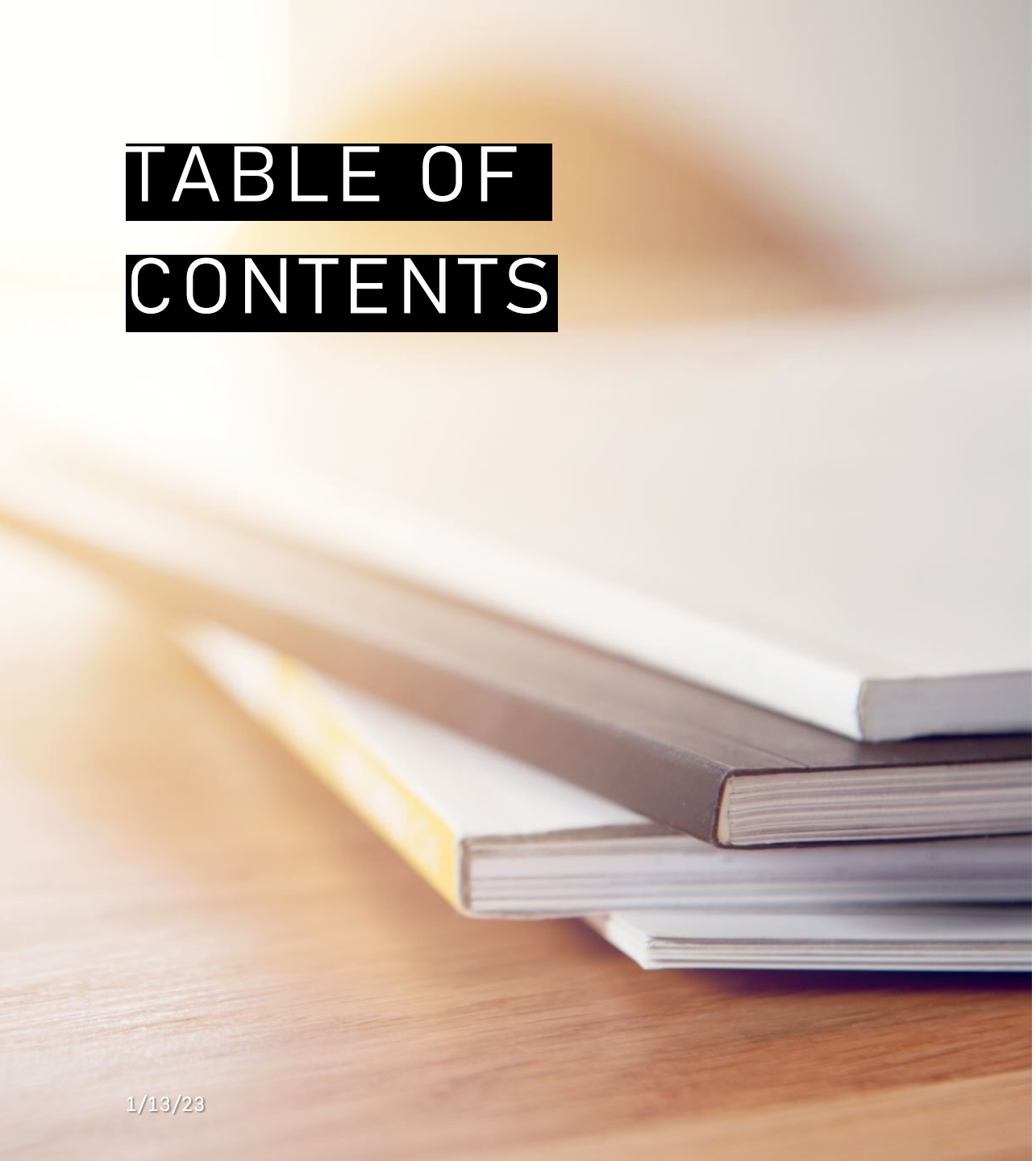
GENES AND DISEASE

A Reference Guide



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ACHONDROPLASIA (ACH)

Gene and inheritance profile:

Gene: FGFR3

Location:

Type: Mutation (gain of function)

MIM #: 100800

Onset age: neonatal - infancy

Inheritance Type: Autosomal dominant

Occurrence: very rare

Symptomology: shortened limbs and digits, short stature, abnormal growth of spine, hypotonia, hyperextensible joints, midface hypoplasia, obstructive apnea, otitis media, hydrocephalus, skeletal dysplasia, large head, prominent forehead, flattened nasal bridge, crowded and misaligned teeth. Lower spine curvature, flat short broad feet, trident hand, bowed lower legs, low muscle tone, associated middle ear infections, possible delay. In developmental milestones.

Overview

Achondroplasia is a mutation of the FGFR3 gene, leading to dwarfism. In patient cases we will often see a ratio of about 80% of parents that do not display the characteristic features due to dominant associated inheritance. Only about 20% of cases are associated with inherited FGFR3 mutation. Patients will have an overall shortened height of about 4'6" or less due to spinal cord compression and lessened bone growth of the arms and legs. In addition, patients may experience delayed motor development. Due to brain steam compression 3-7% of patients die in their first year of life. 50% of people with Achondroplasia will pass it onto their children but only 20% of cases are due to inheritance. Occurrence of live births with ACH is 1-20,000-30,000. Achondroplasia can be tested for prenatally via ultrasound or genetic testing.

