Monogenic disorders introduced (3,4)

GeneReviews® website may be helpful in learning more about various disorders (https://www.ncbi.nlm.nih.gov/books/NBK1116/) (14).

Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), September 16, 2024. World Wide Web URL: https://omim.org/ (15).

1p36 deletion syndrome

1p36 deletion syndrome is a disorder of intellectual disabilities, and individuals either cannot speak or speak only a few words. They present with hypotonia and dysphagia. They may have behavioral issues such as temper tantrums, self-biting or some others. Most individuals have brain structural abnormalities, and more than half of individuals develop seizures. An estimated prevalence of 1p36 deletion syndrome is 1 in 5,000 newborns annually in the United States.

Most cases of 1p36 deletion syndrome arise *de novo* and not inherited. About 20% of individuals with 1p36 deletion syndrome are inherited from an unaffected parent. In those cases, the parent carries a balanced translocation, but children who inherit the translocation in an unbalanced form develop the syndrome.

About 50% of individuals with 1p36 deletion syndrome have the deleted segment which includes the tip of the p arm of chromosome 1. Around 29% have deletions that include a segment near the end of the chromosome 1. The remaining 21% deletions have complex rearrangements of genetic segments which involve this region of chromosome 1. The size of the deletion is variable among individuals with the syndrome.

The deletion in 1p36 deletion syndrome typically affects the brain, heart, and skeleton. Individual present with microbrachycephaly, and distinctive facial features, including deep-set eyes with straight eyebrows, a midface hypoplasia, a broad-flat nose, a long philtrum, and a pointed chin. The ears are abnormally shaped, low-set and backward rotated. They also have brachydactyly, camptodactyly, and short feet. Visual and hearing problems are common. Some have gastrointestinal, kidney, and genital abnormalities.

These individuals can survive into early adulthood, but their life-expectancy is quite variable.

22q11.2 deletion syndrome

22q11.2 deletion syndrome is a contiguous deletion syndrome with multiple known names. The syndrome has widely variable features which can affect any part of the body. Features can be variable even among individuals within the same family. 22q11.2 deletion syndrome can present at birth with recurrent infection due to immune dysfunction, and distinctive facial features. Individuals often have a high arched palate, bifid uvula, and submucosal cleft palate. An estimated prevalence of 22q11.2 deletion syndrome is about 1 in 4,000 individuals worldwide, but it may be more common than this estimation.

22q11.2 deletion syndrome is caused by the deletion of a small segment of chromosome 22 at q11.2. The deletion or mutation is often *de novo*, and it is not inherited in most cases. However, in about 10% of cases are inherited from a parent with an autosomal dominant inheritance pattern. The deleted segment typically contains about 30 to 40 genes although many of them have not been well characterized.

The loss of T-box transcription factor 1 (*TBX1*), is probably responsible for many of the characteristics in this syndrome such as heart defects, a cleft palate, distinctive facial features, hearing loss, and hypocalcemia. The loss of another gene, catechol-o-methyl transferase (*COMT*) in the same regions may also help explain the increased risk of behavioral problems and mental illness. Other deleted genes are likely to be responsible for other features.

Skeletal features such as asymmetry including abnormal spine. They present with delayed growth and short stature. Intellectual and learning disabilities as well as delayed speech development. Behavioral issues are common such as attention-deficit-hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) associated with difficulty with communication and social interactions.

This condition has numerous names including DiGeorge syndrome, velocardiofacial syndrome, Shprintzen syndrome, and conotrucal anomaly face syndrome.

Adrenal hypoplasia congenita (AHC), X-linked AHC or *NR0B1*-related AHC

Adrenal hypoplasia congenita (AHC) is an X-linked disorder, which typically manifests from birth in males, and affects the development of the adrenal glands. It is caused by a variant in the nuclear receptor subfamily 0 group B member 1 (*NR0B1*) gene which encodes for the protein DAX1. An estimated prevalence of AHC is 1 in 12,500 newborns, but the true prevalence is unclear.

Adrenal insufficiency is the main abnormality and begins in infancy or childhood. Clinical features associated with adrenal deficiency include feeding difficulty, vomiting, dehydration, hypoglycemia, and shock. If untreated, these complications are life-threatening. Hypogonadotropic hypogonadism with testosterone deficiency occurs. Other features are cryptorchidism, delayed puberty, and infertility. The onset and severity of these features may vary, even among individuals among family members.

Angelman syndrome

Angelman syndrome is one of the very complex imprinting-associated disorders, and most clinical features are related to nervous system abnormalities.

Angelman syndrome is a complex genetic disorder that primarily affects the nervous system

Several different mechanisms are known to cause Angelman syndrome. Most cases of Angelman syndrome (~70%) occur when a segment of the maternal allele of chromosome 15, including ubiquitin-protein ligase E3A (*UBE3A*) is deleted. In other cases (~10-20%), Angelman syndrome is caused by a variant in the maternal copy of *UBE3A*. In a small % cases, the condition is due to paternal uniparental disomy, which is the presence of two chromosome 15 copies only from the father, instead of one copy from each parent. Very rarely, it can be caused by a translocation, or a by a variant or other defect in the region of DNA that controls activation of *UBE3A*, inactivating *UBE3A* or other genes on the maternal chromosome 15.

Still, 10-15% of individuals with Angelman have no known cause identified. It is possible that alterations in other genes or chromosomes may be responsible for features similar to Angelman syndrome in those patients.

An estimated prevalence of Angelman syndrome is 1 in 12,000 to 20,000 individuals worldwide.

