The Difference Between Genetic and Chromosomal Disorders

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Introduction

Throughout the world, millions of people are affected by genetic disorders, which are varied and diverse. Single-gene disorders, such as sickle cell anemia or Huntington's disease, are caused by a change in the DNA sequence that affects a specific gene. Chromosomal disorders, such as Down's Syndrome or Prader Willi Syndrome, are caused by an abnormal chromosome number or constitution [1].

Single-gene changes are caused by mutations in genes or errors in DNA replication in the S phase of the cell cycle [1]. There are multiple ways a mutation - or genetic variant - can occur and affect a person. Inherited variants are variants inherited from parents, and tend to be passed down through generations, while de novo variants are novel mutations that occur in children without being found in parents [2]. The cells in which the variants occur also make a difference, with somatic variants occurring during a person's life in non-reproductive cells, while germline variants occur in the parent's gametes and are then present in the child [2].

Chromosomal disorders occur when there is a change in the number or structure of chromosomes in a person's cell. Numerical abnormalities are when a person's chromosomal copy number varies from the usual two. This is called aneuploidy, and can be an extra chromosome - a trisomy when there are three chromosomes - or one less chromosome - a monosomy, when there is only one chromosome [3]. Structural abnormalities occur when the structure of the chromosomes is altered, in deletions, duplications, inversions, translocations, or the formation of rings [3]. Chromosomal abnormalities can occur during meiosis, with errors in meiotic recombination (or crossing over) being a leading cause of aneuploidy [4].

Single-Gene Disorders

Single-gene mutations are mutations which only affect a single gene in the DNA, instead of whole chromosomes.

Type of Mutations

Germline and Somatic Mutations

There are a variety of different single-gene mutations that can be categorized in a multitude of ways. The first two categories of single-gene mutations are germline mutations and

somatic mutations. Somatic mutations occur in non-reproductive cells with alterations in DNA occurring after conception [5].

A germline mutation is a mutation that is in the gametes (sex cells) of the parents, causing them to pass it onto their child but not to express it themselves [5].

Point Mutations

A point mutation only affects a single base pair (A+T or C+G), and often occurs during mistakes in DNA replication, although they can also be caused by outside factors that modify the DNA, such as x-rays or UV rays [6]. There are multiple categories of point mutations.

Transition mutations occur when the same type of nucleotides are substituted for each other: purine for purine (adenine or guanine), or pyrimidine for pyrimidine (thymine or cytosine) [6] and are less likely to change the amino acid sequence [7]. In a transversion mutation, the opposite of transition mutations, different types of nucleotides are switched out. Purines would be switched for pyrimidines or vice versa [6]. Transversion mutations are far more likely to change the amino acid sequence and affect protein function [7]. Transversion and transition mutations are expressed in different ways, depending on how they change the DNA sequence.

There are two categories for the effect a mutation has on the amino acid sequence: synonymous and non-synonymous. Synonymous mutations do not change the amino acid sequence [8]. Silent mutations are synonymous, occurring when the base pair change creates a different codon that still codes for the same amino acid. This means that the function of the protein does not change since the amino acid sequence is the same [9].

Non-synonymous mutations do change the amino acid sequence, and therefore the protein [8]. Nonsense mutations, a mutation that creates a stop codon, are non-synonymous. A stop codon stops translation before it should, causing an incomplete and non-functional protein [9].

A missense mutation can be synonymous or non-synonymous, as it creates a codon that may or may not code for a different amino acid. Since one change in the amino acid sequence does not necessarily code for a new protein, this may or may not affect protein function [9].

Frameshift Mutations

Frameshift mutations are mutations that affect nucleotide bases in numbers not divisible by 3, so that they shift the codons (groups of nucleotides) and coding sequence out of place,

changing the amino acid sequence drastically as the entire gene sequence is then misread [10]. There are four categories of frameshift mutations: deletions, insertions, duplications, and repeat expansion.

Frameshift deletions are when one or more nucleotides are deleted from the DNA sequence, leaving a gap in the DNA. Insertions are when extra nucleotides are placed in the DNA sequence. Insertions and deletions can happen at the same time. Duplications occur when one or more nucleotides are copied and repeated next to the original gene sequence, creating extra DNA and disrupting the nucleotide sequences around it [10].

A repeat expansion is when *microsatellites,* simple nucleotide sequences of usually around 3 or 4 nucleotides that are repeated multiple times, are repeated more than usual, shifting the other nucleotides in the sequence [11].

Muller's Morphs

Muller's Morphs are a specific way of classifying gene mutations. The categories of Muller's morphs are amorphs (or null), hypomorphs, hypermorphs, neomorphs, and antimorphs.

Amorphs are mutations that cause a complete loss of gene function resulting in the lack of a functional protein [12]. They usually are inherited in a recessive pattern but can be dominant [13].

Hypomorphs only cause partial loss of gene function, leading to a reduced amount of protein expression [12]. Hypomorphs are usually recessive [13].

Hypermorphs are mutations that increase gene function. They code for a normal protein, but increase transcription and translation causing increased protein expression . They are usually inherited in a dominant pattern [13].

Neomorphs cause a gain of gene function that's different from its original function. They create proteins with new functions either due to structural changes brought about by changes in amino acid sequence, or due to protein expression in new tissues [13].

Finally, antimorphic mutations, inherited in a dominant pattern, produce gene functions opposite to the gene's original function. This can happen via creating a protein with a changed function that works opposite to the normal protein's function [13].

Examples of Single-Gene Disorders

Sickle cell anemia

Sickle cell anemia (SCD), is a genetic disease which causes red blood cells to take on a sickle shape, leading to them dying faster than the body can produce new red blood cells[14]. The sickle cells slow or block blood flow because they are rigid and sticky. The disease is caused by a recessive gene, (Hb) which controls hemoglobin production, meaning both the mother and father must carry the gene[15].

Causes

SCD is caused when a hemoglobin S allele (HbS) and a hemoglobin (HBB) pathogenetic variant create a gene that causes abnormal hemoglobin polymerization. This leads to the gene HbSS, a homozygous gene, the most common gene that causes sickle cell disease[16].

