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REVIEW

22q11 deletion syndrome: current perspective

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Abstract: Chromosome 22q11 is characterized by the presence of chromosome-specific low-copy repeats or segmental duplications. This region of the chromosome is very unstable and susceptible to mutations. The misalignment of low-copy repeats during nonallelic homologous recombination leads to the deletion of the 22q11.2 region, which results in 22q11 deletion syndrome (22q11DS). The 22q11.2 deletion is associated with a wide variety of phenotypes. The term 22q11DS is an umbrella term that is used to encompass all 22q11.2 deletion-associated phenotypes. The haploinsufficiency of genes located at 22q11.2 affects the early morphogenesis of the pharyngeal arches, heart, skeleton, and brain. *TBX1* is the most important gene for 22q11DS. This syndrome can ultimately affect many organs or systems; therefore, it has a very wide phenotypic spectrum. An increasing amount of information is available related to the pathogenesis, clinical phenotypes, and management of this syndrome in recent years. This review summarizes the current clinical and genetic status related to 22q11DS.

Keywords: DiGeorge syndrome, velocardiofacial syndrome, *TBX1*

Introduction

Congenital absence of a thymus and parathyroid gland was reported by Dr Angelo M DiGeorge in 1965. Later, cardiac anomalies were added to the phenotype, and the syndrome was named DiGeorge syndrome (DGS; Mendelian Inheritance in Man [MIM] number 188400).[1] Most patients with DGS have monosomic deletions on the long arm of chromosome 22. This deletion might present with a variety of phenotypes, including DGS and velocardiofacial syndrome. 22q11 deletion syndrome (22q11DS) is an umbrella term that describes various clinical phenotypes.[2,3] 22q11DS is the most common microdeletion syndrome in humans, although it is likely to be more prevalent than reported and underrecognized because of its inherent clinical variability and heterogeneity. 22q11DS can affect many organs and systems.[4,5] An increasing amount of information has been reported regarding the pathogenesis, clinical phenotypes, and management of this syndrome in recent years. This review summarizes the current clinical and genetic status of 22q11DS.

Nomenclature

A long-arm deletion of chromosome 22 might present with a variety of phenotypes, including DGS, velocardiofacial syndrome (MIM number 192430), conotruncal anomaly face syndrome (MIM number 217095) (or Takao syndrome), and isolated outflow tract (OFT) defects of the heart.[2] CATCH22 (Cardiac Abnormality/abnormal

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facies, T-cell deficit due to thymic hypoplasia, Cleft palate, Hypocalcemia due to hypoparathyroidism resulting from 22q11 deletion) was proposed as a collective acronym for these differing presentations of a common genetic etiology.[2,3] Many clinicians believe that 22q11.2 deletion is a single syndrome rather than several distinct syndromes.[2] Therefore, the term 22q11DS is an umbrella term used to describe all deletion-associated phenotypes. The term 22q11DS is used in this review to cover all of the phenotypic variations described before.

Pathogenesis

Human chromosome 22 is acrocentric, and is the second-smallest human chromosome. It spans ~51 million DNA building blocks (base pairs) and represents 1.6% of the human genome in cells. Recurrent acquired and somatic rearrangements of chromosome 22 are associated with multiple diseases and developmental abnormalities. Most of these recurrent rearrangements occur within 22q11, suggesting genomic instability of this region of chromosome 22. Deletions of 22q are associated with 22q11DS.[6] The deletion occurs near the middle of the chromosome at a location designated q11.2, and results in a 1.5–3 Mb microdeletion on the long arm of chromosome 22. Although different-sized lesions have been identified, ~90% of patients have a common ~3 Mb deletion, which is defined the typically deleted region (TDR), whereas most other (~7%) patients have a smaller ~1.5 Mb deletion. A small percentage of affected individuals have shorter deletions in the same region.[2]