Clinical features of Angelman syndrome include delayed development, intellectual disability, severe speech impairment, and ataxia. Most children have microcephaly and epilepsy. Delayed development becomes noticeable by the age 6 to 12 months, and other features appear in early childhood.

Children often present with a happy, excitable demeanor with frequent smiling, laughter and hand-flapping movements. Hyperactivity and a short attention span are common behavior features. Sleep issues are common, and individuals with this disorder seem to require less sleep than other children.

As they grow older, individuals with Angelman syndrome become less excitable, and sleep issues typically resolve. However, they continue to have intellectual disability, severe speech impairment and seizures throughout their lives.

Adults have distinctive facies which may appear coarse. They may develop scoliosis. Overall, the life expectancy seems to be nearly normal.

Many features seen in Angelman syndrome are the consequence of the loss of the gene *UBE3A*. Each individual normally inherits one copy of the gene from each parent and both genes are active in most tissues in the body. However, in the central nervous system, only the maternal copy needs to be active, and this parent-specific gene activation is termed imprinting. Therefore, the features in Angelman syndrome manifest when no active maternal copy of *UBE3A* is present in the brain.

The loss of the gene OCA2-melanosomal transmembrane protein (*OCA2*) is responsible for light-colored hair and fair skin in some individuals with Angelman syndrome. *OCA2* is responsible for pigmentation and is also the region of chromosome often deleted in this syndrome. However, the loss of this gene does not explain other features of Angelman syndrome.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is an overgrowth syndrome, and one of the well-known imprinting disorders. It can affect many parts of the body. An estimated prevalence of Beckwith-Wiedemann syndrome is 1 in 10,500 to 13,000 newborns worldwide although this may be underestimated due to the mildness of symptoms in some individuals.

Beckwith-Wiedemann syndrome is typically not inherited (85%), but the parents who have a child with this syndrome have an increased risk of having another child with this syndrome, depending on the type of variant. About 10-15% of families have multiple children with this syndrome.

Clinical features of Beckwith-Wiedemann syndrome are variable. Infants with this syndrome present with macrosomia and often have omphalocele as well as an umbilical hernia, which can interfere with breathing, swallowing, and speaking. They can develop hypoglycemia and kidney abnormalities in infancy. In addition, visceromegaly and pits or creases in the skin near the ears are other unique features.

Children are often taller than their peers in childhood. Growth slows down, and adults with this condition are not typically tall. Hemihyperplasia can become less apparent over time. They are at an increased risk of developing several types of cancerous and noncancerous

tumors, such as Wilms tumor, and hepatoblastoma. Tumors often develop in childhood in 10% of individuals.

The genetic causes of Beckwith-Wiedemann syndrome are complex. Some genes in the region associated with this syndrome, are differentially methylated (DMRs), and only maternally inherited copy is expressed.

About ½ (50%) of all cases of Beckwith-Wiedemann syndrome result from methylation abnormalities, often at imprinting center (ICs) which control the methylation of several genes associated with normal growth, such as cyclin-dependent kinase inhibitor 1C (*CDKN1C*), H19-imprinted maternally expressed noncoding transcript (*H19*), insulin-like growth factor II (*IGF2*), and KCNQ1-opposite strand/antisense transcript 1 (*KCNQ1OT1*) genes. Abnormal methylation disrupts normal regulation of these genes, resulting in overgrowth and other features in this syndrome.

About 20% of individuals with Beckwith-Wiedemann syndrome are caused by uniparental disomy (UPD). Paternal UPD develops early in the embryonic process and can result in mosaicism, which seems to explain some features in this syndrome. Less commonly, variants in *CDKN1C* can cause this syndrome. The *CDKN1C* gene has a role in prenatal growth regulation, and the disruption of regulation due to variants leads to overgrowth features. About up to 6% of individuals have a chromosomal abnormality such as a translocation, duplication, or deletion of the region on chromosome 11.

An individual who inherits the abnormal gene may have no visible features of Beckwith-Wiedemann syndrome, depending on which parent passed the variant. In most cases of Beckwith-Wiedemann syndrome due to *CDKN1C* variants, individuals have inherited the variant from their mother. In rare cases, chromosomal abnormalities may be inherited from a parent, while others occur *de novo*.

Most children and adults with Beckwith-Wiedemann syndrome do not develop serious medical issues, and their life expectancy is typically normal.

Beta-thalassemia

Beta-thalassemia is a type of anemia due to a reduction in beta globin, a subunit of hemoglobin molecule, which is made up of two alpha and two beta submits. Beta-thalassemia is due to variants in the hemoglobin beta locus (*HBB*) gene, leading to a reduction in the amount of beta globin.

Beta-thalassemia is classified into two types depending on the severity of symptoms: thalassemia major (also known as transfusion-dependent thalassemia or Cooley's anemia)

with more severe symptoms, and thalassemia intermedia (also known as non-transfusion-dependent thalassemia). It is common in Mediterranean countries, North Africa, the Middle East, India Central and Southeast Asia.

Thalassemia major and thalassemia intermedia have an autosomal recessive inheritance pattern. On occasions, heterozygous carrier of a *HBB* variant may develop mild anemia, and this condition is called thalassemia minor. In addition, some variants of *HBB* have an autosomal dominant inheritance pattern.