The Hb gene encodes for hemoglobin, a protein in red blood cells that allow them to carry oxygen to the rest of the body. Defects in the gene prevents this function from happening[16].

HbS can also combine with other HBB variants to cause SCD, such as sickle-hemoglobin C disease [Hb S/C], sickle beta-thalassemia [Hb S/β+-thalassemia and Hb S/β0-thalassemia], Hb S/D, Hb S/O-Arab, and Hb S/E, all heterozygous combinations of variant genes[16].

The different abnormal alleles can also determine the severity of the disease, some allele combinations causing sickle cell to be more or less severe. HbS/S and HbS/β0 have more symptoms than Hb S/C or S/β+-thalassemia[16].

The genes are recessive genes, meaning it must be passed down from both mother and father who have heterozygous genes of a variant and a normal HBB gene. People with a heterozygous gene of an HBB gene which makes healthy cells and one which makes sickle cells often also have sickle cells, but the other healthy gene makes enough healthy hemoglobin and cells to make up for the unhealthy calls and prevent them from experiencing symptoms of the disease[16].

Clinical Presentation

When the hemoglobin gene encodes for abnormal hemoglobin, it is no longer able to carry out its function of carrying oxygen in red blood cells to the rest of the body, as the oxygen cannot attach to the red blood cells. The

HbAB

HbSS, Hb S/C,Hb S/β+, Hb S/β0

Heterozygous combinations:
HbAS, HbAC, ect

cells become fragile and sickle-shaped, blocking blood flow. This means that oxygen cannot get around the body[16].

The fragility of the sickle cells causes hemolysis, the destruction of red blood cells. It is common for red blood cells to go through hemolysis, as the body naturally makes more. However sickle cells die faster than normal red blood cells, dying faster than the body can make more. This leads to the body not having enough red blood cells, especially as the cells the body makes are more sickle cells[16].

These sickle cells cause a variety of serious symptoms of SCD such as pallor, jaundice, stroke, swelling, fatigue, pain episodes, severe anemia, an unhealthy spleen, pneumococcal sepsis, meningitis, and increased risk of infections[15].

Since oxygen cannot get to tissues around the body, organs are injured and it creates pain and inflammation in those organs, called a vaso-occlusive crisis[17].

Sickle cell anemia symptoms also lead to the development of various other diseases.

Diagnosis

Newborn screening for SCD and the HbS gene started in 1975 and continues using two main techniques. Isoelectric focusing, in which proteins are separated by their isoelectric points for analysis, is used to analyze the hemoglobin in red blood cells and determine whether they have SCD[16].

High-performance liquid chromatography, in which compounds are separated in a liquid mixture, is also used for blood analysis to look closer at the red blood cells and hemoglobin to determine whether they are sickle cells[16] .

If the disease is not found in the newborn screenings, it can also be identified and diagnosed based on clinical symptoms and traits[16].

Treatment

Sickle cell disease does not have a cure. The easiest way to treat the disease is through prevention of it, with parents receiving genetic testing for the genes ahead of time to know whether their child will have a possibility of developing SCD[16].

Early intervention and medical checkups from a young age are best for treatment from a young age, with specific lifestyle activities to lower the risk of the symptoms associated with the disease[16].

Blood transfusions are used to give people with SCD healthy red blood cells and improve blood function in the body[18].

Stem cell transplants have also been used, with varying results. They attempt to replace sick patient's bone marrow with healthy bone marrow that can start producing healthy hemoglobin, creating healthy red blood cells[18].

FDA approved drugs to treat the symptoms of SCD include hydroxycarbamide, endari, oxbryta, and adakveo[16].

New forms of gene therapy have started testing at Columbia University in a study that found that the gene therapy returned red blood cells to their normal shape and fixed hemoglobin function for up to 3 years. In this therapy, stem cells are collected and given a copy of the hemoglobin gene that creates healthy hemoglobin. The cells are then inserted back into the patient and make healthy red blood cells. Although it is a fairly new therapy, it yields hugely promising results for the treatment of SCD and the future of gene therapy[18].

Huntington's disease

Huntington's disease(HD) is an inherited disease which causes the breakdown of nerve cells in the brain. This breakdown of cells restricts functional abilities and causes cognitive, movement, and psychiatric disorders. It develops later in life, when patients are in their 30s or 40s, with no medicines available to prevent the disorder, only to manage it[19].

Causes

The Huntington gene (HTT) encodes for the huntingtin protein and is on the short arm of chromosome 4 in the region 4p16.3[20].

The Huntington's protein is found in many of the body's cells and is responsible for chemical signaling, transporting materials, binding to other structures, and prevention of apoptosis(cell destruction). It is essential for the program of neural induction, progressive specification of neural progenitor cell types, and the subsequent elaboration of neural lineage species[21].

Huntington's disease is caused by a mutant form of HTT (mHTT), caused by a trinucleotide repeat expansion of the codon, a sequence of 3 nucleotides in the DNA, CAD. In the general population, there are 6-35 repeats. However HD starts to develop when there are 40 or more CAG repeats in the gene. In cases where one has more than 27 repeats, there is a possibility of extension upon transmission to their children, meaning they do not have the disease but their children will because the amount of repeats will increase[22].

Huntington's disease is autosomal dominant, meaning if one parent has it so do their children[22].

Clinical Presentation

The development of Huntington's disease is split into three parts: presymptomatic HD, with no signs yet exhibited; prodromal HD, when mild symptoms first start appearing; and manifest HD, when the disease has fully manifested. It usually starts manifesting when people are in their 30s or 40s[22].

Juvenile Huntington's disease occurs when patients experience onset of the disease before they turn 21. Juvenile HD patients have more CAG repeats than typical HD patients. They often experience seizures on top of other HD symptoms[20] .

A main symptom of HD is motor issues, with patients experiencing a variety of different issues. Chorea, the sudden jerky movements of one's face and limbs is present. Early in the development of the disease, patients hyperkinetic, when there is excessive movement of a body part. As the disease progresses, they become hypokinetic, with slow or reduced movement (in juvenile HD, patients are hypokinetic first before becoming hyperkinetic)[22].