Mechanism of the deletion at 22q11.2

Complex low-copy repeats (LCRs, also termed segmental duplications), which are composed of multiple repeat elements, provide the structural basis for a diverse range of genomic variations and combinations of variations. These regions of chromosomes are susceptible to translocations, inversions, deletions, and duplications. LCRs are region-specific DNA blocks usually sized >5–10 kb that share >95%–97% similarity with each other. Nonallelic homologous recombination (NAHR) is a form of homologous recombination that occurs between two lengths of DNA that share high sequence similarity but are not alleles. NAHR is one of the major genomic rearrangements, and most recurrent genomic rearrangements are caused by NAHR between two LCRs. Due to their high sequence identity, nonallelic copies of LCRs, instead of copies at the usual allelic positions, can sometimes be aligned during meiosis or mitosis. This so-called misalignment and the subsequent crossover between them can result in genomic rearrangements in progeny cells. Thus, the nonallelic copies act as mediators of homologous recombination and are responsible for the observed breakpoint clustering. NAHR between LCRs causes duplication and/or deletions. The misalignment of LCRs during NAHR is an important mechanism underlying chromosomal microdeletion disorders, including 22q11DS.[7–10]

The proximal region of 22q11.2 is enriched with LCRs. This region contains eight chromosome 22-specific LCRs (LCR22s; LCR22-A to LCR22-H). There is a relationship between four LCR22s (LCR22-A, -B, -C, and -D) and 22q11DS (Figure 1). These proximal LCRs are larger than the distal ones, and have a complex modular structure. The typical 3 Mb deletion occurs between the most proximal (LCR22-A) and most distal (LCR22-D) units, whereas a 1.5 Mb deletion could be an A–B or an A–C deletion.[2,7]

The LCR22s comprise 11% of the 22q11.2 region and contain both genes and unprocessed pseudogene copies. The *BCR* pseudogene is present once in LCR22-A, and twice in LCR22-D. The sequences that correspond to the BCR-like module within the LCRs were suggested as a potential rearrangement hotspot.[11,12]

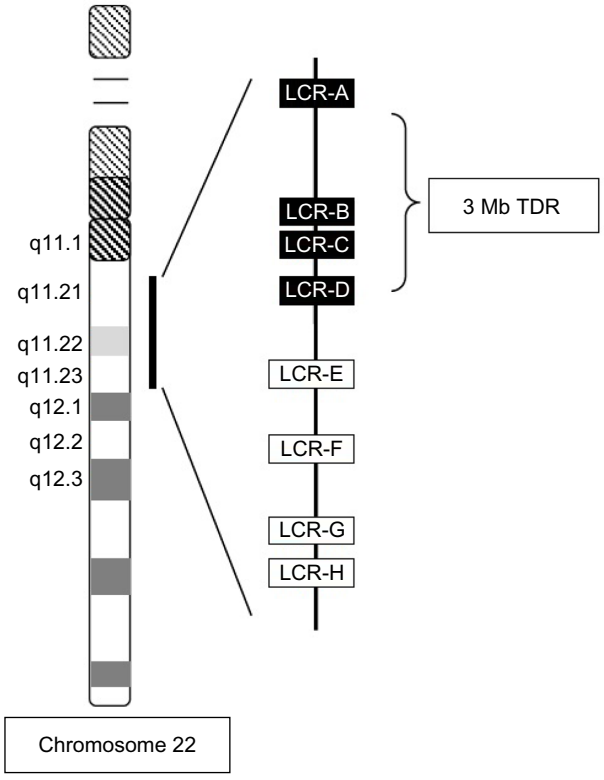

Figure 1 Schematic view of chromosome 22 indicating the position of the low-copy repeats in 22q11.2.
Abbreviations: LCR, low-copy repeat; TDR, typically deleted region.