Typical symptoms of anemia include a pale appearance, weakness, and fatigue. Individuals with beta-thalassemia are at risk of developing blood clots. The onset of symptoms of thalassemia major is within the first 2 years of life. Children may develop life-threatening anemia, and they often have failure to thrive and jaundice. In addition, they have splenomegaly, hepatomegaly, and cardiomegaly, as well as abnormal bones. They are transfusion-dependent, and they can accumulate iron from repeated transfusions, resulting in excess deposition in the liver and heart. Individuals often develop endocrine issues, and adolescents with thalassemia major have delayed puberty.

Thalassemia intermedia is milder than thalassemia major. The onset of symptoms is early childhood or later, and they present with mild anemia. They may also have slow growth, bone abnormalities, and abnormal blood clots.

Some *HBB* variants prevent the production of any beta globin which is referred to as beta-zero (β0) thalassemia. Other *HBB* gene variants result in deficiency of beta globin which is referred to as beta-plus (β+) thalassemia. Having either β0 or β+ thalassemia does not predict the severity of thalassemia, so individuals have been diagnosed with either thalassemia major or intermedia.

Down syndrome

Down syndrome is a chromosomal disorder associated with intellectual disability, characteristic facies, and hypotonia noticeable in infancy. The most common cause of Down syndrome is trisomy 21 with an extra copy of chromosome 21.

Less commonly, translocation Down syndrome can be caused by partial aneusomy of chromosome 21, due to a translocation of partial segment of chromosome 21, in addition to typical two copies of chromosome 21.

In addition, mosaic Down syndrome can be identified in a very small percentage of individuals who have an extra copy of chromosome 21 in some cells of the body, resulting mosaicism of chromosome 21 only in those cells.

Down syndrome occurs in about 1 in 700 newborns. In the United States, 5,300 infants are diagnosed with Down syndrome annually, and currently, about 200,000 individuals have Down syndrome. The risk of having a child with this condition is increased with maternal aging.

Unique facial features of this condition include a flattened appearance, up-slanting palpebral fissures, small ears, a protruding tongue, and a short neck. Other features include small hands and feet as well as a single palmar crease. About 50% may have a heart defect. Gastroesophageal reflux and celiac disease as well as hypothyroidism are common as well as eye and hearing abnormalities. A small percentage of children develop acute leukemia.

All individuals with Down syndrome present with cognitive delay, but intellectual disability is usually mild to moderate. Speech and language are developed slower than age-matched children. Delayed growth and development and behavioral problems are commonly reported. Behavior issues include attention deficit, obsessive and

compulsive behavior, stubbornness and tantrums. A minority of children with Down syndrome are diagnosed with autism spectrum disorders (ASD). Later in life, individuals with Down syndrome are at an increased risk of developing Alzheimer's disease at an earlier age.

Duchenne-Becker muscular dystrophy (Duchenne muscular dystrophy)

Muscular dystrophies are a group of genetic conditions that present with progressive muscle weakness and atrophy. Duchenne and Becker are allelic X-linked muscular dystrophies, and variants in the dystrophin (*DMD*) gene, encoding dystrophin cause these disorders, so they are also known as dystrophinopathies. An estimated prevalence of both conditions is 1 in 3,500 to 5,000 newborn males worldwide, and 400-600 newborn males in the United States have these conditions.

The conditions primarily affect skeletal and cardiac muscles because dystrophin stabilizes and protects muscle fibers. Deficiencies of dystrophin cause Duchenne type of muscular dystrophy (DMD), that lead to damage to the muscle fibers as muscles repeatedly contract and relax. On the other hand, variants with some functionally deficient dystrophin typically cause Becker muscular dystrophy.

Both conditions have similar clinical features which include cardiomyopathy; however, they differ in the age of onset and the rate of progression as well as severity. Males who have Duchenne type tends to present earlier in childhood and worsen rapidly as they grow.

They may have delayed motor skills, such as sitting, standing and walking. They become wheelchair-dependent by adolescence. On the other hand, in Becker muscular dystrophy, symptoms are milder and more variable. Muscle weakness becomes evident in childhood or adolescence, but worsening is much slower than the Duchenne type. Cardiomyopathy can develop into dilated cardiomyopathy, associated with arrhythmia, dyspnea, fatigue, and swelling of the legs and feet due to worsening heart failure.

Individuals with Duchenne muscular dystrophy typically live into their 40's and with Becker, they are able to live into their 40's and beyond.

There is a related condition known as X-linked dilated cardiomyopathy caused by certain variants in *DMD*, and also called, subclinical Becker muscular dystrophy. Individuals with this type do not have skeletal muscle weakness or wasting although changes in the muscles are detectable pathologically.

Familial hypercholesterolemia (FH)

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism presenting with high total cholesterol and high low-density lipoproteins (LDL), associated with premature development of atherosclerotic cardiovascular disease (ASCVD). Individuals with FH have high levels of plasma cholesterol carried in LDL particles and excess cholesterol is deposited in other tissues, such as the skin, tendons, and vasculature. An estimated prevalence of heterozygous FH is one in 200 to 250 individuals in most countries worldwide. FH is more common in certain populations including Afrikaners in South Africa, Lebanese, and Tunisians.

Variants in the *LDLR*, *APOB*, *PCSK9*, with an autosomal dominant inheritance, and *LDLRAP1* with an autosomal recessive inheritance, are known to cause FH. Mutations in one of the causal genes affect the ability or efficiency of LDL particle removal from the circulation. Mutations in *LDLR* are the most common cause of FH. The gene encodes low-density lipoprotein receptors on the hepatic surface, and they facilitate the uptake of low-density lipoproteins. Only variants at the LDL receptor binding regions in *APOB* cause FH.