Patients also experience bradykinesia, slowness or halts of movements; dystonia, where muscles contract involuntary; and dysphagia, swallowing difficulties[22].

The destruction of neurons in the brain that characterize Huntington's create frontal lobe dysfunctions. This damage to the frontal lobe causes poor attention span, irritability with outbursts of anger and aggression, lack of awareness or insight, impulsivity, poor mood regulation, and loss of initiative, curiosity, and creativity. Patients also experience depressive symptoms among other mental health issues[22].

HD also causes cognitive issues, as patients exhibit difficulty in decision making, planning, organization and multitasking. The deterioration of neurons eventually leads to dementia and subcortical-the inability to search one's memory efficiently[22].

Diagnosis

The diagnosis of Huntington's is made based on clinical signs and symptoms and if the patient has a parent with diagnosed HD. Prenatal testing is used when parents are aware that they have Huntington's, using chorionic villi sampling for DNA testing[20].

Lab and genetic testing look for repetitions in the genes and differentiate HD from other diseases to confirm that the patient has HD. MRIs are used to view the brain and its current state[20].

Treatment

Standard treatment of HD is occupational and psychiatric therapy accompanied by various medications to help manage the disease, since there is no cure for HD[20.

Gene therapy has started to be used as a treatment for Huntington's by silencing the mutant genes and repressing transcription and translation, especially blocking protein translation. The gene therapy has been found to make neurons that have not yet died healthy again and protect against disease progression[20].

Cystic Fibrosis

Cystic Fibrosis (CF) is a genetic disease found in about 40,000 people in the US[23]. The disease causes a buildup of mucus in the lungs, pancreas, and other organs throughout the body [23], leading to further complications. The genetic root of the problem is a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene[23].

Causes

Cystic Fibrosis is an inherited disease passed down from parents, and one has to be homozygous for the mutations for the disease to be expressed. CF is caused by one of hundreds of mutations possible in the CFTR gene on chromosome 7 [24]. The most common mutation is F508, which accounts for approximately 70% of all mutations and causes defective protein processing, leading to abnormal folding of the protein and premature protein destruction [24].

Cystic Fibrosis mutations are divided into 5 classes: defective protein synthesis, defective protein processing, disordered regulation, defective chloride conductance, and accelerated channel turnover [24]. Defective protein synthesis occurs in 2%-5% of all patients, and is characterized by a nonsense, frameshift, or splice-site mutation which then causes early termination of the mRNA sequence so that it cannot code for and create the protein[24].

Defective protein processing is the second class of mutations, which occurs when defective processing causes the protein to be unable to move to the correct part of the cell, rendering it useless if it is not in the right place to do its job [24].

The 3rd class, disordered regulation, is when protein activity is impaired due to intracellular signaling. This leads to a fully formed but non-functional protein channel [24], and once again the CFTR protein is unable to carry out its function.

Class 4 is defective chloride conductance, in which the length of the channel is activated and the chloride iron flow is less than normal, even though the protein is produced and moved to the correct place in the cell[24].

Finally, accelerated channel turnover, a class 5 mutation, is characterized by the degrading of the channels by cellular processes leading to a decreased amount of CFTR channels in the cellular membrane[24].

Clinical Presentation

The CFTR gene that is inhibited in the mutation that causes CF encodes for a protein, also called CFTR, which helps regulate salt and water balances in the cell[25]. Without it, too much sodium is being reabsorbed into the body, which then causes more water to be reabsorbed, leading to a thick mucus building up in the organs because of the dehydration, then causing further health issues [24]. This also directly leads to a higher level of salt in the sweat [25].

The buildup of mucus affects the lungs, pancreas, upper airways, liver, intestine, and reproductive organs [26], leading to health issues, especially disease, in most of them [27]. Lung troubles and disease are the most common identifiers of CF, as the buildup of mucus leads to patients to not be able to clear the bacteria and blocks their airways so they can't breathe. Inflammation and infection then occurs, leading to disease [27]. Lung disease is the leading cause of death in Cystic Fibrosis patients [24].

Issues in the pancreas are also common, as the pancreatic duct is blocked by buildups of mucus, leading to the enzyme releasing process of the pancreas not working properly[24]. This can sometimes lead to pancreatic failure.

In the intestine, the intestinal chyme acid is neutralized due to sodium levels being imbalanced, and any enzymes that make it to the intestine are degraded [24]. This leads to symptoms such as abdominal pain, greasy stool, and deficiency in absorbing nutrients, with vitamins A, D, E, and K most absent [24]. The overabsorption of water due to the deficient proteins also leads to dehydration in the intestine, then causing inflammation and obstruction [24].

Other common symptoms include sinus disease and issues with the sweat glands in which one has salty skin because the chlorine channel cannot reabsorb chloride, leading to loss of fluids [24].

Diagnosis

The disease is suspected when people present with the clinical symptoms, such as cough, coughing up mucus, or wheezing of more than three months' duration, clubbed fingers, and the continuous finding of bacterial culture in respiratory mucus[26], among others.

The most common test to confirm the diagnosis is measuring the sweat electrolyte levels to check for regular concentrations of sodium and chloride[27]. If they are abnormal, the person most likely has Cystic Fibrosis.

Since CF is an inherited mutation, screening programmes do exist for the genes in both parents and prenatal babies, and can be used to look for the gene before the baby is born [27].

Treatment

The main focus of Cystic Fibrosis treatment is treating the lung disease, with antibiotics for chest infections, various treatments to clear mucus from lungs such as medicines to make the mucus in the lungs thinner, medicine to widen the airways and reduce inflammation, and commonly lung transplants as the disease progresses and further degrades the patient's lungs [28]

Treatments for issues beyond the lungs include a variety of medicines, treatments and medicines to help absorb food better, and special diets to prevent malnutrition [28].

Gene therapy is a newer, more experimental form that is currently showing promising results, with the basic idea that a new, healthy CFTR gene would be inserted into the cells so that they would make a healthy protein [29]. There are two types of gene therapy being considered, integrating and non-integrating. Integrating gene therapy is when the healthy CFTR gene is inserted into and incorporated into the genome so that it would become a permanent part of the DNA, theoretically lasting forever. Non-integrating gene therapy is when the DNA is inserted into the cell, making the correct healthy protein but is not a permanent part of the genome and therefore the effects do not last forever [29].

