some cases, people will reach adulthood before developing any symptoms.

There are two forms of the disease: a type that responds well to treatment with vitamin B6 and a type that does not. People with B6-responsive CBS deficiency sometimes, but not always, have a less severe course of the disease than those with the B6-non-responsive form.

The majority of people with CBS deficiency are nearsighted as infants. Those who go untreated will experience a dislocation of the lenses in their eyes (ectopia lentis) before the age of 8.

CBS deficiency can cause abnormal blood clots called thromboembolisms. If these blood clots form in or travel to the heart, brain, or other vital organs, they can be fatal. Thromboembolisms are frequently the cause of death in people with the disease.

People with the disease tend to be tall and thin with long arms and legs and an angular appearance. They are more likely than average to develop fragile, porous bones, a condition known as osteoporosis, at an early age. Roughly half of people with CBS deficiency will show signs of osteoporosis by their teenage years. They are also prone to scoliosis, a curvature of the spine.

The IQs of some people with CBS deficiency have been recorded as high as 138, which is well above the general population average of 100 and would be considered “gifted.” The average IQ score for a person with the disease, however, ranges between 57 and 79, depending on the genetic mutations he or she inherited. These IQs are generally considered borderline to mild intellectual disability. IQs for people with the disease have been recorded as low as 10, which indicates profound disability.

The disease can cause neurological or mental health problems such as seizures, anxiety, depression, obsessive-compulsive behavior, and psychosis. Roughly half of people with CBS deficiency have some kind of clinically significant psychiatric illness.

The disease can also cause abnormal muscle twitching, inflammation of the pancreas, the loss of skin color, and liver problems.

How common is Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency?

The exact prevalence of homocystinuria caused by CBS deficiency is unknown. Studies have reported that 1 in every 250,000 people in the general population is affected by the disease, but this figure is widely believed to be too low. Several studies estimate the populations in particular countries and regions as follows: Ireland (1 in 65,000), Germany (1 in 17,800), Norway (1 in 6,400), and Qatar (1 in 3,000).

How is Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency Treated?

A main goal of treatment for a person with homocystinuria caused by CBS deficiency is to control the concentration of homocysteine in the blood, thereby preventing symptoms of the disease. Medical professionals can help design a particular diet which includes vitamins and supplements such as vitamin B6, vitamin B12, folate, and betaine, and avoids certain types of food, notably those with the amino acid methionine. It is important that this treatment begin in infancy so as to limit any damage to the child’s body and intellect.

In order to lower the risk of blood clots, people with the disease should avoid unnecessary surgery and women should not take oral contraceptives. Women with the disease who become pregnant should work with their doctor to avoid pregnancy-related clotting problems.

Typically eye surgery is performed to correct the lens of the eye in people who have ectopia lentis.

What is the prognosis for a person with Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency?

Homocystinuria with CBS deficiency is thought to shorten the lives of people affected by the disease, however there is no known average lifespan. About 1 in 4 people with the disease will die before age 30 from a blood clot. The outlook is much better when the diagnosis is made early in life and the person's diet can be carefully planned.

Hydrolethalus Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: HYLS1.
Exon Sequenced: NM_001134793:3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Hydrolethalus Syndrome?

Hydrolethalus syndrome is an inherited disease that is characterized by severe craniofacial abnormalities and malformations of the limbs, heart, genitalia, respiratory system, and central nervous system (CNS). The most common CNS defects include hydrocephaly (abnormal buildup of fluid around the brain) with absent upper midline structures and a keyhole-shaped defect in the occipital bone (located at the back and lower part of the skull); however, other brain abnormalities can be seen. Other specific more common symptoms include preaxial polydactyly (extra digits), large septal defect (heart defect), and narrowing of the airway with irregular lobulation of the lungs. These malformations are considered lethal.

Today, HLS can be detected by an ultrasound scan around 13-15 weeks gestation primarily due to the brain malformation being visible, but cleft lip/palate, limb defects (especially double big-toe and/or club-feet), and heart defects may also be seen. Polyhydramnios is typically present in the later parts of the pregnancy.

How common is Hydrolethalus Syndrome?

The prevalence of Hydrolethalus syndrome in the general population is unknown. Among people of Finnish descent, approximately 1 in 20,000 individuals will be affected.

How is Hydrolethalus Syndrome treated?

At this time, there is no cure or treatment option for individuals with Hydrolethalus syndrome.

What is the prognosis for a person with Hydrolethalus Syndrome?

The prognosis for an infant with Hydrolethalus syndrome is poor. There have been rare cases where individuals with Hydrolethalus syndrome have lived for several months. However most individuals are either stillborn or die shortly after birth.

Hypophosphatasia, Autosomal Recessive

Available Methodology: sequencing with copy number analysis.
Gene: ALPL.
Exons Sequenced: NM_000478:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Hypophosphatasia, Autosomal Recessive?

Hypophosphatasia is an inherited disorder that disrupts a process called mineralization, in which the body deposits minerals like calcium and phosphorus into teeth and bones. Proper mineralization is necessary to make bones strong and rigid, and make teeth strong enough to withstand years of chewing.

Hypophosphatasia can have two types of inheritance patterns: autosomal recessive (symptoms are seen when both disease genes have mutations) or autosomal dominant (symptoms occur when only one of two disease genes has a mutation). With autosomal recessive hypophosphatasia, symptoms can vary greatly depending upon which mutations a person carries. Some forms of the disease are severe while other forms are extremely mild.

The most severe form of hypophosphatasia appears before birth or in early childhood. In many cases, infants are stillborn because their skeletons fail to form. Other affected infants are born with short limbs, soft skull bones, and an abnormally shaped chest caused by soft, weak ribs. Approximately half the infants born with the condition die of respiratory failure in the first few weeks of life. Those who survive may have life-threatening complications such as breathing problems, seizures, or high blood calcium levels leading to kidney damage.

In a less severe form, children show the first signs of the condition by losing their baby teeth before the age of five. As they grow, they may be below average in height, with bowed legs or knock knees, large wrist and ankle joints, and an abnormally shaped skull. They are more prone to broken bones, bone pain, and arthritis. They may have trouble learning to walk or may develop a waddling gait. Their teeth may crack or decay more easily than normal.

The mildest form of the disorder is called odontohypophosphatasia. It only affects the teeth. People with this form of the condition have abnormal tooth development and lose their teeth early, but do not have skeletal abnormalities.

Occasionally, people with hypophosphatasia do not develop any symptoms until middle age. The most common symptoms are early tooth loss and frequent, slow-healing stress fractures in the feet. They may also develop arthritis.

How common is Hypophosphatasia, Autosomal Recessive?

Hypophosphatasia affects approximately 1 in 100,000 people and is most common in Caucasians. The disease is particularly common in a particular Mennonite population in Ontario, Canada, where it affects 1 in 2,500 people.

How is Hypophosphatasia, Autosomal Recessive treated?

Infants with the most severe form of the condition usually require mechanical help to breathe and may need surgery to release pressure within the skull. Vitamin B6 may relieve seizures.

Children and adults with hypophosphatasia should see a dentist every year, beginning at the age of one, to preserve teeth as long as possible. Adults will eventually need false teeth.

Aspirin, ibuprofen, and other pain relievers help with bone pain and arthritis. Although preventing bone fractures is difficult, orthotics may help with common fractures in the feet.

People with the condition should not take bisphosphonates, which are drugs commonly prescribed to treat other bone loss conditions such as osteoporosis. They should also avoid excess vitamin D, which can make calcium build up in the blood.

What is the prognosis for a person with Hypophosphatasia, Autosomal Recessive?

Approximately 50% of infants born with the severe form of the condition will die of respiratory failure in infancy. Exact lifespan for the rest is not known. People with the milder forms of the condition have normal lifespans.

Inclusion Body Myopathy 2

Available Methodology: sequencing with copy number analysis.
Gene: GNE.
Exons Sequenced: NM_001128227:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Inclusion Body Myopathy 2?

Inclusion body myopathy 2 (IBM2) is an inherited disease that causes a progressive weakening of the legs and arms, typically beginning in the late teens or early 20s and almost always before the age of 40. Typically people with the disease lose the ability to walk 20 years after symptoms appear.

The muscles of the lower leg are typically affected first. As these muscles slowly weaken, walking becomes more difficult and the person's gait changes. The weakness will spread to the thighs, hand muscles, and certain muscles of the shoulder and neck. A small number of people will also have weakness in the facial muscles. Often the large thigh muscles (quadriceps) are unaffected until late in the course of the disease.

For reasons not well understood, a small number of people who have the genetic mutations that cause IBM2 do not have symptoms of the disease.

How common is Inclusion Body Myopathy 2?

IBM2 is most common among Middle Eastern Jews, particularly of Iranian descent. The disease has also been found in small numbers of non-Jews, both within and outside of the Middle East. Roughly 220 individuals with IBM2 have been reported in medical literature, making the disease very rare in the general population.

Studies estimate that among Iranian Jewish communities in Israel and Los Angeles, 1 in 15 people are carriers of mutations that cause IBM2. These studies also estimate that 1 in every 500 to 1000 Iranian Jews in these communities are affected by IBM2.

How is Inclusion Body Myopathy 2 treated?

There is no cure or treatment for IBM2 that can reverse or delay the progression of muscle weakness. Neurologists, rehabilitation specialists, and physical and occupational therapists can aid in relieving symptoms as they appear.

What is the prognosis for a person with Inclusion Body Myopathy 2?

The disease often does not cause noticeable symptoms until the late teens or early 20s when muscle weakness begins. Movement of the arms and legs will become progressively impaired and typically people with IBM2 are wheelchair-bound 20 years after symptoms begin. The disease's effect on lifespan is not well-studied.

Isovaleric Acidemia

Available Methodology: sequencing with copy number analysis.
Gene: IVD.
Exons Sequenced: NM_002225:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Isovaleric Acidemia?

Isovaleric acidemia (IVA) is an inherited disorder in which the body is unable to properly process proteins, leading to a toxic buildup of isovaleric acid in the blood.

Some people with the genetic mutations that cause IVA do not show symptoms of the disease. The reason for this lack of symptoms is not entirely understood.

As the body digests proteins, it breaks them into smaller parts called amino acids. People with IVA lack a properly-working enzyme necessary to break down a common amino acid called leucine. As a result, an organic acid called isovaleric acid reaches toxic levels in the blood and can cause damage to the brain and nervous system. If left untreated, IVA can lead to seizures, coma, and death. Treatment with an appropriate low-protein diet, however, can lead to fairly normal growth, development, and lifespan.

There are two forms of IVA, one which appears shortly after birth and is rapidly life-threatening, and another which may appear later in childhood as episodes of illness.

The form of IVA seen in newborns appears within two weeks of birth. Initial symptoms include lack of energy, poor appetite, vomiting, and difficulty staying warm. The buildup of isovaleric acid often gives them an odor of sweaty feet. If untreated, these infants will progress to a more serious metabolic crisis, suffering seizures, coma, swelling or bleeding of the brain, and even death.

The childhood form of IVA often appears around the child's first birthday and its symptoms—nearly identical to the infantile form of the disease—may come and go over time, flaring up particularly during times of illness, high protein consumption, or long periods without food. Between periods of crisis, the child can be healthy, however overall these children may show poor growth, muscle weakness, or learning problems. Some infants who have the more severe, early-onset form of the disease can progress to the more episodic form later in life.

IVA is part of a group of diseases known as organic acid disorders.

How common is Isovaleric Acidemia?

IVA affects at least 1 in 250,000 Americans.

How is Isovaleric Acidemia treated?

People with IVA must eat a diet low in proteins, minimizing foods such as dairy products, meat, fish, eggs, legumes, and nuts. The body does need protein, however, and a nutritionist or other medical professional can help devise an appropriate diet. This may include foods made especially for people with organic acid disorders. Supplements of carnitine and/or glycine may be prescribed. These supplements bind with isovaleric acid and turn it into a less harmful compound.

People with IVA should have close contact with a physician during times of illness. At these times, the body may break down its own protein, leading to a buildup of isovaleric acid. Typically people with IVA need to eat more carbohydrates and drink more fluids during times of illness, even if they are not hungry or thirsty.

Any time a child with IVA experiences a metabolic crisis, he or she needs prompt treatment, which may include a hospital visit.

What is the prognosis for a person with Isovaleric Acidemia?

If the disease is recognized promptly and treated diligently, children with IVA can live near-normal lives. It is possible, however, that they will have episodes of metabolic crisis, although these episodes tend to decrease with age. If these episodes are not treated, irreversible learning problems or mental disability can occur.

Those who do not develop any symptoms of the disease can be expected to live a normal lifespan.

Joubert Syndrome 2

Available Methodology: sequencing with copy number analysis.
Gene: TMEM216.
Exons Sequenced: NM_001173990:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Joubert Syndrome 2?

Joubert syndrome 2 (JBTS2) is a disease that causes abnormalities in the brain structure leading to developmental delay, the inability to coordinate muscle movement, involuntary eye movements, and difficulty moving the eyes from side to side. Individuals may also have intellectual disability.

At birth, children with JBTS2 have poor muscle tone. Their eyes rapidly move involuntarily and may rotate inward. They often have difficulty eating due to problems coordinating their muscle movement and breathing problems due to the brain structure abnormalities. Some children with JBTS2 have additional fingers and/or toes (polydactyly). Some children with JBTS2 will have kidney problems leading to kidney failure in adolescence.

Children with JBTS2 all have delayed mental and physical development. They may be mildly to severely mentally retarded, though a few individuals have attended college. In the first few years of life, their eye problems often improve, leading to normal vision.

How common is Joubert Syndrome 2?

JBTS2 is most common in Ashkenazi Jews, of whom 1 in 34,000 is affected.

How is Joubert Syndrome 2 treated?

There is no cure for Joubert syndrome 2. A medical team can address symptoms as they arise. Regular examinations are necessary, since individuals vary from one another in the symptoms they will have. For example infants with difficulty eating should be monitored to ensure they're receiving proper nutrition. Physical and occupational therapy may also be helpful. Children with JBTS2 should also be monitored for eye and kidney problems.

What is the prognosis for a person with Joubert Syndrome 2?

The prognosis for a person with JBTS2 varies. Some will have milder forms of mental retardation and less severe ataxia (lack of muscle control) while others will have more severe mental retardation and movement problems. A minority will have a shorter lifespan due to kidney or liver failure and breathing abnormalities.

KCNJ11-related Familial Hyperinsulinism

Available Methodology: sequencing with copy number analysis.
Gene: KCNJ11.
Exon Sequenced: NM_000525:1.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is KCNJ11-related Familial Hyperinsulinism?

KCNJ11-related familial hyperinsulinism (FHI), also called familial hyperinsulinemic hypoglycemia type 2, is an inherited condition in which the pancreas releases inappropriately large quantities of the hormone insulin, leading to low blood sugar (hypoglycemia). When blood sugar drops to dangerously low levels, seizures and permanent brain damage may occur. If untreated, the condition could ultimately be fatal.

The pancreas normally secretes insulin in response to rising blood sugar. In people with KCNJ11-related FHI, the pancreas secretes insulin even without sugar consumption, thereby removing too much sugar from the blood.

Infants with KCNJ11-related FHI tend to have significantly low blood sugar within the first few days of life. They often require immediate infusions of the sugar glucose to prevent seizures. These newborns are typically born larger than normal and may show difficulty feeding, poor muscle tone, and breathing problems.

In some people with KCNJ11-related FHI, symptoms do not appear until later in childhood. The low blood sugar associated with the condition can also range from mild to severe depending on the individual, and varies even among members of the same family. Early and aggressive treatment is important to avoid permanent brain damage.

How common is KCNJ11-related Familial Hyperinsulinism?

The incidence of all types of FHI is approximately 1 in 25,000 to 1 in 50,000 births in most countries. *KCNJ11* accounts for about 5% of all cases of FHI.

How is KCNJ11-related Familial Hyperinsulinism treated?

Treatments for KCNJ11-related FHI include dietary modification, medications, and surgical intervention. The aim of treatment is to keep the affected person's blood sugar level in the normal range to avoid brain damage.

If a child shows symptoms of KCNJ11-related FHI at birth, intravenous glucose is often given to raise and stabilize the blood sugar level. Babies may need frequent feedings with large amounts of carbohydrates, even overnight. A feeding tube may be helpful to ensure that a child gets sufficient quantities of carbohydrates and may facilitate automatic feedings overnight.

There are several types of medication to treat KCNJ11-related FHI. These are typically taken orally and/or injected several times daily.

When diet and medication do not sufficiently manage blood sugar levels, the person may require surgery to remove part of the pancreas.

After an extended period of successful treatment, many people with KCNJ11-related FHI find their symptoms lessen in severity or even go into remission.

People with KCNJ11-related FHI may find their symptoms aggravated by viral infections and should take particular precautions when they become ill, even if their symptoms have gone into remission. They should also avoid long periods of time without eating.

What is the prognosis for a person with KCNJ11-related Familial Hyperinsulinism?

The long-term outlook for someone with KCNJ11-related FHI depends upon the severity of the symptoms and the vigilance of the efforts to treat it. Permanent brain damage can occur from episodes of low blood sugar. Even with treatment, people with the disease can develop some degree of brain damage or have learning difficulties. They also may be at an elevated risk of diabetes. In the most serious cases, when the disease is not recognized and properly treated, it can be fatal. However with careful treatment, people with KCNJ11-related FHI can live normal lifespans.

Krabbe Disease

Available Methodology: sequencing with copy number analysis.
Gene: GALC.
Exons Sequenced: NM_000153:1-17.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Krabbe Disease?

Krabbe disease, also known as globoid cell leukodystrophy, is an inherited degenerative disease of the nervous system. Leukodystrophies are a group of diseases which affect the myelin sheath, a fatty covering that insulates and protects nerve cells. People with Krabbe disease lack an enzyme called galactocerebrosidase, and the result is a build-up of toxic substances in cells that produce the myelin sheath. Without this protective covering, brain cells die and nerves in the body cannot function properly.

There are two forms of the disease: infantile and late-onset.

INFANTILE FORM

The infantile form, which affects 85 to 90% of people with Krabbe disease, appears in the first few months of life and causes irritability, muscle weakness, unexplained fever, deafness, blindness, seizures, and slowed mental and physical development. Usually death occurs by the age of two, often due to respiratory failure.

LATE-ONSET FORM

The late onset form of Krabbe disease, which affects 10 to 15% of people with the disease, can appear at any time between the ages of six months and fifty years. These individuals slowly develop vision loss, difficulty walking, rigid muscles, and mental impairment. Symptoms among people with late onset Krabbe disease are highly variable. The disease is often fatal 2 to 7 years after symptoms begin.

How common is Krabbe Disease?

About 1 in 100,000 people in the United States and Europe have Krabbe disease, and 1 in 150 are thought to be carriers. Several Druze and Muslim communities in and around Israel have an abnormally high incidence of Krabbe disease. There, as many as 1 in 6 adults may be carriers of the disease.

How is Krabbe Disease treated?

Treatment for Krabbe disease will depend on which form of the disease a person has. Treatment options for both forms are listed below.

INFANTILE FORM

For infants with this form of Krabbe disease who have not yet started showing symptoms, treatment with umbilical cord blood stem cells has shown promise in enabling normal or near normal lives. This procedure can take place within weeks of birth. In many cases neural deterioration is slowed following the procedure and symptoms seem less severe.

Bone marrow stem cells may be used in place of umbilical cord blood stem cells, however cord blood stem cells are less particular and do not require the donor to be a perfect match. With cord blood stem cells, there is also less risk of immune system complications.

Infants who have already started showing symptoms of the disease do not seem to benefit from this treatment. For them and others not suitable for the procedure, the only treatment is to address symptoms as they arise.

LATE-ONSET FORM

Some people with late onset Krabbe disease have benefited from treatment with umbilical cord stem cells, although this treatment has been most successful in pre-symptomatic patients with the infantile form of the disease. In cases where the treatment has been successful, neural deterioration is slowed and symptoms are less severe.

Bone marrow stem cells may be used in place of umbilical cord blood stem cells, however cord blood stem cells are less particular and do not require the donor to be a perfect match. With cord blood stem cells, there is also less risk of immune system complications.

For those not suitable for the procedure, the only treatment is to address symptoms as they arise.

What is the prognosis for a person with Krabbe Disease?

The infantile form of Krabbe disease is usually fatal before the age of two. Those infants who receive cord blood stem cells before the appearance of symptoms have longer lifespans.

Those with late-onset Krabbe disease typically live between 2 and 7 years after the onset of symptoms. The exact symptoms and rate of neurological deterioration varies greatly from person to person, even among those in the same family who have the same genetic mutations.

LAMA2-related Muscular Dystrophy

Available Methodology: sequencing with copy number analysis.
Gene: LAMA2.
Exons Sequenced: NM_000426:1-65.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is LAMA2-related Muscular Dystrophy?

LAMA2-related muscular dystrophy is a disorder that causes muscle weakness and wasting. The condition is a result of mutations in the *LAMA2* gene that contains instructions for the body to make the laminin alpha2 protein. This protein is part of the laminin 2 (also called merosin) and laminin 4 complexes, which are important skeletal muscle components. There are at least two types of this condition:

EARLY-ONSET LAMA2-RELATED MUSCULAR DYSTROPHY

Early-onset LAMA2-related MD is the most common presentation of this condition. It is apparent at birth or within the first few months of life, and thus, considered part of a class of muscle disorders called congenital muscular dystrophies. Low muscle tone and muscle weakness are severe and most affected infants experience delays or fail to reach many motor milestones. Most affected infants can sit unsupported and some can stand without assistance. Very few children with the severe form are ever able to walk without help. In addition, affected newborns may experience breathing difficulties that progressively worsen with age. Feeding difficulties can result in poor weight gain and growth. Other symptoms can include stiff joints, dislocation of the hip, progressive curvature of the spine, weak eye muscles, and seizures. Intellectual disability is only seen in a small percentage of patients, who mostly have structural malformations of the brain and/or seizures.

LATE-ONSET LAMA2-RELATED MUSCULAR DYSTROPHY

Late-onset LAMA2-related MD occurs later in childhood or in adulthood. Signs and symptoms of this form tend to be milder than the early-onset type and are similar to those of a group of muscle disorders classified as limb-girdle muscular dystrophies. In the late-onset form, the muscles most affected are those closest to the body, such as the shoulders, upper arms, pelvic area, and thighs. Children with late-onset LAMA2-related MD sometimes have delayed development of motor skills such as walking, but typically achieve the ability to walk without assistance. Over time, they may develop rigidity of the back, joint stiffness, progressive curvature of the spine, breathing problems, and heart issues (arrhythmia or weakening of the heart muscles, known as cardiomyopathy).

How common is LAMA2-related Muscular Dystrophy?

The worldwide occurrence of LAMA2-related MD is unknown. Where estimated, the occurrence of congenital muscular dystrophies are estimated to be between 1 in 26,000 and 1 in 132,000. However, the number of cases attributed to mutations in *LAMA2* varies by country and has been reported between ~6% and ~66%. Of note, one large study from northern England estimated the occurrence of LAMA2-related MD to be approximately 1 in 166,000 births, and a high frequency of the disease has been described in the Irish and Kenyan populations.

How is LAMA2-related Muscular Dystrophy treated?

Treatment is symptomatic, with the objective of optimizing each patient's abilities, and is usually managed by a team of doctors. For infants and children with early-onset LAMA2-related MD, it may include supplemental feeding, breathing support, physical therapy, orthotics for joint stiffness, occupational therapy, and speech therapy. Seizures or other neurological complications generally require specific medications. Those with the late-onset form benefit from regular physical therapy to stretch the joints and spine, and may need care for progressive breathing difficulties. Monitoring for issues over time, like breathing and heart complications, is also typically recommended for any individual with this condition.

What is the prognosis for a person with LAMA2-related Muscular Dystrophy?

Because of the serious health problems that occur in the early-onset form of the disorder, especially breathing issues, many affected individuals do not survive past adolescence. Those with the rarer, late-onset form have progressive muscle weakness, but life expectancy is typically unaffected.

Leigh Syndrome, French-Canadian Type

Available Methodology: sequencing with copy number analysis.
Gene: LRPPRC.
Exons Sequenced: NM_133259:1-38.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Leigh Syndrome, French-Canadian Type?

Though multiple forms of Leigh syndrome exist with more than 30 causative genes identified, Leigh syndrome, French-Canadian type (LSFC) is exclusively caused by mutations in the LRPPRC gene. Individuals with LSFC often appear normal at birth, but begin to lose basic skills such as head control, sucking, walking, and talking in infancy or early childhood. They may also present with intellectual disabilities, dysmorphic features, irritability, vomiting, and seizures.

Intellectual and neurological symptoms associated with this condition are the result of lesions that develop in the midbrain and/or brainstem. The cells in these regions of the brain also begin to lose their protective coating (myelin sheath) which decreases the ability to process and respond to stimuli and initiate movement in voluntary muscles. In addition, LSFC often causes periods of metabolic crisis wherein symptoms may rapidly worsen, ultimately leading to significant breathing difficulties, heart problems, and vision loss.

How common is Leigh Syndrome, French-Canadian Type?

LSFC has never been reported outside of the French-Canadian population. Among those from the Saguenay-Lac Saint Jean of Quebec, the disorder is observed in approximately 1 in 2000 births.

How is Leigh Syndrome, French-Canadian Type treated?

Currently, there is no cure for LSFC and treatment is only supportive with the goal of alleviating symptoms as they arise. Medications may be provided for treatment of seizures, cardiac, metabolic, and respiratory issues, and muscle/movement disorders as they develop.

What is the prognosis for a person with Leigh Syndrome, French-Canadian Type?

Typically, symptoms of Leigh syndrome present during the first year of life and progress rapidly. The average life expectancy for children with LSFC is approximately five to six years. However, some individuals do not develop symptoms until adulthood and/or have a slowly progressing course of the disorder.

Lipoamide Dehydrogenase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: DLD.
Exons Sequenced: NM_000108:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Lipoamide Dehydrogenase Deficiency?

Lipoamide dehydrogenase deficiency (E3) is a rare inherited disease that causes metabolic abnormalities, neurological damage, poor muscle tone, developmental delay, and movement problems. In some people, it is fatal in childhood. Infants with E3 often appear normal until the age of 8 weeks to 6 months when they develop severe lactic acidosis, a buildup of lactic acid in the body that causes vomiting, abdominal pain, and rapid breathing. If untreated, it can be fatal.

In addition to lactic acid buildup, a number of other substances accumulate in the bodies of people with E3. These include blood pyruvate, alpha-ketoglutarate, branched-chain amino acids, alpha-hydroxyisovalerate, and alpha-hydroxyglutarate.

Infants and children with the disease show developmental delay and a progressive breakdown of their nervous system. They often have poor muscle tone (hypotonia) and abnormal movements. The diseases is also called maple syrup urine disease type 3 due to the characteristic "maple syrup" smell of their urine.

How common is Lipoamide Dehydrogenase Deficiency?

E3 is extremely rare. Fewer than 20 cases are known worldwide. The majority of known cases come from families of Ashkenazi Jewish background.

How is Lipoamide Dehydrogenase Deficiency treated?

There is no established treatment for E3 due to the rarity of the disease. Combinations of diet, vitamins, and supplements have been tried without much success.

What is the prognosis for a person with Lipoamide Dehydrogenase Deficiency?

While the number of known cases does not allow for a well-established prognosis, it is thought that most people with E3 will die during childhood.

Lipoid Congenital Adrenal Hyperplasia

Available Methodology: sequencing with copy number analysis.
Gene: STAR.
Exons Sequenced: NM_000349:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Lipoid Congenital Adrenal Hyperplasia?

Lipoid congenital adrenal hyperplasia (LCAH) is the most severe form of congenital adrenal hyperplasia. The majority of cases are due to mutations in the *STAR* gene that produces the steroidogenic acute regulatory (StAR) protein.

Individuals with LCAH have a significantly diminished ability to produce almost all adrenal (gland located above the kidneys) and gonadal (testis or ovary) steroid hormones due to improper conversion of cholesterol in the body. The resulting hormone deficiencies cause a classic severe form of the disease, but a milder, non-classic form has also been described.

CLASSIC

Severe disease results from mutations that leave little to no enzyme activity of the StAR protein. However, onset of symptoms can be variable. Affected individuals usually experience salt-wasting crises in early infancy, where the body cannot retain salt leading to dehydration and other complications that can be life-threatening. In addition, they may also experience lethargy, poor feeding, and/or darkened (hyperpigmented) skin. Almost all affected individuals also have female genitalia regardless of genetic sex, and some have been described with neurological abnormalities.

NON-CLASSIC

Non-classic disease results from mutations that do not completely eliminate activity of the StAR enzyme, however this does not prevent salt-wasting crises. Although there have only been a handful of cases, individuals with non-classic LCAH seem to present in infancy or early childhood. The condition has been described as a form of non-autoimmune Addison disease. The improper adrenal function can result in darkening of skin (hyperpigmentation), low blood sugar (hypoglycemia), vomiting, and other symptoms.

How common is Lipoid Congenital Adrenal Hyperplasia?

LCAH has been reported in many ethnic groups, however the global incidence is unknown. It has been repeatedly seen in the Japanese, Korean, Palestinian, Saudi Arabian, and Swiss populations, possibly due to founder effects (high frequency of disease because the group arose from a small, isolated population) in some of those populations.

How is Lipoid Congenital Adrenal Hyperplasia treated?

Currently, there is no cure for LCAH. However, hormone replacement therapy is indicated for affected individuals and early, consistent adherence to medication may extend the lifespan into adulthood. A multidisciplinary team of physicians, including an endocrinologist, will likely monitor the medication dosage, medication side effects, growth, and development (both general and sexual) of patients who continue to receive treatment.

What is the prognosis for a person with Lipoid Congenital Adrenal Hyperplasia?

In the absence of any interventions or treatment, LCAH is typically fatal in early infancy, although some individuals have survived to adulthood with treatment.

Lysosomal Acid Lipase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: LIPA.
Exons Sequenced: NM_000235:2-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Lysosomal Acid Lipase Deficiency?

Lysosomal acid lipase (LAL) deficiency is an inherited disease characterized by an absence or deficiency of acid lipase, an enzyme that is necessary for the body to properly metabolize lipids (fatty substances). The effects of LAL deficiency are directly correlated to the body's ability to break down cholesteryl esters (a form of cholesterol) and triglycerides (a type of fat). The end result is an accumulation of lipids in the organs, mainly the spleen, liver, bone marrow, small intestine, adrenal glands, and lymph nodes, which is damaging. LAL deficiency likely represents a spectrum of disease, but sub-categories of the disease have been described, including Wolman disease and cholesteryl ester storage disease (CESD).