Lifestyle modifications including diet, exercise, and smoking strongly influence lipoprotein homeostasis and the risk of ASCVD development. In addition, age, sex, and other conditions such as diabetes and obesity affect the rate or severity of ASCVD.

FH associated well-described clinical features include tendon xanthomas, xanthelasmas, and arcus corneae. Tendon xanthomas develop especially at the Achilles tendons, the hands, elbows, and knees. Xanthelasmas are yellowish papules on the eyelids or around

the eyes. Arcus corneae are grayish colored rings around the pupils, similar to the ones seen in older individuals.

Fragile X syndrome

Fragile X syndrome is a trinucleotide repeat (TNR) expansion disorder associated with developmental disorder which includes learning disability and cognitive impairment, mostly affecting males. Females can also be affected, but much milder than males. Variants in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene

cause fragile X syndrome. *FMR1* encodes for FMRP which regulates the production of proteins involved in the development of synapses of the nervous system. An estimated prevalence of the disorder is about 1 in 400 males and 1 in 8,000 females worldwide.

Almost all cases of fragile X syndrome are caused by trinucleotide repeats (CGG, cytosine, guanine, guanine) within *FMR1*. "Normal" number of repeats are from 5 to about 40. Over 200 repeats result in fragile X syndrome. The abnormal expansion silences *FMR1*, and the gene product FMRP is not produced. Deficiency of FMRP can disrupt nervous system functions which is the underlying pathology of fragile X syndrome.

Individuals with the full mutation or fragile X syndrome have mild to moderate intellectual disability while about one-third of affected females have intellectual disability. Delayed speech and language development are notable by age 2 years. They may present with anxiety and hyperactive behavior such as impulsive actions or fidgeting. They may be diagnosed with attention deficit disorder (ADD), with impaired ability to maintain attention and difficulty focusing on specific tasks. One-third may be diagnosed with autism spectrum disorder (ASD) which affects communication and social interactions. About 15% males and 5% of females may have seizure disorder.

Characteristic features of fragile X syndrome become apparent as individuals grow older, such as a long and narrow facies, large ears, a prominent jaw and forehead. Individuals with this condition typically have unusually flexible fingers, flat feet, and macroorchidism in males after puberty.

Males and females with 55 to 200 repeats have a *FMR1* premutation status. Due to the low levels of FMRP, they may have milder features compared to individuals with full mutation. Most of them are intellectually "normal", but some have emotional issues such as anxiety or depression, as well as exhibiting autistic-like behavior.

Individuals with the premutation are at risk of developing specific entities known as fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X associated tremor/ataxia syndrome (FXTAS).

Glycerol kinase deficiency

Glycerol kinase deficiency may be part of a contiguous deletion syndrome associated with Duchenne muscular dystrophy and X-linked adrenal hypoplasia congenita. However, isolated glycerol kinase also exists.

Isolated glycerol kinase deficiency

Isolated glycerol kinase deficiency (GKD) is a rare X-linked disorder of glycerol metabolism. Isolated GKD is caused by either deletions or variants with the glycerol kinase (*GK*) gene itself. The prevalence of this condition is unknown although less than 200,000 individuals are reported to have isolated GKS in the United States. Since many of them may not have any symptoms, the number may be greatly underestimated.

Individuals with GKD have elevated plasma and urine glycerol levels. Clinically, symptoms are quite variable, Symptoms are due to inability of glycerol to enter the gluconeogenesis pathway. In juvenile-onset GKD, individuals may present with severe hypoglycemic episodes with metabolic acidosis, vomiting, and lethargy, as well as hypotonia. Episodes are often triggered by fasting, illness, or prolonged exercise. Fasting tolerance improves with age because an increase in hepatic gluconeogenic capacity to incorporate nonglycerol precursors increases, and symptoms often disappear. In adult-onset GKD, most individuals are asymptomatic, and only identified incidentally with pseudohypertriglyceridemia because TG analysis uses glycerol for quantification. The baseline glycerol is often >40X greater than the normal baseline glycerol.

The adult-onset, individuals do not require any treatment, but avoidance of fasting and a low-fat and high-carbohydrate diet are recommended for other forms.

Glycogen storage disease

Glycogen storage diseases is a group of heterogenous disorders of carbohydrate metabolism due to abnormal processing of glycogen.

Glycogen storage disease type I

Glycogen storage disease type I (GSDI or von Gierke disease) is a disorder of abnormal accumulation of glycogen in cells of the body, due to defective metabolism of glycogen, especially in the liver, kidneys, and small intestine. Biallelic variants in glucose-6-phosphatase, catalytic 1 (*G6PC1*) causes GSDIa and in glucose-6-phosphate transporter, member 4 (*SLC37A4*) causes GSDIb. An estimated prevalence of GSDI is 1 in 100,000, and GSDIa is more common than GSDIb.

The onset of symptoms is around the ages 3-4 months old which coincides with the time when infants start to sleep throughout the night and do not eat as frequently. The disorder results in non-ketotic or hypoketotic hypoglycemia associated with lactic acidosis and hypertriglyceridemia, and hyperuricemia. Hypoglycemia can lead seizures. In addition, diarrhea is fairly common.

Individuals with GSDI have short stature and thin arms and legs. They may develop hepatomegaly and nephromegaly. Other clinical features in GSDI may are delayed puberty, osteoporosis, gout, kidney disease and pulmonary hypertension. Females may have polycystic ovaries. Noncancerous hepatic adenoma with malignant potential may develop during adolescence and in adulthood.