It was demonstrated that deletions in individuals with 22q11DS had more frequently maternal origin than paternal origins (56% versus 44%). But maternal age does not act as an etiologic factor for the finding of enhanced maternal origin of the deletion. Also, there is no association between the paternal age and the frequency of the deletion.[13]

Results of 22q11.2 deletion and its contribution to clinical phenotypes

The diminished gene expression on 22q11.2 is responsible for the clinical findings associated with 22q11DS; however, little is known about how such changes lead to the phenotypes of 22q11DS. The 3 Mb chromosomal region contains >35 genes, many of which have not been well characterized (Figure 2). The diminished dose of these genes, or their haploinsufficiency, likely compromises early morphogenesis in the pharyngeal arches, heart, skeleton, and brain. However, there is no correlation between the size or type of deletion and the resulting phenotype.[2,7,8]

Numerous candidate genes have been linked with the 22q11DS phenotype. In 1999, murine models identified *TBX1* as a candidate gene for this syndrome. *TBX1*, which encodes a T-box-containing transcription factor that belongs to a large family of transcription factors, has distinct roles in a wide range of embryonic differentiation or response pathways. *TBX1* is the most important gene for 22q11DS.[14]

The pharyngeal apparatus is an embryonic structure that becomes remodeled to form the face, neck, and cardiac OFT. The transcription factors expressed in pharyngeal mesoderm progenitors form a regulatory network that coordinates normal heart and craniofacial development. *TBX1* is expressed in the endoderm and mesoderm of pharyngeal arches, and the ectoderm of the distal pharyngeal apparatus. Animal models have shown that the haploinsufficiency of *TBX1* causes abnormal growth and remodeling in the pharyngeal apparatus and related structures. This information might explain many of the clinical findings of the syndrome, including facial dysmorphia, palatal defects, hypoplasia of the parathyroid glands and thymus, and dental, feeding, and swallowing problems.[14,15]

New data are available in the literature about molecular mechanism of dental anomalies in 22q11DS. It was shown that *TBX1* regulates the proliferation of dental progenitor cells and craniofacial development through microRNA-96-5p.[16]

Neuroepithelium-derived cardiac neural crest cells (cNCCs) are needed for the proper septation of the OFT into the aorta and pulmonary trunk, as well as for the development of the cardiac valves. *TBX1* regulates the differentiation and migration of cNCCs. Cardiac progenitor cells from the second heart field (SHF) contribute to the rapid growth of the embryonic heart, giving rise to the right ventricle and OFT, the myocardium at the arterial pole of the heart, and the atrial myocardium at the venous pole. *TBX1* is required for both inflow tract and OFT morphogenesis because it regulates the segregation and deployment of progenitor cells in the posterior SHF. The primary heart field gives rise to the primitive linear tube, and is not dependent on *TBX1*. *TBX1* knockout animal models supported the importance of this gene in cardiac development. In summary, *TBX1* haploinsufficiency contributes to the conotruncal and cardiac OFT anomalies that are observed commonly in 22q11DS.[17–19]

WNT5A is an important gene for embryogenesis and is critically required for SHF deployment. Recent study showed that *TBX1* is likely to be promoting SHF development through activating *WNT5A* transcription, and disruption of WNT5A-mediated SHF deployment may contribute significantly to the pathogenesis of OFT malformations in 22q11DS.[20]

Various pathways downstream of *TBX1* and modifiers of *TBX1* activity seem to play an important role in the pathogenesis of 22q11DS. *TBX1* regulates the expression of several growth factors and transcription factors, including *FGF8,*

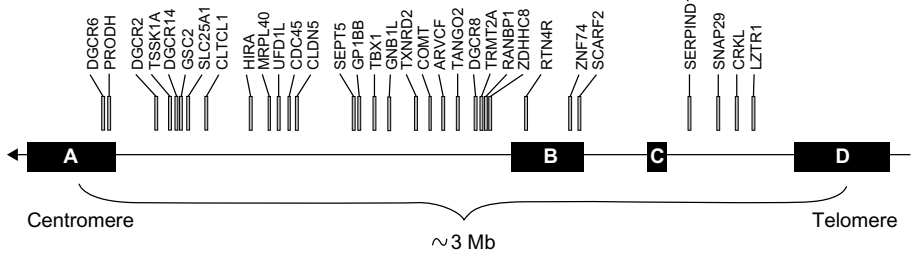

Figure 2 Genes in the typically deleted region of chromosome 22.
Note: The typical 3 Mb deletion occurs between the most proximal (LCR22-A) and most distal (LCR22-D) units.
Abbreviation: LCR22, chromosome 22-specific LCR.