WOLMAN DISEASE

Individuals with Wolman disease typically have little to no acid lipase activity and tend to develop symptoms within the first few weeks of life. Symptoms include an enlarged liver and spleen (hepatosplenomegaly), an enlargement of the abdomen, vomiting, diarrhea, excess fat in the feces, a deficiency of red blood cells, yellowing of the skin or eyes, calcium deposits in the adrenal glands, and a failure to maintain a healthy weight for age.

CHOLESTERYL ESTER STORAGE DISEASE (CESD)

Individuals with CESD, who tend to have higher levels of acid lipase activity, may develop symptoms from the first year of life to adulthood. Symptoms are usually milder than those of Wolman disease and the disease generally progresses more slowly. Most individuals present with liver enlargement that indicates varying degrees of organ damage (such as an accumulation of fat in liver cells or liver cirrhosis). Enlargement of the spleen is also possible and affected individuals frequently develop high cholesterol, elevated triglycerides, and reduced levels of HDL ("good cholesterol"), which results in the formation of plaques in the arteries (coronary artery disease).

How common is Lysosomal Acid Lipase Deficiency?

It is currently unknown how often LAL deficiency occurs in the general population. Recent data suggest that the frequency of the condition may have previously been underestimated, primarily because of a lack of disease recognition and the wide disease spectrum. In addition, the frequency of the condition varies depending on the population studied. Wolman disease has been estimated to occur in 1 in 4,200 individuals in the Iranian Jewish population alone, and in 1 in 8,100 individuals in the Iranian and Uzbekistani/Bukharan populations together. CESD is estimated to be most common in the Caucasian and Hispanic populations, occurring in at least 1 in 225,000 to 1 in 350,000 individuals. Overall, it is thought that Wolman disease is less common than CESD.

How is Lysosomal Acid Lipase Deficiency treated?

Bone marrow transplantation has been shown to successfully cure Wolman disease, but there is a high mortality rate associated with the procedure. When bone marrow transplantation is not performed, the condition is considered fatal and treatment is palliative. The treatment of CESD generally focuses on the patient's symptoms. Affected individuals are typically monitored by laboratory examinations, imaging studies, and evaluation of heart function. Medications (such as statins) may be used to treat high cholesterol and high triglycerides, and liver transplantation may become necessary.

Enzyme replacement therapy is available for both subtypes of LAL deficiency and studies have shown that it may prolong survival.

What is the prognosis for a person with Lysosomal Acid Lipase Deficiency?

Because of the damage to organs and the malnutrition that results from the inability to metabolize fatty acids, infants with Wolman disease typically die within the first year of life, without a successful bone marrow transplant or enzyme replacement therapy. Lifespan for individuals with CESD is expected to be longer than individuals with Wolman disease, and available treatments may prolong life into adulthood. However, approximately 50% of individuals with CESD die in the second decade of life due to complications of liver disease or heart disease.

Maple Syrup Urine Disease Type 1B

Available Methodology: sequencing with copy number analysis.
Gene: BCKDHB.
Exons Sequenced: NM_183050:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Maple Syrup Urine Disease Type 1B?

Maple syrup urine disease (MSUD) type 1B is an inherited metabolic disorder named for the characteristic maple syrup smell of the affected person's urine. If carefully treated with a low-protein diet, people with MSUD can live fairly normal lives.

MSUD is caused by the lack of an enzyme needed to break down three amino acids: leucine, isoleucine, and valine, which are collectively known as the branched-chain amino acids. These amino acids are found in all foods containing protein. Without the needed enzyme, known as branched-chain ketoacid dehydrogenase (BCKAD), these amino acids and their byproducts accumulate and cause damage to the body. MSUD type 1B is due to a defect in one of the four components of the BCKAD enzyme.

Maple syrup urine disease can be classified into four general types: classic, intermediate, intermittent, and thiamine-responsive. Classic MSUD is the most severe type. People with other types exhibit milder symptoms, but are prone to periods of crisis in which symptoms closely resemble classic MSUD. In all types of the disease, there is a risk of mental and physical disability.

CLASSIC

The most common type, classic MSUD is characterized by little or no enzyme activity. Symptoms in people with classic MSUD will appear in the first week of life. Within 12 to 24 hours, or upon first consumption of protein, the infant's urine will take on a maple syrup smell. (Mediterranean populations unfamiliar with maple syrup describe the odor as similar to fenugreek.)

Within several days, the infant will show poor feeding, vomiting, and irritability, followed by lack of energy, weight loss, seizures, a tense arched posture, muscle tone which alternates between stiff and limp, and swelling of the brain. If untreated, life-threatening coma or respiratory failure could occur within 7 to 10 days and most will die within several months.

Upon any lapse of treatment, classic MSUD can cause brain damage. People with the disease are particularly prone to crisis during illness, infection, fasting, or after surgery.

INTERMEDIATE

People with intermediate MSUD have 3 to 8% of the normal amount of BCKAD enzyme activity. As a result, their bodies can tolerate higher amounts of the amino acid leucine. When ill, however, this tolerance drops.

Intermediate MSUD is similar to but less severe than the classic form. During periods of crisis, however, symptoms and risks are nearly identical.

INTERMITTENT

With intermittent MSUD, BCKAD enzyme activity is often between 8 and 15% of normal. Symptoms of the disease may not appear until the first or second year of life. Symptoms often appear during illness, fasting, or periods of high protein consumption.

This form of the disease is rare, but in times of crisis its risks and symptoms are similar to the classic form.

THIAMINE-RESPONSIVE

Thiamine-responsive MSUD is distinct in that people with this form of the disease will respond to large doses of thiamine. One study found that people with thiamine-responsive MSUD have 30 to 40% the normal activity of the BCKAD enzyme. Many people with this form of the disease can tolerate some protein in their diet.

In times of crisis, the risks and symptoms of thiamine-responsive MSUD are similar to the classic form. The ability to treat the disease with thiamine, however, makes it easier to control than the other forms, whose treatment hinges largely on diet.

How common is Maple Syrup Urine Disease Type 1B?

Worldwide, MSUD type 1B is estimated to affect 1 in 185,000 infants. It is most common among the Old Order Mennonite population, where about 1 in 385 infants is affected by the disease. Among Mennonites of eastern Pennsylvania, the frequency has been reported as high as 1 in 176 infants. The disease is also more common among Ashkenazi Jews, with roughly 1 in 50,000 affected by MSUD type 1B.

How is Maple Syrup Urine Disease Type 1B treated?

MSUD type 1B is primarily controlled by diet, using foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, wholegrain flour, beans, and nuts. Often people with MSUD type 1B are given a special liquid formula that supplies nutrients without the amino acids they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the person's entire life.

Amino acid levels in the blood should be monitored regularly by a physician. Blood test findings can help to calibrate the diet, and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Illnesses should always prompt a consultation with a physician, as these are vulnerable periods for a person with MSUD type 1B. He or she may need a special "sick day diet" to avoid hospital stays.

Those with thiamine-responsive MSUD may be prescribed thiamine supplements.

What is the prognosis for a person with Maple Syrup Urine Disease Type 1B?

With early, careful, and lifelong treatment, people with MSUD type 1B can live healthy lives into adulthood and show normal growth and mental development. It is particularly critical to recognize the disease as soon as symptoms appear in order to avoid brain damage and mental disability. Despite careful treatment, some people with the disease will experience periodic flare-ups, particularly during times of illness. These may create learning problems or mental disability and can be life-threatening.

If untreated, MSUD can be fatal.

Maple Syrup Urine Disease Type Ia

Available Methodology: sequencing with copy number analysis.
Gene: BCKDHA.
Exons Sequenced: NM_000709:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Maple Syrup Urine Disease Type Ia?

Maple syrup urine disease (MSUD) type Ia is an inherited metabolic disorder named for the characteristic maple syrup smell of the affected person's urine. MSUD is caused by the lack of an enzyme needed to break down three amino acids (building blocks of proteins): leucine, isoleucine, and valine, which are collectively known as the branched-chain amino acids. These amino acids are found in all foods containing protein. Without the needed enzyme, known as branched-chain ketoacid dehydrogenase (BCKAD) complex, these amino acids and their byproducts accumulate and cause damage to the body. MSUD type Ia is due to a defect in one of the components of the BCKAD complex.

MSUD can be classified into four general types: classic, intermediate, intermittent, and thiamine-responsive. Classic MSUD is the most severe type. People with other types exhibit milder symptoms, but are prone to periods of crisis in which symptoms closely resemble classic MSUD. In all types of the disease, there is a risk of intellectual and physical disability.

CLASSIC TYPE

The most common type, classic MSUD is characterized by little or no enzyme activity. Symptoms in people with classic MSUD will appear in the first week of life. Within 12 to 24 hours, or upon first consumption of protein, the infant's urine will take on a maple syrup smell. (Mediterranean populations unfamiliar with maple syrup describe the odor as similar to fenugreek.) Within several days, the infant will show poor feeding, vomiting, and irritability, followed by lack of energy, weight loss, seizures, a tense, arched posture, muscle tone which alternates between stiff and limp, and swelling of the brain. If untreated, life-threatening coma or respiratory failure could occur within 7 to 10 days. Most will die within several months.

Upon any lapse of treatment, classic MSUD can cause brain damage. People with the disease are particularly prone to crisis during illness, infection, fasting, or after surgery.

INTERMEDIATE TYPE

People with intermediate MSUD have some BCKAD enzyme activity. Thus, intermediate MSUD is similar to, but less severe than, the classic form. Generally, individuals with this form can tolerate higher amounts of the amino acid, leucine, than those with the classic type. During periods of crisis, however, this tolerance drops and symptoms and risks are nearly identical to those of the classic type.

INTERMITTENT TYPE

This form of the disease is rare. In individuals with intermittent MSUD, BCKAD enzyme activity is reduced, not absent. Onset of the disease may not be until the first or second year of life. Symptoms are also often episodic and are more likely to appear during illness, fasting, or periods of high protein consumption. As with the intermediate type, in times of crisis, risks and symptoms are similar to those of the classic form.

THIAMINE-RESPONSIVE TYPE

Thiamine-responsive MSUD is distinct in that people with this form of the disease are expected to show a decrease in symptoms when treated with large doses of thiamine (vitamin B1). Studies suggest that this form exists; however, the evidence is not definitive.

How common is Maple Syrup Urine Disease Type Ia?

Worldwide, MSUD is estimated to affect 1 in 185,000 infants. MSUD type Ia is thought to account for approximately 30-40% of all diagnoses of maple syrup urine disease. Type Ia is most common among the Old Order Mennonite population, where about 1 in 385 infants is affected by the disease. Among Mennonites of eastern Pennsylvania, the frequency has been reported as high as 1 in 176 infants. The disease is also more common among Portuguese Gypsies, where it is estimated to affect 1 in 20,000 infants.

How is Maple Syrup Urine Disease Type Ia treated?

MSUD type Ia is primarily controlled by diet, using foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, wholegrain flour, beans, and nuts. Often people with MSUD type Ia are given a special liquid formula that supplies nutrients without the amino acids they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the person's entire life.

Management is also key to proper treatment. Amino acid levels in the blood should be monitored regularly by a physician. Blood test findings can help to calibrate the diet and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Illnesses should always prompt a consultation with a physician, as these are vulnerable periods for a person with MSUD type Ia. He or she may need a special "sick-day diet" to avoid hospital stays.

Those with thiamine-responsive MSUD may be prescribed thiamine supplements. To date, no patients with any form of MSUD have been treated only with thiamine supplementation. Instead, a combination of thiamine supplementation and restriction of dietary protein intake has been utilized, therefore making it difficult to determine the true impact of a thiamine-only treatment plan.

What is the prognosis for a person with Maple Syrup Urine Disease Type Ia?

If untreated, MSUD can be fatal. With early, careful, and lifelong treatment and a low-protein diet, people with MSUD type Ia can live healthy lives into adulthood and show normal growth and mental development. It is particularly critical to recognize the disease as soon as symptoms appear in order to avoid brain damage and intellectual disability. Despite careful treatment, some people with the disease will experience periodic flare-ups, particularly during times of illness. These episodes may create learning problems or intellectual disability and can be life-threatening.

Maple Syrup Urine Disease Type II

Available Methodology: sequencing with copy number analysis.
Gene: DBT.
Exons Sequenced: NM_001918:1-11.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
96%	Finland
95%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe

What is Maple Syrup Urine Disease Type II?

Maple syrup urine disease (MSUD) type II is an inherited metabolic disorder named for the characteristic maple syrup smell of the affected person's urine. MSUD is caused by the lack of an enzyme needed to break down three amino acids (building blocks of proteins): leucine, isoleucine, and valine, which are collectively known as the branched-chain amino acids. These amino acids are found in all foods containing protein. Without the needed enzyme, known as branched-chain ketoacid dehydrogenase (BCKAD) complex, these amino acids and their byproducts accumulate and cause damage to the body. MSUD type II is due to a defect in one of the components of the BCKAD complex.

MSUD can be classified into four general types: classic, intermediate, intermittent, and thiamine-responsive. Classic MSUD is the most severe type. People with other types exhibit milder symptoms, but are prone to periods of crisis in which symptoms closely resemble classic MSUD. In all types of the disease, there is a risk of intellectual and physical disability.

CLASSIC TYPE

The most common type, classic MSUD is characterized by little or no enzyme activity. Symptoms in people with classic MSUD will appear in the first week of life. Within 12 to 24 hours, or upon first consumption of protein, the infant's urine will take on a maple syrup smell. (Mediterranean populations unfamiliar with maple syrup describe the odor as similar to fenugreek.) Within several days, the infant will show poor feeding, vomiting, and irritability, followed by lack of energy, weight loss, seizures, a tense, arched posture, muscle tone which alternates between stiff and limp, and swelling of the brain. If untreated, life-threatening coma or respiratory failure could occur within 7 to 10 days. Most will die within several months.

Upon any lapse of treatment, classic MSUD can cause brain damage. People with the disease are particularly prone to crisis during illness, infection, fasting, or after surgery.

INTERMEDIATE TYPE

People with intermediate MSUD have some BCKAD enzyme activity. Thus, intermediate MSUD is similar to, but less severe than, the classic form. Generally, individuals with this form can tolerate higher amounts of the amino acid, leucine, than those with the classic type. During periods of crisis, however, this tolerance drops and symptoms and risks are nearly identical to those of the classic type.

INTERMITTENT TYPE

This form of the disease is rare. In individuals with intermittent MSUD, BCKAD enzyme activity is reduced, not absent. Onset of the disease may not be until the first or second year of life. Symptoms are also often episodic and are more likely to appear during illness, fasting, or periods of high protein consumption. As with the intermediate type, in times of crisis, risks and symptoms are similar to those of the classic form.

THIAMINE-RESPONSIVE TYPE

Thiamine-responsive MSUD is distinct in that people with this form of the disease are expected to show a decrease in symptoms when treated with large doses of thiamine (vitamin B1). Studies suggest that this form exists and may be more likely in MSUD type II cases; however, the evidence is not definitive.

How common is Maple Syrup Urine Disease Type II?

Worldwide, MSUD is estimated to affect 1 in 185,000 infants. MSUD type II is thought to account for approximately 13-27% of all diagnoses of maple syrup urine disease. Type II may be more common in Filipinos and the Austronesian indigenous people of Taiwan due to founder effects (high frequency of disease because the group arose from a small, possibly isolated population).

How is Maple Syrup Urine Disease Type II treated?

MSUD type II is primarily controlled by diet, using foods low in protein. This often means severe restrictions on meat, fish, eggs, dairy foods, wholegrain flour, beans, and nuts. Often people with MSUD type II are given a special liquid formula that supplies nutrients without the amino acids they cannot digest. These dietary restrictions should begin immediately upon diagnosis and must continue for the person's entire life.

Management is also key to proper treatment. Amino acid levels in the blood should be monitored regularly by a physician. Blood test findings can help to calibrate the diet and are particularly important during pregnancy for a mother with MSUD. Any swelling of the brain requires immediate medical attention. Illnesses should always prompt a consultation with a physician, as these are vulnerable periods for a person with MSUD type II. He or she may need a special "sick-day diet" to avoid hospital stays.

Those with thiamine-responsive MSUD may be prescribed thiamine supplements. To date, no patients with any form of MSUD have been treated only with thiamine supplementation. Instead, a combination of thiamine supplementation and restriction of dietary protein intake has been utilized, therefore making it difficult to determine the true impact of a thiamine-only treatment plan.

What is the prognosis for a person with Maple Syrup Urine Disease Type II?

If untreated, MSUD can be fatal. With early, careful, and lifelong treatment and a low-protein diet, people with MSUD type II can live healthy lives into adulthood and show normal growth and mental development. It is particularly critical to recognize the disease as soon as symptoms appear in order to avoid brain damage and mental disability. Despite careful treatment, some people with the disease will experience periodic flare-ups, particularly during times of illness. These episodes may create learning problems or intellectual disability and can be life-threatening.

Medium Chain Acyl-CoA Dehydrogenase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: ACADM.
Exons Sequenced: NM_000016:1-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Medium Chain Acyl-CoA Dehydrogenase Deficiency?

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is a treatable inherited disease in which the body cannot turn certain fatty acids into energy due to a deficient enzyme. As a result, partially metabolized fatty acids can accumulate in body tissues, causing damage to the brain, liver, and other organs. If treated early and consistently, people with MCAD deficiency can live normal lives.

Children with untreated MCAD deficiency are prone to quick-developing, life-threatening health problems including seizures, breathing problems, brain damage, coma, and death. The liver may also be enlarged. It is thought that a small percentage of sudden infant death syndrome is due to undiagnosed MCAD deficiency.

The first symptoms of the disease usually appear in infancy or early childhood. These include vomiting, lack of energy, and low blood sugar. Rarely, these symptoms do not appear until adulthood. Often the episodes of metabolic crisis can be triggered by long periods without eating or by illness.

Women whose fetuses have MCAD deficiency are more prone to certain pregnancy complications and should speak with their physician.

How common is Medium Chain Acyl-CoA Dehydrogenase Deficiency?

MCAD deficiency is most common in Caucasians from Northern Europe. In the United States, the disease affects approximately 1 in 17,000 people. Affected Americans are often of Northern European ancestry. The disease is rare among Hispanics, African Americans, Asians, and Native Americans in the United States.

Studies have found high rates of MCAD deficiency in Northern Germany (1 in 4,900) and Southern Germany (1 in 8,500). One study found that Germans and Turks are equally affected.

How is Medium Chain Acyl-CoA Dehydrogenase Deficiency treated?

The key to treatment for people with MCAD deficiency is to avoid fasting, or long periods without eating. Infants will need to be fed frequently with a special diet low in fat. Consuming cornstarch can provide a sustained release of energy and allow for longer gaps between meals. Certain types of fat should be avoided while high amounts of carbohydrates can be beneficial. If the person is unable to consume food, intravenous glucose may be necessary. People with MCAD deficiency should speak with their medical team to devise a specialized diet.

What is the prognosis for a person with Medium Chain Acyl-CoA Dehydrogenase Deficiency?

If a person affected by MCAD deficiency is diagnosed early and treated promptly, the prognosis is good. He or she can lead a normal or near-normal life.

Because the metabolic crises caused by the disease can quickly progress from first symptom to death, it is possible for people who remain undiagnosed to die during their first episode.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

Available Methodology: sequencing with copy number analysis.
Gene: MLC1.
Exons Sequenced: NM_015166:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Megalencephalic Leukoencephalopathy With Subcortical Cysts?

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an inherited disease that causes seizures and mild developmental delay in affected infants and children followed by deterioration in motor and mental skills later in life.

Many infants with MLC are born with disproportionately large heads while the remainder will develop this symptom in the first year of life. After the first year, the growth of the head usually normalizes, becoming proportionate to the body. This is typically accompanied by a mild delay in motor skills development and epileptic seizures.

Most, though not all, people with MLC learn to walk independently for at least several years. While some retain the ability to walk for decades, many will experience deteriorating motor skills beginning in early childhood. Initially their walking will become unstable and they may fall. As time goes on, they often develop the inability to coordinate muscle movement in their torso and limbs. Their movements may become uncontrollably jerky. The majority of these children will require wheelchairs by their early teens or in their 20s.

The decline in mental abilities begins after the decline in motor skills and is usually slower. People with MLC often develop speech problems

Brain scans typically show abnormal structures in the brains of people affected by MLC.

How common is Megalencephalic Leukoencephalopathy With Subcortical Cysts?

MLC is extremely rare, though its exact frequency in the general population is unknown. Mutations screened by Counsyl have been found in people of Middle Eastern, Turkish, Japanese, and Libyan Jewish descent, among others. One mutation is common in the Agrawali community in India. In the Libyan Jewish community, 1 in 34000 are affected.

How is Megalencephalic Leukoencephalopathy With Subcortical Cysts treated?

There is no successful treatment for MLC, though anti-epileptic drugs can control seizures associated with the disease and physical therapy may help improve motor skills.

What is the prognosis for a person with Megalencephalic Leukoencephalopathy With Subcortical Cysts?

The prognosis for a person with MLC is not well understood, however people with the disease are often confined to a wheelchair in their early teens or 20s. Some people with the disease have died in their teens or 20s while other are known to be alive in their 40s.

Metachromatic Leukodystrophy

INCLUDING EARLY-ONSET FORM AND LATE-ONSET FORM

Available Methodology: sequencing with copy number analysis.
Gene: ARSA.
Exons Sequenced: NM_000487:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Metachromatic Leukodystrophy?

Metachromatic leukodystrophy (MLD) is an inherited genetic disease which damages the nervous system. People with MLD will progressively lose intellectual and motor functions. Symptoms may include spasticity, seizures, personality changes, and progressive dementia. As the disease progresses, the person loses the ability to walk, talk, see, and hear. Eventually he or she become paralyzed and unresponsive.

MLD is the most common in a group of diseases known as leukodystrophies. These diseases affect the myelin sheath, a fatty covering that insulates and protects nerve cells.

MLD results from a deficiency in an enzyme called arylsulfatase A. The lack of arylsulfatase A causes a fatty substance called sulfatide to build up to toxic levels in the body. This gradually destroys the myelin sheath, without which brain cells die and nerves in the body cannot function properly.

Metachromatic leukodystrophy can be divided into early-onset and late-onset forms. The early-onset form is also called the infantile form, and the late-onset form can be further divided into juvenile or adult forms. The course of the disease is similar, but the age at which symptoms appear varies, as does the rate at which symptoms progress. The age at which symptoms begin is usually similar among family members.

INFANTILE FORM

This is the most common form of MLD, accounting for 50-60% of all cases. Symptoms appear between the first and second years of life. Initially, affected children lose any language abilities they have developed and have trouble walking. Gradually their muscles waste away and become rigid. They will lose mental function and often experience seizures and loss of sensation in their limbs. By the final stages of the disease, children with infantile MLD become blind and deaf and require a feeding tube. They are unresponsive to their surroundings and become paralyzed. Infantile MLD is usually fatal by the age of 10.

JUVENILE FORM

In the juvenile form of MLD, symptoms appear after the age of 3 but before adolescence (12 to 14). Between 20-30% of people with MLD have the juvenile form. Initial signs of the disease are often difficulties in school and behavioral problems. Clumsiness, slurred speech, incontinence, and strange behavior often prompt parents to seek a diagnosis. As the disease continues, symptoms are similar to infantile MLD, but progress more slowly. The disease is usually fatal 10 or 20 years after symptoms appear.

ADULT FORM

In the adult form of MLD, symptoms appear after puberty and may not appear until a person's 40s or 50s. Roughly 15 to 20% of people with MLD have the adult form. Early signs of the disease often include personality changes, problems at school or work, numbness in the extremities of one's limbs, muscle weakness and loss of coordination, psychiatric problems such as delusions or hallucinations, or drug and alcohol abuse. It can be initially misdiagnosed as schizophrenia, depression, or multiple sclerosis.

Over time, an affected person's behavior will grow inappropriate and he or she will have trouble making good decisions. Everyday skills become difficult and movement will grow spastic and awkward. Eventually a person affected by the adult form will lose the ability to carry on a conversation. In the final stages of the disease, symptoms are similar to the infantile form—blindness, deafness, unresponsiveness, and paralysis.

This form of the disease progresses more slowly than the other forms. Those affected may experience periods of stability or periods of particularly rapid decline. People with the adult form of MLD may live 20 or 30 years after their initial diagnosis.

How common is Metachromatic Leukodystrophy?

Worldwide, 1 in every 40,000 to 160,000 people have metachromatic leukodystrophy. In certain populations, the prevalence can be much higher. These populations include Habbanite Jews in Israel (1 in 75), Israeli Arabs (1 in 8,000), Christian Israeli Arabs (1 in 10,000), and those in western portions of the Navajo Nation (1 in 2,500).

How is Metachromatic Leukodystrophy treated?

There is no cure for MLD. Bone marrow transplantation may be an option for some people with MLD. It has shown the most promise in people who are not yet showing symptoms of MLD. At best it slows, but does not stop, the progression of the disease. This is a controversial treatment because of its substantial health risks.

Other treatments aim to manage symptoms of the disease as they arise. Seizures and muscle tightness may be treated with medication. Physical therapy may help preserve movement as long as possible. Also helpful may be walking aids, wheelchairs, and feeding tubes.

What is the prognosis for a person with Metachromatic Leukodystrophy?

All people with metachromatic leukodystrophy will experience mental and motor deterioration, eventually reaching a state of paralysis and unresponsiveness.

Most children with the infantile form die by the age of 10. Those with the juvenile form typically develop symptoms between the ages of 3 and 14 and can live 10 to 20 years after the onset of symptoms. The adult form of the disease is more variable, but affected adults may not develop symptoms until their 40s or 50s and can live 20 to 30 years after symptoms begin. Death most commonly occurs from pneumonia or other infections.

Methylmalonic Acidemia, cblA Type

Available Methodology: sequencing with copy number analysis.
Gene: MMAA.
Exons Sequenced: NM_172250:2-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Methylmalonic Acidemia, cblA Type?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. In general, symptoms of methylmalonic acidemia can occur from any time between the neonatal period and adulthood. However, the cblA type is usually associated with onset of symptoms in infancy or early childhood. Symptoms often first present as an episode due to infection or other external stressors (metabolic decompensation) and may include vomiting, dehydration, and lethargy. Long-term complications can include low muscle tone (hypotonia), developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), chronic kidney disease, and pancreatitis.

How common is Methylmalonic Acidemia, cblA Type?

The estimated incidence of methylmalonic acidemia is 1 in 50,000 to 1 in 100,000 people. The portion of methylmalonic acidemia attributed to cblA Type is ~25%.

How is Methylmalonic Acidemia, cblA Type treated?

There is no cure for methylmalonic acidemia. Treatment is divided between managing an acute crisis (metabolic decompensation) and management of symptoms between crises. Metabolic crisis is managed in a hospital and involves increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring laboratory work for signs of further complications (like those related to elevated ammonia levels), which is best done by a metabolic expert. Long-term management includes a high-calorie diet that is low in protein, hydroxocobalamin (vitamin B12) intramuscular injections, carnitine and other supplements, and antibiotics. Transplant may become necessary if organ failure occurs.

What is the prognosis for a person with Methylmalonic Acidemia, cblA Type?

Methylmalonic acidemia is associated with a number of chronic issues and higher than average mortality rates. Even with treatment, the cblA type can be associated with symptoms, like intellectual disability or kidney disease. In a small percentage of cblA cases, a metabolic crisis can lead to coma and death, especially if the individual is left untreated.

Methylmalonic Acidemia, cblB Type

Available Methodology: sequencing with copy number analysis.
Gene: MMAB.
Exons Sequenced: NM_052845:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Methylmalonic Acidemia, cblB Type?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. In general, symptoms of methylmalonic acidemia can occur at any time between the neonatal period and adulthood. The cblB type is usually associated with onset of symptoms shortly after birth. During metabolic decompensation (episodic crisis due to infection or other external stressors) symptoms include vomiting, dehydration, lethargy, seizures, metabolic acidosis (too much acid in the blood), and hyperammonemia (elevated ammonia levels). Long-term complications can include increased risk for infections, low muscle tone (hypotonia), encephalopathy (brain damage), epilepsy, developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), pancreatitis, enlarged liver (hepatomegaly), and chronic kidney disease that progresses to kidney failure.

How common is Methylmalonic Acidemia, cblB Type?

The estimated incidence of methylmalonic acidemia is 1 in 50,000 to 1 in 100,000 people. The portion of methylmalonic acidemia attributed to cblB type is ~13%.

How is Methylmalonic Acidemia, cblB Type treated?

There is no cure for methylmalonic acidemia. Treatment is divided between managing an acute crisis (metabolic decompensation) and management of symptoms between crises. Metabolic crisis is managed in a hospital and involves increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring laboratory work for signs of further complications (such as those related to elevated ammonia levels), which is best done by a metabolic expert. Long-term management includes a high-calorie diet that is low in protein, carnitine and other supplements, antibiotics, and hydroxocobalamin (vitamin B12) intramuscular injections in rare cases. Transplant may become necessary if organ failure occurs.

What is the prognosis for a person with Methylmalonic Acidemia, cblB Type?

Methylmalonic acidemia is associated with a number of chronic issues and higher than average mortality rates. Even with treatment, the cblB type can be associated with symptoms, like intellectual disability or kidney failure. Metabolic crisis can lead to coma, especially if left untreated. The median age of death for patients with the cblB type is ~3 years.

Methylmalonic Aciduria and Homocystinuria, cblC Type

Available Methodology: sequencing with copy number analysis.
Gene: MMACHC.
Exons Sequenced: NM_015506:1-4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Methylmalonic Aciduria and Homocystinuria, cblC Type?

Methylmalonic aciduria and homocystinuria, cblC type is a metabolic disorder that affects the body's ability to process a protein called cobalamin. Cobalamin is also known as vitamin B12. The most well-described form of methylmalonic aciduria and homocystinuria is type cblC, or methylmalonic aciduria and homocystinuria, cblC type; it is also the most common of these disorders.

The age of initial presentation of cblC ranges from (1) newborns who can be small for gestational age with unusually small head size; to (2) infants who can have poor feeding, failure to thrive, and neurologic/developmental abnormalities; to (3) toddlers who can have failure to thrive, poor head growth, developmental delay, low muscle tone, and seizures; and to (4) young adults/adults who may develop confusion, mental illness, cognitive decline, and anemia.

How common is Methylmalonic Aciduria and Homocystinuria, cblC Type?

The estimated incidence is estimated to be approximately 1 in 100,000 births.

How is Methylmalonic Aciduria and Homocystinuria, cblC Type treated?