Pathology

FGFr3 is a transmembrane tyrosine kinase receptor protein which is part of the signaling pathway in bone growth differentiation and regulation. The activation of FGFR3 impedes chondrocytes in the growth plate enabling regulated growth of cartilage and bone. The gain of function mutation in FGFR3 associated with the disease allows the activation of FGFR3 to be overstimulated and therefore impedes growth of bones in patients. The FGFR3 gene has a substitution of the nucleotide G for either A or C at position 1138, both of which result in the substitution of glycine for arginine at position 380 amino acid in the protein sequence. 100% of achondroplasia cases are associated with this substitution, 80% of which are de novo(father germline linked to advanced progression of paternal age). This slows down bone growth and leads to shorter possibly malformed bones. This slowing can cause compression of the brain stem, spinal cord, spinal nerve roots, and cerebral spinal fluid due to the children growing faster than their bones. Risk of foramen magnum compress which can lead to motor skill, nerve and behavioral abnormalities as well as influence dietary habits. Extreme cases may be life threatening.

Treatment

- X-ray monitoring for spine and lower extremities
- MRI of brain and spine to monitor occurrence of spinal stenosis
    - If positive patient may need to undergo surgical decompression and fusion
- Hormone therapy to increase height
- Surgery to correct spinal curvature, foramen magnum compression and lower limb development (bowlegedness)
- Ventriculoperitoneal shunt in patients with hydrocephalus

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Achondroplasia. Achondroplasia | Johns Hopkins Medicine. (n.d.). Retrieved December 13, 2022, from https://www.hopkinsmedicine.org/health/conditions-and-diseases/achondroplasia
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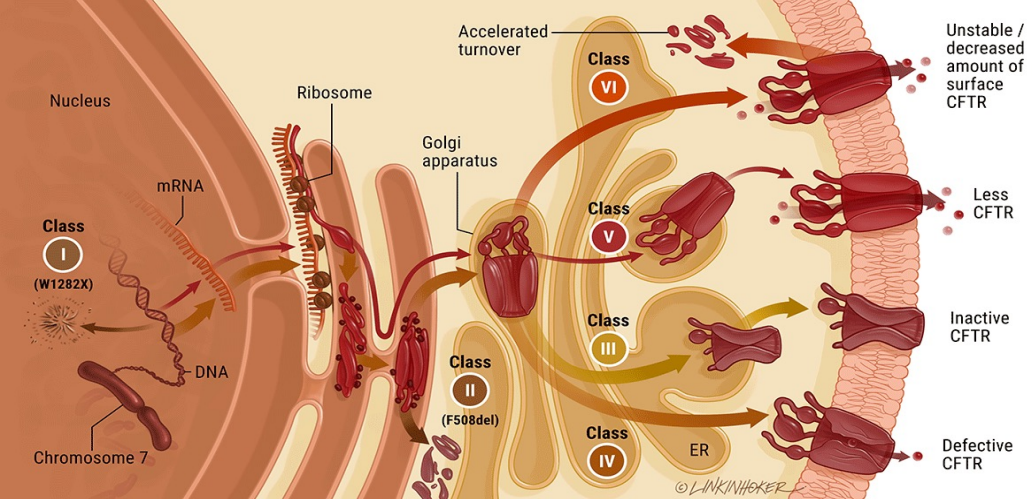

CYSTIC FIBROSIS (CF)

Gene and inheritance profile:

Gene: CFTR

Location: ch7q31 (length: 27 exons, 1480 aa protein)

Type: Mutation

MIM #: 219700

Onset age: infancy - toddler

Inheritance Type: Autosomal recessive

Occurrence: rare (most popular in north European descendants)

Symptomology: Wheezing, shortness of breath, poor growth and weight gain (due to malnutrition), greasy stool, bowel obstruction, chronic lung infections, chronic sinusitis, chronic production of thick mucus, elevated chloride concentration in sweat.

Overview

Cystic fibrosis is a disorder of epithelial ion transport due to mutations in CFTR proteins. It is characterized by thick sticky mucus which blocks airways and organ systems. Patients are more likely to have infections as well as problems with breathing a digestion. Obstructions of the pathways in the digestive system and pulmonary tract may become severe and require supplemental nutrition, enzyme replacement, and possibly even organ transplant. Occurrence of CF is 1: 2,500-3,500 in Caucasian decent with 1:17,000 African American and 1:31,000 Asian descendants. In America about 1:30 are carriers. Sweat testing is most common confirmation of CF which measures the amount of chloride expressed from sweat glands.

Pathology

The associated gene, CFTR, is responsible for hydration in anion channels within the cell membrane via the production of sweat, mucus, saliva, digestive enzymes, and tears. This hydration allows the transfer of chloride ions (-) as well as sodium ions (+) into and out of the cell. Lack of hydration leads to retention of secretions in various organ systems which can lead to organ damage and blockages in the digestive and pulmonary tracts. Due to the different components of a CFTR transmembrane protein, transmembrane domains (TMD1/TMD2) and nucleotide binding domains (NBD1 and NBD2) there can be varying levels of secretion depending on the mutation location. In addition to structural changes in the domains, mutations can cause the CFTR protein to not reach the cellular membrane. Multiple classes are associated with the functionality of the CFTR protein, see picture above, which range from no production of CFTR protein to non/defective function of the CFTR protein

Treatment

- No cure, management of the disease through treatment of symptoms.
- Clear pulmonary secretions, Reduce pulmonary infection
- Enzyme replacement in pancreases
- Fat soluble vitamin
- Improve nutrition (possible caloric substitution may be required)
- Prevent obstructions in the digestive system
- In the case of advanced pulmonary disease: lung transplant

