



## Disease Reference Book



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### 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

#### Summary

3-hydroxy-3-methylglutaryl-CoA lyase deficiency, also called HMG-CoA lyase deficiency, is an autosomal recessive disorder that prevents the body from processing a particular chemical called leucine and keeps it from producing enough ketones, which are substances that provide energy during periods without food.

Signs and symptoms of the condition typically appear within the first year of life but can vary in age of onset and severity. Symptoms may include vomiting, a lack of energy, diarrhea, dehydration, weak muscle tone, and low blood sugar. If left untreated, breathing problems, seizures, coma, and death could occur. Episodes may be triggered by fasting (periods without food), illness, and infection. Roughly 20% of affected individuals will not survive past childhood. Individuals are generally symptom-free between episodes, and those who receive treatment and survive past childhood often are asymptomatic during adulthood.

HMG-CoA lyase deficiency is caused by mutations in the HMGCL gene.

#### Treatment

There is no cure for HMG-CoA lyase deficiency. Treatment consists of a modified diet low in fat and protein. Supplements may also be recommended. Treatment must occur quickly during episodes of crisis and infection. Individuals should take great care to avoid periods without food.

### 3-Methylglutaconic Aciduria, Type 3

#### Summary

3-methylglutaconic aciduria, type 3, also called Costeff optic atrophy, is an autosomal recessive disorder that results in a loss of vision, difficulty with movement, and intellectual disability.

Signs and symptoms appear during infancy to early childhood starting with a loss of vision that worsens over time. This is due to the breakdown of the optic nerves, which are responsible for carrying information from the eyes to the brain. Additional symptoms include rapid and involuntary eye movements (nystagmus) and crossed eyes. Additional problems with movement may include lack of muscle coordination, muscle stiffness, and involuntary, jerking movements of the body. Severe forms of 3MGA-3 may result in a loss of the ability to walk and need for a wheelchair. Life expectancy is shortened, with most individuals surviving into their 30s. Life expectancy beyond 30 is unknown.

3MGA-3 caused by mutations in the OPA3 gene.

#### Treatment

There is currently no cure for 3MGA-3. Treatment is aimed at managing symptoms. Treatment should include a multidisciplinary team of physicians, including neurologists, orthopedic surgeons, ophthalmologists, and physical therapists.

## Abetalipoproteinemia

### Summary

Abetalipoproteinemia is an autosomal recessive disorder that affects the body's ability to absorb dietary fats, cholesterol, and fat-soluble vitamins, which are important for development and maintenance of the body's cells and tissues, including the nervous system and eyes. The signs and symptoms of abetalipoproteinemia generally appear shortly after birth. Symptoms may include diarrhea, failure to grow at a normal rate, abnormally shaped red blood cells, and unusually foul-smelling bowel movements. Additional symptoms may develop later in childhood such as poor coordination and difficulty with balance and movement. Individuals may also develop an eye disorder called retinitis pigmentosa, causing loss of vision. If left untreated, individuals typically will not survive past their 40s.

Abetalipoproteinemia is caused by mutations in the MTTP gene.

### Treatment

There is no cure for abetalipoproteinemia. Treatment is aimed at managing symptoms. Dietary modification including a low-fat diet in conjunction with vitamin supplements may improve symptoms involving the nervous system and eyes.

## Achalasia-Addisonianism-Alacrima Syndrome

### Summary

Achalasia-addisonianism-alacrima syndrome, also known as Triple A syndrome, is an autosomal recessive disorder characterized by three features: Addison disease (a kidney disorder), achalasia (problems swallowing), and alacrima (an inability to make tears).

Signs and symptoms vary from individual to individual, but generally appear between infancy to childhood. Alacrima and achalasia typically appear first. Most individuals will develop all three features, though some may only develop two. Addison disease will result in tiredness, loss of appetite, loss of weight, low blood pressure, and skin darkening. This condition can also affect the nervous system resulting in abnormal sweating, muscle weakness, problems with movement, eye problems, and intellectual disability. Individuals may also develop patches of callused skin on the palms of their hands and soles of their feet. Treatment can greatly improve prognosis.

Achalasia-addisonianism-alacrima syndrome is caused by mutations in the AAAS gene.

### Treatment

There is no cure for Achalasia-addisonianism-alacrima syndrome. Treatment is aimed at managing symptoms and may consist of artificial teardrops, esophageal dilation, and medications.

## Achromatopsia

### Summary

Achromatopsia is a rare autosomal recessive disorder that causes a loss of color vision (color blindness).

In a complete absence of color vision, individuals only see in black, white, and shades of gray. Affected individuals typically experience additional vision problems including abnormal eye movements (nystagmus), increased sensitivity to light, and reduced visual clarity. Symptoms generally will not worsen over time and will not lead to blindness. Other parts of the body are not usually affected.

Mutations in different genes may cause achromatopsia, including *CNGA3* (type 2) and *CNGB3* (type 3). Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for achromatopsia. Treatment is aimed at managing symptoms. Individuals may wear specialized glasses with a dark brown, red, or gray tint to reduce sensitivity to light.

## Acrodermatitis Enteropathica (Zinc-deficiency Type)

### Summary

Acrodermatitis enteropathica (zinc-deficiency type), or AEZ, is an autosomal recessive disorder caused by the body's inability to absorb zinc.

Signs and symptoms generally appear within the first year of life. AEZ is characterized by three features: diarrhea, inflammation of the skin (dermatitis), and an absence of hair (alopecia). Dermatitis typically affects the face, fingers, toes, and genital area. It is characterized by pink, scaly lesions that can develop into pustules, blisters, erosions, or crusts that are at risk for severe infections. Occasionally, individuals will also exhibit immune system problems, poor wound healing, anemia, delayed puberty, and slow growth rate. If left untreated, infants may die from organ failure. If left untreated, AEZ can be fatal.

AEZ is caused by mutations in the SLC39A4 gene.

### Treatment

There is no cure for AEZ, however, symptoms may disappear with treatment. Lifelong zinc supplementation, along with monitoring zinc and copper levels in the blood, can be very effective in most individuals.

## Adams-Oliver Syndrome, Type 4

### Summary

Adams-Oliver syndrome, type 4 is an autosomal recessive disorder that causes scalp and limb abnormalities.

Signs generally appear during infancy. Symptoms may range in severity from individual to individual. Common symptoms include missing areas of skin on the top of the head, and abnormalities of the limbs (hands, feet, arms, and legs). Some individuals will have scarring and lack growth of hair in affected areas (particularly the head).

In severe cases, infants may also experience problems with the development of bone in that same area of the head. Some individuals may develop high blood pressure or heart defects that may be life-threatening. Some may also have developmental delay, seizures, and learning disabilities.

Adams-Oliver syndrome, type 4 is caused by mutations in the EOGT gene.

### Treatment

There is no cure for Adams-Oliver syndrome, type 4. Treatment is aimed at managing symptoms and may include a team of healthcare professionals such as pediatricians, orthopedic surgeons, cardiologists, and physical therapists. Individuals often require orthopedics, prosthetics, and physical therapy to address abnormalities of the limbs. Scalp defects sometimes heal without treatment but may require skin grafting or surgery. Some individuals will require the use of a helmet to prevent injury to the head. Individuals should also be closely monitored for heart abnormalities.



## Adenosine Deaminase 2 Deficiency

### Summary

Adenosine deaminase 2 (ADA2) deficiency, also known as childhood-onset polyarteritis nodosa, is an autosomal recessive disorder that causes inflammation of the blood vessels.

Age of onset and severity of symptoms vary from individual to individual, but generally appear during childhood. Inflammation of the blood vessels may cause damage to the skin, nervous system, kidneys, and gastrointestinal system. Inflammation may be life-threatening in some cases. Symptoms may include intermittent fevers, skin discoloration, enlarged liver and spleen, and recurrent strokes. Some individuals also experience immune system abnormalities.

ADA2 deficiency is caused by mutations in the CECR1 gene.

### Treatment

There is no cure for ADA2 deficiency. Treatment is aimed at managing symptoms and may include immunosuppression therapy and medication.

## Adenosine Deaminase Deficiency

### Summary

Adenosine deaminase deficiency (ADA) is an autosomal recessive disorder characterized by severe immune system problems that can lead to recurrent life-threatening infections.

Age of onset may vary from individual to individual but typically first appear within the first 6 months of life. Symptoms may include recurrent infection (to the ears, sinuses, and respiratory system), failure to grow at a normal rate, pneumonia, diarrhea, liver problems, hearing loss, and swollen/itchy skin. Over time, chronic lung damage and other health problems may occur. If diagnosis and treatment are not made early, individuals with the severe form of ADA typically will not survive past the age of 2.

Less frequently, individuals may not experience symptoms until childhood or even adulthood. Symptoms tend to be milder in these cases and typically consist of recurrent upper respiratory and ear infections.

Adenosine deaminase deficiency is caused by mutations in the ADA gene.

### Treatment

There is no cure for ADA. Treatment is aimed at managing infections and restoring immune function. Medications, bone marrow transplant, or lifelong enzyme replacement therapy has been used to restore the immune system.

## Adrenoleukodystrophy

### Summary

Adrenoleukodystrophy (ALD) is an X-linked inherited disorder that affects the nervous system and glands on the kidney (adrenal glands) that produce certain hormones.

ALD results from a breakdown of the myelin sheath (a fatty covering of the nerves in the brain and spinal cord) reducing the ability of the nerves to deliver information to the brain. There is also damage to the adrenal glands which results in a reduction in certain hormones that can cause weight loss, changes in the skin, vomiting, and coma. There are three forms of X-linked adrenoleukodystrophy are: childhood cerebral form, adrenomyeloneuropathy form, and Addison disease only.

The childhood cerebral form is the most severe form of ALD with signs and symptoms appearing between the ages of 4 to 10 years. Initial signs in males are typically behavioral and learning problems. Over time, individuals will experience adrenal gland damage, difficulty with speech, reading, and writing. Additionally, affected individuals may exhibit difficulty swallowing, aggressive behavior, problems with vision, and poor coordination. Many will suffer from complete disability within a few years of diagnosis and experience a shortened lifespan.

The adrenomyeloneuropathy form generally appears from early to mid-adulthood. Symptoms may include weakness and stiffness in the legs, urinary tract disorders, genital tract disorders, and intellectual and behavioral changes. Those with more severe symptoms may suffer from a shortened life expectancy.

The mildest form of ALD presents as Addison disease only. Individuals with Addison disease show signs of adrenal damage between childhood and early adulthood but will progress to the adrenomyeloneuropathy features as they reach middle age.

ALD is caused by mutations in the ABCD1 gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one ABCD1 gene is enough to cause ALD. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their ABCD1 gene to cause the condition. For this reason, males are affected by this condition much more than females. Some females with symptoms have been reported, but they are later onset and usually present with the adrenomyeloneuropathy type.

### Treatment

There is no cure for ALD. Treatment is aimed at managing symptoms. Corticosteroid replacement therapy may be used to help treat impaired adrenal glands. Bone marrow transplant may be recommended for individuals with early neurological symptoms.

## Afibrinogenemia

### Summary

Afibrinogenemia is an autosomal recessive disorder that caused by a missing protein in the blood that plays an important role in blood clotting.

Signs and symptoms may appear shortly after birth. Blood of individuals affected with afibrinogenemia doesn't clot properly, and they experience uncontrolled bleeding such as frequent bleeds in the nose or mouth, bleeding following minor trauma, and spontaneous bleeding for seemingly no reason. This can also lead to bleeding in the joints, organs, or brain. Affected females may also experience recurrent miscarriages. Uncontrolled bleeding in the brain and internal organs may be life-threatening.

Afibrinogenemia is caused by mutations in the FGB gene.

### Treatment

There is no cure for afibrinogenemia. Treatment consists of managing symptoms and may include fibrinogen replacement therapy.

## Aicardi-Goutieres Syndrome, Type 5

### Summary

Aicardi-Goutieres syndrome, type 5 (AGS5) is an autosomal recessive disorder that affects the brain, immune system, and skin.

Severity of symptoms vary from individual to individual but generally appear shortly after birth with poor feeding, vomiting, irritability, problems with the nervous system, and a build-up of calcium in the brain. Damage may be severe and permanent.

Additional symptoms may include developmental delay or developmental regression, intellectual disability, skin lesions, seizures, vision problems, joint stiffness, muscle weakness, abnormal muscle tone, and an abnormally small head size. Individuals with severe symptoms may not survive past childhood or may survive past childhood but experience severe intellectual disability and permanent neurological damage.

AGS5 is caused by mutations in the SAMHD1 gene.

### Treatment

There is no cure for AGS5. Treatment is aimed at managing symptoms and improving quality of life. Individuals may need special adjustments for feeding, medication for seizures, and are closely monitored by healthcare professionals throughout their lives.

## Alpha-Mannosidosis

### Summary

Alpha-mannosidosis is an autosomal recessive disorder that causes problems in multiple organs and tissues throughout the body. Problems may include intellectual disability, skeletal abnormalities, weak immune system, poor motor skills, muscle weakness, enlarged liver, enlarged spleen, and speech impairment. Affected individuals often have typical similar facial features which may include a large head, prominent forehead, large ears, rounded eyebrows, low hairline, flattened nasal bridge, protruding jaw, and widely spaced teeth.

There are three forms of alpha-mannosidosis that determine age of onset and severity of symptoms.

Symptoms in the mildest form (type I) typically appear after the age of 10. Individuals generally will not experience skeletal abnormalities or muscle weakness. Symptoms may be so mild that cases can only be diagnosed through laboratory testing.

Symptoms in the moderate form (type II) typically appear before the age of 10. Individuals will experience skeletal abnormalities and muscle weakness, but symptoms progress very slowly. This form is the most common among the three types.

Symptoms in the most severe form (type III) typically appear during infancy with a rapid progression. Affected pregnancies may miscarry or be stillborn, and most individuals will not survive past childhood.

Alpha-mannosidosis is caused by mutations in the MAN2B1 gene.

### Treatment

There is no cure for alpha-mannosidosis. Treatment is aimed at managing symptoms, preventing complications, and increasing quality of life. Treatment may include antibiotics to treat infections, hearing aids, glasses, tubes to drain fluid in the ear, and orthopedics or the use of a wheelchair. Physical therapy, speech therapy, and special educational support is often beneficial. Bone marrow transplant has been used for treatment.

## Alpha-Thalassemia

### Summary

Alpha-thalassemia is a disorder that affects the part of the red blood cells called hemoglobin, which carries oxygen to tissues throughout the body. Hemoglobin is made up of four chains (2 alpha and 2 beta chains). Individuals with alpha-thalassemia do not produce enough of the alpha chains and thus cannot make as much hemoglobin. This low level of hemoglobin can lead to a lack of oxygen and nutrients in many areas of the body. Individuals may have low levels of red blood cells (anemia), fatigue, jaundice, weakness, and serious health complications.

There are two main types of alpha-thalassemia that differ in severity of symptoms: Hemoglobin-Bart (Hb Bart) and Hemoglobin H (HbH). Hb Bart is the more severe form of alpha-thalassemia. Prior to birth, there is a build-up of fluid around the body and organs (called hydrops fetalis). Liver and heart defects may also be present. Death usually occurs shortly after birth. Women pregnant with a baby suffering from Hb Bart are also at risk for various pregnancy complications and should be closely monitored.

HbH is a milder, but still serious, form of alpha-thalassemia. Symptoms usually appear during the first year, they can also be absent until later in life. Children with HbH have yellowing of the eyes and skin (jaundice), enlarged liver and spleen, anemia, and bone abnormalities that affect the facial features. Unlike Hb Bart, individuals with HbH can live into adulthood.

Alpha-thalassemia is caused by changes in the HBA1 and HBA2 genes. Most commonly this change is a deletion of the gene (90% of the time), but it can also be due to slight DNA changes within the gene that cause it to malfunction. Because everyone has 2 copies of each gene, there are a total of 4 gene copies that can be affected in alpha-thalassemia, leading to different combinations of changes.

All four copies deleted/malfunctioning (–/–) causes Hb Bart.

Three copies deleted/malfunctioning (–/–a or a/–) causes HbH.

Two copies deleted/malfunctioning creates alpha-thalassemia trait (also called alpha-thalassemia 0). The 2 changes can be on the same gene (–/aa or aa/–) or in combination on the two different genes (–a/–a). These individuals are considered carriers of alpha-thalassemia and are at high risk for passing the condition on to their children. This risk is dependent on the status of their partner. These individuals may show signs of mild anemia.

One copy deleted/malfunctioning (–a/aa or aa/–a) creates silent alpha thalassemia trait (also called alpha-thalassemia +). The chance of having a child with Hb Bart or HbH is lower than with alpha-thalassemia 0. The exact risk will be dependent on how many copies the partner has. These individuals are not at risk for any symptoms.

### Treatment

There is no effective treatment for Hb Bart. For HbH, blood transfusions are used as needed to maintain blood cell levels. Routine blood monitoring is needed every 6-12 months.



## Alport Syndrome

### Summary

Alport Syndrome is an inherited genetic disorder that affects the kidney, ears, and eyes.

Individuals affected with Alport syndrome suffer from a loss of kidney function over time, which often results in kidney failure. Hearing loss is another feature of Alport syndrome that can appear later in childhood. They may also have eye abnormalities, but generally will not experience a loss of vision. Symptoms are typically more severe in males than in females. More than half of the affected individuals will experience kidney failure by the age of 30, with most of the remaining suffering from it by age of 40.

Alport syndrome can be caused by different genes with different types of inheritance. Mutations in the COL4A5 cause an X-linked form of Alport syndrome. Males only have one X chromosome, so a mutation in that one COL4A5 gene is enough to cause this form of Alport syndrome. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their COL4A5 gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for Alport syndrome. Treatment is aimed at managing symptoms. Medication, dialysis and kidney transplant may be available for individuals suffering from kidney disease or kidney failure. Hearing aids may be beneficial to manage hearing loss.

## Alstrom syndrome

### Summary

Alstrom syndrome is an autosomal recessive disorder that affects multiple systems in the body with signs and symptoms usually appearing between infancy and early childhood. Initial symptoms typically involve problems with vision such as random eye movements and sensitivity to light. Loss of vision gets worse over time, and some individuals eventually become blind.

Additional symptoms include hearing loss, an enlarged and weakened heart that could result in heart failure, type 2 diabetes, obesity, and developmental delays. Many also exhibit deep-set eyes, a rounded face, thin hair, and experience premature balding. Children may also exhibit short fingers and toes and wide, flat feet.

Alstrom syndrome is caused by mutations in the *ALMS1* gene.

### Treatment

There is no cure for Alstrom syndrome. Treatment is aimed at monitoring and managing symptoms. Treatment may include special prescription lenses, special education, hearing aids, and medication. In severe cases, kidney transplants have been performed. Early onset of treatment may help to increase life expectancy and quality of life.

## Amegakaryocytic Thrombocytopenia

### Summary

Amegakaryocytic thrombocytopenia (AMT) is an autosomal recessive disorder that causes bone marrow failure, which results in a decreased level of platelets in the blood (thrombocytopenia). Platelets normally help in making blood clots after injury. So, people with this condition are more likely to have excessive bleeding because clots cannot be made as well. This may cause round spots to appear on the skin (as a result of bleeding under the skin), or bleeding in the brain, lungs and/or gastrointestinal tract.

Both severe and mild types of AMT have been reported. The more severe form will start showing signs by the age of 2 years, while the milder type will present later. If left untreated, individuals will most likely end up with bleeding complications and bone marrow failure within the first few years of life.

AMT is caused by mutations in the MPL gene.

### Treatment

Treatment consists of replacement of platelets with transfusions. Stem cell transplant is considered a curative therapy. However, 20% of individuals that receive stem cell transplant will not survive the procedure.

## Analbuminemia

### Summary

Analbuminemia is an autosomal recessive disorder that causes a severe reduction or absence of a protein found in the blood called serum albumin. Signs and symptoms generally include fatigue, low blood pressure, elevated fat levels in the blood, and swelling caused by fluids in tissues. Many individuals only experience mild symptoms; however, some may develop heart problems and early death.

Analbuminemia is caused by mutations in the ALB gene.

### Treatment

Treatment of analbuminemia is aimed at managing symptoms and may include treatment of possible heart complications.

## Andermann Syndrome

### Summary

Andermann syndrome is an autosomal recessive disorder that causes damage to the nerves involved in the senses and movement. The part of body that connects the right and left parts of the brain (corpus callosum) doesn't form properly (agenesis).

Signs and symptoms appear early in life and are associated with a breakdown of nerve tissue creating muscle weakness, delayed development of motor skills, abnormal reflexes, loss of sensation in the hands and feet, and body tremors. Affected children typically learn to walk around the age of 3 but lose this ability by their early teens. Symptoms get worse over time, and many develop joint deformities and scoliosis later in life. Most individuals will have some degree of intellectual disability, ranging from mild to severe, and psychosis has also been seen in adolescence.

Those affected with Andermann syndrome may also show distinct features including a small head, widely spaced eyes, and large ears. Facial muscle weakness and drooping eyelids may result problems affecting the nerves in the face. The average lifespan is 30 to 40 years.

Andermann syndrome is caused by mutations to the SLC12A6 gene.

### Treatment

There is no cure for Andermann syndrome. Treatment is aimed at managing current symptoms but does not prevent the worsening of disease. Walking aids, physical therapy, and special education may be beneficial. Medication may be prescribed for psychiatric manifestations.

## Argininemia

### Summary

Argininemia is an autosomal recessive disorder that causes a toxic build-up of ammonia in the blood. High levels of ammonia affect different systems in the body, particularly the nervous system.

Onset and severity can vary from person to person. Signs typically first appear close to the age of 3 years as overall stiffness (especially in the legs). Other symptoms include slow growth, delays in development and loss of previously learned physical skills, intellectual disability, balance and coordination problems, and seizures. These can be made worse during times of stress, illness, or fasting.

Argininemia is caused by mutations in the ARG1 gene.

### Treatment

There is no cure for argininemia. Treatment consists of lowering levels of ammonia and may include a diet of restricted protein intake, supplements, dialysis, or liver transplant.

## Argininosuccinic Aciduria

### Summary

Argininosuccinic aciduria is an autosomal recessive disorder that causes a chemical called ammonia to build-up in the blood. At high levels, ammonia is toxic to the body, particularly to the brain, nerves, and liver.

Signs and symptoms typically appear a few days after birth and may include a lack of energy, poor feeding, irritability, and vomiting. Infants may also experience breathing problems, poorly controlled body temperature, build-up of fluid in the brain, seizures, coma, and possibly death. Complications from this disorder may include intellectual disability, developmental delay, liver disease, high blood pressure, skin lesions, and brittle hair. In some cases, individuals may inherit a milder form of argininosuccinic aciduria in which symptoms are only present during times of stress or illness.

Argininosuccinic aciduria is caused by mutations in the *ASL* gene.

### Treatment

There is no cure for argininosuccinic aciduria. Treatment is aimed at preventing the build-up of ammonia in the bloodstream with changes to the diet and medications and/or supplements.



## Arthrogryposis, Intellectual Disability, and Seizures

### Summary

Arthrogryposis, intellectual disability, and seizures (AIS) is an autosomal recessive disorder that affects the joints and causes intellectual disability and seizures. Affected individuals are born with arthrogryposis, a disorder that affects the joints causing them to be permanently bent and limited in movement. The joints that are most likely to be affected include the shoulders, elbows, wrists, hands, hips, knees, and feet. The muscles around the joints may be thin, weak, or stiff.

In addition to the joint problems, affected individuals also exhibit differing degrees of intellectual disability and suffer from seizures that may begin anywhere from ages 3 to 11.

AISS is caused by mutations in the SLC35A3 gene.

### Treatment

There is no cure for AIS. Treatment is aimed at managing symptoms and increasing quality of life.

## Arthrogryposis, Renal Dysfunction, and Cholestasis, Type 1

### Summary

Arthrogryposis, renal dysfunction, and cholestasis, type 1 (ARC1) is an autosomal recessive disorder that affects many systems in the body. Symptoms are generally observed at birth. Affected individuals may have skeletal fractures at birth and experience arthrogryposis, a disorder that can cause the joints to be permanently bent and limited in movement. The joints that are most likely to be affected include the shoulders, elbows, wrists, hands, hips, knees, and feet. The muscles around the joints may be thin, weak, or stiff. In addition, individuals may experience hip dysplasia where the hip socket is abnormally formed.

Other symptoms include developmental delay, low muscle tone, extremely dry skin, kidney dysfunction, yellow discoloration of the skin and eyes (jaundice), and cholestasis (a condition where bile cannot flow from the liver to the stomach). Affected individuals may also have certain facial features such as a sloping forehead, low set ears, and an abnormally small head size. Death often occurs during infancy, normally due to infection, dehydration, or too much acid in the blood.

ARC1 is caused by mutations in the VPS33B gene.

### Treatment

There is no cure for ARC1. Treatment is aimed at managing symptoms and improving quality of life. Treatment may include fluid infusion, medication, and orthopedic intervention. Liver transplant has been performed in at least one case.



## Asparagine Synthetase Deficiency

### Summary

Asparagine synthetase deficiency is an autosomal recessive disorder affecting the nervous system.

Signs and symptoms start at birth or before and include a small head (microcephaly), small chin, large hands/feet, brain malformations, seizures, blindness, breathing difficulties, and exaggerated startled response. The abnormalities will worsen over time resulting in early death during infancy.

ASD is caused by mutations in the ASNS gene.

### Treatment

There is no cure for ASD. Treatment is focused on managing symptoms and making the patient comfortable.

## Aspartylglycosaminuria

### Summary

Aspartylglycosaminuria (AGU) is an autosomal recessive disorder that causes a decline in mental function over time.

Signs and symptoms typically first appear around the age of 2 or 3 years. The initial sign is generally delayed speech followed by mild intellectual disability that becomes first shows up as a slower learning ability. Intellectual disability continues to get worsen, with most adolescents eventually losing most of their speech. Adults may develop other physical problems and seizures. Individuals with AGU may have typical similar facial features including widely spaced eyes, small ears, a broad nose, square-shaped face, and full lips. Children may suffer from frequent respiratory infections, and bones may become weak and prone to breaking. Affected individuals generally only survive into mid-adulthood.

Aspartylglycosaminuria is caused by mutations in the AGA gene.

### Treatment

There is no cure for aspartylglycosaminuria. Treatment is aimed at managing symptoms and may include anti-seizure medication, orthopedic aids, and special education.

## Ataxia with Isolated Vitamin E Deficiency

### Summary

Ataxia with vitamin E deficiency (AVED) is an autosomal recessive disorder that results in the body's inability to use vitamin E. Lack of vitamin E affects the nervous system, causing problems with movement (ataxia), speech, reflexes in the legs, and a loss of sensation in the arms and legs. Some individuals may also develop retinitis pigmentosa, causing loss of vision.

If treatment is initiated prior to the appearance of symptoms, individuals can live a symptom-free life. If left untreated, most individuals will require the use of a wheelchair between the ages of 11 and 50.

Symptoms typically appear between the ages of 4 and 18 with problems in movement worsening with age.

AVED is caused by mutations in the TTPA gene.

### Treatment

There is no cure for AVED, however, symptoms can be effectively managed with lifelong doses of vitamin E. If treatment is initiated prior to the appearance of symptoms, symptoms may never develop. If treatment is initiated after the appearance of symptoms, vitamin E will be able to reverse and/or stop the progression of symptoms.

## Ataxia with Oculomotor Apraxia, Type 1

### Summary

Ataxia with oculomotor apraxia, type 1 (AOA1) is an autosomal recessive disorder that causes a continued loss of nerve structure and function and problems with movement. Individuals AOA1 generally experience the first signs and symptoms during childhood with difficulty coordinating movements. Additional symptoms may include difficulty with eye movement, limited peripheral vision, jerky and involuntary movements, abnormal muscle tone in the upper limbs, and muscle twitching. Individuals with AOA1 may also have hands and feet that are short and experience atrophy (wasting). Intellectual disability occurs in some affected individuals. AOA1 gets worse over time, and most affected individuals require the use of a wheelchair within 10 years of the first symptoms.

AOA1 is caused by mutations in the APTX gene.

### Treatment

There is no cure for AOA1. Treatment consists of managing symptoms and may include physical therapy, special education to assist with reading, writing and speaking, a low cholesterol and high protein diet, and routine follow-up with a neurologist.

## Ataxia-telangiectasia

### Summary

Ataxia-telangiectasia is an autosomal recessive disorder that affects the nervous system, immune system, and other body systems. This disorder is characterized by the progressive difficulty in controlling movement.

Signs and symptoms typically appear early in childhood and may include difficulty walking, involuntary movement, muscle twitches, problems with balance and coordination, slurred speech, and difficulty moving the eyes side to side. Most individuals will require wheelchair assistance by the age of 10.

A characteristic feature of ataxia telangiectasia is the appearance of small clusters of enlarged blood cells in the eyes and surface of the skin, giving an appearance of red spider-like veins. This is called telangiectasia.

Many individuals affected with ataxia-telangiectasia have a weakened immune system, making them prone to chronic lung infections. Affected individuals are also at an increased risk of developing cancer, particularly leukemia and lymphoma. They are sensitive to radiation exposure such as radiation found in medical X-rays. Life expectancy is typically shortened with most individuals surviving into early adulthood. Nearly all individuals need wheelchair assistance by the age of 10. Many will develop cancer.

Ataxia-telangiectasia is caused by mutations in the ATM gene.

### Treatment

There is no cure for ataxia-telangiectasia. Treatment is aimed at managing symptoms. Medications may be given for those with weakened immune systems or to help reducing tremor and improve movement. Physical therapy and occupational therapy may also be beneficial to help minimize the loss of muscle control and aid in movement. Monitoring for early signs of malignancy is recommended.

## Autoinflammation, Lipodystrophy, and Dermatitis Syndrome

### Summary

Autoinflammation, lipodystrophy, and dermatitis syndrome (ALDS), also known as Nakajo-Nishimura syndrome, is an autosomal recessive disorder that affects multiple parts of the body. Signs and symptoms generally appear during infancy to early childhood. Affected individuals experience red and swollen areas on the skin (particularly the face, fingers, and toes) and recurrent fevers. Over time, affected individuals develop problems with the way their bodies produce, uses, and stores fat. Additional symptoms include movement limitations due to severe stiffness, joint pain, poor growth, and muscle weakness and atrophy (wasting).

Additional symptoms that may appear include an enlarged liver and spleen or anemia (a shortage of red blood cells). A few cases of intellectual disability and seizures have been reported. Some individuals have experienced a shortened life expectancy due to heart failure.

ALDS is caused by mutations in the PSMB8 gene.

### Treatment

There is no cure for autoinflammation, lipodystrophy, and dermatitis syndrome. Treatment is aimed at managing symptoms and may include medication to treat fevers and skin lesions.



## Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

### Summary

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), is an autosomal recessive disorder that affects muscle movement, and worsens over time.

The first sign of ARSACS generally appears between the ages of 12 months to 18 months. Symptoms include muscle wasting, difficulty with coordination, involuntary eye movements, abnormal tensing of the muscles, and speech problems as well as weakness in the arms and legs, vision problems, and deformities in the hands and feet. Symptoms become worse over time, and most affected individuals will require a wheelchair by the age of 30 to 40 years. Affected individuals usually do not survive past the age of 60.

ARSACS is caused by mutations in the SACS gene.

### Treatment

There is no cure for ARSACS. Treatment is aimed at managing symptoms. Medications, physical therapy, occupational therapy, and speech therapy may be beneficial in helping affected individuals.

## Bardet-Biedl Syndrome

### Summary

Bardet-Biedl syndrome (BBS) is a group of autosomal recessive disorders that affect multiple parts of the body. Symptoms of BBS vary widely, even within the same family. Main features include vision loss and obesity.

Vision loss generally first appears as night blindness around mid-childhood and gets worse over time. Most individuals become legally blind by adolescence or early adulthood. Obesity starts in early childhood and continues to get worse over time leading to complications such as high blood pressure, high cholesterol, and type 2 diabetes.

Other symptoms include kidney problems, extra fingers/toes, abnormal genitalia, behavioral problems, and intellectual disability. Many individuals have a shortened life expectancy and suffer from severe loss of vision and learning difficulties. Kidney failure is a frequent cause of death.

Many different genes can cause Bardet-Biedl syndrome, including ARL6, BBS1, BBS2, BBS4, BBS5, BBS7, BBS10, BBS12, and MKKS. Although most of the time two mutations in the same gene are needed to cause the condition, sometimes 1 change in 2 different genes can also create the symptoms of Bardet-Biedl syndrome.

### Treatment

There is no cure for BBS. Treatment is focused on addressing symptoms. Surgery may be recommended to remove extra fingers and toes. Visual aids and special education can help address the vision loss, learning problems, and intellectual disability. Modified diet, exercise, and a nutritionist is beneficial for obesity. Kidney transplant may become necessary if kidney failure occurs.

## Bartter Syndrome, Type 4A

### Summary

Bartter syndrome is a group of autosomal recessive disorders that affect the kidneys and causes a build-up of minerals in the body that can cause various health problems.

Signs and symptoms are often life-threatening and typically appear before or right after birth. Bartter syndrome may cause an excess amount of amniotic fluid, increasing the risk for premature birth. Affected individuals fail to grow at a normal rate, are often dehydrated, constipated, and have an increased frequency of urination. Large amounts of calcium are lost through urine causing weakness in the bones. Additional symptoms may include hardening of the kidney tissue, muscle weakness, cramping, and fatigue. A specific form of Bartter syndrome called Bartter syndrome, type 4A also causes hearing loss due to abnormalities in the inner ear. Individuals may experience normal growth following treatment; however, some individuals may still experience kidney failure or gallstones.

Bartter syndrome type 4A is caused by mutations in the BSND gene.

### Treatment

Treatment involves potassium, calcium, and magnesium supplements. Medication may be required to treat many of the symptoms.

## Beta-Ketothiolase Deficiency

### Summary

Beta-ketothiolase deficiency is an autosomal recessive disorder that causes the body to be unable to breakdown a chemical called isoleucine which comes from food resulting in the blood being too acidic. This is often triggered by periods of fasting or eating a high amount of protein-rich foods. Signs and symptoms typically appear during infancy to early childhood and may include vomiting, extreme fatigue, dehydration, and problems breathing. Occasionally, individuals may also experience seizures which may lead to coma.

If diagnosed and treated early, episodes can be prevented, and individuals may experience normal intelligence and healthy lives. Even with treatment, some individuals may still exhibit symptoms and experience some degree of intellectual disability.

Beta-ketothiolase deficiency is caused by mutations in the ACAT1 gene.

### Treatment

There is no cure for beta-ketothiolase deficiency. Treatment is aimed at preventing symptoms and may include modifying one's diet to be low in protein and high in carbohydrates. Treatment may also include monitoring ketone levels, taking supplements, and avoiding periods without food.

## Beta-Thalassemia

### Summary

Beta-thalassemia is a group of disorders that affect the part of the red blood cells called hemoglobin, which carries oxygen to tissues throughout the body. Hemoglobin is made up of four chains (2 alpha and 2 beta chains). Individuals with beta thalassemia do not produce enough of the beta chains and thus cannot make as much hemoglobin. This low level of hemoglobin can lead to a lack of oxygen and nutrients in many areas of the body. Individuals may have low levels of red blood cells (anemia), fatigue, jaundice, weakness, and serious health complications.

There are two main types of beta thalassemia that differ in severity of symptoms: thalassemia major (also known as Cooley's anemia) and thalassemia intermedia. Thalassemia major is the more severe form of beta thalassemia with signs and symptoms generally appearing within the first 2 years of life. Individuals may exhibit a failure to grow at a normal rate, jaundice, enlarged liver and spleen, skeletal abnormalities, and delayed puberty. Individuals often develop life-threatening anemia and need frequent blood transfusions to replenish their red blood cell supply. However, chronic blood transfusions can result in a build-up of iron in the body, leading to complications of the liver, heart, and hormones.

Thalassemia intermedia is the milder form of beta thalassemia. Signs and symptoms generally appear during early childhood to adulthood. Individuals typically have milder anemia and may exhibit skeletal abnormalities and slow growth.

Beta-thalassemia is caused by mutations in the HBB gene. Two mutations are needed to cause symptoms. The beta-thalassemia mutations in HBB can combine with mutations that cause structural changes to beta-hemoglobin (including mutations of hemoglobins S, C, E, D-Punjab and O-Arab) or problems with the alpha hemoglobin chain caused by a different gene. If someone is known to be positive for a beta thalassemia mutation, it is highly recommended that a second blood test (called hemoglobin electrophoresis) be performed on that person and his/her partner in order to assess for over 300 different changes that can affect beta hemoglobin to ensure there is not a second mutation that would put them at risk. Carriers of just one mutation are not expected to show any symptoms.

### Treatment

The most common treatment for beta thalassemia is blood transfusions to maintain proper levels of red blood cells. Chelation therapy may be administered to help eliminate excess iron caused by repeated transfusions. Some individuals may require a bone marrow transplant.

## Bilateral Striatal Degeneration and Progressive Polyneuropathy

### Summary

Bilateral striatal degeneration and progressive polyneuropathy is also known as thiamine metabolism dysfunction syndrome-4 (THMD4). THMD4 is an autosomal recessive disorder that causes skeletal and neurological problems.

Signs and symptoms generally begin during childhood. Individuals have periodic dysfunction of the nervous system, causing muscle weakness and wasting (atrophy). The lower limbs are more often affected than the upper limbs. Periods of brain dysfunction, fever, infection, walking difficulty, and tiredness are also common. Affected individuals may recover from these episodic attacks but usually experience some lasting weakness.

Skeletal abnormalities may include foot deformities and joint stiffness.

THMD4 is caused by mutations in the SLC25A19 gene.

### Treatment

There is no cure for THMD4. Treatment is aimed at managing symptoms and increasing quality of life.

## Biotinidase Deficiency

### Summary

Biotinidase deficiency is an autosomal recessive disorder in which the body is unable to process the vitamin biotin.

Signs and symptoms generally appear within the first few months of life. Those with the more severe form may suffer from seizures, poor muscle tone, breathing problems, and delayed development. If left untreated, individuals may suffer from hearing and vision loss, skin rash, hair loss, fungal infections, and problems with movement and balance.

Individuals with a milder form of biotinidase deficiency (or a partial deficiency) may have symptoms that only appear during times of stress, illness, or infection. With early diagnosis and treatment, individuals are expected to live a normal lifespan.

Biotinidase deficiency is caused by mutations in the BTD gene.

### Treatment

There is no cure for biotinidase deficiency. This disorder is typically treated with a daily biotin supplement. Hearing and vision aids may also be recommended.

## Bisphosphoglycerate Mutase Deficiency

### Summary

Bisphosphoglycerate mutase (BPGM) deficiency is an autosomal recessive disorder that causes anemia. Anemia is a condition in which there are not enough healthy red blood cells to carry an adequate amount of oxygen to the tissues. This lack of oxygen can damage different tissues of the body.

