Genotypic and Phenotypic Abnormalities Linking 22q11.2 Deletion Syndrome and Psychiatric Disorders

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Abstract

22q11.2 deletion syndrome (22q11.2DS), otherwise known as DiGeorge syndrome, is a disease that causes many physical deformities as well as neurological abnormalities. Of all the diseases linked to microdeletions, 22q11.2DS has the highest prevalence due to its large unstable low copy number repeat blocks (LCR). Previous studies have shown associations between the 22q11.2DS and psychiatric illnesses, particularly schizophrenia, with potential connections to significant changes in white and grey matter in the brain. It is difficult to diagnose this disease due to the various symptomatologies; currently, the only way to confirm this disease is through genetic testing. In this review, the genotypic and phenotypic differences in addition to the clinical symptomatology and diagnostic tools of 22q11.2DS and their links to psychiatric illnesses are examined.

Introduction

Chromosome 22q11.2 deletion syndrome, also known as DiGeorge syndrome, is most often a result of a microdeletion of chromosome 22. It was first described in 1965 by Dr. Angelo DiGeorge, who studied a group of infants that exhibited conotruncal cardiac anomalies, hypoplastic thymus, and hypocalcemia (preceding parathyroid hypoplasia), otherwise known as the clinical triad. Molecularly, four blocks of low copy number repeats (LCRs) found in this DNA region of chromosome 22 undergo unequal meiotic recombination due to mispairing of the DNA repeats, leading to the chromosomal deletions (1). The LCRs on chromosome 22 contain more DNA than other LCRs and are highly unstable, leading to an increased number of patients with 22q11.2 deletion syndrome in comparison to other chromosomal deletions. This can occur by autosomal inheritance of mutated DNA from parents with low penetrance (2).

Some clinical characteristics include autoimmune disease, hearing loss, learning difficulty, abnormal facial morphology, congenital heart disease, and psychiatric illness (3). Patients with chromosome 22q11.2 deletion syndrome are at a 25-fold higher risk for developing schizophrenia or a schizoaffective disorder (4). A majority of the clinical features are indistinguishable from schizophrenia or related schizoaffective disorders and can be genetically verified using molecular testing by fluorescence in situ hybridization (FISH) and a standard fluorescently-labeled DNA probe from the deleted area (4). It has been found that patients with schizophrenia and 22q11.2DS have a lower IQ and may differ in auxiliary clinical features such as myofascial dysmorphic features, palatal defects, and velocardiofacial defects (5).

In conjunction with major schizophrenic symptoms, such as delusions, hallucinations, movement difficulty, reduced speaking, and reduced feelings (20), the median age of disease onset in genetically predisposed children ranges from 12 to 26 years, and those with parents who did not transmit the deletion commonly exhibit less severe symptoms (5). Unique to the 22q11.2 deletion syndrome, some patients show signs of neurobehavioral characteristics different to the standard schizophrenic symptomatology, such as increased levels of excitement and impulsive reactions, which are linked to short temper or emotional outbursts (5).

The exact mechanism leading to these characteristics is currently unknown, and there are many theories as to why it may occur. Researchers speculate that the deletion region could be linked to a unique locus sensitive to psychiatric illnesses, or that it could be a step in allowing more mutations to occur which would lead to psychiatric disorders (4, 6).

There are various names that apply to the phenotypic features of the syndrome, such as cardiofacial syndrome, velocardiofacial, or conotruncal anomaly face syndrome, in addition to DiGeorge syndrome or 22q11.2 deletion syndrome. The multitude of names often leads to diagnostic confusion when treating these patients. Other patients may also present with clinical characteristics associated with this syndrome, but not in conjunction with chromosomal deletion, generating further uncertainty. This leads to confusion between other disorders such as such as coloboma-heart-atresia-retarded-genital-ear (CHARGE) syndrome, Smith-Lemli-Optiz syndrome, Kabuki syndrome, and Goldenhar syndrome. As such, it is standard to only diagnose patients presenting with the chromosomal 22q11.2DS and the clinical presentations associated with the syndrome with DiGeorge syndrome, and not consider other cases without 22q11.2 chromosome deletion as 22q11.2DS (1).

Due to the issues pertaining to the diagnosis of this syndrome as well as the prevalence of syndrome, it is important to review the potential link that the genetic background can contribute to this phenomenon.

Methods

Literature on chromosomal abnormalities as well as psychiatric symptomatology related to the 22q11.2DS were reviewed from a variety of sources, such as PubMed and Google Scholar. Articles were found using the search strategies of: “22q11.2 deletion syndrome” or “DiGeorge Syndrome” in addition to “schizophrenia,” “brain,” and “psychiatric disorders.” Articles referencing psychiatric illness alongside the deletion syndrome or DiGeorge syndrome were examined, and those

including other significant psychiatric illnesses were included. Importance was weighted based on the mechanism proposed by the articles and the link between the syndrome and the disorder. Case studies connecting psychiatric disorders and the chromosomal deletion were included.