References:
CFTR. Johns Hopkins Cystic Fibrosis Center. (2020, January 28). Retrieved December 12, 2022, from https://hopkinscf.org/knowledge/cftr/
Nussbaum, R. L., McInnes, R. R., & Willard, H. F. (2015). case 12: cystic fibrosis. In *Thompson & Thompson Genetics in medicine*. essay, Elsevier Health Sciences.
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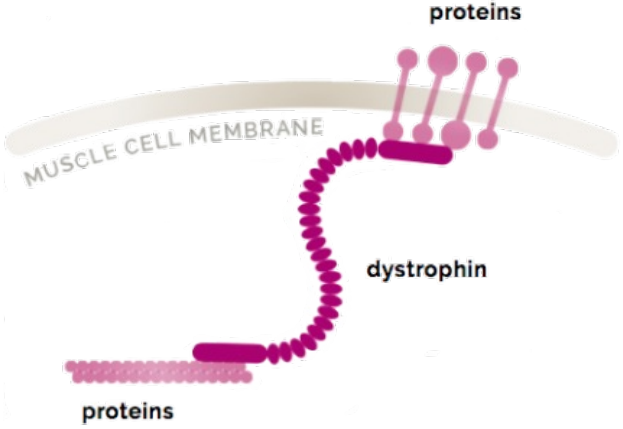

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Gene and inheritance profile:

Gene: DMD (protein: Dystrophin)

Location: chXp21.2

Type: Mutation (duplications, deletions, insertions, and nucleotide changes)

MIM #: 310200

Onset age: 3 – 5 years old

Inheritance Type: X-Linked

Occurrence: rare (primarily in males) 1 in 3,500 - 5,000

Symptomology: muscle weakness, waddling gait, learning disabilities and neurological disorders (ADHD, anxiety, autism, epilepsy), memory issues, delayed speech, opposing behavior (depression, anger), difficulty walking and standing, enlarged calves, fatigue, dilated cardiomyopathy

Overview

DMD is a muscle disorder which primary effects males, though females can be a carrier of the syndrome. It is extremely rare for females to be symptomatic. The disease causes muscle weakness which is apparent from a very young age with delayed walking (around 18 months), differing gait (such as walking on toes with legs apart and/or walking with stomach pointed outward, needing help to stand (Gower's maneuver), and falling often. The patient's loss of muscle tissue cannot be reversed so the disease is progressive in nature, primarily affecting the lower body such as hip and thigh muscles. Age at onset is most often 3-5 years. Children often need wheelchair assistance around 8-11 years of age and require ventilation support around age 12-19. DMD occurs in 1:3,500-5,000 male births worldwide with about 1:10,000 women being carriers. Genetic Blood testing can confirm the absence of dystrophin to diagnosis patients with DMD.

Pathology

Dystrophin is cytoplasmic protein that is part of a protein complex, costamere, which provides a structural connection between the muscle fiber's cytoskeleton, actin, and the dystoglycan complex, a transmembrane sarcolemma protein complex. The sarcolemma is a thin sheath of lipid bilayer which envelopes muscle fibers that provide anchor support and protection from damage. Dystrophin also has this same functional complex in the heart and nerves. Over time the absence of dystrophin fibrosis occurs causing damage of muscle cells and replacing them with scarring and fat tissue.

Treatment

- no cure
- Steroids to slow muscle damage and reduce inflammation – corticosteroids
- Exon skipping therapy to allow the body to produce a shorter variant of dystrophin
- Psychological and behavioral therapy
- Physical therapy
- Monitoring and management of associated effects such as heart disease

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U.S. National Library of Medicine. (n.d.). *DMD gene: Medlineplus genetics*. MedlinePlus. Retrieved December 12, 2022, from https://medlineplus.gov/genetics/gene/dmd/#references
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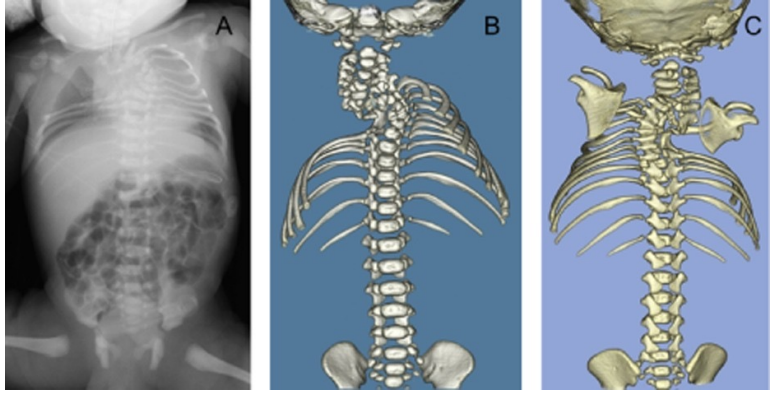

DIAPHANOSPONDYLODYSOSTOSIS (DSD)AND ISCHIOSPINAL DYSOSTOSIS(ISD)

Gene and inheritance profile:

Gene: BMPER gene

Location: ch7p14.3

Type: Mutation

MIM #: 608022

Onset age: prenatal-neonatal

Inheritance Type: autosomal recessive

Occurrence: rare (primarily in males) 1 in 3,500 - 5,000

Symptomology:

DSD: small chest, posterior rib gaps, abnormalities of the spine, clusters of embryonic cells in kidneys in the forms of dysplasia, nephrogenic rests, nephroblastomatosis, and/or cysts. ocular hypertelorism, epicanthal folds due to low nasal bridge with short nose, and low-set ears, delayed maturation of bone, abnormal or absence of ossified vertebral bodies, motor delay, inability to control head

ISD: scoliosis, minor facial dysmorphism, ischial hypoplasia, and vertebral malformations such as lumbosacral hypoplasia, motor delay

Overview

Ischiospinal dysostosis and diaphanospondylodysostosis are a type of spinal dysostoses which are both derived from the BMPER gene. Until recent years they were thought of as two separate diseases however recent studies have shown that these diseases are in fact phenotypes of the same disease, characteristic of abnormally formed spine and ribs. Due to this abnormality the spine is often malformed and may exhibit fused portions (see associated picture). This disease is a perinatal lethal disorder that is primarily associated with the spine and ribs, though kidneys as well as facial features are commonly affected as well. The disease can range from mild to severe forms with DSD being the more severe and ISD being milder. DSD is found in less than 1 in 1,000,000 individuals with 1-2 to 100,000 carrier rate. DSD can be confirmed blood testing via karyotyping,

Pathology

In this disease, BMPER, bone morphogenetic protein-binding endothelial regulator, gene shows a homozygous or heterozygous compound variant. Multiple variants, such as missense and nonsense, in the gene region are associated, though studies are still taking place due to the rarity of the disease. The non-variated form of BMPER works to regulate BMP, bone morphogenetic protein, through inhibition which further regulates BMP's interaction with osteoblasts and chondrocytes. Due to SNV occurring in a gene that regulates early formation of bone growth children will experience the effects of the disease during growth development in the womb and can have severe symptoms shortly after birth. This also shows as undeveloped/undifferentiated mesenchymal tissue in full term children. In the case of the more severe DSD, death can occur shortly after birth due to respiratory failure, however, there are cases of survival beyond this period.

Treatment

- Oxygen at birth and as needed (either full or supplementary)
- Orthopedic care support
- Neurology care support
- Occupational therapy
- Physical therapy
- Prenatal scans such as ultrasound to determine risk of disease in unborn baby

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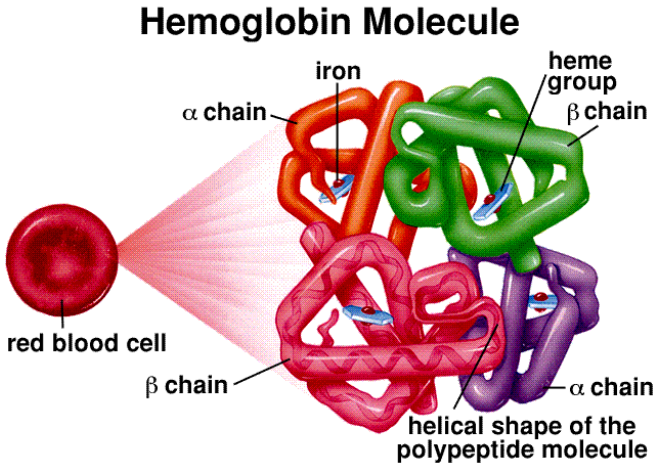

THALASSEMIA

Gene and inheritance profile:

Gene: HBA1 and/or HBA2 (alpha thalassemia), HBB (beta thalassemia)

Location: ch16p13.3 (alpha1 & 2) ch11p15.4 (beta)

Type: Mutation (deletions, variants)

MIM #: 613985

Inheritance Type: autosomal recessive

Onset age: 6-24 months of age

Occurrence: rare (most common in Asian, and African American ancestry)

Symptomology: mild to severe anemia, fatigue, weakness, shortness of breath, pale skin, dizziness, fast heartbeat, headaches, leg cramps, concentration difficulties, enlarged liver and/or spleen, hypochromia, microcytosis, hemolytic anemia, ineffective erythropoiesis,

Overview

Thalassemia is an inherited blood disorder that is caused by a lack of hemoglobin in the blood causing malfunction and reduced longevity of RBCs. There are two types, alpha and beta, corresponding to the type of hemoglobin which is affected. Therefore, alpha thalassemia refers to a patient with a disorder of the alpha globulin where beta thalassemia would refer to a patient with a disorder of the beta globulin. These two portions of globulin come together in pairs to create a full hemoglobulin in the blood. Being deficient in either alpha or beta globulin results in lower overall hemoglobulin levels. There are also severities of the disorder termed minor, intermedia, and major. As their names suggest major is the most severe and minor is the least. Patients are often immunosuppressed and have enlarged spleen and thin bones due to the body trying to overcompensate for lack of hemoglobin. Thalassemia occurs in 4.4: 10,000 live births with about 5% of the population being carriers. Blood testing can confirm abnormalities in RBCs associated with the disorder (size, shape, and color).

Pathology

Multiple mutations of the HBA or HBB genes which result in thalassemia determine the severity of the disease. The greater the imbalance between alpha and beta subunits, the more serve the disease. 4 subunits are required to create 1 hemoglobin, 2 alpha and 2 beta. An imbalance causes a lack of of hemoglobin which can result in overall issues in the blood such as shorter lifespan of individual red blood cells, hemolytic anemia and hypochromia. Overtime organs can also become damaged due to lack of oxygen and increased iron intake due to anemia symptoms. Genetic deletions are associated with 80% of alpha thalassemia patients while 90% of beta thalassemia is caused by mutations.