Many individuals with GSDIb may have severe recurrent bacterial infections due to neutropenia that becomes apparent by age 1. Inflammatory bowel disease is a common feature. They also develop oral problems such as cavities, gingivitis, periodontal disease, abnormal tooth development and oral ulcers.

Glycogen storage disease type III

GSD type III, also known as Cori disease, is caused by biallelic variants in the amylo-1,6-glucosidase, 4-alpha-glycanotransferase (*AGL*) gene which encodes for the glycogen debranching enzyme, involved in the breakdown of glycogen. Partially broken-down glycogen molecules accumulate throughout the body. The prevalence of GSDIII is 1 in 100,000 individuals in the United States. This disorder is more common in individuals of North African Jewish ancestry in which an estimated incidence is 1 in 5,400 individuals.

GSDIII has four subtypes, distinguishable by clinical features. GSDIIIa is the most common among GSDIII subtypes, accounting for about 85% of all cases. GSDIIIb accounts for about 15%. GSD types IIIc and IIIc are extremely rare and poorly

defined. GSDIIIa and GSDIIIc typically affect the liver and muscles. GSDIIIb and GSDIIId mainly affect the liver.

Individuals present with failure to thrive, fasting ketotic hypoglycemia and fluctuating HTG, as well as hepatomegaly with elevated transaminases in childhood. Slow growth and short stature are common clinical features.

As they grow older, children typically develop hepatomegaly. However, the enlarged liver may return to normal size during adolescence, though some may develop cirrhosis and liver failure later in life. A small percentage of people may develop non-cancerous hepatic adenoma, some of which have malignant potential.

Individuals with GSDIIIa may develop myopathy later in life, affecting both skeletal and cardiac muscles. The severity of myopathy is very variable, and hypotonia and mild myopathy may develop in early childhood. Myopathy may become severe by early to mid-adulthood. Some individuals with GSDIIIa may also develop cardiomyopathy or cardiac hypertrophy, though it often does not progress to heart failure. Others have no cardiac muscle issues.

Huntington's disease (HD)

Huntington's is one of trinucleotide repeat (TNR) disorders with an autosomal dominant inheritance resulting in debilitating neurodegenerative disorder. An estimated prevalence of this condition is 3 to 7 per 100,000 individuals of European ancestry, and less common in other populations including Japanese, Chinese, and people of African descent. It is caused by an expansion of trinucleotide repeats (CAG; cytosine, adenine, and guanine) within the huntingtin (*HTT*) gene. The "normal" repeat length is 10-35 repeats, and individuals with 36 to 39 may or may not develop any signs or symptoms. Individuals typically develop Huntington's disease with >40 repeats.

Adult-onset type is most common, typically appearing in thirties or forties. Early signs may include irritability, depression, poor coordination, involuntary movements, and difficulties with learning and making decisions. Many develop progressive worsening of chorea, which is involuntary jerking or twitching movements. Affected individuals may have trouble walking, speaking, and swallowing, and they typically live about 16-20 years after the onset of signs and symptoms.

Lipodystrophy

Lipodystrophy is a group of heterogeneous disorders associated with a variable loss of adiposity in the body.

Congenital generalized lipodystrophy

Congenital generalized lipodystrophy (also known as Berardinelli-Seip congenital lipodystrophy) is associated with a virtual lack of adiposity in the body and may result in muscular appearance. Multiple inheritance patterns (autosomal dominant and autosomal recessive) are known to cause this subtype, and causal genes include, but not limited to 1-acylglyceriol-3-phosphate o-acyltransferase 2 (*AGPAT2*), BSCL2 gene (*BSCL2*), caveolin 1 (*CAV1*), caveolae-associated protein 1 (*CAVIN1*), and lamin A/C (*LMNA*). An estimated prevalence of congenital generalized lipodystrophy is about 1 in 10 million individuals worldwide. Although the condition has been reported around the world, it seems to be more prevalent in certain regions of Lebanon and Brazil.

A lack of adipose tissues leads to the ectopic storage of fats in other organs such as in the muscles and the liver. The disease onset is variable, from birth to adolescence. Due to lack of adipose hormone, leptin, some individuals are hyperphagic. Insulin resistance, diabetes mellitus (DM), hypertriglyceridemia (HTG), and acute pancreatitis are common features. In addition, hepatic steatosis and hepatomegaly are other additional features. In addition, myopathy, cardiomyopathy, arrhythmia, atherosclerotic cardiovascular disease (ASCVD), immune dysfunction and renal abnormalities are common features. Some may develop orbital ridges, large hands, large feet, and a prominent umbilicus. Acanthosis nigricans may be observed due to insulin resistance. Females may have clitoromegaly, and hirsutism, irregular menstrual periods, cystic ovaries, and infertility.

Familial partial lipodystrophy

Familial partial lipodystrophy is another subtype of lipodystrophy with partial lack of adiposity. Well-known causal genes are the lamin A/C (*LMNA*), peroxisome

proliferator-activated receptor-gamma (*PPARG*), AKT serine/threonine kinase 2 (*AKT2*), perilipin1 (*PLIN1*), and others. The condition is inherited in both autosomal dominant and recessive patterns. An estimated prevalence of this condition is 1 in 1,000,000 individuals worldwide. However, females are diagnosed more often than males, probably due to the fat loss from the hips and limbs is easily recognized in females.