Currently, there is no treatment that cures or alleviates all the symptoms of methylmalonic aciduria and homocystinuria, cblC type. Critically ill individuals must be stabilized, preferably in consultation with a metabolic specialist, by treating their metabolic disease. Dietary modifications may improve symptoms and gastrostomy tube placement for feeding is often required. Seizures are treated using standard protocols. Medications have proven effective in some cases.

During the first year of life, infants may need to be evaluated once or twice a month. Routine medical care should include special attention to growth and development; neurologic evaluation for early signs of delay, behavioral disturbances, and seizures; and ophthalmologic evaluation for retinal and optic nerve changes. Prolonged fasting and excessive dietary protein intake should be limited.

What is the prognosis for a person with Methylmalonic Aciduria and Homocystinuria, cblC Type?

Some affected individuals have early and severe symptoms, while others reach adulthood without evidence of ongoing disease progression. In some cases, severe neurologic symptoms and/or cognitive impairment persist. It is difficult to discern whether or not such impairments are due to the disease progression prior to treatment or ongoing neurological decline.

MKS1-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: MKS1.
Exons Sequenced: NM_017777:1-18.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are MKS1-related Disorders?

Mutations in MKS1 are found in 2 different inherited syndromes:

Meckel-Gruber syndrome is caused by mutations in at least 13 different genes, including *MKS1*. Meckel-Gruber syndrome is an inherited genetic condition that causes central nervous system (CNS) malformations, fluid-filled sacs (cysts) in the kidney and polydactyly (extra fingers and toes). Other birth defects, including defects of the heart, cleft lip and cleft palate, and abnormalities of the liver and genitalia, are also features of Meckel-Gruber syndrome. Due to the severity of symptoms, those affected with Meckel-Gruber syndrome are stillborn or die soon after birth. The common birth defects associated with Meckel-Gruber syndrome can often be seen on prenatal ultrasound.

In some cases, mutations in this gene may cause a more mild condition called Bardet-Biedl syndrome (BBS13). Bardet-Biedl syndrome is an inherited disease that causes vision problems, kidney abnormalities, genital anomalies, extra fingers or toes, and mild obesity, among other symptoms. About half of people with the disease have developmental delay or mental disability.

How common are MKS1-related Disorders?

Meckel-Gruber syndrome affects an estimated 1/13,250 - 1/140,000. It is more common in certain specific populations such as the Finnish (1/9000) and Belgians (1/3000).

Bardet-Biedl syndrome is rare, affecting about 1 in 100,000 in North America and 1 in 125,000 in Europe. It is more or less common in specific populations such as Kuwaiti Bedouins (1 in 13,500), residents of Newfoundland, Canada (1 in 17,500), and the Swiss (1 in 160,000). It is estimated that *MKS1* accounts for 4.5% of all Bardet-Biedl syndrome.

How are MKS1-related Disorders treated?

There is no cure for Meckel-Gruber syndrome. For those affected, treatment is supportive.

For those individuals affected with Bardet-Biedl syndrome, extra fingers and toes can often be surgically removed in childhood. The vision and kidney problems associated with the disease can be treated in the standard fashion by medical specialists. If kidney problems reach life-threatening levels, dialysis and/or kidney transplantation may be necessary. Diet and exercise can help control obesity. In women, vaginal malformations can be surgically corrected.

What is the prognosis for a person with an MKS1-related Disorder?

Meckel-Gruber syndrome is a lethal condition and prognosis is poor. Those affected are either stillborn or die in the first few hours or days of life.

Kidney disease is a major cause of early death for people with Bardet-Biedl syndrome. However, a majority of individuals may have a normal or near-normal life expectancy with some impairments.

Mucolipidosis III Gamma

Available Methodology: sequencing with copy number analysis.
Gene: GNPTG.
Exons Sequenced: NM_032520:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucolipidosis III Gamma?

Mucolipidosis III gamma is an inherited lysosomal storage disorder that slowly progress over time. People with Mucolipidosis III gamma lack an enzyme called GlcNAc-1-phosphotransferase which is important for the proper functioning of lysosomes, the digestive system of the cell.

Mucolipidosis III gamma is primarily associated with progressive skeletal abnormalities. Joint stiffness, loss of flexibility, and pain are typically the first symptoms to present in early childhood; the fingers, shoulders, and hips are particularly impacted. Other skeletal abnormalities include slow growth, short stature (short height), osteoporosis (low bone mineral density) that may cause an increased risk for fractures, scoliosis (spinal curvature, and gradual mild coarsening of facial features.

Other symptoms include heart valve abnormalities, problems with the ribs which may impact lung function, and clouding of the cornea in the eyes. Many individuals will develop thickened facial features (broad nose, large tongue, and thick lips). The majority of individuals have intellectual ability within the normal range, but mild intellectual disability has been reported.

How common is Mucolipidosis III Gamma?

Mucolipidosis III gamma is a rare disorder, its exact incidence is unknown.

How is Mucolipidosis III Gamma treated?

There is no cure for mucolipidosis III gamma and no known treatments to slow the limitations caused by progressive stiffness of the joints. Treatment may include pain management and/or physical therapy. Surgery may be done if hip replacement or heart valve replacement is necessary.

What is the prognosis for a person with Mucolipidosis III Gamma?

Mucolipidosis III gamma is a progressive condition that causes problems with mobility and accompanying pain. Individuals affected with mucolipidosis III gamma have survived into adulthood, but prognosis is difficult to predict due to the rarity of the condition.

Mucolipidosis IV

Available Methodology: sequencing with copy number analysis.
Gene: MCOLN1.
Exons Sequenced: NM_020533:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucolipidosis IV?

Mucolipidosis IV is a rare inherited condition that affects the development of the nerves. In about 15% of cases, it also causes existing nerves to degenerate. Most infants with the condition are unable to sit up, crawl, or control their hand motions. They also chew and swallow very slowly, because the muscles of their mouth and face move slowly or not at all.

Children with the condition never learn to walk independently, although a few have learned to use a walker. When they are able to speak, they tend to do so either very slowly or very quickly and slur words, mumble, or whisper. In addition, they rarely learn more than a few words, although some children with mucolipidosis IV have learned to communicate with a few dozen basic signs. In general, people with the disease only reach a developmental age of 12 to 15 months.

Mucolipidosis IV leads to poor vision caused by cloudy corneas (the clear front part of the eye) and degeneration of the retina (the part inside the eye which translates light into images). People with the disease are also prone to dry, irritated eyes, crossed eyes, and pupils that respond slowly to changes in light levels. Although infants with the condition may be born with nearly normal vision, their vision almost always starts to deteriorate by the age of 5. Virtually everyone with the condition is severely visually impaired by the early teens.

About 5% of people with the condition have an atypical variation with less severe movement and vision problems.

How common is Mucolipidosis IV?

Fewer than 100 cases of mucolipidosis IV have been reported in medical literature. More than 80% of those affected are of Ashkenazi Jewish background, and the disease is rare outside this population. Roughly 1 in 100 Ashkenazi Jews is a carrier.

How is Mucolipidosis IV treated?

Treatment for mucolipidosis IV focuses on ensuring comfort and improving function. Physical therapy, foot and ankle orthotics, walkers, and wheelchairs can help maximize mobility. Speech therapy may improve the ability to communicate. Younger children frequently develop eye irritation, which lubricating eye drops, gels, or ointments can soothe.

What is the prognosis for a person with Mucolipidosis IV?

Mucolipidosis IV typically shortens one's lifespan, but people with the disease commonly reach adulthood and some are known to be alive in their mid-40s.

Mucopolysaccharidosis Type I

Available Methodology: sequencing with copy number analysis.
Gene: IDUA.
Exons Sequenced: NM_000203:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucopolysaccharidosis Type I?

Mucopolysaccharidosis type I (MPS I) is an inherited disease in which the body lacks an enzyme called alpha-L-iduronidase. Without this enzyme, the body cannot properly break down long chains of sugar molecules called glycosaminoglycans. As a result, these molecules accumulate in the body, causing numerous health problems. There are 2 forms of MPS I, a severe form and an attenuated form. Children with the severe form, also known as Hurler syndrome, typically die before the age of 10, but may live longer with treatment.

SEVERE MUCOPOLYSACCHARIDOSIS TYPE I

Children with the disease appear normal at birth, but around the age of 9 months they typically begin developing some or all of the following symptoms:

- Appearance: Coarse facial features (broad mouth, square jaw), short neck, large head, small stature
- Brain: Progressive and profound intellectual and developmental disabilities, tendency toward a dangerous accumulation of fluid around the brain
- Heart: Heart disease including valve problems and narrowed arteries
- Eyes: Cloudy corneas leading to limited vision, glaucoma, and blindness
- Bones: Spinal abnormalities, back pain, joint disease leading to restricted movement, claw hand, carpal tunnel syndrome, misshapen bones
- Ears: Moderate to severe hearing loss
- Skin: Darkened areas
- Digestive System: Enlarged liver and spleen, diarrhea and constipation
- Lungs and Breathing: Progressive lung disease, frequent infection, chronic runny nose, airway blockages, sleep apnea

ATTENUATED MUCOPOLYSACCHARIDOSIS TYPE I

This form is also known as Hurler-Scheie syndrome or Scheie syndrome. Children usually develop symptoms between the ages of 3 and 10 years. The severity of disease varies from serious life-threatening complications leading to death in the second to third decades to a normal life span complicated by significant disability from progressive arthropathy and cardiorespiratory disease. Learning disabilities can be present, and hearing loss and cardiac valvular disease are common.

How common is Mucopolysaccharidosis Type I?

Approximately 1 in 100,000 people have the severe form and 1 in 500,000 have the attenuated form. It has been found in people of all ethnicities.

How is Mucopolysaccharidosis Type I treated?

Depending on the severity of MPS I and the age of the child, one of several treatments may prevent or ameliorate some symptoms of the disease.

Bone marrow transplants can be effective in relieving physical aspects of Hurler syndrome, although it does not seem to help the bone or eye symptoms. Children who receive bone marrow transplants early—before the age of 2—tend to have better mental development, although they still have learning problems and progressive mental decline. Outcomes of the procedure do vary, but a bone marrow transplant can prolong the lifespan of a person with Hurler syndrome, even though it will still be significantly shortened. Note that the procedure itself carries a high risk of fatality.

Umbilical cord blood is a more recent treatment for MPS I, allowing for an unrelated donor and eliminating the need for total body radiation, as is the norm with a bone marrow transplant. This treatment can prolong the lifespan of an affected child, but also does not help the bone and eye issues. A cord blood transplant can help prevent a certain measure of mental decline if it is performed before significant damage is done to the intellect, often before the age of 18 months. Like bone marrow transplants, the procedure itself carries a high risk of fatality and can result in a variety of outcomes.

Enzyme replacement therapy using recombinant human alpha-L-iduronidase has also been shown to benefit people with MPS I, relieving many of the physical symptoms. Enzyme replacement may be used in tandem with the above surgical options. This treatment is relatively new and further study is needed to determine its long-term success.

Other symptoms of the disease can be addressed as they arise. Examples of these treatments include special education for developmental delays, heart valve replacement, shunting to remove excess fluid and relieve pressure from around the brain, sunglasses or hats to promote better vision, and physical therapy to aid in movement.

What is the prognosis for a person with Mucopolysaccharidosis Type I?

The prognosis for people with severe MPS I is generally poor. They need special education and assistance to perform ordinary daily functions, and are often wheelchair-bound. Death usually occurs within the first 10 years of life, although early treatment such as a bone marrow transplant can extend the lifespan. Heart and breathing problems are often the cause of death among children with the disease. Patients with attenuated MPS I have a variable lifespan.

Mucopolysaccharidosis Type II

Available Methodology: sequencing with copy number analysis.
Gene: IDS.
Exons Sequenced: NM_000202:1-9.

Detection Rate	Population
88%	African American
88%	Ashkenazi Jewish
88%	Eastern Asia
88%	Finland
88%	French Canadian or Cajun
88%	Hispanic
88%	Middle East
88%	Native American
88%	Northwestern Europe
88%	Oceania
88%	South Asia
88%	Southeast Asia
88%	Southern Europe

What is Mucopolysaccharidosis Type II?

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a lysosomal storage disorder that almost always affects males. Lysosomal storage disorders are a group of diseases characterized by the build up of toxic materials in the body. MPS II is caused by deficiency in the enzyme, iduronate-2-sulphatase. Deficiency in iduronate-2-sulphatase leads to the build-up of glycosaminoglycans (GAGs), important complex carbohydrates responsible for many regulatory functions in the body. The build-up of GAGs occurs in numerous organs and tissues leading to symptoms of MPS II.

Onset of symptoms and disease severity can be variable, but characteristic features include coarse facial features (broad nose, large tongue, and thick lips), enlarged head, recurrent ear infections, enlarged liver and spleen, hernias, thickened, pebbled skin, and short stature. Generally, severe cases present with symptoms between 18 months and 4 years of age. Approximately two-thirds of affected males will have central nervous system (CNS) involvement, leading to severe neurological decline and intellectual disability. Other major features include skeletal abnormalities (short stature as well as joint deformities and limited joint mobility), hearing loss, heart abnormalities, and airway obstruction that leads to pauses in breathing and progressive respiratory disease.

For individuals with a milder form of MPS II, onset of non-CNS related symptoms can occur in infancy or early childhood, although onset can also occur later than those with a severe form of MPS II. The severity of disease and progression can vary significantly, but heart disease and hearing loss are still common. Individuals with a milder form of MPS II often have normal neurologic and motor development.

It is important to note that symptomatic carrier females have been documented. These rare cases in females are due to chromosomal structural abnormalities or inactivation of the paternal X chromosome. Symptoms may be milder due to residual enzyme activity.

How common is Mucopolysaccharidosis Type II?

The occurrence of MPS II varies by region but is approximately 1 in 100,000 to 1 in 170,000 males.

How is Mucopolysaccharidosis Type II treated?

There is no cure for MPS II. Treatment focuses on management of symptoms, for example, physical and occupational therapy for developmental delays or surgical valve replacement for heart abnormalities. Enzyme replacement therapy (idursulfase) is also available for treatment of non-CNS related complications, though the success of treatment is dependent on the severity of disease. Treatment via bone marrow transplant and stem cell transplant have been attempted, though more data is needed to determine their long-term effectiveness.

What is the prognosis for a person with Mucopolysaccharidosis Type II?

For those with severe disease, death typically occurs in the first or second decade of life. Individuals with a milder form of MPS II can have complications that lead to death in their twenties or thirties, though survival into the fifties and sixties has been reported.

Mucopolysaccharidosis Type IIIA

Available Methodology: sequencing with copy number analysis.
Gene: SGSH.
Exons Sequenced: NM_000199:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucopolysaccharidosis Type IIIA?

Mucopolysaccharidosis type IIIA (MPS IIIA), also known as Sanfilippo syndrome type A, is a subtype of MPS III and is considered the most severe form of MPS III. The features of MPS IIIA are due to the build up of glycosaminoglycans (GAGs), important complex carbohydrates responsible for many regulatory functions in the body. This build up primarily affects the central nervous system. Although symptoms can range from mild to severe, even among affected individuals in the same family.

Infants with MPS IIIA appear normal at birth. Developmental delay and speech delay typically begin before 1 year of age, with the average age of onset at 7 months. Recurrent ear, nose, and throat infections are common. Behavioral issues, such as aggressiveness, sleeplessness, and hyperactivity typically develop in early childhood, often between ages 3 and 5 years. Intellectual disability becomes more severe during this time period, in part, because seizures frequently develop. Verbal communication is often lost before age ten. Motor problems, such as difficulty swallowing and spasticity (stiff or rigid muscles) will also develop. Most individuals with MPS IIIA lose the ability to walk by their mid-teens. Hearing loss is common. The physical features of the disease, such as coarse facial features, skeletal abnormalities, and macrocephaly (large head) are often mild.

How common is Mucopolysaccharidosis Type IIIA?

The incidence of MPS IIIA varies significantly by region. Where estimates have been made, the incidence ranges from 1 in 60,000 to 1 in 4,600,000, with an average incidence of approximately 1 in 172,000.

How is Mucopolysaccharidosis Type IIIA treated?

There is currently no approved treatment or cure for MPS IIIA.

What is the prognosis for a person with Mucopolysaccharidosis Type IIIA?

MPS IIIA is a condition with chronic issues and limited treatment options. Death typically occurs by the second or third decade of life, with an average lifespan of approximately 15 years.

Mucopolysaccharidosis Type IIIB

Available Methodology: sequencing with copy number analysis.
Gene: NAGLU.
Exons Sequenced: NM_000263:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucopolysaccharidosis Type IIIB?

Mucopolysaccharidosis type III B (MPS IIIB) also known as Sanfilippo syndrome type B, is a progressive lysosomal storage disorder. The features of MPS IIIB are due to the build up of glycosaminoglycans (GAGs), important complex carbohydrates responsible for many regulatory functions in the body. This build up primarily affects the central nervous system. Severity of the disease can range from mild to severe, even among affected individuals in the same family.

Infants with MPS IIIB appear normal at birth. The onset of symptoms including developmental delay and speech delay usually occurs between one to four years of age. Behavioral issues, such as aggressiveness and hyperactivity, typically develop in early childhood, often between ages of three and six years. Intellectual disability becomes more severe during this time period. Motor problems, such as difficulty swallowing and spasticity (stiff or rigid muscles), will also develop. The physical features of the disease, such as coarse facial features, skeletal abnormalities, and macrocephaly (large head) are often mild.

How common is Mucopolysaccharidosis Type IIIB?

The incidence of MPS IIIB varies significantly by region. Where estimates have been made, the occurrence ranges from 1 in 125,000 and 1 in 5,000,000 with an average incidence of approximately 1 in 374,000.

How is Mucopolysaccharidosis Type IIIB treated?

There is currently no approved treatment or cure for MPS IIIB.

What is the prognosis for a person with Mucopolysaccharidosis Type IIIB?

MPS IIIB is a condition with chronic issues and limited treatment options. Death typically occurs in the second or third decade of life, though survival into the fourth decade has been reported.

Mucopolysaccharidosis Type IIIC

Available Methodology: sequencing with copy number analysis.
Gene: HGSNAT.
Exons Sequenced: NM_152419:1-18.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Mucopolysaccharidosis Type IIIC?

Mucopolysaccharidosis type IIIC (MPS IIIC), also known as Sanfilippo Type C syndrome, is a progressive lysosomal storage disorder. The features of MPS IIIC are due to the build up of glycosaminoglycans (GAGs), important complex carbohydrates responsible for many regulatory functions in the body. This build up primarily affects the central nervous system. Severity of the disease can range from mild to severe, even among affected individuals in the same family.

Infants with MPS IIIC appear normal at birth. The onset of symptoms including developmental delay and speech delay usually occurs between one to four years of age. Behavioral issues, such as aggressiveness and hyperactivity, typically develop in early childhood, often between ages of three and six years. Intellectual disability becomes more severe during this time period. Motor problems, such as difficulty swallowing and spasticity (stiff or rigid muscles), will also develop. The physical features of the disease, such as coarse facial features, skeletal abnormalities, and macrocephaly (large head) are often mild.

Some individuals have developed retinitis pigmentosa, which causes deterioration of the light sensing cells of the eye leading to progressive vision loss.

How common is Mucopolysaccharidosis Type IIIC?

The incidence of MPS IIIC varies significantly by region. Where estimates have been made, the incidence ranges from 1 in 235,000 and 1 in 3,200,000 with an average incidence of approximately 1 in 737,000.

How is Mucopolysaccharidosis Type IIIC treated?

There is currently no approved treatment or cure for MPS IIIC.

What is the prognosis for a person with Mucopolysaccharidosis Type IIIC?

Symptoms begin in early childhood. Death typically occurs in the second or third decade of life, though survival into the fourth decade has been reported.

Muscle-eye-brain Disease

Available Methodology: sequencing with copy number analysis.
Gene: POMGNT1.
Exons Sequenced: NM_017739:2-22.

Detection Rate	Population
96%	African American
96%	Ashkenazi Jewish
96%	Eastern Asia
98%	Finland
96%	French Canadian or Cajun
96%	Hispanic
96%	Middle East
96%	Native American
96%	Northwestern Europe
96%	Oceania
96%	South Asia
96%	Southeast Asia
96%	Southern Europe

What is Muscle-Eye-Brain Disease?

Muscle-eye-brain disease (MEB) is an inherited condition causing a number of symptoms including muscle weakness, vision abnormalities, brain structure abnormalities, and severe intellectual and developmental disabilities.

MEB causes congenital muscular dystrophy, a form of muscle weakness that is present from birth or develops shortly after birth. It causes an infant to feel floppy in all of his or her muscles, including those of the face. He or she may also exhibit involuntary muscle jerks or twitches.

Eye problems associated with MEB include severe near-sightedness and glaucoma, among others.

Another hallmark of MEB is a brain abnormality known as cobblestone lissencephaly (or type II lissencephaly). The brain develops a bumpy “cobblestone” appearance and lacks the normal folding structure. Other structural changes in the brain are also present. Children with MEB may have a buildup of fluid around the brain that can create a dangerous amount of pressure.

The severity of symptoms can vary among people with MEB.

How common is Muscle-Eye-Brain Disease?

MEB is very rare, although its exact prevalence is unknown.

How is Muscle-Eye-Brain Disease treated?

There is no successful treatment or cure for MEB. Medical specialists can help treat specific symptoms, such as using medication to control seizures, physical and occupational therapy to aid in movement, and special eye glasses to help make the most of the child's vision.

What is the prognosis for a person with Muscle-Eye-Brain Disease?

The prognosis for a person with MEB varies depending on the severity of the symptoms, but is generally poor. Studies have shown people with MEB typically die between the ages of 6 and 16.

MUT-related Methylmalonic Acidemia

Available Methodology: sequencing with copy number analysis.
Gene: MUT.
Exons Sequenced: NM_000255:2-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is MUT-related Methylmalonic Acidemia?

Methylmalonic acidemia represents a group of disorders that affect the way a person breaks down proteins and fats. In general, symptoms of methylmalonic acidemia can occur from any time between the neonatal period and adulthood. There are two enzymatic subtypes of MUT-related methylmalonic acidemia:

MUT0 ENZYMATIC SUBTYPE

The mut0 enzymatic subtype is usually associated with onset of symptoms shortly after birth. During metabolic decompensation (episodic crisis due to infection or other external stressors), symptoms include vomiting, dehydration, lethargy, seizures, too much acid in the blood (metabolic acidosis), and elevated ammonia levels in the blood (hyperammonemia). Long-term complications can include increased risk for infections, low muscle tone (hypotonia), brain damage (encephalopathy), epilepsy, developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), pancreatitis, enlarged liver (hepatomegaly), and chronic kidney disease that progresses to kidney failure.

MUT- ENZYMATIC SUBTYPE

The mut- enzymatic subtype is usually associated with onset of symptoms by early infancy/childhood. Symptoms may be similar to the mut0 type, but there may be fewer complications. Symptoms often first present during metabolic decompensation and may include vomiting, dehydration, and lethargy. Long-term complications can include low muscle tone (hypotonia), developmental delay and intellectual disability, anorexia and poor growth (failure to thrive), chronic kidney disease, and pancreatitis.

How common is MUT-related Methylmalonic Acidemia?

The worldwide incidence of methylmalonic acidemia has not been studied. However, overall estimates for those populations studied are between 1 in 6,000 and 1/300,000. These incidences vary significantly likely due to regional differences, which may be in part due to founder effects (high frequency of disease because the group arose from a small, possibly isolated population). The portion of methylmalonic acidemia attributed to mutations in *MUT* is estimated to be ~63% based on one study in Europe.

How is MUT-related Methylmalonic Acidemia treated?

There is no cure for methylmalonic acidemia. Treatment is divided between managing an acute crisis (metabolic decompensation) and management of symptoms between crises. Metabolic crisis is managed in a hospital and involves increasing the amount of fluid in the body, ensuring proper nutrition (reduced or no protein and increased glucose-intake), and monitoring laboratory work for signs of further complications (like those related to elevated ammonia levels), which is best done by a metabolic expert. Long-term management includes a high-calorie diet that is low in protein, hydroxocobalamin (vitamin B12) intramuscular injections for the mut- type, carnitine and other supplements, and antibiotics. Transplant may become necessary if organ failure occurs.

What is the prognosis for a person with MUT-related Methylmalonic Acidemia?

Methylmalonic acidemia is associated with a number of chronic issues and higher than average mortality rates. Even with treatment, the mut type can be associated with symptoms, like intellectual disability or kidney failure. Metabolic crisis can lead to coma, especially if left untreated, and the average age of death for patients with the mut type is ~3 years.

MYO7A-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: MYO7A.
Exons Sequenced: NM_000260:2-49.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are MYO7A-related Disorders?

MYO7A-related disorders represent a group of disorders associated with hearing loss with or without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems.

USHER SYNDROME TYPE IB

There are three types of Usher syndrome, identified as type I, type II and type III. The different types of Usher syndrome are grouped by the severity of the disease and the age when symptoms appear. Mutations in MYO7A cause Usher syndrome type 1B (USH1B).

Usher syndrome type I is an inherited disease that causes hearing loss, balance problems, and progressive vision loss. Infants with USH1B are profoundly deaf in both ears at birth. They have severe balance problems caused by abnormalities of the inner ear (vestibular system) that can lead to delayed development. In general, children with USH1B sit and walk at later ages and have difficulties sensing changes in speed or direction. In childhood or by early adolescence, individuals with USH1B develop retinitis pigmentosa (RP), an eye disease which causes night blindness and a gradual loss of peripheral vision. Eventually only the central vision remains, creating “tunnel vision.” This central vision too can be impaired and can lead to blindness in a small number of people with the disease. In some cases, people with Usher syndrome type 1 develop cataracts, which can further impair vision.

DFNB2

Some mutations in *MYO7A* have been reported in recessive nonsyndromic hearing loss and deafness (hearing loss but no vision loss), referred to as DFNB2. Individuals with DFNB2 develop profound hearing loss anywhere from birth to adolescence, and may also develop balance problems. Though the progressive vision loss typical in Usher syndrome is not expected in this condition, some individuals reevaluated later in life had developed symptoms of retinitis pigmentosa indicating variability/overlap in the conditions associated with this gene.

DFNA11

In rare cases, a mutation in *MYO7A* causes dominant nonsyndromic hearing loss and deafness. A dominant condition is one where only one mutation is sufficient to cause the condition. Individuals with DFNA11 seem to develop moderate to severe progressive

hearing loss after learning how to talk (late childhood or adolescence). However, though they may have nystagmus or balance issues (milder than USH1B), they do not experience the vision loss typical in Usher syndrome. This condition seems to be the mildest associated with *MYO7A*.

How common are MYO7A-related Disorders?

The global incidence is unknown for all three conditions. The incidence/prevalence of Usher syndrome type I overall has been estimated in a few countries. In most countries, the frequency ranges from ~1 in 45,000 to ~1 in 65,000, with the exception of Germany where the frequency is ~1 in 90,000. Approximately 53-63% of people with Usher syndrome type I have USH1B. There are regions where founder effects (high frequency of disease because the group arose from a small, possibly isolated population) occur, such as in indigenous populations in South Africa.

DFNB2 and DFNA11 are rare disorders. DFNB2 has been been reported in at least 3 families and DFNA11 in at least 5 families of various ethnicities. Other presentations of or variability in these two disorders may not be recognized as of yet.

How are MYO7A-related Disorders treated?

There is no cure for MYO7A-related disorders, however early treatment is important to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal. People with Usher syndrome type 1B generally do not respond to hearing aids, however cochlear implants may help regain some form of hearing. Sign language is a good option for communication. Specialists can introduce other tools and methods of instruction available to people with hearing loss. It is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example in tactile signing) help children adapt to their limited vision. Individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What is the prognosis for a person with a MYO7A-related Disorder?

Usher syndrome type IB results in severe hearing and vision impairment and DFNB2/DFNA11 results in hearing impairment only. However, none of the conditions affect one's lifespan or intelligence.

NEB-related Nemaline Myopathy

Available Methodology: sequencing with copy number analysis.
Gene: NEB.
Exons Sequenced: NM_001271208:3-80,117-183.

Detection Rate	Population
92%	African American
>99%	Ashkenazi Jewish
92%	Eastern Asia
92%	Finland
92%	French Canadian or Cajun
92%	Hispanic
92%	Middle East
92%	Native American
92%	Northwestern Europe
92%	Oceania
92%	South Asia
92%	Southeast Asia
92%	Southern Europe

What is NEB-related Nemaline Myopathy?

Nemaline myopathy (NEB-related) is a genetic disease that causes weakness in the muscles of the face, neck, arms, and legs. Along with a tendency toward decreased muscle tone, this weakness can delay motor functions such as walking. In some cases, it can also cause difficulty eating and breathing, notably in infancy.

There are at least six different forms of nemaline myopathy, caused by mutations in several genes. Counsyl screens for a form of the disease caused by a mutation in the NEB gene. This form, most common in Ashkenazi Jews, usually causes a milder form of the disease known as "typical" or "typical congenital" nemaline myopathy.

People with typical nemaline myopathy are usually born with the muscle weakness typical of the disease, but eventually develop the strength to walk. In most affected people, the disease does not become progressively worse, allowing for active adult lives. In early childhood, they may have difficulty eating.

The muscle problems associated with nemaline myopathy are caused by an abnormal buildup of thread-like structures (nemaline bodies) in certain muscle tissue.

How common is NEB-related Nemaline Myopathy?

The form of nemaline myopathy for which Counsyl provides screening is most commonly found in the Ashkenazi Jewish community, where 1 in 47,000 are affected. This mutation has also been found in families not known to be of Ashkenazi Jewish descent.

How is NEB-related Nemaline Myopathy treated?

For all people with nemaline myopathy, physical therapy can significantly improve their mobility and strength. As a child with nemaline myopathy learns to walk, this will be particularly important. If weakness in facial muscles impairs speech, a speech therapist can be helpful. If feeding is a problem, it will be important to monitor the child's nutrition.

Infants with severe nemaline myopathy usually require a feeding tube to help them swallow properly and mechanical breathing support at least some of the time. They also need aggressive treatment for respiratory infections.

What is the prognosis for a person with NEB-related Nemaline Myopathy?

Individuals with typical nemaline myopathy tend to have a good prognosis. While they are delayed in their ability to walk, they usually gain that ability and live normal, active adult lives.

The more severe forms of nemaline myopathy cause breathing problems and lung infections which can be fatal in early childhood.

Niemann-Pick Disease Type C

Available Methodology: sequencing with copy number analysis.
Gene: NPC1.
Exons Sequenced: NM_000271:1-25.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Niemann-Pick Disease Type C?