Treatment

- No cure
- Blood transfusion (in thalassemia major)
- B vitamin supplement (folic acid)
- Iron chelation
- Judicious transfusion
- Bone marrow transplant

Resources:
Centers for Disease Control and Prevention. (2022, April 29). *What is thalassemia?* Centers for Disease Control and Prevention. Retrieved December 13, 2022, from https://www.cdc.gov/ncbddd/thalassemia/facts.html
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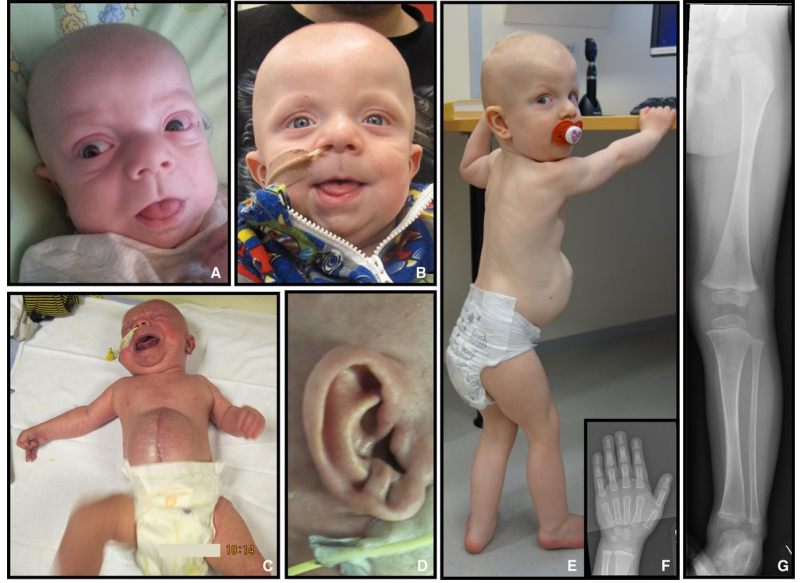

BECKWITH-WIEDEMANN SYNDROME (BWS)

Gene and inheritance profile:

Gene: CDKN1C, H19, and KCNQOT1

Location: ch11p15.5

Type: mutation or deletion of imprinted genes

MIM #: 130650

Onset age: prenatal - newborn

Inheritance Type: Imprinting, autosomal dominant

Symptomology: hemihypertrophy, macroglossia, exomphalos (omphalocele, umbilical hernia, and diastasis recti), visceromegaly, gigantism, possible tumor development, abnormal growth rate of bone structure, hypoglycemia, dysplasia, nephrocalcinosis, and nephrolithiasis, slight risk of mental disability, and possibility of congenital heat defects, enlarged placenta, variable facial morphology, hypercalciuria, low blood sugar, pits and creases in the skin around ears.

Overview

Beckwith-Wiedemann Syndrome is associated as an overgrowth disorder due to increased growth rate in the second half of gestation which continues into childhood. Enlarged placenta was also associated with pregnancies of children affected by BWS. Abnormal growth such as hemihypertrophy (increased growth on one side of the body) or macroglossia (enlarged tongue) is often associated with the mutation as well as exomphalos (defect of abdominal wall causing organ protrusion through belly button), giganticism, visceromegaly (increased size of the spleen, liver, pancreas, kidneys, and/or adrenals) and possible tumor development. Renal abnormalities such as dysplasia, nephrolithiasis, and nephrocalcinosis may also be present in BWS individuals. Due to increased rate of growth, tumor growth is also associated with BWS and should be monitored in children up to age 8. BWS occurs in 1 in every 11,000 births with only about 15% inheritance. Carrier information is complex and unknown and reoccurrence varies greatly due to variations. Prenatal and physical appearance as well as genetical testing confirm BWS.

Pathology

There are multiple genetic factors which are causative factors of BWS in the location 11p15.5. These include CDKN1C(p57), H19, and KCNQOT1 (LIT1). BWS can sometimes be caused by loss of expression of CDKN1C, which is involved in regulation of fetal growth through restriction. Commonly maternal LIT1 will display hypomethylation which will lead to the disease in about 60% pf cases. H19 is a regulator of IGF2 insulin growth factor 2, which promotes growth and development in the prenatal stages of development. Variation and hypermethylation of maternally expressed H19 is associated with the overexpression of IGF2 gene imprinting region in 2 -7% of cases. CDKN1C variants are normally inherited from mothers and will only express the phenotype if the maternal gene is affected.

Treatment:

- ultrasound followed by maternal serum alpha-fetoprotein assay and possible genetical testing
- Managed care and surgery as needed (ie. repair of the abdominal wall)
- Speech and feeding therapy/techniques in presence of macroglossia
- Reduce calcium excretions to reduce hypercalciuria
- Tumor monitoring via abdominal ultrasound (every 3 months), annual renal ultrasound and alpha-fetoprotein level (every 6 weeks) to monitor for hepatoblastoma for first 8 years of life