Angelman Syndrome

Angelman Syndrome (AS), is a rare neurogenetic disorder, occuring in around 500,000 people around the world, caused by issues with the UBE3A gene, which is located on the 15th maternal chromosome [30]. The first signs and symptoms of the disorder, such as developmental delays and intellectual disability, appear when a person is about 6-12 months of age [31].

Causes

Angelman Syndrome is caused when the UBE3A gene, which lies on 15q11-13, on the maternal chromosome is not expressed, which has consequences due to factors such as genomic imprinting(when only one copy of a gene is expressed) silencing the paternal chromosome and the UBE3A gene altogether [32].

UBE3A encodes for a protein named E6-associated protein, which is essential for the proper functioning of neurons and synaptic plasticity (how a synapse can change for communication between them). Without the UBE3A properly encoding for the protein, it is not in the cells and then causes the degradation of various other proteins necessary for neuron health, such as p53 and p27, and synapse health, such as arc and ephexin5 [32]. Without these proteins, the neurons degrade and die, leading to several neurological consequences.

70-75% of AS cases are caused by deletion of the 12q11-13 region on the maternal chromosome, 2-3% are caused by a paternal uniparental disomy (UPD), when there are two copies of the paternal chromosome, 3-5% are caused by an imprinting defect(defect in which chromosomes are expressed), and 5-10% are caused by a single gene point mutation in the maternal UBE3A allele, when a single base pair is added or deleted [32].

Clinical Findings

The symptoms of Angelman Syndrome include developmental delays, intellectual disabilities, limited or nonexistent speech, ataxia(issues with movement and balance), seizures, and walking difficulties [33].

In childhood, more specific symptoms occur, such as a happy, excitable attitude, hand-flapping motions, hyperactivity and short attention span, difficulty sleeping and needing less sleep, and a fascination with water, along with all of the long-term symptoms [33].

Diagnosis

DNA methylation analysis detects 80% of Angelman Syndrome, while UBE3A sequence analysis detects pathogenetic variants in another 11% of cases [34]. FISH and DNA marker analysis are used to determine which parent the deletion came from [33].

Treatment

Drugs such as sodium valproate, clonazepam, and phenobarbital are used to treat seizures [34]. Patients also undergo speech, language, and physical, and occupational therapies [34].

Gene therapy shows promising results for Angelman's Syndrome, in which researchers make a healthy version of the UBE3A gene to deliver to neurons, which then creates a healthy protein [35]. However, the research is in early stages at UNC.

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD), is in a of a group of diseases named dystrophinopathies which cause progressive muscle degeneration and weakness [36]. DMD includes a less severe form of the disorder called Becker Muscular Dystrophy and an intermediate form of the disorder [37]. The disorder, which occurs in about every 6 in 100,000 births, is caused by issues with a protein called dystrophin that keeps muscle cells intact [36].

Causes

DMD is inherited in an X-linked recessive pattern, which leads to more males having the disorder, about 1 in 3500 [38], and occurs when the gene that codes for dystrophin is mutated. The dystrophin gene is located on chromosome Xp21, on the bottom of the chromosome, and is one of the largest genes in the gene sequence [37].

The dystrophin protein is used for structural support of the muscle cells [38] by coming together with the dystrophin-associated glycoprotein complex (DGC) forming the dystrophin-associated glycoprotein complex [39]. This complex structure then supports the structure of the cell. Without it, the membrane becomes permeable and outside particles enter the cell, heightening internal pressure until the cell dies [39]. This occurs in the skeletal and cardiac muscle as well as a bit in the brain, places where the gene is expressed.

About 65% of mutations in the dystrophin gene are deletions, 6-10% are duplications, and the last 25% are smaller mutations and rearrangements. A small number of cases, about 2%, are caused by complex rearrangements and changes in introns - parts of genes that are not transcribed into mRNA[39].

Female carriers of the disease, females who have one mutated dystrophin allele and one healthy one, are usually asymptomatic but can develop symptoms if there is another issue preventing both their X chromosomes from being expressed, such as variations of Turner Syndrome, translocations between the two chromosomes, or inactivation of the healthy chromosome [37].

Clinical Findings

The degradation and destruction of the muscle cells then cause a variety of symptoms. Physical presentations are calf muscle hypertrophy, when the calf muscles are bigger than usual [40]; flexion contracture, a bent joint, usually in the hand, that cannot be straightened [40]; and a waddling gait [37].

The main characteristic of DMD is the chronic weakening of muscles [40], affecting most of the body and causing issues such as cardiomyopathy, when the heart is too weak to pump blood[40]. Other health issues such as issues with breathing and scoliosis also occur [37].

Patients with Duchenne Muscular Dystrophy experience multiple developmental delays: global developmental delay, speech language delay, and motor delays [40]. They also commonly have mild cognitive and intellectual disabilities, but the severity of these do not correlate with the severity of the other symptoms [37].

Diagnosis

Multiple different methods are used to diagnose DMD. Patients are tested for elevated levels of creatine kinase, an enzyme that helps muscles produce energy, which is a sign of

muscle, heart, or brain damage. Taking a muscle biopsy(a small piece of muscle) is also used for testing to study the muscle cells for signs of degeneration and the absence of the dystrophin protein. Finally, electromyography, the recording of the electrical activity in the muscle tissue, is used to determine whether the muscle tissue and cells are as active as they should be, as low levels are a sign of degeneration and therefore DMD [37].

Gene analysis is also used to test for the disorder, with methods such as multiplex ligation-dependent probe amplification (MLPA), which studies the DNA for variations using a polymerase-based reaction; oligonucleotide-based array comparative genomic hybridization (CGH), which studies a patient's DNA for duplications or deletions; and next-generation sequencing (NGS), which is sequencing multiple sets of DNA at the same time [39].

Treatment

The treatments for DMD vary and are specific to each symptom of the disorder they are treating. Glucocorticoid therapy is a type of therapy commonly used that uses drugs such as prednisone and deflazacort to slow the degradation of muscle and brain cells [37].