Niemann-Pick disease type C is an inherited condition in which the body cannot properly metabolize cholesterol and fats, resulting in an excess of these substances in the body. Cholesterol buildup in the liver causes severe liver disease, and fat accumulation in the brain leads to learning disabilities and progressive neurological symptoms.

The first symptom of the disease, which can appear at any age from infants to adults, is an enlarged liver, enlarged spleen, or jaundice. In some cases, it is possible to detect the disease in an unborn child via ultrasound, but the disease is most commonly diagnosed in school-aged children. Symptoms may include sudden muscle problems such as seizures, clumsiness, tremors, problems walking, sudden falls, slurred speech, and trouble moving the eyes up and down. As the condition progresses, these children develop learning disabilities, psychological problems, or even dementia, and often lose the ability to speak. Eventually, people with Niemann-Pick disease type C lose the ability to move their facial muscles or swallow, making feeding through a stomach tube necessary.

For those diagnosed during childhood, the disease is usually fatal in the late teens or twenties due to pneumonia. People diagnosed in adulthood generally survive 10 to 20 years after diagnosis.

At the cellular level, Niemann-Pick disease type C can be caused by two different genetic mutations. Type C1 is caused by a mutation in the NPC1 gene, and type C2 is caused by a mutation in the NPC2 gene. Although the genetic mutations are different, the resulting symptoms are the same because NPC1 and NPC2 must work together to remove cholesterol and lipids from body cells. Of the known cases of Niemann-Pick disease type C, 95% have been type C1 while 5% have been C2.

How common is Niemann-Pick Disease Type C?

Niemann-Pick disease type C is estimated to affect 1 in 150,000 people. It is more common among French Acadians in Nova Scotia, people of Hispanic descent in specific parts of Colorado and New Mexico, and a small Bedouin group in Israel.

How is Niemann-Pick Disease Type C treated?

At this time, there is no cure for Niemann-Pick disease type C. Treatment focuses on managing symptoms with medication for seizures, sedatives for sleep disturbances, physical therapy to maintain mobility, and speech therapy to preserve communication as long as possible. Chest physiotherapy and antibiotics may help to prevent regular lung infections. People with the condition need a gastronomy tube for feeding when they can no longer swallow well enough to avoid choking or malnutrition.

What is the prognosis for a person with Niemann-Pick Disease Type C?

Niemann-Pick disease type C is usually fatal 10 to 20 years after diagnosis. In children who show symptoms at an early age, disease progression is usually faster compared to people whose symptoms appear later in life. Over half of people with this disease will be diagnosed by the age of 10.

Niemann-Pick Disease Type C2

Available Methodology: sequencing with copy number analysis.
Gene: NPC2.
Exons Sequenced: NM_006432:1-5.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Niemann-Pick Disease Type C2?

Niemann-Pick disease type C is an inherited condition in which the body cannot properly metabolize cholesterol and fats, resulting in an excess of these substances in the body. Cholesterol buildup in the liver causes severe liver disease, and fat accumulation in the brain leads to learning disabilities and progressive neurological symptoms.

The first symptom of the disease, which can appear at any age from infants to adults, is an enlarged liver, enlarged spleen, or jaundice. In some cases, it is possible to detect the disease in an unborn child via ultrasound, but the disease is most commonly diagnosed in school-aged children. Symptoms may include sudden muscle problems such as seizures, clumsiness, tremors, problems walking, sudden falls, slurred speech, and trouble moving the eyes up and down. As the condition progresses, these children develop learning disabilities, psychological problems, or even dementia, and often lose the ability to speak. Eventually, people with Niemann-Pick disease type C lose the ability to move their facial muscles or swallow, making feeding through a stomach tube necessary.

For those diagnosed during childhood, the disease is usually fatal in the late teens or twenties due to pneumonia. People diagnosed in adulthood generally survive 10 to 20 years after diagnosis.

At the cellular level, Niemann-Pick disease type C can be caused by two different genetic mutations. Type C1 is caused by a mutation in the *NPC1* gene, and type C2 is caused by a mutation in the *NPC2* gene. Although the genetic mutations are different, the resulting symptoms are the same because *NPC1* and *NPC2* must work together to remove cholesterol and lipids from body cells. Of the known cases of Niemann-Pick disease type C, 95% have been type C1 while 5% have been C2.

How common is Niemann-Pick Disease Type C2?

It is currently unknown how often Niemann-Pick disease type C2 occurs in the general population. It is estimated that Niemann-Pick disease type C affects 1 in 150,000 individuals, with approximately 5% of these cases being attributed to *NPC2*.

How is Niemann-Pick Disease Type C2 treated?

At this time, there is no cure for Niemann-Pick disease type C. Treatment focuses on managing symptoms with medication for seizures, sedatives for sleep disturbances, physical therapy to maintain mobility, and speech therapy to preserve communication as long as possible. Chest physiotherapy and antibiotics may help to prevent regular lung infections. People with the condition need a gastronomy tube for feeding when they can no longer swallow well enough to avoid choking or malnutrition.

What is the prognosis for a person with Niemann-Pick Disease Type C2?

Niemann-Pick disease type C is usually fatal 10 to 20 years after diagnosis. In children who show symptoms at an early age, disease progression is usually faster compared to people whose symptoms appear later in life. Over half of people with this disease will be diagnosed by the age of 10.

Niemann-Pick Disease, SMPD1-associated

Available Methodology: sequencing with copy number analysis.
Gene: SMPD1.
Exons Sequenced: NM_000543:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Niemann-Pick Disease, SMPD1-associated?

SMPD1-associated Niemann-Pick disease (NPD) is an inherited disease in which the body cannot properly metabolize a certain fatty substance called sphingomyelin due to a deficient enzyme called acid sphingomyelinase. As a result, sphingomyelin builds up in the body, causing cells to die and making it harder for certain organs to work properly. Mutations in SMPD1 can cause either type A or type B NPD.

Niemann-Pick disease type A causes mental disability, loss of motor skills, and enlargement of the liver and spleen, among other symptoms. The disease is often fatal by the age of 2 or 3. Symptoms of Niemann-Pick disease type A usually begin within the first few months of life. By the age of six months, infants with the disease have difficulty feeding, display an enlarged abdomen, and will begin to lose the motor skills they have developed. Seizures and spastic movement are common. Most will not learn to sit independently, crawl, or walk. They have poor muscle tone and develop cherry-red spots in their eyes. Many have a yellow tinge to the skin and whites of the eye (jaundice). Intellectual and motor skills will progressively and rapidly decline. These children may show vomiting, irritability, lung infections, and difficulty sleeping.

Unlike type A, which is fatal in early childhood, people with NPD type B have a less severe course of the disease and often live into adulthood. The most common symptoms include an enlargement of the liver and spleen (hepatosplenomegaly), a progressive decline in lung function and repeated respiratory infection, and poor or slower physical growth leading to shorter stature. They typically have abnormal lipid levels in their blood, with low HDL cholesterol and high LDL and triglycerides. This can lead to coronary artery disease later in life. People with NPD type B may also have a decreased number of blood platelets, which are needed to form blood clots. These symptoms may not be present from birth, developing in late childhood or adolescence. People with NPD type B usually do not have the nervous system complications (i.e. loss of motor skills) found in type A, however some people with the disease develop symptoms that combine features of both type A and type B.

How common is Niemann-Pick Disease, SMPD1-associated?

Niemann-Pick disease (including both types A and B) is thought to affect 1 in 250,000 people. Niemann-Pick disease type A occurs most frequently in Ashkenazi Jews, among whom 1 in 100 is a carrier. The disease is not limited to Ashkenazi Jews, however, and has occurred in people of all ethnicities. Type A is the most common form of Niemann-Pick disease, accounting for 85% of cases. Type B affects people of many different ethnicities. Cases have been reported in 29 countries. NPD type B is most common in the Maghreb region of North Africa, which includes Algeria, Morocco, and Tunesia.

How is Niemann-Pick Disease, SMPD1-associated treated?

Unfortunately there are no effective treatments for Niemann-Pick disease type A. Medical professionals can attempt to treat the symptoms through physical therapy, monitoring of nutrition, and medication to help sleep disorders. Such treatment cannot stop the decline caused by the disease, however.

There is no treatment to address the cause of NPD type B. However, individual symptoms such as high cholesterol can be addressed. Those with clotting problems may need blood transfusions while those with breathing problems may need supplemental oxygen. The person's diet will be monitored to ensure they are getting the proper nutrition for growth.

What is the prognosis for a person with Niemann-Pick Disease, SMPD1-associated?

The prognosis for a person with Niemann-Pick disease type A is poor. It is a severe disease which is typically fatal by the age of 2 or 3. People with NPB type B often survive into adulthood, however lifespan will likely be affected.

Nijmegen Breakage Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: NBN.
Exons Sequenced: NM_002485:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Nijmegen Breakage Syndrome?

Nijmegen breakage syndrome (NBS) is an inherited disease in which the body's DNA is prone to breakages. People with NBS often develop cancer at an early age and experience frequent lung and sinus infections. They also show intellectual decline, eventually leading to mild-to-moderate mental disability. People with NBS can live into adulthood, but typically not beyond their 30s or 40s.

Infants with NBS are often born with a small head size. Their physical growth is often slow, leaving them smaller than average for their age. They have characteristic features, including a sloping forehead, small chin, big ears, and prominent nose, which become more apparent later in childhood.

In one study, 35% of the 70 people studied who had NBS developed cancer—most commonly a type known as B-cell lymphoma—between the ages of 1 and 34. People with NBS cannot tolerate the high doses of ionizing radiation often used to treat cancer, and must find alternate treatment methods.

Immunodeficiency—the reduced ability of the body to fight off infection—is another symptom frequently associated with NBS. As a result, the disease causes frequent infections in the lungs, ears, sinuses, and urinary tract. Recurrent bronchitis can be life-threatening.

Intellect appears to develop normally or near-normally in early childhood, but typically declines until the person reaches mild-to-moderate levels of mental disability around the age of 10.

Carriers of NBS do not show symptoms of the disease, however recent studies have shown that some carriers may be at a greater than average risk of developing cancer.

How common is Nijmegen Breakage Syndrome?

Scientists estimate that 1 in 100,000 births is affected by NBS. The disease is most common in people of Eastern European or Slavic background, specifically those from Poland, the Czech Republic, and the Ukraine. There the carrier frequency may reach as high as 1 in 155. More than 40 cases of NBS have been diagnosed in North America.

How is Nijmegen Breakage Syndrome treated?

There is no treatment to address the underlying cause of NBS, but certain symptoms can be treated.

Vitamin E and folic acid supplements may be helpful. In some people, intravenous infusions with immunoglobulin may help reduce infections. Preventative antibiotics are another option for treating infection. Special education and speech therapy can be helpful as well.

Large doses of radiation must be avoided in people with NBS, even before birth. Cancer treatments therefore must be adapted.

What is the prognosis for a person with Nijmegen Breakage Syndrome?

Some people with NBS do live into adulthood, though typically the lifespan does not extend beyond one's 30s or 40s. The longest known lifespan of a person with NBS is 53. Cancer is the most common cause of death among people with NBS, followed by lung infections leading to respiratory failure.

Northern Epilepsy

Available Methodology: sequencing with copy number analysis.
Gene: CLN8.
Exons Sequenced: NM_018941:2-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Northern Epilepsy?

Northern epilepsy is an inherited disease that causes seizures and leads to severe mental disability in adulthood.

Children with Northern epilepsy appear normal until they begin to develop seizures between the ages of 5 and 10. The seizures increase in frequency until puberty, after which they decline in frequency, but do not disappear. Within 2 to 5 years of the first seizure, the child begins to decline mentally. This decline is progressive and by the age of 30, the person is mentally disabled (an IQ less than 70), regardless of whether the seizures were controlled by medication. After age 30, people with the disease may also become clumsy in their movements and have problems with balance.

One third of people with the disease will also develop mild loss of visual acuity in adulthood.

Northern epilepsy belongs to a heterogenous group of diseases known as neuronal ceroid lipofuscinoses. Northern epilepsy is caused by a mutation in the gene CLN8. This gene carries the instructions for a particular protein, but the function of this protein is unknown.

How common is Northern Epilepsy?

In Finland, 1 in 135 people are carriers of the disease. All cases to date have been among Finnish people, particularly in the northern part of the country. Fewer than 50 cases have been described in the medical literature.

How is Northern Epilepsy treated?

There is no effective treatment for Northern epilepsy. Seizures can be controlled with medication, however this will not slow the progression of the disease towards mental disability.

What is the prognosis for a person with Northern Epilepsy?

People with Northern epilepsy often live to the age of 50 or 60, but have significant mental and physical impairments for much of their lives.

Ornithine Transcarbamylase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: OTC.
Exons Sequenced: NM_000531:1-10.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Ornithine Transcarbamylase Deficiency?

Ornithine transcarbamylase (OTC) deficiency is a metabolic disorder that results from problems in the urea cycle, a metabolic pathway necessary for the removal of ammonia from the body. The symptoms of OTC deficiency, which is the most common urea cycle disorder, result from elevated levels of ammonia in the blood (hyperammonemia). While ammonia is a normal byproduct of protein breakdown, it is toxic if there is too much in the body. An excess of ammonia is particularly damaging to the liver and nervous system. However, the condition is quite variable, with affected individuals presenting from birth to adulthood and with differing levels of disease severity, based on the degree of OTC enzyme deficiency. As this is an X-linked disorder (the gene that causes the condition is located on the X chromosome), OTC deficiency most often affects males, although some females may show signs of the condition.

NEONATAL ONSET FORM

This severe form of OTC deficiency, which results from absent or near-absent enzyme activity, first presents at or shortly after birth. Symptoms may include poor feeding, lethargy, low muscle tone, seizures, breathing difficulties, and potentially a hyperammonemic coma. Recurrent hyperammonemic crises (periods of high ammonia levels) lead to continued liver and brain damage and resulting complications.

LATER ONSET FORM

Partial OTC deficiency results in a later onset of symptoms (anywhere from infancy to adulthood). Individuals with this form may present with recurrent vomiting, a history of protein intolerance or avoidance, a Reye-like syndrome (with brain and liver swelling), developmental delays, intellectual disability, and/or seizures.

CARRIER FEMALES

While most carrier females (females that have one altered copy of the *OTC* gene and one copy that functions normally) show no signs of OTC deficiency, it is estimated that at least 15-20% will have a partial enzyme deficiency and may develop symptoms of the condition. It is important to know, however, that all carrier females (even those who have previously shown no signs of the condition) are more prone to experience symptoms of OTC deficiency during and just after pregnancy.

How common is Ornithine Transcarbamylase Deficiency?

It is not yet known precisely how common OTC deficiency is worldwide. While some sources estimate that OTC deficiency may occur in as many as 1 in 14,000 individuals, others estimate that it may affect approximately 1 in 50,000 to 1 in 80,000 individuals.

How is Ornithine Transcarbamylase Deficiency treated?

The treatment of OTC deficiency is focused on managing metabolic crises by reducing ammonia levels. If an infant presents with suddenly high ammonia levels, dialysis is performed, intravenous medications are given, and dietary restrictions are utilized to clear the body of problematic proteins. Liver transplantation is almost always necessary in those with the neonatal onset form, and may be considered in some cases of partial OTC deficiency. Seizures are treated with medications, while developmental delays and intellectual disabilities are managed with supportive therapies.

To avoid manifestations of OTC deficiency, affected individuals are prescribed intravenous medications, specialized formulas, and a restricted diet with less protein intake. People with OTC deficiency should also avoid exposure to valproic acid (Depakote, an anti-seizure medication), prolonged fasting or starvation, intravenous steroids, and high levels of protein or amino acids, which may trigger a metabolic crisis.

What is the prognosis for a person with Ornithine Transcarbamylase Deficiency?

The overall outcome for an individual with this condition depends on the severity of the enzyme deficiency and the extent of damage that occurs during hyperammonemic episodes. If an individual remains asymptomatic or mildly symptomatic, their prognosis may be good. However, if there is significant brain and liver damage as a result of metabolic crises, neuropsychological, gastrointestinal, and/or liver complications may occur. Adequate management of the condition during and between crises may improve prognosis, although hyperammonemic crises may lead to coma and even death, if untreated.

PCCA-related Propionic Acidemia

Available Methodology: sequencing with copy number analysis.
Gene: PCCA.
Exons Sequenced: NM_000282:1-24.

Detection Rate	Population
95%	African American
95%	Ashkenazi Jewish
95%	Eastern Asia
95%	Finland
95%	French Canadian or Cajun
95%	Hispanic
95%	Middle East
95%	Native American
95%	Northwestern Europe
95%	Oceania
95%	South Asia
95%	Southeast Asia
95%	Southern Europe

What is PCCA-related Propionic Acidemia?

Propionic acidemia is an inherited condition caused by a deficiency in the enzyme propionyl-CoA carboxylase. This results in the body being unable to properly process certain parts of proteins and fats, causing harmful substances to build up in the the body. This build up in the blood, urine, and tissues can be toxic and cause serious health problems.

Symptoms of propionic acidemia most often begin within the first few days after birth. Initial symptoms include poor feeding, lack of energy, weak muscle tone, and vomiting. If untreated, these symptoms can progress to more serious medical complications, including organ damage, seizures, coma, and possibly death. Propionic acidemia may be associated with developmental regression, intellectual disability, frequent infection, nutritional problems, and heart problems. The severity of symptoms can be variable amongst individuals with the condition. Typically, if an individual has symptoms beginning in infancy and does not receive treatment, they do not live past the first year of life.

Less commonly, the signs and symptoms of propionic acidemia appear during childhood or later in life. In individuals with this later-onset form, symptoms may be triggered by periods of fasting, fever, or infection. In some cases, the only symptom present is thickening of the heart muscle (cardiomyopathy).

At a cellular level, propionic acidemia is caused by mutations in either the *PCCA* or *PCCB* gene. Although the genetic mutations are different, the resulting symptoms are the same because PCCA and PCCB combine together to make the enzyme propionyl-CoA carboxylase. Of the known cases of propionic acidemia, approximately 35-50% have been attributed to mutations in *PCCA*, while 50-65% have been attributed to *PCCB* mutations.

How common is PCCA-related Propionic Acidemia?

The worldwide incidence of propionic acidemia has not been estimated, but is generally accepted to be 1 in 100,000 overall. However, the incidence of this condition varies significantly across the world. Where estimates are available, the incidence is between 1 in 1,500 and 1 in 520,000. It is more common among in Japan (1 in 17,400 including an asymptomatic form identified in newborn screening),

the Middle East (1 in ~27,000 in Saudi Arabia and 1 in 2000-5000 in specific tribes, 1 in 10,000 in Bahrain, and as high as 1 in 20,000 in the United Arab Emirates), and in Greenland (1 in 1600 in the Inuit population). Again, depending on region, the percent of cases attributed to the PCCA gene is between 10% and 70% with most countries showing that 40% of cases are due to *PCCA* mutations.

How is PCCA-related Propionic Acidemia treated?

At this time, there is no cure for propionic acidemia. Treatment primarily focuses on individualized dietary management to ensure proper nutrition. Dietary supplements and medication to manage medical complications may be used. Regular assessment for growth, nutritional needs, feeding, kidney function, cardiac problems, and development is recommended. Prompt identification and treatment of stressors such as fasting, fever, illness, and injury may decrease the chance of organ damage. Any time a child with propionic acidemia experiences an event causing fasting or illness, he or she needs prompt treatment, which may include a hospital visit. Liver transplant may be beneficial in some cases.

What is the prognosis for a person with PCCA-related Propionic Acidemia?

If an individual presenting with symptoms of propionic acidemia is not treated early in infancy, they do not usually live past the first year of life. If the condition is recognized promptly and treated diligently, survival and long term outcome is potentially improved. Even with treatment, affected individuals may still have significant intellectual and neurological impairment. Normal development is possible in some patients with later onset forms of the condition, with strict dietary management and close monitoring.

PCCB-related Propionic Acidemia

Available Methodology: sequencing with copy number analysis.
Gene: PCCB.
Exons Sequenced: NM_001178014:1-16.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is PCCB-related Propionic Acidemia?

Propionic acidemia is an inherited condition caused by a deficiency in the enzyme propionyl-CoA carboxylase. This results in the body being unable to properly process certain parts of proteins and fats, causing harmful substances to build up in the the body. This build up in the blood, urine, and tissues can be toxic and cause serious health problems.

Symptoms of propionic acidemia most often begin within the first few days after birth. Initial symptoms include poor feeding, lack of energy, weak muscle tone, and vomiting. If untreated, these symptoms can progress to more serious medical complications, including organ damage, seizures, coma, and possibly death. Propionic acidemia may be associated with developmental regression, intellectual disability, frequent infection, nutritional problems, and heart problems. The severity of symptoms can be variable amongst individuals with the condition. Typically, if an individual has symptoms beginning in infancy and does not receive treatment, they do not live past the first year of life.

Less commonly, the signs and symptoms of propionic acidemia appear during childhood or later in life. In individuals with this later-onset form, symptoms may be triggered by periods of fasting, fever, or infection. In some cases, the only symptom present is thickening of the heart muscle (cardiomyopathy).

At a cellular level, propionic acidemia is caused by mutations in either the *PCCA* or *PCCB* gene. Although the genetic mutations are different, the resulting symptoms are the same because PCCA and PCCB combine together to make the enzyme propionyl-CoA carboxylase. Of the known cases of propionic acidemia, approximately 35-50% have been attributed to mutations in *PCCA*, while 50-65% have been attributed to *PCCB* mutations.

How common is PCCB-related Propionic Acidemia?

The worldwide incidence of propionic acidemia has not been estimated, but is generally accepted to be 1 in 100,000 overall. However, the incidence of this condition varies significantly across the world. Where estimates are available, the incidence is between 1 in 1500 and 1 in 520,000. It is more common among in Japan (1 in 17,400 including an asymptomatic form identified in newborn screening),

the Middle East (1 in ~27,000 in Saudi Arabia and and 1 in 2000-5000 in specific tribes, 1 in 10,000 in Bahrain, and as high as 1 in 20,000 in the United Arab Emirates), and in Greenland (1 in 1600 in the Inuit population). Again, depending on region, the percent of cases attributed to the *PCCB* gene is between 10% and 80% with most countries showing that 60% of cases are due to *PCCB* mutations.

How is PCCB-related Propionic Acidemia treated?

At this time, there is no cure for propionic acidemia. Treatment primarily focuses on individualized dietary management to ensure proper nutrition. Dietary supplements and medication to manage medical complications may be used. Regular assessment for growth, nutritional needs, feeding, kidney function, cardiac problems, and development is recommended. Prompt identification and treatment of stressors such as fasting, fever, illness, and injury may decrease the chance of organ damage. Any time a child with propionic acidemia experiences an event causing fasting or illness, he or she needs prompt treatment, which may include a hospital visit. Liver transplant may be beneficial in some cases.

What is the prognosis for a person with PCCB-related Propionic Acidemia?

If an individual presenting with symptoms of propionic acidemia is not treated early in infancy, they do not usually live past the first year of life. If the condition is recognized promptly and treated diligently, survival and long term outcome is potentially improved. Even with treatment, affected individuals may still have significant intellectual and neurological impairment. Normal development is possible in some patients with later onset forms of the condition, with strict dietary management and close monitoring.

PCDH15-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: PCDH15.
Exons Sequenced: NM_033056:2-33.

Detection Rate	Population
93%	African American
93%	Ashkenazi Jewish
93%	Eastern Asia
93%	Finland
93%	French Canadian or Cajun
93%	Hispanic
93%	Middle East
93%	Native American
93%	Northwestern Europe
93%	Oceania
93%	South Asia
93%	Southeast Asia
93%	Southern Europe

What are PCDH15-related Disorders?

PCDH15-related disorders represent a group of disorders associated with hearing loss with/without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems.

USHER SYNDROME TYPE 1F (USH1F)

Usher syndrome type 1F is an inherited disease that causes hearing loss, balance problems and difficulty with gaze stabilization (secondary to vestibulopathy), and progressive vision loss. Infants with USH1F are profoundly deaf in both ears typically at birth. They have severe balance problems that can lead to delayed development (children sit and walk at later ages and have difficulties sensing changes in speed or direction). In childhood or by early adolescence, individuals with USH1F will develop retinitis pigmentosa, an eye disease which causes night blindness and a gradual loss of peripheral vision. Eventually only the central vision remains, creating a “tunnel vision” effect. Central vision can be impaired too and can lead to blindness in a small number of people with the disease, in part due to the occasional development of cataracts.

DFNB23

Some mutations in USH1F have been reported in recessive nonsyndromic hearing loss and deafness (isolated hearing loss), referred to as DFNB23. Individuals with DFNB23 typically have severe-profound hearing loss at birth. Unlike other forms of hearing loss, DFNB23 does not affect movement or balance.

How common are PCDH15-related Disorders?

The global incidence is unknown for both conditions. The incidence/prevalence of Usher syndrome type I overall has been estimated in a few countries. In most countries, the frequency ranges from ~1 in 45,000 to ~1 in 65,000, with the exception of Germany where the frequency is ~1 in 90,000. Approximately 7-12% of people with Usher syndrome type I have USH1F. There are regions where founder effects (high frequency of disease because the group arose from a small, possibly isolated population) occur. Individuals of

Ashkenazi Jewish descent have been noted to have one common mutation with an estimated carrier frequency of ~1 in 134 individuals. In the Hutterite population, ~1 in 40 individuals is a carrier of a different common mutation.

DFNB23 is a rare disorder. It has only been reported in 5 families, and the global incidence is unknown. Other presentations of or variability in this disorder may not be recognized as of yet.

How are PCDH15-related Disorders treated?

There is no cure for PCDH15-related disorders, however early treatment is important to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal.

People with Usher syndrome type 1F generally do not respond to hearing aids, however cochlear implants may help regain some form of hearing. Sign language is a good option for communication. Specialists can introduce other tools and methods of instruction available to people with hearing loss. It is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example in tactile signing) help children adapt to their limited vision. Individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What is the prognosis for a person with a PCDH15-related Disorder?

Usher syndrome type IF results in severe hearing and vision impairment and DFNB23 results in hearing impairment only. However, neither condition affects one's lifespan or intelligence.

Pendred Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: SLC26A4.
Exons Sequenced: NM_000441:2-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Pendred Syndrome?

Pendred syndrome is an inherited condition that affects the body's ability to make a protein called pendrin, which is important for normal functions of the inner ear and thyroid.

People with the condition are usually born severely to profoundly deaf, although some lose their hearing rapidly in infancy or early childhood and others have only moderate hearing loss that does not worsen over time. The inner ear malformations that are typical of Pendred syndrome may also cause balance problems.

Affected individuals may develop a goiter, a large swelling at the base of the neck caused by thyroid enlargement. This symptom usually appears several years after hearing loss is diagnosed. It can happen at any time during late childhood, adolescence, or adulthood. Pendred syndrome does not usually affect thyroid function, however goiters can put pressure on the esophagus and windpipe, interfering with swallowing and breathing.

How common is Pendred Syndrome?

The frequency of Pendred syndrome is unknown, but some researchers believe it is responsible for 1 in 10 infants who are born deaf.

How is Pendred Syndrome treated?

Treatment for Pendred syndrome focuses on addressing hearing loss. Children with the condition should be fitted for hearing aids early in life. Cochlear implants show some promise for restoring some hearing to people who are severely to profoundly deaf. Children should receive special educational programs for the hearing-impaired.

For those who develop goiters large enough to cause breathing or swallowing difficulties, treatment may include radioactive iodine to shrink the swelling or surgery to remove all or part of the thyroid.

What is the prognosis for a person with Pendred Syndrome?

Pendred syndrome causes moderate to profound hearing loss, but does not affect lifespan.

Peroxisome Biogenesis Disorder Type 3

Available Methodology: sequencing with copy number analysis.
Gene: PEX12.
Exons Sequenced: NM_000286:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Peroxisome Biogenesis Disorder Type 3?

Peroxisome biogenesis disorder type 3 (also known as *PEX12*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 3?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 3-9% of cases are attributed to mutations in *PEX12*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 3 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 3?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 4

Available Methodology: sequencing with copy number analysis.
Gene: PEX6.
Exons Sequenced: NM_000287:1-17.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Peroxisome Biogenesis Disorder Type 4?

Peroxisome biogenesis disorder type 4 (also known as *PEX6*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 4?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 9-16% of cases are attributed to mutations in *PEX6*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 4 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 4?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 5

Available Methodology: sequencing with copy number analysis.
Gene: PEX2.
Exon Sequenced: NM_000318:4.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Peroxisome Biogenesis Disorder Type 5?

Peroxisome biogenesis disorder type 5 (also known as *PEX2*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 5?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 1-4% of cases are attributed to mutations in *PEX2*. However, the incidence of *PEX2*-related ZSS in the Ashkenazi Jewish population may be higher and the incidence of all peroxisomal biogenesis disorders in Japan may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 5 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 5?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

Peroxisome Biogenesis Disorder Type 6

Available Methodology: sequencing with copy number analysis.
Gene: PEX10.
Exons Sequenced: NM_153818:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Peroxisome Biogenesis Disorder Type 6?

Peroxisome biogenesis disorder type 6 (also known as *PEX10*-related Zellweger syndrome spectrum, ZSS) is an inherited disease that stops part of the body's cells, called a peroxisome, from forming correctly. Peroxisomes normally break down waste products in a cell. Not everyone with ZSS will have the same symptoms and some may have more severe symptoms than others. The disease is generally grouped into three subtypes: Zellweger syndrome or ZS (the most severe), neonatal adrenoleukodystrophy or NALD (intermediate severity), and Infantile Refsum disease or IRD (the mildest form). Individuals with ZSS usually show symptoms of the disease as newborns or as children, but some people may not have symptoms until they are older.

ZELLWEGER SYNDROME (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical developmental milestones. Infants born with ZS have developmental delay leading to severe intellectual disability. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some cases, the infant cannot move and may not be able to suck or swallow because their muscles are too weak. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice). Some have bleeding in their digestive tract. Abnormally shaped bones are also common.

NEONATAL ADRENOLEUKODYSTROPHY (NALD) AND INFANTILE REFSUM DISEASE (IRD)

The symptoms of NALD and IRD are less severe than those of ZS, with IRD being the mildest form of the disease. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly. Infants and children with NALD or IRD may have developmental delays with mild to severe intellectual disability. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is Peroxisome Biogenesis Disorder Type 6?

Peroxisomal biogenesis disorders generally affect approximately 1 in 50,000 infants, and approximately 3% of cases are attributed to mutations in *PEX10*. In Japan, the incidence of all peroxisomal biogenesis disorders may be lower than 1 in 500,000.