References:
Entry - #130650 - beckwith-wiedemann syndrome; BWS - OMIM. (n.d.). Retrieved December 15, 2022, from https://omim.org/entry/130650
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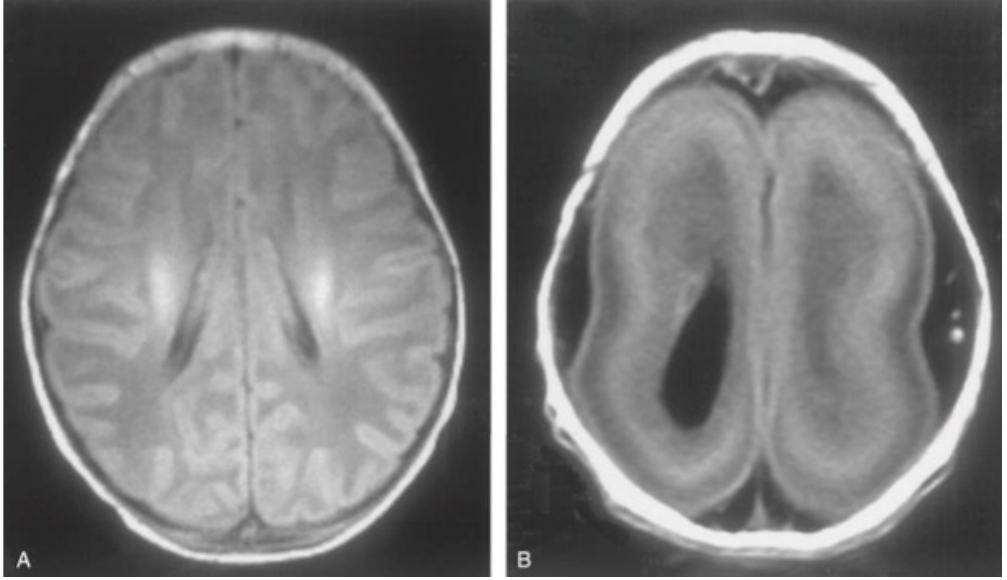

MILLER-DIEKER SYNDROME (MDLS)

Gene and inheritance profile:

Gene: LIS1

Location: 17p13.3

Type: chromosomal microdeletion

MIM #: 247200

Onset age: neonatal-toddler

Inheritance Type: chromosomal rearrangement(balanced translocation), though most cases occur at random

Symptomology: seizures, severe intellectual disability, facial dysmorphism, Lissencephaly type 1 or type 2, microcephaly, smoothness of the cerebral cortex, aspiration, poor feeding habits, early death (often in childhood), very rarely hydrocephalus

Overview

Patients will also exhibit signs Lissencephaly type 1 or type 2, (smooth brain), see associated picture comparing a normal brain to a brain affected by lissencephaly. Note that parents that may posses the balanced translocation in this region are carriers and do not show signs of the disease. Children will display symptomology from Unfortunately, due to the complications of the disease, most children do not survive to adulthood. Due to the similarities in cases Miller-Dieker Syndrome can often be confused with Walker-Warburg syndrome or typical lissencephaly. In the general population MDLS occurs in 1:1,000,000 babies and carrier information cannot be provided as the disease is typically not inherited. During pregnancy genetical testing of amniotic fluid or ultrasound is commonly used to detect MDLS.

Pathology

LIS1 encodes for a protein that is part of the platelet activating factor acetyl hydrolase 1B (PAFAH1B). This complex works in regulation PAF in the brain which directs migration of nerve cells, a process called neuronal migration. In the absence of this process the folds of the brain do not develop since the neurons that cause the folds do not move to there intended locations. As neurons do not have proper connections or placement in the brain, nerve circuits and neuronal functions are decreased and cause defects such as seizures. Though lissencephaly is only associated with LIS1 gene, other factors of the disease, such as facial dysmorphism, are not, however they are associated with surrounding genes on the 17p13.3 region. Therefore, though the smoothing of the brain occurs due to LIS1, it is apparent that the deletion in this gene directly affects surrounding genes, causing mutation. As the child ages onset of microcephaly can become apparent as well as feeding and intellectual disability.

Treatment

- No cure
- Management of symptoms, such as seizures
- Possible oxygen supplementation
- Management to prevent aspiration
    - Tube feeding via nasogastric or gastric tube i.e. mickey
    - Possible surgical intervention

References:
U.S. Department of Health and Human Services. (n.d.). *Lissencephaly*. National Institute of Neurological Disorders and Stroke. Retrieved December 17, 2022, from https://www.ninds.nih.gov/health-information/disorders/lissencephaly
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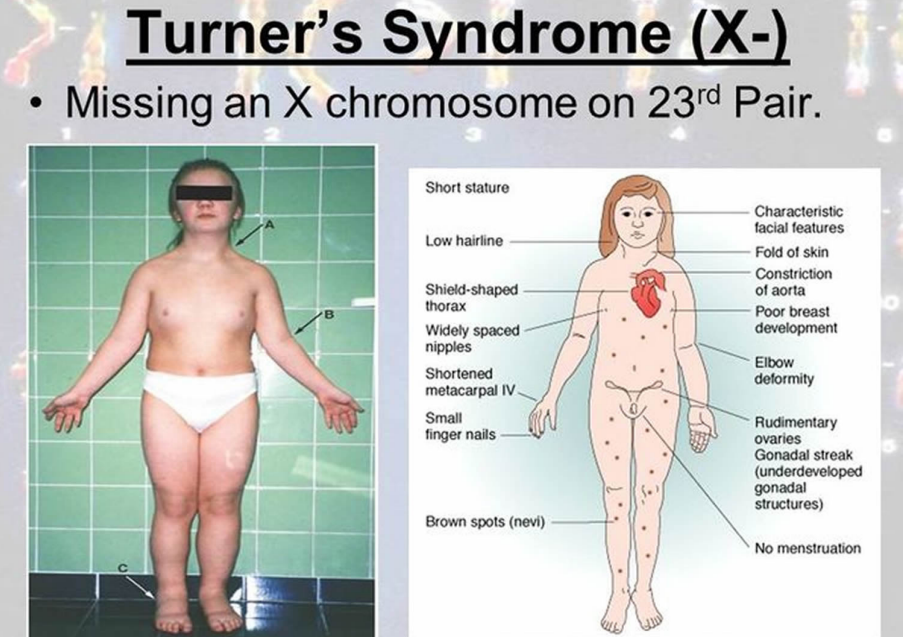