Anemia generally appears during infancy in those affected with BPGM deficiency. Additional symptoms include jaundice (yellowing of the skin and eyes), an enlarged spleen, gallstones, and inflammation of the gallbladder.

BPGM deficiency is caused by mutations in the BPGM gene.

### Treatment

There is no cure for BPGM deficiency. Treatment is aimed at managing symptoms.



## Bjornstad Syndrome

### Summary

Bjornstad syndrome is an autosomal recessive disorder that causes hearing loss and hair abnormalities. Signs and symptoms generally appear during childhood but may vary in severity from individual to individual. Hearing loss is caused by changes to the inner ear and affects both ears. Hearing loss ranges from mild to severe, with some individuals experiencing a complete loss of hearing. The hair abnormality (pili torti) is a condition where the hair appears to be flat and twisted and becomes very brittle, breaking easily. The hair on the head, and the eyebrows and eyelashes are usually the only hair affected.

Bjornstad syndrome is caused by mutations in the BCS1L gene.

### Treatment

There is no cure for Bjornstad syndrome. Treatment is aimed at managing symptoms and may include hair replacement therapy, special education for speech, and monitoring by a team of specialists. Early diagnosis and intervention are important.

## Bloom Syndrome

### Summary

Bloom syndrome is an autosomal recessive disorder characterized by weight and growth deficiency before and after birth and sensitivity to the sun that causes a distinct skin rash (a butterfly patch across nose and cheeks). Other symptoms can include a high-pitched voice, reduced fertility, increased risk for infection, learning disabilities, and possibly chronic obstructive pulmonary disease (COPD).

Bloom syndrome is in a class of disorders known as chromosome breakage syndromes, which have a high chance for multiple cancers, especially at an early age. The lifespan of individuals affected with Bloom syndrome is shortened, with death due to cancer in the late teens to early 20s. Regular cancer screenings beginning at a young age can help to extend life expectancy.

Bloom syndrome is caused by mutations in the BLM gene.

### Treatment

There is no cure for Bloom syndrome. Treatment is typically aimed at monitoring nutrition to maximize growth and regular cancer screening during childhood. Affected individuals are advised to stay out of the sun and to avoid infections.

## Brittle Cornea Syndrome, Type 1

### Summary

Brittle cornea syndrome, type 1 is an autosomal recessive connective tissue disorder. People with this condition are at high risk for their corneas in their eyes to become damaged after only mild injury. Other signs and symptoms can include hearing loss, vision loss, dental abnormalities, curvature of the spine (scoliosis), joints with a large range of motion (hypermobility), and very stretchy skin. Most individuals affected with brittle cornea syndrome type 1 will eventually lose their vision.

Brittle cornea syndrome type 1 is caused by mutations in the ZNF469 gene.

### Treatment

There is no cure for brittle cornea syndrome type 1. Treatment is aimed at managing symptoms and may include special education to address vision and hearing loss, protection for the joints, and close monitoring by a team of healthcare professionals.

## Canavan Disease

### Summary

Canavan disease is an autosomal recessive disorder that affects myelin. Myelin is the protective covering around the nerves, and if it is damaged, the result can be damage to the brain and nerves.

Although there is a rare form of Canavan disease that is milder, most affected individuals have a severe, infantile form of the disease. This is characterized by overall poor muscle tone, enlarged head size, lack of head control, and delays in reaching milestones. Affected children may seem healthy at birth, but symptoms typically appear by 3 to 5 months of age and become more obvious over time. Most children are unable to sit, stand, or walk. Paralysis, difficulty feeding, and swallowing, seizures, and sleep problems may also develop. Most affected individuals die during childhood.

Canavan disease is caused by mutations in the ASPA gene.

### Treatment

There is no cure for Canavan disease. Treatment is directed at providing proper nutrition, hydration, managing infections, and controlling seizures. Children may benefit from physical therapy and other therapies to maximize physical abilities and enhance communication skills.

## Carbamoyl Phosphate Synthetase 1 Deficiency

### Summary

Carbamoyl phosphate synthetase 1 deficiency (CPS1 deficiency) is an autosomal recessive disorder that causes a toxic buildup of a chemical called ammonia in the blood, causing damage to the brain, liver, and intestines.

Signs and symptoms typically appear during infancy and may include poor feeding, excessive sleepiness, recurrent vomiting, irregular breathing, poor muscle tone, uncontrolled body temperature, seizures, and coma. Individuals who survive the newborn period may develop intellectual disability and experience delayed development. Less frequently, onset of this disorder may be delayed until childhood or later resulting in a milder form of the disorder. Episodes may be triggered by illness, infection, or stress.

CPS1 deficiency is caused by mutations in the CPS1 gene.

### Treatment

There is no cure for CPS1 deficiency. Treatment includes a life-long strict diet of limited protein. Supplements and other medications are often prescribed. Life-long monitoring from a team of healthcare providers is recommended.

## Carnitine Palmitoyltransferase 1A Deficiency

### Summary

Carnitine palmitoyltransferase 1A (CPT1A) deficiency is an autosomal recessive disorder in which the body is unable to process certain fats to be used as energy. Symptoms can be triggered during times of fasting, illness, or infection.

Signs and symptoms typically appear during early childhood and may include an enlarged liver, liver malfunction, and muscle weakness. Individuals may also experience a low level of ketones (a byproduct of fat breakdown) and low sugar in the blood. These two symptoms together are called hypoketotic hypoglycemia. If left untreated, individuals are at risk for liver failure, brain damage, seizures, coma, and death.

CPT1A deficiency is caused by mutations in the CPT1A gene.

### Treatment

There is no cure for CPT1A deficiency; however, symptoms can be managed well through treatment including a diet high in carbohydrates and low in fat and frequent feedings.

## Carnitine Palmitoyltransferase 2 Deficiency

### Summary

Carnitine palmitoyltransferase 2 (CPT2) deficiency is an autosomal recessive disorder in which the body is unable to process certain fats to be used as energy.

There are three different forms of CPT2 deficiency that range in severity of symptoms and age of onset. The lethal neonatal form is the most severe with symptoms appearing shortly after birth including liver failure, respiratory failure, seizures, a weakened heart with an irregular heartbeat, as well as brain and kidney abnormalities. Infants with this form of CPT2 usually only survive for a few months. Individuals also experience recurring low blood sugar levels in conjunction with low level of ketones. Symptoms can be triggered by illness, infection, and fasting. Individuals are at risk for liver failure, damage to the nervous system, coma, and death.

The severe infantile hepato-cardio-muscular has similar symptoms that show up within the first year of life. The myopathic form is the most common but least severe form of CPT2 deficiency. Symptoms can appear at any time from childhood through adulthood and may include recurrent episodes of muscle pain and weakness from breakdown of muscle tissue that are triggered by extreme temperatures, infection, fasting, exercise or stress. This breakdown also causes an increase in a chemical called myoglobin that can damage the kidneys and cause a reddish-brown color to the urine. Many individuals with the myopathic form are symptom-free in between episodes.

The lethal neonatal form has a poor prognosis as affected individuals typically die within the first year of life. Those affected with the severe infantile hepato-cardio-muscular form typically have a shortened life expectancy, while those with the myopathic form are expected to have a relatively normal lifespan.

All three types of CPT2 deficiency are caused by mutations in the CPT2 gene.

### Treatment

There is no cure for CPT1A deficiency; however, symptoms can be well-managed through treatment including a diet high in carbohydrates and low in fat and frequent feedings.

## Carnitine Uptake Deficiency

### Summary

Carnitine uptake deficiency, also called primary carnitine deficiency, is an autosomal recessive disorder that prevents the body from properly using fats into energy.

Symptoms of carnitine uptake deficiency vary widely from individual to individual, and there are reports of some people not showing any signs of the condition. Symptoms typically appear in infancy or early childhood and may include muscle weakness, vomiting, low blood sugar, a weakened or enlarged heart, and severe brain dysfunction. Without treatment, affected individuals may experience heart failure, permanent brain damage, coma, and sudden death. Episodes may be triggered during times of fasting, infection, or illness.

The severity of symptoms varies from individual to individual, with some individuals remaining asymptomatic. With a regular treatment regimen, individuals can live a normal life expectancy. If left untreated, individuals may experience permanent brain damage, serious health problems, and potential death.

Carnitine uptake deficiency is caused by mutations to the SLC22A5 gene.

### Treatment

There is no cure for carnitine uptake deficiency. Treatment is aimed at managing symptoms. Frequent feedings and lifelong supplements of L-carnitine may be recommended.



## Carnitine-Acylcarnitine Translocase Deficiency

### Summary

Carnitine-acylcarnitine translocase deficiency (CACT deficiency) is an autosomal recessive disorder that causes the body to be unable to use certain fats for energy.

Symptoms generally appear shortly after birth with many individuals showing signs within the first 48 hours of life. Symptoms may include severe hypoglycemia (low blood sugar), breathing problems, excess levels of ammonia (a chemical that can be toxic) in the blood, seizures, and an irregular heartbeat. Additional symptoms that may develop include an enlarged liver, weak heart muscle, hypothermia, and developmental delay. Affected individuals are at risk for liver failure, coma, and sudden death. Many will not survive past the newborn period, but some may have milder symptoms which may be brought on by fasting (periods without food). Individuals with severe symptoms have a poor prognosis, with many dying before the age of 3 months. Individuals with milder symptoms have a more favorable prognosis if treated.

CACT deficiency is caused by mutations in the SLC25A20 gene.

### Treatment

There is no cure for CACT deficiency. Treatment includes a diet low in fats along with possible supplements and medications.

## Cataract, Type 18

### Summary

Cataract, type 18 is an autosomal recessive disorder that causes a clouding of the eye which can affect vision. Signs and symptoms are either present at birth or will develop shortly thereafter during infancy. Severity of vision loss is dependent on the location and density of the cloudy covering. The degree of impact on vision may be less severe in some cases. Other parts of the body are unaffected.

Cataract, type 18 is caused by mutations in the FYCO1 gene.

### Treatment

Treatment for cataract, type 18 may involve eyeglasses, contacts, or vision aids. If there is a large degree of vision loss, surgery may be required to remove the cataract.

## Cerebral Dysgenesis-Neuropathy-Ichthyosis-Palmoplantar Keratoderma Syndrome (CEDNIK)

### Summary

Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome (CEDNIK) is a rare autosomal recessive disorder that affects the nervous system causing severe problems in development.

Signs and symptoms of CEDNIK generally appear early in life and may include severe intellectual disability, delay of motor skills, failure to grow at a normal rate, gastrointestinal bleeding, a small head size, weakness or tingling in the hands and feet, and a thickening of the skin on the palms of the hands and soles of the feet (palmoplantar keratoderma). Individuals often develop dry, scaly skin (ichthyosis). Characteristic facial features include a long face and downward slanting eyes. Most will not survive past the age of 12.

CEDNIK is caused by mutations in the SNAP29 gene.

### Treatment

There is no cure or effective treatment known for CEDNIK.

## Cerebrotendinous Xanthomataosis

### Summary

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder that causes an accumulation of certain fats, particularly cholesterol, which can build-up to abnormal levels and affect many areas of the body.

Signs and symptoms typically develop during infancy with chronic diarrhea and potential liver dysfunction. Cataracts (clouding of the eye) and brittle bones generally appear during late childhood. This disorder progresses with new symptoms appearing over time including intellectual disability, dementia, seizures, psychiatric problems, hallucinations, and difficulty with speech and movement. During early adulthood, fat may begin to accumulate under the skin, particularly in the tendons. This causes discomfort and problems with flexibility. If left untreated, the build-up will increase, and symptoms will worsen over time.

Individuals who are diagnosed and treated early on may be able to prevent a continued build-up of fats in the body, new symptoms, and in some cases reverse symptoms. If left untreated, individuals generally will not survive beyond their 50s to 60s, with some individuals dying during childhood.

CTX is caused by mutations in the CYP27A1 gene.

### Treatment

There is no cure for CTX, but early treatment is important. Medications can help make some of the symptoms better. Surgery for cataracts is generally required by the age of 50.

## Chanarin-Dorfman Syndrome

### Summary

Chanarin-Dorfman syndrome is an autosomal recessive disorder that affects the metabolism of certain fats called triglycerides, causing a buildup in various organs and tissues.

Signs and symptoms vary from individual to individual, but will generally appear during infancy as red, itchy, and scaly skin. Other symptoms include an enlarged liver, hearing loss, muscle weakness, lack of coordination, slow growth and development, random eye movement, and some intellectual disability. Some individuals will only experience the skin symptoms, while others will have other problems and be more severely affected.

Chanarin-Dorfman syndrome is caused by mutations in the ABHD5 gene.

### Treatment

There is no cure for Chanarin-Dorfman syndrome. Treatment is aimed at managing symptoms and may include the use of skin softening medication/creams.

## Chloride Diarrhea, Type 1

### Summary

Chloride diarrhea, type 1 (CD1) is an autosomal recessive condition that causes severe chronic diarrhea. Affected individuals lose a lot of a chemical called chloride through watery stools causing dehydration and in imbalance of various chemicals in the blood. Many of the affected children are born premature, and the diarrhea begins shortly after birth. Some may even experience problems prior to birth causing excess fluid in the womb. Early growth and development may be delayed. Additional symptoms caused by the recurrent diarrhea include a distended abdomen, low blood pressure, and dehydration. If left untreated, it can be fatal.

Chronic hereditary diarrhea can be caused by mutations in different genes. Two mutations in the same gene are needed to cause symptoms. Chloride diarrhea, type 1 is caused by mutations in the SLC26A3 gene.

### Treatment

There is no cure for CD1. Supplements, medications, and maintaining hydration are all recommended treatment, which is focused on increasing quality of life and avoiding fecal incontinence.

## Choreo-acanthocytosis

### Summary

Choreo-acanthocytosis (ChAc) is an autosomal recessive disorder that affects movement.

Signs and symptoms generally appear during adulthood, but some individuals experience an earlier onset during childhood. Initial signs are typically seizures, but additional symptoms can include involuntary jerking movements, abnormal star-shaped red blood cells, and involuntary tensing of muscles causing excessive tongue and lip biting. Intellectual disability is common, and affected individuals may have difficulty learning, remembering, and processing information. The disorder slowly progresses for about 15 to 30 years. Life expectancy is shortened with individuals surviving to the ages of 28 to 61 years. Sudden death from seizure has been reported.

ChAc is caused by mutations in the VPS13A gene.

### Treatment

There is no cure for ChAc. Treatment is aimed at managing symptoms and may include speech therapy and various medications.

## Choroideremia

### Summary

Choroideremia is an X-linked inherited disorder that causes a loss of vision over time due to a loss of cells in the eye and surrounding blood vessels (choroid).

Signs and symptoms generally appear between childhood and adolescence. The initial symptom is a loss or impairment of night vision. Over time, individuals will experience a loss of central vision, which is necessary for tasks such as reading and driving. Eventually, individuals will lose the ability to see details, but the speed of worsening can vary. Eventually, all affected individuals will become legally blind. Life expectancy is usually unaffected.

Choroideremia is caused by mutations in the CHM gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one CHM gene is enough to cause choroideremia. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their CHM gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for choroideremia. Treatment is focused on managing symptoms. Vision aids may help with making the most of remaining vision while UV exposure from sunlight should be avoided. Surgical correction of vision may also be required depending on the individual's condition.



## Chronic Granulomatous Disease (Cytochrome B-negative)

### Summary

Chronic granulomatous disease (CGD) is an inherited disorder characterized by a poorly functioning immune system that is unable to protect the body from infection as it should. People with CGD suffer from frequent and serious infections at least once every few years beginning in early childhood. Over time, the body may start to attack itself even when healthy and cause conditions like arthritis or other autoimmune disorders. Areas of inflammation (granulomas) will also occur in different tissues of the body. Damage can include stomach or intestinal abscesses, stomach blockage (leading to pain, vomiting, and weight loss), and it can also affect the kidneys, bladder, genitalia, and bone marrow. Individuals experience a shortened lifespan, but with treatment, many are able to survive into mid to late adulthood.

Several different genes may be associated with CGD with different types of inheritance. One of these genes is CYBA, which is inherited in an autosomal recessive fashion.

### Treatment

There is no cure for CGD. Treatment is focused on managing infections with medication. Stem cell transplant may be considered as an early treatment option. Individuals should avoid substances that are known to cause infections.

## Chronic Granulomatous Disease (Cytochrome B-positive, Type 1)

### Summary

Chronic granulomatous disease (CGD) is an inherited disorder characterized by a poorly functioning immune system that is unable to protect the body from infection as it should. People with CGD suffer from frequent and serious infections at least once every few years beginning in early childhood. Over time, the body may start to attack itself even when healthy and cause conditions like arthritis or other autoimmune disorders. Areas of inflammation (granulomas) will also occur in different tissues of the body. Damage can include stomach or intestinal abscesses, stomach blockage (leading to pain, vomiting and weight loss), and it can also affect the kidneys, bladder, genitalia, and bone marrow. Individuals experience a shortened lifespan, but with treatment, many are able to survive into mid to late adulthood.

Several different genes may be associated with CGD with different types of inheritance. CGD, type 1 is caused by mutations in the NCF1 gene, which is inherited in an autosomal recessive fashion.

### Treatment

There is no cure for CGD. Treatment is focused on managing infections with medication. Stem cell transplant may be considered as an early treatment option. Individuals should avoid substances that are known to cause infections.

## Chronic Granulomatous Disease (X-linked)

### Summary

Chronic granulomatous disease (CGD) is an inherited disorder characterized by a poorly function immune system that is unable to protect the body from infection as it should. People with CGD suffer from frequent and serious infections at least once every few years beginning in early childhood. Over time, the body may start attack itself even when healthy and cause conditions like arthritis or other autoimmune disorders. Areas of inflammation (granulomas) will also occur in different tissues of the body. Damage can include stomach or intestinal abscesses, stomach blockage (leading to pain, vomiting and weight loss), and it can also affect the kidneys, bladder, genitalia, and bone marrow.

The outcome for an individual affected with CGD is variable depending on the severity and frequency of infections. Individuals experience a shortened lifespan, but, with treatment, many are able to survive into mid-to late adulthood.

Several different genes may be associated with CGD with different types of inheritance. One of these genes is CYBB, which is on the X chromosome (one of two sex chromosomes) and inherited in an X-linked fashion. Males only have one X chromosome, so a mutation in that one CYBB gene is enough to cause this form of CGD. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their CYBB gene.

### Treatment

There is no cure for CGD. Treatment is focused on managing infections with medication. Stem cell transplant may be considered as an early treatment option. Individuals should avoid substances that are known to cause infections.

## Chudley-McCullough Syndrome

### Summary

Chudley-McCullough syndrome is an autosomal recessive disorder that causes sensorineural hearing loss (hearing loss caused by damage to the inner ear) and brain malformations.

Signs and symptoms generally appear during infancy and include severe hearing loss, structural abnormalities in the brain, and a build-up of fluid in the brain. Although rare, some individuals have also experienced seizures, intellectual disability, and developmental delays.

Chudley-McCullough syndrome is caused by mutations in the GPSM2 gene.

### Treatment

There is no cure for Chudley-McCullough syndrome. Treatment is aimed at managing symptoms and may include hearing aids and regular monitoring by medical specialists.

## Ciliary Dyskinesia

### Summary

Ciliary dyskinesia is a group of autosomal recessive disorders that causes breathing problems, recurrent infections, and infertility. These problems are largely due to abnormal hairs called cilia that are located in the lining of the airway and help to clear the area of mucus and dirt. Cilia is also present in structures that help move sperm cells forward.

Signs and symptoms generally appear during infancy, often first appearing as breathing problems. Infants may require the use of oxygen, and affected individuals often develop recurrent respiratory infections which can lead to life-threatening lung damage.

Additional symptoms include a chronic wet cough, daily nasal congestion, possible fluid build-up in the brain, recurrent ear infections, potential hearing loss, and infertility. Roughly half of affected individuals will have abnormally placed internal organs in their chests and abdomens often being on the opposite side of the body from what you would expect.

Ciliary dyskinesia can be caused by many different genes including DNAL1 and RSPH9.

### Treatment

There is no cure for ciliary dyskinesia. Treatment consists of managing symptoms and may include aggressive treatment to clear mucus, medication for bacterial infections in the airway and sinus disease, hearing aids, and potential surgery as needed. Routine immunizations are recommended to help prevent respiratory tract infections.

## Citrullinemia

### Summary

Citrullinemia is an autosomal recessive disorder that causes a build-up of a chemical called ammonia that can cause damage to various parts of the body.

Citrullinemia belongs to a group of inherited disorders called urea cycle disorders. The urea cycle is a reaction in the body that helps break down chemicals like ammonia and remove them from the body. When this cycle doesn't function normally, you get a build-up of these chemicals. Signs and symptoms generally appear within the first few days after birth as a lack of energy, poor feeding, vomiting, and seizures that may lead to a loss of consciousness. Symptoms may be life-threatening if left untreated.

There is a milder form of citrullinemia, which may not appear until childhood or adulthood. This form of the disorder presents with intense headaches, difficulty with balance and muscle coordination, a lack of energy, and partial loss of vision. Some individuals affected with the milder form of citrullinemia may go a long time without showing signs or never experience any problems associated with this disorder.

If left untreated, this disorder is typically fatal early in infancy. Treatment can help people with citrullinemia live longer, but the length of time is unknown. Neurological damage that occurs before treatment is usually severe and is not reversible.

Most cases of citrullinemia are caused by mutations in the *ASS1* gene.

### Treatment

Treatment is aimed at regulating the levels of ammonia in an affected individuals' blood, which may involve diet changes, medications, or dialysis. Individuals are required to be monitored closely and regularly by healthcare providers.

## Cockayne Syndrome, Type A

### Summary

Cockayne syndrome, type A is an autosomal recessive condition causing short height and premature aging. People with Cockayne syndrome are unable to repair damage to their DNA that occurs with environmental exposures (e.g., chemicals, sunlight, free radicals). This damage can build-up and cause cells to malfunction and die creating the premature aging effects.

Symptoms can first appear anytime between birth and late childhood. Affected individuals have small heads (microcephaly), eye and bone abnormalities, hearing and vision loss, tooth decay, failure to thrive and gain weight, and short stature. Problems with the nervous system can lead to muscle tremors, muscle weakness, intellectual disability, seizures, and dementia. They also have an increased sensitivity to the sun resulting in sunburns even with only a little exposure. Lifespan is usually reduced.

Cockayne syndrome is caused by 2 genes. Two mutations in the same gene are needed to cause disease. Cockayne syndrome, type A is caused by mutations in the ERCC8 gene, and type B is caused by mutations in the ERCC6 gene.

### Treatment

There is no cure for Cockayne syndrome. Treatment is focused on managing symptoms. Physical therapy, feeding tubes, sun protection, and medications may be used.

## Cohen Syndrome

### Summary

Cohen syndrome is an autosomal recessive disorder that affects physical and intellectual development.

Symptoms vary widely from individual to individual but generally appear shortly after birth. Symptoms may include poor feeding, failure to grow at a normal rate, low muscle tone, small head size, delay in reaching physical milestones, and unusually flexible joints. The majority of affected individuals will have narrow hands and feet, short height, and be overweight around the torso. Recurring infections are also common.

Individuals affected by Cohen syndrome have characteristic distinct facial features including thick hair and eyebrows, long eyelashes, a low hairline, and prominent upper-central teeth. Many tend to be overly cheerful and very sociable.

Individuals over the age of 40 often suffer from cataracts (clouding of the eye) and other severe vision problems. Life expectancy is thought to be unaffected.

Cohen syndrome is caused by mutations in the VPS13B gene (also referred to as COH1).

### Treatment

There is no cure for Cohen syndrome. Treatment is aimed at managing symptoms and may include physical, occupational, and speech therapy. Special education may be required for individuals with intellectual disability. Respiratory infections may be treated with antibiotics, while low vision aids or glasses may be needed for vision problems.



## Combined Pituitary Hormone Deficiency, Type 1

### Summary

Combined pituitary hormone deficiency (CPHD) is an autosomal recessive disorder that causes a decrease of certain hormones made in the pituitary gland and affects the development of different parts of the body. CPHD type 1 (CPHD1) is one form of this disorder and is associated with low levels of thyroid-stimulating hormone (TSH), growth hormone (GH), and prolactin. The levels of adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are usually normal.

Symptoms range in severity but generally appear during early childhood. Initial signs of the disorder are a severe failure to grow with short height due to a low levels of growth hormone. Additional symptoms may include jaundice (yellowing of eyes and/or skin), swelling, poor muscle tone, hypothyroidism (a condition where the thyroid gland does not produce enough thyroid hormone), fertility problems, and intellectual disability. Individuals with CPHD1 also exhibit facial characteristics that include a prominent forehead, deep-set eyes, a short nose, and an unusually large tongue. Treatment is effective, and individuals are typically able to live a normal, healthy life.

CPHD1 is caused by mutations in the POU1F1 gene.

### Treatment

CPHD1 is generally treated with hormone replacement therapies. Biosynthetic growth hormone is often administered through injections throughout childhood to aid in growth.

## Combined Pituitary Hormone Deficiency, Type 2

### Summary

Combined pituitary hormone deficiency, type 2 (CPHD2) is an autosomal recessive disorder that causes low levels of certain hormones made by the pituitary gland, affecting the development of different parts of the body.

Signs and symptoms range in severity from individual to individual and generally appear during early childhood. Initial signs of the disorder are a failure to grow at a normal rate and a short stature due to a deficiency in growth hormone. Additional symptoms may include weight gain, fatigue, delayed or absent puberty, and infertility. Life expectancy is usually unaffected.

CPHD2 is associated with deficiencies in the following hormones produced by the pituitary gland: thyroid-stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and occasionally adrenocorticotrophic hormone (ACTH). People with CPHD2 are also at higher risk for infection. Rare cases of intellectual disability or vision problems have also been reported.

CPHD2 is caused by mutations in the PROP1 gene.

### Treatment

CPHD2 is generally treated with various hormone replacement therapies.

## Cone-rod Dystrophy, Type 18

### Summary

Cone-rod dystrophy (CORD), is a rare autosomal recessive eye disorder that affects the retina of the eye. The retina is the light sensitive tissue at the back of the eye that triggers nerve impulses to the brain to form an image. The cones and rods are parts of the retina that help with this process.

There are several different forms of CORD. CORD type 18 (CORD18) is variable and may appear from childhood to adolescence or adulthood. Symptoms may include decreased visual clarity, a partial loss of vision, and a reduced ability to see colors. Loss of peripheral vision and night blindness can also occur. Other parts of the body outside of the eyes are usually unaffected.

CORD18 is caused by mutations in the RAB28 gene.

### Treatment

There is no cure for CORD. Treatment involves slowing down the progression of vision loss, treating complications as they arise, and helping patients adjust to the impact of losing their vision.

## Congenital Adrenal Hyperplasia (11-Beta-Hydroxylase Deficient)

### Summary

Congenital adrenal hyperplasia (CAH) describes a group of disorders that affects hormone production. The type of CAH will vary depending on the hormone that is lacking, but most forms will cause extra male hormones (androgens) to be made.

Classic forms of 11-beta hydroxylase deficient-CAH will have external genitalia in females may appear to look more male (called ambiguous genitalia). The internal reproductive organs are not affected, but both males and females will start to develop body hair, deepening of their voices, and growth spurts early due to the extra levels of androgens. Since an early growth spurt can prevent normal growth later on, many people with CAH are shorter than average as an adult. As females get older they may experience problems with fertility. People with the classic form, may also have high blood pressure.

The non-classic form is milder and does not involve high blood pressure or the external genitalia. However, they do tend to be shorter as adults with an increased amount of body hair and irregular menstruation.

Whether someone inherits the classic or non-classic form will depend on how much of the hormone is missing. Non-classic forms tend to have higher levels of remaining hormone compared to the classic forms.

11-beta-hydroxylase deficient CAH is caused by mutations in the CYP11B1 gene.

### Treatment

Treatment for 11-beta-hydroxylase deficient CAH consists primarily of medications to fix the hormone levels and treat high blood pressure.

## Congenital Adrenal Hyperplasia (3-Beta-Hydroxysteroid Dehydrogenase Deficient)

### Summary

Congenital adrenal hyperplasia (CAH) describes a group of disorders that affects hormone production. The type of CAH will vary depending on the hormone that is lacking, but most will cause extra male hormones (androgens) to be made.

Classic forms of 3-beta-hydroxysteroid dehydrogenase deficient CAH is often referred to as the salt-wasting type. People with this type lose large levels of salt (sodium) in their urine. Symptoms include dehydration, problems feeding, and vomiting. The loss of salt can eventually be life-threatening. Males and females can both have abnormalities with their external genitalia and fertility issues in adulthood, and females can have problems with excessive hair growth. External genitalia in females may appear to look more male (called ambiguous genitalia). The internal reproductive organs are not affected, but both males and females will start to develop body hair, deepening of their voices, and growth spurts early due to the extra levels of androgens. Since an early growth spurt can prevent normal growth later on, many people with CAH are shorter than average as an adult. As females get older they may experience problems with fertility.

The non-classic form is milder and does not involve salt-wasting issues and is limited to problems related to genitalia and sexual development.

Whether someone inherits the classic or non-classic form will depend on how much of the hormone is missing. Non-classic forms tend to have higher levels of remaining hormone compared to the classic forms.

3-beta-hydroxysteroid dehydrogenase deficient CAH is caused by mutations in the HSD3B2 gene.

### Treatment

Treatment for 3-beta-hydroxysteroid dehydrogenase deficient CAH consists primarily of medications to maintain proper hormone levels.

## Congenital Adrenal Hyperplasia (Cholesterol Desmolase Deficient)

### Summary

Congenital adrenal hyperplasia (CAH) describes a group of disorders that affects hormone production. The type of CAH will vary depending on the hormone that is lacking. Cholesterol desmolase deficient CAH (also called lipoid adrenal hyperplasia) is the most severe form of CAH.

Both males and females with cholesterol desmolase deficient CAH will have female-looking external genitalia. They will also all lose a high amount of sodium (salt) in their urine during early infancy causing dehydration, feeding problems, and vomiting. If not treated immediately, it can be life-threatening, and many die early from this condition.

Cholesterol desmolase deficient CAH is caused by mutations in the STAR gene.

### Treatment

There is no cure for cholesterol desmolase deficient CAH. Treatment is centered around treating the salt-wasting complications. For those that survive the early medical crises, hormone therapy and surgery may also be recommended to address the other hormonal and genitalia concerns.

## Congenital Disorder of Glycosylation, Type 1A

### Summary

Congenital disorders of glycosylation (CDG) are a set of disorders that affect how the body gets nutrients from certain proteins. The lack of nutrients can affect many parts of the body. Severity of symptoms can vary widely from individual to individual. Some individuals are greatly affected while others are only mildly affected. Symptoms generally appear during infancy and may include weak muscle tone, developmental delay, and failure to grow at a normal rate.

Additional symptoms that include difficulty with coordination and balance, intellectual disability, stroke-like episodes that may cause temporary paralysis, blood clotting issues, hormonal abnormalities, eyes that are crossed, loss of vision, and seizures. Females with CDG-IC have problems with the production of hormones that affect sexual development and often will not go through puberty. Some infants will not survive past their first year, typically due to organ failure. Others that have milder symptoms may survive into adulthood.

CDG can be caused by many different genes. Two mutations in the same gene are needed in order to cause symptoms. CDG, type 1C is caused by mutations in the ALG6 gene.

### Treatment

There is no cure for CDG, type 1C. Treatment is aimed at managing symptoms. Physical therapy, speech therapy, and occupational therapy are recommended to address developmental delay. Proper nutrition, medications, and supplements are also used, and some may require feeding tubes or surgery.

## Congenital Disorder of Glycosylation, Type 1B

### Summary

Congenital disorders of glycosylation (CDG) are a set of disorders that affect how the body gets nutrients from certain proteins. The lack of nutrients can affect many parts of the body. Severity can vary widely from individual to individual, but generally appear during the first 3 months of life for CDG, type 1B. Signs and symptoms include chronic diarrhea, vomiting, failure to grow at a normal rate, low blood sugar, blood clotting issues, liver disease, and problems with the small intestine.

Unlike other forms, CDG, type 1B does not affect the nervous system, therefore, affected individuals will not exhibit intellectual disability. Without treatment, symptoms of this disorder may be life-threatening.

CDG can be caused by many different genes. Two mutations in the same gene are needed in order to cause symptoms. CDG, type 1B is caused by mutations in the MPI gene.

### Treatment

Treatment of CDG-1B involves a life-long administration of certain medications which may make current symptoms better and prevent new ones from occurring.



## Congenital Disorder of Glycosylation, Type 1M

### Summary

Congenital disorders of glycosylation (CDG) are a set of disorders that affect how the body gets nutrients from certain proteins. The lack of nutrients can affect many parts of the body.

Symptoms for type 1M generally appear during infancy, and may include a failure to thrive, weak muscle tone, heart disease, and dry, scaly skin. Over time, affected individuals will develop an abnormally small head (microcephaly).

Additional symptoms may include seizures, muscle weakness, immune deficiency, coagulation disorders (difficulty with blood clotting), involuntary eye movements, and minimal hair growth. Some will not survive past infancy, often due to heart failure or heart disease.

Individuals affected with CDG, type 1M generally experience a shortened life expectancy with some dying during early infancy.

CDG can be caused by many different genes. Two mutations in the same gene are needed in order to cause symptoms. CDG, type 1M is caused by mutations in the DOLK gene.

### Treatment

There is no cure for CDG, type 1M. Treatment is aimed at managing symptoms and increasing quality of life.

## Congenital Disorder of Glycosylation, Type 2K

### Summary

Congenital disorders of glycosylation (CDG) are a set of disorders that affect how the body gets nutrients from certain proteins. The lack of nutrients can affect many parts of the body.

Symptoms for type 2K vary from individual to individual, but generally appear during early childhood. Affected individuals experience poor growth, feeding problems, psychomotor impairment (slowing down of thoughts and physical movement), and exhibit a short stature. Other symptoms may include poor muscle tone, unexplained recurrent fevers, eye abnormalities, an enlarged liver, skeletal abnormalities, and an abnormally small sized head (microcephaly).

CDG can be caused by many different genes. Two mutations in the same gene are needed in order to cause symptoms. CDG, type 2K is caused by mutations in the TMEM165 gene.

### Treatment

There is no cure for CDG, type 2K. Treatment is aimed at managing symptoms and increasing quality of life.

## Congenital Insensitivity to Pain

### Summary

Congenital insensitivity to pain is an autosomal recessive disorder that affects the ability of people to feel physical pain.

Signs and symptoms are present from birth. People are aware of the situation (i.e., they can feel the difference between hot and cold) but have lost the ability to perceive pain (e.g., when a hot drink is burning their mouth). Due to the inability to feel pain, affected individuals often experience many bruises, broken bones, injuries, and health problems that may go undetected since they don't always realize they have suffered an injury. Children may experience injuries to the tongue, lips, and fingers from accidental self-biting. Many affected individuals also have a reduced ability to smell or a complete loss of the sense of smell.

Congenital insensitivity to pain is caused by mutations in the SCN9A gene.

### Treatment

There is no cure for congenital insensitivity to pain. Treatment most commonly involves early education for both the affected individual and relatives of the affected individual. Extreme care and close healthcare provider supervision is required. In some cases, baby teeth may be removed to prevent injury.

## Congenital Insensitivity to Pain with Anhidrosis

### Summary

Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive disorder that affects the ability of people to feel physical pain.

Signs and symptoms are present from birth. People are aware of the situation (i.e., they can feel the difference between hot and cold) but have lost the ability to perceive pain (e.g., when a hot drink is burning their mouth). Due to the inability to feel pain, affected individuals often experience many bruises, broken bones, injuries, and health problems that may go undetected since they don't always realize they have suffered an injury. Malnutrition may also be an issue as they may also be unable to feel hunger pains and know it is time to eat. Children may experience injuries to the tongue, lips, and fingers from accidental self-biting. Many affected individuals also have a reduced ability to smell or a complete loss of the sense of smell. Additional signs may include misshapen fingernails and toenails, thick and leathery skin, bald patches on the scalp, hyperactivity, and intellectual disability.

Sweating plays an important role in cooling the body temperature, but people with CIPA have a decrease or absence of sweating (anhidrosis), resulting in recurrent high fevers and potential seizures brought on by high body temperature. If diagnosed and monitored carefully, individuals may live into adulthood.

CIPA is caused by mutations in the NTRK1 gene.

### Treatment

There is no cure for CIPA. Treatment primarily revolves around education of relatives and patients in taking care to help prevent injuries. Medical supervision is required from a very young age. In some extreme cases, affected individuals have their baby teeth removed to prevent self-injury.

## Corneal Dystrophy and Perceptive Deafness

### Summary

Corneal dystrophy and perceptive deafness (CDPD) are an autosomal recessive disorder characterized by loss of vision and hearing.

Signs and symptoms are typically apparent at birth and may include clouding of the eye (cataracts), blurred vision, involuntary/random eye movement, and loss of vision.

Hearing loss is gets worse over time, often beginning between the ages of 10 to 25 years, but it also has been present as young as the age of 4 years in some patients. Individuals typically will not exhibit any additional symptoms outside of hearing and vision loss and can live a normal lifespan.

CDPD is caused by mutations in the SLC4A11 gene.

### Treatment

Individuals with CDPD may be treated with a topical solution to improve eye abnormalities, and corneal transplant can result in a large improvement in vision. Monitoring of hearing is recommended, and hearing aids may be necessary later in life.

## Crigler-Najjar Syndrome

### Summary

Crigler-Najjar syndrome is an autosomal recessive disorder that results from high levels of bilirubin in the body. Bilirubin is made as blood cells breakdown. If it is not removed by the body by the liver, it can be toxic to various organs.

Signs and symptoms are typically apparent at birth or during infancy and include jaundice (yellowing of the skin or whites of the eyes) due to the orange-yellow tint of bilirubin. A severe form of the disorder (type I) may lead to a condition called kernicterus, which can cause brain damage, involuntary movement, hearing problems, intellectual disability, fatigue, and weak muscle tone. If left untreated, individuals may not survive past childhood. Individuals with the milder form of the disorder (type II) often survive into adulthood.

Crigler-Najjar syndrome is caused by mutations in the UGT1A1 gene.

### Treatment

There is no cure for Crigler-Najjar syndrome. Life-long treatments using special lights/lamps are can be helpful if implemented before the age of 4. Treatment may also include blood transfusions or liver transplant.