How is Peroxisome Biogenesis Disorder Type 6 treated?

There is no cure for ZSS and there is no standard way to treat it. In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems. Physicians can also address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

What is the prognosis for a person with Peroxisome Biogenesis Disorder Type 6?

ZSS usually reduces a person's lifespan. The prognosis for an infant with ZS is poor. Most pass away within the first year of life without reaching any physical or mental developmental milestones. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of intellectual disability. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

PEX1-related Zellweger Syndrome Spectrum

Available Methodology: sequencing with copy number analysis.
Gene: PEX1.
Exons Sequenced: NM_000466:1-24.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is PEX1-related Zellweger Syndrome Spectrum?

PEX1-related Zellweger syndrome spectrum (ZSS) is an inherited disease that impairs the proper functioning of the body's peroxisomes, a cellular structure that normally breaks down fatty acids and other metabolic waste products.

As indicated by the word "spectrum," people with ZSS vary widely in the type and severity of their symptoms. The disease is generally grouped into three subtypes: Zellweger syndrome (the most severe), neonatal adrenoleukodystrophy (intermediate severity) and infantile Refsum disease (the mildest form). Each is described below. Individuals with ZSS usually show symptoms of the disease as newborns or as children.

While specific genetic mutations cannot fully predict which form of the disease a person will inherit, some genetic mutations are more closely associated with milder or more severe symptoms. Please consult a healthcare professional for more information.

Zellweger Syndrome (ZS)

ZS is the most severe form of ZSS. Infants with ZS usually die before their first birthday without reaching many mental or physical milestones.

Infants born with ZS have developmental delay leading to severe mental retardation. They often have seizures and typically have facial deformities such as a high forehead, abnormal ear lobes, a large "soft spot" on the top of their heads, and a small chin. In some, the lack of muscle tone is so severe that the infant cannot move and may not be able to suck or swallow. They often show poor feeding. Their livers are usually enlarged and their skin and the whites of their eyes may have a yellowish tinge (jaundice.) Some have bleeding in their digestive tract. Bone deformities are also common.

Neonatal Adrenoleukodystrophy (NALD) and Infantile Refsum Disease (IRD)

The symptoms of NALD and IRD are similar to that of ZS, but typically less severe, with NALD being more severe than IRD. Symptoms in these children often begin in late infancy or early childhood and may progress more slowly.

Infants and children with NALD or IRD may have developmental delays leading to mild to severe mental retardation. Hearing loss and vision impairment typically grow worse over time and may lead to blindness and/or deafness. Many people with the disease have liver problems and some have developed episodes of spontaneous bleeding, particularly around the brain. Some children with the disease learn to walk, while others lack the muscle tone needed for such movement. Similarly many children with the disease learn to talk, though some do not.

How common is PEX1-related Zellweger Syndrome Spectrum?

ZSS affects 1 in 50,000 infants.

How is PEX1-related Zellweger Syndrome Spectrum treated?

There is no cure for ZSS and there is no standard way to treat it. Physicians can address certain symptoms as they arise, such as prescribing medication for seizures. Children with milder forms of the disease may benefit from hearing aids, glasses, and/or surgery to remove cataracts. In those who reach school age, special education is likely necessary. Modifications to the child's diet may also be recommended.

In children with severe forms of the disease, the main goal of treatment is to protect the child from infections and breathing problems.

What is the prognosis for a person with PEX1-related Zellweger Syndrome Spectrum?

ZSS usually reduces a person's lifespan. One study showed that children with NALD or IRD who survive the first year of life have a 77% chance of reaching school age. These children will all have some degree of learning disabilities or mental retardation. Most people with NALD survive into childhood while those with IRD can live into their teens or 20s, and perhaps even longer.

The prognosis for an infant with ZS is poor. Most die within the first year of life without reaching any physical or mental milestones.

Phenylalanine Hydroxylase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: PAH.
Exons Sequenced: NM_000277:1-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Phenylalanine Hydroxylase Deficiency?

Phenylalanine hydroxylase deficiency is a treatable inherited disease in which the body cannot properly process the amino acid phenylalanine due to a deficient enzyme called phenylalanine hydroxylase. If severe forms of the disease go untreated, the buildup of phenylalanine can be toxic to the brain, causing impaired development and leading to severe and irreversible mental disability. If treated early and consistently however, people with phenylalanine hydroxylase deficiency can lead completely normal lives.

The disease can be divided into several categories based on the amount of enzyme deficiency: Classic phenylketonuria (PKU), variant PKU, and non-PKU hyperphenylalaninemia (non-PKU HPA). Since the mid-1960s, it has been standard for hospitals in North America to screen newborns for phenylalanine hydroxylase deficiency using a drop of blood obtained from a heel prick. This is now a routine practice in most developed countries.

It can be difficult to predict how severely affected a child will be based on the particular genetic mutations they carry. Children with any form phenylalanine hydroxylase deficiency should be evaluated by a specialist immediately after birth.

CLASSIC PKU

Classic PKU is the most common and severe form, resulting from an absence or near absence of the phenylalanine hydroxylase enzyme.

If PKU is not promptly diagnosed and treated with a special diet, mental disability will occur, along with a number of other symptoms including a small head, seizures, behavior problems, a "mousy" or "musty" odor, abnormal gait, low bone density, and eczema (a skin condition). These are all avoidable if the proper diet is instituted shortly after birth.

VARIANT PKU

Variant PKU is an intermediate form of the disease, less severe than classic PKU but more severe than non-PKU HPA. A child with variant PKU is at risk for developing the symptoms associated with classic PKU. Though the symptoms may be milder, there is still a risk for impaired mental development if the child's intake of phenylalanine is not monitored.

NON-PKU HYPERPHENYLALANINEMIA

Non-PKU HPA is the mildest form of phenylalanine hydroxylase deficiency. People with non-PKU HPA have a higher level of phenylalanine hydroxylase than do people with classic or variant PKU and are consequently at lower risk for developing brain damage. Some people with non-PKU HPA are able to tolerate a normal diet and do not require treatment. This will vary from person to person and must be determined by a medical professional based on the levels of phenylalanine in the person's blood.

How common is Phenylalanine Hydroxylase Deficiency?

The frequency of carriers and affected individuals in select populations is listed below.

Ethnic Group	Carrier Rate	Affected Rate
Turkish	1 in 26	1 in 2,600
Irish	1 in 33	1 in 4,500
Caucasian American	1 in 50	1 in 10,000
East Asian	1 in 51	1 in 10,000
Finnish	1 in 200	1 in 160,000
Japanese	1 in 200	1 in 160,000
Ashkenazi Jewish	1 in 225	1 in 200,000

How is Phenylalanine Hydroxylase Deficiency treated?

The degree of enzyme deficiency varies among people with phenylalanine hydroxylase deficiency, and therefore the treatment must also be individualized based on the levels of phenylalanine in the blood. An infant with any form of phenylalanine hydroxylase deficiency should be evaluated immediately after birth to determine whether or not he or she requires treatment. A blood test can reveal the amount of functioning phenylalanine hydroxylase in the body and this will indicate the amount of phenylalanine the person can safely consume.

While people with classic PKU must adhere to a strict low-phenylalanine diet, others with milder form of the disease are able to safely consume small amounts of the amino acid. For people with non-PKU HPA, treatment may not even be necessary.

Generally speaking, a diet low in protein and free from phenylalanine is important in preserving mental function in a person with classic PKU. Phenylalanine-free formulas are available for infants. Maintaining appropriate levels of phenylalanine in the brain can be achieved through blood testing and diet adjustment. This must be closely supervised by medical professionals. In most cases, this special diet must be maintained for life.

People with any form of phenylalanine hydroxylase deficiency should be conscious to avoid consuming aspartame, an artificial sweetener that contains phenylalanine.

Women with phenylalanine hydroxylase deficiency who become pregnant must be particularly careful to maintain safe levels of phenylalanine in their own bodies in order to avoid birth defects in their children. Ideally this begins prior to conception.

In late 2007, the medication sapropterin dihydrochloride (brand name: Kuvan) was approved by the FDA for use in people with phenylalanine hydroxylase deficiency. In some, it can enhance the activity of the deficient enzyme and lower levels of phenylalanine

in the body, allowing for a relaxation of the dietary restrictions. Some people with the disease do not respond to the drug, however. The people who do respond to this treatment usually have milder forms of the disease.

What is the prognosis for a person with Phenylalanine Hydroxylase Deficiency?

If a person with classic or variant PKU is treated early and consistently for the disease, the prognosis can be excellent. Many people with PKU have gone on to lead normal lives with normal intelligence and lifespan. If treatment is not begun early or adequately maintained, a person with a more severe form of PKU is at risk for severe and irreversible brain damage.

The prognosis is good for a person with non-PKU HPA. He or she may lead a normal life without treatment.

PKHD1-related Autosomal Recessive Polycystic Kidney Disease

Available Methodology: sequencing with copy number analysis.
Gene: PKHD1.
Exons Sequenced: NM_138694:2-67.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is PKHD1-related Autosomal Recessive Polycystic Kidney Disease?

PKHD1-related autosomal recessive polycystic kidney disease (ARPKD) is an inherited disease in which clusters of fluid-filled sacs (cysts) form in the kidneys, often leading to kidney failure by the age of 10 and a reduced lifespan. According to studies, between 23 and 30% of infants with ARPKD die hours or days after birth due to breathing difficulties.

The majority of infants with ARPKD show enlarged, cyst-filled kidneys within the first month of life. These cysts will impair the kidneys' ability to filter waste from the body. About 50% of infants with the disease will also have an enlarged liver. These anomalies are often detectable through ultrasound before the child is born. More than half of children will develop kidney failure by the age of 10. Without dialysis or transplantation, the disease is often fatal.

A minority of people with ARPKD do not show symptoms of the disease until later in childhood or early in adulthood, with liver disease being the dominant symptom. In these people, the kidney disease is often mild.

Extremely high blood pressure is common in people with ARPKD. They are also prone to urinary tract infections, frequent urination, low blood cell counts, pain in the back or the sides, varicose veins, and hemorrhoids. Many are also smaller than normal in stature.

How common is PKHD1-related Autosomal Recessive Polycystic Kidney Disease?

ARPKD affects 1 in every 20,000 to 40,000 infants. However, the disease may actually be more common since people with milder forms of the disease may not be diagnosed without genetic testing. About 1 in 70 U.S. adults is thought to be a carrier of ARPKD.

How is PKHD1-related Autosomal Recessive Polycystic Kidney Disease treated?

The initial concern with infants who have ARPKD is to protect their ability to breathe. Eating a nutritious diet can help the child's growth, and in some cases, growth hormones are recommended. Infants and children may require feeding tubes in order to ensure proper growth.

If faced with kidney failure, people with ARPKD frequently undergo dialysis (a "cleansing" of the blood through a machine that remove wastes) or kidney transplants. If the liver is extremely damaged, transplantation of this organ may also be recommended. Some people with ARPKD must undergo dialysis or a kidney transplant while they are still in infancy.

In all people with ARPKD, medications can lower blood pressure and clear up urinary tract infections.

What is the prognosis for a person with PKHD1-related Autosomal Recessive Polycystic Kidney Disease?

Between 20 and 30% of infants with ARPKD die hours or days after birth due to breathing difficulties. Of those who survive infancy, about 85% survive their first year of life, 82% survive to age 10, and 73% live past the age of 15. In one study, 58% of individuals required dialysis or kidney transplantation by age 20.

As transplantation methods improve, it is expected that people with ARPKD will live longer lives.

Polyglandular Autoimmune Syndrome Type 1

Available Methodology: sequencing with copy number analysis.
Gene: AIRE.
Exons Sequenced: NM_000383:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Polyglandular Autoimmune Syndrome Type 1?

Polyglandular Autoimmune Syndrome Type 1 (PAS-1) is an inherited disease in which the body's immune system mistakenly attacks healthy cells, notably the glands that produce the body's hormones. People with PAS-1 have at least two of the disease's main symptoms: fungal infections of the skin and mucous membranes, decreased function in the parathyroid glands, and decreased function in the adrenal glands (Addison disease). Many people with the disease have all three main symptoms. There are also numerous and diverse other symptoms which can occur.

In the majority of people with PAS-1, the first symptom to appear is recurrent and persistent fungal infections of the skin and mucous membranes, such as the in the moist lining of the nose and mouth. These infections typically begin between the ages of 3 and 5, although they can occur any time before one's 30s.

Frequently the second symptom of the disease to appear is an underactive parathyroid gland (hypoparathyroidism). This typically occurs before the age of 10. The parathyroid glands normally secrete a hormone used to regulate the amount of calcium and phosphorous in the bone and blood. An underactive parathyroid gland can cause numerous symptoms including tingling in the lips, fingers, and toes; muscle cramps; pain in the abdomen, face, legs, and feet; weakness or fatigue; and dry hair and skin.

Often the third symptom to appear is underactive adrenal glands, a condition known as Addison disease. This disease typically appears before the age of 15. Addison disease can cause fatigue, muscle weakness, weight loss, low blood pressure, and changes in skin coloration.

There are numerous other symptoms which can also occur in people with PAS-1. These include chronic liver disease, extreme fatigue due to a problem with red blood cells, skin disease, total body hair loss, an underactive pituitary gland, abnormalities in the ovaries and testes, diarrhea, difficulty absorbing nutrients from food, and eye problems, among others.

The most common pattern with PAS-1 is that the three main symptoms of the disease—fungal infections of the skin, underactive parathyroid gland, and Addison disease—develop in that order before the age of 20. The other symptoms associated with the disease may then begin sporadically over time until one's 50s, when the symptoms typically stabilize. This does not hold true for all

people with PAS-1, however. Generally speaking, the earlier in life that the main symptoms appear, the more likely it is that additional symptoms will develop.

How common is Polyglandular Autoimmune Syndrome Type 1?

PAS-1 is a rare condition in the United States, but it is more common among certain ethnic groups. The number of people affected include:

- Iranian Jews: 1 in 6,500 to 9,000
- Sardinians: 1 in 14,000
- Finns: 1 in 25,000
- Slovenians: 1 in 43,000
- Norwegians: 1 in 80,000 to 90,000
- Poles: 1 in 129,000

How is Polyglandular Autoimmune Syndrome Type 1 treated?

There is no cure for PAS-1. Each symptom must be treated as it arises and lifelong regular checkups are necessary to look for any new symptoms. It is important to discover and treat new symptoms as soon as possible to prevent permanent damage to the body.

Physicians often prescribe hormone replacement therapy or intravenous steroids for people with PAS-1. Calcium and vitamin D are often helpful to treat an underactive parathyroid gland. Fungal infections can be treated with medication.

Other symptoms are treated as they arise. For example, people with diabetes can take insulin and monitor their diet.

What is the prognosis for a person with Polyglandular Autoimmune Syndrome Type 1?

The prognosis for a person with PAS-1 varies depending on the number and severity of his or her symptoms. Early detection of the disease and its component symptoms is important for preventing life-threatening scenarios. With careful monitoring, it is possible to have a normal or near-normal lifespan. Women with PAS-1 can give birth, and men with PAS-1 can father healthy children.

Pompe Disease

Available Methodology: sequencing with copy number analysis.
Gene: GAA.
Exons Sequenced: NM_000152:2-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
98%	Hispanic
>99%	Middle East
>99%	Native American
98%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
98%	Southern Europe

What is Pompe Disease?

Pompe disease, also known as glycogen storage disease type II, is an inherited disorder whose primary symptom is progressive weakness in the muscles used for mobility and breathing. In infants with Pompe disease, the heart muscles are often severely affected as well. These symptoms are caused by a mutation in an enzyme called alpha-glucosidase (also called maltase) that breaks down glycogen, a stored form of sugar used for energy. As a result, glycogen builds up in the body, notably in the muscles, and damages individual cells.

There are two main types of Pompe disease: infantile-onset and late-onset forms. The severity of symptoms, age at which symptoms begin, and rates of disease progression are related to the degree of alpha-glucosidase deficiency.

INFANTILE-ONSET FORM

The infantile form is the most common and most severe type of Pompe disease. Babies with the disease may appear normal at birth, but begin to show symptoms in the first few months of life. They develop general muscle weakness and poor muscle tone, which causes their bodies to seem limp as they are unable to move, hold up their heads, or feed. They fail to gain weight and grow at the expected rate. Breathing problems can be compounded by lung infections. These infants have enlarged hearts and livers, and many also have enlarged tongues. The disease progresses rapidly and most infants with Pompe disease will die within the first year of life, often from heart or lung failure. In people with the infantile form of the disease, alpha-glucosidase is either entirely missing or inactive.

LATE-ONSET FORM

The late onset form of Pompe disease is due to a partial deficiency in alpha-glucosidase. Symptoms can begin at any time, from childhood to adulthood. In this form of the disease, muscle weakness eventually leads to breathing problems and death from lung failure. The heart may be involved, but it will not be enlarged. These people will lose mobility and eventually require a wheelchair or become bedridden. Machines may become necessary in order to breathe.

This form of the disease progresses more slowly, and life expectancy is better than in the infantile-onset form. People who develop symptoms of Pompe disease in late childhood often die in their 20s and 30s. Those who develop symptoms later may experience a slower progression, but unfortunately their lifespan will also be curtailed.

How common is Pompe Disease?

Pompe disease affects roughly 1 in 100,000 people. The infantile-onset form is the most common type of Pompe disease.

How is Pompe Disease treated?

In 2006, the FDA approved an enzyme replacement therapy called Myozyme for people with Pompe disease. Myozyme has been shown to decrease heart size, maintain normal heart function, and improve muscle tone and strength in people with the infantile-onset form of the disease. It is too soon to gauge how it will affect people with the disease long-term.

Adults and children with Pompe disease are often prescribed a protein-rich diet and a daily exercise regimen to help muscle tone and strength. They must also carefully monitor and treat lung infections.

What is the prognosis for a person with Pompe Disease?

Babies born with the infantile-onset form of Pompe disease typically die within the first year of life, though enzyme replacement therapy can now prolong that lifespan. For people with the late-onset forms of the disease, lifespan will depend upon the age at which symptoms begin and the degree of alpha-glucosidase impairment. In general, the later in life symptoms develop, the slower they will progress. Unfortunately, this disease will greatly curtail the lifespan of those affected. Most people with Pompe disease will die from lung failure.

PPT1-related Neuronal Ceroid Lipofuscinosis

Available Methodology: sequencing with copy number analysis.
Gene: PPT1.
Exons Sequenced: NM_000310:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is PPT1-related Neuronal Ceroid Lipofuscinosis?

PPT1-related neuronal ceroid-lipofuscinosis (NCL) is an inherited disease that causes degeneration of the brain leading to a progressive loss of mental and motor skills. It can also cause blindness, and typically leads to an early death. In the final stages of the disease, affected individuals will be motionless and in a vegetative state.

There are several forms of NCL, largely differentiated by the gene responsible and the age at which symptoms begin. Mutations in the PPT1 gene typically result in the infantile or juvenile form of NCL.

INFANTILE FORM

The infantile form of NCL (INCL) usually begins to cause noticeable symptoms between the ages of 6 months and 24 months. Initially, infants will show developmental delays and experience seizures or jerking movements. Often these infants will have small heads. Blindness and seizures will be present by 24 months, after which mental functions will deteriorate. The child's movement will become spastic and uncontrolled and he or she will develop dementia.

JUVENILE FORM

The symptoms of juvenile NCL (JNCL), also called Batten disease, often begin between the ages of 4 and 10. These children rapidly lose their vision, which is often the first noticeable symptom. They typically become completely blind within two years. People with JNCL often develop periodic seizures between the ages of 5 and 18.

Between the ages of 8 and 14, mental functions typically decline. Children may have difficulty with speech and show behavioral problems. Some people with JNCL also develop psychiatric problems including disturbed thoughts, attention problems, and aggression. These problems can eventually progress to dementia.

People with JNCL also show a decline in motor function and may have difficulty controlling their own movement.

How common is PPT1-related Neuronal Ceroid Lipofuscinosis?

Approximately 1 in 25,000 people globally are affected by some form of NCL. These diseases are most common in Scandinavian countries, but occur elsewhere as well. In the United States, an estimated 25,000 families are affected by some form of NCL. A subset of all NCLs are caused by mutations in the PPT1 gene. The remainder are caused by mutations in multiple other genes.

INCL is most common in Finland, where 1 in 20,000 births is affected by the disease and 1 in 70 people is a carrier. About half the world's cases of INCL are in Finland. Although many genes may be associated with various forms of NCLs, mutations in the PPT1 gene are frequently seen among the Finnish population.

In Iceland, 7 in 100,000 births are affected by JNCL. Other countries experience fewer cases of JNCL. One study showed 0.7 cases per 100,000 births in Germany.

Exactly how many cases of NCL are caused by mutations in the PPT1 gene is unknown.

How is PPT1-related Neuronal Ceroid Lipofuscinosis treated?

There is no treatment for the underlying cause of NCL. Treatments can only address the symptoms as they arise. Various medications can be useful for treating seizures, poor muscle tone, sleep disorders, mood disorders, excessive drooling, and digestion. In some people, a feeding tube is also helpful.

What is the prognosis for a person with PPT1-related Neuronal Ceroid Lipofuscinosis?

The prognosis for a person with NCL depends upon the type of the disease he or she has. People with INCL or JNCL will become blind and will deteriorate mentally. They will eventually enter a vegetative state and become totally dependent on others to care for them.

Among those with INCL, death usually occurs in childhood.

Among those with JNCL, death usually occurs between one's late teens to 30s.

Primary Carnitine Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: SLC22A5.
Exons Sequenced: NM_003060:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Primary Carnitine Deficiency?

Primary carnitine deficiency is a condition in which the body cannot properly process fats into energy. It is caused by a defect in the protein that transports carnitine, a natural substance derived from an amino acid. The condition is typically treatable by the daily use of L-carnitine supplements. However without early detection and treatment, the condition can cause permanent brain damage and may even prove fatal.

If left untreated, primary carnitine deficiency causes a weakening of the heart muscles, leading to a diminished ability to pump blood around the body (cardiomyopathy). Both the heart and liver may become enlarged. It also causes a weakness in skeletal muscles and dangerously low blood sugar (hypoglycemia) that can lead to brain damage. While this brain damage can cause irreversible learning problems or even mental retardation, the remaining symptoms tend to disappear once the person begins taking L-carnitine supplements.

Without supplements, a person with primary carnitine deficiency is particularly vulnerable to "metabolic crisis"-sleepiness, irritability, fever, nausea, vomiting, low blood sugar-when they go long periods without eating or are ill. If the crises are not treated, the child may experience seizures, swelling of the brain, and other life-threatening symptoms.

How common is Primary Carnitine Deficiency?

Primary carnitine deficiency affects approximately 1 in 100,000 newborns and is known to be more common-1 in 40,000-in Japan.

How is Primary Carnitine Deficiency treated?

People with primary carnitine deficiency will need to take supplements of L-carnitine for their entire lives. If these children have begun to experience heart problems or muscle weakness, they can typically reverse those symptoms by taking L-carnitine. A

physician may also recommend that people with primary carnitine deficiency eat more frequently, even if they don't feel hungry. This is particularly important when they are young and/or sick.

What is the prognosis for a person with Primary Carnitine Deficiency?

With regular treatment begun at birth, the prognosis for a person with primary carnitine deficiency is very good. They can typically live normal lives. If treatment is not begun soon enough, these children can experience permanent brain damage, leading to learning difficulties or even mental retardation. Without any treatment, the disease causes numerous serious health problems and would likely be fatal.

Primary Hyperoxaluria Type 1

Available Methodology: sequencing with copy number analysis.
Gene: AGXT.
Exons Sequenced: NM_000030:1-11.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Primary Hyperoxaluria Type 1?

Primary hyperoxaluria type 1 (PH1) is an inherited disease in which the lack of a particular liver enzyme causes the body to accumulate excess amounts of a substance called oxalate. This oxalate leads to a buildup of insoluble calcium salts in the kidneys and other organs. If untreated, it results in life-threatening kidney failure.

People with PH1 are prone to recurrent kidney stones that can lead to kidney failure. Among people with PH1, 50% experience kidney failure by the age of 15, 80% by the age of 30.

In addition to the kidneys, PH1 also leaves insoluble calcium deposits in other body tissues. This can lead to bone pain; vision loss; tingling, numbness, or pain in the extremities; enlargement of the liver and spleen; and problems with the electrical system of the heart (heart block).

Symptoms typically begin between the ages of 1 and 25, with roughly 80% showing signs of the disease in late childhood or early adolescence. Another 10% of people with PH1 show symptoms in early infancy (before the age of 6 months) while the remaining 10% do not show symptoms until their 40s or 50s.

How common is Primary Hyperoxaluria Type 1?

PH1 is quite rare, with estimates placing its frequency worldwide between 1 in 100,000 and 1 in 1,000,000. In Europe, it affects an estimated 1 in 120,000 people. It is thought to be more common in Tunisia, Iran, and Israeli Arab and Druze populations.

How is Primary Hyperoxaluria Type 1 treated?

About half of people with PH1 respond to high doses of vitamin B6, which can reduce the amount of oxalate in the body. In some of these people, the oxalate level can be normalized, while in others it is merely reduced to a healthier level.

People with the condition should drink plenty of water. A physician may prescribe medication or other vitamins to help lower oxalate levels and inhibit the formation of kidney stones.

One important option in treating PH1 is organ transplantation of the liver and kidneys. Because a deficient liver enzyme leads to kidney failure, early liver transplantation may avoid the need to also transplant new kidneys. Kidney replacement alone is not a sufficient treatment as the liver could destroy the new kidneys as well.

People with PH1 should avoid extremely large doses of vitamin C as well as foods high in oxalate, including chocolate, rhubarb, and starfruit.

What is the prognosis for a person with Primary Hyperoxaluria Type 1?

The prognosis for a person with PH1 is variable and depends on how early the disease is detected and treated. Among people with PH1, 50% experience kidney failure by the age of 15, 80% by the age of 30. In more severe cases, children will develop kidney failure between the ages of 3 and 6 and will require organ transplants in order to survive. Early detection and treatment with vitamin B6 can help avoid kidney failure in some cases.

Following organ transplant, some people have lived normal or near-normal lifespans.

Women with PH1 have successfully given birth to healthy babies following a liver/kidney transplant.

Primary Hyperoxaluria Type 2

Available Methodology: sequencing with copy number analysis.
Gene: GRHPR.
Exons Sequenced: NM_012203:1-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Primary Hyperoxaluria Type 2?

Primary hyperoxaluria type 2 (PH2) is an inherited disease in which the lack of a particular liver enzyme causes the body to accumulate excess amounts of a substance called oxalate. This oxalate leads to a buildup of insoluble calcium salts in the kidneys and other organs. If untreated, it can result in life-threatening kidney failure.

People with PH2 are prone to recurrent kidney stones that can lead to kidney failure. The disease has similar symptoms to primary hyperoxaluria type 1 (PH1), but PH2 tends to be a less aggressive form of the disease, even when symptoms start early in life. PH1 and PH2 are caused by different missing liver enzymes.

In addition to the kidneys, PH2 also leaves insoluble calcium deposits in other body tissues, causing problems with bones, eyes, teeth, nerves, and the heart.

Symptoms typically begin between the ages of 1 and 25, with roughly 80% showing signs of the disease in late childhood or early adolescence. Another 10% of people with PH2 show symptoms in early infancy (before the age of 6 months) while the final 10% do not show symptoms until their 40s or 50s.

How common is Primary Hyperoxaluria Type 2?

PH2 is very rare, though its exact incidence is unknown. As of 2002, only 37 individuals with the disease have been described in medical literature.

How is Primary Hyperoxaluria Type 2 treated?

People with the condition should drink plenty of water. A physician may prescribe medications or other vitamins to help lower oxalate levels and inhibit the formation of kidney stones.

While people with PH2 are less likely to develop kidney failure than people with PH1, organ transplantation remains an option if kidney failure does occur. Because a deficient liver enzyme leads to kidney failure, early liver transplantation may avoid the need to also transplant new kidneys. Kidney replacement alone is not a sufficient treatment as the liver could destroy the new kidneys as well.

People with PH2 should avoid extremely large doses of vitamin C as well as foods high in oxalate, including chocolate, rhubarb, and starfruit.

What is the prognosis for a person with Primary Hyperoxaluria Type 2?

The prognosis for a person with PH2 is variable and depends on how early the disease is detected and treated. Some people with the disease will develop kidney failure that may require liver and kidney transplantation. In other cases, hydration and medication will be sufficient to control the disease.

Generally, people with PH2 have a better long-term outcome than people with PH1 and they require fewer surgeries.

Following organ transplant, some people have lived normal or near-normal lifespans.

Primary Hyperoxaluria Type 3

Available Methodology: sequencing with copy number analysis.
Gene: HOGA1.
Exons Sequenced: NM_138413:1-7.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Primary Hyperoxaluria Type 3?

Primary hyperoxaluria type 3 (PH3) is an inherited disease where lack of a particular liver enzyme causes the body to accumulate excess amounts of a substance called oxalate. Oxalate leads to a buildup of insoluble calcium salts in the kidneys. There are three types of primary hyperoxaluria. Unlike types 1 and 2, which can impact other organs, buildup of oxalate in PH3 has not been seen outside of the kidneys.

People with PH3 are at increased risk for developing kidney stones. Symptoms can develop anytime from infancy to adulthood. Approximately 50% of affected individuals developed kidney stones by age 5, but many experience a decrease by adulthood. Some people with the disease do not have symptoms until adulthood. Kidney function can be impacted by frequent kidney stones; however, kidney failure has rarely been reported in individuals with PH3.

How common is Primary Hyperoxaluria Type 3?

Approximately 1 in 165,000 individuals worldwide are expected to be affected with PH3. Reports of higher and lower carrier frequencies have been reported in the Ashkenazi Jewish and African American populations, respectively.

How is Primary Hyperoxaluria Type 3 treated?

People with the condition should drink plenty of water. Intravenous (IV) fluids may be necessary during periods of illness or times of limited fluid intake. A physician may prescribe medication or vitamins to help lower oxalate levels and inhibit the formation of kidney stones. Dietary restriction of foods high in oxalate may be beneficial. Unlike with other type of primary hyperoxaluria, individuals with PH3 rarely require dialysis or kidney/liver transplantation.

What is the prognosis for a person with Primary Hyperoxaluria Type 3?

Individuals with PH3 often have formation of multiple kidney stones, which can be managed by increased fluid intake and supplements. Kidney stone formation in many individuals with PH3 often decrease as they reach adulthood. Thus far, only one individual with PH3 has been reported to have progressed to kidney failure, and transplant is not necessary in most individuals with PH3.