Discussion

22q11.2 deletion syndrome

22q11.2 deletion syndrome (22q11.2DS) is one of the most common microdeletion syndromes, also known as DiGeorge syndrome. It was originally used to diagnose children who presented with the symptomatology of immunodeficiency (~77%), hypoparathyroidism (hypocalcemia 49%), and congenital heart disease (~77%) (1). These children would often also present with thymic aplasia, or the lack of a fully functional thymus. Other symptoms were later discovered to be part of the syndrome and usually present alongside the clinical triad listed above; these symptoms include but are not limited to congenital anomalies (cleft palate 11%, polyhydramnios 16%, polydactyly 6%), autoimmune diseases (~10%), variable cognitive delays (nonverbal learning disability 65%, cognitive disability 30%, borderline cognitive disability 32%, low average 20%), behavioral presentations (anxiety 17–29%, phobia 23–61%, ADHD 3–46%, autism 14–45%), and later-onset psychiatric disorders (schizophrenia 10-30%) (1, 8). However, these symptoms vary case by case and are part of the reason for diagnostic difficulty.

Deletions of LCR blocks

22q11.2DS consists of a chromosomal deletion in a region surrounded by four distinct blocks of LCRs (LCR A-D), each composed of multiple repeats with LCR A being the most proximal (1). It is known that these LCR blocks are larger and more complex than any other LCR blocks associated with human chromosomal deletion syndromes, and the commonality of their deletion underlies the theory that these blocks are inherently unstable. The LCRs are >96% identical, leading to a higher chance of meiotic error (9). It has been found that LCR A and LCR D are the largest segmental repeats and surround a 3-Mb 22q11.2 region hemizygous in most patients (8). This deletion is seen in 70–80% of patients (1) and occurs due to asynchronous replication at the 22q11.2 locus, leading to unequal meiotic recombination (10). This mechanism also results in proximal and distal nested deletions. Patients having proximal (centromeric) nested deletions, including LCR22A-LCR22B and LCR22A-LCR22C, show similar features to the 5–10% of patients that have the LCR22A-LCR22D deletion. The distal nested deletions include LCR22B-LCR22D and LCR22C-LCR22D deletions, which are associated with synchronous yet less penetrant presentations in comparison to individuals with LCR22A-LCR22D deletions. These deletions are more frequently inherited and show symptomatology such as palatal defects and developmental differences, along with a few others (8).

TBX1, *COMT*, and *PRODH* genes

Deletions of certain genes in 22q11.2DS have begun to be identified with various symptoms associated with the microdeletion syndrome. It is thought that T-box1 (*TBX1*) gene deletion leads to cardiac and craniofacial features, while the catechol-O-methyl-transferase (*COMT*) and proline dehydrogenase (oxidase) 1 (*PRODH*) gene deletions lead to psychiatric presentations (1, 18). *COMT* gene encodes the enzyme involved in the breakdown of dopamine mainly in the prefrontal cortex. Hemizygosity leads to low activity, allowing dopamine to aggregate and potentially increase the risk for psychiatric illnesses. In the prefrontal cortex, dopamine plays a role in prepulse and latent inhibition (21), which can affect an individual's ability to focus and avoid distractions (7). *PRODH* gene encodes the mitochondrial enzyme proline dehydrogenase, a catalyst used during the conversion of proline to glutamate. The low conversion levels observed due to *PRODH* deletion result in increased plasma proline levels, which affects N-methyl-D-Aspartate (NMDA) receptor signaling and may lead to damaged brain tissue.

Type I hyperprolinemia (HPI) is an autosomal recessive disorder correlated with seizures, intellectual disability, and psychiatric symptoms, all of which are also associated with 22q11.2DS. HPI is caused by an inherited deficiency of *PRODH*, of which the polymorphic *PRODH* gene has had several SNPs studied for an association with schizophrenia, supporting the observations made by de Kong et al. in their study of the *PRODH* rs450046 polymorphism (18).

Connection to psychiatric illnesses

Patients with the 22q11.2DS have presented with higher rates of psychiatric illnesses. While it is uncommon for young children to be diagnosed, young adults and older individuals with this chromosomal deletion have shown increasing symptomology for depression and psychiatric illnesses. Patients diagnosed as psychotic and non-psychotic with velocardiofacial syndrome (VCFS) both show a negative correlation with respect to cognitive testing (i.e., the higher the patient's age, the lower the patient's cognitive scores) (12). While there are associations between mood and anxiety disorders with the microdeletion syndrome, there is a significant increase in the comorbidity between schizophrenia or schizoaffective disorders and 22q11.2DS (13).