## Cystic Fibrosis

### Summary

Cystic fibrosis (CF) is an autosomal recessive genetic disorder that severely affects the respiratory, digestive, and reproductive systems. CF is a chronic condition that worsens over time and is characterized by the build-up of thick, sticky mucus that can damage many of the body's organs. Mucus is a substance that lines various organs and tissues. In a healthy person mucus is slippery, keeping the organs and tissues moist and protected. However, individuals with CF have overly thick and sticky mucus, resulting in blockage in different parts of the body especially the lungs and airways leading to problems with breathing and higher chance for infections. Permanent lung damage including the formation of scar tissue and cysts can occur.

Mucus can also block the pancreas, preventing digestive chemicals from reaching the small intestine. This results in diarrhea, malnutrition, dehydration, and poor growth.

The majority of men with CF are born missing a part of their reproductive system called the vas deferens (CAVD) leading to infertility. The severity of symptoms varies from individual to individual. "Classic CF" refers to the more common and severe form of the disorder, which is generally diagnosed in early childhood. "Non-classic CF" refers to the milder form of the disorder, which may not be diagnosed until later in life or present only as CAVD. Other genetic and environmental factors are also likely to contribute to the severity of the disorder. With improved treatment and better ways to manage the disorder, many individuals with CF now live into adulthood. The average life expectancy is late 30s, with some living into their 40s, 50s, and longer.

CF is caused by mutations in the CFTR gene.

### Treatment

Cystic fibrosis has no cure. However, treatment for symptoms have improved greatly over recent years. The goal of treatment is to ease the symptoms and slow the progression of the disease. This is done with a combination of antibiotics, diet, and other medications. Physical therapy and special exercises may be used to help break up the mucous. Lung transplant may be an option for those with severely damaged lungs.

## Cutis Laxa, Type 2A

### Summary

Cutis laxa, type 2A (CL2A) is an autosomal recessive disorder that affects the connective tissue. Connective tissue works to connect, support, and separate muscles, joints, organs, and skin. This disorder is characterized by loose, wrinkled, saggy, and non-stretchy skin. Symptoms affecting the skin can get better with age.

Severity of symptoms vary from individual to individual but generally appear at birth. Affected individuals have typical facial features that may include large ears, a small mouth, and a flat nasal bridge with a short nose. Some may also experience developmental delay, worsening problems with movement, low muscle tone, feeding issues, problems with the eyes and vision, seizures, and intellectual disability.

There are many different types of cutis laxa caused by different genes. CL2A is caused by mutations in the ATP6V0A2 gene.

### Treatment

There is no cure for CL2A. Treatment is aimed at managing symptoms and may include surgery and special education for developmental and learning difficulties.



## Cystinosis

### Summary

Cystinosis is an autosomal recessive disorder in which the chemical cystine accumulates within the body causing damage to organs and tissues, particularly the kidneys and eyes.

There are three forms of cystinosis: nephropathic cystinosis, intermediate cystinosis, and non-nephropathic or ocular cystinosis. Nephropathic cystinosis is the most severe form and appears during infancy. Symptoms may include poor growth, kidney damage, increased urination, thirst, dehydration, and soft, bowed bones. By 2 years of age, individuals may experience eye pain with an increased sensitivity to light due to cystine crystals building up in the eye. If left untreated, children typically experience kidney failure by the age of 10. Additional complications may include blindness, diabetes, thyroid and nervous system problems, infertility in males, and muscle break down.

Intermediate cystinosis generally appears during adolescence with similar symptoms as nephropathic cystinosis. Kidney and eye problems are typically the first signs in this form of the disorder. If diagnosed and treated early, some individuals may survive into their 50s. If left untreated, individuals will generally experience kidney failure by the late teens to mid-twenties. Age of onset for non-nephropathic or ocular cystinosis is variable and although they will generally experience the problems associated with the crystals in the eye, they will not develop kidney malfunction or most of the other symptoms associated with the more severe forms.

Cystinosis is caused by mutations in the CTNS gene.

### Treatment

Medication has been shown to delay or prevent kidney failure and greatly improves the life expectancy for individuals with nephropathic cystinosis. It has also been shown to delay kidney failure. Individuals should also remain well hydrated. Vitamins and minerals may be recommended. Kidney transplant may be required for those that have experienced kidney failure.

## D-Bifunctional Protein Deficiency

### Summary

D-bifunctional protein deficiency, also known as peroxisomal bifunctional enzyme deficiency, is an autosomal recessive disorder that causes deterioration of the nervous system.

Signs and symptoms first appear shortly after birth. Newborns exhibit poor muscle tone and seizures. Most individuals will never reach any developmental milestones, and the ones who do will regress within a few months. Symptoms worsen over time with individuals experiencing severe and recurrent seizures, vision and hearing loss, exaggerated reflexes, and intellectual disability.

Affected individuals may also exhibit typical similar facial features including a high forehead, widely spaced eyes, and a lengthened space between the nose and mouth. The majority of affected individuals will not survive past the age of 2 years.

D-bifunctional protein deficiency is caused by mutations in the HSD17B4 gene.

### Treatment

There is no cure for D-bifunctional protein deficiency. Treatment is supportive and includes ensuring a proper nutrition as well as medications for seizures.

## Desmosterolosis

### Summary

Desmosterolosis is a very rare autosomal recessive disorder that causes neurological problems and elevated levels of desmosterol (a precursor of cholesterol) that may build-up in the blood, kidneys, liver, and brain.

Signs and symptoms generally appear during childhood and may include delays in reaching milestones, particularly with speech and motor skills. Individuals may also experience brain abnormalities that may include a malformation in the tissue that connects the right and left halves of the brain called the corpus callosum. Additional symptoms include muscle and joint stiffness, short height, random eye movement, abnormal head size, heart problems, and seizures. Individuals may also exhibit typical similar facial features including a small lower jaw and cleft palate (an opening in the roof of the mouth).

Desmosterolosis is caused by mutations in the DHCR24 gene.

### Treatment

There is no cure for desmosterolosis. Treatment is supportive. Medication may be prescribed for seizures. Physical therapy and occupational therapy may be beneficial in aiding mobility.

## Diaphanospondylodysostosis

### Summary

Diaphanospondylodysostosis (DSD) is a rare autosomal recessive disorder that affects the bones.

Signs and symptoms generally appear shortly after birth and may include a short neck, unusual ribs, abnormalities with the vertebrae, an enlarged soft spot on an infant's skull, a short and wide chest, and breathing problems. Kidney problems are also common. Infants that are born generally will not survive very long due to breathing difficulties.

DSD is caused by mutations in the BMPER gene.

### Treatment

There is no cure for DSD. Treatment is aimed at managing symptoms.

## Dihydrolipoamide Dehydrogenase Deficiency

### Summary

Dihydrolipoamide dehydrogenase deficiency (DLD), also known as maple syrup urine disease type 3, is a rare autosomal recessive disorder that affects several systems in the body. A chemical called lactic acid builds up in the tissues and causes breathing problems, irregular heartbeat, and vomiting. Infants have weak muscles, extreme tiredness, some intellectual disability, trouble feeding, liver disease, and seizures.

Signs and symptoms are variable from individual to individual but generally appear shortly after birth and most are symptom-free between episodes that can be brought on by stress, injury, or fever. However, because the episodes can be severe, many will not live longer than a few years. Those that do survive will still have continued occurrence of the various muscle and neurological problems. Most infants die within the first few years of life. Those that survive into childhood often have neurological problems and delayed growth.

DLD is caused by mutations in the DLD gene.

### Treatment

There is no cure for DLD. Currently, there is no agreement on treatment for affected individuals. Dietary changes, vitamins, and supplements have been used to help slow the worsening of the disease but are largely unsuccessful.

## Dilated Cardiomyopathy, Type 1GG

### Summary

Cardiomyopathies are common disorders that refer to abnormalities of the heart muscle that often result in heart failure. Dilated cardiomyopathies (DCM) are the most common form of cardiomyopathies. DCM is characterized by widening of a certain part of the heart called the ventricles, that makes the heart unable to pump blood properly.

DCM may cause irregular heartbeats, blood clots, and possibly sudden death. DCM is a major cause of heart transplants in children, accounting for over 50% of the cases performed in individuals between the ages of 1 to 10 years. DCM, type 1GG is a rare autosomal recessive type of DCM that appears during infancy or childhood and has a very high rate of death. Studies of individuals affected with this form of DCM have shown over two-thirds dying from heart failure in childhood.

There are many different genes that can cause dilated cardiomyopathy. DCM, type 1GG is caused by mutations in the *SDHA* gene.

### Treatment

There is no cure for DCM, type 1GG. Treatment may include medication or implantable devices such as pacemakers and internal defibrillators may be used. Some individuals may require a heart transplant.

## Du Pan Syndrome

### Summary

Du Pan syndrome is an autosomal recessive disorder that causes a short height and skeletal abnormalities.

Individuals with Du Pan syndrome are missing a bone in their lower leg called the fibula. Additionally, they have a severe shortening of the bones in their forearms, lower legs, and toes. Intelligence and life expectancy are seemingly unaffected.

Du Pan syndrome is caused by mutations in the GDF5 gene.

### Treatment

There is no cure for Du Pan syndrome. Treatment is focused on addressing skeletal abnormalities. Physical therapy, casting, and braces are beneficial. Surgery may be recommended certain cases.

## Duchenne Muscular Dystrophy

### Summary

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that causes muscle weakness and muscle degeneration (wasting) that worsens over time.

Signs and symptoms of DMD generally appear during early childhood with muscle weakness in the hips and pelvic area, thighs, and shoulders. Eventually it also affects the arms, legs, and trunk. Affected individuals may also experience frequent falls and delayed development of motor skills (i.e., sitting and walking). Symptoms worsen rapidly, and many need wheelchair assistances by adolescence.

By early adolescence, affected individuals will experience cardiomyopathy. This is a heart abnormality causing a weakened heart muscle, making it harder for the heart to pump and deliver blood to the rest of your body. This heart condition creates extreme tiredness, irregular heartbeat, limb swelling, and shortness of breath. All of this can worsen over time and become life-threatening. Males with DMD usually die in their 20s, although advancements in care for heart and breathing problems can increase survival.

DMD is caused by mutations in the DMD gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one DMD gene is enough to cause Duchenne muscular dystrophy. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their DMD gene to cause the condition. For this reason, males are affected by this condition much more than females. About 20% of females who carry one mutation will experience mild muscle weakness, and 8% may have heart abnormalities.

### Treatment

Currently there is no cure for DMD. Treatment is aimed at managing the symptoms of the disorder and may include physical therapy, respiratory therapy, orthopedic devices (such as a leg brace), and potential surgery. Medication may help slow muscle the decline of muscle or heart function.



## Dyserythropoietic Anemia

### Summary

Dyserythropoietic anemia (CDA) is an autosomal recessive disorder that causes a shortage of red blood cells (called anemia). Red blood cells carry oxygen and nutrients to the different tissues and organs of the body so if there is a shortage of these cells, there will be damage to multiple parts of the body.

Signs and symptoms of CDA generally appear in childhood and can have different levels of severity. Symptoms may include jaundice (yellowing of the skin and eyes), an enlarged liver and spleen, heart problems, diabetes, and liver disease. On rare occasion, individuals with CDA also have bone abnormalities. Individuals with anemia also experience tiredness, weakness, and pale skin.

The prognosis for an individual affected with CDA is generally favorable, but individuals still suffer from lifelong anemia with jaundice and an enlarged spleen. Frequent monitoring by a healthcare professional is needed.

There are three types of CDA. Two mutations in the same gene are needed to cause symptoms. CDA, type 1A is caused by mutations in the CDAN1 gene, while CDA, type 1B is caused by mutations in SEC23B. The gene behind CDA, type 3 has not yet been identified.

### Treatment

There is no cure for CDA. Treatment involves managing symptoms and may include medication to increase red blood cells and decrease iron levels. Transfusion may be necessary in some cases.

## Dyskeratosis Congenita, Type 5

### Summary

Dyskeratosis congenita is a rare disorder that affects multiple parts of the body causing abnormally shaped nails, abnormal skin coloring, and white patches that form on the inside of the mouth. Dyskeratosis congenita, type 5 (DKC5) is a severe autosomal recessive form of this disorder that also causes bone marrow failure and immune system problems.

Signs and symptoms of DKC5 generally appear during early childhood with the bone marrow failure leading to a condition where not enough new blood cells are being made. Additional symptoms include higher rates of infection, poor growth both before and after birth, delays in reaching developmental milestones, liver and lung damage, and osteoporosis (weakening of the bones). Affected individuals generally will not survive past childhood with death often occurring due to bone marrow failure, infections, cancer, or lung complications.

DKC5 is caused by mutations in the RTEL1 gene.

### Treatment

There is no cure for DKC5. Treatment is aimed managing symptoms. Individuals should be closely monitored by healthcare professionals. Stem cell transplant may be considered for bone marrow failure.

## Dyskeratosis Congenita, X-linked

### Summary

X-linked dyskeratosis congenita (DKCXL) is a rare disorder that affects multiple parts of the body causing abnormally shaped nails, abnormal skin coloring, and white patches that form on the inside of the mouth.

Signs and symptoms of DKCXL generally appear during early childhood with the bone marrow failure leading to a condition where not enough new blood cells are being made and possibly leukemia. These children also have a higher risk of developing other cancers as well. Additional symptoms may include hearing loss, poor vision, liver disease, osteoporosis, build-up of scar tissue in the lungs, dental problems, and hair loss. Some individuals with a severe form of the disorder may also experience intellectual disability. Males can also have moving urine out of the bladder causing painful urination or infection.

Many individuals with the severe form of this disorder will not survive past childhood as most individuals are at higher risk for different forms of cancer and lung complications.

DKCXL is caused by mutations in the DKC1 gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one DKC1 gene is enough to cause this type of congenital dyskeratosis. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their DKC1 gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for DKCXL. Treatment is aimed managing symptoms. Individuals should be closely monitored by healthcare professionals. Stem cell transplant may be considered for bone marrow failure.

## Dystrophic Epidermolysis Bullosa

### Summary

Epidermolysis bullosa is a group of autosomal recessive disorders in which the skin is very fragile and blisters easily.

Individuals with the severe type of dystrophic epidermolysis bullosa (DEB) generally born with blisters covering the entire body from the birthing process. Blisters can also affect the inside of the mouth and digestive tract. As these blisters heal, they cause scarring that may result in difficulty eating which can lead to slow growth. Additional symptoms include fusion of the fingers and toes, nail loss, joint abnormalities (contractures) that limit movement, and loss of vision due to eye inflammation. Children are at greater risk of certain cancers, which can shorten lifespan.

Those with a milder form of the disorder tend to have blistering limited to their hands, elbows, knees, and feet with more limited scarring.

All types of DEB are caused by mutations in the COL7A1 gene. There can be both autosomal recessive and autosomal dominant forms of inheritance for this condition. This test is only looking at mutations inherited in an autosomal recessive fashion where 2 mutations are needed to cause disease.

### Treatment

There is no cure for autosomal recessive DEB. Treatment is focused on preventing and reducing blistering, scarring, and potential infections through protecting the skin and taking care of wounds. Regular skin checks and biopsies are recommended to screen for squamous cell carcinoma.

## Ehlers-Danlos Syndrome, Type 7C

### Summary

Ehlers-Danlos syndrome is a condition that affects the connective tissues that offer support to the skin, bones, blood vessels, and organs.

Signs and symptoms include soft, doughy skin that is extremely fragile and sags/bruises easily. Individuals also exhibit loose joints that may cause delay in the development of motor skills such as sitting, standing, and walking. People with Ehlers-Danlos, type 7C (also called dermatosparaxis type) will also show shorter limbs, tooth abnormalities, a bluish tint to the whites of their eyes, and mild overgrowth of body hair. Affected individuals are also at risk for organ rupture.

Mutations in various genes may cause different forms of EDS. EDS7C is caused by mutations in the ADAMTS2 gene.

### Treatment

There is no specific treatment available for EDS7C. Affected individuals, particularly children, are advised to wear protective pads or bandages over areas of the body most likely to become bruised or torn, such as the forehead, knees, and shins. Contact sports and other trauma should be avoided.

## Ellis-van Creveld Syndrome

### Summary

Ellis-van Creveld syndrome is an autosomal recessive disorder that affects bone growth, resulting in dwarfism (very short height).

Signs and symptoms of this disorder include short forearms and lower legs along with a narrow chest with short ribs. Other features include small or abnormally shaped teeth, extra fingers and toes, abnormal nails, and half are born with a heart defect. For many individuals, life expectancy depends on the severity of heart defects. Intelligence is unaffected.

Ellis-van Creveld syndrome is caused by mutations in the EVC or EVC2 genes. Two mutations in the same gene would need to be present in order to cause symptoms of the condition.

### Treatment

There is no cure for Ellis-van Creveld syndrome. Treatment is aimed at managing symptoms and may include treatment for breathing problems, tooth abnormalities, and orthopedic intervention to limit the impact of bone deformities.

## Emery-Dreifuss Muscular Dystrophy, X-linked

### Summary

X-linked Emery-Dreifuss muscular dystrophy (EDMD-XL), is an X-linked inherited disorder that causes problems with the joints and heart.

Signs and symptoms vary, but generally appearing during childhood with joint deformities called contractures. Contractures restrict the movement of certain joints, typically affecting the ankles, elbows, and neck. Most individuals will experience a continued muscle weakness and atrophy (wasting) starting with the muscles in the upper arms and lower legs, moving to the muscles in the shoulders and hips. The majority of affected individuals will experience heart problems by the age of 20 years that may present as an irregular heartbeat, heart palpitations, fainting, and stroke that can lead to sudden death.

There are different types of Emery-Dreifuss muscular dystrophy caused by mutations in different genes with different inheritance patterns. EDMD-XL is caused by mutations in the EMD gene, which is on the X chromosome (one of two sex chromosomes) and inherited in an X-linked fashion. Males only have one X chromosome, so a mutation in that one EMD gene is enough to cause this type of muscular dystrophy. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their EMD gene to cause the condition. For this reason, males are affected by this condition much more than females. Some female carriers of only one mutation may still experience the heart-related complications.

### Treatment

There is no cure for EDMD-XL. Treatment may include implantable pacemakers and defibrillators. Anti-arrhythmic agents such as beta blockers, diuretics, and ACE inhibitors may be prescribed. Heart transplant may be necessary. Physical therapy and walking aids may improve mobility.

## Enhanced S-cone Syndrome

### Summary

Enhanced S-cone syndrome, also known as Goldman-Favre syndrome, is an autosomal recessive disorder that affects vision.

Signs and symptoms generally appear during childhood; however, severity of symptoms may vary widely from individual to individual. Symptoms may include a progressive loss of visual clarity, far-sightedness, and night blindness. Peripheral (side) vision may decrease, and many individuals develop cataracts (clouding of the eyes). Affected individuals may also experience increased sensitivity to blue light and reduced vision in bright light. Some individuals will experience vision loss during childhood, while others may maintain their vision into older age. Life expectancy is unaffected, and most cases will not involve complications in any other parts in the body.

Enhanced S-cone syndrome is caused by mutations in the NR2E3 gene.

### Treatment

There is no cure for enhanced S-cone syndrome. Treatment typically involves managing symptoms with vision aids or medication.



## Epilepsy, Progressive Myoclonic, Type 1B

### Summary

Progressive myoclonic epilepsy, type 1B (PME-1B) is a rare autosomal recessive disorder that causes recurrent seizures and difficulty with movement.

Signs and symptoms generally appear between the ages of 5 and 10 years as problems with balance and coordination. These children may start to fall frequently. Additional symptoms may include muscle twitching, problems swallowing, and slurred speech. Seizures also begin to occur and usually happen at night during sleep. Intellectual ability is unaffected. Although some may not survive past childhood, most individuals die prior to adulthood.

PME-1B is caused by mutations in the *PRICKLE1* gene.

### Treatment

There is no cure for PME-1B. Treatment consists primarily of medication to control seizures. Problems with movement may require the assistance of walking aids or a wheelchair.



## Epilepsy, Pyridoxine-dependent

### Summary

Pyridoxine-dependent epilepsy (PDE) is an autosomal recessive disorder that causes various types of seizures that are hard to control.

Seizures generally appear between birth and infancy and may occur prior to birth in some cases. These prolonged seizures are not usually controlled with normal antiepileptic medication. Seizures involve muscle rigidity, loss of consciousness, and convulsions. Additional symptoms may include low body temperature, involuntary muscle contractions, and possible lasting neurological damage. If left untreated, individuals may develop abnormal brain function.

PDE is caused by mutations in the ALDH7A1 gene.

### Treatment

Individuals with PDE will require a life-long treatment of certain supplements.

## Epileptic Encephalopathy, Type 18

### Summary

Epileptic encephalopathy, type 18, also known as EE18, is an autosomal recessive disorder that causes a severe form of epilepsy (seizures).

Seizures appear shortly after birth, and delays in reaching milestones becomes evident during infancy. Additional symptoms include low muscle tone that causes floppy baby syndrome, reduced or absent reflexes, and a lack of speech. Individuals with EE18 also exhibit typical features that include a high forehead, drooping of the upper eyelids, and arched eyebrows.

EE18 is caused by mutations in the SZT2 gene.

### Treatment

There is no cure for EE18. Treatment is aimed at managing symptoms and increasing quality of life, however, currently there is no effective treatment for EE3.

## Epileptic Encephalopathy, Type 3

### Summary

Epileptic encephalopathy, type 3 (EE3), is an autosomal recessive disorder that causes a severe form of epilepsy (seizures).

Signs and symptoms appear very shortly after birth. Symptoms include involuntary muscle contractions that occur in bursts that can last up to 10 seconds. Additional symptoms include random seizures that can occur hundreds of times per day, low muscle tone that causes floppy baby syndrome and a wasting away (atrophy) of brain tissue. Affected individuals also have an unusually small head. Many will not survive past infancy, with those that survive often living in a vegetative state.

EE3 is caused by mutations in the SLC25A22 gene.

### Treatment

There is no cure for EE3. Treatment is aimed at managing symptoms and increasing quality of life, however, currently there is no effective treatment for EE3.

## Ethylmalonic Encephalopathy

### Summary

Ethylmalonic encephalopathy, is an autosomal recessive disorder that creates a build-up of a chemical (called ethylmalonic acid) in the several of the body's systems, particularly the nervous system, causing various symptoms.

These symptoms generally appear at birth or shortly after birth, and may include delay in reaching developmental milestones, muscle weakness, abnormal movements, seizures, rashes, chronic diarrhea, bleeding under the skin, and blue discoloration of the hands and feet (due to reduced oxygen). Many symptoms continue to worsen over time. Most individuals will not survive past childhood, although some mild cases have been described.

Ethylmalonic encephalopathy is caused by mutations in the ETHE1 gene.

### Treatment

There is no cure for ethylmalonic encephalopathy. Treatment of ethylmalonic aciduria includes administration of medications and supplements.

## Exfoliative Ichthyosis

### Summary

Exfoliative ichthyosis (EI) is a rare disorder that affects the skin.

Signs and symptoms generally appear shortly after birth. Affected individuals have dry and scaly skin covering most of their bodies, and experience peeling of the skin on the palms of the hands and the soles of the feet. Symptoms may be worsened by an increased amount of moisture or an injury to the skin. The prognosis for an individual affected with EI is generally favorable if treated.

EI is caused by mutations in the CSTA gene.

### Treatment

Treatment of EI is aimed at managing symptoms and may include skin creams.

## Fabry Disease

### Summary

Fabry disease is an X-linked inherited disorder in which there is a build-up of a certain fat (called globotriaosylceramide) in various tissues in the body, particularly in the kidneys, heart, and nervous system.

Signs and symptoms of Fabry disease generally appear during childhood. Symptoms include pain in the hands and feet, clusters of dark red spots on the skin, an inability to sweat, a cloudy covering over the eye (cataract), ringing in the ears, loss of hearing, and gastrointestinal problems. As the disorder progresses, individuals typically experience damage to their vital organs and health complications including kidney damage, heart attack, and stroke. Some individuals may experience a milder form of Fabry disease in which onset occurs later in life and symptoms only involves the heart and/or kidneys.

Fabry disease is caused by mutations in the GLA gene which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one GLA gene is enough to cause Fabry disease. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their GLA gene to cause the condition. For this reason, males are affected by this condition much more than females. When females are affected, it is usually milder and later in life. Life expectancy for males is generally shortened by 20 years, and life expectancy for females is generally shortened by 10 years.

### Treatment

There is no cure for Fabry disease. Treatment consists primarily of providing pain relief with medications and implanting a pacemaker or defibrillator. Dialysis or transplant may be required to help with kidney failure. Enzyme replacement therapy may also be a treatment option.

## Factor V and VIII Combined Deficiency

### Summary

Factor V and VIII combined deficiency is an autosomal recessive bleeding disorder. This disorder occurs when levels of factor V protein and factor VIII protein in the blood are lower than normal. Both factor V and factor VIII play a role in the creation of blood clots.

Individuals with factor V and VIII combined deficiency experience easy bruising and longer than normal bleeding following injury and/or surgery. Individuals with severe cases of factor V and VIII combined deficiency may experience spontaneous bleeding (bleeding for no reason) or uncontrolled bleeding after minor injuries. Severe symptoms may also include bleeding into the joints, muscles, brain, and internal organs. Females may experience these bleeding issues after giving birth or during menstruation.

Factor V and VIII combined deficiency can be caused by mutations in the LMAN1 gene.

### Treatment

Treatment consists primarily of administration of recombinant factor FVIII as replacement therapy. Fresh frozen plasma that contain factor V and factor VIII is another treatment option, however, it has been known to cause blood clots in certain individuals. Slow injections of the hormone desmopressin (DDVAP) can help stimulate more clotting factor. Clot preserving medications may also be prescribed.



## Familial Dysautonomia

### Summary

Familial dysautonomia (FD) is an autosomal recessive disorder that affects the nerve cells, which can affect things like digestion, regulation of blood pressure and body temperature, breathing, and tear production. It can also affect the sensory nervous system, which is related to senses like taste or the perception of heat and cold.

Signs and symptoms typically appear during infancy. Affected individuals experience feeding problems, gastrointestinal issues, inability to make tears, poor muscle tone, altered sensitivity to temperature and pain, vomiting, poor bone quality, recurrent pneumonia, heart problems (such as high blood pressure and irregular heartbeat), and breathing difficulties. Some affected children will experience learning disabilities. By adulthood, those with FD can experience a hard time with balance and walking as well as possible worsening vision. Most individuals experience a significantly shortened lifespan. Improved treatment has extended life expectancy somewhat, as approximately 60% of affected individuals now reach the age of 20.

FD is caused by mutations in the IKBKAP gene.

### Treatment

There is no cure for FD. Treatment is aimed at managing symptoms and improving quality of life. Some treatments include maintenance of proper nutrition, intravenous fluids, medications, physical therapies, or support devices. Adults may require walkers or wheelchairs.

## Familial Meconium Ileus

### Summary

Meconium ileus is an intestinal blockage that occurs in newborns and prevents the passage of the first stool or bowel movement (called meconium) due it being thicker and stickier than normal. Although meconium ileus can be a sign of other conditions, it can occur on its own.

Signs and symptoms in newborns may include a swollen abdomen, poor feeding, prolonged diarrhea, green colored vomit, and a failure to have the first bowel movement.

Meconium ileum may be caused by mutations in the *GUCY2C* gene.

### Treatment

One of the first steps in treating meconium ileus is to identify the area of intestine where blockage is occurring often through an x-ray or ultrasound. While some cases of meconium ileus may be treated without surgery, a surgical removal is often required.

## Familial Mediterranean Fever

### Summary

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent episodes of fever and inflammation and pain in the abdomen, chest, and joints. Occasionally the heart, spinal cord, and testicles can also be affected.

There are two types of FMF. In FMF type I, the first episode typically occurs during childhood, and episodes generally last 12 to 72 hours. Periods in between episodes are symptom free, and affected individuals generally feel normal during these times. The length of time from one episode to the next is variable and can range from days to years. Without preventive treatment, a build-up of protein deposits in the kidneys may occur, potentially leading to kidney failure.

Roughly half of the individuals experience mild signs and symptoms prior to an episode known as a prodrome. These signs and symptoms consist of uncomfortable sensations in parts of the body that will later become inflamed, followed by general feelings of discomfort.

In FMF type II, individuals may exhibit no physical symptoms. However, amyloidosis (buildup of amyloid protein deposits in the internal organs) may occur, potentially leading to kidney failure.

FMF is caused by mutations in the MEFV gene.

### Treatment

There is no cure for FMF, and treatment is targeted to prevent episodes through the use of medications. With early diagnosis and regular treatment, individuals can live a normal life expectancy. Kidney transplant may be an option for those that have developed kidney failure.

## Fanconi Anemia, Type A

### Summary

Fanconi anemia is a group of autosomal recessive blood disorders characterized by bone marrow failure, physical abnormalities, defects in the heart, kidney and gastrointestinal system, and an increased risk for leukemia and other types of cancer. Affected individuals may also have learning disabilities and intellectual disability.

Approximately 60%-75% of affected individuals suffer from physical abnormalities such as short height, spotted skin, and malformations of body parts and organs. Bone marrow failure can start as early as the first decade of life. By the age of 40 to 50, bone marrow failure is estimated to occur in 90% of individuals, with 10-30% having blood cancers (primarily leukemia), and 25-30% having other solid tumor cancers, however, most die by the age of 30.

Fanconi anemia is caused by many different genes. Two mutations in the same gene are needed to cause symptoms. Fanconi anemia, type A is caused by mutations in the FANCA gene.

### Treatment

There is no cure for Fanconi anemia. Treatment is focused on the management of symptoms. Oral medication is available to help improve blood count, however, individuals often develop resistance to medication. Bone marrow transplant may be an option to cure leukemia, however, it will not prevent solid tumors from developing in other areas of the body. Stem cell treatment via cord blood is an option.

## Fanconi Anemia, Type C

### Summary

Fanconi anemia is a group of autosomal recessive blood disorders characterized by bone marrow failure, physical abnormalities, defects in the heart, kidney and gastrointestinal system, and an increased risk for leukemia and other types of cancer. Affected individuals may also have learning disabilities and intellectual disability.

Approximately 60%-75% of affected individuals suffer from physical abnormalities such as short height, spotted skin, and malformations of body parts and organs. Bone marrow failure can start as early as the first decade of life. By the age of 40 to 50, bone marrow failure is estimated to occur in 90% of individuals, with 10-30% having blood cancers (primarily leukemia), and 25-30% having other solid tumor cancers, however, most individuals die by the age of 30.

Fanconi anemia is caused by many different genes. Two mutations in the same gene are needed to cause symptoms. Fanconi anemia, type C is caused by mutations in the FANCC gene.

### Treatment

There is no cure for Fanconi anemia. Treatment is focused on the management of symptoms. Oral medication is available to help improve blood count, however, individuals often develop resistance to medication. Bone marrow transplant may be an option to cure leukemia, however, it will not prevent solid tumors from developing in other areas of the body. Stem cell treatment via cord blood is an option.

## Fanconi Anemia, Type G

### Summary

Fanconi anemia is group of autosomal recessive blood disorders characterized by bone marrow failure, physical abnormalities, defects in the heart, kidney and gastrointestinal system, and an increased risk for leukemia and other types of cancer. Affected individuals may also have learning disabilities and intellectual disability.

Approximately 60%-75% of affected individuals suffer from physical abnormalities such as short height, spotted skin, and malformations of body parts and organs. Bone marrow failure can start as early as the first decade of life. By the age of 40 to 50, bone marrow failure is estimated to occur in 90% of individuals, with 10-30% having a blood cancers (primarily leukemia), and 25-30% having other solid tumor cancers. Most individuals die by the age of 30.

Fanconi anemia is caused by many different genes. Two mutations in the same gene are needed to cause symptoms. Fanconi anemia, type G is caused by mutations in the FANCG gene.

### Treatment

There is no cure for Fanconi anemia. Treatment is focused on the management of symptoms. Oral medication is available to help improve blood count, however, individuals often develop resistance to medication. Bone marrow transplant may be an option to cure leukemia, however, it will not prevent solid tumors from developing in other areas of the body. Stem cell treatment via cord blood is an option.

## Fatty Acid Hydroxylase-Associated Neurodegeneration

### Summary

Fatty acid hydroxylase-associated neurodegeneration (FAHN), also called spastic paraplegia type 35, is an autosomal recessive disorder that affects movement and vision.

Signs and symptoms most commonly begin between the ages of 3 and 11 years as frequent falls and changes in the way a child walks due to muscle stiffness and problems with coordination. These issues get worse over time and a wheelchair is eventually required. Eye problems are due weak eye muscles and a destruction of the nerves that carry messages from the eyes to the brain (optic atrophy). Issues include problems with seeing color, loss of visual clarity, involuntary eye movements, and trouble controlling the eyes. Additional symptoms may include seizures, intellectual disability, loss of speech, increased infections, and problems swallowing or chewing.

Individuals with SLS also experience intellectual disability, speech difficulties, and seizures. Children may also experience delay in motor skills (such as crawling and walking). Roughly 50% will need to use a wheelchair. Those with SLS may also be nearsighted and have a sensitivity to light.

SLS is caused by mutations in the FA2H2 gene.

### Treatment

There is no cure for FAHN. Treatment may include medications, surgery, walking-assistance devices, and monitoring of diet.

## Foveal Hypoplasia, Type 2

### Summary

Foveal hypoplasia, type 2 is an autosomal recessive disorder that affects the eyes. Other systems of the body are usually unaffected. Signs and symptoms generally appear at birth with poor vision and random movement of the eyes. The fovea is the center of the back of the eye, and it is responsible for the sharpest and most detailed part of our vision. Individuals affected with this disorder have a poorly formed fovea, causing problems with the eyes and sight.

Foveal hypoplasia, type 2 is caused by mutations in the SLC38A8 gene.

### Treatment

There is no cure for foveal hypoplasia, type 2. Currently there is no standard of treatment for this disorder.



## Fragile X Syndrome

### Summary

Fragile X syndrome (FRAX) is the most common cause of inherited intellectual disability. Males are affected more severely and more commonly affected than females.

Early signs of FRAX include delayed speech and developmental milestones, which then continue into mild to moderate intellectual disability. Females are affected to a lesser degree, with approximately one-third experiencing intellectual disability. Children with FRAX often show anxiety, hyperactivity, attention deficit disorder, and aggression. Females often have milder symptoms and may appear to have depression, shyness, or avoidance of social interactions. About one third of males will also have autism or autism-like behavior.

Affected males often display features that include a long narrow face, large ears, and a prominent jaw and forehead that become more noticeable with age. Approximately 20% of males and 5% of females will experience seizures (epilepsy). Although there can be rare cases of eye abnormalities (strabismus) or heart issues (mitral valve prolapse), these are often not life-threatening.

FRAX is caused by mutations in the FMR1 gene, which is on the X chromosome. The inheritance of FRAX is more complex than other X-linked conditions. In addition to inheriting the changed FMR1 gene, the degree to which the gene is changed also plays a role in who will show signs of the condition and what those symptoms may be.

The FMR1 gene has a particular section of DNA that is repeated (called CGG repeats). Although these repeats are found in everyone, the more repeats that are present, the greater the likelihood the gene is not to be working properly. These repeats can grow in number from generation to generation, increasing the risk for problems. The number of repeats, and thus the category of FRAX, can be divided into 4 categories:

**Non-carrier:** 5 to 44 repeats – This is considered a “stable” amount of repeats, and this person is not at risk for any symptoms or for having a child with FRAX.

**Intermediate carrier:** 45 to 54 repeats – This person is not at risk for having a child with FRAX, but his/her children could experience an expansion in the number of repeats making the person a carrier and putting this individuals’ grandchildren at risk for having a premutation or full mutation.

**Premutation carrier:** 55 to 200 repeats – This person is considered a carrier. Females are at risk for having children with FRAX. Carriers usually do not have any intellectual disabilities but can be more vulnerable to anxiety or depression.

- Males and females with a premutation are also at a higher risk for developing fragile X-associated tremor/ataxia syndrome (FXTAS) after the age of 50. This condition can cause short-term memory loss, mental/behavioral changes, leg weakness, involuntary shaking (tremors), problems with balance (ataxia), and other neurological problems. The overall the risk for FXTAS is 46% in males and 17% in female carriers but may vary depending on age and is likely to increase with age.

- Approximately 21% of female premutation carriers can also develop fragile X-associated primary ovarian insufficiency (FXPOI). FXPOI is characterized by decreased ovarian function, which may result in infertility and early menopause.

- The higher the number of repeats in this category, the more likely females are to have a child with over 200 repeats (full mutation), and the more likely males and females are to show signs of FXTAS or FXPOI.

Full mutation: more than 200 repeats – Males with over 200 repeats will be affected with FRAX. The higher the number of repeats, the more severe the condition will be. Approximately 50% of females with more than 200 repeats on one copy of FMR1 will suffer from intellectual disability, although it is usually milder than what is experienced by males.

#### Treatment

There is no cure for fragile X syndrome; therefore, treatment focuses on improving the lives of the affected individuals. Early diagnosis and intervention can help provide a child with early educational support services as well as speech, occupational, and behavioral therapies. There are many specialty clinics opening across the United States that are designed to provide support for families dealing with fragile X syndrome.

## Fructose Intolerance

### Summary

Fructose Intolerance is an autosomal recessive disorder that affects the ability to digest the specific sugar called fructose (a common sugar found in many fruits).

Signs and symptoms typically first appear during infancy and may include convulsions, excessive sleepiness, irritability, jaundice, poor feeding, and vomiting. After eating fructose, individuals may also experience bloating, abdominal pain, diarrhea, and low blood sugar. If left untreated, affected individuals may not grow or gain weight at a normal rate. Continued eating of fructose may lead to kidney and liver damage, an enlarged spleen, and jaundice (yellowing of the skin and eyes). Long-term exposure to fructose without treatment could cause seizures, coma, or death.

The earlier the diagnosis, the less damage is done to the body. Most symptoms resolve within 3 to 4 weeks of a fructose-free diet allowing people to live symptom free with a normal life expectancy. Affected individuals generally develop a strong dislike for foods and juices that contain fructose. Without dietary restrictions, affected individuals may develop severe and life-threatening liver disease or kidney failure. Despite careful dietary monitoring, some individuals may still experience serious liver disease.

Fructose intolerance is caused by mutations in the ALDOB gene.

### Treatment

Treatment for fructose intolerance consists of a strict fructose-free diet. Liver transplant may be required in cases of serious liver disease.

## Fundus Albinpunctatus

### Summary

Fundus albinpunctatus is an autosomal recessive disorder that causes night blindness which is the inability to see well at night or in poor light. Signs and symptoms generally appear during early childhood. Affected individuals have small yellow-white dots over the retina of the eye, called a flecked-retina.

Fundus albinpunctatus is caused by mutations in the RDH5 gene.

### Treatment

There is no full cure for fundus albinpunctatus. Treatment may involve high doses of beta-carotene to help improve night blindness. Vision aids may also be utilized.