PROP1-related Combined Pituitary Hormone Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: PROP1.
Exons Sequenced: NM_006261:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is PROP1-related Combined Pituitary Hormone Deficiency?

PROP1-related combined pituitary hormone deficiency (CPHD) is an inherited disease that causes a shortage of certain hormones in the body. This typically leaves affected people small in stature and reliant on hormone replacement therapy in order to develop secondary sex characteristics.

The severity of hormone deficiencies can vary from person to person, even among those who share the same disease-causing genetic mutation(s).

Infants with PROP1-related CPHD are often born with a normal height and weight. At some point between the ages of 9 months to 8 years, they fail to grow at the expected rate due to a deficiency in growth hormone. Without treatment, they will be extremely small in stature.

In addition to being deficient in growth hormone, people with PROP1-related CPHD show a deficiency in one or all of the following hormones produced by the pituitary gland: thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, and occasionally adrenocorticotrophic hormone. People with PROP1-related CPHD often develop an underactive thyroid gland in childhood, although the deficiency is usually mild.

People with the disease often have delayed or incomplete development of secondary sex characteristics. They are often infertile. Men usually have a small penis and testes and women may begin to menstruate, but will require hormone replacement in order to avoid early menopause.

There may also be some degree of deficiency in the adrenal gland, leading to symptoms such as persistent weakness, fever, abdominal pain, and weight loss.

PROP1-related CPHD does not affect intelligence.

How common is PROP1-related Combined Pituitary Hormone Deficiency?

PROP1 is one of several genes known to be responsible for CPHD. Combined these genes cause CPHD in roughly 1 in 20,000 people. Among people with CPHD, 30 to 50% have mutations in PROP1.

How is PROP1-related Combined Pituitary Hormone Deficiency treated?

Injections of biosynthetic growth hormone are often begun when PROP1-related CPHD is detected until roughly age 17. The replacement of other hormones is often recommended as their deficiencies are noted.

Hormone replacement can induce the development of secondary sexual characteristics in both boys and girls and it is possible that they will be able to have children.

What is the prognosis for a person with PROP1-related Combined Pituitary Hormone Deficiency?

People with PROP1-related CPHD are typically able to live a normal lifespan.

Pycnodysostosis

Available Methodology: sequencing with copy number analysis.
Gene: CTSK.
Exons Sequenced: NM_000396:2-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Pycnodysostosis?

Pycnodysostosis (PYCD), also spelled pyknodysostosis, is an inherited disease that causes the bones to be abnormally dense while also creating certain bone deformities.

The bones of people with PYCD are brittle and can break easily, even under minimal stress. Fractures are common in affected people's legs, feets, jaws, and collar bone.

People with the disease are abnormally short—less than five feet in height and often much shorter. They are susceptible to a curved spine (scoliosis), and the collarbone is often deformed as well. People with PYCD also have significantly shorter finger bones and their nails are small or absent.

People with pycnodysostosis often have characteristic features including a prominent nose, protruding forehead, and small jaw. Their teeth can be late in coming in, may be missing or irregular, and are prone to cavities. The skull is typically deformed, with the “soft spot” on the top of the head failing to close.

Many scientists believe that 19th-century French painter Henri de Toulouse-Lautrec had PYCD, though the disease was unknown at the time.

How common is Pycnodysostosis?

The frequency of PYCD is unknown, however the disease is very rare.

How is Pycnodysostosis treated?

There is no treatment for the cause of PYCD, however injections of growth hormone have been shown to improve height. Plastic surgery can help correct deformities of the face and jaw.

Dental care will be necessary as people with PYCD are prone to cavities and may be missing teeth. Orthodontia is an option for improving the overall look to the teeth.

People with PYCD need to be careful with their bodies to avoid bone fractures. Exercise should be limited to low-impact activities such as swimming.

What is the prognosis for a person with Pycnodysostosis?

The prognosis for a person with PYCD is generally good. He or she will be prone to fractures, but with care, lifespan can be normal or near-normal.

Pyruvate Carboxylase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: PC.
Exons Sequenced: NM_022172:2-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Pyruvate Carboxylase Deficiency?

Pyruvate carboxylase (PC) deficiency is an inherited enzyme defect that leads to an accumulation of lactic acid and other metabolites in the blood. The build up of these substances can affect the nervous system and cause organ damage. There are three different forms of this condition.

INFANTILE FORM (TYPE A)

The infantile form of PC deficiency presents with developmental delays, failure to thrive, low muscle tone, and seizures. The build up of lactic acid (lactic acidosis) can cause vomiting and difficulty breathing, especially after illness or periods of fasting. Type A is most common in North America, specifically in those of Native American ancestry.

SEVERE NEONATAL FORM (TYPE B)

The severe neonatal form of PC deficiency presents shortly after birth with low blood sugar, severe lactic acidosis, enlarged liver, seizures, low muscle tone, and abnormal movements. Type B is most common in people of European descent, especially France, England, and Germany.

INTERMITTENT/BENIGN FORM (TYPE C)

The intermittent/benign form of PC deficiency is the mildest form of the condition. Affected individuals may have normal neurologic development or mild delays and slightly increased levels of lactic acid.

How common is Pyruvate Carboxylase Deficiency?

Overall, pyruvate carboxylase deficiency is rare, with an estimated 1 new case in every 250,000 births. Type A, however, is more frequent in the Native American population (Algonquin-speaking tribes) with as many as 1 in 10 individuals carrying one mutated copy of the gene (a carrier). Type C has only been reported in a small number of individuals in general.

How is Pyruvate Carboxylase Deficiency treated?

There is no cure for pyruvate carboxylase deficiency, but management involves a high carbohydrate- high protein diet, hydration, and correction of the biochemical abnormalities via supplementation. Fasting and a high fat- low carbohydrate (ketogenic) diet should be avoided, as this can worsen symptoms.

What is the prognosis for a person with Pyruvate Carboxylase Deficiency?

Children with the infantile form generally live into early childhood, while the severe neonatal form leads to death within the first few months of life. Individuals with the intermittent/benign form would be expected to live a normal lifespan with limited symptoms.

Rhizomelic Chondrodysplasia Punctata Type 1

Available Methodology: sequencing with copy number analysis.
Gene: PEX7.
Exons Sequenced: NM_000288:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Rhizomelic Chondrodysplasia Punctata Type 1?

Rhizomelic chondrodysplasia punctata type 1 (RCDP1) is an inherited disease that causes small physical size, certain characteristic bone problems, mental disability, and cataracts. Most children with the classic form of RCDP1 do not live beyond the age of 10, and some will die in infancy. There is also a mild form of the disease, but it is less common.

CLASSIC FORM

Children with the classic form of RCDP1 typically have shortened arm and leg bones. They are often born smaller than average and fail to grow at the expected rate, leaving them much smaller than normal children. The cartilage in children with RCDP1 typically has round or oval areas of calcification. Affected children have stiff, painful joints which may lose the ability to bend normally. They will also have characteristic facial features.

Children with this disease are often severely mentally disabled and fail to develop skills beyond the level of a normal six month-old. The majority also develop seizures.

Other symptoms that may be seen include rough and scaly skin, a cleft palate, and malformations of the spinal column. These children usually develop cataracts early in life that obscure their vision. Most have recurrent lung infections which can be life-threatening.

MILD FORM

In the mild form of the disease, mental and growth disability are less severe. Some have shortened limbs while others do not. All children with this form of the disease have areas of calcification in their cartilage and cataracts.

How common is Rhizomelic Chondrodysplasia Punctata Type 1?

Fewer than 1 in 100,000 infants worldwide is affected by RCDP1. The disease affects children of every ethnicity, however one common mutation known as L292X is most common in Caucasians of Northern European descent.

How is Rhizomelic Chondrodysplasia Punctata Type 1 treated?

There is no cure for RCDP1. Surgery to remove cataracts can restore some vision. Physical therapy may help preserve movement. Other bone surgery may also be helpful. Many children with the disease require a feeding tube. Their lung function must be closely monitored to avoid infection and choking hazards.

Those with milder forms of the disease may benefit from a specialized diet.

What is the prognosis for a person with Rhizomelic Chondrodysplasia Punctata Type 1?

The prognosis for a child with the classic form of RCDP1 is poor. Many die in the first or second year of life, and few survive beyond the age of 10. Breathing problems are often the cause of death.

Those with milder forms of the disease may live longer, however there have been relatively few known cases with which to determine average longevity.

RTEL1-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: RTEL1.
Exons Sequenced: NM_032957:2-35.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are RTEL1-related Disorders?

The *RTEL1* gene is associated with two disorders called Hoyeraal-Hreidarsson syndrome and dyskeratosis congenita. These inherited disorders impair the proper maintenance of chromosome ends (telomeres) and DNA repair leading to a wide variety of symptoms.

Hoyeraal-Hreidarsson syndrome (HHS) is associated with growth restriction in utero and after birth, a small or missing cerebellum (part of the brain that coordinates movement), severe developmental delay, microcephaly (small head size), and immunodeficiency as a result of bone marrow failure. Most individuals with HHS die in childhood as a result of these symptoms.

Dyskeratosis congenita (DKC) is clinically less severe than HHS and is characterized by three main symptoms: abnormal skin coloring specifically in the upper body, leukoplakia (white patches on the tongue and inside of the mouth), and abnormal nails of the fingers and toes. Other symptoms of DKC include short stature, dental abnormalities, fibrosis (thick scarring) in the lungs and liver, narrowing of the esophagus, narrow urethra (typically only in males), osteoporosis (weak or brittle bones), progressive bone marrow failure, and cancer (most commonly leukemia). Progressive bone marrow failure and cancer are the most common causes of death. Most people with DKC have normal intelligence and development, but there are reports of individuals who are more severely affected may have varying degrees of intellectual disability or developmental delay. These symptoms are variable, as not all individuals with DKC will have the same presentation. Mutations in *RTEL1* make up to 2-8% of all cases of DKC.

How common are RTEL1-related Disorders?

Approximately 1 in 100 individuals in the Ashkenazi Orthodox and 1 in 222 individuals in the Ashkenazi Jewish population are reported to be carriers for a mutation in the *RTEL1* gene. In the general population, RTEL1-related disorders affect about 1 in 1,000,000 individuals.

How are RTEL1-related Disorders treated?

There is no cure for RTEL1-related disorder. Regular screening for bone marrow failure and leukemia is recommended with hematopoietic stem cell transplantation used as a treatment option if needed. Annual pulmonary function tests to assess for fibrosis as well as periodic follow-up with a multidisciplinary team of specialists is recommended to assess for other symptom development.

What is the prognosis for a person with an RTEL1-related Disorder?

The prognosis for an individual with HHS is typically poor as it often leads to early bone marrow failure and premature death in childhood. The prognosis for an individual with DKC is variable and is dependent on the severity. The average life expectancy is about 30 years, although many die around the age of 15 as a result of bone marrow failure, lung complications, or cancer.

Salla Disease

Available Methodology: sequencing with copy number analysis.
Gene: SLC17A5.
Exons Sequenced: NM_012434:1-11.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
>99%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is Salla Disease?

Salla disease, also called free sialic acid storage disease, is an inherited condition causing a slow, progressive decline in motor and mental skills. Adults with the disease are profoundly disabled, but live normal lifespans. Salla disease belongs to a group of diseases known as lysosomal storage disorders.

Children with Salla disease appear normal at birth, but show poor muscle tone in the first year of life. Delays in their motor and mental skills become more obvious with age. They become spastic and will have difficulty coordinating their voluntary movements. Most will be able to walk in adulthood, though some cannot.

Loss of intellect is progressive over time, beginning in the first or second year of life. Children with Salla disease typically have delayed language skills. By adulthood, all people with Salla disease have profound intellectual and developmental disabilities with IQs between 20 and 40. Most can speak some words in short sentences.

In a more severe form of Salla disease, also called intermediate severe Salla disease, symptoms appear between the ages of 1 and 6 months. Infants have extremely poor muscle tone, growth delay, and may have seizures. Their loss of motor and mental functions are more rapid, and lifespan may be shortened.

How common is Salla Disease?

Salla disease is rare except in Northern Finland, where 1 in 40 people are carriers. Only 30 cases of intermediate severe Salla disease have been documented outside of Finland.

How is Salla Disease treated?

There is no effective treatment for Salla disease other than to address symptoms as they arise. Special education or physical, occupational, or speech therapy may be helpful.

What is the prognosis for a person with Salla Disease?

People with Salla disease have normal lifespans, but all will be profoundly disabled and will have difficulty with movement. Most will be able to walk, but some will not.

Those with the severe form of Salla disease will have a reduced lifespan. The small number of cases known worldwide make an exact prognosis difficult.

Sandhoff Disease

Available Methodology: sequencing with copy number analysis.
Gene: HEXB.
Exons Sequenced: NM_000521:1-14.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
>99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
>99%	Southern Europe

What is Sandhoff Disease?

Sandhoff disease is an inherited, lysosomal storage disorder caused by the absence or deficiency of two enzymes; hexosaminidase A and hexosaminidase B. These enzymes are located in lysosomes, which are structures in cells that normally break down certain substances and act as recycling centers. Without these critical enzymes, a fatty substance, called GM2 ganglioside, and other molecules accumulate at harmful levels and cause progressive destruction of the nerve cells. Symptoms of the condition vary based on the form of presentation.

INFANTILE (CLASSIC) FORM

The most common and severe form of Sandhoff disease appears in infancy. Infants with this disorder typically appear normal until the age of 3 to 6 months, when their development slows and muscles used for movement weaken. Affected infants lose motor skills such as turning over, sitting, and crawling. They also develop an exaggerated startle reaction to loud noises. As the disease progresses, children with Sandhoff disease experience seizures, vision and hearing loss, intellectual disability, and paralysis. An eye abnormality called a cherry-red spot is characteristic of this disorder. Some affected children also have enlarged organs (organomegaly) or bone abnormalities.

JUVENILE-ONSET FORM

A milder, more rare form of Sandhoff disease occurs when a person has mutations that only cause a partial enzyme deficiency. Signs and symptoms vary widely and can begin in childhood or adolescence. Affected individuals may experience muscle weakness, difficulty coordinating movement, speech problems, recurrent respiratory infections, and seizures.

LATE-ONSET FORM

The late-onset form can be difficult to diagnose. Early signs can include clumsiness and muscle weakness in the legs. Over time, people with late-onset Sandhoff disease may require mobility assistance and experience speech and swallowing difficulties. About 40% of affected adults experience mental illness, such as bipolar disorder or psychotic episodes.

How common is Sandhoff Disease?

One large U.S. population study estimated that the carrier frequency for Sandhoff disease is approximately 1 in 300 in non-Jewish individuals and less common (1 in 500) in those of Jewish descent. Clusters of cases have been reported in certain regions, such as locales of Canada, Argentina, Lebanon, and Central America, suggesting that the carrier frequency may be higher in some specific isolated populations.

How is Sandhoff Disease treated?

There is no specific treatment or cure for Sandhoff disease. Treatment includes supportive care for symptoms, such as medications to control seizures and nutritional and respiratory support.

What is the prognosis for a person with Sandhoff Disease?

Children with the severe infantile-onset form will typically experience recurrent seizures by age 2 and will eventually lose muscle function, mental function, and sight, becoming mostly non-responsive to their environment. Death usually occurs by age 3 and is generally caused by respiratory infections. Children with juvenile-onset Sandhoff disease will show similar health problems but at an older age and will also progressively decline. Though challenging and debilitating, the late-onset form does not always shorten life span.

Segawa Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: TH.
Exons Sequenced: NM_000360:1-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Segawa Syndrome?

Segawa syndrome, also called dopa-responsive dystonia, is an inherited disease that can cause physical rigidity and developmental delay. There are two forms: mild and severe.

In the mild form, symptoms typically begin in childhood. Children develop jerky movements that quickly progress to physical rigidity. These children show spastic movements, and make very little voluntary movement. If untreated, children with Segawa syndrome may have expressionless faces, drooping eyelids, tongue tremors, and drooling problems. They will show both intellectual and physical developmental delays. Some children with Segawa syndrome show a diurnal pattern, meaning their symptoms tend to be less severe early in the day and more severe late in the day. With early treatment, children with Segawa syndrome can avoid many or all of the disease's symptoms.

The severe form of the disease will appear in infancy, usually before six months of age. Affected infants have delayed motor skills, weakness in the chest and abdomen, rigidity in the arms and legs, and problems with movement. These children will eventually have learning disabilities, problems with speech, and behavioral/psychological problems. In addition, some people with the disease have problems with their autonomic nervous system, which regulates unconscious functions such as body temperature regulation, digestion, blood sugar level, and blood pressure. Treatment of the severe form of the disease is often less successful.

Segawa syndrome is caused by a deficiency in an enzyme called tyrosine hydroxylase. Without it, the amino acid tyrosine cannot properly be converted to dopamine, a key neurotransmitter in the brain. Dopamine is important for many functions, including muscle control and cognition.

Note that there is another type of Segawa syndrome with a different genetic basis that is not addressed here.

How common is Segawa Syndrome?

The prevalence of Segawa syndrome is unknown, and only a small number of cases have been diagnosed globally. Cases have been reported in Japan and in the Netherlands.

How is Segawa Syndrome treated?

Individuals with the mild form of Segawa syndrome respond well to treatment with supplements of L-dopa and carbidopa. If taken before symptoms appear, the symptoms may be avoided completely. Even if symptoms have already begun, children with the disease often respond extremely well to the medication. If the disease has gone untreated for some time, certain symptoms may remain, including an irregular gait and other mild movement and speech difficulties.

Treatment with L-dopa and carbidopa supplements has been less beneficial for individuals with severe Segawa syndrome, but this treatment may improve motor skills over time.

If symptoms have gone untreated, physical, occupational, and/or speech therapists may prove helpful.

What is the prognosis for a person with Segawa Syndrome?

With early and consistent treatment, the prognosis for a person with mild Segawa syndrome is good. Many symptoms can be reversed with treatment. If treatment is not begun early and/or the course of the disease is severe, the person may be shorter than they would otherwise have been and may have an irregular walk and/or learning disabilities.

Short Chain Acyl-CoA Dehydrogenase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: ACADS.
Exons Sequenced: NM_000017:1-10.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Short Chain Acyl-CoA Dehydrogenase Deficiency?

Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is an inherited disease in which the body cannot turn certain fats (known as short-chain fatty acids) into energy due to a deficient enzyme. Its symptoms can be triggered by illness or long periods without food.

Infants affected by the disease may display episodes of vomiting, low blood sugar, and fatigue. These episodes can be fatal. Affected infants may have difficulty feeding and fail to grow at the expected rate. Some show poor muscle tone, seizures, and small head size. If the disease is untreated, the child may show developmental delays and permanent learning difficulties.

Some people with SCAD deficiency do not display any symptoms until adulthood. In these cases, the main symptom is chronic muscle weakness. Some may experience periods of pain, nausea, and shortness of breath. It is thought that many cases are so mild that they are never diagnosed.

SCAD deficiency belongs to a group of diseases known as fatty acid oxidation disorders.

How common is Short Chain Acyl-CoA Dehydrogenase Deficiency?

SCAD deficiency affects 1 in every 40,000 to 100,000 newborns. Researchers have hypothesized that this disease may be more common because some people with the disease are asymptomatic or have mild symptoms.

How is Short Chain Acyl-CoA Dehydrogenase Deficiency treated?

It is critical that people with SCAD deficiency avoid going long periods of time without food. Infants and children with SCAD deficiency may require feedings at regular intervals throughout the night. A cornstarch paste is often recommended to provide a sustained release of energy between meals. Foods high in carbohydrates and low in fat are also recommended. During times of illness, dietary

rules must be very carefully followed. If the child cannot eat food for any reason, intravenous glucose must be administered promptly.

Some physicians recommend carnitine supplements for people with SCAD deficiency.

What is the prognosis for a person with Short Chain Acyl-CoA Dehydrogenase Deficiency?

The prognosis for a person with SCAD deficiency varies widely and depends upon the severity of his or her symptoms. In some cases, infants with the disease can die early in life. The prognosis for those who live into adolescence and adulthood and/or develop symptoms of muscle weakness later in life is not known. Some people with the mutations that cause this disease do not develop symptoms, or have mild undiagnosed symptoms.

Sjogren-Larsson Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: ALDH3A2.
Exons Sequenced: NM_000382:1-10.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Sjogren-Larsson Syndrome?

Sjogren-Larsson syndrome (SLS) is an inherited condition with symptoms including dry, thickened, scaling skin (ichthyosis), spastic movement in the legs, and intellectual and developmental disabilities.

People with SLS cannot properly break down molecules called fatty aldehydes. The accumulation of these and related molecules results in the symptoms of SLS.

Children with SLS are often born several weeks prematurely and the majority either have ichthyosis at birth or develop it in the first few months of life. Most of the remainder will develop this symptom within the first year of life. People with SLS will have thicker than normal skin that frequently itches. Scales on the skin can range in form from fine particles to large plate-like scales and they may be dark in color. Often the facial skin is unaffected.

Within the first two years, the nervous system often shows signs of the disease. These signs may include developmental delay, speech abnormality, and seizures. Many people with the disease have mild to moderate intellectual disability. In terms of mental development, people with SLS do not worsen over time and can learn new skills.

Many people with SLS have spastic movement in their legs and the majority never learn to walk. They may also lose mobility in the joints of their lower body, contributing to motor problems. Spastic movement can also affect the arms. Overall, people with SLS tend to be shorter than average.

Some people with SLS are extremely sensitive to bright light and many have glistening white dots in the retina of the eye.

How common is Sjogren-Larsson Syndrome?

The disease is most common in Sweden, where an estimated 0.4 out of 100,000 are affected by it. In northern Sweden, 1% of the population is a carrier of the disease.

Cases of SLS have been seen in people of all ethnicities. It is rare, though its exact frequency is unknown.

How is Sjogren-Larsson Syndrome treated?

There is no treatment for the root cause of SLS, but its symptoms can be addressed.

Treatments for the skin problems caused by ichthyosis include daily baths, moisturizing creams, and creams or lotions with active ingredients that slough off dead skin cells. Drugs called retinoids may improve skin condition, although they are not often used in children. Recent research has shown that a drug called zileuton can help reduce skin itching associated with SLS, but it is not yet FDA approved for this purpose. Some studies suggest that eating a diet with limited fats and taking medium-chain triglyceride supplements can help ichthyosis, but the evidence so far has been mixed.

If a person with SLS has seizures, these usually can be controlled with anti-seizure medication.

Physical therapy may help build or regain motor skills including walking. Surgery may help reduce the spastic movements of the leg. Mechanical braces or other aids may be useful in helping people with SLS to walk.

What is the prognosis for a person with Sjogren-Larsson Syndrome?

With good medical care, most people with SLS survive into adulthood. Their life expectancy may be related to the degree of neurological symptoms.

Smith-Lemli-Opitz Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: DHCR7.
Exons Sequenced: NM_001360:3-9.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Smith-Lemli-Opitz Syndrome?

Smith-Lemli-Opitz syndrome, or SLO syndrome, is an inherited disorder in which the body's ability to make cholesterol is impaired due to a deficient enzyme. Cholesterol is critical for the structure of cells, and is necessary for normal fetal development. It also plays an important role in the production of hormones and digestive acids. In addition to low cholesterol levels, SLO syndrome also causes toxic byproducts of cholesterol production to build up throughout the body, further disrupting growth and development.

In children with little or no ability to make cholesterol, symptoms are severe. These infants are commonly born with an abnormally small head, cleft palate, and weak muscle tone. They often have difficulty feeding because they lack the sucking reflex or have an abnormally small stomach that causes persistent vomiting. Some have extra fingers or toes as well as the typical fused second and third toes on both feet. Male infants may have deformed or underdeveloped genitalia.

Infants with the severe form of SLO syndrome grow slowly and 90% have moderate to severe mental disability. Severely affected infants may also have heart defects and problems with their kidneys, causing death in the first months of life.

Some children are born with a milder form of the condition in which the body can produce some cholesterol. Symptoms may include developmental delays, feet with the second and third toes fused together, slow growth, and short stature. These children generally learn to walk and talk and can acquire other skills, although they can rarely live independently as adults. Adults with the disease often show aggressive behavior.

Symptoms of the disease can vary from person to person. Some affected people have only minor symptoms of the condition.

How common is Smith-Lemli-Opitz Syndrome?

Smith-Lemli-Opitz syndrome affects an estimated 1 in 20,000 to 60,000 people. This disease is more common in those of European ancestry, particularly those in Slovakia and the Czech Republic. It is very rare among people of African and Asian descent.

How is Smith-Lemli-Opitz Syndrome treated?

There is no cure for SLO syndrome, but its symptoms can be addressed. The primary treatment is to supplement the person's diet with large amounts of dietary cholesterol, either in the form of purified cholesterol or in foods such as egg yolks and cream. This has been shown to improve symptoms. Early intervention and therapy helps with speech and physical disabilities. Medication may treat symptoms such as vomiting, constipation, and gastroesophageal reflux. Surgery and orthotics can help muscle spasms and improve mobility.

Because the condition can cause extreme sun sensitivity, people with SLO syndrome should always wear sunblock, sunglasses, and appropriate clothing when they go outdoors.

What is the prognosis for a person with Smith-Lemli-Opitz Syndrome?

Although serious internal malformations can lead to early death, with good nutrition and medical care many people with SLO syndrome can have a normal lifespan. Mental disability typically prevents people from living independently.

Spastic Paraplegia Type 15

Available Methodology: sequencing with copy number analysis.
Gene: ZFYVE26.
Exons Sequenced: NM_015346:2-42.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Spastic Paraplegia Type 15?

Hereditary spastic paraplegias are a group of disorders that cause progressive muscle stiffness (spasticity) in the lower limbs that leads to paralysis (paraplegia). Complex hereditary spastic paraplegias, such as spastic paraplegia type 15 (SPG15), impact the lower limbs and also cause neurological impairment, which may include intellectual disability or dementia. Less commonly, some affected individuals also have vision and hearing problems.

Onset of symptoms in SPG15 typically occurs in childhood or adolescence and the first symptom is often either leg stiffness or intellectual disability. Neurological symptoms may include learning difficulties and intellectual disability, structural brain malformations (e.g., thinning of the tissue that connects the left and right halves of the brain, the corpus callosum), loss of nerve cells in different parts of the brain, involuntary movements, and dementia. These issues may be progressive. Additional symptoms may include numbness, tingling or pain in the arms and legs, problems with muscle movements and reflexes, and issues with bladder control. Some individuals with SPG15 also have problems with the retina in the eye, which can cause visual impairment. The severity of each of these symptoms is variable in affected individuals.

How common is Spastic Paraplegia Type 15?

The worldwide frequency of SPG15 has not been established. It is estimated that autosomal recessive hereditary spastic paraplegias occur in approximately 1 in 50,000 births. SPG15 has been reported to account for 3 to 15% of all cases of autosomal recessive hereditary spastic paraplegias, depending on region. In areas where consanguinity (relatedness between parents of offspring) is common, the frequency of cases is likely higher.

How is Spastic Paraplegia Type 15 treated?

There is no cure for the underlying cause of this condition. SPG15 is treated symptomatically and may include physical therapy, occupational therapy, and devices to assist with walking or use of a wheelchair. Various medications may be used to reduce muscle stiffness and pain. Patients with hearing impairment may use a hearing device.

What is the prognosis for a person with Spastic Paraplegia Type 15?

Individuals with SPG15 typically have progressive spasticity that will often necessitate assistance with walking or a wheelchair approximately 15 years after the diagnosis. Remaining outcomes will vary based on the severity of symptoms. However, this condition is not expected to shorten lifespan.

Spinal Muscular Atrophy

Available Methodology: spinal muscular atrophy.
Gene: SMN1.
Variant (1): SMN1 copy number.

Detection Rate	Population
71%	African American
94%	Ashkenazi Jewish
93%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
91%	Hispanic
92%	Middle East
93%	Native American
95%	Northwestern Europe
93%	Oceania
93%	South Asia
93%	Southeast Asia
94%	Southern Europe

What is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a disease in which certain nerves in the brain and spinal cord die, impairing the person's ability to move. Called motor neurons, these nerves control our ability to sit up, crawl, and walk. In severe cases, a person will not be able to sit up independently and their breathing and swallowing may also be impaired. In the mildest cases, symptoms begin in adulthood and make independent movement such as walking more difficult, but still possible. There are five main subtypes of spinal muscular atrophy, each described below. It is not always possible to predict which type of SMA a child could have based on the genetic mutation he or she inherits. This is true of the mutation (exon 7 deletion) for which Counsyl tests.

TYPE 0

Type 0 is the most severe form of SMA. Symptoms can often be seen in the later stages of pregnancy as the fetus is less active than expected. Once born, the infant will have little ability to move and may not be able to breathe and swallow independently. Infants with type 0 SMA often die before the age of 6 months.

TYPE I – ALSO CALLED WERDNIG-HOFFMANN DISEASE

Type I is another severe form of the disease. Symptoms develop within the first six months of life. Infants with SMA type I often have trouble breathing and swallowing. Their muscle tone and strength are extremely poor; they cannot sit up without support and will not meet any motor skills milestones. Their intellect, however, is normal. Most children with type I SMA will die before the age of two.

TYPE II – ALSO CALLED DUBOWITZ DISEASE

In children with type II SMA, muscle weakness becomes apparent between the ages of 6 and 12 months. When placed in a sitting position, people with type II SMA can usually maintain the position without support, however they often lose this ability by their mid-teens. People with SMA type II cannot stand or walk without assistance. They have poor muscle tone and strength and their fingers usually tremble uncontrollably. Their intelligence is typically normal or above average.

TYPE III – ALSO CALLED KUGELBERG-WELANDER DISEASE

Type III SMA is a milder form of the disease. Its symptoms begin sometime between the age of one year and early adulthood. As young children, they may fall repeatedly and have trouble walking down stairs. While their muscles are weaker than normal, people with type III SMA can usually stand and walk without assistance, although they may lose this ability later in life. The legs are often more severely affected than the arms.

TYPE IV

Type IV is the mildest form of spinal muscular atrophy. With this form of the disease, muscle weakness does not begin until one's 20s or 30s, or even later. This weakness is often mild to moderate, and the person can still walk and move independently. These individuals may experience mild to moderate tremors and/or twitching. The disease typically does not diminish lifespan. With all types of SMA, there can be difficulties in sleeping and gaining weight. Frequent pneumonia is common. A curvature of the spine and stiff joints are also common. Women with milder forms the disease have been known to give birth to healthy children, although many of the pregnancies had complications.The disease is caused by a shortage in SMN protein, which helps preserve motor neurons. Without it, the neurons cannot pass messages from the brain to the muscles of the body.