FGF10, PITX2, CHD7, VEFR3, EYA1, WNT5A, BMPER, and Otog-MyoD.[18,19] Disruption of the expression of these genes by the loss of function of *TBX1* contributes to the pathogenesis of 22q11DS. *TBX1* expression is regulated negatively by retinoic acid, and positively by *SHH* via *FOXA2*.[17–19] The manipulation of these pathways might be a cornerstone of future advances in 22q11DS.

TBX1 is the best-known and most studied gene on 22q11.2. The current literature suggests that *TBX1* is largely responsible for the clinical findings in patients with 22q11DS, particularly the physical malformations. However, *TBX1* haploinsufficiency cannot explain all the clinic phenotypes of 22q11DS. Nevertheless, as mentioned above, the TDR that causes 22q11DS contains many genes.[7,19]

Recently, it was shown that haploid 22q11 gene insufficiency, including but not limited to *TBX1*, disrupts orofacial and cranial nerve development by modifying retinoic acid-modulated anterior–posterior hindbrain differentiation. These disruptions likely contribute to dysphagia in infants and young children with 22q11DS.[21]

Recent studies showed that reduced doses of 22q11 genes could modify the initial forebrain patterning, subsequent cortical neurogenesis and migration, and the mitochondrial support of activity-dependent synapse formation and elimination in the early postnatal brain. Nevertheless, it remains unclear which genes have a cause-and-effect relationship with these processes.[22]

Catechol-*O*-methyl transferase (COMT) degrades catecholamines such as dopamine and epinephrine; its gene is located on chromosome 22q11.2. The proline dehydrogenase (oxidase) 1 (*PRODH*) gene is also located in the same region, which encodes a mitochondrial enzyme that degrades proline. The deficiency of this enzyme results in hyperprolinemia. *COMT* and *PRODH* haploinsufficiency was implicated by some studies in the behavioral and psychiatric disturbances associated with 22q11DS.[23] *SMARCB1* is a tumor suppressor gene that is also located on 22q11.2 distal of the TDR for 22q11DS. The haploid deficiency of this gene might be associated with head-and-neck tumors such as rhabdoid tumors in some 22q11DS patients.[24] In addition, the haploinsufficiency of glycoprotein Ib β (*GP1BB*) might contribute to the mild thrombocytopenia observed in patients with 22q11DS. *GP1BB* is also located on chromosome 22q11.2. Bernard–Soulier syndrome, which is characterized by giant platelets, thrombocytopenia, and a prolonged bleeding time, was also described in patients with 22q11DS.[25] Several other genes in the 22q11 region, such as histone cell cycle regulator gene (*HIRA*), ubiquitin fusion degradation 1-like gene (*UFD1L*), and Crk-like protein gene (*CRKL*), have been implicated in the pathogenesis of 22q11DS.[7,19]

Epidemiology

22q11DS is the most common microdeletion syndrome in humans. However, population-based estimates of the incidence and prevalence of 22q11DS differ. Most studies reported a prevalence of one in every 4,000 newborns; however, reports range from one in 2,000 to one in 6,395.[3,26,27] Nevertheless, many researchers believe that this number is artificially low due to under-diagnosis. Consistent with this, familial occurrence is the most frequent cause of diagnosis in adults at some genetic centers.[28]

Male and female sexes are affected equally by 22q11DS. In addition, the deletion of 22q11.2 is more prevalent within certain ethnic groups. Specifically, 22q11DS occurs more frequently among Hispanics compared with Whites, African Americans, and Asians.[26]

Generally, >90% of DGS cases are de novo or novel deletions caused by a random occurrence during fetal development. An unaffected parent might then carry the deletion in his or her eggs or sperm, and the risk of recurrence is ~1%. However, it can also be inherited, and familial autosomal dominant recurrence is reported in ~8%–28% of patients in various series.[29] Some cases appear to have a vigorous diagnosis but no deletion; 35%–90% of patients with DGS and 80%–100% of velocardiofacial syndrome patients have the 22q deletion.[2,30]