TURNER SYNDROME (TS)

Gene and inheritance profile:

Gene: X chromosome copy deletion

Location: Xq; X:61,000,001-156,040,895

Type: chromosomal deletion

MIM #: 300082

Onset age: neonatal, female, may not be diagnosed till puberty

Inheritance Type: random from reproductive cell arrangement, not inherited

Symptomology: short stature, broad chest, webbed neck, low set ears, gonadal dysgenesis, cystic hygroma, lymphedema, cardiac abnormalities, renal abnormalities, sensorineural hearing deficit, edema of the hands and feet, and dysplastic nails, bicuspid aortic valve, Increased risk of osteoporotic fractures, hyroiditis, diabetes mellitus type 1 and type 2, inflammatory bowel disease, and cardio-vascular disease, estrogen deficiency, no menstrual cycle

Overview

Turner Syndrome is due to a partial or complete loss of one of the x chromosomes in females. This syndrome is female based and does not occur in males. The greatest associations with the disease are infertility and ovarian regulation as well as lower estrogen levels. Most women with turner's syndrome are not able to reproduce, however, the small percentage that are would be considered high risk pregnancies. Turner syndrome occurs in 1 – 2000:2500 live female births according to data in Europe, Japan, and the United States. As parents are not normally carriers, carrier information is not available. Karyotyping is the most common form of testing to confirm Turner Syndrome in suspected individuals.

Pathology

The secondary X chromosome in females are required for reproduction and ovary fitness. The absence of a second X chromosome causes the ovaries to atropine into fibrous tissue streaks and/or remain undeveloped in most cases, leading to infertility and lack of normal menstrual cycle. Gonadal development still occurs however, in most cases the reproductive organs are not functional. In healthy individuals, both X chromosomes remain active, the entirety of effects which has not been fully researched. However, effects on the kidneys, hearing, and heart suggest that there are many different correlated genes on both X chromosomes that work on different organ systems beyond reproduction. The lack of estrogen levels associated with heathy individuals may be a causative factor in some of the additional symptoms.

Treatment

- Hormone therapy
  - Growth hormone
  - Estrogen therapy
- Mental health professional referral and/or support therapy for people with the disease
- Maintenance checkups with various doctors if problems arise; such as:
  - Gynecologist
  - Urologist
  - ENT
  - audiologist

References:
Entry - %300082 - cognitive function 1, social; CGF1 - OMIM. (n.d.). Retrieved December 19, 2022, from https://www.omim.org/entry/300082
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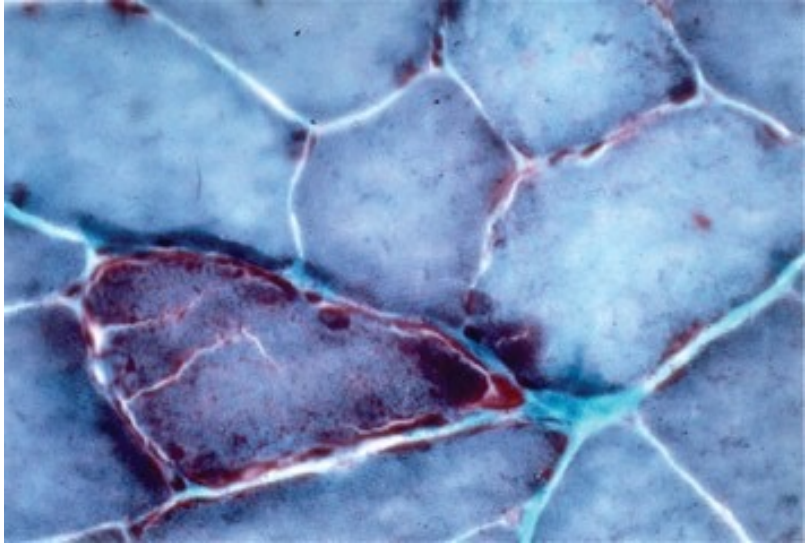

MYOCLONIC EPILEPSY WITH RAGGED-RED FIBERS (MERRF)

Gene and inheritance profile:

Gene: MT-TK (mitochondrial gene)

Location: Chr MT

Type: Pathogenetic Variant of Mitochondrial DNA

MIM #: 545000

Onset age: 2-11 years; 19-65 years

Inheritance Type: Mitochondrial Inheritance, maternal

Symptomology: myoclonus, myopathy, epilepsy, ataxia, weakness, dementia, hearing loss, short stature, cardiomyopathy with WPW (Wolff-Parkinson-White), ragged red muscle fibers, cognitive impairment, lipomas(multiple), optic atrophy, nervous system issues

Overview

The first signs of the disease are often characterized by myoclonus, twitching and jerking type movement of muscles suddenly and involuntarily. The disease's name comes from the myoclinical epilepsy, a generalized motor seizure which is sudden and bilateral in nature, along with the appearance of muscle fibers in the disease which appear red, as opposed to green myofibrils, and ragged. This occurs due to the abnormal mitochondrial pooling under the plasma membrane of muscle fibers, enhancing the red appearance. Mitochondrial expression can affect all or some mitochondria in the same tissue and is not consistent throughout the body so different tissues/muscles can be affected and the degree of affected individuals can vary. Current statistics show that occurrence of the disease is less than 1 in 1,000,000 in European individuals with exact penetrance and carrier statistics being unknown. Genetical testing of the 8344 A>G site can be performed as well as diagnosis of myoclonus, generalized epilepsy, ataxia, and ragged-red fibers via muscle biopsy.