How common is Spinal Muscular Atrophy?

In the United States, 1 in every 6,000 to 10,000 people develop spinal muscular atrophy and 1 in 50 is a carrier of the disease. It has been found in people of every race, but is most common in Caucasians, of whom 1 in 35 is a carrier. Carrier rates for other populations include: Ashkenazi Jews (1 in 41 to 62), Asians (1 in 53), African Americans (1 in 66), and Hispanics (1 in 117). Studies done in specific populations have found carrier rates of 1 in 50 in Germany, 1 in 57 in Italy, and 1 in 62 in China.

How is Spinal Muscular Atrophy treated?

There is no cure for spinal muscular atrophy, however some of its symptoms can be addressed.

For children with the more severe forms of spinal muscular atrophy, mechanical breathing aids may prolong lifespan. In some cases, breathing is more difficult at night, leading to a lack of sleep. In those cases, certain types of respiratory assistance may be helpful. If getting enough nutrition is an issue, some people with SMA have turned to feeding tubes.

Those with milder forms of the disease sometimes choose to have surgery to correct curvature of the spine (scoliosis) or joint problems. In forms of the diseases that are fatal in early childhood, these surgeries are often not done.

What is the prognosis for a person with Spinal Muscular Atrophy?

The prognosis for a person with SMA varies greatly depending on which type of the disease he or she has.

TYPE 0

The disease is typically fatal between 2 and 6 months of age. These infants do not develop any motor skills expected of infants their age.

TYPE I

This type of SMA is usually fatal within two years. With mechanical breathing aids, children with type I SMA may live longer. There are a few known cases of SMA type I in which the child survived to adolescence or adulthood.

TYPE II

With type II SMA, 75% of those affected live to the age of 25. They are often able to sit independently when placed in a sitting position, but lose this ability by their mid-teens.

TYPE III

People with type III SMA may live a normal lifespan. Many learn to walk independently, though most lose the ability to do so by their 30s or 40s.

TYPE IV

A normal lifespan is possible for people with type IV SMA. They do not develop symptoms until their 20s or 30s and usually retain the ability to walk independently.

Spondylothoracic Dysostosis

Available Methodology: sequencing with copy number analysis.
Gene: MESP2.
Exons Sequenced: NM_001039958:1-2.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Spondylothoracic Dysostosis?

Spondylothoracic dysostosis (STD) is an inherited condition characterized by skeletal abnormalities of the vertebrae and ribs. For patients with STD, their bones do not form properly resulting in fusion of the ribs to the vertebrae, giving a fan-like appearance. This fusion results in a shortened neck and torso and a small chest. These abnormalities of the upper-body can cause significant breathing complications as the chest in unable to expand correctly. This can be life-threatening. Affected patients have normal length arms and legs, but due to the shortened torso, have short stature. Many patients with STD develop hernias due to the excess pressure placed on the diaphragm when breathing.

Mutations in the *MESP1* gene cause STD and can also cause a related, but thought to be distinct condition, called spondylocostal dystosis type 2 (SCDO2). SCDO2 is thought to be milder than STD, but also more rare. Due to the rarity of SCDO2 the exact characteristics are unknown.

How common is Spondylothoracic Dysostosis?

Spondylothoracic dysostosis affects approximately 1 in 200,000 people worldwide. The condition is more common in Puerto Rico where 1/12,000 people are affected.

How is Spondylothoracic Dysostosis treated?

There is no cure for STD, and treatment focuses on symptoms as they arise. Infants usually require mechanical help to breathe. Hernias are repaired as necessary. Respiratory and cardiac function, as well as growth and development, are monitored by physicians.

What is the prognosis of a person with Spondylothoracic Dysostosis?

Generally the prognosis for a person with STD is poor. Approximately half of all patients die in infancy from respiratory failure. Of those who survive infancy, prognosis is good with minimal medical complications and normal intelligence.

Steroid-resistant Nephrotic Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: NPHS2.
Exons Sequenced: NM_014625:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Steroid-Resistant Nephrotic Syndrome?

Steroid-resistant nephrotic syndrome type 2 is a disease that causes significant abnormalities in kidney function, often leading to kidney failure.

The age at which symptoms begin varies; in some cases, symptoms have begun before age 2 while in others, symptoms did not appear until later in childhood.

Symptoms include an excess of protein in the urine, a shortage of protein in the blood, an excess of cholesterol and triglycerides in the blood, and generalized swelling in the body tissues. The water-retention that causes swelling can also cause weight gain and high blood pressure. The disease can cause scar tissue to form in the kidney's glomeruli, which are structures responsible for filtering waste products. This is known as focal segmental glomerulosclerosis.

The disease typically leads to kidney failure, necessitating transplantation in many before the age of 20. Even after receiving a kidney transplant, symptoms of the disease can recur. It is described as "steroid-resistant" because unlike other forms of nephritic syndrome, it does not respond to steroid medications.

The disease is caused by a mutation in the gene that provides the instructions for making podocin, a protein used by the kidney's glomeruli.

How common is Steroid-Resistant Nephrotic Syndrome?

The frequency of steroid-resistant nephritic syndrome type 2 is unknown. Several cases have been reported among Israeli-Arab children, however it has been found in other populations as well.

How is Steroid-Resistant Nephrotic Syndrome treated?

The goal of treatment is to minimize damage to the kidneys, partially by controlling blood pressure. Medication may also be required for high cholesterol. Often children with steroid-resistant nephritic syndrome require kidney transplants. They many also need medication to control for infection.

What is the prognosis for a person with Steroid-Resistant Nephrotic Syndrome?

The prognosis for a person with steroid-resistant nephritic syndrome type 2 is varied, however with transplantation and careful medical management, these children can live into adulthood.

Sulfate Transporter-related Osteochondrodysplasia

INCLUDING ACHONDROGENESIS TYPE 1B, DIASTROPHIC DYSPLASIA, AND RECESSIVE MULTIPLE EPIPHYSEAL DYSPLASIA

Available Methodology: sequencing with copy number analysis.
Gene: SLC26A2.
Exons Sequenced: NM_000112:2-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Sulfate Transporter-Related Osteochondrodysplasia?

Sulfate transporter-related osteochondrodysplasias are a group of inherited diseases caused by mutations in a gene important in cartilage and bone formation, called SLC26A2. These diseases include: achondrogenesis type 1B, diastrophic dysplasia, and recessive multiple epiphyseal dysplasia.

Achondrogenesis type 1B

Achondrogenesis type 1B (ACG1B) is a severe skeletal disease that is fatal either before or shortly after birth.

Infants born with the disease have extremely short arms, legs, fingers, and toes. The fingers and toes may be rotated inward. Infants with the disease also tend to have flat faces, protruding abdomens, narrow chests, and short necks that show thickening of the soft tissue. Many are born with hernias.

Fetuses with ACG1B are often in the breech position, “upside-down” with their feet toward the birth canal. Mothers of fetuses with ACG1B are prone to certain other pregnancy complications.

Diastrophic dysplasia

Diastrophic dysplasia, also called diastrophic dwarfism, causes a person to be extremely small in stature. It also causes joint pain, difficulty with movement, and bone and joint abnormalities.

People with diastrophic dysplasia have very short arms and legs, although their skulls are often normally sized. They are often born with bone deformities such as club foot, cleft palate, a curved spine, and "hitchhiker thumbs" which are bent back. The outside of the ears are often swollen at birth and this can result in abnormal-looking ears later in life. People with the disease also tend to have small chests and protruding abdomens. The disease can cause breathing problems in infants, particularly due to the small size of the ribcage.

Those with the disease develop joint pain from an early age and have difficulty moving their joints. These symptoms worsen with age. Walking may become difficult for people with the disease. Adult height of people with diastrophic dysplasia often ranges from 3.2 feet to 4.6 feet.

Diastrophic dysplasia does not typically affect intelligence or mental function.

Recessive multiple epiphyseal dysplasia

Recessive multiple epiphyseal dysplasia (rMED) causes bone deformities and joint pain. Unlike people with related diseases, those with rMED typically reach normal height and live normal lifespans.

Half of people with rMED are born with an obvious bone abnormality such as cleft palate, club foot, or an inwardly-curved pinky finger. Some also have a mild curvature of the spine (scoliosis).

All people with the disease develop joint pain, often late in childhood. Pain is most common in the hips and knees but can also occur in the wrists, fingers, and elsewhere.

How common is Sulfate Transporter-Related Osteochondrodysplasia?

ACG1B is very rare, and its frequency is unknown. One particular mutation that causes the disease is most common in Finland, but other mutations are found globally.

Diastrophic dysplasia has been estimated to affect 1 in 100,000 people worldwide. It has been found in people of all ethnicities, but is most common in Finland.

Recessive multiple epiphyseal dysplasia is also rare, but researchers believe it may be more common than realized due to people with mild symptoms who go undiagnosed.

How is Sulfate Transporter-Related Osteochondrodysplasia treated?

There is no treatment for ACG1B. Infants with the disease can only be made as comfortable as possible.

For people with diastrophic dysplasia, the goal of treatment is to improve and maintain mobility while relieving pain. This can be done with a combination of muscle exercises, surgery, and the use of plaster casts to hold childrens' joints in place. In particular, surgery can be used to correct club foot, to reduce compression of the spinal cord, or to correct knee joints. Surgery may need to be repeated as bone deformities tend to re-form after surgery. It is important that people with diastrophic dysplasia do not become obese, as this puts harmful weight on their knee and ankle joints.

Recessive multiple epiphyseal dysplasia is usually treated through a combination of targeted muscle strengthening exercises and non-steroidal anti-inflammatory drugs (NSAIDs). People with the disease should avoid sports and activities that stress their joints. Obesity too can put strain on the joints. In some circumstances, surgery may be useful.

What is the prognosis for a person with Sulfate Transporter-Related Osteochondrodysplasia?

The prognosis for an infant with ACG1B is poor. They will die before or shortly after birth.

Infants with diastrophic dysplasia rarely face life-threatening breathing problems. Most people with diastrophic dysplasia live into adulthood. All will face physical challenges with walking and other movement, and may rely on various mechanical aids for mobility. They usually have normal intelligence and mental function.

People with recessive multiple epiphyseal dysplasia can live normal lifepans and can perform most daily activities, provided these don't stress the joints. Despite joint pain and some bone and joint abnormalities, people with rMED can live normal, healthy lives.

TGM1-related Autosomal Recessive Congenital Ichthyosis

Available Methodology: sequencing with copy number analysis.
Gene: TGM1.
Exons Sequenced: NM_000359:2-15.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is TGM1-related Autosomal Recessive Congenital Ichthyosis?

TGM1-related autosomal recessive congenital ichthyosis (ARCI) is a genetic skin condition caused by a disruption in the proper formation of proteins that are found in the outer layer of the skin (epidermis). *TGM1* accounts for 38%-55% of ARCI.

Infants with this disorder typically are born with a tight, clear covering over their skin called a collodion membrane. This membrane usually dries up and peels off in the first few weeks of life, leaving scaly skin. The eyelids and lips are turned outward (ectropion). Some newborns will have contractures of their fingers. Generally, individuals with TGM1-related ARCI have large, dark scales that cover most of their skin. Infants will commonly develop infections, and are at risk for dehydration and respiratory problems. Affected individuals may also have hair loss (alopecia), a decreased ability to sweat (hypohidrosis), increased sensitivity to heat and thick skin on their hands and feet.

How common is TGM1-related Autosomal Recessive Congenital Ichthyosis?

TGM1-related ARCI is thought to occur in less than 1 in 200,000 people worldwide. Although the data is somewhat limited, increased incidence of TGM1-related ARCI has been reported in Norway (1 in 91,000 individuals), Spain, and Southern India.

How is TGM1-related Autosomal Recessive Congenital Ichthyosis treated?

Treatment for newborns with TGM1-related ARCI generally requires a moist environment and minimizing the risk for infections and immediate treatment of infections. Topical petrolatum-based creams and ointments are used to keep the skin soft and hydrated. As affected individuals grow, daily use of petroleum or lanolin based creams, long baths to help with lubrication, and alpha-hydroxy acid treatments are required. For those with a severe form of the disease, oral retinoids may be indicated. Additionally, all affected individuals require continued surveillance for respiratory infection and dehydration.

What is the prognosis for a person with TGM1-related Autosomal Recessive Congenital Ichthyosis?

Individuals affected with TGM1-related ARCI generally have a good prognosis with early treatment. The disease will usually remain stable over the lifetime of the affected individual. In the newborn period, the risk for infection (sepsis) is great, therefore it is important that appropriate therapies be initiated immediately following delivery.

TPP1-related Neuronal Ceroid Lipofuscinosis

Available Methodology: sequencing with copy number analysis.
Gene: TPP1.
Exons Sequenced: NM_000391:1-13.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is TPP1-related Neuronal Ceroid Lipofuscinosis?

TPP1-related neuronal ceroid lipofuscinosis (NCL) is an inherited disease that causes degeneration of the brain leading to a progressive loss of mental and motor skills. It can also cause blindness and typically leads to an early death. In the final stages of the disease, an affected person will be in a vegetative state.

There are several forms of NCL, largely differentiated by the gene that carries the mutation and the age at which symptoms begin. Mutations in the TPP1 gene typically result in the classic late infantile form or juvenile form of NCL.

CLASSIC LATE INFANTILE FORM (LINCL)

The symptoms of classic LINCL typically begin between the ages of 2 and 4. Seizures are often the first sign, followed by a loss of the physical and mental milestones already achieved. Dementia soon follows along with a loss of motor coordination. Children with classic LINCL become blind between the ages of 4 and 6. They are often bedridden after the age of 6 and are unable to take care of themselves. Their life expectancy ranges from 6 to 40, with many succumbing to the disease by their 20s.

JUVENILE FORM (JNCL)

The symptoms of JNCL, also called Batten disease, often begin between the ages of 4 and 10. These children rapidly lose their vision, becoming completely blind within two to four years. People with JNCL often develop periodic seizures between the ages of 5 and 18.

Between the ages of 8 and 14, mental functions typically decline. Children may have difficulty with speech and show behavioral problems. Some people with JNCL also develop psychiatric problems including disturbed thoughts, attention problems, and aggression. These problems can eventually progress to dementia.

People with JNCL also show a decline in motor function and may have difficulty controlling their own movement.

How common is TPP1-related Neuronal Ceroid Lipofuscinosis?

Approximately 1 in 25,000 people globally are affected by some form of NCL. These diseases are most common in Scandinavian countries, but occur elsewhere as well. In the United States, it is estimated that 25,000 families are affected by some form of NCL.

Worldwide, 0.46 per 100,000 infants are born with TPP1-related NCL.

Mutations that cause TPP1-related NCL are more common in Iceland, Germany, and Finland than in other nations.

How is TPP1-related Neuronal Ceroid Lipofuscinosis treated?

There is no treatment for the underlying cause of TPP1-related NCL. Treatments can only address the symptoms as they arise. Various medications can be useful for treating seizures, poor muscle tone, sleep disorders, mood disorders, excessive drooling, and digestion. In some people, a feeding tube is also helpful.

What is the prognosis for a person with TPP1-related Neuronal Ceroid Lipofuscinosis?

The prognosis for people with TPP1-related NCL is generally poor. They will become blind and have severe mental deterioration. They will enter a vegetative state in childhood and become totally dependent on others to care for them. Death can occur between the ages of 6 and 40.

Tyrosinemia Type I

Available Methodology: sequencing with copy number analysis.
Gene: FAH.
Exons Sequenced: NM_000137:1-14.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Tyrosinemia Type I?

Tyrosinemia type I is an inherited metabolic disorder in which the body lacks an enzyme needed to break down the amino acid tyrosine, an important building block of proteins. The deficiency in this enzyme, which is called fumarylacetoacetate hydrolase, leads to an accumulation of tyrosine and related substances in the body, which can damage tissues and organs.

There are several forms of tyrosinemia, but type I is the most severe. Symptoms will begin within the first few months of life. Early symptoms include diarrhea, vomiting, an enlarged liver, failure to grow at a normal rate, yellowing of the skin and whites of the eyes (jaundice), a softening of the bones, irritability, and a boiled cabbage or rotten mushroom-like odor. Tyrosine will build up in the cornea, causing itchy, irritated eyes. The liver is progressively damaged, as are the kidneys and central nervous system. If left untreated, children with tyrosinemia type I may have episodes of abdominal pain, an altered mental state, pain or numbness in the extremities, and/or respiratory failure. A mechanical ventilator may be necessary for episodes of respiratory failure, which often last between one and seven days.

If not recognized and promptly treated, tyrosinemia type I is usually fatal before the age of 10. Death is often due to liver or kidney failure, a neurological crisis, or hepatocellular carcinoma, a type of liver cancer. Some children may die within weeks of experiencing the first symptoms. With treatment, however, 90% of people with the disease will live to adulthood and experience fairly normal lives.

How common is Tyrosinemia Type I?

Tyrosinemia type I affects 1 in 100,000 to 120,000 people worldwide. In the U.S., an estimated 1 in 100 to 150 people are carriers of a genetic mutation that causes tyrosinemia type I. This disease is more common in Norway and Finland, where it affects 1 in 60,000 births. It is also common in Quebec, Canada, where it affects 1 in 16,000 people. In the Saguenay-Lac-Saint-Jean region of Quebec, the disease is especially common, affecting 1 in 1,846 people.

How is Tyrosinemia Type I treated?

The drug nitisinone (brand name: Orfadin) was FDA approved in 2002 to treat tyrosinemia type I. It prevents an accumulation of specific metabolic compounds in people with the disease and is typically taken as soon as the disease is diagnosed.

The earlier the disease is recognized and treated, the less damage is done to the body and the better the prognosis. It is important that people with tyrosinemia type I manage their diets closely in a prescribed manner to control intakes of tyrosine and another amino acid, phenylalanine.

Daily nitisinone intake and careful diet monitoring will be necessary throughout the life of someone with tyrosinemia type I. Failure to comply with recommended treatments may result in the return of severe, potentially-fatal symptoms and damage to the body.

In severe cases where the affected person cannot take nitisinone or already has cancerous cells in the liver, liver transplantation is an option. The procedure does carry serious risks, however. Prior to the development of nitisinone, liver transplantation was the only treatment for tyrosinemia type I.

What is the prognosis for a person with Tyrosinemia Type I?

Without treatment, tyrosinemia type I is usually fatal by the age of 10 due to liver or kidney failure, neurological crisis, or liver cancer. However if promptly diagnosed and treated with nitisinone and a managed diet, outcomes can be quite good with a survival rate greater than 90%. Children who receive this treatment can grow to normal size and show improved liver and kidney function as well as more normal bone structure.

Tyrosinemia Type II

Available Methodology: sequencing with copy number analysis.
Gene: TAT.
Exons Sequenced: NM_000353:2-12.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Tyrosinemia Type II?

Tyrosinemia type II (TYRII) is an amino acid disorder that causes the body to have reduced production of an enzyme called hepatic tyrosine aminotransferase. Without this enzyme a protein called tyrosine builds up in the body and can cause symptoms such as pain and redness in the eye, painful skin thickening of the palms of the hand and soles of the feet, and intellectual disability. Not everyone diagnosed with TYRII will have the same symptoms and some may have more severe symptoms than others. While there are not many reported cases, available reports indicate that if a pregnant mother with TYRII is not treated it can cause growth problems or developmental delay in the unborn baby.

How common is Tyrosinemia Type II?

TYRII is reported to be rare, affecting less than 1/250,000 individuals. It has been reported in individuals of Italian, Ashkenazi Jewish, French, Scottish, Northern European, Japanese, and Middle Eastern ancestry. The diagnosis may be most common in individuals of Arab or Mediterranean ancestry, based on documented case reports.

How is Tyrosinemia Type II treated?

A low protein diet and restricting food sources of tyrosine and phenylalanine (such as artificial sweeteners) can improve symptoms associated with TYRII for some affected individuals. Beginning treatment early in life appears to reduce the severity of mental impairment, as well as the eye and skin symptoms for some individuals. There are special supplements and foods for babies and adults with TYRII. Additional medications such as oral retinoids may be useful in the treatment of the skin abnormalities.

What is the prognosis for a person with Tyrosinemia Type II?

The symptoms of an individual affected with TYRII tend to progress and persist unless the dietary restrictions are implemented. Many affected individuals see improvement in the eye and skin symptoms after removing tyrosine and phenylalanine from the diet. Infants who are diagnosed with TYRII very early and who start treatment right away can usually have a healthy and normal life. About half of individuals with TYRII have some sort of intellectual disability, but early treatment may reduce this risk.

USH1C-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: USH1C.
Exons Sequenced: NM_153676:1-27.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What are USH1C-related Disorders?

USH1C-related disorders represent a group of disorders associated with hearing loss with or without vision loss. This group of disorders does not affect intelligence or cause any other primary health problems.

USHER SYNDROME TYPE IC

There are three types of Usher syndrome, identified as type I, type II and type III. The different types of Usher syndrome are grouped by the severity of the disease and the age when symptoms appear. Mutations in *USH1C* cause Usher syndrome type 1.

Usher syndrome type I is an inherited disease that causes hearing loss, balance problems, and progressive vision loss. Infants with this disorder are profoundly deaf in both ears at birth. They have severe balance problems caused by abnormalities of the inner ear (vestibular system) that can lead to delayed development. In general children with Usher syndrome type I sit and walk at later ages and have difficulties sensing changes in speed or direction. In childhood or by early adolescence, affected individuals develop retinitis pigmentosa (RP), an eye disease which causes night blindness and a gradual loss of peripheral vision. Eventually only the central vision remains, creating “tunnel vision.” This central vision too can be impaired and can lead to blindness in a small number of people with the disease. In some cases, people with Usher syndrome type 1 develop cataracts, which can further impair vision.

DFNB18A

Some mutations in *USH1C* have been reported in recessive nonsyndromic hearing loss and deafness (isolated hearing loss), referred to as DFNB18A. Individuals with DFNB18A typically have severe-profound hearing loss at birth. Unlike other forms of hearing loss, DFNB18A does not affect movement or balance.

How common are USH1C-related Disorders?

The global incidence is unknown for both conditions. The incidence/prevalence of Usher syndrome type I overall has been estimated in a few countries. In most countries, the frequency ranges from ~1 in 45,000 to ~1 in 65,000, with the exception of Germany where

the frequency is ~1 in 90,000. Approximately 1-15% of people with Usher syndrome type I have *USH1C*. It is estimated that 1 in 100 to 1 in 225 French Canadians/Acadians (in Quebec and Louisiana) are a carrier of USH1C-related disorders.

How are USH1C-related Disorders treated?

There is no cure for USH1C-related disorders, however early treatment is important to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. It is also important to take advantage of the time when the child's vision is normal.

People with Usher syndrome type 1C generally do not respond to hearing aids, however cochlear implants may help regain some form of hearing. Sign language is a good option for communication. Specialists can introduce other tools and methods of instruction available to people with hearing loss. It is often helpful if the whole family undergoes such instruction and, as a family unit, helps the child adapt.

For those individuals that develop vision loss, visual aids and specialized instruction (for example in tactile signing) help children adapt to their limited vision. Individuals can be prone to accidental injury due to their vision loss and balance problems. Well-supervised participation in sports may help an individual with Usher syndrome type 1 compensate for balance issues, but swimming may be particularly difficult and strategies to ensure safety are needed. Use of UV-A and UV-B blocking sunglasses is recommended, and other optical aids may increase eye comfort. Therapy with vitamin A palmitate may slow retinal degeneration for some.

What is the prognosis for a person with an USH1C-related Disorder?

Usher syndrome type IC results in severe hearing and vision impairment and DFNB18A results in hearing impairment only. However, neither condition affects one's lifespan or intelligence.

USH2A-related Disorders

Available Methodology: sequencing with copy number analysis.
Gene: USH2A.
Exons Sequenced: NM_206933:2-72.

Detection Rate	Population
94%	African American
94%	Ashkenazi Jewish
94%	Eastern Asia
94%	Finland
94%	French Canadian or Cajun
94%	Hispanic
94%	Middle East
94%	Native American
94%	Northwestern Europe
94%	Oceania
94%	South Asia
94%	Southeast Asia
94%	Southern Europe

What are USH2A-related Disorders?

There are three types of Usher syndrome, identified as type I, type II, and type III. The different types of Usher syndrome differ in the severity and the age of onset. Mutations in the *USH2A* gene cause Usher syndrome type II.

Usher syndrome type II causes mild to severe hearing loss beginning at birth (congenital) and progressive loss of vision, typically beginning in adolescence or adulthood. The hearing loss with this form is usually not progressive and mainly affects the ability to detect high frequency sounds. The degree of hearing loss varies both among individuals and within families with Usher syndrome type II. Unlike other forms of Usher syndrome, Usher syndrome type II is generally not associated with balance problems.

Vision loss in Usher syndrome type II is due to a condition called retinitis pigmentosa (RP) and usually begins in the late teens or early twenties. The vision loss is progressive but does not usually lead to complete blindness. Typically the first sign of vision loss is night blindness that progresses to loss of peripheral (side) vision, eventually causing tunnel vision. This progression generally takes place over years or decades.

Some affected individuals have retinitis pigmentosa (RP) without hearing loss, a condition known as retinitis pigmentosa 39 (RP39).

How common are USH2A-related Disorders?

In the United States, Usher syndrome is conservatively thought to affect 4.4 in 100,000 people. The frequency of Usher syndrome type II is not known. Usher syndrome is likely responsible for 3-6% of all childhood deafness.

How are USH2A-related Disorders treated?

Currently there is no cure for Usher syndrome type II, but early treatment is important to give an affected child the best opportunity to develop communication skills. While a child is young, his or her brain is most receptive to learning language, either spoken or signed. Cochlear implants may improve hearing loss symptoms for some individuals. Specialists can introduce other tools and methods of instruction available to people with hearing loss. It is often helpful if the family undergoes such instruction together to help the child adapt.

Routine hearing and vision evaluations are important to detect potentially treatable complications, such as cataracts. Use of UV-A and UV-B blocking sunglasses and other low vision aids may ease the discomfort and difficulties associated with RP. Affected individuals are sometimes prone to accidental injury due to their vision loss and may need to devise systems to avoid such problems. Activities such as sports and driving a car may be difficult or dangerous. Therapy with vitamin A palmitate may slow retinal degeneration for some. Counseling and lifestyle therapy may help affected individuals cope with the difficulties associated with vision loss.

What is the prognosis for a person with an USH2A-related Disorder?

Although the hearing loss symptoms are moderate to severe, most children with Usher syndrome type 2A can use oral communication. Cochlear implants may improve hearing loss in some children. Symptoms of vision loss typically begin in late childhood or early adolescence and the narrowing of the visual field progresses over time. This condition is not associated with balance problems associated other types of Usher syndrome. Usher syndrome type II does not affect intellectual ability or life span.

Usher Syndrome Type 3

Available Methodology: sequencing with copy number analysis.
Gene: CLRN1.
Exons Sequenced: NM_174878:1-3.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Usher Syndrome Type 3?

Usher syndrome type 3 is an inherited disease that causes progressive hearing loss and vision impairment. The rate at which hearing and vision decline varies greatly from person to person, even among those in the same family. In some people, the hearing and/or vision loss can be profound, while in others it can be milder.

People with Usher syndrome type 3 are born with normal hearing and most commonly develop hearing loss in their teenage years, requiring hearing aids by mid- to late-adulthood. By middle age, they are often completely deaf.

Usher syndrome type 3 causes an eye disease known as retinitis pigmentosa. Often arising during puberty, this causes night blindness that progresses to blind spots in the late teens or early adult years. Peripheral (side) vision is often the first to be reduced. Often by mid-life, the person is legally blind.

Unlike other forms of Usher syndrome, type 3 does not usually cause major problems with balance. Some problems may arise later in life, however.

The disease does not affect intelligence nor does it cause any other health problems.

How common is Usher Syndrome Type 3?

Usher syndrome type 3 is rare, making up just 2% of all cases of Usher syndrome. Type 3 is more common in Finland and among Ashkenazi Jews. One study showed that in the New York City area, 0.7% of Ashkenazi Jews are carriers of a particular mutation, which would mean that 1.2 in 100,000 Ashkenazi Jewish children would be affected.

How is Usher Syndrome Type 3 treated?

There is no cure for Usher syndrome, however there are ways to negotiate the vision and hearing loss it causes.

People with the disease will learn to speak normally before their hearing declines. They can explore a range of options including cochlear implants, hearing aids, or sign language.

A person with Usher syndrome will eventually require low vision aids and specialized instruction on how to cope with their limited vision. They can be prone to accidental injury due to their vision loss and may need to devise systems to avoid such problems.

Specialists in both hearing loss and vision loss can guide people to the best options to fit their needs.

What is the prognosis for a person with Usher Syndrome Type 3?

Usher syndrome type 3 will cause severe hearing and vision impairment by mid-life, however it does not affect one's lifespan or intelligence.

Very Long Chain Acyl-CoA Dehydrogenase Deficiency

Available Methodology: sequencing with copy number analysis.
Gene: ACADVL.
Exons Sequenced: NM_000018:1-20.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Very Long Chain Acyl-CoA Dehydrogenase Deficiency?

Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency is a condition in which the body does not properly convert certain types of fat into energy, particularly during periods of fasting, illness, or exercise.

There are three different forms of VLCAD deficiency, ranging from severe symptoms present at birth to very mild symptoms that develop during adulthood:

Severe Early-Onset Form

Infants with the most severe form of VLCAD deficiency develop symptoms within the first few months of life. It causes a thickening of the heart muscle or other weakness of the heart (cardiomyopathy) which impairs its function. It can also cause an abnormal heart rhythm and/or fluid around the heart. These symptoms can be fatal if not recognized and treated promptly. The disease can also cause poor muscle tone, lack of energy, an enlarged liver, and periods of low blood sugar (hypoglycemia).

Hepatic or Hypoketotic Hypoglycemic Form

This form of VLCAD deficiency often appears in early childhood, and is similar to the more severe version except that it does not affect the heart. People with the hepatic or hypoketotic form typically have low blood sugar and an enlarged liver.

Late-Onset Episodic Myopathic Form

People who have the late-onset form of VLCAD deficiency, which is thought to be the most common form of the disease, typically experience mild symptoms beginning in adolesence or adulthood, and some do not experience any symptoms at all. This form also does not normally affect the heart and may not cause low blood sugar. People with this form of the disease may experience occasional periods of muscle cramps or muscle pain and rhabdomyolysis, which is when the body breaks down muscle fibers,

releasing a protein into the bloodstream that can damage the kidneys and turn one's urine a dark brown or red color. These symptoms may occur more frequently after exercise.