## Galactosemia

### Summary

Galactosemia is an autosomal recessive disorder that affects the body's ability to process a sugar called galactose. Galactose is a part of lactose and is found in many types of food such as dairy products and baby formula.

There are several different types of galactosemia. The three main forms are classic galactosemia (type 1) and galactokinase deficiency (type 2), and galactose epimerase deficiency (type 3).

Classic galactosemia is the most common and severe form of this disorder. Signs and symptoms typically appear within a few days after birth. Affected infants may exhibit feeding difficulties, lack of energy, a failure to grow at a normal rate, jaundice, liver damage, loss of appetite, and vomiting. Without treatment, individuals may suffer from infections, delayed development, speech problems, and intellectual disability. Children are at risk for cataracts (clouding of the eyes), and females may experience reproductive problems. For classic galactosemia, if diagnosed and treated early, most individuals can live a normal life expectancy. There may still be risk for intellectual disability, cataracts, and reproductive problems.

Galactokinase-deficient galactosemia is less severe than classic galactosemia. Individuals rarely experience serious health complications, with the only associated symptom generally being the development of cataracts.

Galactose epimerase-deficient galactosemia can have a wide range of symptoms including cataracts, delayed growth and development, liver and kidney problems, and intellectual disability.

Classic galactosemia is caused by mutations in the GALT gene. Galactokinase deficiency is caused by mutations in the GALK1 gene. Galactose epimerase deficiency is caused by mutations in the GALE gene.

### Treatment

Individuals with classic galactosemia will need to modify their diets to restrict foods containing lactose (i.e., dairy products). They will also need to monitor galactose levels through blood tests. Calcium and vitamin supplements may be recommended. Speech therapy and surgery for removal of cataracts may be optional.

Individuals with galactokinase deficiency should also modify their diets to restrict foods containing lactose. Surgery may be an option for removal of cataracts.

## Gaucher Disease

### Summary

Gaucher disease (GD) is an autosomal recessive disorder in which the body fails to produce an enzyme needed to break down fatty materials. This results in a wide range of symptoms in various organs and tissues.

Severity and age of onset vary from individual to individual. Symptoms may include an enlarged liver and spleen (causing a bulging abdomen), anemia, bone pain, skeletal abnormalities, and lung disease. Intelligence is unaffected. There are 5 different forms of GD.

Type 1 is the most common. It can affect people of any age with a range of severity but typically does not involve problems with the brain or spinal cord.

Type 2 usually appears before the age of 2 years and is one of the more severe types involving brain damage, seizures, abnormal eye movements, intellectual disability, and dementia. Most people with GD type 2 will not survive beyond 4 years of age.

Type 3 is also one of the more severe types, but it can start a little later and worsens slower than type 2. While some individuals may not survive past childhood, others may live into their 40s.

The perinatal-lethal form is the most severe but is also rare. Symptoms can start before birth and include extensive swelling due to fluid accumulation, enlarged liver and spleen, dry and scaly skin, and life-threatening neurological abnormalities leading to death shortly after birth.

The fifth form of GD is the cardiovascular form which primarily affects the heart although individuals can also have an enlarged liver and spleen, bone disease, and eye abnormalities.

All forms of GD are caused by different mutations in the GBA gene.

### Treatment

Enzyme replacement therapy (ERT) is the standard treatment available for most individuals affected with GD, types 1 and 3. ERT does not prevent or improve neurological symptoms but is effective in preventing bone and spleen damage. Additional treatments include blood transfusions, joint replacement, heart valve replacement, and medication for pain. Bone marrow transplant is a rare procedure that may help to reverse non-neurological symptoms of GD, type 1.

There is no effective treatment for severe brain damage that may occur with GD types 2 and 3.

## Giant Axonal Neuropathy

### Summary

Giant axonal neuropathy is an autosomal recessive disorder that causes abnormal function of the brain and nerves, often causing weakness and numbness. Signs and symptoms generally appear between infancy to early childhood. Symptoms may progress to a problems with coordination, loss of reflexes in the limbs, hearing problems, poor vision, seizures, and intellectual disability. Most individuals become dependent on a wheelchair or are bedridden by early adolescence. Symptoms worsen over time, and most will not survive past early adulthood.

Giant axonal neuropathy is caused by mutations in the GAN gene.

### Treatment

There is no cure for giant axonal neuropathy. Treatment is aimed at managing symptoms.

## GJB6-related DFNB1A Non-syndromic deafness

### Summary

Non-syndromic deafness is an inherited disorder that causes isolated deafness but is not associated with symptoms that affect other parts of the body.

Most cases of non-syndromic deafness are associated with hearing loss caused by damage to the inner ear. The inner ear serves as the area that helps to process sound, holds nerves that send information from the cochlea to the brain, and is involved with balance. Age of hearing loss is variable and can occur at any age.

Loss of hearing prior to an individual learning to speak is called prelingual hearing loss. Loss of hearing that occurs after the development of speech is called post lingual hearing loss.

There are several forms of non-syndromic deafness that are grouped according to the affected gene and the pattern of inheritance.

A certain form of non-syndromic deafness, called DFNB1A, is inherited in an autosomal recessive pattern. This form of non-syndromic deafness generally is apparent at birth and is characterized by a non-progressive, prelingual hearing impairment that varies from mild to severe hearing loss. Deafness results from damage to the neural receptors of the inner ear. Loss of hearing caused by changes to the inner ear are called sensorineural deafness.

GJB6-related non-syndromic deafness is caused by mutations in the GJB6 gene, which is responsible for providing instructions for making a protein called connexin 30. This protein plays a role in allowing communication between cells. Mutations in the GJB6 gene affect the communication between cells, potentially affecting the function or survival of the cells needed for hearing. Sometimes a GJB6 gene mutation can be found in combination with a GJB2 gene mutation and can also cause DFNB1A non-syndromic deafness.

### Treatment

There is no cure for GJB6-related non-syndromic deafness. Treatment should include a speech therapist and a hearing aid specialist. Special educational programs may be beneficial. Individuals may show improvement by using hearing aids or cochlear implants.



## Glanzmann Thrombasthenia

### Summary

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder that causes an abnormality in blood platelets, resulting in easy bruising and bleeding.

Symptoms vary from individual to individual but generally appear at birth or shortly after birth. Symptoms may include prolonged easy bleeding (particularly after surgery or injury), bleeding from the gums, easy bruising, nosebleeds, and heavy menstrual bleeding for women. Some bleeds may be life-threatening.

Glanzmann thrombasthenia may be caused by mutations in the ITGA2B or ITGB3 genes.

### Treatment

There is no cure for Glanzmann thrombasthenia. Treatment is aimed at managing symptoms and may include transfusions to help control bleeding. Affected individuals should talk with their doctor before taking drugs that could make bleeding last even longer such as nonsteroidal anti-inflammatory drugs (i.e., ibuprofen and naproxen).

## Glutaric Acidemia, Type 1

### Summary

Glutaric acidemia, type 1 (GA1) is an autosomal recessive disorder in which the body is unable to properly break down certain proteins. So, as the proteins build-up in the body it can cause potential brain damage, particularly in the region that controls movement.

Signs and symptoms of GA1 generally appear during infancy to early childhood but can sometimes appear during adolescence or adulthood. Severity of symptoms vary widely from individual to individual. In many cases, symptoms first appear as a metabolic crisis, which is an episode marked by low blood sugar, vomiting, lack of energy, irritability, and difficulty feeding. If left untreated, a metabolic crisis may lead to seizures, swelling/bleeding of the brain, intellectual disability, coma, and death. Periods of stress, illness, and infection may trigger episodes or worsen symptoms. These children also have muscles that are stiff or have spasms and can also have bleeding in the brain.

If diagnosed and treated early, individuals can live relatively normal lives. If metabolic crises have already occurred, the physical and intellectual damage that results are irreversible. If left untreated, GA1 can be fatal.

GA1 is caused by mutations in the GCDH gene.

### Treatment

There is no cure for GA1. Treatment is focused on preventing metabolic crises. Treatment includes frequent meals and a low levels of certain proteins. Vitamins, supplements, and staying well-hydrated are also recommended.

## Glutathione Synthetase Deficiency

### Summary

Glutathione synthetase deficiency, also called pyroglutamic acidemia, is an autosomal recessive disorder in which individuals are unable to produce an antioxidant called glutathione which plays a role in protecting cells from damage and in building DNA and other proteins in the body.

Age of onset and severity of symptoms vary from individual to individual. People with a mild form of glutathione synthetase deficiency typically only exhibit mild anemia (low amount of red blood cells) which can make a person feel weak or tired along with chest pain, dizziness, or shortness of breath. A more intermediate form also shows the sign of high acid levels in the blood and tissues (acidosis). Individuals with severe glutathione synthetase deficiency exhibit the symptoms found in the intermediate form as well as neurological symptoms, including seizures, delay of motor skills, intellectual disability, loss of coordination, decline in speech, and a slowing of physical reactions. Some individuals may also develop recurrent bacterial infections.

Glutathione synthetase deficiency is caused by mutations in the GSS gene.

### Treatment

There is no cure for glutathione synthetase deficiency. Long-term complications may be avoided or minimized with early treatment, which can include vitamin supplements and medications to correct acidosis.

## Glycine Encephalopathy

### Summary

Glycine encephalopathy (GCE), also known as nonketotic hyperglycinemia, is an autosomal recessive disorder that causes a toxic build-up of a molecule called glycine in the tissues and organs of the body, particularly in the brain.

Signs and symptoms usually appear shortly after birth and may include a lack of energy, poor muscle tone, feeding issues, jerky movements, and potentially life-threatening breathing problems. Individuals that survive the initial symptoms go on to develop severe intellectual disability and seizures. Females tend to be more severely affected than males. Some rarer forms may not show signs until later in childhood or adulthood and can vary in severity.

Mutations in different genes can cause GCE, including the GLDC or AMT genes. Two mutations in the same gene would be needed to cause symptoms of the disease.

### Treatment

There is no cure for GCE. Treatment is aimed at managing symptoms and may include medication to control seizures or lower glycine levels, physical therapy, a feeding tube to assist with swallowing, and medication for gastroesophageal reflux.

## Glycogen Storage Disease, Type 1 (von Gierke)

### Summary

Glycogen storage disease, type 1 (GSD1), also called von Gierke disease, is an autosomal recessive disorder that is characterized by the buildup of a sugar called glycogen in the body. This build-up affects the way certain organs and tissues will function.

Shortly after birth, affected infants begin difficulty maintaining proper sugar levels in the blood. As these levels drop too low (hypoglycemia), they can cause seizures. Additional symptoms, especially if untreated, include an enlarged liver causing a large abdomen, developmental delays, irritability, short height, delayed puberty, bone thinning (osteoporosis), kidney disease, and high blood pressure. Early diagnosis and treatment have improved life expectancy and quality of life.

There are two types of glycogen storage disease, type 1. They are very similar and share many features. GSD1B has the features listed above in addition to high risk of infection, inflammation of the intestines, high risk for cavities and gum disease, as well as abnormal teeth and mouth sores. GSD1A is caused by mutations in the G6PC gene, while GSD1B is caused by mutations in the SLC37A4 gene. Two mutations in the same gene would be needed to cause symptoms.

### Treatment

There is no cure for GSD1. Treatment is aimed at maintaining healthy blood sugar levels. Diet changes (e.g., more frequent eating, avoiding certain sugars) can prevent many complications of the disorder. Medication may also be prescribed to treat symptoms.

## Glycogen Storage Disease, type 2 (Pompe)

### Summary

Glycogen storage disease, type 2 (GSD2), also known as Pompe disease or acid maltase deficiency, is an autosomal recessive disorder caused by the build-up of a sugar called glycogen in the body. This build-up affects the way certain organs and tissues will function.

There are three types of Pompe disease differing in age of onset and severity of symptoms. In the classic infantile-onset form of Pompe disease, symptoms appear within a few months after birth. Symptoms include muscle weakness, enlarged liver, heart defects, and poor muscle tone, which can affect movement and feeding. Affected individuals may also experience breathing problems and fail to grow at a normal rate. Most infants will not live past their first year of life, often experiencing heart or lung failure.

In the non-classic infantile-onset form, symptoms appear by age 1 and may include delayed motor skills, enlarged heart, and muscle weakness. Unlike the classic infantile-onset form, individuals affected with this type rarely experience heart failure. However, muscle weakness often leads to serious breathing problems, often leading to death in early childhood.

With the late-onset form of GSD2, start of the disease is in late childhood and tends to worsen more slowly. Individuals will still experience continued muscle weakness, particularly in the legs, trunk, and muscles that control breathing. Breathing problems may cause life-threatening respiratory failure, with the average lifespan reaching 55 years of age.

Typically, the later in age that symptoms develop, the more slowly the disorder will progress, although life expectancy will be shortened regardless, usually due to lung failure.

GSD2 is caused by mutations in the GAA gene.

### Treatment

There is no cure for GSD2. Treatment is aimed at managing symptoms. Enzyme replacement therapy has been shown to decrease heart size, improve muscle function, and reduce glycogen buildup, helping decrease some symptoms and prolonging life expectancy. Proper nutrition, physical therapy, and an exercise routine may be recommended.

## Glycogen Storage Disease, Type 3

### Summary

Glycogen storage disease, type 3 (GSD3), also known as Cori or Forbes disease, is an autosomal recessive disorder caused by the build-up of a sugar called glycogen in the body. This build-up affects the way certain organs and tissues will function, particularly the liver and muscles.

Symptoms typically appear during infancy or early childhood. However, a milder form of this disorder may not appear until adulthood. Symptoms may include low blood sugar, enlarged liver causing a swollen abdomen, slow growth with short height. The liver typically returns to a normal size by adolescence, but some individuals may still experience liver disease (cirrhosis) or failure. A small percentage of affected people will develop non-cancerous tumors in the liver. Many symptoms can be managed, increasing life expectancy and quality of life. There is, however, an increased risk of infant death from seizures caused by low blood sugar (hypoglycemia).

There are 4 subtypes of GSD3. Types A and C mainly affect the liver and muscles. Muscle weakness may develop later in life and can affect the heart and movement. In contrast, type B and D usually involve just the liver. Muscle weakness may develop later in life and can affect the heart and movement.

All types of GSD3 are caused by mutations in the AGL gene.

### Treatment

There is no cure for GSD3. Dietary changes such as a high protein and frequent feeding are the main treatment for infants.

## Glycogen Storage Disease, type 5 (McArdle)

### Summary

Glycogen storage disease, type 5 (GSD5), also known as McArdle disease, is an autosomal recessive disorder in which skeletal muscles are unable to break down a certain sugar called glycogen to make energy.

Symptoms of this disorder generally begin during early adolescence but can appear during infancy or adulthood. Individuals affected with GSD5 have difficulty exercising and will typically feel fatigue, pain, and cramps within the first few minutes of exercise. After a period of rest, many individuals will experience a second wind in which they are able to resume exercise with little to no symptoms. In some individuals, muscle weakness can become worse over time. Roughly half of those affected with GSD5 will experience a breakdown of muscle tissue that releases a protein called myoglobin, which causes urine to turn a reddish-brown color and can result in kidney failure. With proper management of exercise, individuals should be able to lead healthy lives with a normal life expectancy.

GSD5 is caused by mutations in the PYGM gene.

### Treatment

There is no cure for GSD5. Treatment consists of carefully monitoring exercise. Studies have shown that consuming the sugar sucrose prior to activity may decrease muscle pain and fatigue.



## GM1-gangliosidosis

### Summary

GM1-gangliosidosis is an autosomal recessive disorder that causes a continued breakdown of the nerve cells in the brain and spinal cord.

Type I GM1-gangliosidosis (infantile form) is the most severe of the disorder, typically appearing before the age of 6 months. Initial signs are a slowing of development, muscle weakness, and a loss of skills previously learned. As the disorder progresses, individuals will develop skeletal abnormalities, an enlarged liver and spleen, intellectual disabilities, loss of vision, and seizures. Most will not survive beyond early childhood.

Type II (late infantile or juvenile form) typically appears between the ages of 1 to 5 years. Symptoms include loss of previously learned skills, enlarged organs, and delayed neurological development. Type II progresses more slowly than type I but will still shorten life expectancy. Most individuals survive into mid-childhood or early adulthood.

Type III (adult or chronic form) is the mildest form of the disorder generally appearing between the teens to twenties. Symptoms primarily consist of involuntary muscle tensing. Life expectancy is variable.

GM1-gangliosidosis is caused by mutations in the GLB1 gene.

### Treatment

There is no cure for GM1-gangliosidosis. Treatment is aimed at managing symptoms. There are ongoing clinical trials for new medical treatments, but they are not currently available.

## GRACILE Syndrome

### Summary

GRACILE syndrome is a severe autosomal recessive disorder that is fatal during infancy. GRACILE stands for the different main features:

GR: Growth retardation

A: Aminoaciduria

C: Cholestasis

I: Iron overload

L: Lactic acidosis

E: Early death

Affected pregnancies suffer from poor growth prior to birth and deliver smaller than average newborns who continue to experience slow growth (growth retardation) after birth. Individuals suffer from large amounts of iron in the liver and a build-up of lactic acid in the body (lactic acidosis) which can cause damage to various organs. Lactic acidosis can cause symptoms such as vomiting, abdominal pain, weakness, rapid breathing, irregular heartbeat, and mental status changes. Additionally, kidney problems create high levels of amino acids in urine (aminoaciduria) and a reduced ability to produce a digestive fluid called bile which leads to damaging levels of bile in the liver (cholestasis). Half of affected individuals die within a few days after birth, and the majority will not survive past their first few months of life.

GRACILE syndrome is caused by mutations in the BCS1L gene.

### Treatment

There is no cure for GRACILE syndrome. Treatment generally will not extend life expectancy.

## Gray Platelet Syndrome

### Summary

Gray platelet syndrome (GPS) is an autosomal recessive bleeding disorder caused by abnormal platelets, which are blood cells that help form clots.

Signs and symptoms generally appear during infancy or early childhood and may include low platelet counts that make it harder to form clots and thus results in easy bruising, nosebleeds, and excessive bleeding. Individuals affected with GPS may also experience heavy bleeding following surgery or injury. Females tend to have irregular and heavy menstruation.

Individuals with GPS often have myelofibrosis, which is the buildup of scar tissue in the bone marrow, which further reduces the number of total blood cells being made, which can lead to an enlarged spleen. Since the condition can worsen with age, adults are at greater risk for life-threatening bleeding events.

GPS is caused by mutations in the NBEAL2 gene.

### Treatment

There is no cure for GPS. Treatment involves predicting and preventing bleeding events or minimizing the risk for one. Individuals should take great care to avoid contact sports and activities that may result in trauma or injury. Individuals may require medication and may also need to have platelet transfusions prior to any surgery. Splenectomy (spleen removal) may also be considered if the spleen becomes enlarged.

## Growth Hormone Deficiency, Type 1B

### Summary

Growth hormone deficiency is an autosomal recessive disorder caused by the absence or severe shortage of growth hormone.

Signs and symptoms are generally evident by early childhood when affected individuals fail to grow at the expected rate and exhibit an unusually short height (less than 3rd percentile for their age group). Additional signs may include an immature appearance when compared to peers, a prominent forehead, a heavier build, and a decreased level of energy. Most affected individuals reach normal height with treatment. Intelligence and life expectancy are unaffected.

There are three different types of isolated growth hormone deficiency (not occurring with other abnormalities in the body). Type 1A is the most severe form and is due to a complete absence of growth hormone. Those affected with type 1A are shorter than normal at birth.

Type 1B and Type 2 are milder than type 1A due to a small amount of growth hormone that remains. The short stature in these children do not show until early to mid-childhood.

Growth hormone deficiency, type 1B is caused by mutations in the GHRHR gene.

### Treatment

There is no cure for PME-1B. Treatment consists primarily of medication to control seizures. Problems with movement may require the assistance of walking aids or a wheelchair.

## Growth Retardation, Developmental Delay, Coarse Facies, and Early Death

### Summary

Growth retardation, developmental delay, coarse facies, and early death (GDFD) is a very rare autosomal recessive disorder that causes a delay in growth, neurological problems, and facial abnormalities.

Signs and symptoms generally appear during infancy and include a failure to thrive, slow growth, small head size, severe developmental delay, brain abnormalities, seizures, and heart defects. Typical facial features include abnormal nostrils, a protruding tongue, and overall coarse facial features. Additional problems include genital abnormalities, hearing loss, eye problems, and a cleft palate (an opening in the roof of the mouth). Most will not survive past the age of 3 years.

GDFD is caused by mutations in the FTO gene.

### Treatment

There is no cure for GDFD. Treatment is supportive and aimed at managing symptoms to help increase quality of life.

## Guanidinoacetate Methyltransferase Deficiency

### Summary

Guanidinoacetate methyltransferase deficiency (GAMT deficiency) is an autosomal recessive disorder that affects the brain and muscles.

Signs and symptoms generally appear between 3 months and 3 years of age, though some individuals may have symptoms that appear in adulthood. Symptoms include severe intellectual disability, limited speech development, delayed development of physical skills, and seizures. Many individuals will also develop autistic-like behaviors and random, involuntary muscle spasms. In severe cases of GAMT, individuals may experience loss of previously obtained milestones and skills. Treatment appears to be effective at reducing the severity of symptoms. However, symptoms developed prior to diagnosis generally cannot be reversed. It is unclear whether or not GAMT affects life expectancy.

GAMT deficiency is caused by mutations in the GAMT gene.

### Treatment

There is no cure for GAMT. Treatment is aimed at managing symptoms and preventing additional symptoms from developing. Treatment may include a modified diet in addition to medication and other supplements.

## Hearing Loss

### Summary

Hearing loss can be syndromic (associated with other abnormalities) or non-syndromic (no other symptoms). Most non-syndromic hearing loss is associated with damage to the inner ear (called sensorineural hearing loss), which serves as the area that helps to process sound, holds nerves that send information from the cochlea to the brain, and is involved with balance. Age of hearing loss is variable and can occur at any age either prior to learning to speak (prelingual) or after (post lingual). The hearing loss can be stable or can get worse over time and possibly lead to complete deafness. Other parts of the body are not affected, and life expectancy is not usually reduced.

Over 50 different genes are involved in non-syndromic hearing loss, with more than 20 inherited in an autosomal recessive fashion. A selective set is listed below.

MYO15A - Causes DFNB3

TMC1 - Causes DFNB7

TMPRSS3 - Causes DFNB8/10

OTOF - Causes DFNB9

STRC - Causes DFNB16

TRIOBP - Causes DFNB28

MYO3A - Causes DFNB30

MYO6 - Causes DFNB37

DFNB59 - Causes DFNB59

SYNE4 - Causes DFNB76

LOXHD1 - Causes DFNB77

### Treatment

There is no cure for non-syndromic hearing loss. Treatment should include a speech therapist, and some may benefit from special educational programs. Individuals may show improvement by using hearing aids or cochlear implants.

## Hearing Loss (DFNB1A, Connexin 26)

### Summary

Hearing loss and deafness can be a result of a syndromic (associated with other abnormalities) or non-syndromic (no symptoms affecting other parts of the body) cause. Hearing loss DFNB1A is a form of hearing loss that is non-syndromic and is associated with damage to the inner ear (called sensorineural hearing loss), which serves as the area that helps to process sound, holds nerves that send information from the cochlea to the brain, and is involved with balance. DFNB1A usually occurs at an early age prior to learning to speak (prelingual). Although the severity of hearing loss can vary, it does not usually get worse over time.

Over 30 different genes have been associated with non-syndromic hearing loss and deafness, with more than 20 inherited in an autosomal recessive fashion. DFNB1A is an autosomal recessive form of hearing loss caused by mutations in the GJB2 gene, which provides instructions for a protein called connexin 26.

### Treatment

There is no cure for GJB2-related deafness. Treatment can include speech therapy, hearing aids, and cochlear implants.



## Hemolytic Anemia (with or without Immune-Mediated Polyneuropathy)

### Summary

Hemolytic Anemia with or without immune-mediated polyneuropathy is an autosomal recessive blood disorder that may also cause damage to the peripheral nerves (polyneuropathy) that can be triggered or made worse when suffering from an infection. This neuropathy may come and go over time. First signs may appear between 3 and 7 months.

Anemia happens when not enough red blood cells are in the body. In hemolytic anemia, the anemia is because the bone marrow cannot make the cells fast enough. It can cause tiredness, pain, irregular heartbeat, and possible heart failure. The episodes of polyneuropathy can cause weak muscles, low reflexes, and weakness in the hands and feet.

This form of hemolytic anemia is caused by mutations in the CD59 gene.

### Treatment

There is no cure for hemolytic anemia. Transfusion, medication, lifestyle changes can be used to treat the anemia. Bone marrow or stem cell transplants may also be considered. The neuropathy can be addressed with therapy and medication.

## Hemophilia B

### Summary

Hemophilia B, also known as Factor 9 deficiency or Christmas disease, is an X-linked inherited disorder that slows the blood clotting process.

Individuals with hemophilia B experience uncontrolled bleeding following trauma or surgery since they are unable to make clots properly. Individuals with severe cases of hemophilia B may experience spontaneous bleeding (bleeding for no reason) or uncontrolled bleeding after even minor injuries. Severe symptoms may also include bleeding into joints, muscles, the brain, and internal organs. Individuals with milder forms of the disorder may not be diagnosed until prolonged bleeding following surgery or serious trauma (if they have one).

Hemophilia B is caused by mutations in the F9 gene which is on the X chromosomes. Hemophilia B is caused by mutations in the F9 gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one F9 gene is enough to cause this type of hemophilia. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their F9 gene to cause the condition. For this reason, males are affected by this condition much more than females. Approximately 10% of females carrying only 1 mutation could be at risk for abnormal bleeding following surgery, injury, or dental work.

### Treatment

Treatment consists primarily of giving factor IX as replacement therapy and other medications. Lifestyle changes may be recommended to prevent bleeding episodes (e.g. avoiding contact sports).

## Hermansky-Pudlak Syndrome, Type 3

### Summary

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder that causes an unusually light coloring of the hair, skin, and eyes (albinism).

Affected individuals typically have fair skin, white or light-colored hair, reduced vision, increased sensitivity to light, and involuntary eye movements. Problems with vision generally stabilize after childhood. Many also experience difficulty with blood clotting causing prolonged bleeding, easy bruising, and a higher risk of skin damage and skin cancers. Some individuals also develop scar tissue in the lungs that may cause life-threatening breathing problems.

There are nine different types of HPS. HPS, type 3 is associated with the eye and sight concerns but has less noticeable skin lightening. They can experience mild bleeding problems but do not suffer the breathing difficulties.

HPS, type 3 is caused by mutations in the HPS3 gene.

### Treatment

There is no cure for HPS, type 3. Treatment is aimed at managing symptoms, such as bleeding. Vision aids may be beneficial in assisting vision. Individuals should take measures to protect themselves from the sun.

## Hexosaminidase A Deficiency (Tay-Sachs Disease)

### Summary

Hexosaminidase A deficiency, more commonly called Tay-Sachs disease (TSD), is a fatal autosomal recessive disorder that causes a rapid and continued destruction of the nerve cells in the brain and spinal cord due to a missing enzyme (hexosaminidase A) that normally breaks down chemicals that otherwise build-up and become toxic to the nervous system.

There are several forms of TSD that are determined by symptoms and age of onset. The infantile form is the most common and the most severe form and causes that results in the continued loss of movement and mental function. Affected individuals generally appear healthy until 3 to 6 months, at which time their development begins to slow, and the muscles used for movement begin to weaken. After 8 to 10 months, the diseases start to worsen faster, and affected infants become unable to sit or crawl. Children will experience weakness, seizures, vision and hearing loss, and intellectual disability that worsens over time. Children with TSD will eventually end up in an unresponsive, vegetative state. Death normally occurring between the ages of 4 and 5 years.

In late-onset/juvenile TSD symptoms may not appear until later childhood. While disease is slower, symptoms are generally the same as the earlier form, with death occurring around the age of 15 years for the juvenile forms.

Adult-onset TSD is very rare. Symptoms typically develop between adolescence to the mid-30s. Affected individuals have milder symptoms than those of the infantile and juvenile forms. Adult-onset TSD has the greatest variability of symptoms that may include loss of mental ability, slurred speech, muscle weakness, muscle cramps, involuntary muscle twitching, unsteady gait, and potential severe mental disorders such as schizophrenia. Life expectancy is variable and may not be fatal.

TSD is caused by mutations in the HEXA gene.

### Treatment

There is no cure for TSD. Treatment is aimed at keeping individuals as comfortable as possible and may include medication, physical therapy, and breathing or feeding assistance.

## Holocarboxylase Synthetase Deficiency

### Summary

Holocarboxylase synthetase deficiency (HLCSD) is an autosomal recessive disorder in which the body is unable to effectively use vitamin B7, also known as biotin.

Signs and symptoms generally develop shortly after birth; however, age of onset may vary. Symptoms may include difficulty feeding, poor muscle tone, a lack of energy, vomiting, irritability, breathing problems, loss of hair, and skin rash. If left untreated, some may develop seizures, developmental delay, and coma. Prognosis is generally favorable with early treatment as it generally reduces symptoms considerably. If left untreated, risk for death is high, and many will not survive past childhood.

HLCSD is caused by mutations in the HLCS gene.

### Treatment

There is no cure for HLCSD deficiency, however, treatment is normally very effective. The primary treatment for HLCSD is life-long biotin supplements. Individuals should be regularly monitored for additional complications and effectiveness of therapy. Dietary modification may also be recommended.

## Homocystinuria (CBS-deficient)

### Summary

Homocystinuria caused by cystathionine beta-synthase (CBS) deficiency is an autosomal recessive disorder in which the body is unable to properly process chemicals, called amino acids, affecting many parts of the body.

Age of onset may vary from individual to individual. Some develop symptoms during infancy, while others may not develop symptoms until adulthood. Symptoms may include skeletal abnormalities, blood clots, vision problems, and brittle bones. Individuals tend to have a tall stature with an angular appearance. Some individuals experience developmental delay, learning problems, and intellectual disability.

There are two forms of CBS-related homocystinuria: B6-responsive form and B6-nonresponsive form. Individuals with the B6 responsive form respond well to treatment with vitamin B6 and generally experience a less severe form of homocystinuria. Individuals with B6-nonresponsive form will not respond to treatment with vitamin B6 and generally have a more severe form of homocystinuria.

If treated early, individuals may develop normal intelligence and prevent the development of further complications. However, some individuals still experience a shortened life expectancy due to complications such as blood clots.

Mutations in various genes are associated with various forms of homocystinuria. CBS-deficient homocystinuria is caused by mutations in the CBS gene.

### Treatment

There is no cure for CBS-deficient homocystinuria. Treatment is focused on preventing symptoms and complications. The primary goal is to control levels of homocysteine in the blood, which can be done by limiting certain things in the diet and supplementing with certain vitamins or vitamin-enriched foods.

## Hyperchlorhidrosis

### Summary

Hyperchlorhidrosis is an autosomal recessive disorder that causes an excessive loss of salt through sweat, which can result in severe dehydration and high levels of potassium in the blood.

Signs and symptoms of hyperchlorhidrosis generally appear during infancy. Symptoms may include periods of dehydration that require hospitalization, difficulty feeding, poor growth and weight gain, and low levels of sodium (salt) in the body. If the levels of salt get too low, people with this condition can experience severe swelling throughout the body which can be life-threatening. The prognosis for an individual with hyperchlorhidrosis is favorable if diagnosed early, and the affected individual is following the treatment plan.

Hyperchlorhidrosis is caused by mutations in the CA12 gene.

### Treatment

There is no cure for isolated hyperchlorhidrosis. Treatment is aimed at replacing sodium and may require medication.

## Hyperinsulinism, Type 1

### Summary

Hyperinsulinism is an autosomal recessive disorder in which individuals have an abnormally high quantity of insulin in the body. Insulin is a hormone that aids in the control of blood sugar levels, and when insulin is too high, sugar levels in the body drop (hypoglycemia). Affected individuals typically show signs and symptoms within the first few days after birth, including poor muscle tone, difficulty feeding, irritability, lack of energy, poor sleeping, and breathing problems. Severe hypoglycemia requires infusions of glucose (sugar) to help prevent serious complications such as seizures, brain damage, coma, and potential death.

In severe cases, permanent brain damage may occur from episodes of low blood sugar. Affected individuals may develop intellectual disability, learning disabilities, and are at an elevated risk of developing diabetes. If left undiagnosed, hyperinsulinism may be fatal. However, with proper treatment, affected individuals may have a normal lifespan.

Signs and symptoms can range from mild to severe, even within the same family. While age of onset typically occurs during infancy, it can range from birth to late childhood.

There are multiple forms of hyperinsulinism caused by different genes. Hyperinsulinism, type 1 is caused by mutations in the ABCC8 gene.

### Treatment

There is no cure for hyperinsulinism. Treatment is focused on maintaining a normal blood sugar level. Dietary modification and medication are most often used to manage the disorder. Intravenous glucose is frequently given to newborns to stabilize their blood sugar level. Newborns may also require frequent feedings to ensure they are receiving sufficient amounts of carbohydrates. Medication to control high insulin levels is also available and is particularly effective in individuals with milder cases of the disorder. Surgery may be required in severe cases to remove parts of the pancreas (an organ involved in making insulin).



## Hyperinsulinism, Type 2

### Summary

Hyperinsulinism is an autosomal recessive disorder in which individuals have an abnormally high quantity of insulin in the body. Insulin is a hormone that aids in the control of blood sugar levels, and when insulin is too high, sugar levels in the body drop (hypoglycemia). Affected individuals typically show signs and symptoms within the first few days after birth, including poor muscle tone, difficulty feeding, irritability, lack of energy, poor sleeping, and breathing problems. Severe hypoglycemia requires infusions of glucose (sugar) to help prevent serious complications such as seizures, brain damage, coma, and potential death.

Signs and symptoms can range from mild to severe, even within the same family. While age of onset typically occurs during infancy, it can range from birth to late childhood. If left undiagnosed, hyperinsulinism can cause permanent brain damage and may be fatal. However, with proper treatment, affected individuals may have a normal lifespan.

There are multiple forms of hyperinsulinism caused by different genes. Hyperinsulinism, type 2 is caused by mutations in the KCNJ11 gene.

### Treatment

There is no cure for hyperinsulinism. Treatment is focused on maintaining a normal blood sugar level. Dietary modification and medication are most often used to manage the disorder. Intravenous glucose is frequently given to newborns to stabilize their blood sugar level. Newborns may also require frequent feedings to ensure they are receiving sufficient amounts of carbohydrates. Medication to control high insulin levels is also available and is particularly effective in individuals with milder cases of the disorder. Surgery may be required in severe cases to remove parts of the pancreas (an organ involved in making insulin).

## Hyperornithinemia-Hyperammonemia-Hemocitrullinemia Syndrome

### Summary

Hyperornithinemia-hyperammonemia-hemocitrullinemia syndrome (HHH), also called ornithine translocase deficiency, is an autosomal recessive disorder in which a chemical called ammonia accumulates in the blood, which can be toxic and damaging to different parts of the body, particularly the nervous system.

Age of onset and severity of symptoms may vary greatly from individual to individual. Infants with the infantile form may experience vomiting, poor feeding, and a lack of energy. Some infants may exhibit seizures or go into comas. Intellectual disability is generally seen by childhood. Meals high in protein, stress, and periods without food (fasting) may cause ammonia to build-up, leading to the appearance of or worsening of symptoms.

HHH is caused by mutations in the SLC25A15 gene.

### Treatment

There is no cure for HHH. Treatment is aimed at managing symptoms and controlling episodes of ammonia accumulation. Taking supplements or medications along with following a low-protein diet is often recommended as treatment. Even with treatment some may continue to experience a worsening of symptoms over time.

## Hyperoxaluria, Type 1

### Summary

Hyperoxaluria is an autosomal recessive disorder in which the body over produces a substance called oxalate, which is a hard chemical found in kidney stones. This build-up leads to kidney damage, kidney failure, and damage to other organs.

Hyperoxaluria, type 1 is the severe form of hyperoxaluria with an onset that varies from the ages of 1 to 25 years. Roughly 19% of individuals will exhibit symptoms during the first 6 months of life. Symptoms may include anemia, failure to grow at a normal rate, and an overproduction of acid in the body. Over 50% exhibit symptoms during late childhood or early adulthood, and the remainder show signs later. If diagnosed and treated early, some individuals may experience a favorable prognosis. If left untreated, individuals may progress to kidney failure which could be fatal.

Different genes can cause hyperoxaluria. Two mutations in the same gene would be needed to cause symptoms. Hyperoxaluria, type 1 is caused by mutations in the AGXT gene.

### Treatment

There is no cure for hyperoxaluria, type 1. Treatment is aimed at managing symptoms. It is very important for affected individuals to stay hydrated and drink large volumes of water regularly to help prevent the formation of kidney stones. Although some vitamins can help reduce the build-up, others will make it worse. Liver or kidney transplants may be an option.

## Hyperoxaluria, Type 2

### Summary

Hyperoxaluria is an autosomal recessive disorder in which the body over produces a substance called oxalate, which is a hard chemical found in kidney stones. This build-up leads to kidney damage, kidney failure, and damage to other organs.

Hyperoxaluria, type 2 has an onset during childhood. Symptoms may include urinary tract blockage, blood in urine, kidney damage, and kidney failure. If left untreated, individuals may progress to kidney failure which could be fatal.

Different genes can cause hyperoxaluria. Two mutations in the same gene would be needed to cause symptoms. PH2 is caused by mutations in the GRHPR gene.

### Treatment

There is no cure for hyperoxaluria, type 2. Treatment is aimed at managing symptoms. It is very important for affected individuals to stay hydrated and drink large volumes of water regularly to help prevent the formation of kidney stones. Liver or kidney transplants may be an option.

## Hyperoxaluria, Type 3

### Summary

Hyperoxaluria is an autosomal recessive disorder in which the body over produces a substance called oxalate, which is a hard chemical found in kidney stones. This build-up leads to kidney damage, kidney failure, and damage to other organs. This build-up is not as severe in hyperoxaluria, type 3 compared to types 1 and 2.

Hyperoxaluria, type 3 is considered to be the milder form of hyperoxaluria since some individuals may not show symptoms or may improve over time. Only a small percentage of cases end up with severe liver damage or failure.

Different genes can cause hyperoxaluria. Two mutations in the same gene would be needed to cause symptoms. PH3 is caused by mutations in the HOGA1 gene.

### Treatment

There is no cure for hyperoxaluria, type 3. Treatment is aimed at managing symptoms. It is very important for affected individuals to stay hydrated and drink large volumes of water regularly to help prevent the formation of kidney stones. Dialysis or transplants may be an option for those cases involving kidney failure.