Cardiomyopathy, or weakness of the heart, is surveilled with tests that measure the beating of the heart such as ECGs and echocardiograms, and then treated with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers to help it pump blood [37].

Occupational, physical, and speech therapies are used to aid developmental delays.

Gene therapy for DMD is being researched, with the idea of delivering a healthy gene to restore the dystrophin protein in unhealthy muscle cells. However the gene is too large to deliver with the current technology, so a smaller version of dystrophin has been developed to be used for such therapies[39]. The therapy would help the symptoms of DMD by preventing the muscle cell death that causes it in the first place.

Chromosomal Disorders

Chromosomal mutations are mutations that cause a change in the chromosome. There are two main types of chromosomal mutations: numerical and structural.

Numerical Abnormalities

Numerical abnormalities are when there is an abnormal number of chromosomes in the cell [41]. There are two types of numerical abnormalities: aneuploidy and polyploidy.

Aneuploidy is the condition of having any number of chromosomes that is different from the normal diploid condition [42]. The main kinds of aneuploidy are monosomies, when there is only one chromosome instead of two, and trisomies, when there are three chromosomes instead of two [42].

Polyploidy is when cells have more than the diploid set of chromosomes for all chromosomes [43].

Structural Abnormalities

A structural chromosomal abnormality is when the structure of the chromosome is changed, but not the number of chromosomes [42]. The types of structural abnormalities are deletions, duplications, translocations, inversions, rings, and isochromosomes.

Chromosomal deletions are when large parts of the chromosome are deleted, such as an arm of the chromosome or a large chunk of it, while chromosomal duplications are different from simply aneuploidies because only a part of the chromosome is duplicated, causing extra genetic material, but the whole chromosome [44].

A translocation is when a part of one chromosome is transferred to another. Reciprocal translocation is when a segment of a chromosome is exchanged with a segment of another chromosome. Reciprocal translocations do not always have harmful effects because they are usually balanced. On the other end, Robertsonian translocations occur when chromosomes are attached to one another. The chromosome can be attached to another at the centromere and lose the two short arms, fusing the long arms together. Another example of a Robertsonian translocation is when one chromosome will join onto the end of the other [45].

Inversions are when the parts of the chromosome are broken off and turned upside down, then reattached. This causes the genetic material to be inverted. Sometimes, genetic material along the edge is lost in the process[44]. A ring chromosome is created when a chromosome breaks, and the broken ends fuse together, making a ring-like shape [44].

An isochromosome is a chromosome where the two arms of the chromosome are mirror images of each other. This can cause the opposite chromosome arm to be deleted, and therefore genetic material to be missing [46].

Examples of Chromosomal Disorders

Prader Willi

Prader Willi syndrome (PWS) is a rare chromosomal disorder caused by germline mutations in chromosome 15 [47] that occurs in about 1 in 20000 to 1 in 30000 births[48]. It leads to issues with hunger, growth, sexual development, body temperature, mood, and sleep as well as mild intellectual disabilities as behavioral problems [49].

Causes

PWS is caused when the genes in the q.11-q.13 regions of chromosome 15 are not expressed in the paternal chromosome. Since the genes in the maternal chromosome of chromosome 15 are never expressed, a defect in the paternal chromosome has serious consequences. There are multiple things that can cause these genes not to be expressed: a paternal deletion, a maternal uniparental disomy, an imprinting defect, or a paternal chromosome translocation [50].

A paternal deletion occurs in about 70% of patients, when parts or the whole of the paternal chromosome is deleted, so the genes cannot be expressed because they aren't there. A maternal uniparental disomy occurs in 25% of patients when the maternal chromosome is duplicated and replaces the paternal chromosome. This leads to two unexpressed maternal chromosomes [50].

Imprinting is the process in which only one copy of a gene is expressed [51]. In an imprinting defect, occurring in only about 5% of people with PWS, a paternal chromosome carries a maternal imprint, leading to the genes not being expressed[50]. About 10% of these imprinting defects are caused by a microdeletion to the imprinting center of chromosome 15, which changes the imprinting of the whole chromosome [51].

Finally, the very rare paternal chromosome translocation is when the q.11-q.13 region is switched between the maternal and paternal chromosomes, silencing both. All of these defects can lead to PWS, and are chromosomal defects that cannot be passed down through families. However, in cases such as the imprinting defect, where the defect is caused by a specific gene, the gene and therefore the defect can be passed down through families [50].

Clinical Presentation

Prader Willi Syndrome causes multiple physical symptoms that progress and appear throughout a patient's life. From ages 0-2, they experience hypotonia, low muscle tone visible in infancy through poor suck and feeding in the neonatal period. From ages 2-6, their hypotonia persists and they also show global developmental delays, being slow to develop and grow

compared to other children [48]. These developmental delays are major, particularly motor and language delays. From ages 6-12, their previous symptoms persist as excessive eating and insatiable hunger appear, often leading to obesity. Around the age of 8, they become hyperphagic, meaning they are always hungry and never feel full[48].From ages 13 and on, they continue to exhibit such symptoms as well as hypothalamic hypogonadism, which prevents the pituitary gland from creating regular sex hormones [48]. This leads to delayed reproductive development and eventually genital hypoplasia(the underdevelopment of reproductive organs), infertility, and incomplete puberty. Scoliosis is also fairly common, present in 40-80% of patients.

Most PWS patients also experience mild intellectual disabilities throughout their lifetime. They have behavior issues such as temper tantrums, stubbornness, skin picking, controlling and manipulative behavior, compulsivity, and difficulty with changes in routine. Symptoms of psychiatric disorders such as Generalized Anxiety Disorder and Obsessive Compulsive Disorder (OCD) also often manifest in PWS patients, along with sleep abnormalities - particularly sleep apnea, where one's breathing becomes shallow or stops altogether during sleep [50].

Prader Willi patients tend to have stunted growth and are usually smaller and shorter. They also present with a narrow face, almond-shaped eyes, narrow nose bridge, thin upper lip with down-turned corners of the mouth [48].