All three types of VLCAD deficiency are caused by an error in the production of an enzyme called very long-chain acyl-coenzyme A dehydrogenase. This enzyme breaks down a type of fat known as very long-chain fatty acids and converts it into energy. People with VLCAD deficiency do not have enough of this enzyme, and as a result, the fats are not converted into energy, leaving the person with low blood sugar (hypoglycemia) and feelings of weakness or tiredness. In addition, a buildup of very long-chain fatty acids in the body can damage the heart, liver, and muscles, causing the additional symptoms of the disease.

How common is Very Long Chain Acyl-CoA Dehydrogenase Deficiency?

VLCAD deficiency affects 1 in every 40,000 to 120,000 people.

How is Very Long Chain Acyl-CoA Dehydrogenase Deficiency treated?

People with VLCAD deficiency may be prescribed a special diet. In severe, early-onset cases of the disease, this is often includes intravenous glucose and/or a low-fat formula designed with types of fat the person is better able to digest. With early and active medical care, any heart problems associated with the severe form of the disease can typically be reversed.

Adults who experience episodes of rhabdomyolysis can be treated through adequate hydration and efforts to lower the acidity of the urine to protect the kidneys.

People with VLCAD deficiency should avoid long periods without eating, dehydration, and a high fat diet.

What is the prognosis for a person with Very Long Chain Acyl-CoA Dehydrogenase Deficiency?

With early diagnosis and treatment, the prognosis for a person with VLCAD deficiency is very good. Many are able to live without symptoms and have normal physical and mental development. If the more severe cases of VLCAD deficiency are not detected and treated early, however, the disease can be fatal.

In milder cases of adult-onset VLCAD deficiency, many people remain symptom-free for life even without treatment.

Wilson Disease

Available Methodology: sequencing with copy number analysis.
Gene: ATP7B.
Exons Sequenced: NM_000053:1-21.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Wilson Disease?

Wilson disease is an inherited disease that causes the body to retain too much copper. Copper deposits in the liver, brain, kidneys, and eyes eventually cause tissue damage and scarring that makes the affected organs stop working properly. If not diagnosed and treated early, the condition causes organ failure and death.

Symptoms typically first appear in childhood or early adolescence, but they can appear as early as age 3 and as late as age 70. The most common symptom is liver disease, which first appears as fatigue, abdominal pain, or jaundice. In some cases, it progresses quickly to liver or kidney failure, and will require a liver transplant.

Symptoms can also include neurological problems such as tremors, poor coordination, loss of fine motor skills, problems walking, muscle rigidity in the body or face, or difficulty swallowing. Some people with the condition also develop psychiatric problems including depression, poor impulse control, phobias, aggression, and compulsive behavior. Wilson disease may also interfere with memory and attention span.

Copper deposits also accumulate in the eyes, creating characteristic brown circles around the colored part of the eye. These circles do not interfere with vision.

Even with ongoing treatment to remove excess copper from the body, people with Wilson disease sometimes develop arthritis, heart problems, and endocrine disorders caused by copper accumulation.

How common is Wilson Disease?

Worldwide, approximately 1 in 30,000 people have Wilson disease. It is most common in China, Japan, and Sardinia, where it may affect as many as 1 in 10,000 people.

How is Wilson Disease treated?

Wilson disease requires lifelong, regular treatment to remove copper from the body. Most people with the condition take a medication called penicillamine (brand name: Cuprimine or Depen) several times a day by mouth, combined with vitamin B6. This traps and removes copper from the body through the urine. However, some people react to penicillamine with fever, rash, and other serious complications. These people may be treated with other oral medications such as trientine or high-dose zinc. For individuals who do not respond to medication or have severe side effects, liver transplant is a final treatment option.

With careful treatment prior to the first symptom's appearance, most symptoms can be prevented. If treatment begins after symptoms appear, these symptoms can often show marked improvement. Stopping treatment, however, will cause health problems to return.

People with Wilson disease should not use copper cooking utensils. They should avoid foods high in copper, such as liver, chocolate, mushrooms, nuts, and shellfish. If they live in an area with copper water pipes, they should drink distilled water.

What is the prognosis for a person with Wilson Disease?

With proper treatment, Wilson disease can be managed for many years after diagnosis. Its effect on lifespan is unclear.

X-linked Adrenoleukodystrophy

Available Methodology: sequencing with copy number analysis.
Gene: ABCD1.
Exons Sequenced: NM_000033:1-6.

Detection Rate	Population
77%	African American
77%	Ashkenazi Jewish
77%	Eastern Asia
77%	Finland
77%	French Canadian or Cajun
77%	Hispanic
77%	Middle East
77%	Native American
77%	Northwestern Europe
77%	Oceania
77%	South Asia
77%	Southeast Asia
77%	Southern Europe

What is X-Linked Adrenoleukodystrophy?

X-linked adrenoleukodystrophy (X-ALD) is a genetic condition that primarily affects the nervous system and adrenal glands. X-ALD is more common and more severe in males because of the way it is inherited. Neurologic problems result from deterioration (demyelination) of the insulating covering (myelin) of the nerves in the brain and spinal cord. This causes a decline in intellectual and motor function and ultimately reduces lifespan. X-ALD is also associated with adrenal insufficiency which results in the decreased production of certain hormones causing abnormalities in blood pressure, heart rate and ability to have children.

There are three major forms of X-ALD that occur in males:

Childhood cerebral form

The childhood form is the most severe. Typcially by age 4 years, children will start to experience learning and/or behavior problems that progress over time to impaired understanding, speech, vision, hearing and motor function. The rate of symptom progression is variable, but can result in significant disability within a few years after symptoms start.

Adrenomyeloneuropathy type (AMN)

This type of X-ALD most often presents in early adulthood. Initial symptoms may include: difficulty walking, speech difficulties, loss of muscle movement coordination, impaired sexual function and behavior changes. An absence of hormones (adrenal insufficiency) may also occur and lead to weakness, weight loss, skin changes, vomiting, and coma.

Addison disease only

This is the mildest form of X-ALD. Individuals with this form, often present with symptoms associated with adrenal insufficiency only sometime between childhood and adulthood. During adulhood, symptoms of the AMN type may start to appear. Adrenal function typically remains normal in female carriers.

Different forms of X-ALD can be observed within the same family.

Female carriers

Approximately 20% of female carriers develop symptoms most closely resembling the AMN type. However, the onset of symptoms in female carriers typically present later on in adulthood.

How common is X-Linked Adrenoleukodystrophy?

Collectively, all forms of X-ALD are estimated to occur in approximately 1 in 20,000 to 1 in 50,000 males. X-ALD occurs at a similar frequency across all ethnicities.

How is X-Linked Adrenoleukodystrophy treated?

Currently, there is no cure for X-ALD. However, treatments are available to address many of the symptoms. Corticosteriod replacement therapy is used to treat symptoms caused by adrenal insufficiency, but does not relieve neurologic symptoms. A multidisciplinary team of healthcare professionals, including: neurologists, physical therapists, urologists, ophthalmologists, audiologists, endocrinologists and other healthcare specialists will need to be involved in the treatment and ongoing management of individuals with X-ALD.

What is the prognosis for a person with X-Linked Adrenoleukodystrophy?

The life expectancy of individuals with this type depends on the severity of the signs and symptoms and how quickly the disorder progresses. Individuals with the cerebral form of X-linked adrenoleukodystrophy usually survive only a few years after symptoms begin but may survive longer with intensive medical support. The prognosis for individuals with the AMN type and Addison disease only type vary; in some cases, neurologic damage may lead to early death.

X-linked Alport Syndrome

Available Methodology: sequencing with copy number analysis.
Gene: COL4A5.
Exons Sequenced: NM_000495:1-51.

Detection Rate	Population
95%	African American
95%	Ashkenazi Jewish
95%	Eastern Asia
95%	Finland
95%	French Canadian or Cajun
95%	Hispanic
95%	Middle East
95%	Native American
95%	Northwestern Europe
95%	Oceania
95%	South Asia
95%	Southeast Asia
95%	Southern Europe

What is X-Linked Alport Syndrome?

Alport syndrome is a genetic condition characterized by progressive kidney disease, hearing loss, and abnormalities affecting the eyes. Alport syndrome can be inherited in an X-linked or autosomal recessive manner. The presentation of X-linked Alport syndrome is variable in severity; some individuals have a milder disease course, while others develop more severe disease with complications. The X-linked form of Alport syndrome is more severe in males than females.

Blood in the urine is often the first sign of kidney disease and typically presents during childhood. This is usually not detectable by the naked eye, but may be visible during periods of illness such as a cold or flu. Individuals with X-linked Alport syndrome also develop protein in the urine during childhood. Kidney disease often progresses to kidney failure by early adulthood. Kidney failure is associated with various symptoms including: high blood pressure, fatigue, poor appetite, swelling of legs and feet, and frequent urination. Kidney insufficiency and associated medical complications will develop in all males with X-linked Alport syndrome. Medications may delay the progress of kidney failure, but most often, either a kidney transplant and/or dialysis is necessary.

X-linked Alport syndrome is also associated with varying degrees of progressive hearing loss. The onset and severity of hearing loss is variable, but it is not uncommon for some degree of hearing loss to develop by adolescence.

Individuals with X-linked Alport syndrome may also develop eye abnormalities. Specific problems with the lens, retina and cornea are the most common in X-linked Alport syndrome and may result in light sensitivity, cataract formation, and blurred vision. Glasses are sometimes required to correct vision.

Limited information exists regarding vascular complications associated with Alport syndrome. However, aneurysms of the abdominal and thoracic aorta have been reported in a small number of males with Alport syndrome, in addition to aortic valve abnormalities. To date, vascular complications are believed to only occur in males. However, the frequency of vascular events remains unclear.

Carrier Females

Most female carriers of X-linked Alport syndrome will have blood in the urine that is not detectable to the naked eye. Some females are also affected by varying degrees of hearing loss, but it tends to occur later in life. By late adulthood, up to 40% of female carriers will progress to kidney failure.

How common is X-Linked Alport Syndrome?

Collectively, all forms of Alport syndrome are estimated to occur in approximately 1 in 50,000 live births. X-linked Alport syndrome is the most common form, accounting for around 85% of all Alport syndrome. X-linked Alport syndrome occurs at a similar frequency amongst all ethnicities. Approximately 10-15% of males affected by X-linked Alport syndrome do not inherit a mutation from a carrier mother (*de novo* mutation).

How is X-Linked Alport Syndrome treated?

Currently, there is no cure for X-linked Alport syndrome. However, treatments are available to address many of the associated symptoms. Medications are utilized to treat high blood pressure, reduce protein in the urine, and slow the progression of kidney disease. However, kidney failure will develop eventually in all males with X-linked Alport syndrome and in some females. Because the onset of kidney failure is variable, transplantation or dialysis may be required as early as the teenage years, but most often, necessary by adulthood.

Hearing aids may be required to treat hearing loss. Additionally, ophthalmologic intervention, such as cataract surgery, may be required for some individuals.

A multidisciplinary team of physicians, including: nephrologists, audiologists, ophthalmologists and other healthcare professionals will need to be involved in the ongoing treatment and management of individuals with X-linked Alport syndrome.

What is the prognosis for a person with X-Linked Alport Syndrome?

While the prognosis of X-linked Alport syndrome is variable, the vast majority of males develop kidney failure by 40 years of age. Renal transplantation and/or dialysis are typically successful as patients approach kidney failure. However, complications from kidney disease may still result in shortened life span. Hearing loss develops in the vast majority of males by 40 years. Many times, the eye complications associated with X-linked Alport syndrome do not cause any severe vision problems; although, cataract surgery and/or corrective lenses may be required.

X-linked Congenital Adrenal Hypoplasia

Available Methodology: sequencing with copy number analysis.
Gene: NR0B1.
Exons Sequenced: NM_000475:1-2.

Detection Rate	Population
99%	African American
99%	Ashkenazi Jewish
99%	Eastern Asia
99%	Finland
99%	French Canadian or Cajun
99%	Hispanic
99%	Middle East
99%	Native American
99%	Northwestern Europe
99%	Oceania
99%	South Asia
99%	Southeast Asia
99%	Southern Europe

What is X-Linked Congenital Adrenal Hypoplasia?

X-linked congenital adrenal hypoplasia (XLCAH), is a disease caused by mutations in the *NR0B1* gene and primarily affects males. This disorder causes the glands located above each kidney (adrenal glands) to not produce important chemicals called hormones. When these hormones are not produced properly, the body cannot retain enough sodium (salt). This is commonly called "salt wasting" and it can lead to serious illness with dehydration, vomiting, diarrhea, failure to thrive, heart rhythm abnormalities (arrhythmias), and shock. If not recognized and properly treated, a salt wasting crisis can be fatal.

XLCAH can also lead to a lack of sex hormones produced by the adrenal glands called hypogonadotropic hypogonadism. This lack of sex hormones can cause males with CAH to have smaller than average sex organs, undescended testes, delayed or incomplete puberty and fertility problems.

Most commonly, affected boys will show signs of the disease from the first few weeks of life to early childhood, but some later-onset cases have been reported. The age of onset and severity of symptoms can be variable, even within the same family.

This is an X-linked disease meaning that the *NR0B1* gene is on the X-chromosome. Males have just one copy of the X-chromosome and *NR0B1* gene while females have two copies. Because they only have one copy of the gene, males who carry a mutation in that gene are affected by the condition while female carriers still have one normal (working) copy of the gene. Because of this, most female carriers do not have symptoms, however, in rare cases female carriers have been reported with adrenal insufficiency or hypogonadotropic hypogonadism.

How common is X-Linked Congenital Adrenal Hypoplasia?

This is a rare disorder. Studies estimate that more than 1 in 600,000 males will have XLCAH, but the true global incidence is unknown. Other presentations of XLCAH may not be recognized as of yet.

How is X-Linked Congenital Adrenal Hypoplasia treated?

Currently, there is no cure for XLCAH. However, treatments are available for the symptoms. Patients benefit from taking hormone replacement medications to restore and maintain the right balance of hormones in the body; most patients will need to take hormone medications for the rest of their lives. A multidisciplinary team of physicians, including an endocrinologist, will need to monitor the hormone levels to determine medication dosage, medication side effects, growth, and sexual development of patients with this condition. The endocrinologist will carefully monitor sex hormones near puberty and supplement hormones if puberty is delayed or not progressing as expected.

Once the condition is diagnosed, illness caused by salt-wasting should be treated in a hospital where the imbalances can be monitored and corrected.

What is the prognosis for a person with X-Linked Congenital Adrenal Hypoplasia?

With early diagnosis and proper medication management, most individuals with XLCAH will have a normal life expectancy. Early death can occur during periods of significant sodium loss (salt crises) if medication dosage is not adequately adjusted, especially during times of illness or trauma. Problems with sexual development and infertility are monitored by physicians on an ongoing basis.

X-linked Juvenile Retinoschisis

Available Methodology: sequencing with copy number analysis.
Gene: RS1.
Exons Sequenced: NM_000330:1-6.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
98%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis is an inherited eye disorder that makes the inner layer of the retina split in a spoke-wheeled pattern. It usually occurs in both eyes at once. This disease affects more males than females.

Boys with the condition may have symptoms in early childhood, but are often not diagnosed until they have their first visual screening before starting school. They usually have vision of 20/60 to 20/120, with tiny lesions, splits, or cysts visible on their retinas. Fewer than 10% of people with the condition experience full retinal detachment or bleeding inside the eye, both of which can cause blindness.

As boys with X-linked juvenile retinoschisis go through their teens, their vision may slowly worsen, but it typically stabilizes in their twenties. When they reach their forties and fifities, their vision may start to deteriorate again. Many people with the condition eventually have vision of 20/200 or worse, making them legally blind.

How common is X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis is estimated to affect 1 in every 5,000 to 25,000 people. Due to its pattern of inheritance, the disease primarily affects males.

How is X-Linked Juvenile Retinoschisis treated?

In general, treatment focuses on monitoring the progress of the disease and helping affected individuals learn to cope with poor vision. For example, children can use large-text books and high-contrast reading materials. Adults can purchase special magnifiers, clocks, and adaptive software to help them at home and at work.

Because X-linked juvenile retinoschisis affects only the inner layers of the retina, surgery is rarely effective in treating the disease. However surgery may help with complete retinal detachment.

Low-vision specialists such as optometrists can help both children and adults make the most of the vision they have. Some people with the condition can get restricted driver's licenses if they wear special telescopic lenses behind the wheel. (Please note that these lenses are not legal in all states.)

Children under the age of 10 should see a pediatric ophthalmologist or retina surgeon every year. Older children and adults need less frequent monitoring.

People with X-linked juvenile retinoschisis should avoid high contact sports and other activities that might cause a hard blow to the head. This minimizes the risk of retinal detachment or bleeding in the eye.

What is the prognosis for a person with X-Linked Juvenile Retinoschisis?

X-linked juvenile retinoschisis does not affect lifespan, but does cause progressive vision problems which can result in legal blindness after middle age.

X-linked Myotubular Myopathy

Available Methodology: sequencing with copy number analysis.
Gene: MTM1.
Exons Sequenced: NM_000252:2-15.

Detection Rate	Population
98%	African American
98%	Ashkenazi Jewish
99%	Eastern Asia
98%	Finland
98%	French Canadian or Cajun
98%	Hispanic
98%	Middle East
98%	Native American
98%	Northwestern Europe
98%	Oceania
98%	South Asia
98%	Southeast Asia
98%	Southern Europe

What is X-Linked Myotubular Myopathy?

X-linked myotubular myopathy (MTMX) is a rare disorder that belongs to a larger group of disorders known as centronuclear myopathies. This condition almost exclusively occurs in males. Presentation of the condition can vary (as described below), but MTMX almost always affects the strength of the muscles used for movement (skeletal muscles) and results in low muscle tone (hypotonia).

SEVERE X-LINKED MYOTUBULAR MYOPATHY

Most affected individuals have the severe or classic form of the disease. Signs of this condition may present before birth with decreased fetal movement or too much amniotic fluid (polyhydramnios). At birth, babies typically show low muscle tone and they develop multiple problems due to this muscle weakness including feeding problems, delayed motor development, and respiratory failure requiring mechanical ventilator support. Some individuals can not move on their own. Many also have weakness in the muscles that control eye movement (ophthalmoplegia), characteristic facial features such as large head, narrow face, high and arched roof of the mouth, and absent reflexes. Less common features that may occur include stiffening of the muscles resulting in tight joints (contractures), curvature of the spine (scoliosis), liver disease, recurrent infections, and seizures. Intellectual disability is also common in affected individuals, though some may develop difficulties as a result of seizures or lack of oxygen (related to mismanaged respiratory failure).

MODERATE AND MILD X-LINKED MYOTUBULAR MYOPATHY

In the moderate form of the disease, individuals may have less severely delayed milestones, and they are more likely to be able to breathe on their own or with minimal support from mechanical ventilation. In the mild form of the disease, muscle weakness may improve. Individuals are more likely to have near-normal motor development and are generally able to walk, ventilator support becomes unnecessary with age, and they tend to not develop the characteristic facial features. It is important to note that it is usually not possible to predict the form of the disease based on the mutations carried, but the moderate and mild forms are less common.

Most female carriers do not have symptoms, however there are reports of carrier females developing mild/moderate symptoms associated with this condition. However, this seems to be a rare occurrence.

How common is X-Linked Myotubular Myopathy?

The worldwide incidence for MTMX is unknown. It has been reported that MTMX affects approximately 1 in 50,000 male newborns, though this is only based on a single estimate from a French registry. Approximately 10-20% of males affected do not inherit a mutation from a carrier mother (de novo mutation).

How is X-Linked Myotubular Myopathy treated?

Currently there is no cure for MTMX. Treatment focuses on trying to maximize functional abilities and minimize complications with a team of specialists, generally those that have expertise in long-term care of children with neuromuscular disorders. For example, a physical therapist and/or rehabilitation medicine specialist will manage movement issues. A neurologist may assist with motor delays and seizures. A pulmonologist will likely manage the need for mechanical ventilation, and a surgeon will determine the need for a tracheostomy and feeding tube. Other specialties are involved as needed.

What is the prognosis for a person with X-Linked Myotubular Myopathy?

Because of their severe breathing problems, the vast majority of individuals affected with X-linked myotubular myopathy do not survive infancy. Some individuals, especially with the milder forms, may live into childhood or adolescence, but survival into adulthood is generally uncommon. Individuals who have survived long-term have developed other medical problems.

X-linked Severe Combined Immunodeficiency

Available Methodology: sequencing with copy number analysis.
Gene: IL2RG.
Exons Sequenced: NM_000206:1-8.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is X-Linked Severe Combined Immunodeficiency?

X-linked severe combined immunodeficiency (X-SCID) is a disorder of the immune system that causes recurrent, severe infections, fevers, and skin rashes. The condition almost exclusively affects males. Patients with X-SCID are missing two important immune system components, T lymphocytes and natural killer lymphocytes. These patients also have B lymphocytes that do no work. Since the immune system is unable to function properly, X-SCID patients are unable to fight off infections.

Symptoms of X-SCID typically start between three and six months of age. Most male infants with untreated X-SCID will show slower than average growth, develop significant diaper and oral rashes, and will have severe, persistent infections despite active treatment. They may also have absent tonsils and lymph nodes. Babies with an atypical form of X-SCID may have immune system dysfunction, rashes, gastrointestinal problems, and short stature.

X-SCID is inherited as an X-linked condition. This means that typically women are unaffected carriers while males that inherit this condition are affected.

How common is X-Linked Severe Combined Immunodeficiency?

The exact incidence of X-SCID is unknown. It is thought to be the most common form of severe combined immunodeficiency, accounting for up to 50% of cases, and has an estimated incidence of approximately 1 in 115,000 to 1 in 300,000 in the US (diverse population). However, the incidence may vary by region. More information about the true incidence of the condition may come as other countries adopt newborn screening and registries become more established.

How is X-Linked Severe Combined Immunodeficiency treated?

Bone marrow transplantation is the most common form of treatment for X-SCID. Replacement of the bone marrow in a person with X-SCID with the bone marrow of a healthy individual allows the body to generate new, functional blood cells and lymphocytes. Bone marrow transplantation has a significantly higher success rate if performed shortly after birth. Cord blood transplantation may also be an affective treatment of X-SCID. Gene therapy may also be considered for patients that are not good candidates for bone marrow or cord blood transplantation.

What is the prognosis for a person with X-Linked Severe Combined Immunodeficiency?

X-linked severe combined immunodeficiency is almost universally fatal unless a successful bone marrow transplantation or gene therapy is completed. Approximately 90% of infants can be successfully treated with a bone marrow transplant. For infants in which a bone marrow transplant is not completely successful, or for those that are not candidates for a bone marrow transplant, administration of proteins to help the immune system function may be beneficial. For infants in whom bone marrow transplantation, gene therapy, or immunoglobulin infusion is unsuccessful, the average life expectancy is approximately 1-2 years.

Xeroderma Pigmentosum Group A

Available Methodology: sequencing with copy number analysis.
Gene: XPA.
Exons Sequenced: NM_000380:1-6.

Detection Rate	Population
>99%	African American
>99%	Ashkenazi Jewish
>99%	Eastern Asia
>99%	Finland
>99%	French Canadian or Cajun
>99%	Hispanic
>99%	Middle East
>99%	Native American
>99%	Northwestern Europe
>99%	Oceania
>99%	South Asia
>99%	Southeast Asia
>99%	Southern Europe

What is Xeroderma Pigmentosum Group A?

Xeroderma pigmentosum (XP) is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from sunlight. Thus, the areas of the body that are most affected by the condition are the skin and eyes. XP's name comes from two of its common characteristics: dry skin (xeroderma) and skin color changes (pigmentosum). There are multiple types of XP, some with different features that are captured by the groupings, but all types include sensitivity to UV light.

The onset of symptoms for individuals with XP group A (XPA) is usually in infancy, but some mutations have been associated with later onset. Typically, XPA is diagnosed in infants who have been sunburned after minimal time in sunlight. Affected children also develop excessive freckling on sun-exposed areas. Damage from the UV rays significantly increases the risk for skin cancer in children with XPA. The average age of onset for non-melanoma skin cancer in children with any type of XP is 9 years and for melanoma is 22 years. The eye is also susceptible to damage from UV light resulting in impaired vision due to clouding of the cornea, inflammation of the cornea, non-cancerous growths on the eye, and/or eye cancer.

Other abnormalities that occur in individuals with XPA, but are unlikely to be related to UV damage, include neurological abnormalities and internal cancers. At least 25 to 30% of individuals with XPA have progressive neurological issues that may include hearing loss, difficulty swallowing and talking, movement problems, seizures, and intellectual disability. The risk for internal cancers is thought to be linked to environmental carcinogens, like cigarette smoke and other, potentially uncontrollable, exposures.

How common is Xeroderma Pigmentosum Group A?

Worldwide, XP has been estimated to affect about 1 in 100,000 individuals. For the Caucasian population in the United States, XP is estimated to affect 1 in 250,000 individuals. In Western Europe, 1 in 1,000,000 new cases are seen annually. Of the XP cases in the United States, ~9% are XPA cases.

Higher frequency of XPA cases has been reported in other areas where marriage between blood relatives (consanguinity) is common, or where a few mutations account for the majority of cases. In Japan, ~55% of cases of XP are attributed to a few mutations in the

XPA gene; thus the XPA disorder is estimated to affect approximately 1 in 40,000 Japanese individuals. Additional countries in North Africa, the Middle East, and South Asia may also have a higher frequency of XPA patients.

How is Xeroderma Pigmentosum Group A treated?

Management for all types of XP involves strictly avoiding sun and UV light especially to the skin and eyes; skin-covering clothing, sunscreen, sunglasses with UV protection are strongly recommended. Avoidance of carcinogens, like cigarette smoke, is also recommended. Treatment of individuals with XP is typically multidisciplinary. Individuals are regularly seen by dermatologists to remove skin growths, and may be prescribed high doses of a special form of vitamin D to prevent additional growths although there are many side effects. Ophthalmologists are also involved in patient care to regularly examine the eyes for damage. A neurologist and audiologist may aid in monitoring, diagnosis, and management of neurological features. Oncologists will become involved if an internal cancer is diagnosed.

What is the prognosis for a person with Xeroderma Pigmentosum Group A?

The prognosis for an individual with XPA is generally poor due to early onset of symptoms and severity of features. The life expectancy is shortened for many individuals with XPA due to the dramatically increased risk for skin cancer and risk for neurodegeneration. The average life expectancy of an individual with any type of XP with neurological features is 29 years (37 years if neurological features are not present).

Xeroderma Pigmentosum Group C

Available Methodology: sequencing with copy number analysis.
Gene: XPC.
Exons Sequenced: NM_004628:1-16.

Detection Rate	Population
97%	African American
97%	Ashkenazi Jewish
97%	Eastern Asia
97%	Finland
97%	French Canadian or Cajun
97%	Hispanic
97%	Middle East
97%	Native American
97%	Northwestern Europe
97%	Oceania
97%	South Asia
97%	Southeast Asia
97%	Southern Europe

What is Xeroderma Pigmentosum Group C?

Xeroderma pigmentosum (XP) is an inherited condition characterized by an extreme sensitivity to ultraviolet (UV) rays from sunlight. Thus, the areas of the body that are most affected by the condition are the skin and eyes. XP's name comes from two of its common characteristics: dry skin (xeroderma) and skin color changes (pigmentosum). There are multiple types of XP, some with different features that are specific to each group, but all types include sensitivity to UV light.

XP is often diagnosed in infants who have been sunburned after minimal time in sunlight. However, not all children with XP group C (XPC) will sunburn, though they may have freckle-like changes in skin areas exposed to the sun. Damage from UV rays, regardless of the amount of sun damage observed, significantly increases the risk for skin cancer in children with XPC. The average age of onset for non-melanoma skin cancer in children with any type of XP is 9 years and for melanoma is 22 years. The eye is also susceptible to damage from UV light resulting in impaired vision or blindness in one or both eyes due to clouding of the cornea, inflammation of the cornea, non-cancerous growths on the eye, and/or eye cancer.

Other abnormalities that occur in a portion of individuals with XPC, but are unlikely to be related to UV damage, include neurological abnormalities and internal cancers. Cognitive and motor issues are less likely with XPC, but hearing loss, intellectual disability, autism, and hypoglycemia which can cause neurologic damage have been reported. Risk for internal cancers, primarily cancers of the brain, may be higher than that in other groups, even if the individual does not have any neurological abnormalities. The increased risk for internal cancers is thought to be linked to environmental carcinogens, like cigarette smoke and other, potentially uncontrollable, exposures.

How common is Xeroderma Pigmentosum Group C?

Worldwide, XP has been estimated to affect about 1 in 100,000 individuals. However, XP has been estimated to affect from as high as 1 in 5000 persons to as low as 1 in 1,400,000 individuals, depending on the population. For the Caucasian population in the United States, XP is estimated to affect 1 in 250,000 individuals. In Western Europe, 1 case of XP is seen per 1,000,000 individuals, annually. Of the XP cases in the United States, approximately 40 to 45% are XP group C cases.

In the Japanese population, XP affects approximately 1 in 22,000 individuals, with ~3.5% being attributed to mutations in the *XPC* gene. A higher frequency of XP cases has been reported in areas where marriage between blood relatives (consanguinity) is common, or where a few mutations account for the majority of cases (founder mutations). A higher frequency of XP cases has been documented in Italy, Turkey, North Africa, and the Middle East. In the Comorian black population of Mayotte, an island off the coast of Africa, XP is found in 1 in 5000 individuals.

How is Xeroderma Pigmentosum Group C treated?

Management for all types of XP involves strictly avoiding sun and UV light especially to the skin and eyes; skin-covering clothing, sunscreen, and sunglasses with UV protection are strongly recommended. Avoidance of carcinogens, like cigarette smoke, is also recommended. Treatment of individuals with XP is typically multidisciplinary. Individuals are regularly seen by dermatologists to remove skin growths, and may be prescribed high doses of a special form of vitamin A to prevent additional growths (though there are many side effects). Ophthalmologists are also involved in patient care to regularly examine the eyes for damage. A neurologist and audiologist may aid in monitoring, diagnosis, and management of neurological features. Oncologists will become involved if an internal cancer is diagnosed.

What is the prognosis for a person with Xeroderma Pigmentosum Group C?

The prognosis for an individual without neurological features may be good and associated with a normal lifespan. However, the life expectancy is shortened for many individuals with XPC due to the dramatically increased risk for cancers. The average life expectancy of an individual with any type of XP and no neurological features is approximately 37 years (29 years if neurological features are present).