Fat loss from the limbs leads to muscular appearance, and instead, fat accumulation is noted in the face and neck as well as in the liver, resulting in hepatic steatosis and hepatomegaly. Due to abnormal deposits of adiposity, individuals may appear cushingoid. These individuals also develop insulin resistance, diabetes mellitus (DM), hypertriglyceridemia (HTG) and acute pancreatitis. Acanthosis nigricans can also be observed. Some females develop ovarian cysts, hirsutism, and infertility. Similar to the

generalized lipodystrophy, cardiomyopathy, atherosclerotic cardiovascular disease, arrhythmia, and myopathy can develop.

McCune-Albright syndrome

McCune-Albright syndrome is a mosaic disorder affecting the bones, skin, and several endocrine organs. It is not inherited and rather, it is caused by a random mutation in the GNAS complex locus (*GNAS*) gene, occurring very early in development. Some cells are normal, while others have a *GNAS* mutation in the body. An estimated prevalence of this condition is one in 100,000 to 1,000,000 individuals worldwide.

Individuals with McCune-Albright syndrome develop polyostotic fibrous dysplasia which is fibrous (scar-like) changes in many bones, often on one side of the body. Bone lesions may become cancerous though very rare (<1%). Individuals may develop an asymmetric facial appearance due to affected skull and jaw and can present with a limp due to deformed and uneven long bone growth. Scoliosis is common due to abnormal curvature of the spine.

Individuals with this condition may have multiple café-a-lait spots (shaped like the coast of Maine) on one side of the body, which may be present at birth. Females may have early puberty, and menstrual bleeding by age 2, due to excess estrogen produced by cysts in one of the ovaries (affected side). Males less commonly may also have early puberty.

Individuals with McCune-Albright syndrome may develop thyroid goiter or thyroid nodules, and about half of individuals may develop hyperthyroidism and its associated symptoms. Other features include acromegaly due to excess growth hormone secretion by the pituitary gland, and Cushing syndrome due to excess cortisol secretion by the adrenal glands which only occurs before age 2. Gastrointestinal polyps may develop, but they are typically noncancerous.

Prader-Willi syndrome

Prader-Willi syndrome is one of the complex imprinting disorders. Hypotonia is often noticed infancy

Prader-Willi syndrome is an imprinting disorder that is caused by the loss of genes in particular loci on chromosome 15. Individuals typically inherit one copy of this chromosome from each parent. Only the paternal copies of some genes are active by the process known as imprinting.

About 70% of cases are caused when the paternal copy of a loci on chromosome 15 is deleted in each cell, while the maternal copies of these genes are inactive. In about 25% of cases, two copies of chromosome 15 are inherited from the mother (maternal copies), instead of biparental copies, resulting in maternal uniparental disomy. In rare cases, Prader-Willi syndrome can be caused by a chromosomal translocation, by a genetic alteration or other changes that inactivate genes on the paternal chromosome 15. An estimated prevalence of Prader-Willi syndrome is 1 in 10,000 to 30,000 individuals worldwide.

In infancy, individuals have hypotonia, feeding difficulties, poor growth and developmental delay. In childhood, they develop hyperphagia and obesity. Some who are obese also develop type 2 diabetes mellitus (T2DM).

Individuals with Prader-Willi syndrome usually have mild to moderate intellectual impairment and learning disabilities. Behavioral problems such as temper outbursts, stubbornness, and compulsive behavior (picking at the skin) are common. They may also have sleep issues. Their distinctive facial features include a narrow forehead, almond-shaped eyes, and a triangular mouth. Short stature and small hands and feet are other features. In some individuals with Prader-Willi syndrome, fair skin and

light-colored hair are noted. Both affected males and females have underdeveloped genitals. Puberty is delayed or incomplete, and infertility is common.

Small nucleolar RNAs (snoRNAs) have a variety of functions including regulating other types of RNA molecules. The loss of a particular group of snoRNA genes, known as the *SNORD116* cluster, may play a major role in the development of some features in Prader-Willi syndrome. It is uncertain that the loss of *SNORD116* cluster contributes to intellectual disability and behavior problems, as well as physical features.

The loss of the OCA2 melanosomal transmembrane protein (*OCA2*) gene which is important in pigmentation of the skin, hair and eyes, is associated with unusually fair skin and light-colored hair. However, the loss of this gene does not cause the other features of Prader-Willi syndrome.

Most cases of Prader-Willi syndrome are not inherited, particularly those due to deletion in the paternal chromosome 15 or by maternal uniparental disomy. There is often no family history of Prader-Willi syndrome, so most cases are *de novo* during the formation of ovum or sperm or in early embryonic development. However, in rare instances, a variant associated with inactivating the paternal chromosome 15 can be heritable.

Primary mitochondrial disorders

Primary mitochondrial disorders are clinically pleotropic and heterogeneous diseases due to dysfunction of the mitochondrial respiratory chain. Many tissues and organs that are dependent on high energy or aerobic metabolism are vulnerable to mitochondrial disorders. Primary mitochondrial disorders are caused by pathogenic variants in genes coding for the mitochondrial respiratory chain and related proteins which are from both nuclear DNA and mitochondrial DNA.

Some examples of primary mitochondrial disorders:

Chronic progressive external ophthalmoplegia (CPEO): external ophthalmoplegia, bilateral ptosis, mild proximal myopathy.

Kearns-Sayre syndrome (KSS): PEO onset age <20 years, pigmentary retinopathy, one of the following: CSF protein >1 g/L, cerebellar ataxia, heart block, bilateral deafness, myopathy, dysphagia, diabetes mellitus, hypoparathyroidism, dementia.