Diagnosis

Full diagnosis of Prader Willi Syndrome is made using DNA testing on the q.11-q.13 regions of chromosome 15 after clinical features are shown [48].

DNA methylation analysis is a process in which methyl groups are added to cytosine or adenine, causing a pattern to develop that shows the genes and is commonly used to diagnose PWS. It is the only technique that can detect all the ways that PWS develops (deletion, imprinting defect, translocation). The data from methylation analysis is enough for diagnosis but not for genetic counseling [52].

The second DNA testing method used for diagnosis is fluorescence in situ hybridization (FISH), which detects 65%-75% of deletions by looking for gene changes in the cells. FISH testing uses probes - short single-stranded DNA sequences that match up with the sequence that one is looking for, with fluorescent dye attached - and looks to see if the single strand binds with a complementary strand, which will tell whether that sequence is in the DNA [53].

Treatment

Although Prader Willi can't be cured, patients undergo a variety of different treatments to manage the disorder. Special tubes or nipples are used for feeding difficulties as a young child. As they grow older, they have a strict diet with supervision of their eating habits and monitoring of their weight and BMI to prevent overeating and obesity [54].

To manage sleep apnea, patients undergo various sleep studies and treatment. To deal with their scoliosis, they are sent to an orthopedist. To treat their eye issues, they are sent to an ophthalmologist. They also undergo physical, occupational, and behavior therapies and are often placed in special needs programs as they move through the schools. Some medicines are given, such as serotonin reuptake inhibitors to help with OCD symptoms [54].

To help with developmental delays, patients undergo growth hormone therapies, which is found to be greatly beneficial in terms of reducing symptoms, as well as specific sex hormone treatments and surgeries to aid with reproductive development [54].

A new type of treatment, experimental gene therapy, has begun to have promising results in slowing or preventing symptoms of PWS. Gene therapy is used to attempt to "turn on" or express the PWS genes in the unexpressed maternal chromosome. It can also be used to replace missing or inactive chromosomes or genes [55].

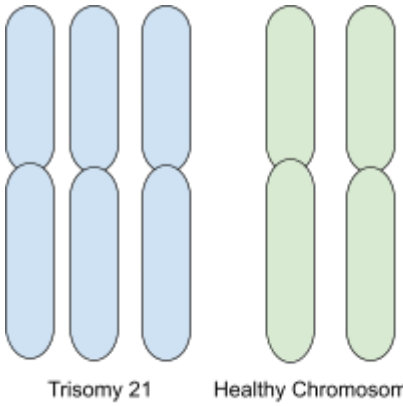
Down Syndrome

Down syndrome is a chromosomal disorder occurring in about 1 in every 700 babies characterized by an extra chromosome in chromosome 21, also called trisomy 21. Most Down syndrome fetuses miscarry during pregnancy. It affects the musculoskeletal, cardiovascular, and neurological systems and it shows most commonly through Lower IQ, intellectual disability, specific facial features, and trouble speaking [56].

Causes

95% of people with Down have a trisomy 21-where one has three copies of chromosome 21. This is caused by errors in meiosis I and meiosis II in both the maternal and paternal gametes [57].

About 3% of people with Down syndrome have Translocation Down Syndrome, in which an extra copy of chromosome 21 is attached to another chromosome in a translocation mutation [57].



About 2% of people with Down syndrome have Mosaic Down Syndrome, in which only some of their cells have a trisomy in chromosome 21, but the other cells don't. This leads to fewer features of the condition being apparent in the patients, and the ones that are are less severe [57].

Very rarely patients with Down syndrome can have a partial trisomy, where only part of a third chromosome is copied [57].

Higher maternal age is found to have higher risk for Down Syndrome, as errors in meiosis I and meiosis II are more likely to occur. Other environmental factors that can heighten risk for down syndrome are usage of tobacco, folic acid supplementation, or oral birth control [58].

There are two theories as to why the trisomy causes Down syndrome. The first is that the third chromosome causes an overexpression of the genes, especially the AAP gene, which encodes the amyloid precursor protein [59]. This protein is found in many of the tissues and organs of the body, including the central nervous system, and is known to play a role in the development of Alzheimer's disease [60].

The second theory is simply that the extra chromosome causes issues with transcription regulation and homeostasis[57]).

Clinical Presentation

There are a few physical features associated with Down Syndrome. Patients tend to have a short stature, with short fingers. They often have epicanthic folds, flat nasal bridge and occiput, small mouth and ears, and up-slanting palpebral fissures[58].

Patients with Down syndrome are more likely to develop certain health conditions. Congenital heart defects are the leading cause of death in younger Down syndrome patients. The heart defects they can have include atrioventricular septal defects (ASVD), where there are holes between the two sides of the heart, and the valves controlling the flow of blood between the left and right chambers may not be formed correctly [61]; ventricular septal defects (VSD), where there is a hole in the heart, which will cause blood with oxygen to be pumped back to the lungs and be mixed with blood that has not been oxidized [62]; and other rarer defects such as secundum atrial defect (occurring 10% of patients), tetralogy of Fallot (occuring in 6% of patients), and isolated PDA (occuring in 4% of patients). Many patients have multiple heart defects [58].

Hypothyroidism, a thyroid dysfunction in which the thyroid gland doesn't produce enough of the hormone, affecting heart rate, metabolism, and body temperature, occurs in >50% of patients [58].

Patients with Down syndrome often develop autoimmune diseases, making them more prone to infections especially as they go through the various treatments for their other health issues, and they often develop recurrent infections [58].

Obstructive sleep apnea, where one's breathing becomes shallow or stops altogether during their sleep, is prevalent in most Down syndrome patients and is heavily treated throughout their lives [58].

About 8% of patients develop epilepsy, whether in early infancy or later on. Epilepsy developing in early infancy usually leads to more severe epilepsy. Late-onset epilepsy is associated with the development of Alzheimer's disease [58].

Other health problems Down syndrome patients face include hearing and vision problems as well as hematological disorders including leukemia [58].