## Hyperphenylalaninemia (BH4-Deficient)

### Summary

Hyperphenylalaninemia is an autosomal recessive disorder that is caused by a build-up in the blood of a substance from the diet (called phenylalanine) which can cause brain damage. In this type of the disorder, the phenylalanine level increases because the chemical that can help break it down (tetrahydrobiopterin or BH4) is low.

BH4-deficient hyperphenylalaninemia typically starts a few months after birth. Symptoms may include intellectual disability, drowsiness, irritability, difficulty swallowing, seizures, developmental delays, inability to control body temperature, and abnormal muscle movements. The neurological signs that can show up as early as 4-5 months are not reversible, even with treatment. Early treatment is needed (even prior to symptoms) in order to prevent many of the symptoms.

BH4-deficient hyperphenylalaninemia can be caused by mutations in multiple genes. The most common form is caused by mutations in the PTS gene.

### Treatment

There is no cure for BH4-deficient hyperphenylalaninemia. Treatment consists primarily of bringing phenylalanine levels back to normal through restricted diet and medications.

## Hyperphenylalaninemia (Phenylketonuria/PKU)

### Summary

Hyperphenylalaninemia, also known as phenylketonuria (PKU), is an autosomal recessive disorder that is caused by a build-up in the blood of a substance from the diet (called phenylalanine) which can cause brain damage.

Signs can start within months of birth and range from mild to severe. Symptoms include seizures, delayed development, behavioral problems, low bone density, and a small head size (microcephaly). If left untreated, individuals will develop permanent intellectual disability. Early detection and treatment are needed in order to prevent some of the symptoms.

PKU is caused by mutations in the PAH gene.

### Treatment

There is no cure for PKU, however, symptoms can be managed and even prevented through a restricted diet. It is important for females with PKU to closely monitor their levels of phenylalanine during pregnancy to avoid loss of pregnancy and birth defects in their children.

## Hyperuricemia, Pulmonary Hypertension, Renal Failure, and Alkalosis Syndrome

### Summary

Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis syndrome (HUPRAS) is an autosomal recessive disorder that affects multiple parts of the body.

Signs and symptoms generally appear during infancy and may include premature birth, abnormal chemical levels in the blood (alkalosis and hyperuricemia) that can lead to weakness, fever, chills, joint pain, or cramping, high blood pressure in the arteries of the lungs (pulmonary hypertension), decreased muscle tone, and delayed development. Individuals often suffer from kidney failure during infancy. Most affected individuals will not survive past their first year of life.

HUPRAS is caused by mutations in the SARS2 gene.

### Treatment

There is no cure or effective treatment for HUPRAS and management is mainly supportive.



## Hypomagnesemia, Type 1

### Summary

Hypomagnesemia, type 1 is an autosomal recessive disorder that affects the body's ability to absorb magnesium from the diet, which causes the parathyroid gland to malfunction and create low levels of calcium as well.

The first signs generally appear during infancy as neurological problems, such as seizures and muscle spasms. If left untreated, the low magnesium and calcium levels in the blood can lead to intellectual disability, developmental delay, failure to gain weight and grow, further neurologic damage, heart failure, or even death. If an individual is diagnosed early and started on treatment, many of the complications can be avoided.

Hypomagnesemia, type 1 is caused by mutations in the TRPM6 gene.

### Treatment

There is no cure for hypomagnesemia, type 1. Treatment is aimed at maintaining proper levels of magnesium and calcium.

## Hypomyelinating Leukodystrophy, Type 3

### Summary

Hypomyelinating leukodystrophy, type 3 (HLD3) is an autosomal recessive disorder that affects the brain and spinal cord. HLD3 is similar to another condition called Pelizaeus-Merzbacher disease.

HLD3 is part of a group of disorders called leukodystrophies, where the main feature is a breakdown of myelin, the protective covering around the nerves. Signs and symptoms generally appear during infancy with involuntary random eye movements. Individuals will experience delayed physical milestones and worsening muscle spasms and stiffness. Many children will never learn to speak and can have intellectual disability, seizures, and problems with vision.

HLD3 can be caused by mutations in the AIMP1 gene.

### Treatment

There is no cure and standard course of treatment for individuals with HLD3. Treatment is symptomatic and supportive. Medication is commonly prescribed for seizures and muscle problems. Physical therapy and speech therapy are often beneficial. Some individuals may require the use of walking aids.

## Hypoparathyroidism-Intellectual Disability-Dysmorphism Syndrome

### Summary

Hypoparathyroidism-intellectual disability-dysmorphism syndrome, also known as Sanjad-Sakati syndrome, is a rare autosomal recessive disorder characterized by hypoparathyroidism (a condition in which the body secretes abnormally low levels of a hormone made by the parathyroid). Hypoparathyroidism may cause muscle aches or cramps, fatigue, dry and coarse skin, brittle nails, headaches, and changes in mood.

Signs and symptoms generally occur between infancy and childhood. Affected individuals often have a long and narrow face, a prominent forehead, deep set small eyes, large ears, and a small jaw. Individuals may also have tooth abnormalities and short hands and feet. Growth retardation, intellectual disability, physical skill delays, and seizures are also common features.

Hypoparathyroidism-intellectual disability-dysmorphism syndrome is caused by mutations in the TBCE gene.

### Treatment

There is no cure for hypoparathyroidism-intellectual disability-dysmorphism syndrome. Treatment may consist of growth hormone and large doses of vitamin D.

## Hypophosphatasia

### Summary

Hypophosphatasia is an inherited disorder that affects the development of teeth and bones. This disorder disrupts a process called mineralization, which plays a role in the formation of strong, rigid bones and teeth.

There are several different forms of hypophosphatasia that vary widely in age of onset and severity of symptoms. The most severe form of hypophosphatasia typically appears prior to birth or during infancy. Infants may have short limbs, soft skull bones, an abnormally shaped chest, and weak ribs. Additional symptoms may include a failure to gain weight, poor feeding, vomiting, and breathing problems. Many children with this type are often stillborn due to the skeletal abnormalities.

The milder forms of hypophosphatasia may appear anytime from childhood through adulthood, with an early loss of baby teeth, short height, bowed legs, enlarged wrist and ankle joints, and/or an abnormally shaped skull. Adults have softened bones, making them prone to recurrent breaks of the foot and thigh bones. Additional symptoms may include arthritis and a premature loss of adult teeth. Some may only have the symptoms involving abnormal tooth development.

Those affected with the most severe form have an unfavorable prognosis as many are stillborn, and about 50% of the remaining individuals will not survive past infancy. The prognosis for individuals with the milder form of hypophosphatasia is unknown.

The severe form of hypophosphatasia is inherited in an autosomal recessive fashion and is caused by mutations to the ALPL gene.

### Treatment

There is no cure for hypophosphatasia. Treatment is aimed at managing symptoms. Those with the severe form may require breathing assistance. Medications may be used to treat arthritis and joint pain.

## Hypophosphatemic Rickets with Hypercalciuria

### Summary

Hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disorder that causes rickets (softening of the bones), low levels of phosphate in the blood (hypophosphatemia), and high levels of calcium in urine (hypercalciuria). Phosphate is a mineral that is needed for the development of bones and teeth.

Signs and symptoms generally appear during early childhood and may include slow growth, a short stature, skeletal abnormalities, muscle weakness, dental abnormalities, and bone pain. Many individuals will experience bowed legs or knock knees. If left untreated, symptoms generally worsen over time.

HHRH is caused by mutations in the SLC34A3 gene.

### Treatment

Treatment for HHRH primarily consists of supplements and regular monitoring. With treatment, individuals may experience normal lives and a normal life expectancy.

## Inclusion Body Myopathy, Type 2

### Summary

Inclusion body myopathy type 2 (IBM2) is an autosomal recessive disorder that affects the skeletal muscles, particularly in the legs and arms. Individuals experience muscle weakness that worsens over time.

The first symptom of IBM2 is weakness in the muscles of the lower legs. This weakness will affect an individual's ability to walk and can also make climbing stairs and running difficult. Over time, weakness will spread into the muscles of the upper legs, hips, shoulders, neck, and hands, but the quadriceps (muscle on front part of the upper leg) remain unaffected. Most individuals will require the use of a wheelchair within 20 years after the first symptoms appear. Life expectancy is usually unaffected.

IBM2 is caused by mutations in the GNE gene.

### Treatment

There is no cure for IBM2. Neurologists, physical therapists, and occupational therapists may be beneficial in helping to treat symptoms as they appear.

## Infantile Cerebellar-Retinal Degeneration

### Summary

Infantile cerebellar-retinal degeneration (ICRD) is an autosomal recessive disorder that causes neurodegeneration (loss of nerve function and structure).

Signs and symptoms generally appear during infancy and can include seizures, severe motor and cognitive impairment (such as memory and decision-making), and a failure to meet developmental milestones. Affected individuals experience optic nerve and retinal deterioration, resulting in loss of vision and other eye problems (such as abnormal eye movements). Individuals will get worse over time and have a shortened life expectancy.

ICRD is caused by mutations in the ACO2 gene.

### Treatment

There is no cure for ICRD. Treatment is aimed at managing symptoms and increasing quality of life.

## Infantile Hypercalcemia

### Summary

Infantile hypercalcemia is an autosomal recessive disorder that results in an increased level of calcium in the blood. Signs and symptoms appear shortly after birth and cause vomiting, dehydration, and an overall failure to thrive. Additional symptoms may include low muscle tone and tiredness as well as an over-sensitivity to vitamin D.

Infantile hypercalcemia is caused by mutations in the CYP24A1 gene.

### Treatment

There is no cure for infantile hypercalcemia. Treatment is aimed at managing and preventing symptoms and may include medication and avoidance of vitamin D.



## Infantile Transient Liver Failure

### Summary

Infantile Transient Liver Failure (LFIT) is a rare inherited disorder causing liver dysfunction.

Symptoms include jaundice (yellowing of the skin and eyes), weakened muscles (hypotonia), enlarged liver, problems forming blood clots, and vomiting. If treated properly, affected individuals may survive the initial illness with no further recurrence.

The outcome for an individual affected with LFIT is unknown given so few cases have been reported. In cases where the first signs are treated, normal development is expected. In other cases, affected individuals have died between 2 months and 4 months of age.

LFIT is caused by mutations in the TRMU gene.

### Treatment

There is no cure for LFIT. Treatment is aimed at managing symptoms. Liver transplant may be recommended.

## Joubert Syndrome, Type 2

### Summary

Joubert syndrome is an autosomal recessive disorder that may present with different signs and symptoms. Joubert syndrome causes malformations in the brain stem. As a result, characteristics of Joubert syndrome involve developmental delay, inability to coordinate muscle movements involved in eating and breathing, weak muscle tone, abnormal eye movements, and intellectual disability. Additional signs and symptoms may include kidney or liver disease and skeletal abnormalities. Prognosis and life expectancy are dependent on the severity of intellectual disability and liver/kidney damage.

Joubert syndrome can be caused by mutations in at least 10 genes. Two mutations in the same gene are needed to cause symptoms of the condition. Joubert syndrome, is caused by mutations in the TMEM216 gene.

### Treatment

There is no cure for Joubert syndrome. Treatment is aimed at managing symptoms. Treatment may include proper nutrition, managing breathing problems, and physical or occupational therapy.

## Junctional Epidermolysis Bullosa

### Summary

Junctional epidermolysis bullosa (JEB) is a group of autosomal recessive disorders in which the skin is very fragile and blisters easily even after minor friction or injury.

There are two types of JEB. In the Herlitz type, individuals have blistering over large regions of the skin from birth which can lead to pain, infections, and bleeding. Blistering can occur internally in the lining of the mouth, throat, or digestive tract making eating difficult. Blockage to the airways may lead to difficulty breathing and could be fatal. Other symptoms of the Herlitz type may include joint deformities (contractures) that will restrict movement, hair loss, fevers, and fused fingers and toes. Most infants will not survive beyond their first year of life.

The non-Herlitz type is milder. The blistering is usually limited to the hands, elbows, knees, and feet and can improve over time. Loss of hair, abnormal nails, and teeth can also occur, but breathing difficulties and other severe complications seen in the Herlitz types are rare in the non-Herlitz forms. Lifespan is usually normal.

Multiple genes can cause both types of JEB, including LAMA3, LAMB3, and LAMC2. Two mutations in the same gene are needed to cause symptoms of the condition.

### Treatment

There is no cure for JEB. Treatment is aimed on managing symptoms as they arise, including preventing skin damage, treating open wounds and blisters, preventing infection, and maintaining hydration and proper nutrition.

## Kindler Syndrome

### Summary

Kindler syndrome (KS) is an autosomal recessive disorder that affects the skin and causes an increased sensitivity to light.

Signs and symptoms generally appear at birth with severe skin blistering, particularly on the hands and feet. Their skin is often very thin and fragile and can become discolored. Other symptoms include excessive gum bleeding, a narrowing of the esophagus (throat), and webbing between the toes and fingers. Blistering and sensitivity to light can become milder with age.

KS is caused by mutations in the FERMT1 gene.

### Treatment

There is no cure for KS. Treatment is aimed at managing symptoms and includes preventive measures against light sensitivity, added padding to protect the skin, and regular monitoring by a healthcare professional for cancer.

## Kohlschutter-Tonz Syndrome

### Summary

Kohlschutter-Tonz syndrome (KTS) is a rare autosomal recessive disorder that causes epilepsy, dementia, and intellectual disability.

Signs and symptoms may vary from individual to individual and generally appear during early childhood. Symptoms may include impaired development of motor skills, recurrent seizures (epilepsy), spasticity (abnormal muscle movements), abnormal formation of tooth enamel, and discoloration of the teeth. Many will experience severe intellectual disability. The severity and frequency of seizures may further affect speech and movement. In severe cases, individuals may lose function in all limbs. The majority of individuals are bedridden between their teens and twenties.

KTS is caused by mutations in the *ROGDI* gene.

### Treatment

There is no cure for KTS. Treatment is aimed at preventing seizures, mainly with medication. Regular exams by neurologists and dentists are recommended.

## Krabbe Disease

### Summary

Krabbe disease, also known as globoid cell leukodystrophy, is an autosomal recessive degenerative disorder of the nervous system. Krabbe disease is a part of a larger group of disorders known as leukodystrophies. These disorders affect the development of the myelin, a covering that acts as a protective layer around nerve cells.

Krabbe disease has two forms that vary in age of onset: infantile form and late-onset form. The infantile form of Krabbe disease typically shows signs before 1 year of age and is the more common form of this disorder. Initial symptoms may include irritability, feeding problems, muscle weakness, hearing and vision loss, seizures, stiff posture, and impaired mental and physical development. Over time, individuals will experience difficulty moving, chewing, swallowing, and breathing. The late-onset form of Krabbe disease varies widely in age of onset and can appear during childhood, adolescence, or adulthood. Symptoms also vary widely and may include vision loss, difficulty walking, and intellectual disability. Those affected with the infantile form typically will not survive past the age of 2 years. Those affected with the late-onset form typically only survive for 2 to 7 years following initial symptoms.

Krabbe disease is caused by mutations in the GALC gene.

### Treatment

There is no cure for Krabbe disease. Treatment is aimed at managing symptoms. If diagnosis is made extremely early (or before birth), individuals with the infantile form can sometimes be treated with cord blood stem cells after birth to slow the disease. Individuals with the late-onset form have shown some benefit from treatment from umbilical cord stem cells.



## Laron Syndrome

### Summary

Laron syndrome is an autosomal recessive disorder that causes a deficiency in growth hormone, resulting in an unusually short height of affected individuals.

Although these children may seem to have normal size at birth, they will start to grow more slowly overtime. They can also experience delays in motor skills, tooth development, and puberty. Hair is often thin and affected individuals often suffer from obesity.

Laron syndrome is caused by mutations in the GHR gene.

### Treatment

There is no cure for Laron syndrome. Treatment includes medications and frequent feeding.

## Leber Congenital Amaurosis, Type 13

### Summary

Leber congenital amaurosis (LCA) is an eye disorder caused by the breakdown of a part of the eye called the retina. The retina plays a role in detecting light and color.

Symptoms can start between infancy and childhood, but the severity will vary from person to person. People with LCA will experience sensitivity to light, involuntary eye movements, slow or absent pupil response to light, and extreme farsightedness. Some individuals will also exhibit an abnormally thin or cone-shaped cornea (the outermost part of the eye). The prognosis for an individual affected with LCA, type 13 is generally favorable since there are no major health complications outside of vision problems. Life expectancy is usually unaffected.

Over 13 forms of LCA have been discovered. Each form varies by genetic mutation, pattern of vision loss, and other related eye abnormalities. When the condition is autosomal recessive, two mutations in the same gene are needed to cause symptoms. LCA, type 13 is caused by mutations in the RDH12 gene.

### Treatment

There is no cure for LCA, type 13. Treatment is focused on management of vision loss; however, treatment options are limited. Low vision aids may be beneficial, and individuals may require special educational opportunities.



## Leber Congenital Amaurosis, Type 2

### Summary

Leber congenital amaurosis (LCA) is an eye disorder caused by the breakdown of a part of the eye called the retina. The retina plays a role in detecting light and color.

Symptoms can start between infancy and childhood, but the severity will vary from person to person. People with LCA will experience sensitivity to light, involuntary eye movements, slow or absent pupil response to light, and extreme farsightedness. Some individuals will also exhibit an abnormally thin or cone-shaped cornea (the outermost part of the eye). The prognosis for an individual affected with LCA, type 2 is generally favorable since there are no major health complications outside of vision problems. Life expectancy is usually unaffected.

Over 13 forms of LCA have been discovered. Each form varies by genetic mutation, pattern of vision loss, and other related eye abnormalities. LCA, type 2 is caused by mutations in the RPE65 gene.

### Treatment

There is no cure for LCA, type 2. Treatment is focused on management of vision loss; however, treatment options are limited. Low vision aids may be beneficial, and individuals may require special educational opportunities.

## Leigh Syndrome (COX-Deficient)

### Summary

Leigh syndrome is a disorder that causes neurological defects including a continued loss of mental and physical abilities due to lesions that appear on the brain and cause damage. The protective covering over the nerves (myelin) can also be destroyed making it hard to send nerve signals back and forth.

Signs and symptoms typically appear in the first year of life, however, in some cases, have not appeared until adulthood. Initial signs include vomiting, diarrhea, feeding problems, and difficulty swallowing. Additional symptoms may include weak muscles, problems with coordination, involuntary muscle contractions, failure to grow at a normal rate, rapid involuntary eye movements, and developmental delay. Some individuals will exhibit a thickening of the heart muscle and experience a build-up of lactate in the body. Many will experience severe breathing problems that worsen over time, eventually causing respiratory failure. Individuals generally will not survive past a couple years past the appearance of initial symptoms. Death typically occurs from respiratory failure. Some individuals who have an adult-onset form of this disorder may experience symptoms that progress more slowly.

Over 30 different genes with different types of inheritance can cause Leigh syndrome. With autosomal recessive types, two mutations in the same gene are needed to cause symptoms. COX-deficient Leigh syndrome is caused by mutations in the SURF1 gene.

### Treatment

There is no cure for Leigh syndrome. Treatment is aimed at managing symptoms. Medication is available to treat seizures and involuntary muscle contractions.

## Leigh Syndrome (French-Canadian Type)

### Summary

Leigh syndrome is a disorder that causes neurological defects including a continued loss of mental and physical abilities due to lesions that appear on the brain and cause damage. The protective covering over the nerves (myelin) can also be destroyed making it hard to send nerve signals back and forth.

Signs and symptoms typically appear in the first year of life, however, in some cases have not appeared until adulthood. Initial signs include vomiting, diarrhea, feeding problems, and difficulty swallowing. Additional symptoms may include weak muscles, problems with coordination, involuntary muscle contractions, failure to grow at a normal rate, rapid involuntary eye movements, and developmental delay. Some individuals will exhibit a thickening of the heart muscle and experience a build-up of lactate in the body. Many will experience severe breathing problems that worsen over time, eventually causing respiratory failure. Individuals generally will not survive past a couple years past the appearance of initial symptoms. Death typically occurs from respiratory failure. Some individuals who have an adult-onset form of this disorder may experience symptoms that progress more slowly.

Over 30 different genes with different types of inheritance can cause Leigh syndrome. With autosomal recessive types, two mutations in the same gene are needed to cause symptoms. The French-Canadian type of Leigh syndrome is caused by mutations in the LRPPRC gene.

### Treatment

There is no cure for Leigh syndrome. Treatment is aimed at managing symptoms. Medication is available to treat seizures and involuntary muscle contractions.

## Lethal Congenital Contracture Syndrome, Type 2

### Summary

Lethal congenital contracture syndrome, type 2 (LCCS2) is a severe autosomal recessive disorder. The primary symptoms of LCCS2 are breathing problems and joint contractures (stiffness or constriction in the joints that causes decreased flexibility and limitations in movement).

Diagnosis of LCCS2 prior to birth has been made as early as 15 weeks gestation using prenatal ultrasound. Symptoms are evident immediately following birth and include severe joint contractures, urinary and bladder abnormalities, enlarged or swollen kidneys, extreme underdeveloped muscles, and eye abnormalities with vision problems. Most infants die shortly after birth due to breathing difficulties.

LCCS2 is caused by mutations in the ERBB3 gene.

### Treatment

There is no cure or effective treatment for LCCS2.

## Lethal Congenital Contracture Syndrome, Type 3

### Summary

Lethal congenital contracture syndrome 3 (LCCS3) is an autosomal recessive disorder. The primary symptoms are breathing problems and joint contractures (stiffness or constriction in the joints that causes decreased flexibility and limitations in movement).

Signs and symptoms are generally evident shortly after birth, but contractures may even be detected prior to birth by ultrasound. The muscles around the joints may be underdeveloped, weak, or stiff, especially in the legs and vertebral column. Individuals can die within hours of birth due to severe breathing difficulties.

LCCS3 is caused by mutations in the gene *PIP5K1C* cause LCCS3.

### Treatment

There is no cure or effective treatment for LCCS3.

## Lethal Congenital Contracture Syndrome, Type 4

### Summary

Lethal congenital contracture syndrome, type 4 (LCCS4) is a severe autosomal recessive disorder. The primary symptoms of LCCS4 are breathing problems and joint contractures (stiffness or constriction in the joints that causes decreased flexibility and limitations in movement).

Symptoms are evident immediately following birth. The muscles around the joints may be underdeveloped, weak, or stiff, especially those in the legs. The ability to breathe is severely affected due to these issues. Most will not survive past the first hour after birth, with death often occurring due to the breathing problems.

LCCS4 is caused by mutations in the MYBPC1 gene.

### Treatment

There is no cure or effective treatment for LCCS4.

## Limb-Girdle Muscular Dystrophy

### Summary

Limb-girdle muscular dystrophy (LGMD) is an autosomal recessive disorder that causes the continued weakness of the muscles, particularly in the shoulders, arms, hips, and thighs.

Age of onset and severity of symptoms may vary widely depending on the type and the person affected. Even individuals with the same type in the same family may appear differently. During childhood symptoms may start as an abnormal walk (on the balls of the feet) or problems running. The muscles in the leg as well as those in the hip, shoulder, and abdomen will worsen over time. The earlier the symptoms of LGMD appear, the faster they tend to worsen, and the more severe the disorder tend to be. As the disorder progresses, affected individuals may experience scoliosis (curve of the back), shoulder blades that stick out, joint stiffness that restricts movement, and sometimes an overgrowth of their calf muscles. A small percentage of individuals will experience a weakening in the muscles of the heart or in those muscles that affect breathing. Those that experience more severe symptoms may require wheelchair assistance, while others with milder symptoms may only experience minimal disability and live a normal life expectancy.

Over 15 different genes can cause LGMD, including CAPN3, SGCA, SGCB, and SGCG. Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for LGMD. Treatment is aimed at managing symptoms. Physical therapy and stretching may be beneficial in prolonging muscle strength and movement. Surgery may be an option for scoliosis and other joint problems. Regular monitoring for heart problems is recommended.

## Lipoprotein Lipase Deficiency

### Summary

Lipoprotein lipase deficiency is an autosomal recessive disorder that prevents the normal breakdown of fats (lipoproteins) so that they build-up in different areas of the body.

Signs and symptoms generally appear during childhood and may include abdominal pain due to swelling of the pancreas. Individuals can manage symptoms with appropriate treatment. If left untreated, it can turn into pancreatitis damaging the pancreas, which can be life-threatening. Additional symptoms include the appearance of small, yellow skin lesions (xanthomas), an enlarged liver and spleen, a milky appearance to the blood, depression, memory loss, and mild dementia. These signs can get better if fat levels are brought back to normal.

Lipoprotein lipase deficiency is caused by mutations in the LPL gene.

### Treatment

There is no cure for lipoprotein lipase deficiency. Treatment is based on maintaining levels of fat through a diet extremely low in fat.



## Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency

### Summary

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) is an autosomal recessive disorder in which the body is unable to convert certain fats into energy, particularly during times of fasting and illness.

Signs and symptoms typically appear during infancy or early childhood. Initial symptoms generally include a lack of energy, low blood sugar, poor muscle tone, feeding difficulties, liver problems, and abnormalities in the retina (a part of the eye). In childhood, individuals may experience muscle pain and a loss of sensation in the hands and feet. If left untreated, affected individuals can develop heart problems, breathing issues, seizures, coma, and sudden death.

If diagnosed and treated early, individuals can live relatively normal and healthy lives. However, some individuals will continue to experience episodes that may affect the brain, muscles, heart, liver, and eyes. If left untreated, LCHAD can be fatal.

LCHAD is caused by mutations in the HADHA gene.

### Treatment

There is no cure for LCHAD. Treatment is aimed at modifying the diet to be high in fats and carbohydrates and avoiding periods of fasting. Other supplements may be added to provide additional energy.

## Lysosomal Acid Lipase Deficiency

### Summary

Lysosomal acid lipase (LAL) deficiency is an autosomal recessive disorder that prevents the body from breaking down fats and cholesterol, causing a toxic build-up in different cells and tissues of the body.

There are two forms of LAL deficiency. The later-onset form, known as cholesteryl ester storage disease or CESD, generally appears before the ages of 10 to 12 years, but some individuals will not present with symptoms until adulthood. Severity of symptoms vary but include an enlarged liver followed by the development of chronic liver disease (cirrhosis). Affected individuals may experience a build-up of fatty deposits in the artery walls possibly causing blockage, which increases the risk of stroke or heart attack.

The infantile-onset form, known as Wolman disease, presents as early as a few days to a few months after birth and is characterized by an enlarged liver and spleen, malabsorption of nutrients, poor weight gain, poor muscle tone, low iron in the blood, and malfunctioning of the adrenal glands (small hormone-producing glands on top of each kidney) due to abnormal collection of fats. Affected individuals usually do not survive beyond the first year of life due to severe malnutrition and organ failure.

CESD and Wolman disease are caused by mutations in the LIPA gene.

### Treatment

There is no cure for CESD or Wolman disease. Treatment for CESD is aimed at lowering cholesterol and fat levels through a low-fat diet and cholesterol-lowering medications. A liver transplant may also be required in cases with severe liver damage. Treatment for Wolman disease is very limited. Management is aimed at maintaining optimal nutrition and treatment of symptoms. Stem cell transplantation has been shown to increase chances of survival.

## Mal de Meleda

### Summary

Mal de Meleda (MDM) is a rare autosomal recessive disorder that causes a thickening of the skin on the palms of the hands and soles of the feet (palmoplantar keratoderma).

Signs and symptoms generally appear before the age of 1 and include facial redness, unusually short bones in the fingers and toes, recurrent skin lesions, and nail abnormalities. Thickening of the skin appears shortly after birth on the palms of the hands and soles of the feet, progressing onto the surface of the hands and feet, elbows, knees, and other organs. Excessive sweating and repeat fungal infections are also common. While symptoms may get worse over time, they typically only affect the skin. Life expectancy is unaffected.

MDM is caused by mutations in the *SLURP1* gene.

### Treatment

There is no cure for MDM. Treatment primarily consists of medications and creams.

## Maple Syrup Urine Disease

### Summary

Maple syrup urine disease (MSUD) is an autosomal recessive disorder in which the body is unable to process certain chemicals properly in the body. This disorder is named for the sweet smell similar to maple syrup in the urine of untreated infants.

Symptoms can present soon after birth or may not show until later in infancy or childhood. Signs and symptoms of MSUD include an extreme lack of energy, developmental delay, irritability, vomiting, weight loss, and poor feeding. If left untreated, MSUD may cause seizures, breathing problems, swelling of the brain, coma, or death. If left untreated, most infants will die within the first few months of life. Individuals are prone to episodes during times of stress, illness, and infection.

Most affected individuals can live normal life expectancies with a strict diet, however, some may still experience symptoms even with these changes. If treatment is not initiated early, individuals may experience brain damage and impaired intellect. Episodes of metabolic crises can flare up during times of stress, illness, or infection, and may be fatal. If left untreated, affected individuals generally will not survive past infancy.

There are three types of classic MSUD caused by mutations in different genes: BCKDHA (type 1A), BCKDHB (type 1B), and DBT (type 2) genes. Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for MSUD. Treatment is aimed at preventing complications with a lifelong protein-free diet. Careful supervision and frequent blood tests will be required.

## Meckel Syndrome, Type 1

### Summary

Meckel syndrome is a group of disorders that causes different medical problems throughout the body.

Signs and symptoms generally include large kidneys full of cysts (fluid filled sacs), an opening in the brain or spinal column (neural tube defect), and extra fingers or toes. Meckel syndrome can also cause heart defects, enlarged spleen, cleft lip or palate (opening in the roof of the mouth or lips), small eyes and chin, small head size (microcephaly), genital abnormalities, and slow growth. Many of these features may be seen before birth by ultrasound. For those that make it to birth, most still die shortly after birth from kidney failure and breathing difficulties.

Over 8 genes are known to cause Meckel syndrome. Two mutations in the same gene are needed to cause disease. Meckel syndrome, type 1 is caused by mutations in the MKS1 gene.

### Treatment

There is no cure or effective treatment for Meckel syndrome.

## Medium-chain Acyl-CoA Dehydrogenase Deficiency

### Summary

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is an autosomal recessive disorder in which the body is unable to convert certain fats into energy, particularly during periods without food or during times of infection and illness.

Signs and symptoms typically appear during infancy or early childhood, though there have been rare cases of adult-onset. Initial symptoms generally include vomiting, a lack of energy, and low blood sugar. If left untreated, affected individuals are prone to health complications such as brain damage, liver problems, breathing issues, seizures, coma, and sudden death. If diagnosed and treated early, individuals can live a normal lifespan, but if left untreated, MCAD can be fatal.

MCAD is caused by mutations in the ACADM gene.

### Treatment

There is no cure for MCAD. Treatment is aimed at managing the diet and avoiding periods of fasting and large amounts of carbohydrates. Supplements are also sometimes prescribed.

## Megalencephalic Leukoencephalopathy with Subcortical Cysts

### Summary

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal recessive disorder that affects brain development and function.

Signs and symptoms generally appear at birth or shortly thereafter. Individuals often have an enlarged brain (megalencephaly) that will slowly increase the size of their head. Leukoencephalopathy is an abnormality in the white matter of the brain, which is a bundle of nerves. Affected individuals may develop brain cysts that can cause spasticity (abnormal tensing of the muscles) and difficulty with movement.

Additional symptoms may include poor muscle tone, involuntary movement of the limbs, difficulty swallowing, and difficulty with speech. Many individuals will suffer from some degree of intellectual disability and may also have seizures. Life expectancy is typically shortened.

Most cases of MLC are caused by mutations in the MLC1 gene.

### Treatment

There is no cure for MLC. Treatment may consist of medication to control seizures and physical therapy to help keep motor skills.

## Megaloblastic Anemia (Imerslund-Grasbeck syndrome)

### Summary

Megaloblastic anemia, also known as Imerslund-Grasbeck syndrome, is a rare autosomal recessive blood disorder characterized by low levels of vitamin B12 in the body causing a shortage of red blood cells (anemia). The cells that are present are abnormally large making them more likely to die faster. Anemia prevents the tissues in the body from getting the nutrients and oxygen they need to function properly.

Signs and symptoms generally appear during infancy or childhood. Symptoms may include vomiting, loss of appetite, diarrhea, pale skin, recurrent infections, enlarged liver and spleen, loss of weight, weakness, problems with breathing, and irritability. Additional symptoms may include numbness in the hands or feet, delayed development, and confusion.

Megaloblastic anemia can be caused by mutations in the AMN or CUBN genes. Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for megaloblastic anemia. Treatment may consist of lifelong B12 supplements and a diet high in meat.



## Megaloblastic Anemia (Thiamine-Responsive Type)

### Summary

Thiamine-responsive megaloblastic anemia (TRMA) is a rare autosomal recessive disorder that causes hearing loss, diabetes, and a blood disorder called megaloblastic anemia in which there is a shortage of red blood cells and the cells that are present are abnormally large making them more likely to die faster. Anemia prevents the tissues in the body from getting the nutrients and oxygen they need to function properly.

Signs and symptoms generally appear between infancy and adolescence. Initial signs include a decreased appetite, headaches, pale skin, a lack of energy, diarrhea, tingling in the hands and feet, and diabetes. Affected individuals often develop hearing loss during early childhood due to abnormalities in the inner ear, known as sensorineural hearing loss. Some individuals will also develop optic atrophy (a degeneration of the nerves that carry information from the eyes to the brain), heart problems, and seizures. Normal life expectancy is possible with treatment. Megaloblastic anemia is reversible, and diabetes can be improved with treatment.

TRMA is caused by a mutation in the SLC19A2 gene.

### Treatment

Treatment for TRMA is aimed at managing and preventing symptoms. This may include thiamine supplements to treat anemia and potentially improve diabetes. It is unclear whether vitamin B1 can improve or prevent hearing loss. It is recommended that affected individuals undergo annual hearing, ophthalmologic, and cardiac evaluations.

## Metachromatic Leukodystrophy

### Summary

Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder in which there is an abnormal build-up of fats called sulfatides in the body resulting in damage to the nervous system. MLD is one of the disorders in a group of disorders called leukodystrophies, which affect the development of the myelin sheath, a covering that protects nerve cells from damage.

Although children will seem normal at birth, individuals with MLD experience a worsening of intellectual and motor skills including a loss of sensation in the hands and feet, blindness, hearing loss, loss of speech, seizures, loss of bladder control (incontinence), and eventual paralysis.

Symptoms generally appear by the age of 2 years in 50-60% of cases, and most will not survive past childhood. Approximately 20-30% of all cases will start to show signs from 3 years to adolescence. Initial signs generally present as problematic behavior at school and progress to include clumsiness, slurred speech, and seizures. This form of MLD worsens more slowly than the infantile form, but life expectancy is still affected. Individuals typically survive for 20 years after symptoms first appear.

The remaining cases show an age of onset between the teenage years and adulthood. Initial symptoms include loss of coordination, difficulty at school, alcoholism or drug abuse, and other changes in personality. Affected individuals may also experience psychiatric symptoms such as delusions or hallucinations. Individuals with this form of MLD may survive 20 to 30 years after symptoms first appear.

MLD is caused by mutations to the ARSA gene.

### Treatment

There is no cure for MLD. Treatment focuses on managing symptoms and preserving quality of life and include medications, physical therapy, walking aids, and feeding tubes.

## Methylmalonic Aciduria

### Summary

Methylmalonic aciduria is a group of autosomal recessive disorders that prevent the body from processing certain proteins and fats properly.

Signs and symptoms typically appear between infancy to early childhood; however, age of onset and severity of symptoms may vary widely. Symptoms typically include a lack of energy, vomiting, dehydration, weak muscle tone, developmental delay, failure to grow at a normal rate, and coma. Individuals may also exhibit intellectual disability, chronic kidney disease, inflammation of the pancreas, and feeding problems. Methylmalonic aciduria may be fatal if left untreated. Individuals that survive past childhood will most likely suffer from kidney failure at some point in their lives. Individuals with MMAA-related methylmalonic aciduria have a more favorable prognosis than the other forms of the disorder.

Methylmalonic aciduria can be caused by many different genes. Two mutations in the same gene are needed to cause symptoms. Two of these genes are MMAA and MMAB.

### Treatment

There is no cure for methylmalonic aciduria. Treatment primarily consists of a protein-restricted diet, nutritional supplements, and avoiding periods without food. MMAA- and MMAB-related methylmalonic aciduria may be responsive to injections of vitamin B12. Kidney transplant may be required for individuals who have suffered kidney failure.

## Methylmalonic Aciduria (cblC type with homocystinuria)

### Summary

Methylmalonic aciduria (cblC type with homocystinuria), also known as cobalamin C disease, is an autosomal recessive disorder that results from a defect in the processing of vitamin B12 (cobalamin) by different parts of the body.

Symptoms typically appear during infancy but may sometimes appear during adolescence or adulthood. Symptoms may include developmental delay, feeding difficulties, intellectual disability, vision problems, small-sized head, poor muscle tone, tiredness, anemia, and seizures. Symptoms may be triggered by fasting (periods without food), illness, and infection. Symptoms can be reduced through life-long treatment. If left untreated, symptoms may be fatal.

Late-onset methylmalonic aciduria and homocystinuria may appear as dementia, mental problems, and difficulty with coordination.

Methylmalonic aciduria (cblC type with homocystinuria) is caused by mutations in the MMACHC gene.

### Treatment

There is no cure for Methylmalonic aciduria (cblC type with homocystinuria). Treatment is focused on managing symptoms and may include a low protein diet, nutritional supplements, and medications.

## Methylmalonic Aciduria (MUT type)

### Summary

Methylmalonic aciduria is a group of autosomal recessive disorders that prevent the body from processing certain proteins and fats properly.

Signs and symptoms typically appear between infancy to early childhood; however, age of onset and severity of symptoms may vary widely from individual to individual. Symptoms typically include a lack of energy, vomiting, dehydration, weak muscle tone, developmental delay, failure to grow at a normal rate, and coma. Individuals may also exhibit intellectual disability, chronic kidney disease, inflammation of the pancreas, anemia, and feeding problems. If left untreated, individuals may not survive past childhood.

One type of methylmalonic aciduria is due to a missing chemical in the body called mutase, which works to help breakdown protein and fat. Individuals with complete absence of mutase suffer from more severe symptoms than those with partial MUT deficiency.

Methylmalonic aciduria can be caused by many different genes. Two mutations in the same gene are needed to cause symptoms. Mutase-related methylmalonic aciduria is caused by mutations in the MUT gene.

### Treatment

There is no cure for methylmalonic aciduria. Treatment primarily consists of a protein-restricted diet, nutritional supplements, and avoiding periods without food. Although individuals with complete mutase deficiency will not respond to vitamin B12 therapy, some individuals with partial deficiency may. Kidney transplant may be required for individuals who have suffered kidney failure.