Pearson syndrome: sideroblastic anemia of childhood, pancytopenia, exocrine pancreatic failure, renal tubular defects.

Leigh syndrome: subacute relapsing encephalopathy, cerebellar & brain stem signs, infantile onset, basal ganglia lucencies, maternal history of neurologic disease or Leigh syndrome, mitochondrial DNA variants and nuclear DNA variants are causes.

Neurogenic weakness with ataxia and retinitis pigmentosa (NARP): late-childhood or adult-onset, peripheral neuropathy, ataxia, pigmentary retinopathy, basal ganglia lucencies, abnormal electroretinogram, sensorimotor neuropathy.

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS): stroke-like episodes at age <40 years, seizures and/or dementia, ragged-red fibers and/or lactic acidosis, diabetes mellitus, cardiomyopathy (initially hypertrophic; later dilated), bilateral deafness, pigmentary retinopathy, cerebellar ataxia.

Myoclonic epilepsy with ragged-red fibers (MERRF): myoclonus, seizures, cerebellar ataxia, myopathy, dementia, optic atrophy, bilateral deafness, peripheral neuropathy, spasticity, multiple lipomata.

Leber hereditary optic neuropathy (LHON): Subacute painless bilateral visual failure, Male:female =4:1, median age of onset 24 years, dystonia, cardiac pre-excitation syndromes.

Disorders with nDNA variants

Barth syndrome: dilated cardiomyopathy, skeletal myopathy, neutropenia, almost exclusively in males. Mutations in the tafazzin, phospholipid-lysophospholipid translacylase (*TAFAZZIN*) gene cause Barth syndrome.

Coenzyme Q10 deficiency: encephalopathy, cerebellar ataxia, hypotonia, dystonia, spasticity, nystagmus, optic atrophy, retinopathy, sensorineural hearing loss. Variants in the coenzyme Q2, polyprenyltransferase, (*COQ2*) conenzyme Q4 (*COQ4*), coenzyme Q6, monooxygenase (*COQ6*), coenzyme Q8A (*COQ8A*), and coenzyme Q8B (*COQ8B*) genes cause CoQ10 deficiency.

***Mitochondrial phosphate carrier deficiency (MPCD)*:** respiratory failure soon after birth, early-onset hypertrophic cardiomyopathy, lactic acidosis. Variants in the solute carrier family 25, member 3 (*SLC25A3*) gene cause MPCD.

Hutchinson-Gilford progeria syndrome (Progeria)

Hutchingson-Gilford progeria syndrome, also known as Progeria, is a rapid aging disorder beginning in childhood. An estimated prevalence of Progeria is one in 4 million newborns worldwide. It is caused by a pathogenic variant or mutation in the lamin A/C (*LMNA*) gene. The *LMNA* gene encodes for lamin A and lamin C proteins. The lamin A is an essential scaffolding (supporting) component of the nuclear envelope that is the membrane surrounding the nucleus. The mutation (*LMNA*, c.1824C>T) produces a flawed version of lamin A, named progerin, which lacks 50 amino acid residues, including an important cleavage site, resulting in abnormal length of lamin A or specifically named progerin. Ultimately, the cell accumulates progerin and the nucleus and then, cells become damaged. The mutation is typically *de novo* and has an autosomal dominant inheritance pattern.

Affected children typically appear “normal” at birth and during early infancy. Then, they develop failure to thrive and develop a characteristic facial appearance including prominent eyes, a thin nose with a beaked tip, thin lips, a small chin, and protruding ears. They also have alopecia (hair loss), aged-looking skin, joint abnormalities, and a loss of subcutaneous fat.

The condition does not affect intellectual development or motor skills such as sitting, standing, and walking. Individuals with Progeria are prone to develop arteriosclerotic cardiovascular disease (ASCVD) beginning in childhood and have increased risk of having myocardial infarction (MI) and cerebral vascular accident (CVA) at a young age.

Sickle cell disease (SCD)

A group of disorders that affect hemoglobin molecules that lead to anemia due to the presence of hemoglobin S. Variants in the hemoglobin-beta locus (*HBB*) cause SCD. The most common cause of SCD is Glu6Val, but other variants can lead to different types of SCD. The presence of hemoglobin S can distort red blood cells into a sickle or crescent shape. SCD is the most common inherited hemoglobinopathies, and about

100,000 individuals are estimated to have SCD. An estimated prevalence of SCD is 1 in 500 African Americans and 1 in 1,000 to1,400 Hispanic Americans. Millions of people are estimated to have SCD worldwide, and most common among individuals of African ancestry and of the Mediterranean countries such as Greece, Turkey, Italy, the Arabian Peninsula, India, Spanish-speaking regions in South and Central America as well as parts of Caribbean islands.

The onset of symptoms in SCD is during early childhood. Anemia, recurrent infection, and pain syndrome are common clinical features. Some individuals have mild symptoms, while others require frequent hospitalizations due to serious complications.

Each hemoglobin typically consists of 2 subunits of alpha-globin and 2 subunits of beta-globin which is encoded by *HBB*. Different variants in HBB produce abnormal versions of beta-globin such as hemoglobin S (HbS) and hemoglobin C (HbC), and hemoglobin E (HbE). Beta-thalassemia is caused by variants in *HBB* which lead to unusually low levels of beta-globin.

In individuals with SCD, at least one beta-globin subunit is replaced by HbS. In sickle cell anemia, also known as homozygous SCD or HbSS, which is the most common form of SCD, and both beta-globin subunits are replaced by HbS. The other beta-globin subunit can be replaced by a different version of beta-globin that results in HbSC, known as hemoglobin C. In individuals who have HbS and beta-thalassemia, hemoglobin S-beta-thalassemia (HbSbetaThal) disease results.