A prominent characteristic of Down Syndrome is the neurological development, as most patients have mild to moderate intellectual disabilities. They often express difficulty in language and speaking, verbal working memory (remembering information given verbally), and episodic memory (remembering specific times and places). Autism spectrum disorder is common among patients. Down syndrome patients also have an increased risk of anxiety and depression disorders [58].

Early-onset Alzheimer's disease (AD) is very common in Down syndrome patients, as it is related to APP overproduction. Around 70% of adult patients die of dementia from AD [60].

Diagnosis

The diagnosis of Down syndrome is made using prenatal screening and testing such as ultrasounds, FISH, QF-PCR (which uses DNA polymorphic markers to detect abnormalities), and Paralogue sequence quantification (PSQ), which uses paralogue genes to detect abnormal amounts of chromosomes [57].

Treatment

To first confirm the diagnosis of Down syndrome and to be sent to a geneticist, karyotyping is used. Multiple treatments are then suggested to address the various health issues associated with the disorder [58].

Hearing and vision are assessed for cataracts, tests for thyroid function are done yearly, patients are sent for a cardiac referral, and receive physical therapy. Sleep apnea is treated with various devices to monitor breathing and keep the patient breathing during sleep [58].

Turner Syndrome

Turner Syndrome (TS), also known as congenital ovarian hypoplasia syndrome, is a common sex chromosome abnormality that occurs when one of the X chromosomes isn't working properly, being either missing or partially missing. The disorder only affects females, occuring in 1 in 2000 to 1 in 2500 female births. It leads to several medical and developmental problems such as short stature and the ovaries not being properly developed [63].

Causes

Patients with TS have a partially or completely absent X chromosome. 50% of patients have monosomy X, where the X chromosome is completely missing, with the karyotype 45, X. This is typically caused by nondisjunction (errors in chromosome segregation) in the gametes of the parent [64].

The other 50% can have 3 other kinds of chromosomal mutations: isochromosome Xq, in which two copies of the long arm of the chromosome are connected head to head, ring chromosome, in which parts of the ends of the arms are missing and have fused together at the ends to form a ring, and Xp or Xq deletion, a deletion of part of the arms of the chromosome [64].

Typically, one of the X chromosomes is inactivated, in a phenomenon called lyonization. However, usually some of the genes on the chromosome escape lyonization and are still expressed. When the X chromosome becomes inactive in TS, these genes are also deactivated and no longer function, causing the disorder [64].

A gene candidate for the cause of Turner Syndrome is short stature homeobox (SHOX), a gene which is connected to short stature and the skeletal system and is located on the X chromosome. The deactivation of this gene through the X chromosomal abnormalities could contribute to many of the symptoms of TS [64].

Clinical Presentation

A main physical trait in patients with Turner Syndrome is short stature, caused by growth delays. Patients also present with a webbed neck [65].

TS causes there to be a lack of estrogen in the body, leading to delayed puberty and premature ovarian failure, where the ovaries are not fully developed and they lose function. The patients also experience primary amenorrhea, or not having a period, because of this [65].

Cardiac abnormalities occur in 41% of Turner patients and they must be monitored for proper heart function constantly. These abnormalities include having a smaller aortic diameter, heart valve disease, aortic bicuspid deformity, when the valve only has two leaflets instead of the normal three, and aortic dissection aneurysm, when a tear occurs in the inner layer of a large blood vessel connected to the heart [66].

TS patients generally have autoimmune disease and develop many issues because of it, most commonly thyroiditis, the inflammation of the thyroid gland. Patients can also develop colitis, inflammation of the colon, celiac's disease, when eating gluten causes infections that damage the small intestine, psoriasis, scaly rashes, and type 1 diabetes. They commonly also have low glucose tolerance [66].

Patients with Turner's have skeletal abnormalities related to the cause of short stature, and they are at high risk for fractures, scoliosis, and osteoporosis. TS patients tend to fracture their bones fairly commonly [66].

Patients with TS have normal intelligence but learning disabilities, usually being placed in special needs programs in schools [65].

Renal abnormalities, such as collecting system malformations, when the kidney's collecting system is abnormal and can't collect the sodium and water that it usually does, positional/horseshoe kidney, when the kidney is positioned or rotated abnormally, and mal-rotated kidneys, also an issue with position or rotation of the kidney, are common among TS patients [65].

Other symptoms associated with Turner Syndrome are hearing loss and low visual-spatial skills [65].

Diagnosis

Turner syndrome is suspected prenatally when ultrasounds show fetal hydrops, fluid building up in a baby's tissues and organs, cystic hygroma, a sac-like birth defect on a baby's head or neck, or cardiac defects [64].

A karyotype is used to officially diagnose to determine whether the X chromosome is present or not, but can make mistakes in cases of mosaicism, in which case FISH is used [64].

Appearance of clinical presentation can also be used as a sign to diagnose if it was not caught prenatally [64].

Treatment

Growth hormone and estrogen therapies are used to help with growth and puberty development, yielding positive results in TS patients [66].

Patients receive regular checkups and observation for other symptoms which then are specifically treated, such as EKGs and surgery to monitor and correct cardiac abnormalities [64].

Gene therapy treatment with stem cells are currently being experimented with and considered for Turner Syndrome, but have not yet been fully developed.

Cri-du-Chat syndrome

Cri-du-Chat Syndrome (CdCS), is a rare chromosomal disorder caused by a partial deletion of chromosome 5 [67], more specifically the p arm of chromosome 5 [68]. Occurring in 1 in 20,000 to 1 in 50,000 newborns, it leads to symptoms such as intellectual disability and delayed development [67]. Its name, Cri-du-Chat, comes from the high-pitched, cat-sounding cry in newborns that characterizes the disease [68].

Causes

Cri-du-Chat syndrome is caused by a deletion of the p arm of chromosome 5, and the deletion of specific regions and genes have been linked to the main symptoms of the disorder. The main clinical findings of CdCS, especially the intellectual disabilities, are caused by a deletion of the area 5p15.2 and the typical cat cry is linked to the deletion of the 5p15.3 area [69].

The deletion of the specific genes Semaphorin F (*SEMAF*) and **δ**-catenin (*CTNND2*), found in 5p15.31, have been linked to the intellectual disabilities and mental delays that occur in CdCS [70], while the deletion of telomerase reverse transcriptase (*hTERT*) gene, located in 5p15.33, is suspected to contribute to the phenotypic manifestations of the disorder.