Clinical presentation

22q11DS presents with a very wide phenotypic spectrum, including the following: facial dysmorphisms; congenital cardiac defects; velopharyngeal insufficiency with or without cleft palate; thymic hypoplasia; immune deficiency; parathyroid hypoplasia; developmental delay; learning disabilities; psychiatric disorders; renal, ocular, and skeletal malformations; hearing loss; and laryngeal abnormalities. The phenotypes associated with the syndrome might be recognized during the prenatal period, or in newborns, children, and even adults.[31–33] Clinical phenotypes of 22q11DS are summarized in Table 1.

Fetal phenotype

Congenital heart defects are the major prenatal sonographical feature of 22q11 deletions. Among these, conotruncal defects are the most common cardiac anomalies, although vascular abnormalities and hypoplastic left hearts were also reported.[34] Thymus abnormalities are also an important prenatal sonographic feature of this syndrome. Urinary tract defects,

Table 1 Clinical phenotypes of 22q11 deletion syndrome

Fetal phenotype
Cardiac anomalies; mostly conotruncal defects, rarely vascular abnormalities, and hypoplastic left heart
Thymus abnormalities
Others; urinary tract defects, neurological problems such as neural tube defects, cerebral anomalies, and polyhydramnios
Neonatal and childhood phenotype
Typical facial findings; a long face, malar flattening, hypertelorism, short palpebral fissures, a wide and prominent nasal root, a wide nasal bridge, a bulbous nasal tip, micrognathia, a small mouth, and small, low-set ears
Congenital heart disease;* mostly conotruncal and aortic arch defects, and rarely nonconotruncal defects
Hypoparathyroidism
Velopharyngeal insufficiency; hypernasal speech, increased nasal resonance, and nasal regurgitation
Recurrent infection; mainly respiratory tract infections and acute otitis media
Neuropsychological manifestations; cognitive deficits, attention difficulties, visual spatial abnormalities, impaired executive function, attention-deficit/hyperactivity disorders, anxiety disorders, depression, and autism spectrum disorders
Gastrointestinal problems; feeding difficulties, gastroesophageal reflux, chronic constipation, abdominal pain, and vomiting
Renal problems; renal agenesis, obstructive abnormalities, and vesicoureteric reflux
Ophthalmological abnormalities; strabismus, amblyopia, and structural ocular abnormalities
Musculoskeletal system problems; hypotonia, ligamentous laxity, spinal deformities, and idiopathic leg pain
Laryngeal abnormalities
Head-and-neck vascular anomalies
Dental problems – enamel hypoplasia/chronic caries
Autoimmune diseases
Endocrine problems; thyroid hypoplasia, hypothyroidism, and growth hormone deficiency
Adult phenotype
Typical facial features
Developmental delays with psychiatric disorders such as schizophrenia
Cardiac anomalies
Voice abnormalities; hypernasality
Hypoparathyroidism
Early-onset Parkinson's disease

Note: *Tetralogy of Fallot is the most prevalent cardiac defect, but interrupted aortic arch type B is the most specific defect for 22q11 deletion syndrome.

neurological problems such as neural tube defects, cerebral anomalies, and polyhydramnios have also been reported.[35] However, facial anomalies in fetuses are difficult to diagnose.