Studies done on patients with the 22q11.2DS reveal a higher prevalence of midline brain abnormalities, such as the presence of a cava septum pellucidum et vergae, which is also a common feature of other genetic and neurodevelopmental disorders (14). Cava septum pellucidum, also known as the cave of septum pellucidum, is a cavity in the septum pellucidum present in fetuses. It usually fuses during infancy. If this cavity is not closed during infancy, cognitive and developmental problems can occur during childhood (19). In addition, it has been found that affected patients with the microdeletion can have significant increases or decreases of their grey matter up to 27%, as well as white matter decreases up to 33% (16). The reductions in the grey matter of the cerebellum, medial temporal-occipital lobe, and posterior cingulate cortex suggest that the loss of grey matter plays an important role in the pathways of neural processing in comparison to the frontal cortex (16). White matter anomalies predominate in regions specific to connectivity, mostly projection fibers and tracts (17). Behavioral features such as schizotypal traits may also result from the anatomical differences in brain regions such as the hippocampus,

cerebral ventricles, and temporal lobes (15). Previous studies have shown abnormal brain development in autistic patients exhibiting social behavior problems (22, 23), and an increase of the grey matter has been thought to have a positive correlation with schizophrenia in addition to social behavioral issues (15).

Diagnosis, treatment, and management

Most of the symptoms associated with chromosome 22 microdeletions are variable, and the differing severity of symptoms can lead physicians to misdiagnose 22q11.2DS under different names, including VCFS syndrome (Shprintzen-Goldberg Syndrome), conotruncal anomaly face syndrome, and Optiz G/BBB syndrome, and Cayler cardiofacial syndrome (24). Thus, molecular methods like fluorescent in situ hybridization (FISH) have been used to diagnose the disease in cytogenetics laboratories since 1992. FISH specifically targets chromosome 22 and identifies the absence of commonly deleted regions. If a region is missing, DiGeorge syndrome is confirmed. Even though FISH is a common method used to identify the syndrome, there are two potential complications that can arise. The results can take up to 3–14 days to receive, leaving the patient's family anxious. Also, FISH lacks the precision necessary to detect atypical deletions. Two emerging methods, PCR-based technology and SNP arrays, provide quicker results. However, they still are similar to FISH in the sense that they can only detect typical deletions. Also, these methods are expensive compared to FISH. Most patients are diagnosed in utero using prenatal ultrasound. If cardiac anomalies are found on the ultrasound, chromosome 22q11.2 deletion tests are ordered and performed (1).

Treatment of 22q11.2DS includes medications to treat associated symptoms, genetic counseling, and patient-centered therapy. While there is no cure for the syndrome, symptoms can be managed if carefully monitored and addressed as needed. If the patient is functioning normally, regular follow-up is needed to make sure no new health concerns arise. Physicians only consider prescribing medication if the patient has severe immunodeficiency stopping the body from preventing secondary infections. Since many drugs are still in the developmental and testing phase, adverse side effects can occur in patients with pre-existing autoimmune conditions. These side effects are currently not fully understood because there is insufficient research determining the harm of these drugs on immunocompromised patients. Because of the uncertainties surrounding the medications, physicians utilize genetic counseling in order to detect possible genetic abnormalities in utero, as well as inform parents of the risk of having additional affected children. Siblings are therefore also tested for the possibility of being carriers. Various forms of therapy dependent on the patient's direct needs are also used to help people with DiGeorge syndrome smoothly navigate their everyday lives (1, 25) These findings suggest areas for future research to optimize patient care and advance diagnostic tools used to detect the syndrome early (1).

Conclusion

22q11.2DS is a debilitating disease resulting in variable clinical features, leading to diagnostic confusion with other diseases. It affects an estimated 1 in 4,000 people, but researchers suspect it is underdiagnosed due to the variable associated symptoms (24). It is also the most common deletion syndrome due to the unstable large LCR blocks with the deletion of the *TBX1*, *PRODH*, and *COMT* genes, and has a possible correlation to psychiatric illnesses. However, there is currently no existing data supporting the exact links between the genetic abnormalities and the psychiatric symptomatology. While there are many characteristics to this disease, the defining features influencing the brain are the variable changes in white and grey matter. Connections between the abnormal anatomy of the brain and schizotypal presentations are still not fully understood, and future studies are needed to further extend our knowledge on the exact mechanisms behind the progression of psychiatric disorders and brain anomalies in patients with 22q11.2DS.

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