## Microcephaly, Postnatal Progressive, with Seizures and Brain Atrophy

### Summary

Microcephaly, postnatal progressive, with seizures and brain atrophy (MCPHSBA) is an autosomal recessive disorder that causes a continued decrease in head size (microcephaly), along with deterioration of brain tissue (atrophy) and severe intellectual disability.

Signs and symptoms generally appear shortly after birth and may include seizures, difficulty with movement, jitteriness, severe muscle tightness (spasticity), failure to grow at a normal rate, difficulty swallowing, and poor visual focus.

MCPHSBA is caused by mutations in the MED17 gene.

### Treatment

There is no cure for MCPHSBA. Medication is available for seizures, and a feeding tube may be necessary for individuals who have problems swallowing.

## Microcephaly, Type 9

### Summary

Microcephaly is a condition in which children are born with a very small head. Because of the small skull, the brain is also smaller than usual though still normal in shape and structure.

Signs and symptoms generally present at birth and may be seen prenatally by ultrasound. Children with microcephaly suffer from delays in speech, sitting, walking, and standing. Intellectual delays are mild to moderate and do not get worse with age. This condition does not normally affect other parts of the body.

Different genes are known to cause microcephaly. Two mutations in the same gene are needed to cause the disease. Microcephaly, type 9 is caused by mutations in the CEP152 gene.

### Treatment

There is no cure for microcephaly. Special education and therapy to address the physical and mental delays may be recommended.

## Mitochondrial Complex I Deficiency

### Summary

Mitochondrial complex I deficiency is an autosomal recessive disorder that causes continued damage to the nervous system. This disorder affects many organs and tissues that require high levels of energy, such as the brain and skeletal muscles.

Symptoms of mitochondrial complex I deficiency may vary widely from individual to individual. Age of onset is also variable and may appear anywhere between childhood to adulthood. Symptoms include eye problems, vision loss, hearing loss, movement problems, muscle weakness and seizures. Heart and liver problems are also possible.

Mitochondrial complex I deficiency can be caused by mutations in various different genes, such as *NDUFA11*, *NDUFAF5*, *NDUF54*, *NDUF56*, *NDUFAF3*, *FOXRED1*. Two mutations in the same gene would be needed to cause symptoms of this condition.

### Treatment

There is no cure for mitochondrial complex I deficiency. Treatment options will vary depending on symptoms.



## Mitochondrial Complex III Deficiency (Nuclear Type 4)

### Summary

Mitochondrial complex III deficiency (nuclear type 4) is an autosomal recessive disorder that affects many areas of the body including the brain, kidneys, liver, heart, and skeletal muscles.

Signs and symptoms usually appear during infancy but can appear later in life. Severity of symptoms vary widely from individual to individual. Those that have milder symptoms generally exhibit muscle weakness and extreme fatigue and may live into adolescence or adulthood. Individuals who have more severe symptoms may exhibit liver disease leading to liver failure, kidney problems, brain dysfunction, delayed development, failure to grow at a normal rate, problems with movement, weak muscles, and difficulty communicating. Some individuals will experience cardiomyopathy (a form of heart disease), possibly leading to heart failure. Many of the severe cases do not live past childhood.

Mitochondrial complex III deficiency (nuclear type 4) can be caused by mutations in the UQCRCQ gene.

### Treatment

There is no cure or standard treatment for mitochondrial complex III deficiency. Some affected individuals have responded well to certain vitamins.

## Mitochondrial Complex V Deficiency (Nuclear Type 2)

### Summary

Mitochondrial complex V deficiency (nuclear type 2) is an autosomal recessive disorder that causes a continued neurodegeneration. This disorder affects many organs and tissues that require high levels of energy to function well.

Onset generally occurs at birth or prior to birth. Severity of symptoms vary widely from individual to individual. Affected individuals often have a low birth weight and experience poor growth, high blood pressure, respiratory difficulties, lactic acidosis (a buildup of too much lactic acid in the body), and a failure to thrive. Additional symptoms may include heart disease, heart arrhythmia (irregular heartbeat), psychomotor impairment (slowed speech, movement, and impaired thinking), poor muscle tone, and an enlarged liver. On occasion, seizures may also occur. This condition can cause early death, and those that survive often develop problems with coordination and tremors.

Mitochondrial complex V deficiency (nuclear type 2) can be caused by mutations in the TMEM70 gene.

### Treatment

There is no cure for mitochondrial complex V deficiency. Treatment is aimed at managing symptoms and increasing quality of life.

## Mitochondrial Depletion Syndrome, Type 1 (MNGIE)

### Summary

Mitochondrial depletion syndrome, type 1 (MDS1), also known as mitochondrial neurogastrointestinal encephalopathy (MNGIE), is an autosomal recessive disorder that affects multiple parts of the body, particularly the digestive and nervous system.

Signs and symptoms can appear anywhere from infancy to adulthood but will most often appear by the age of 20. The most common sign is difficulty with the digestion, since MDS1 affects the movement of food through the digestive tract. This results in feeling full after eating only a small portion of food, difficulty with swallowing, nausea, vomiting, abdominal pain, diarrhea, weight loss, decreased muscle mass, and blockage in the intestines. Additional symptoms related to the nervous system include tingling and numbness in the hands and feet, droopy eyelids, hearing loss, and difficulty controlling eye movement. Symptoms worsen over time and affected individuals experience a shortened life expectancy. Life expectancy is shortened, with one study showing the average age of death occurring at 37.

MDS1 is caused by mutations in the TYMP gene.

### Treatment

There is no cure for MNGIE. Treatment may include airway protection, antibiotics, morphine, specialized education, physical therapy, and occupational therapy. Affected individuals should avoid mitochondrial interfering drug use.

## Mitochondrial Depletion Syndrome, Type 2 (Myopathic)

### Summary

Mitochondrial depletion syndrome, type 2 (MDS2) is an autosomal recessive disorder belonging to a group of disorders that are characterized by a severe reduction in mitochondrial DNA (mtDNA), which has a lot of genes that convert food and chemicals to the energy our body needs to function. This disorder affects tissues and organs in the body, causing progressive muscle weakness.

Signs and symptoms of MDS2 generally appear during early childhood. Initial signs may appear as muscle weakness that progresses over time causing a loss of motor skills such as standing, walking, and talking. Some affected individuals will experience muscle weakness in the muscles that control eye movement, leading to an appearance of droopy eyelids. Additional symptoms may include an enlarged liver, seizures, and hearing loss. As the disorder progresses, individuals may experience severe breathing problems, requiring the assistance of a ventilator. Most individuals will not survive past childhood with respiratory failure being the most common cause of death.

TK2-MDS is caused by mutations in the TK2 gene.

### Treatment

There is no cure for MDS2. Treatment consists of physical therapy exercises and wheelchair use to ease mobility. Anti-epileptic medication may be prescribed. Some individuals may require the use of a ventilator to assist with breathing.

## Mitochondrial Depletion Syndrome, Type 3 (Hepatocerebral)

### Summary

Mitochondrial depletion syndrome, type 3 (MDS3), also called the hepatocerebral type, is an autosomal recessive disorder belonging to a group of disorders that are characterized by a severe reduction in mitochondrial DNA (mtDNA), which has a lot of genes that convert food and chemicals to the energy our body needs to function. This results in the impaired function of the cells and tissues throughout the body.

Signs and symptoms generally appear between infancy to early childhood. Symptoms include neurological (cerebral) and liver (hepato) dysfunction, involuntary movement of the eyes (nystagmus), muscle weakness, and loss of previously learned physical skills.

Many individuals affected by MDS3 also have a severe form of deoxyguanosine kinase deficiency causing isolated liver disease, which may develop later in infancy or childhood and may cause liver failure.

MDS3 is caused by mutations in the DGUOK gene.

### Treatment

There is no cure for MDS3. Individuals who have isolated liver disease rather than a multisystem form of the disorder may undergo a liver transplant. Physical therapy is common and may be beneficial for those with milder forms of the disorder or isolated liver disease.

## Mitochondrial Depletion Syndrome, Type 5 (Encephalomyopathic)

### Summary

Mitochondrial DNA depletion syndrome, type 5 (MDS5), also known as the encephalomyopathic type, is an autosomal recessive disorder belonging to a group of disorders that are characterized by a severe reduction in mitochondrial DNA (mtDNA), which has a lot of genes that convert food and chemicals to the energy our body needs to function. Tissues and organs that require large amounts of energy are affected, such as the brain and muscles.

Signs and symptoms of this form of MDS5 generally appear during infancy. Initial symptoms may include a severe loss of muscle tone affecting movement. Additional symptoms may include involuntary muscle contraction, recurrent seizures, progressive curvature of the spine, failure to grow at a normal rate, and severe hearing impairment. Most individuals will not survive past childhood, though some have survived into their teens. Death most frequently occurs due to infection.

SUCLA2-related MDS is caused by mutations in the SUCLA2 gene.

### Treatment

There is no cure for SUCLA2-related MDS. Physical therapy and stretching exercises may help to increase mobility. Wheelchair assistance may be necessary. Respiratory aids such as a ventilator may be required to assist with breathing. Braces can be used for scoliosis, anti-epileptic medication may be prescribed to treat seizures, and cochlear implants may be recommended to assist with hearing impairment.

## Molybdenum Cofactor Deficiency, Type A

### Summary

Molybdenum cofactor deficiency (MCD) is an autosomal recessive disorder characterized by brain damage that worsens over time.

Although the child may look healthy at birth, signs and symptoms generally appear during infancy. The child can have problems feeding and experience seizures that will not respond to treatment. Additional signs include breakdown of the brain tissue leading to intellectual and physical delays with many kids never being able to sit or speak. Symptoms worsen over time, and most will not survive past childhood.

MCD is caused by mutations in multiple genes. Two mutations in one gene are needed to show symptoms. MCD, type A is caused by mutations in the MOCS1 gene.

### Treatment

There is no cure for MCD. Early diagnosis is very important. MCD may be detected on a newborn screen depending on the laboratory.

## Mucopolipidosis II/III

### Summary

Mucopolipidosis II/III (ML II/III) are autosomal recessive disorders that affect many parts of the body.

Symptoms in individuals with ML II (also called I-cell disease) typically appear at birth and may include multiple skeletal abnormalities along with joint problems that restrict movement. Individuals can develop an enlarged liver and spleen, hoarse voice, frequent ear infections leading to hearing loss, heart abnormalities, and suffer from recurrent respiratory infections that affect breathing. Many will stop growing by the age of 3 years, and most do not survive past childhood due to congestive heart failure or recurrent infections.

ML III is milder than ML II with symptoms often not appearing until closer to age 3 years, and many survive into their 40s or 50s. People with ML III grow slowly and have short heights. Their joints are stiff, and they suffer from multiple skeletal abnormalities including weak bones (osteoporosis). These problems can become more severe over time. Learning disabilities or mild intellectual disability, coarse facial features, frequent infections, and heart abnormalities are also common.

Both ML II and ML III are caused by mutations in the GNPTAB gene.

### Treatment

There is no cure for ML II/III. Treatment is aimed at managing symptoms. Physical therapy and low-impact therapies such as aqua-therapy may be useful for joint pain.



## Mucopolipidosis, Type 3 Gamma

### Summary

Mucopolipidosis, type 3 gamma (ML-3G) is an autosomal recessive disorder that affects many different parts of the body.

Symptoms of ML-3G typically appear before the age of 3 years and may include slow growth, short stature, stiff joints, skeletal abnormalities, brittle bones that are prone to fracture (osteoporosis), and pain. Problems such as lung disease and heart valve abnormalities can be significant. A small percentage will experience intellectual disability and learning problems. Individuals usually live into adulthood.

ML-3G is caused by mutations in the GNPTG gene.

### Treatment

There is no cure for ML-3G. Surgery may be needed to help with breathing or address heart abnormalities. Low-impact physical therapy can be beneficial. Individuals will require life-long regular monitoring by healthcare providers.

## Mucopolidosis, Type 4

### Summary

Mucopolidosis, type 4 (ML4) is a severe autosomal recessive neurological disorder that causes delayed development and vision loss over time.

Infants affected by ML4 experience difficulty sitting, crawling, walking, and grasping objects, which can start as early as the first year of life. Most children are never able to walk due to weak muscles that become stiff as they get older. Individuals with ML4 also have intellectual disabilities as well as problems with speech, chewing, and swallowing. Although vision is normal at birth, it will continue to get worse over the first 10 years of life. Most will be blind by their teenage years. While most individuals reach adulthood, overall life expectancy is reduced.

Approximately 5% of people with ML4 have a form of the condition that has milder effects on development, walking, and vision.

ML4 is caused by mutations in the MCOLN1 gene.

### Treatment

There is no cure for ML4. Treatment may include various therapies, orthotics, walkers, vision aids, and wheelchairs. It is focused on increasing quality of life and improving function.

## Mucopolysaccharidosis, Type 1 (Hurler Syndrome)

### Summary

Mucopolysaccharidosis, type 1 (MPS1) is an autosomal recessive disorder affecting many body parts.

Signs and symptoms of Hurler syndrome typically appear within the first year of life and become rapidly worse over time. Affected individuals have skeletal abnormalities that may affect the skull, hip, limbs, and hands in addition to joint deformities (contractures) that limit movement. They often have a narrowing of the spinal column, which may need surgery to prevent damage to the spinal cord. Other features include an enlarged head, coarse facial features, an enlarged liver and spleen, hearing loss, and a cloudy covering over the eye (cataract) leading to a loss of vision. A narrow airway can cause breathing problems and recurrent infections. Individuals typically experience a decline in intellectual function as well as loss of previously learned motor skills between the ages of 1 and 2 years. Most affected individuals will experience a shortened life expectancy due to heart and breathing complications.

MPS1 is divided into three types (Hurler, Hurler-Scheie, and Scheie syndrome) depending on severity. Hurler syndrome is the most severe, while Scheie is the least severe. All these types are caused by the same gene, IDUA.

### Treatment

There is no cure for MPS1. Treatment is aimed at preventing and managing symptoms. Stem cell transplant is the primary treatment for individuals under the age of 2 years before children start to lose previously learned skills. This treatment may prolong survival, protects neurological functions, and helps improve many of the other symptoms. Enzyme replacement therapy (ERT) has been shown to provide benefit for individuals affected with MPS1. Additional treatment may include physical therapy, occupational therapy, and speech therapy. Surgery may be needed to replace heart valves, repair hernias, and to remove excess fluid from the brain.

## Mucopolysaccharidosis, Type 2 (Hunter Syndrome), X-linked

### Summary

Mucopolysaccharidosis, type 2 (MPS2), also called Hunter syndrome, is an X-linked inherited disorder affecting many body parts. The condition worsens over time but varies widely from individual to individual.

The first signs appear between the ages of 2 and 4 years as a change in facial features to include widening of the lips, rounded cheeks, and a broad nose and tongue. They suffer from a narrow airway that can lead to recurrent infections, airway blockage, and breathing problems. Many individuals may also develop a build-up of fluid in the brain (hydrocephalus), enlarged liver and spleen, joint deformities that limit movement, thick non-stretchy skin, and heart abnormalities. Some individuals will also develop a loss of vision and hearing.

Children with MPS2 grow normally until the age of 5 years at which time their growth slows, and they end up with short height. Life expectancy is between 10 to 20 years of age, although some milder cases may live further into adulthood.

MPS2 is caused by mutations in the IDS gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one IDS gene is enough to cause this type of mucopolysaccharidosis. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their IDS gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for MPS2. Treatment is aimed at managing symptoms. Surgery for heart, airway, or skeletal problems may be needed.

## Mucopolysaccharidosis, Type 3 (Sanfilippo Syndrome)

### Summary

Mucopolysaccharidosis, type 3 (MPS3), also called Sanfilippo syndrome, is an inherited autosomal recessive disorder that affects the brain and spinal cord due to the body's inability to breakdown certain chemicals called glycosaminoglycans (GAGs).

MPS3 generally appears during childhood. Initial symptoms may include delayed speech and problems such as restless, aggressive, or anxious behavior. Other issues include trouble sleeping, an enlarged liver, short height, joint stiffness, recurrent diarrhea, frequent respiratory and ear infections, and a larger head size. As the disorder progresses, individuals may lose previously learned physical or intellectual skills and suffer from loss of hearing and/or vision. Symptoms worsen over time, and most individuals will only survive into adolescence or early adulthood.

MPS3 is caused by mutations in 4 different genes, all with similar symptoms. The genes that cause MPS3 include SGSH (type A), NAGLU (type B), HGSNAT (type C), and GNS (type 4).

### Treatment

There is no cure or effective treatment for MPS3. Medication may be prescribed to treat seizures and sleep disturbances. Physical therapy and special educational classes may be beneficial.

## Mucopolysaccharidosis, Type 3 (Sanfilippo Syndrome)

### Summary

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MPS3 generally appears during childhood. Initial symptoms may include delayed speech and problems such as restless, aggressive, or anxious behavior. Other issues include trouble sleeping, an enlarged liver, short height, joint stiffness, recurrent diarrhea, frequent respiratory and ear infections, and a larger head size. As the disorder progresses, individuals may lose previously learned physical or intellectual skills and suffer from loss of hearing and/or vision. Symptoms worsen over time, and most individuals will only survive into adolescence or early adulthood.

MPS3 is caused by mutations in 4 different genes, all with similar symptoms. The genes that cause MPS3 include SGSH (type A), NAGLU (type B), HGSNAT (type C), and GNS (type 4).

### Treatment

There is no cure or effective treatment for MPS3. Medication may be prescribed to treat seizures and sleep disturbances. Physical therapy and special educational classes may be beneficial.

## Mucopolysaccharidosis, Type 4A (Morquio Syndrome)

### Summary

Mucopolysaccharidosis, type 4A (MPS4A), also called Morquio syndrome A, is an inherited autosomal recessive disorder that affects the skeletal system.

Signs and symptoms generally appear during early childhood when affected individuals start to display bone abnormalities that become more pronounced over time. These abnormalities are found in the chest, spine, hips, limbs, and hands. Due to these abnormalities, affected individuals often experience difficulty with walking and will be short in height. Many will also have overly flexible joints.

Additional symptoms may include breathing problems due to narrow airways, recurrent ear infections, hearing loss, upper respiratory infections, heart and dental abnormalities, and a cloudy covering over the eye (cataract) causing vision loss. Intelligence is not affected. Some individuals with severe symptoms may only survive through late childhood or adolescence, while others with milder symptoms may survive well into adulthood.

MPS4A is caused by mutations in the GALNS gene.

### Treatment

There is no cure for MPS4A. Treatment is aimed at managing symptoms and increasing quality of life.

## Mucopolysaccharidosis, Type 6 (Maroteaux-Lamy Syndrome)

### Summary

Mucopolysaccharidosis, type 6 (MPS6), also called Maroteaux-Lamy syndrome, is an inherited autosomal recessive disorder that affects many parts of the body, and the severity and speed of worsening will vary from person to person.

Age of onset generally occurs during early childhood. Affected individuals have skeletal abnormalities that may affect the skull, hip, limbs, and hands in addition to joint deformities (contractures) that limit movement. They often have a narrowing of the spinal column which may need surgery to prevent damage to the spinal cord. Unlike other forms of MPS, MPS6 does not affect intellectual ability. Other features include an enlarged head, coarse facial features, a large tongue, an enlarged liver and spleen, hearing loss, and a cloudy covering over the eye (cataract) leading to a loss of vision. Many will also experience heart disease, short height, and frequent upper respiratory infections. Heart disease and airway obstruction cause many cases of death.

MPS6 is caused by mutations in the ARSB gene.

### Treatment

There is no cure for MPS6. Treatment is aimed at managing symptoms and may include supplemental oxygen, skeletal or heart surgery, and physical and speech therapy.



## Mucopolysaccharidosis, Type 7 (Sly Syndrome)

### Summary

Mucopolysaccharidosis, type 7 (MPS7), also called Sly syndrome, is an inherited autosomal recessive disorder that affects many parts of the body, and the severity will vary from person to person.

The most severe cases of MPS7 exhibit an overall swelling of the body due to a build-up of fluids prior to birth, which can often result in death before the baby is even born. Others show the first signs during early childhood. Symptoms of MPS7 include skeletal abnormalities, joint contractures that decrease mobility, an abnormally large head, intellectual disability that worsens over time, hearing loss and vision loss, short height, and a build-up of fluid in the brain (hydrocephalus), which can cause damaging levels of pressure. Individuals may also experience heart abnormalities, frequent respiratory infections, and sleep apnea (temporary stop of breathing during sleep).

Many affected individuals also have characteristic facial features that are described as being coarse. Life expectancy is shortened with death often occurring due to heart disease or airway blockage.

MPS7 is caused by mutations in the GUSB gene.

### Treatment

There is no cure for MPS7. Treatment is aimed at managing symptoms to improve quality of life and may include orthopedics to treat bone abnormalities.

## Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome, Type 1

### Summary

Multiple congenital anomalies-hypotonia-seizures syndrome, type 1 (MCAHS1) is an autosomal recessive disorder that causes a wide variety of symptoms in affected individuals.

Signs and symptoms generally appear shortly after birth and include poor muscle tone, lack of physical skills development, and seizures. Affected individuals also have heart defects, bladder or kidney abnormalities, or seizures. MCAHS1 syndrome may also cause signs prior to birth such as increased growth or increase in amniotic fluid levels. Individuals typically will not survive past the age of 3 years.

MCAHS1 is caused by mutations in the PIGN gene.

### Treatment

There is no cure for MCAHS1. Treatment is aimed at managing symptoms and may include medication to help control seizures or physical therapy to assist in motor function.

## Multiple Sulfatase Deficiency

### Summary

Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder that affects the brain, skin, and bones.

There are three types of MSD characterized by age of onset and severity of symptoms. The three types of MSD are: neonatal, late-infantile, and juvenile. Affected individuals will usually only survive a few years after the first signs appear.

The neonatal form of MSD is the most severe form with symptoms generally appearing shortly after birth. Symptoms include a breakdown of the tissue in the nervous system causing problems with movement, seizures, developmental delay, and delayed growth. Additional symptoms include dry and scaly skin, excess growth of hair, skeletal abnormalities, and joint stiffness. Individuals also have typical facial features that are described as coarse. Some individuals will experience loss of hearing, heart abnormalities, and an enlarged liver and spleen. Symptoms generally worsen over time.

The late-infantile form of MSD is the most common form of the disorder, generally appearing during early childhood. Initial signs include a continued loss of mental abilities and physical skills, dry/scaly skin, skeletal abnormalities, and the typical coarse facial appearance.

The juvenile form of MSD is the rarest form of the disorder, generally appearing during mid-to-late childhood. Symptoms include a slower loss of mental and physical skills and dry/scaly skin.

MSD is caused by mutations in the SUMF1 gene.

### Treatment

There is no cure for MDS. Treatment is supportive and aimed at managing symptoms.

## Muscular Dystrophy-Dystroglycanopathy

### Summary

Muscular Dystrophy-Dystroglycanopathy (MDD) is an autosomal recessive disorder that affects the muscles, eyes, and brain.

Severity of symptoms vary from individual to individual. Symptoms typically appear at or right after birth. Muscular symptoms may include weak muscle tone and involuntary muscle contractions that worsen over time. Children with this disorder are often missing the normal “wavy” appearance to the brain and instead is bumpier (like cobblestones). Fluid can also build-up in the brain causing pressure. These two brain abnormalities can result in both physical and intellectual delays. The eyes in people with MDD can be abnormally sized or cloudy (cataracts), and most people with the condition have some degree of vision loss.

Walker-Warburg syndrome (WWS) is often used to describe a severe form of the disorder. Muscle-Eye-Brain disease may be used to describe a form with severity that is somewhere between that of WWS and MDD. Most experience a shortened lifespan.

MDD has many types that can be caused by different genes, including POMGNT1 (type 3), FKTN (type 4), and FKRP (type 5). Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for MDD. Treatment is aimed at managing symptoms and may include physical or occupational therapy to aid in movement. Medication may also be used to help control seizures.

## Myasthenic Syndrome, Type 10

### Summary

Myasthenic syndromes are a group of disorders causing muscle weakness that worsens with physical activity. Myasthenic syndrome, type 10 (CMS10) is an autosomal recessive form of this disorder that appears during early childhood.

Severity of symptoms vary from individual to individual. The muscles that are most commonly affected include facial muscles (including muscles responsible for eyelid control and eye movement) and muscles used for chewing and swallowing. Muscle weakness may cause many individuals to experience difficulty feeding, delayed development of physical milestones, and possible breathing problems. Individuals with severe breathing problems may experience pneumonia or respiratory failure. The severity of muscle weakness varies. Those with severe muscle weakness may be unable to walk, while others experience minor weakness and are fairly unaffected.

Myasthenic syndrome can be caused by mutations in many different genes. Two mutations in the same gene are needed to cause disease. CMS10 is caused by mutations in the DOK7 gene.

### Treatment

There is no cure for CMS10. Treatment may include various medications.

## Myasthenic Syndrome, Type 4

### Summary

Myasthenic syndromes are a group of disorders causing muscle weakness that worsens with physical activity. Myasthenic syndrome, type 4 (CMS4) is an autosomal recessive form of this disorder that appears during early childhood.

Severity of symptoms vary from individual to individual. The muscles that are most commonly affected include facial muscles (including muscles responsible for eyelid control and eye movement) and muscles used for chewing and swallowing. Muscle weakness may cause many individuals to have trouble feeding, delayed development of physical milestones, and possible breathing problems. Individuals with severe breathing problems may experience pneumonia or respiratory failure. The severity of muscle weakness varies. Those with severe muscle weakness may be unable to walk, while others experience minor weakness and are unaffected.

Myasthenic syndrome can be caused by mutations in many different genes. Two mutations in the same gene are needed to cause disease. CMS4 is caused by mutations in the CHRNE gene.

### Treatment

There is no cure for CMS4. Treatment may include various medications and therapies.

## Myasthenic Syndrome, Type 5

### Summary

Myasthenic syndromes are a group of disorders causing muscle weakness that worsens with physical activity. Myasthenic syndrome, type 5 (CMS5) is an autosomal recessive form of this disorder that appears during early childhood.

Severity of symptoms vary from individual to individual. The muscles that are most commonly affected include facial muscles (including muscles responsible for eyelid control and eye movement) and muscles used for chewing and swallowing. Muscle weakness may cause many individuals to experience difficulty feeding, delayed development of physical milestones, and possible breathing problems. Individuals with severe breathing problems may experience pneumonia or respiratory failure. The severity of muscle weakness varies. Those with severe muscle weakness may be unable to walk, while others experience minor weakness and are fairly unaffected.

Myasthenic syndrome can be caused by mutations in many different genes. Two mutations in the same gene are needed to cause disease. CMS5 is caused by mutations in the COLQ gene.

### Treatment

There is no cure for CMS5. Treatment may include various medications.

## Myopia with Cataract and Vitreoretinal Degeneration

### Summary

Myopia with cataract and vitreoretinal degeneration (MCVD) is an autosomal recessive disorder that affects the eyes usually leading to blindness in at least one eye.

Signs and symptoms generally develop during childhood. Affected individuals experience severe nearsightedness (myopia), breakdown (deterioration) of the retina, and cataracts (cloudiness to the eye). Some individuals also experience a dislocated or unstable lens within the eye. If the retina becomes detached, it could cause complete loss of vision.

MCVD is caused by mutations in the P3H2 gene (previously known as the LEPREL1 gene).

### Treatment

There is no cure for myopia with cataract and vitreoretinal degeneration. Treatment is aimed at managing symptoms and may include surgery.



## Myotubular Myopathy (X-linked)

### Summary

Myotubular myopathy is an X-linked inherited disorder that affects the muscles involved in movement.

Signs and symptoms generally appear at birth and include muscle weakness and poor muscle tone. Additional symptoms include impaired motor skills (sitting, walking, crawling, etc.), feeding and breathing problems, involuntary eye movement, undescended testicles, and absent reflexes. Bone development is often disrupted leading to curvature of the spine (scoliosis), fragile bones, joint deformities, a large head, and a long face. Individuals may also experience liver disease, recurrent respiratory infections, and seizures. Individuals who survive past childhood often continue to struggle with recurrent breathing problems and respiratory infections, which is the leading cause of death in these children.

Myotubular myopathy is caused by mutations in the MTM1 gene which is on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one MTM1 gene is enough to cause this type of myotubular myopathy. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their MTM1 gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for myotubular myopathy. Treatment involves managing symptoms with a wide team of healthcare providers and specialists. Ventilators are often needed to assist with breathing.

## Nemaline Myopathy

### Summary

Nemaline myopathy is an autosomal recessive disorder that causes muscle weakness (myopathy), especially in the muscles of the limbs, face, and neck. Nemaline myopathy causes problems with breathing, feeding and swallowing, abnormal curvature of the spine (scoliosis), as well as joint and foot deformities. Signs and symptoms are typically present at birth or appear shortly after. Motor milestones may be delayed. Most affected individuals are eventually able to walk and lead normal lives with no long-term effects. There is a small percentage of individuals that experience a more severe case of Nemaline myopathy. This may cause respiratory difficulties and lung infections and may potentially be fatal in childhood.

There are at least six forms of Nemaline myopathy, caused by different genes with different types of inheritance. Two mutations in the same gene would be needed to cause symptoms. 50% of nemaline myopathy is caused by mutations in the NEB gene.

### Treatment

There is no cure for Nemaline myopathy. Treatment is focused on managing symptoms and may include physical therapy, speech therapy, and monitoring of a child's nutrition. Infants often require a feeding tube to help with swallowing, and a ventilator may be used to assist with breathing. Aggressive treatment may be required for respiratory infections.

## Nephronophthisis, Type 2

### Summary

Nephronophthisis is an autosomal recessive disorder that damages the kidneys. It can start in childhood and lead to kidney failure when the kidneys are no longer able to filter fluids and waste from the body. Nephronophthisis, type 2, also known as infantile nephronophthisis, is an early onset form of this disorder that can worsen quickly. Most individuals progress to kidney failure by the age of 3 years.

Most cases of nephronophthisis only present with symptoms involving the kidneys. However, additional symptoms (such as anemia, liver and heart abnormalities) are present in 10%-15% of cases. Some individuals may have organs in the body that are positioned in the opposite position they are meant to be in (right side versus left side), called situs inversus.

Nephronophthisis can be caused by mutations in many different genes. Two mutations in the same gene are needed to cause symptoms of the disease. Nephronophthisis, type 2 is caused by mutations in the *INVS* gene.

### Treatment

There is no cure for nephronophthisis. At present, there is no effective treatment to prevent the disease from getting worse. Kidney dialysis or transplant may be required for individuals who have developed kidney failure.

## Nephrotic Syndrome, Type 1 (Finnish Nephrosis)

### Summary

Nephrotic syndrome, type 1, also known as congenital Finnish nephrosis, is an autosomal recessive disorder characterized by abnormal kidney function.

Signs and symptoms of nephrotic syndrome, type I typically appear during birth or shortly thereafter, and premature birth can be common. Some cases presenting in infancy or late childhood have also been reported. Symptoms may include swelling due to fluid retention, high blood pressure, and kidney failure. Most individuals will not survive past the age of 5 years. Kidney transplants have increased the survival rate to a relatively normal life expectancy.

Nephrotic syndrome, type 1 is caused by mutations in the NPHS1 gene.

### Treatment

There is no cure for nephrotic syndrome, type 1. If diagnosed early, intensive medical therapy including dialysis, medications, feeding tubes, and antibiotics may be used to extend lifespan to the point of kidney transplant.

## Nephrotic Syndrome, Type 2

### Summary

Nephrotic syndrome, type 2, also known as steroid-resistant nephrotic syndrome, is an autosomal recessive disorder characterized by abnormal kidney function that cannot be treated with steroids.

Signs and symptoms of nephrotic syndrome, type 2 typically appear during childhood but can occur shortly after birth. Symptoms may include swelling due to fluid retention, high blood pressure, and kidney scarring and failure.

Nephrotic syndrome, type 2 is caused by mutations in the NPHS2 gene.

### Treatment

There is no cure for nephrotic syndrome, type 2. It is hard to treat due to the resistance to steroids. Other medications may still be used to treat the high blood pressure and other symptoms. Treatment is usually done to extend lifespan to the point of kidney transplant.

## Netherton Syndrome

### Summary

Netherton syndrome is an autosomal recessive disorder that causes abnormal skin and hair.

Signs and symptoms generally appear shortly after birth as infants are often born with red and scaly skin. The severity of skin abnormalities may vary from individual to individual and may change over time. This skin can be very dry causing dehydration and problems regulating body temperature, and the itchy skin can cause recurring infections also due to scratching and breaks in the skin. Skin cells also die at a faster rate causing a build-up of dead skin, particularly in the ears that can cause hearing difficulties if not removed.

Abnormalities of the hair are also seen shortly after birth with many having sparse and brittle hair that breaks easily. Eyelashes and eyebrows may also be affected. Individuals with Netherton syndrome can also develop asthma, food allergies, and immune system problems.

Netherton syndrome is caused by mutations in the SPINK5 gene.

### Treatment

There is no cure for Netherton syndrome. Treatment is aimed at managing symptoms and may include medications or creams for the skin.

## Neuroaxonal Dystrophy (Infantile)

### Summary

Infantile neuroaxonal dystrophy (INAD) is a rare autosomal recessive disorder that affects the nervous system due to swelling and breakdown of the nerve endings inside and outside of the brain and spinal cord.

Signs and symptoms generally appear between 6 and 18 months and include a loss of head control and a delay of physical skills and intellectual skills. Individuals also experience a decline in vision and speech, as well as hearing loss, difficulties with movement, involuntary eye movements, muscle weakness, difficulty feeding and breathing, or seizures. Many have typical facial features that may include a prominent forehead, crossed eyes, a small jaw, and low-set ears. Individuals will eventually lose the ability to move independently and can develop dementia (not be aware of their surroundings). The disorder worsens over time. Many individuals end up in a vegetative state, and most will not survive beyond childhood.

INAD is caused by mutations in PLA2G6 gene.

### Treatment

There is no cure for INAD, and treatment cannot stop the worsening of the disorder. Treatment is aimed at managing symptoms and may include medication for pain relief, seizures, and muscle spasms. Individuals may require a feeding tube and physical therapy.

## Neuronal Ceroid Lipofuscinosis

### Summary

Neuronal ceroid-lipofuscinosis (NCL), sometimes referred to as Batten disease, is a group of autosomal recessive disorders that causes a breakdown of the brain leading to a continued loss of intellectual and physical abilities, seizures, and death.

The different types of NCL are based on the age of onset (infantile, late-infantile, juvenile, and adult). Infantile NCL typically appears between 6 months and 24 months. Most individuals will never be able to walk or speak. Symptoms become worse over time, and most individuals will not survive past childhood.

Late-infantile NCL generally shows signs between 2 and 8 years. They will often lose the skills they acquired at earlier ages and are wheelchair bound by late childhood. Vision can also be affected in this type, and most will not survive past their teenage years.

Juvenile NCL generally appears between the ages of 4 and 10 years. These children will also lose their previously learned physical and intellectual skills. They have a quick loss of vision and experience seizures, heart problems, and behavioral issues. Most people with the juvenile form of NCL live into their 20s or 30s.

Mutations in multiple genes can cause different types of NCL that can present in the different forms listed above, including PPT1 (type 1), TPP1 (type 2), CLN3 (type 3), CLN5 (type 5), CLN6 (type 6), MFSD8 (type 7). Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for NCL. Treatment is aimed at managing symptoms. Medication can be prescribed for seizures, muscle twitches, and behavioral problems. Physical therapy and occupational therapy may be beneficial in prolonging movement.



## Neuronal Ceroid Lipofuscinosis, Type 8 (including Northern Epilepsy)

### Summary

Neuronal ceroid-lipofuscinosis (NCL), sometimes referred to as Batten disease, is a group of autosomal recessive disorders that causes a breakdown of the brain leading to a continued loss of intellectual and physical abilities, seizures, and death.

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Late-infantile NCL generally shows signs between 2 and 8 years. They will often lose the skills they acquired at earlier ages and are wheelchair bound by late childhood. Vision can also be affected in this type, and most will not survive past their teenage years.

Juvenile NCL generally appears between the ages of 4 and 10 years. These children will also lose their previously learned physical and intellectual skills. They have a quick loss of vision and experience seizures, heart problems, and behavioral issues. Most people with the juvenile form of NCL live into their 20s or 30s.

Mutations in multiple genes can cause different types of NCL that can present in the different forms listed above, including PPT1 (type 1), TPP1 (type 2), CLN3 (type 3), CLN5 (type 5), CLN6 (type 6), MFSD8 (type 7) and CLN8 (type 8). Two mutations in the same gene are needed to cause symptoms.

Mutations in the CLN8 gene can cause late-infantile NCL as well as a condition called Northern epilepsy. The seizures seen in Northern epilepsy can start to occur between the ages of 5 and 10 years at a frequency of 1-2 times a month, but they become less frequent with age. A few years after the start of seizures, affected individuals will experience a loss of motor skills (such as writing, buttoning, using silverware) and intellectual abilities. Problems with balance, walking, and visual clarity will worsen over time. Northern epilepsy is considered one of the mildest forms of NCL.

### Treatment

There is no cure for NCL. Treatment is aimed at managing symptoms. Medication can be prescribed for seizures, muscle twitches, and behavioral problems. Physical therapy and occupational therapy may be beneficial in prolonging movement.

## Neutropenia, Type 3

### Summary

Neutropenia is a disorder that leads to recurrent infections in various parts of the body. Affected individuals have a deficiency of neutrophils, which are a type of white blood cell that helps fight infection and inflammation.

Signs and symptoms generally appear after the age of 2 years. Neutropenia often leads to recurrent infections in many areas of the body, particularly the sinuses, lungs, and liver. Additional symptoms that may occur include inflammation of the gums and skin, brittle bones that are prone to fracture, developmental delay, and seizures. If left untreated, infections may be fatal. Roughly 20% of affected individuals will also develop cancer in the form of acute leukemia or blood and bone marrow disease (called myelodysplastic syndrome).

Mutations in several different genes can cause neutropenia. Neutropenia, type 3 is caused by mutations in the HAX1 gene.

### Treatment

There is no cure for neutropenia, type 3. Medications to prevent and treat infection are usually recommended. In severe cases, bone marrow transplant may be considered.

## Neutropenia, Type 4

### Summary

Neutropenia is a disorder that leads to recurrent infections in various parts of the body. Affected individuals have a deficiency of neutrophils, which are a type of white blood cell that helps fight infection and inflammation.

Signs and symptoms generally appear after the age of 2 years. Neutropenia often leads to recurrent infections in many areas of the body, particularly the sinuses, lungs, and liver. Additional symptoms that may occur include inflammation of the gums and skin, brittle bones that are prone to fracture, developmental delay, and seizures. If left untreated, infections may be fatal. Roughly 20% of affected individuals will also develop cancer in the form of acute leukemia or blood and bone marrow disease (called myelodysplastic syndrome).