Pathology

Age of onset for the disease varies greatly. In about 80% of cases the mutation in MT-TK occurs at nucleotide position 8244 which typically codes for adenine in healthy individuals and guanine in individuals affected by the disease. 8356T>C and 8363G>A are responsible for about 10% of cases. Genes other than MT-TK in the mitochondria may also be a causative factor of MERRF however, when other genes are affected, additional symptoms are also seen. Other genes associated with MERRF include TRNP, ND5, TRNL1, TRNK, TRNH, and TRNS1. When the MT-TK gene is altered, mitochondrial complexes I and IV, which generate energy via oxidative phosphorylation, have the greatest rate of reduction in energy synthesis. The disease is progressive throughout the lifetime of the patient due to the mutation rate of mitochondria being higher due to frequent productivity as well as the lack of introns in genes.

Treatment

- No cure
- Seizure management
- Managed care of the disease for oxidative phosphorylation activity
    - Coenzyme Q10
    - L-carnitine supplements

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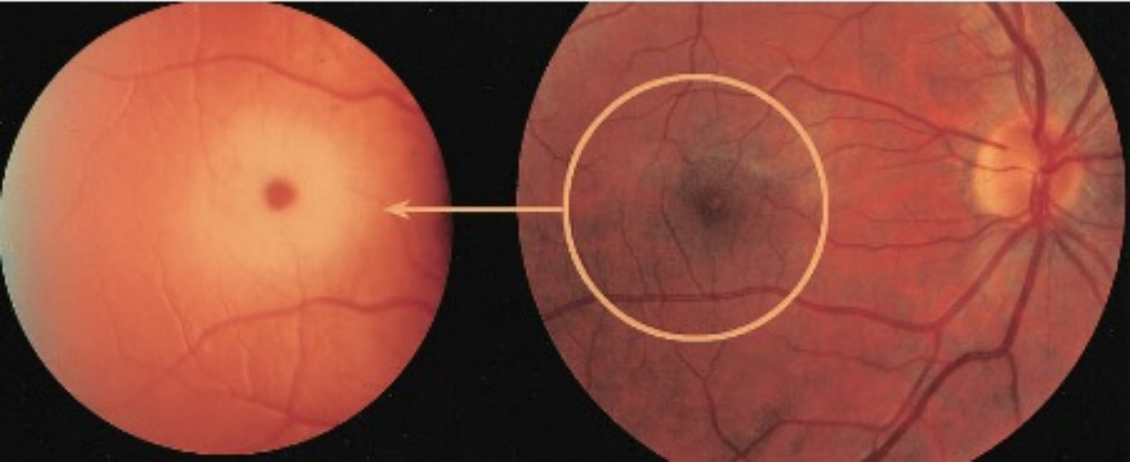

TAY-SACHS DISEASE (TSD)

Gene and inheritance profile:

Gene: HEXA

Location: 15q23

Type: mutation

MIM #: 272800

Onset age: infancy (about 3-6 months), common in eastern Ashkenazi Jewish ancestry

Inheritance Type: Autosomal Recessive

Symptomology: Slowed growth during infancy, slowed milestone progression, lose of milestone accomplishment, fatality at young age due to progression, weakness leading to paralysis, loss of vision and hearing, muscle stiffness, seizures, dysphagia, myoclonic jerks, cherry red spot in the eye (see picture above)

Overview

Tay-Sachs is a disorder of the nerves. Most commonly the disease progresses extremely early in life starting onset at 3-6 months, however, other forms exist including juvenile Tay-Sachs (later childhood progression) and late-onset Tay-Sachs (early adult hood progression. The later the start of the disease the less fatality risk associated with it and symptoms are milder overall. Overall, the disease is most prevalent in Ashkenazi Jewish ancestry with 1 in 27 being a carrier verses the general population of 1 in 250 being a carrier. Actual disease incidence is 1 in 1,000,000 live births. Testing is performed via blood sample to test for hexosaminidase A enzyme in the blood.

Pathology

The HEXA gene produces the alpha subunit of beta-hexosaminidase A which aids lysosome break down of GM2 gangloside in cell membranes. GM2 gangloside is a fatty substance that is toxic to neurons in large quantities. A common variant which causes TS is a 4-bp insertion on exon 11 of HEXA which causes a frameshift. The resulting protein produced There are a number of variants within the HEXA gene, however, the variants which still allow for production of some of the alpha subunit normally experience milder symptoms later in life, while the patients that have early onset of TS are associated with extremely low or complete loss of production of the subunit. As the disease progresses neurons of the brain and spinal cord die due to toxicity leading to neurological and motor development issues in the disease.

Treatment

- No cure
- Seizure and stiffness medicines
- Physiotherapy
- Speech and language therapy
- Antibiotics to treat pneumonia
- Psychiatrist
- Symptoms progress until fatality often at around 3-5 years of age
    - Fatality commonly occurs due to pneumonia

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