Neonatal and childhood phenotype

The clinical presentation of 22q11DS in pediatric patients and neonates is highly variable. The manifestations involve multiple organ systems and vary in severity and from patient to patient; the symptoms also vary depending on the age of the patient. Nevertheless, they commonly include the following classic findings: behavioral problems, developmental and/or learning disabilities, conotruncal cardiac anomalies, palatal defects, hypernasal speech, immunodeficiency, hypocalcemia, and characteristic facial features.[2,3,31,32]

Congenital heart disease is present in ~80% of patients with 22q11DS, and conotruncal and aortic arch defects are the most typical cardiac malformations associated with 22q11DS. The conotruncal defects include tetralogy of Fallot, pulmonary atresia, truncus arteriosus, an interrupted aortic arch, and a double outlet right ventricle. Nonconotruncal defects such as ventricular septal defects, atrial septal defects, and atrioventricular septal defects have also been reported. Tetralogy of Fallot is the most prevalent cardiac defect in 22q11DS, but interrupted aortic arch type B (distal to the left common carotid artery) is the most specific defect. Cardiopathies might appear shortly after birth with cyanosis or cardiovascular collapse, or could be defined in adulthood. An aberrant subclavian artery might present with feeding difficulties or respiratory symptoms.[31,32,35]

Although hypoparathyroidism is a rare endocrine disorder in pediatric-aged patients, the hypocalcemia caused by hypoparathyroidism is one of the classic symptoms of 22q11DS, and is present in 16%–70% of patients.[2] Hypoparathyroidism can be diagnosed in children of all ages with 22q11DS; diagnosis occurs commonly in the newborn period but can also occur during the late adolescent period.[36] Mild hypocalcemia without symptoms might last for several years.[37] Hypoparathyroidism is often transient and resolves after the neonatal period, but it may manifest later in life as episodes of hypocalcemia during stresses such as infectious diseases, surgery, or pregnancy. Patients develop permanent hypoparathyroidism only rarely. Neonatal hypocalcemia is not associated with the later development of permanent hypoparathyroidism.[38] However, the early onset of hypoparathyroidism is associated with a high risk of later recurrence.[39] A recent study concluded that the occurrence of neonatal seizures related to hypocalcemia might increase the risk of more severe intellectual deficits in patients with 22q11DS.[40]

The metabolic features of hypoparathyroidism include hypocalcemia, hyperphosphatemia, and reduced or low-range parathyroid hormone levels. The usual signs and symptoms are muscle cramps and tingling, numbing, seizures, tetany, positive Chvostek signs, and positive Trousseau signs. Stridor can also be a symptom, but it must be differentiated from laryngeal web. Hypocalcemia in 22q11DS has a wide clinical manifestation, ranging from only paresthesia and numbness to convulsions.[3,31,32,41]

The congenital cardiac defects associated with neonatal hypocalcemia are the most frequent features that lead

to diagnosis in the first 2 years of life. The most common symptoms leading to diagnosis in patients older than 2 years are neuropsychological manifestations, otorhinolaryngologic manifestations, and typical facial findings.[2,3,28,31–33]

Hypotonia and ligamentous laxity are very common in the infantile period. An unsteady gait, a lack of coordination, and clumsy hand skills are also observed commonly. Patients with 22q11DS also have an increased risk of spinal deformities such as cervical spinal abnormalities and scoliosis, and idiopathic leg pains are seen commonly in childhood.[3,31–33,42]

The neurocognitive profile of 22q11DS is also highly variable, both among individuals and throughout its development. Almost all individuals with 22q11DS cope with the resulting cognitive deficits. Borderline intellectual function (an IQ of 70–75) is the most common intellectual disability in these patients. The mathematic ability is usually weak, but their memory is good. Attention difficulties, visual spatial abnormalities, and impaired executive function are also common. Most children with 22q11DS achieve higher scores in verbal tasks than in non-verbal tasks. In addition, learning difficulties are very common during the preschool and in primary school-aged children. Psychiatric problems related to 22q11DS have also been described in children and adolescents, including attention-deficit/hyperactivity disorders, anxiety disorders, depression, and autism spectrum disorders.[43–46]

Most 22q11DS patients have speech or language difficulties. The most common speech abnormality is velopharyngeal insufficiency, which manifests typically as hypernasal speech, increased nasal resonance, and nasal regurgitation. Velopharyngeal insufficiency that becomes increasingly apparent with age and submucous cleft palate might also be observed, although overt cleft palate is rare. In addition to immune deficiency, palatal weakness and Eustachian tube dysfunction lead to recurrent ear infections in these patients. Hearing loss is a frequent problem in patients with 22q11DS.[31,32,47,48]