Hemoglobin molecules are important oxygen carriers in the body. In individuals with SCD, red blood cells degrade quickly, and result in anemia. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children. Excess breakdown of red blood cells can cause jaundice and painful episodes because sickled cells are stiff and inflexible and can become stuck in small vessels. Deficiency of oxygen delivery to organ systems such as the lungs, kidneys, spleen, and the brain can lead to organ dysfunction and damages. A serious consequence of SCD is pulmonary hypertension in about 10% of adults with SCD which can result in heart failure.

Turner syndrome

Turner syndrome is a chromosomal disorder that affects development. Females typically have two X chromosomes, but in Turner syndrome, only one copy of the X chromosome is present or one of the pair of X chromosomes is altered. Most cases of

Turner syndrome are not inherited. An estimated prevalence of Turner syndrome is about 1 in 2,000 newborns worldwide who are assigned female at birth. However, this condition is often found to cause miscarriages and still births.

The most common feature of Turner syndrome is short stature, becoming evident by about age 5. About 30% of individuals have webbed neck, a low hairline at the back of the neck, lymphedema of the hands and feet, skeletal and kidney abnormalities. One-third to 50% of individuals with Turner syndrome are born with a coarctation of the aorta or abnormalities of the aortic valve, and complications associated with the heart defects can be life-threatening.

Many individuals with Turner syndrome do not undergo puberty unless they receive hormone therapy, and most have infertility. Only a small % of people retain normal ovarian function through young adulthood. Premature ovarian failure (POF) occurs although the ovaries develop normally, ova usually die prematurely even before birth.

Most individuals have normal intelligence. Developmental delays, nonverbal learning disabilities, and behavioral issues have been observed.

About half of individuals with Turner syndrome have monosomy X. Turner syndrome can be caused even by when one of the X chromosomes is partially missing or rearranged rather than being completely absent. Chromosomal abnormality, monosomy X, or nondisjunction result in a loss of X during the formation of eggs or sperm of the parents of the patient, resulting in zygote without one X chromosome. Mosaic Turner syndrome is not inherited either. In an individual, it can occur randomly during cell division in early fetal development. Thus, some cells have two X chromosomes, while others only have one X chromosome. In rare cases, Turner syndrome can be caused by a partial deletion of the X chromosome which can be heritable.

Currently, it is unclear which genes on the X chromosome are responsible for the features of Turner syndrome. However, the loss of one copy of short stature homeobox *SHOX* gene is likely the cause of short stature and skeletal abnormalities.

Williams-Beuren syndrome

Williams-Beuren syndrome or Williams syndrome is a developmental disorder that affects many parts of the body. The main features are mild to moderate intellectual disability and learning problems. Individuals also have unique personalities,

distinctive facies, and a supravalvular aortic stenosis. An estimated prevalence of Williams syndrome is 1 in 7,500 to 18,000 individuals. Williams syndrome is caused by the deletion of genetic regions of chromosome 7 which includes 25 to 27 genes. The elastin (*ELN*), general transcription factor II-I (*GTF2I*), GTF2I-repeat domain-containing protein I (*GTF2IRD1*), and LIM-domain kinase I (*LIMK1*) are genes often deleted in Williams syndrome.

A defect in *ELM* is responsible for connective tissue abnormalities, and the cause of supravalvular aortic stenosis. Difficulties with visual-spatial tasks, unique behavioral features, and other cognitive abnormalities are associated with the deletion of *GTF2I*, *GTF2IRD1*, and *LIMK1*. The deletion of *GTF2IRD1* gene is thought to contribute to the unique facial features. The presence or absence of neutrophil cytosolic factor I (*NCF1*) may have an impact on the risk of developing hypertension in individuals with Williams syndrome. When *NCF1* is deleted, less individuals develop hypertension so a loss of this gene may be protective.

Children with Williams syndrome have distinctive facies, including a broad forehead, puffiness around the eyes, and a flat nasal bridge, full cheeks, and a small chin. Dental issues are common, and teeth are small, widely spaced, crooked, or missing. Older children and adults typically have a longer face with a wide mouth and full lips.

Other features include joint and soft, and loose skin due to abnormalities of connective tissues. They have short stature, and they may develop hypercalcemia in infancy, developmental delay, and coordination issues. Hyperacusis, visual problems as well as gastrointestinal and urinary issues are also common. Obesity or diabetes can develop in adulthood.

Individuals with Williams syndrome have difficulty with visual-spatial tasks such as drawing and puzzles, but they tend to do well tasks with spoken language, music, and learning by repetition (rote memorization). They have outgoing, engaging personalities and are interested in other people. Attention deficit disorder (ADD), anxiety, and phobias are common.

If the supravalvular aortic stenosis is not repaired, individuals develop shortness of breath, chest pain, and ultimately, heart failure. Pulmonary arterial stenosis and coronary artery

stenosis can occur. Hypertension and stiffness of vasculature are noted. Therefore, individuals often cannot tolerate the use of anesthesia.

Most cases of Williams syndrome are not inherited, and the chromosomal variant is typically *de novo*. Thus, there is no family history of Williams syndrome in the family.

However, the risk of having a child with Williams syndrome is higher if a parent who is unaffected has an inversion of the region of chromosome associated with Williams syndrome. Williams syndrome can be inherited in an autosomal dominant inheritance pattern when a parent has the deletion.