Mutations in several different genes can cause neutropenia. Neutropenia, type 4 is caused by mutations in the G6PC3 gene.

### Treatment

There is no cure for neutropenia, type 4. Medications to prevent and treat infection are usually recommended. In severe cases, bone marrow transplant may be considered.

## Neutropenia, Type 5

### Summary

Neutropenia type 5 is a severe autosomal recessive disorder that leads to recurrent infections in different parts of the body. Affected individuals have a deficiency of neutrophils, which are a type of white blood cell that helps fight infection and inflammation.

Symptoms generally appear during infancy. Aside from the immune system problems, individuals may experience poor weight gain, an enlarged liver and spleen, bone marrow dysfunction, enlarged kidneys, and delayed development.

Mutations in several different genes can cause neutropenia. Neutropenia, type 5 is caused by mutations in the VPS45 gene.

### Treatment

There is no cure for neutropenia, type 5. Medications to prevent and treat infection are usually recommended. In severe cases, bone marrow transplant may be considered.

## Niemann-Pick Disease, type C1

### Summary

Niemann-Pick disease is an autosomal recessive disorder that causes an inability of the body to breakdown, transport, and use fats and cholesterol.

Signs and symptoms of Niemann-Pick disease, type C1 typically appear during childhood, though an onset during infancy and adulthood are possible. Symptoms may include severe liver and lung disease, breathing difficulties, developmental delay, seizures, lack of coordination, poor muscle tone, involuntary muscle contraction, difficulty feeding, and an inability to move the eyes up and down. Adults are more likely to experience dementia and psychiatric symptoms.

There are 4 different types of Niemann-Pick disease caused by 3 different genes. Niemann-Pick disease, type C1 is caused by mutations in the NPC1 gene.

### Treatment

There is no cure for Niemann-Pick disease, type C1. Treatment is aimed at managing symptoms and increasing quality of life. Treatment may include medications, physical therapy, a feeding tube, and management of infections.

## Niemann-Pick Disease, type C2

### Summary

Niemann-Pick disease is an autosomal recessive disorder that causes an inability of the body to breakdown, transport, and use fats and cholesterol.

Signs and symptoms of Niemann-Pick disease, type C2 typically appear during childhood, though an onset during infancy and adulthood is possible. Symptoms may include severe liver and lung disease, breathing difficulties, developmental delay, seizures, lack of coordination, poor muscle tone, involuntary muscle contraction, difficulty feeding, and an inability to move the eyes up and down. Adults are more likely to experience dementia and psychiatric symptoms.

There are 4 different types of Niemann-Pick disease caused by 3 different genes. Niemann-Pick disease, type C2 is caused by mutations in the NPC2 gene.

### Treatment

There is no cure for Niemann-Pick disease, type C2. Treatment is aimed at managing symptoms and increasing quality of life. Treatment may include medications, physical therapy, a feeding tube, and management of infections.

## Niemann-Pick Disease, types A and B

### Summary

Niemann-Pick disease is an autosomal recessive disorder that causes an inability of the body to breakdown, transport, and use fats and cholesterol.

Signs and symptoms of Niemann-Pick disease, type A typically appear by 3 months of age as a failure to gain weight and a failure to thrive with an enlarged liver and spleen. After 1 year, affected individuals will start to show a continued decline in mental and physical abilities. Severe lung disease can develop causing infection and respiratory failure. A routine examination can pick up the characteristic “cherry-red spot” in the eye.

Signs for Niemann-Pick, type B usually appear later during mid-childhood and although similar to type A, they are milder. They will often be shorter heights due to delayed bone growth. Only 33% will have the “cherry-red spot” seen on eye exam. Most people with Niemann-Pick, type B can survive into adulthood.

There are 4 different types of Niemann-Pick disease caused by 3 different genes. Both types A and B in Niemann-Pick disease are caused by mutations in the SMPD1 gene.

### Treatment

There is no cure for Niemann-Pick disease, types A or B. Treatment is aimed at managing symptoms and increasing quality of life. Treatment may include medications, physical therapy, a feeding tube, and management of infections.

## Nijmegen Breakage Syndrome

### Summary

Nijmegen Breakage syndrome (NBS) is an autosomal recessive disorder that can cause many different health problems.

Infants have unusually small heads and are slow to grow throughout infancy and childhood. Growth becomes more normal later in childhood, but affected individuals may still be shorter than other children their age. Individuals affected with NBS often suffer from a weakened immune system causing frequent infections, intellectual disability, and have up to a 50 times higher chance for cancer. Individuals are also highly sensitive to the effects of radiation treatment; therefore, alternative methods for cancer care must be used. Females with this condition are also likely to experience problems having children.

The average life expectancy may be near 30-40 years of age. Cancer is the leading cause of death with approximately half of affected individuals developing non-Hodgkin's lymphoma by 15 years of age.

NBS is caused by mutations in the NBN gene. Two copies of a mutation in this gene are needed to cause symptoms. Most carriers of one mutation will not normally show symptoms of the disorder. However, several studies have reported that carriers for specific NBS mutations are also at an increased risk for certain cancers.

### Treatment

There is no cure for NBS. Treatment is aimed at management of symptoms through continued monitoring by healthcare professionals and the use of various medications.



## Non-syndromic Hydrocephalus

### Summary

Non-syndromic hydrocephalus (HYC1) is an autosomal recessive disorder that affects the cerebrospinal fluid (the clear fluid that surrounds the brain and spinal cord). This fluid is housed in an area of the brain called ventricles.

Individuals with HYC1 experience enlarged ventricles due to a build-up of this fluid which can affect the way the surrounding brain tissue develops and result in neurological damage. This fluid build-up will generally start before birth. Severity of symptoms varies from individual to individual with some experiencing mild seizures and others experiencing severe intellectual disability and muscles weakness/lack of muscle control.

HYC1 is caused by mutations in the *CCDC88C* gene.

### Treatment

There is no cure for HYC1. Treatment is aimed at managing symptoms and increasing quality of life. In certain cases, surgery may be needed to relieve the pressure on the brain caused by the fluid build-up.

## Oculocutaneous albinism type 1A

### Summary

Oculocutaneous albinism (OCA) is a group of conditions that affect coloring (pigmentation) of the skin, hair, and eyes. Oculocutaneous albinism type 1A (OCA1A), caused by mutations in the TYR gene, is the most severe form of OCA. Individuals with this condition produce no pigmentation at all and are characterized by white hair and skin, light-colored translucent irises, nystagmus and misrouting of the optic nerves. Long-term sun exposure greatly increases the risk of skin damage and skin cancers, including an aggressive form of skin cancer called melanoma, in people with this condition.

### Treatment

There is no cure for the albinism, but treatment may relieve symptoms and prevent sun damage. Treatment may include corrective lenses for vision problems, sunglasses to protect the eyes from UV rays, protective clothing and sunscreen to protect skin and surgery on the eye muscles to correct abnormal eye movements.

## Ornithine Transcarbamylase Deficiency

### Summary

Ornithine transcarbamylase deficiency (OTC) is an X-linked disorder that causes a toxic build-up of ammonia in the blood. OTC is a part of a class of inherited disorders called urea cycle disorders, which is the process in the liver that breaks down and rids the body of ammonia. High levels of ammonia affect different systems in the body, particularly the nervous system.

Signs and symptoms of OTC deficiency vary in severity but generally appear within a few days after birth. Symptoms may include a lack of energy, poor feeding, poor growth, low muscle tone, and a poorly controlled rate of breathing and body temperature. Symptoms may lead to seizures and coma. Additional complications include developmental delay, intellectual disability, and worsening liver damage. Some individuals also exhibit skin lesions and brittle hair. If diagnosed and treated early, coma and death may be prevented.

Ornithine transcarbamylase deficiency is caused by mutations in the OTC gene, which is located on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one OTC gene is enough to cause ornithine transcarbamylase deficiency. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their OTC gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for OTC deficiency. Treatment consists of lowering levels of ammonia and may include a diet of restricted protein intake, supplements, dialysis, or liver transplant.

## Osteochondrodysplasias (Sulfate Transporter-related)

### Summary

Sulfate transporter-related osteochondrodysplasias (STROs) are a group of autosomal recessive disorders that affect the bones and cushioning between the bones (cartilage). There are four forms of STROs that all share similar features but range in severity: Achondrogenesis 1B, recessive multiple epiphyseal dysplasia, diastrophic dysplasia, and atelosteogenesis 2. All four forms result in short arms and legs as well as a short overall height.

Achondrogenesis 1B is the most severe form of STROs, which is typically fatal prior to birth or shortly after birth. Symptoms include extremely short limbs, a rounded and protruding abdomen, and a narrow chest. Fingers and toes may also be rotated inwards, and some infants may experience an abnormal build-up of fluid in the body causing overall swelling.

Diastrophic dysplasia is diagnosed at birth or shortly thereafter. Symptoms include a short stature, short limbs, scoliosis (curvature of the spine), swelling of the ears, clubfoot (inward and upward turn to the foot), cleft palate (opening in the roof of the mouth), thumbs that are turned outwards (often called hitchhiker thumbs), a small chest, a rounded stomach, and bone/joint abnormalities. Some infants may have problems breathing due to the small size of their chests.

Atelosteogenesis 2 resembles diastrophic dysplasia. Symptoms are usually more severe, and affected individuals typically will not survive past infancy.

Although not tested for in this screen, multiple epiphyseal dysplasia is another mild form of the STROs. Symptoms may include malformation of the bones, hands, feet, and knees, early onset arthritis, joint pain, and cleft palate. Symptoms typically appear during childhood but may not be diagnosed until adulthood.

All four types of STROs are caused by mutations in the SLC26A2 gene.

### Treatment

There is no cure for STROs. Treatment is aimed at managing symptoms and increasing comfort and quality of life. Treatment for achondrogenesis 1B and atelosteogenesis 2 consists of making the affected individual as comfortable as possible. Diastrophic dysplasia is typically treated with physical therapy, muscle exercises, plaster casts, and surgery.

## Osteopetrosis, Type 1

### Summary

Osteopetrosis is an inherited bone disorder that causes abnormally dense bones that have a very high risk for breaks even during minor falls or injuries.

First signs appear during infancy, and additional symptoms include a loss of vision, loss of hearing, slow growth, enlarged liver and spleen, short height, and paralysis of muscles in the face (due to pinched nerves from dense skull bones). Affected individuals are also at risk for abnormal bleeding, anemia, and recurrent infections due to bone marrow problems. If left untreated, most individuals will not survive past their first few years of life with death often occurring from infection and/or bone marrow failure.

Osteopetrosis can be caused by many different genes with different types of inheritance. Osteopetrosis, type 1 can be caused by mutations in the *TCIRG1* gene, and it is inherited in an autosomal recessive fashion.

### Treatment

There is no cure for osteopetrosis. Treatment consists of blood transfusions, medication to treat infections, and management of vision loss, hearing loss, and developmental problems. Bone marrow transplant may improve many symptoms if performed early in life.

## Osteopetrosis, Type 8

### Summary

Osteopetrosis is an inherited bone disorder that causes abnormally dense bones that have a very high risk for breaks even during minor falls or injuries.

First signs appear during infancy, and additional symptoms include a loss of vision, loss of hearing, slow growth, enlarged liver and spleen, short height, and paralysis of muscles in the face (due to pinched nerves from dense skull bones). Affected individuals are also at risk for abnormal bleeding, anemia, and recurrent infections due to bone marrow problems. If left untreated, most individuals will not survive past their first few years of life with death often occurring from infection and/or bone marrow failure.

Osteopetrosis can be caused by many different genes with different types of inheritance. Osteopetrosis, type 8 can be caused by mutations in the *SNX10* gene, and it is inherited in an autosomal recessive fashion.

### Treatment

There is no cure for osteopetrosis. Treatment consists of blood transfusions, medication to treat infections, and management of vision loss, hearing loss, and developmental problems. Bone marrow transplant may improve many symptoms if performed early in life.

## Otospondylomegaepiphyseal Dysplasia

### Summary

Otospondylomegaepiphyseal dysplasia (OSMED) is an autosomal recessive disorder that causes skeletal abnormalities and hearing loss.

Signs and symptoms generally appear shortly after birth. In addition to the hearing loss, affected individuals typically exhibit similar facial features that may include a short nose, flat nasal bridge, cleft palate, undersized jaw, and an abnormally large distance between the eyes. People with this condition also have abnormally shaped and shortened limb bones as well as flat spinal bones which can lead to back and joint pain, problems with movement, and early-onset arthritis. Some symptoms that involve the bones may lessen during childhood, however, hearing loss and joint pain will continue into adulthood.

OSMED is caused by mutations in the COL11A2 gene.

### Treatment

There is no cure for OSMED. Treatment is aimed at managing symptoms and may include surgery for cleft palate and treatment for joint pain and hearing loss.

## Pendred Syndrome

### Summary

Pendred syndrome, also called non-syndromic hearing loss type 4, is an autosomal recessive disorder characterized by moderate to severe hearing loss in both ears and a thyroid condition called goiter.

Individuals with Pendred syndrome are typically born with severe hearing loss caused by changes to the inner ear (sensorineural). Some individuals may not experience hearing loss until later in infancy or early childhood. Due to problems with the inner ear, affected individuals may have problems with balance.

In late childhood or adolescence, children with Pendred syndrome may develop a goiter (a swelling of the thyroid gland), which can interfere with swallowing and breathing.

50% of Pendred syndrome cases are caused by mutations in the *SLC26A4* gene.

### Treatment

There is no cure for Pendred syndrome. Treatment is focused on addressing hearing loss. Affected children may need hearing aids or cochlear implants. Educational programs for the hearing impaired may also be helpful. Goiter may be treated with radioactive iodine to shrink the size, and surgery may be an option to remove part of the thyroid.



## Peroxisomal Acyl-CoA Oxidase Deficiency

### Summary

Peroxisomal acyl-CoA oxidase deficiency (PAOD), also called pseudo-neonatal adrenoleukodystrophy, is a rare autosomal recessive disorder that causes a weakening of the nervous system.

Signs and symptoms typically appear shortly after birth as low muscle tone and seizures. Individuals have distinct facial features including widely spaced eyes and a low nasal bridge. Most individuals will learn to walk and develop speech, however, as the disease progresses, they will lose these skills between the ages of 1 and 3 years. Over time, they will also develop vision and hearing loss, exaggerated reflexes, and increasingly severe and recurrent seizures. Muscle weakness is replaced by increased muscle tone (hypertonia). Most individuals will not survive past early childhood due to breathing complications.

Acyl-CoA oxidase deficiency is caused by mutations in the ACOX1 gene.

### Treatment

There is no cure for PAOD, and treatment is aimed at managing symptoms.

## Phosphoglycerate Dehydrogenase Deficiency

### Summary

Phosphoglycerate dehydrogenase deficiency (PDD) is an autosomal recessive disorder that causes a progressive loss of brain tissue leading to an unusually small head, impaired motor and speech development, seizures, and difficulty feeding.

There are different forms of PDD that vary in severity and age of onset. The most common and severe form which shows the first signs during infancy. Affected infants develop seizures shortly after birth and show little to no development of motor skills. Juvenile and adult forms are very rare, and present with milder symptoms.

PDD is caused by mutations in the PHGDH gene.

### Treatment

There is no cure for PDD. Affected individuals may be prescribed medication to help control seizures.

## Polycystic Kidney Disease

### Summary

Polycystic kidney disease (PKD) is an autosomal recessive disorder that affects the kidneys and other organs. In PKD, clusters of fluid-filled sacs (cysts) develop in the kidneys, interfering with their function, potentially leading to kidney failure. These cysts can also develop in other organs, especially the liver.

Signs and symptoms of PKD typically appear shortly after birth or during infancy although cases of seeing these cysts by ultrasound prior to birth have been noted. Other symptoms include dangerously high blood pressure, pain in the back and sides, recurrent urinary tract infections, kidney stones, frequent need to urinate, low blood counts, hemorrhoids, and heart abnormalities.

Secondary effects from dysfunctional kidneys include very low amniotic fluid during pregnancy, which may cause the baby's lungs to develop improperly (pulmonary hypoplasia), possibly causing death. Roughly 33% of affected infants will die within a few hours to a few days after birth. Of those that survive beyond their first year of life, the one-year survival rate is 85-87%, and the ten-year survival rate is 82%. Roughly half will experience kidney failure by the age of 10 years.

PKD is caused by mutations in the PKHD1 gene.

### Treatment

There is no cure for PKD. Treatment is focused on aiding newborns with their ability to breathe. Feeding tubes, medications, and growth hormones may be needed. Kidney dialysis is frequently used for individuals suffering from kidney failure, but kidney transplant may also be recommended.

## Polyglandular Autoimmune Syndrome, Type 1

### Summary

Polyglandular autoimmune syndrome, type 1 (PAS-1) is an autosomal recessive disorder that affects the body's immune system, causing the immune system to attack the body's healthy cells.

Signs and symptoms of PAS-1 typically appear in childhood or adolescence. It is often characterized by three features: mucocutaneous candidiasis (fungal infection of the nose and mouth), hypoparathyroidism (underactive parathyroid gland), and Addison disease.

The first feature to appear is generally mucocutaneous candidiasis followed by hypoparathyroidism, which causes weakness, tiredness, dry hair and skin, muscle pain and cramping, and a tingling sensation in the lips, fingers, and toes. The third feature to appear is generally Addison disease, which is a result of a malfunction of the adrenal gland. This leads to tiredness, loss of appetite, weight loss, low blood pressure, muscle weakness, and changes in skin coloration. Additional signs and symptoms that may occur less frequently include abnormalities in the reproductive organs, complications of the eyes, skin, nails and digestive system, and potential type I diabetes. Generally, the earlier the first features appear, the more likely multiple features will develop. Early detection and management are important.

PAS-1 is caused by mutations in the AIRE gene.

### Treatment

There is no cure for PAS-1. Treatment focuses on managing symptoms. Hormone replacement therapy, intravenous steroids, calcium, and vitamin D are often prescribed to manage symptoms. Medication is also available to treat fungal infections.

## Polymicrogyria

### Summary

Polymicrogyria is a severe disorder that affects the brain. The surface of the brain is normally covered with folds/ridges (gyri). But these folds are too small (micro) and too plentiful (poly) in people with polymicrogyria. Symptoms may vary depending on the area and percentage of the brain that is affected.

Signs and symptoms develop prior to birth and include an abnormal development of the brain that results in developmental delay, muscle weakness, paralysis, seizures, failure of the eyes to turn in the same direction at the same time, and problems with speech. Seizures seen in this disorder may be difficult to control with medication.

Although different types of polymicrogyria occur with differing types of inheritance, only one gene has been identified. Polymicrogyria that affects the frontoparietal regions on both sides of the brain is caused by mutations in the ADGRG1 gene (previously called GPR56).

### Treatment

There is no cure for polymicrogyria. Treatment is aimed at managing symptoms and may include medication and various therapies to help with motor skills.

## Pontocerebellar Hypoplasia, Type 1A

### Summary

Pontocerebellar hypoplasia is an autosomal recessive disorder that is caused by an underdevelopment (hypoplasia) of the pons and cerebellum (two parts of the brain). The pons helps the different parts of the brain communicate with each other, and the cerebellum coordinates movements in the body.

Signs and symptoms generally appear within the first year of life. Affected individuals may experience an atrophy (wasting) in the brain over time causing severe intellectual disability and a small head size. Individuals with PCH, type 1 have very weak muscles, joint contractures limiting movement, loss of vision, breathing difficulties, and feeding problems.

Many different genes can cause pontocerebellar hypoplasia. Two mutations in the same gene are needed to cause symptoms of the disorder. PCH, type 1A is caused by mutations in the VRK1 gene.

### Treatment

There is no cure or effective treatment for PCH, type 1A. Treatment is aimed at managing symptoms and improving quality of life. Physical therapy and special education may be beneficial.

## Pontocerebellar Hypoplasia, Type 1B

### Summary

Pontocerebellar hypoplasia is an autosomal recessive disorder that is caused by an underdevelopment (hypoplasia) of the pons and cerebellum (two parts of the brain). The pons helps the different parts of the brain communicate with each other, and the cerebellum coordinates movements in the body.

Signs and symptoms generally appear within the first year of life. Affected individuals may experience an atrophy (wasting) in the brain over time causing severe intellectual disability and a small head size. Individuals with PCH, type 1 have very weak muscles, joint contractures limiting movement, loss of vision, breathing difficulties, and feeding problems.

Many different genes can cause pontocerebellar hypoplasia. Two mutations in the same gene are needed to cause symptoms of the disorder. PCH, type 1B is caused by mutations in the EXOSC3 gene.

### Treatment

There is no cure or effective treatment for PCH, type 1B. Treatment is aimed at managing symptoms and improving quality of life. Physical therapy and special education may be beneficial.

## Pontocerebellar Hypoplasia, Type 2D

### Summary

Pontocerebellar hypoplasia is an autosomal recessive disorder that is caused by an underdevelopment (hypoplasia) of the pons and cerebellum (two parts of the brain). The pons helps the different parts of the brain communicate with each other, and the cerebellum coordinates movements in the body.

Signs and symptoms generally appear within the first year of life. Affected individuals may experience an atrophy (wasting) in the brain over time causing severe intellectual disability and a small head size. Individuals with PCH, type 2 are lacking voluntary movement skills (e.g., sitting, walking, reaching for things). They also have problems swallowing, vision loss, seizures, and periods of both stiff and shaky muscles in addition to a lack of communication (including speech).

Many different genes can cause pontocerebellar hypoplasia. Two mutations in the same gene are needed to cause symptoms of the disorder. PCH, type 2D is caused by mutations in the SEPSECS gene.

### Treatment

There is no cure or effective treatment for PCH, type 2D.



## Pontocerebellar Hypoplasia, Type 2E

### Summary

Pontocerebellar hypoplasia is an autosomal recessive disorder that is caused by an underdevelopment (hypoplasia) of the pons and cerebellum (two parts of the brain). The pons helps the different parts of the brain communicate with each other, and the cerebellum coordinates movements in the body.

Signs and symptoms generally appear within the first year of life. Affected individuals may experience an atrophy (wasting) in the brain over time causing severe intellectual disability and a small head size. Individuals with PCH, type 2 are lacking voluntary movement skills (e.g., sitting, walking, reaching for things). They also have problems swallowing, vision loss, seizures, and periods of both stiff and shaky muscles in addition to a lack of communication (including speech).

Many different genes can cause pontocerebellar hypoplasia. Two mutations in the same gene are needed to cause symptoms of the disorder. PCH, type 2E is caused by mutations in the VPS53 gene.

### Treatment

There is no cure or effective treatment for PCH, type 2E.

## Progressive Familial Intrahepatic Cholestasis, Type 2

### Summary

Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive disorder that causes liver disease that gets worse over time, often leading to liver failure. Individuals with PFIC have difficulty getting rid of bile, a digestive fluid, which can build-up in the liver causing damage.

Signs and symptoms of PFIC generally appear during infancy and may include severe itching, jaundice (yellowing of the skin and eyes), failure to grow at a normal rate, high blood pressure, gallstones, and an enlarged liver and spleen.

There are different types of PFIC. Individuals with PFIC, type 2 generally have symptoms only related to liver disease which is often more severe and develops into liver failure before adulthood. Initial symptoms may include discolored stool and dark urine. Individuals with PFIC, type 2 are also at a greater risk of developing a liver cancer.

PFIC, type 2 is caused by mutations in the ABCB11 gene.

### Treatment

There is no cure for PFIC. Treatment may include nutritional therapy and medications. However, half of affected individuals will still need a liver transplant. Close monitoring for cancer is also recommended.

## Prolidase Deficiency

### Summary

Prolidase deficiency is an autosomal recessive disorder that causes a wide variety of symptoms including enlarged liver and/or spleen, diarrhea, vomiting, dehydration, and delayed development. People with prolidase deficiency are also at high risk for recurring skin, ear, and respiratory infections. Skin lesions often develop on the hands, feet, and legs. Signs and symptoms range in severity from individual to individual but typically appear during infancy. Roughly two-thirds of affected individuals will also experience intellectual disability.

Some individuals with severe symptoms may suffer from recurrent life-threatening respiratory infections. Other individuals may have milder symptoms that can be controlled through treatment.

Prolidase deficiency is caused by mutations in the PEPD gene.

### Treatment

There is no cure for prolidase deficiency. Treatment is aimed at managing symptoms, particularly skin ulcerations and infections through creams and medications.

## Propionic Acidemia

### Summary

Propionic acidemia is an autosomal recessive disorder in which the body is unable to process certain proteins and fats properly. This disorder is characterized by a buildup of organic acids in the blood, urine, and tissues that can lead to serious health problems. If left untreated, an infant with early onset propionic acidemia typically will not survive past the first year of life.

Signs and symptoms typically appear shortly after birth and may include vomiting, poor feeding, poor muscle tone, and a lack of energy. If left untreated, symptoms can progress to more serious health problems such as heart abnormalities, seizures, coma, and potential death. Some individuals will experience intellectual disability and delayed development.

Less frequently, individuals will experience an onset of propionic acidemia during childhood. In these cases, symptoms may come and go over time, but serious health problems may be triggered by illness, infection, or periods without food.

Long term effects of propionic acidemia may include tight muscles, inflammation of the pancreas, recurrent infections, vision problems, irregular heartbeat, poor growth, and low bone density.

Propionic acidemia is caused by mutations in the PCCA and PCCB genes. Two mutations in the same gene are needed to cause symptoms.

### Treatment

There is no cure for propionic acidemia. Treatment is aimed at managing symptoms. Treatment may include a low protein and high calorie diet, consistent monitoring by a healthcare professional, nutritional supplements, antibiotics, and avoiding long periods without food.

## Pseudocholinesterase deficiency

### Summary

Pseudocholinesterase deficiency, also known as butyrylcholinesterase deficiency, is an autosomal recessive disorder that results in increased sensitivity to certain muscle relaxant drugs used during general anesthesia, called choline esters.

Individuals with this condition are unable to break down (metabolize) certain muscle relaxant drugs or anesthetics that is usually used during surgical procedures or in emergencies. As a result, the effect of the anesthetic agent does not wear off for a few hours, and these individuals are unable to breathe on their own until the anesthetic wears off.

The main complication that can result, if this condition is overlooked during a procedure, is respiratory arrest or failure due to paralysis of the lung muscles.

Pseudocholinesterase deficiency caused by mutations in the BCHE gene provides instructions for making the pseudocholinesterase enzyme, also known as butyrylcholinesterase, that is involved in the breakdown of choline ester drugs (e.g. succinylcholine and mivacurium).

### Treatment

Treatment of pseudocholinesterase deficiency is aimed at supporting the individuals breathing during and after a procedure requiring an anesthetic agent. A mechanical ventilator machine is used to support breathing until the anesthetic agent wears off. It is recommended that individuals with this condition avoid certain anesthetic agents that contain choline esters to prevent complications.

## Pseudorheumatoid Dysplasia

### Summary

Pseudorheumatoid dysplasia (PRD) is an autosomal recessive disorder that causes progressive joint stiffness due to the breakdown of the cushioning between the bones, called cartilage.

Signs and symptoms generally appear during childhood, often beginning joint stiffness in the hips. Affected individuals may develop an abnormal walk, stiffness in the other joints, decreased ability to move, swelling in the joints, and overall weakness. As they age, additional symptoms may include enlarged joints (particularly in the fingers and knees), bent fingers, curvature of the spine (scoliosis), and more limited joint movement. Many individuals will be shorter than average by adulthood. Life expectancy is usually unaffected.

PRD is caused by mutations in the WISP3 gene.

### Treatment

There is no cure for PRD. Treatment is not clearly defined. Joint replacement may be required by early adulthood.

## Pycnodysostosis

### Summary

Pycnodysostosis is an autosomal recessive disorder that causes certain bone abnormalities.

Age of onset is variable and may range from infancy to adulthood. Symptoms include a short height, abnormal feet, fingers, jaws, and collar bone. Individuals are prone to bone fractures, even under minimal stress. Many also have a curvature of the spine (scoliosis).

Pycnodysostosis causes similar typical facial features including a large skull, small jaw, and a protruding forehead. Many will experience abnormally shaped teeth or a delay in teeth coming in and have a higher risk for cavities and decay. Fingernails may be irregular and cracked. On occasion, individuals may also experience anemia (low number of blood cells) that can lead to tiredness and weakness. With proper medical care, individuals can live a normal lifespan.

Pycnodysostosis is caused by mutations in the CTSK gene.

### Treatment

There is no cure for pycnodysostosis. Treatment involves preventing fractures by avoiding high impact exercises and activities. Growth hormone injections may help with height.

## Pyruvate Dehydrogenase E1-alpha Deficiency, X-linked

### Summary

Pyruvate dehydrogenase deficiency is a disorder in which a chemical called lactic acid builds up in the body and causes a variety of medical problems.

Signs and symptoms of pyruvate dehydrogenase deficiency typically first appear shortly after birth and include vomiting, nausea, serious breathing problems, and an irregular heartbeat. The build-up of lactic acid also causes neurological problems including delayed motor skills (such as sitting up and crawling), intellectual disability, poor muscle tone, and seizures. Some individuals may exhibit abnormal brain development (such as a breakdown of the cerebral cortex and underdevelopment of the tissue that connects the right and left halves of the brain) as a result of damage to the sensitive tissues in the brain. Most individuals will not survive past childhood.

Pyruvate dehydrogenase deficiency may be caused by mutations to several different genes. One of the genes is the PDHA1 gene which is on the X chromosome causing males to be more likely affected.

### Treatment

There is no cure for pyruvate dehydrogenase deficiency. Treatment is aimed at managing symptoms and consists mostly of dietary changes. Individuals are recommended to follow a diet high in fats, low in carbohydrates, and with adequate protein. Supplements may also be added.



## Pyruvate Dehydrogenase E1-beta Deficiency

### Summary

Pyruvate dehydrogenase deficiency is a disorder in which a chemical called lactic acid builds up in the body and causes a variety of medical problems.

Signs and symptoms of pyruvate dehydrogenase deficiency typically first appear shortly after birth and include vomiting, nausea, serious breathing problems, and an irregular heartbeat. The build-up of lactic acid also causes neurological problems including delayed motor skills (such as sitting up and crawling), intellectual disability, poor muscle tone, and seizures. Some individuals may exhibit abnormal brain development (such as a breakdown of the cerebral cortex and underdevelopment of the tissue that connects the right and left halves of the brain) as a result of damage to the sensitive tissues in the brain. Most individuals will not survive past childhood due to their multiple medical problems.

Pyruvate dehydrogenase deficiency may be caused by mutations to several different genes. One of the genes is the PDHB gene which is inherited as an autosomal recessive disorder.

### Treatment

There is no cure for pyruvate dehydrogenase deficiency. Treatment is aimed at managing symptoms and consists mostly of dietary changes. Individuals are recommended to follow a diet high in fats, low in carbohydrates, and with adequate protein. Supplements may also be added.

## Retinitis Pigmentosa

### Summary

Retinitis pigmentosa (RP) is a group of disorders that affect the retina (a part of the eye) and cause a loss of vision over time.

Signs and symptoms typically appear during childhood as a decrease or loss of night vision and/or an inability to see in low lights. As the disease worsens, there is a loss of peripheral (or side) vision causing tunnel vision. Central vision is eventually lost, affecting the ability to perform tasks such as reading and driving, with many individuals becoming legally blind by adulthood. Some may also develop cataracts (a clouding of the eye) and reduced ability to distinguish colors.

Symptoms of non-syndromic RP are generally limited to loss of vision, and other parts of the body are not usually affected. Other conditions can have RP as one of the features, but have other symptoms not associated with vision. These are called syndromic.

Over 50 different genes can cause non-syndromic RP with different types of inheritance. Some examples of autosomal recessive non-syndromic RP are listed below. In autosomal recessive inheritance, two mutations in the same gene would be needed to cause disease.

C8orf37 - Causes RP type 64 (can also cause another eye condition called cone-rod dystrophy)

CRB1 - Causes RP type 12 (can also cause another eye condition called leber congenital amaurosis, type 8)

DHDDS - Causes RP type 59

EYS - Causes RP type 25

FAM161A - Causes RP type 28

PDE6G - Causes RP type 57

PRCD - Causes RP type 36

TULP1 - Causes RP type 14 (can also cause another eye condition called leber congenital amaurosis, type 15)

### Treatment

There is no cure for RP. Treatment is aimed at slowing the progression of this disorder and using low vision aids.

## Retinoschisis (X-linked)

### Summary

Retinoschisis is an inherited eye disorder that affects specific cells (macula) in the retina (a part of the eye) and impairs vision. It is part of a group of disorders called macular degeneration.

Males may have symptoms that appear in early childhood but are typically not diagnosed until poor vision becomes an issue when they begin school. Individuals experience a continued decline in vision until their 20s when it stabilizes temporarily. Once affected individuals reach their 40s and 50s, they experience another decline in vision. A small percentage will go on to complete blindness. Life expectancy is usually unaffected.

Most cases of X-linked juvenile retinoschisis are caused by mutations in the RS1 gene, which is on the X chromosome (one of two sex chromosomes). Males only have one X chromosome, so a mutation in that one RS1 gene is enough to cause this type of retinoschisis. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their RS1 gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

There is no cure for retinoschisis. Treatment is aimed at addressing visual needs. Individuals may require large-printed text books or assistive technologies to help with work and school. Retinal detachments may be treated with surgery. Younger children should be monitored closely each year. Affected individuals should avoid contact sports and other activities that might result in a blow to the head in order to decrease the risk of retinal detachment or bleeding in the eye.

## Rhizomelic Chondrodysplasia Punctata, Type 1

### Summary

Rhizomelic chondrodysplasia punctata, type 1 (RCDP1) is an autosomal recessive disorder that causes skeletal abnormalities, intellectual disability, and breathing problems.

Symptoms generally appear at birth or during infancy. Affected individuals have shortened bones in the upper arms and thighs, develop stiff and painful joints, fail to grow at a normal rate, and have severe intellectual and developmental disabilities. Most individuals will not develop normal speech, the ability to sit up, or be able to feed themselves. People with RCDP1 are also at higher risk for recurrent infections and seizures.

The majority of individuals die before the age of 10 years usually due to breathing problems. Occasionally, individuals will experience milder symptoms and survive into early adulthood.

RCDP1 is caused by mutations in the PEX7 gene.

### Treatment

There is no cure for RCDP1. Treatment is focused on managing symptoms and increasing quality of life. Medication may be prescribed to treat seizures. Physical therapy may be beneficial to preserve movement, and a feeding tube may be needed to assist with eating. Regular monitoring of lungs for respiratory infection is recommended.

## Sandhoff Disease

### Summary

Sandhoff Disease, also referred to as GM2-gangliosidosis, is an autosomal recessive disorder that causes a progressive destruction of the nerves in the brain and spinal cord.

The infantile form of Sandhoff disease is the most common form of this disorder. Symptoms generally appear during infancy and may include muscle weakness, delayed development, loss of motor skills, and becoming highly startled with loud noises. Over time, individuals will experience loss of vision and hearing, enlarged organs, intellectual disability, recurrent respiratory infections, paralysis, and seizures. Most individuals only survive into early childhood.

Less common forms are milder with symptoms appearing later during childhood or adulthood. Symptoms vary widely from individual to individual and may include muscle weakness, loss of coordination, clumsiness, speech problems, gastrointestinal problems, and mental illness.

Sandhoff disease is caused by mutations in the HEXB gene.

### Treatment

There is no cure for Sandhoff disease. Treatment includes respiratory support and medication to control seizures.

## Mucopolysaccharidosis, Type 3 (Sanfilippo Syndrome)

### Summary

Mucopolysaccharidosis, type 3 (MPS3), also called Sanfilippo syndrome, is an inherited autosomal recessive disorder that affects the brain and spinal cord due to the body's inability to breakdown certain chemicals called glycosaminoglycans (GAGs).

MPS3 generally appears during childhood. Initial symptoms may include delayed speech and problems such as restless, aggressive, or anxious behavior. Other issues include trouble sleeping, an enlarged liver, short height, joint stiffness, recurrent diarrhea, frequent respiratory and ear infections, and a larger head size. As the disorder progresses, individuals may lose previously learned physical or intellectual skills and suffer from loss of hearing and/or vision. Symptoms worsen over time, and most individuals will only survive into adolescence or early adulthood.

MPS3 is caused by mutations in 4 different genes, all with similar symptoms. The genes that cause MPS3 include SGSH (type A), NAGLU (type B), HGSNAT (type C), and GNS (type 4).

### Treatment

There is no cure or effective treatment for MPS3. Medication may be prescribed to treat seizures and sleep disturbances. Physical therapy and special educational classes may be beneficial.

## Seckel Syndrome

### Summary

Seckel syndrome is a group of conditions characterized by growth delays and small head size (microcephaly).

Signs and symptoms generally appear prior to birth as slow growth and microcephaly. Affected individuals have typical features including sloping forehead, small chin, ear malformation or missing earlobes, cleft palate (opening in roof of the mouth), tooth anomalies, and a beaked nose. Children with Seckel syndrome also have multiple brain malformation that result physical and intellectual delays.

Different genes are known to cause Seckel syndrome. Two mutations in the same gene are needed to cause the disease. Seckel syndrome, type 5 is caused by mutations in the CEP152 gene.

Some children with changes in this gene have a similar condition called microcephaly, type 9. They will have the same delays in growth and small head size as well as delays in speech, sitting, walking, and standing. However, even with the smaller head size, their brains are often likely to be normal in shape and structure. Intellectual delays are mild to moderate and do not get worse with age. This particular type does not normally affect other parts of the body.

### Treatment

There is no cure or effective treatment for Seckel syndrome or microcephaly. Special education and therapy to address the physical and mental delays may be recommended.

## SeSAME Syndrome

### Summary

SeSAME syndrome is a rare autosomal recessive disorder that causes seizures, sensorineural deafness (deafness caused by damage to the inner ear), ataxia (loss of coordination and muscle control), intellectual disability, and electrolyte imbalance. Examples of electrolytes are sodium, chloride, potassium, calcium, and magnesium. Seizures can be one of the first symptoms, usually appearing during infancy. The ataxia can lead to difficulty with walking.

SeSAME syndrome is caused by mutations in the *KCNJ10* gene.

### Treatment

There is no cure for SeSAME syndrome. Treatment is aimed at managing symptoms and have included electrolyte supplements. Hearing aids, canes, and wheelchairs may provide assistance for the ataxia and hearing loss. Affected individuals should be closely monitored by healthcare professionals.

## Severe Combined Immunodeficiency (-T/+B/-NK), X-linked

### Summary

Severe combined immunodeficiency (SCID) is a group of rare inherited disorders that cause is due to an inadequate immune system.