Immunodeficiency is another key feature of 22q11DS. The observed immunodeficiencies are secondary to thymic aplasia or hypoplasia with subsequent impaired thymocyte development. The degree of immunodeficiency seen in patients with 22q11DS is highly variable, and might include defects in T-lymphocyte number and function, as well as humoral defects. The thymus and the T-cells are absent completely (complete DGS) in a very small number of patients, but most subjects have a milder form of immunodeficiency (incomplete DGS). Despite the low-for-age T-cell counts in most patients in infancy, this usually improves during the first year of life.[43,49] Antibody deficiencies (hypogammaglobulinemia) have also been described in a minority of patients, most commonly IgA deficiency. An increased frequency of infections, mainly respiratory tract infections, is common in children with 22q11DS, but the frequency commonly diminishes with increasing age.[43,49,50] An increased prevalence of autoimmune conditions was reported in both children and adults with 22q11DS.[49]

Despite the phenotypic variability, most children with 22q11DS share a combination of features and have a characteristic dysmorphic facial appearance (Figure 3).[36] The facial characteristics described in individuals with 22q11DS are a long face, malar flattening, hypertelorism, short palpebral fissures, hooded/swollen eyelids, a wide and prominent nasal root, a wide/broad nasal bridge, a low nasal bridge, a bulbous nasal tip (becoming evident with age), hypoplastic alae nasi, micrognathia, a small mouth, asymmetric facial movements, and malformed, small, low-set ears. Children with 22q11DS usually have a mild pattern of the characteristic facial features, which might not be recognized easily. However, a physician experienced in 22q11DS could observe the typical facial features in most patients. Postaxial polydactyly might also occur.[30,51]

Renal problems are frequent in patients with 22q11DS, including structural renal anomalies such as renal agenesis or dysplastic kidneys, obstructive abnormalities, and vesicoureteric reflux.[2,3,30–33] Morphological and functional thyroid alternations have also been reported. Thyroid hypoplasia is common, but hypothyroidism is rare in 22q11DS.[52] Gastrointestinal involvement is observed sometimes in patients, including gastroesophageal reflux, chronic constipation, abdominal pain, and vomiting. However, intestinal

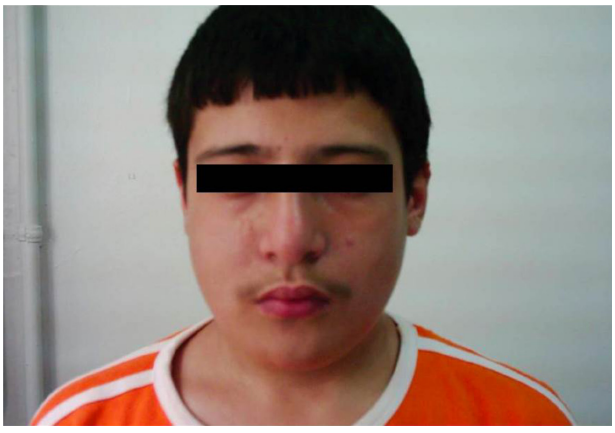

Figure 3 Characteristic facial features might not be recognized easily.
Notes: Prominent nose with a bulbous tip, small mouth and eyes, and long face in a patient diagnosed with 22q11DS. He also had hypoparathyroidism and attention deficit.

malrotation is rare. Refractive errors, strabismus, amblyopia, and structural ocular abnormalities are encountered frequently in children with 22q11DS.[2,3,30–33] Growth deficiencies are common in patients, particularly during infancy and early childhood. Nevertheless, growth hormone deficiency has been described only rarely.[53]