The severity and manifestation of the disorder depends on the size and location of the deletion, as well as whether it is interstitial or terminal [69]. An interstitial deletion is when the chromosome has broken in two places and the part that is broken off is deleted while the two broken ends fuse together, leaving a part out [71]. A terminal deletion is simply a deletion that occurs towards the end of the chromosome.

Clinical Presentation

At birth, the common phenotypic presentation is low weight, microcephaly(when the head is smaller than usual), eyes that are far apart, large nasal bridge, down-turned mouth, low ears, undersized jaw (micrognathia), and the identifying cat cry [70], among others.

Common neonatal issues are asphyxia, when the body is deprived of oxygen, leading to cyanotic crises where the parts of the body not receiving enough oxygen turn blue; difficulty with suction; and hypotonia, or low muscle tone [70].

In the early years of life, infections in the respiratory and intestinal symptoms are common, although the cause is still unclear [70].

With age, issues such as hypertonia, having too much muscle tone so that limbs are stiff and hard to move; microcephaly (large head); dental malocclusions, when the teeth are not aligned properly; sensitivity to sound; cardiac disorders, especially congenital heart defects; cutaneous hemangioma, when blood vessels build up in the skin or organs; and issues with the kidneys, among others [69]. Deafness is also a recurring problem among patients.

Intellectual disabilities are another characteristic of the disease, with symptoms such as hyperactivity, repetitive movements, trouble communicating, and obsessive attachment to objects [69].

Diagnosis

Cri-du-Chat syndrome is able to be diagnosed in the neonatal period by using amniocentesis [69], genetically testing a small group of cells taken from the amniotic fluid in the womb [72].

After birth, diagnoses can be made based on the patient showing the clinical symptoms of CdCS, after which karyotyping, looking at a lab image of the chromosomes for shape or numerical abnormalities, is used to confirm the diagnosis [69].

FISH (fluorescence in-situ hybridization), a way to map people's cells and DNA, is also a method used to confirm and test the genome for CdCS, more often used in further testing than just for diagnosis confirmation [73].

Treatment

There is no specific treatment for CdCS due to how rare it is, but rehabilitation and early intervention are the typical procedures, usually involving physical and speech therapies as well as psychomotricity (though less popular), a type of psychotherapy using body meditation to improve motor function [69]

Treatments then become specific to the issue associated with the disorder, with hearing aids and exams for deafness, surgeries for specific issues such as heart disease, special diets, and a healthy lifestyle [69].

There are no current gene therapies specific to Cri-du-Chat Syndrome yet, although there are most certainly some being studied.

Klinefelter syndrome

Klinefelter syndrome (KS), otherwise known as XXY, is a chromosomal disorder where a male individual has 2 or more sex chromosomes [74]. The disorder occurs randomly and only in males [75], causing a variety of symptoms, the most prominent of which is infertility [76].

Causes

Klinefelter syndrome is the most common form of aneuploidy (when there is an abnormal number of chromosomes), and occurs in 1 in 500 to 1000 males [74], and is characterized by a male individual born with two or more X chromosomes. About 80-90% of patients have the classic form of KS, where the genotype is XXY [77].

The remaining 10-20% of patients have other genotypes, including when there are more than three chromosomes (XXXY or XXYY), a structural abnormality in an X chromosome, or a mosaicism, in which only some of the cells have extra X chromosomes [77]. The higher the number of X chromosomes, the more severe the disease.

The extra X chromosome causes shortage of testosterone, which is the hormone that stimulates the growth of male's physical and sexual characteristics, leading to the development of the symptoms associated with Klinefelter's [78].

Clinical Presentation

There is a very broad range of phenotypes of Klinefelter Syndrome due to its commonality and variation in genotype. Patients tend to have the physical appearance of tall stature, small testes, gynecomastia (the growth of breast tissue),less body hair, and broad hips [77].

KS also causes less visible signs like imbalanced hormones such as androgen deficiencies, low testosterone, and high gonadotropins, all hormones associated with sex and reproduction [77]. It also causes issues with fertility, most notably low sperm count.

Diagnosis

Many cases of Klinefelter syndrome go undiagnosed due to the variations in the phenotype. Testing is conducted prenatally (before birth) when genetic abnormalities are noticed, at birth when genetic abnormalities or hypotonia (low muscle tone) are apparent, in teenagers once symptoms are presented, and in adults when infertility is diagnosed [74].

The main types of testing used to diagnose KS are karyotypes, a picture of all the chromosomes in a cell, or chromosomal microarrays, a test used to determine whether there are an abnormal number of chromosomes [74]. Testing also includes a workup testing for hypogonadism, which is when the sex organs do not produce enough gametes, or sex cells [74].

Treatment

Treatments for KS depend on the severity of the disorder. Speech-language delays are treated with speech therapy and motor delays are treated with occupational therapy. Testosterone therapy is used to manage phenotypes and minimize symptoms associated with hormone issues [74]. Breast reduction surgery is also used to reduce breast tissue [75].

There are no prominent gene therapy treatments for Klinefelter Syndrome.

Conclusion

In this paper, I have reviewed the different genetic disorders: single-gene and chromosomal.

Although single-gene mutations and chromosomal disorders are both types of genetic disorders, they have fairly different characteristics. Single-gene mutations only affect a single gene, causing very specific issues. These single-gene mutations can fall under multiple categories; germline or somatic, point or frameshift, and Muller's Morphs. On the other hand, chromosomal disorders occur when an individual has an abnormal number of chromosomes, and usually have a wider variety of symptoms than single-gene genetic disorders. Chromosomal disorders are further sorted into two categories: structural abnormalities and aneuploidies.

Although they differ, researchers treating both single-gene and chromosomal disorders are looking to gene therapy as a new form of treatment. With promising results across the board, gene therapy looks to replace faulty genes or chromosomes with lab-made healthy versions to help treat these disorders, and has been successful in treating a variety of genetic disorders, although most experiments are still in testing stages.

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