Signs and symptoms of SCID are generally apparent at birth or within the first few months of life. Symptoms include a failure to thrive, high risk of severe, frequent, and prolonged infections. There are different cells (T cells, B cells, and natural killer cells) that help the immune system work properly. Any time some of these cells are missing, the immune system cannot protect the body the way it needs to. If left untreated, individuals typically will not survive past their first year of life. Treatment has shown to be effective in some cases, but the outcome still remains variable.

SCID can be part of many conditions and involve different genes. SCID that is negative for T and natural killer cells, but positive for B cells is caused by mutations in the IL2RG gene, which is on the X chromosome (one of two sex chromosomes) and is inherited in an X-linked fashion. Males only have one X chromosome, so a mutation in that one IL2RG gene is enough to cause this form of SCID. Females have two X chromosomes, so typically the mutation would need to occur on both copies of their IL2RG gene to cause the condition. For this reason, males are affected by this condition much more than females.

### Treatment

It is important that diagnosis is made prior to a serious infection as the effectiveness of treatment greatly decreases after. Great care should be taken to provide affected individuals with protected and germ-free environments. Treatment for IL2RG-related SCID consists of various antibiotics and medications to treat current infections and prevent new ones from occurring. Bone marrow or stem-cell transplant may also be helpful in most types of SCID.



## Severe Combined Immunodeficiency (-T/-B/+NK)

### Summary

Severe combined immunodeficiency (SCID) is a group of rare inherited disorders are due to an inadequate immune system.

Signs and symptoms of SCID are generally apparent at birth or within the first few months of life. Symptoms include a failure to thrive, high risk of severe, frequent, and prolonged infections. There are different cells (T cells, B cells, and natural killer cells) that help the immune system work properly. Any time some of these cells are missing, the immune system cannot protect the body the way it needs to. If left untreated, individuals typically will not survive past their first year of life. Treatment has shown to be effective in some cases, but outcome still remains variable.

SCID can be part of many conditions and involve different genes. Two mutations in the same gene would be needed to cause symptoms of the conditions. SCID that is negative for T and B cells, but positive for natural killer cells is caused by mutations in the either the RAG1 or RAG2 gene.

### Treatment

It is important that diagnosis is made prior to a serious infection as the effectiveness of treatment greatly decreases after. Great care should be taken to provide affected individuals with protected and germ-free environments. Treatment for RAG1- and RAG2-related SCID consists of various antibiotics and medications to treat current infections and prevent new ones from occurring. Bone marrow or stem-cell transplant may also be helpful in most types of SCID.

## Severe Combined Immunodeficiency, Athabascan Type

### Summary

Severe combined immunodeficiency (SCID) is a group of rare inherited disorders that cause is due to an inadequate immune system.

Signs and symptoms of SCID are generally apparent at birth or within the first few months of life. Symptoms include a failure to thrive, high risk of severe, frequent, and prolonged infections. People with the Athabascan type are also extremely sensitive to ionizing radiation and can also suffer from recurrent diarrhea and oral or genital ulcers. SCID, Athabascan type is negative for T and B cells, but is positive for natural killer cells. It gets its name from a group of North American Navajo and Jicarilla Apache Indians that has a very high frequency of the condition and belong to the Athabascan language group.

There are different cells (T cells, B cells, and natural killer cells) that help the immune system work properly. Any time some of these cells are missing, the immune system cannot protect the body the way it needs to. If left untreated, individuals typically will not survive past their first year of life. Treatment has shown to be effective in some cases, but prognosis still remains variable.

SCID can be part of many conditions and involve different genes. Two mutations in the same gene would be needed to cause symptoms of the conditions. SCID, Athabascan type is caused by mutations in the DCLRE1C gene.

### Treatment

There is no cure for SCID. It is important that diagnosis is made prior to a serious infection as the effectiveness of treatment greatly decreases after. Great care should be taken to provide affected individuals with protected and germ-free environments. Treatment for RAG1- and RAG2-related SCID consists of various antibiotics and medications to treat current infections and prevent new ones from occurring. Bone marrow or stem-cell transplant may also be helpful in most types of SCID.

## Short Stature, Onychodysplasia, Facial Dysmorphism and Hypotrichosis (SOFT Syndrome)

### Summary

Short stature, onychodysplasia, facial dysmorphism and hypotrichosis (SOFT syndrome) is an autosomal recessive disorder affecting the bones, hair, face and nails. Signs and symptoms are generally seen via ultrasound prior to birth as poor growth, and infants generally are underweight at birth. Affected individuals experience very short upper arm and upper leg bones. Most will reach a final height equal to someone 6 years to 8 years of age.

Individuals with SOFT syndrome also exhibit similar facial features that include a long and triangular face, small ears, and a prominent nose. Many will also have a high-pitched voice. Additional symptoms include nail abnormalities, a small head size during childhood, a waddling walk, and noticeably less hair after puberty.

SOFT syndrome is caused by mutations in the POC1A gene.

### Treatment

There is no cure for SOFT syndrome. Treatment is unknown.

## Short-chain acyl-CoA dehydrogenase (SCAD) deficiency

### Summary

Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is an autosomal recessive disorder characterized by the bodies impaired ability to convert certain fats into energy, especially during periods without food (fasting).

SCAD deficiency may be triggered by fasting or illnesses such as viral infections and may appear during infancy or early childhood. Signs and symptoms can include vomiting, low blood sugar (hypoglycemia), a lack of energy (lethargy), poor feeding, and failure to gain weight and grow at the expected rate (failure to thrive). Other features of this disorder may include poor muscle tone (hypotonia), seizures, developmental delay, and a small head size (microcephaly).

The severity of this condition varies widely, even among members of the same family. In some individuals the condition could be life threatening, while some individuals may never develop any symptoms at all.

SCAD deficiency is caused by mutations in the ACADS gene, which is responsible for providing instructions for making an enzyme called short-chain acyl-CoA dehydrogenase (SCAD), that is required to break down (metabolize) a group of fats called short-chain fatty acids. Short-chain fatty acids are a major source of energy for the heart and muscles and other tissues during periods fasting.

### Treatment

There is no specific treatment or management requirements for SCAD deficiency as most affected individuals are asymptomatic. However, an age-appropriate heart-healthy diet; avoidance of fasting longer than age-appropriate fasting periods for infants and toddlers and longer than 12 hours for older children is recommended.

## Sialic Acid Storage Disorder

### Summary

Sialic acid storage disease, also called sialuria, is an autosomal recessive disorder that causes damage to the nervous system. Sialuria appears shortly after birth with symptoms including developmental delay, failure to grow at a normal rate, weak muscles, poor coordination, and an enlarged heart, liver, and spleen. Infants may also suffer from intellectual disability, seizures, and a build-up of fluid in the abdomen. Affected individuals develop facial features that are described as being coarse.

Salla disease is a name given to a milder form of sialuria since symptoms appear a little later (during the first year), but they still get worse over time. Most individuals with sialuria will only survive into early childhood, but people with Salla disease have been shown to live into adulthood.

All forms of sialic acid storage disease are caused by mutations in the SLC17A5 gene.

### Treatment

There is no cure for sialuria. Treatment is aimed at managing symptoms. Therapy to assist in mobility, motor function, and speech may be helpful.

## Sickle Cell Disease

### Summary

Sickle cell disease is a group of disorders that affect a part of the red blood cells called hemoglobin, which carries oxygen to tissues throughout the body. Hemoglobin is made up of four chains (2 alpha and 2 beta chains). There are different changes to the beta chain of hemoglobin that create different hemoglobin types (S, C, E, D-Punjab, and O-Arab).

Individuals with hemoglobin S have a specific condition called sickle cell anemia. In this condition, the shape of red blood cells is shaped more like a sickle or crescent than a circle. This abnormal shape makes it more likely for the cells to breakdown and makes it harder for blood to flow through the arteries and veins, leaving the body lacking oxygen and nutrients that the blood would normally deliver. Signs and symptoms of sickle cell anemia generally appear during childhood and may include a low red blood cell count (anemia), recurrent infections, and episodes of pain (crisis). Anemia can cause fatigue, jaundice, shortness of breath, and delayed growth and development. Severity can vary from individual to individual, with some requiring frequent hospitalization. Sickle cell anemia also causes high blood pressure, resulting in potential complications such as pulmonary hypertension, which may lead to heart failure. Many people with sickle cell anemia live well into adulthood, but shortened lifespans have been reported.

Hemoglobins C, E, D-Punjab, and O-Arab are other beta-hemoglobin chain variants that cause different shaped/sized red blood cells, but their symptoms are usually milder than with hemoglobin S. Individuals with hemoglobins C, D, E, and O may have mild to moderate anemia in conjunction with an enlarged spleen.

All of these different types of beta hemoglobin are caused by different mutations in the HBB gene. Someone can inherit two copies of the same mutation (e.g., SS or CC) or two different mutations (e.g., SC or CE). The symptoms and severity will vary depending on the combination of mutations. Those with only one copy of a mutation are called carriers and often referred to as having the trait (e.g., hemoglobin S trait or hemoglobin C trait). Carriers are not expected to show the disease symptoms you would see in someone with two mutations.

If someone is known to be positive for a hemoglobin S, C, E, D-Punjab, or O-Arab mutation, it is highly recommended that a second blood test (called hemoglobin electrophoresis) be performed on that person and their partner in order to assess for over 300 different changes that can affect beta hemoglobin to ensure there is not a second mutation that would put them at risk.

### Treatment

Hemoglobins C, E, D-Punjab, and O-Arab often do not require treatment. Individuals with sickle cell anemia should stay hydrated, avoid extreme physical activity, infections, and excess sun exposure. Proper nutrition is beneficial. Medication may be available for infection and pain. Blood transfusions may be required periodically to treat anemia. Other treatments may include joint replacement, blood dialysis, kidney transplant, and surgical removal of the gallbladder or spleen. Bone marrow transplant may be an option for some individuals but is not without risks. Stem cell transplant via cord blood banking has also been performed.

## Sjogren-Larsson Syndrome

### Summary

Sjogren-Larsson syndrome (SLS) is an autosomal recessive disorder characterized by skin, eye, and neurological problems.

Affected infants are generally born prematurely. Skin is red at birth but becomes dry, rough, and scaly later in infancy. Itchiness is also a constant problem, but luckily, the skin on the face is typically unaffected.

Individuals with SLS also experience intellectual disability, speech difficulties, and seizures. Children may also experience delay in motor skills (such as crawling and walking). Roughly 50% will need to use a wheelchair. Those with SLS may also be nearsighted and have a sensitivity to light. With good medical care, most individuals with SLS can survive into adulthood.

SLS is caused by mutations in the ALDH3A2 gene.

### Treatment

There is no cure for SLS. Treatment is focused on the management of symptoms. Individuals should keep their skin as moisturized and hydrated as possible. Daily baths, creams, and lotions are often beneficial. Medications may also be used to address the skin issues or seizures. Physical therapy may be useful in helping those with difficulty walking. Wheelchairs, walkers, and mechanical braces may be necessary.

## Smith-Lemli-Opitz Syndrome

### Summary

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder that impairs the body's ability to make cholesterol. Cholesterol is essential during pregnancy for the structure of cells and normal development of the fetus, and it is also important for many different processes after birth.

SLOS is characterized by birth defects, intellectual disability, and behavioral problems. Multiple medical problems affecting the heart, lungs, kidneys, gastrointestinal tract, and genitalia have been noted. Many have symptoms of autism and can also have a cleft palate (opening in the roof of the mouth), small head size (microcephaly), weak muscles, feeding problems, vomiting, extra fingers, and webbing in between the toes.

Signs and symptoms of SLOS may vary widely from individual to individual. Some of the more mildly affected individuals may only have minor physical abnormalities with learning and behavioral difficulties. The more severely affected individuals may experience life-threatening physical abnormalities and serious intellectual disability, and some may be unable to live independently. Some individuals with severe symptoms may have a shortened lifespan, but with proper nutrition and good medical care, many affected individuals may have a normal life expectancy.

SLOS is caused by mutations in the DHCR7 gene.

### Treatment

There is no cure for SLOS. Treatment is aimed at managing symptoms. Supplementing diet with large amounts of cholesterol can help alleviate some symptoms. Medication, physical therapy, occupational therapy, speech therapy, surgery, and orthotics may also be recommended.



## Spastic Paraplegia, Type 2

### Summary

Spastic paraplegia, type 2 (SPG2) is an autosomal recessive disorder that affects the muscles over time.

Age of onset generally occurs during adolescence. Symptoms include a loss of muscle coordination, speech difficulties, and spasticity (stiffness) of the lower limbs. Individuals also develop a gait ataxia (uncoordinated walking) which may lead to frequent falls. Additional symptoms include muscle atrophy (wasting away of muscle tissue), overactive reflexes, and tremors. Intellectual ability is usually not affected. Individuals should retain the ability to walk, and life expectancy appears to be unaffected.

SPG2 is caused by mutations in the KIF1C gene.

### Treatment

There is no cure for SPG2. Treatment is aimed at managing symptoms and increasing quality of life.

## Spastic Paraplegia, Type 47

### Summary

Spastic paraplegia is a group of disorders that cause neurodegeneration that results in stiff or rigid muscles (spasticity) with that weaken over time.

There are various types of spastic paraplegia. Signs and symptoms of spastic paraplegia, type 47 generally appear during early childhood. Symptoms may include spasticity, seizures, severe intellectual disability, low muscle tone, and a lack of speech. This can worsen over time and lead to the need for a wheelchair.

There are many different forms of spastic paraplegia. When the condition is autosomal recessive, two mutations in the same gene are needed to cause symptoms. SPG47 is caused by mutations in the AP4B1 gene.

### Treatment

There is no cure for spastic paraplegia type 47. Treatment is aimed at preventing and slowing symptoms and may include medication such as muscle relaxants and physical therapy. Some individuals will require the assistance of a wheelchair, walker, or cane.

## Spastic Paraplegia, Type 49

### Summary

Spastic paraplegia, type 49 (SPG49) is an autosomal recessive disorder that causes progressive muscle stiffness and weakening of the lower limbs along with developmental delays and intellectual disability.

Signs and symptoms of SPG49 generally appear during early childhood. As they get older, children with SPG49 develop an unsteady gait (walk), an absence of reflexes, some degree of intellectual disability, difficulty with speech, and a reduced degree of facial expressions. Affected individuals also have features that include a chubby appearance, a short and broad neck, a round face, and a short height. Many also have gastrointestinal reflux disease, causing chronic respiratory infections.

There are many different forms of spastic paraplegia. SPG49 is caused by mutations in the *TECP2* gene.

### Treatment

There is no cure for SPG49. Treatment is aimed at managing symptoms and may include physical and occupational therapy, medication, and orthotic devices. Some individuals may require the assistance of a wheelchair.

## Spastic Paraplegia, Type 53

### Summary

Hereditary spastic paraplegia, type 53 (SPG53) is an autosomal recessive neurodegenerative disorder that causes increasing muscle stiffness over time, developmental delays, and intellectual disability.

Signs and symptoms of SPG53 generally appear during early childhood and begin with difficulty with balance and muscle spasms. Muscle stiffness usually starts in the lower limbs and eventually progresses to the arms and hands. Additional symptoms that develop include problems walking, neurological problems such as seizures, and some degree of intellectual disability.

There are many different forms of spastic paraplegia. SPG53 is caused by mutations in the VPS37A gene.

### Treatment

There is no cure for SPG53. Treatment is aimed at managing symptoms and may include physical and occupational therapy, medication, and orthotic devices. Surgery to lengthen ligaments have been performed. Some individuals have improved their ability to walk through botulinum injections.

## Spinal Muscular Atrophy

### Summary

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects muscle movement and is characterized by continued muscle breakdown (atrophy) and weakness due to a loss of neurons in the brain and spinal cord. These neurons are needed for activities such as sitting up, crawling, walking, and movement of the head. Intelligence is unaffected.

Patients affected with SMA are generally grouped into four different types (I, II, III, IV) that range in severity and age of onset.

Type I SMA, also called Werdnig-Hoffman Disease, is the most common and severe type of this disorder. Symptoms develop within the first few months of life and may even be evident at birth. Affected infants have poor muscle tone and strength and are often unable to support their own heads and sit unassisted. Those with type I often have trouble breathing and swallowing. Life expectancy is typically two years to four years of age.

Type II SMA is also called Dubowitz Disease. Symptoms of muscle weakness typically appear between the ages of 6 months and 12 months. Those affected with type II can normally maintain a sitting position without support but cannot stand or walk without assistance. More than 75% live into their mid-20s.

Type III SMA, also called Kugelberg-Welander Disease, is a milder form of this disorder. Symptoms typically appear between early childhood and adolescence. These individuals may have weaker muscles but are still able to stand and walk without support up to their 30s to 40s. Many with type III SMA will require wheelchair assistance later in life.

Type IV SMA is the mildest form of this disorder, with symptoms generally appearing during adulthood. Individuals with type IV SMA may experience mild to moderate muscle weakness, tremors, twitching, and potential breathing problems. Individuals can still move and walk without support, and life expectancy is typically unaffected.

Although different genes can cause different types of SMA, the type of SMA discussed here is caused by mutations in the SMN1 gene. Another gene, SMN2, modifies the severity of SMA. The more copies there are of SMN2, the less severe the disorder.

### Treatment

There is currently no cure for SMA. Treatment is directed at supporting and managing the symptoms of the disorder to improve quality of life. For children with type I SMA, treatment may include respiratory assistance to maximize their ability to breathe. As there is often difficulty swallowing, these children also need their nutrition monitored and may require a feeding tube. Those with milder forms of SMA often develop scoliosis or joint problems and may require appropriate orthopedic care including potential surgery.

## Spinal Muscular Atrophy with Respiratory Distress, Type 1

### Summary

Spinal muscular atrophy with respiratory distress, type 1 (SMARD1) is an autosomal recessive disorder that causes muscle weakness and respiratory failure.

Signs and symptoms generally appear during infancy with breathing problems, a weak cry, difficulty feeding, foot deformities, and recurrent episodes of pneumonia. Around the age of 13 months, affected individuals will experience paralysis of their diaphragm, causing further breathing issues and will require a ventilator to assist with breathing. Soon after, affected individuals exhibit muscle weakness that begins as distal weakness (muscles further away from the center of the body), eventually spreading throughout the entire body, severely limiting movement. Excessive sweating, irregular heartbeat, loss of bowel and bladder control, and a reduced sensitivity to pain are also seen. Occasionally, individuals will not develop symptoms until later in childhood. Most affected individuals will not usually survive past early childhood.

SMARD1, also called distal hereditary motor neuropathy, type VI, is caused by mutations in the IGHMBP2 gene.

### Treatment

There is no cure for SMARD1. Treatment is primarily supportive and consists of breathing support that may include a ventilator or tracheal intubation. Physical therapy and/or medications may also be recommended.

## Spondyloenchondrodysplasia with Immune Dysregulation (SPENCDI)

### Summary

Spondyloenchondrodysplasia with immune dysregulation (SPENCDI) is an autosomal recessive disorder that causes skeletal abnormalities and problems with the immune system.

Signs and symptoms may appear between infancy to adolescence. Symptoms may include skeletal abnormalities such as flattened spinal bones, bone damage in the limbs, and abnormalities to the cushioning of the joints (cartilage). The bone abnormalities often result in a shorter than average height. Individuals may also experience an autoimmune reaction (where the body attacks its own tissues and organs), leading to a decrease in blood cells, chronic inflammation, problems with the thyroid gland, and recurrent respiratory infections. Some individuals may also experience neurological symptoms such as problems with coordination, muscle stiffness, and intellectual disability.

SPENCDI is caused by mutations in the ACP5 gene.

### Treatment

There is no cure for SPENCDI. Treatment is aimed at managing symptoms and increasing quality of life.

## Spondyloepimetaphyseal Dysplasia (Short Limb-Hand Type)

### Summary

Spondyloepimetaphyseal dysplasia, short limb-hand type (SEMD-SL) is an autosomal recessive disorder of the bones.

Signs and symptoms generally appear at birth as small stature with short limbs and hands. Additional skeletal features include a joint deformities (contractures), small chin, narrow chest, wide nostrils, high roof of the mouth, and eyes that are far apart. Weak muscles and developmental delay are also possible. Due to the small chest and trunk, there can be a risk for breathing problems and spinal cord compression. Both of these complications can be life-threatening and significantly reduce life expectancy.

SEMD-SL is caused by mutations in the *DDR2* gene.

### Treatment

There is no cure for SEMD-SL. Treatment is focused on managing symptoms and keeping the child comfortable. Medications, physical therapy, and possible surgery all may be recommended over time.



## Stargardt Disease, Type 1

### Summary

Stargardt disease, also called macular degeneration, is an autosomal recessive eye disorder that causes vision loss over time.

The retina is the light sensitive tissue at the back of the eye that triggers nerve impulses to the brain to form an image. The center of the retina is called the macula, and it is in charge of creating clear central vision (the type used for reading, recognizing people, and driving). In Stargardt disease, a yellow substance builds up under the macula and damages the surrounding cells causing vision loss to begin. Seeing in low light, at night, and/or distinguishing colors can also become a problem as Stargardt disease progresses. Individuals will need to learn how to manage worsening vision, but life expectancy is generally unaffected. Other parts of the body are usually unaffected.

There are many different genes that can cause this condition, which usually shows its first signs in late childhood. Stargardt disease, type 1 is caused by mutations in the ABCA4 gene and is the most common form of this disease.

### Treatment

There is no cure for Stargardt disease. Treatment involves slowing down the speed of vision loss, treating complications as they arise, and helping patients adjust to the impact of losing their vision.

## Stuve-Wiedemann Syndrome

### Summary

Stuve-Wiedemann syndrome (SWS), also known as Schwartz-Jampel syndrome type 2, is a rare autosomal recessive bone disorder. SWS belongs to a group of disorders known as the bent-bone dysplasias.

Individuals with SWS are typically of short height with long bowed bones and other skeletal abnormalities. Serious complications of the disorder include breathing, feeding and swallowing difficulties, as well as recurrent episodes of overheating due to the body's inability to regulate temperature. Most affected individuals will not survive past infancy. Those that survive past infancy generally go on to develop curvature of the spine (scoliosis), random bone fractures (seemingly for no reason), bowing of the lower limbs, and malfunctioning of the autonomic nervous system (which controls things like breathing, heartbeat, and digestion).

SWS is caused by mutations in the *LIFR* gene.

### Treatment

There is no cure for SWS. Treatment is focused on managing symptoms.

## Thyroid Dyshormonogenesis, Type 2A

### Summary

Thyroid dyshormonogenesis, type 2A, a severe form of congenital hypothyroidism, is an autosomal recessive disorder that causes a thyroid deficiency. The thyroid gland plays an important role in growth, brain development, and metabolism.

Symptoms are present at birth. Affected individuals have a thyroid gland that does not produce enough thyroid hormone (hypothyroidism) with recurrent enlargement of the thyroid gland (goiter). If left untreated, congenital hypothyroidism can lead to health problems such as poor growth and intellectual disability. The prognosis for an individual affected with thyroid dyshormonogenesis, type 2A is generally very favorable for individuals that are diagnosed and treated early.

Thyroid dyshormonogenesis, type 2A is caused by mutations in the TPO gene.

### Treatment

Although, there is no cure for thyroid dyshormonogenesis, type 2A, symptoms may be controlled with medication. Frequent monitoring by healthcare providers is recommended.

## Tumoral Calcinosis (Hyperphosphatemic)

### Summary

Tumoral calcinosis is a rare autosomal recessive disorder that causes abnormal deposits of calcium in the body (calcinosis). There are two types of familial tumoral calcinosis: hyperphosphatemic familial tumoral calcinosis (HFTC) and normophosphatemic familial tumoral calcinosis (NFTC). In addition to the increased calcium, HFTC is also shows increased levels of a chemical called phosphate in the blood and other tissues.

Signs and symptoms of HFTC generally appear between early childhood to early adulthood as calcinosis. Calcium masses are deposited in and under the skin and around the joints but may also develop in the soft tissue of the feet, legs, hands, and occasionally in the blood vessels and organs. Affected individuals often develop darkened skin spots during the first year of life followed by hardened nodules that can affect movement. While these can become large, they are not cancerous. Additional symptoms may bone or tooth abnormalities, and eye irritation.

Mutations in various genes are associated with HFTC, including *GALNT3*. Two mutations in the same gene are needed in order to cause symptoms of this condition.

### Treatment

There is no cure for HFTC. Medication is the primary form of treatment. Removal of the parathyroid glands may be necessary if individuals do not respond to treatment.

## Tumoral Calcinosis (Normophosphatemic)

### Summary

Tumoral calcinosis is a rare autosomal recessive disorder that causes abnormal deposits of calcium in the body (calcinosis). There are two types: hyperphosphatemic and normophosphatemic (NPTC) depending on whether the amount of a substance called phosphate is high or normal.

Signs and symptoms of tumoral calcinosis generally develop from early childhood to early adulthood as calcium becomes deposited just under the skin around the joints. It can also develop in the soft tissue of the feet, legs, hands, and occasionally in the blood vessels and organs. Affected individuals often develop darkened skin lesions during the first year of life followed by harder nodules or lesions. Severe skin and bone infections and severe inflammation in the lining of the eyelids and gums can also occur. Life expectancy is usually shortened.

NPTC is caused by mutations in the *SAMD9* gene.

### Treatment

There is no cure for tumoral calcinosis, and medication is the main form of treatment. Removal of the parathyroid glands may be necessary if individuals do not respond to treatment but is often a last resort.

## Tyrosinemia, Type 1

### Summary

Tyrosinemia is an autosomal recessive disorder causing serious medical problems due to the build-up of a chemical called tyrosine in tissues and organs throughout the body.

Tyrosinemia, type 1, also known as hepatorenal tyrosinemia, is the most severe form of tyrosinemia. Symptoms typically appear within the first few months after birth and may include slow growth, diarrhea, vomiting, softening of the bones, cabbage-like odor, enlarged liver, and jaundice (yellowing of skin and eyes). Children that are not treated may have abdominal pain, nerve damage, growth failure, breathing problems, kidney dysfunction, an altered mental state, and liver failure or cancer. These episodes of symptoms can last anywhere from 1 to 7 days.

If left untreated, affected individuals typically die by the age of 10. With treatment, there is a greater than 90% survival rate and improved quality of life.

Tyrosinemia type 1 is caused by mutations in the FAH gene.

### Treatment

Individuals prescribed a certain drug immediately after diagnosis show maximum benefit and a better outcome. Modifying the diet and yearly liver scans are also recommended. Those that have already experienced liver failure or liver cancer may require a liver transplant.

## Usher Syndrome

### Summary

Usher syndrome is a set of autosomal recessive conditions that cause hearing and vision loss. Many infants are born with bilateral (both ears) hearing loss. Without early diagnosis and intervention, affected individuals rarely go on to develop speech. Due to abnormal inner ear function, many individuals have severe balance and coordination difficulties, often appear to be clumsy, and may experience delayed motor milestones.

Within the first decade of life, individuals develop an eye disorder called retinitis pigmentosa that starts as trouble seeing at night or in low light. It then worsens to a loss of peripheral (side) vision causing tunnel-vision. Some individuals develop cataracts (a cloudiness over the eye), which may reduce the remaining vision to senses of light and darkness.

Usher syndrome is divided into three types. Type 1 is the most severe with earliest onset. Type 2 starts a little later in childhood, and people with this type do not have problems with balance or development. Individuals with Usher syndrome, type 3 usually have normal hearing at birth and do not start showing a loss of hearing until late childhood progressing slowly over time until mid-adulthood. Without early treatment, affected individuals may not develop speech abilities. Life expectancy and intelligence are unaffected.

A variety of genes cause the different forms of Usher syndrome, but two mutations in the same gene are needed to cause symptoms. Examples include: MYO7A (type 1B), USH1C (type 1C), CDH23 (type 1D), PCDH15 (type 1F), USH2A (type 2A), CLRN1 (type 3A)

Certain mutations in CDH23 and MYO7A can also cause hearing loss without the vision loss (called non-syndromic hearing loss).

### Treatment

There is no cure for Usher syndrome. Treatment is aimed at managing hearing and vision loss. Early intervention is important to give an individual the best chance at developing normal speech abilities. Individuals typically will not respond to hearing aids, but cochlear implants may restore some level of hearing. Specialists may introduce sign language while the individual is still young and has normal vision. Vision loss may be treated with low vision aids.

## Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

### Summary

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) is an autosomal recessive disorder in which the body is unable to convert certain fats to energy, particularly during times of fasting, illness, and exercise.

People with VLCAD can vary in their age of onset and severity. Those showing their first signs later in childhood or early adulthood tend to be milder and lack heart problems.

The earlier, more severe form of VLCAD usually appears during the first few months of life. Symptoms include poor muscle tone, lack of energy, low blood sugar, and an enlarged liver. If left untreated, individuals are at risk for damage to the heart and other organs, which can be life-threatening. Individuals with the severe early onset form of VLCAD may not survive without treatment. With proper diagnosis and early treatment, many individuals with VLCAD are typically able to live healthy lives.

VLCAD is caused by mutations in the ACADVL gene.

### Treatment

There is no cure for VLCAD. Treatment is aimed at managing and preventing symptoms. Individuals may require changes to their diet and routine heart monitoring. Fasting, dehydration, and excessive exercise should be avoided.



## Vitamin D-Resistant Rickets, Type 2A

### Summary

Vitamin D-resistant rickets (VDRR) is a group of autosomal recessive disorders that causes a softening and weakening of the bones (rickets). Although rickets normally responds well to vitamin D supplements or increased sun exposure, the regular vitamin isn't sufficient for people with VDRR.

Signs and symptoms generally appear shortly after birth. The bones are weak and painful and are at high risk for breaks. People with VDRR grow slowly, have bowed legs, weak muscles, tooth abnormalities, possible hair loss, and may include slow growth, a short stature, skeletal abnormalities, muscle weakness, dental abnormalities, and bone pain. Many individuals will experience bowed legs or knock knees. If left untreated, symptoms generally worsen over time.

VDRR can be caused by two different genes (CYP27B1 and VDR) with slightly different features. Two mutations in the same gene are needed to cause symptoms.

### Treatment

Supplements and medications can be used to help prevent complications in VDRR.

## Werner Syndrome

### Summary

Werner syndrome is an autosomal recessive disorder that causes premature aging. Most people with Werner syndrome develop normally until puberty. However, they will not normally have a growth spurt, and thus be shorter heights. Symptoms that develop in the 20s and 30s include premature graying and loss of hair, cataracts (cloudy lenses in the eyes), thinning of the bones, aging of the skin (such as age spots), and a hoarse voice. As the disorder progresses, individuals may experience type 2 diabetes, severe wasting of muscle tissue, and the build-up of fat and cholesterol in the arteries, many things that usually affect people much older. Affected individuals also have a higher risk of developing cancer.

Most individuals will experience a shortened life expectancy due to cancer or heart disease with many surviving into their late 40s or early 50s.

Werner syndrome is caused by mutations in the WRN gene (previously known as the RECQL2 gene).

### Treatment

There is no cure for Werner syndrome. Treatment is aimed at managing symptoms and often includes regular monitoring by a team of healthcare professionals.

## Wilson Disease

### Summary

Wilson disease is an autosomal recessive disorder in which too much copper is present in the body. Copper builds up in the liver, brain, kidney, and eyes causing damage and scarring that prevents organs from working normally.

Signs and symptoms of Wilson disease typically first appear during childhood or adolescence but may appear as late as the age of 70. The initial and most common symptom is liver disease which shows up as abdominal pain, jaundice (yellowing of skin and eyes), and tiredness. Other symptoms may include loss of physical skills, stiff muscles, clumsiness, difficulty swallowing, tremors, and speech problems. Roughly 33% of individuals will experience psychiatric symptoms such as depression, neurosis, impaired thinking, abrupt personality change, or inappropriate behavior. Some will have copper deposits on the surface of the eye that form a greenish-brownish ring. Despite treatment, some individuals with Wilson disease may develop heart problems, arthritis, and endocrine disorders. If diagnosed and treated early, many individuals can have a normal life expectancy. If left untreated, Wilson disease can lead to brain damage, liver failure, and death.

Wilson disease is caused by mutations in the ATP7B gene.

### Treatment

There is no cure for Wilson disease. Lifelong treatment to remove excess copper from the body is required. Medication and changes to diet are usually recommended. Liver transplant may also be needed in cases of liver failure. Cooking with copper utensils or drinking from copper water pipes should be avoided.

## Woodhouse-Sakati Syndrome

### Summary

Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive disorder that affects many systems in the body.

Signs and symptoms generally appear during adolescence and include intellectual disability, various muscle and movement problems, diabetes, hypogonadism (sex glands that produce little to no hormones), and a loss of hair (alopecia). Additional symptoms that may develop include hearing loss, difficulty speaking, and seizures, affected individuals seem to show similar features such as a high forehead, triangular face, and prominent ears.

WoSaS is caused by mutations in the DCAF17 gene.

### Treatment

There is no cure or effective treatment for WSS at this time.

## Xeroderma Pigmentosum, Type C

### Summary

Xeroderma pigmentosum (XP) is an autosomal recessive disorder that causes extreme sensitivity to ultraviolet (UV) rays from the sun.

Signs and symptoms generally appear between infancy and childhood. Many individuals develop severe sunburns and blistering following only a few moments of exposure. By the age of 2 years, almost all affected individuals will develop freckling of the skin in sun exposed areas, which is uncommon for most children at this age. Additional symptoms may include spider-like blood vessels under the skin, non-cancerous growths on the eyes, over-sensitivity to bright light, loss of eyelashes, clouding of the eye, and dry skin. Affected individuals have a risk (2,000 times higher than normal) of developing skin cancer before the age of 20. Some studies suggest that individuals are also at a greater risk of developing other types of cancers such as brain and lung cancer. The prognosis for an individual affected with XP is variable depending on avoidance of sun exposure and treatment. Individuals who take great care to avoid sun exposure may increase life expectancy and have a more favorable prognosis.

There are several different types of XP caused by different genetic mutations. Two mutations in the same gene are needed to cause symptoms of the condition. XP, type C is caused by mutations in the XPC gene.

### Treatment

There is no cure for XP. Treatment consists primarily of avoiding sun exposure, and using sunscreen, UV protective clothing, and UV blocking films for indoors. Individuals should undergo regular skin and eye exams.

## Zellweger Spectrum Disorder, Type 1

### Summary

Zellweger spectrum disorders (ZSD) are a group of rare autosomal recessive disorders that cause a variety of medical problems due to the body's inability to remove toxins from the body in structures called peroxisomes. Individuals with ZSDs vary greatly in the severity of their signs and symptoms. ZSDs include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Of the different disorders that are included in ZSDs, Zellweger syndrome is the most severe.

Individuals affected with Zellweger syndrome develop signs and symptoms shortly after birth. Symptoms may include poor muscle tone, feeding problems, hearing and vision loss, developmental delay, and seizures. Infants may also have common features such as a high forehead, a flattened face, broad nasal bridge, and a large space between the bones of the skull (causing a soft spot on the top of the head). Individuals may develop life-threatening damage to different organs and tissues, including the liver, heart, and kidneys and will not typically survive past the age of 1 year.

Neonatal adrenoleukodystrophy and infantile Refsum disease are less severe with first signs not developing until late infancy or early childhood. Affected individuals may experience similar features to those in Zellweger syndrome, but the condition does not worsen as fast. Most individuals will reach childhood, and some of those with infantile Refsum disease may survive into adulthood.

ZSD can be caused by mutations in over 10 different genes. Two mutations in the same gene are needed to cause symptoms. ZSD, type 1 is caused by mutations in the PEX1 gene.

### Treatment

There is no cure for ZSD. Treatment is aimed at managing symptoms. This can include feeding tubes, medications, hearing aids, glasses, surgery to remove cataracts (clouding of the eye), and dietary modification.

## Zellweger Spectrum Disorder, Type 5

### Summary

Zellweger spectrum disorders (ZSD) are a group of rare autosomal recessive disorders that cause a variety of medical problems due to the body's inability to remove toxins from the body in structures called peroxisomes. Individuals with ZSDs vary greatly in the severity of their signs and symptoms. ZSDs include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Of the different disorders that are included in ZSDs, Zellweger syndrome is the most severe.

Individuals affected with Zellweger syndrome develop signs and symptoms shortly after birth. Symptoms may include poor muscle tone, feeding problems, hearing and vision loss, developmental delay, and seizures. Infants may also have common features such as a high forehead, a flattened face, broad nasal bridge, and a large space between the bones of the skull (causing a soft spot on the top of the head). Individuals may develop life-threatening damage to different organs and tissues, including the liver, heart, and kidneys and will not typically survive past the age of 1 year.

Neonatal adrenoleukodystrophy and infantile Refsum disease are less severe with first signs not developing until late infancy or early childhood. Affected individuals may experience similar features to those in Zellweger syndrome, but the condition does not worsen as fast. Most individuals will reach childhood, and some of those with infantile Refsum disease may survive into adulthood.

ZSD can be caused by mutations in over 10 different genes. Two mutations in the same gene are needed to cause symptoms. ZSD, type 5 is caused by mutations in the PEX2 gene.

### Treatment

There is no cure for ZSD. Treatment is aimed at managing symptoms. This can include feeding tubes, medications, hearing aids, glasses, surgery to remove cataracts (clouding of the eye), and dietary modification.

## Zellweger Spectrum Disorder, Type 6

### Summary

Zellweger spectrum disorders (ZSD) are a group of rare autosomal recessive disorders that cause a variety of medical problems due to the body's inability to remove toxins from the body in structures called peroxisomes. Individuals with ZSDs vary greatly in the severity of their signs and symptoms. ZSDs include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Of the different disorders that are included in ZSDs, Zellweger syndrome is the most severe.

Individuals affected with Zellweger syndrome develop signs and symptoms shortly after birth. Symptoms may include poor muscle tone, feeding problems, hearing and vision loss, developmental delay, and seizures. Infants may also have common features such as a high forehead, a flattened face, broad nasal bridge, and a large space between the bones of the skull (causing a soft spot on the top of the head). Individuals may develop life-threatening damage to different organs and tissues, including the liver, heart, and kidneys and will not typically survive past the age of 1 year.

Neonatal adrenoleukodystrophy and infantile Refsum disease are less severe with first signs not developing until late infancy or early childhood. Affected individuals may experience similar features to those in Zellweger syndrome, but the condition does not worsen as fast. Most individuals will reach childhood, and some of those with infantile Refsum disease may survive into adulthood.

ZSD can be caused by mutations in over 10 different genes. Two mutations in the same gene are needed to cause symptoms. ZSD, type 6 is caused by mutations in the PEX10 gene.

### Treatment

There is no cure for ZSD. Treatment is aimed at managing symptoms. This can include feeding tubes, medications, hearing aids, glasses, surgery to remove cataracts (clouding of the eye), and dietary modification.