Adult phenotype

Due to variation in the phenotypic features and their severity, the diagnosis of 22q11DS could be missed in children, and the syndrome might be diagnosed during adulthood instead. The main presenting symptoms in adults are developmental delays with psychiatric disorders and cardiac anomalies.[54] A recent study showed that 22q11DS might increase the risk of early-onset Parkinson's disease.[55] Hypoparathyroidism might be the main reason for diagnosis during adulthood. It was reported that familial inheritance is the most frequent reason for adults with 22q11DS to be referred to the genetic clinic. If concomitant findings such as the typical facial features and voice abnormalities (such as hypernasality) associated with 22q11 deletions are observed in patients evaluated at psychiatry and cardiology clinics, the diagnosis of 22q11DS should be considered.[28,54]

Diagnosis

The decision to test for 22q11DS is easy if multiple defects and/or symptoms associated with the syndrome are present simultaneously. However, physicians should note that the signs and symptoms might be subtle; therefore, clinical clues could be overlooked easily. As mentioned above, patients with this syndrome usually have mild facial features. As such, careful physical examinations using anthropometric measures are very important for suspected cases of 22q11DS. It should be noted that the diagnosis of 22q11DS, particularly in adolescents and adults, often requires an enhanced index of suspicion.[30–32] Detailed suggestions for clinicians have been published elsewhere.[56]

Fluorescence in situ hybridization (FISH) is the current method of choice for detecting 22q11.2 microdeletions. FISH is a highly accurate and reliable test that can also be used for prenatal diagnosis. However, it is limited to a single target sequence within the proximal 22q11.2 deletion region, and some atypical deletions do not include the region analyzed using FISH with commonly used probes (such as TUPLE1). A polymerase chain reaction-based assay (multiplex ligand-dependent probe amplification) is used widely in Europe, and is becoming accepted increasingly in the US because it has a rapid turnaround time, it is more cost-effective, and can detect the smaller deletions missed by FISH. This novel technique is capable of detecting atypical 22q11.2 deletions that are not routinely tested or detected using routine FISH.[5,57] Advanced molecular methods that identify the deletion or duplication of genomic sequences at high resolution, such as microarrays, can also be used. The detection capacity of microarrays depends on the density of the probes used. This is particularly important when patients present with classical features of the syndrome but no evidence of gene deletions using FISH; diagnosis is challenging in these patients. For example, point mutations in *TBX1* have been described in a small number of patients.[58]

There is a need for a rapid, cost-effective, and easy laboratory method for screening and diagnosis of 22q11DS. A recent study shows promise in this regard. A multiplex droplet digital polymerase chain reaction is sensitive and specific for the detection of 22q11DS.[59]

Management

22q11DS is a multisystem syndrome with remarkable variability and expression among individuals. Moreover, the presence of one feature does not predict the presence of any other feature. As such, the management of 22q11DS patients is highly dependent on age and phenotype; therefore, treatment is individualized according to the underlying lesion and severity.[31,32]

In infants and young children with feeding problems, recurrent infections, hypocalcemia, and structural cardiac and palatal anomalies might be accompanied by speech, learning, and/or developmental difficulties. The combination of poor suck reflexes, palatal weakness, and dysfunctional swallowing often means that formula rests in abnormal anatomic locations or regurgitates into the Eustachian tube or sinuses. Gastroesophageal reflux is also common in these patients. The management of feeding difficulties includes thickeners, anti-reflux medications, and nasogastric or gastrostomic feeding tubes when necessary.[2,3,31,32]

Hypocalcemia due to hypoparathyroidism is a common problem during the neonatal period, but it could occur at any age, including adulthood. The standard treatment for hypoparathyroidism is to correct hypocalcemia using oral vitamin D analogs and calcium. However, physicians should be careful to avoid overtreatment, which results in hypercalciuria, hypercalcemia, nephrolithiasis, nephrocalcinosis, and renal failure.[60] Teriparatide recombinant human parathyroid hormone (1–34) is a promising novel treatment for chronic hypocalcemia in hypoparathyroid syndromic children, and it might solve this problem in the future.[41] A recent study demonstrated the

efficacy of parental parathyroid transplantation combined with allogeneic thymus transplantation in a patient.[61] Daily vitamin D is advised for 22q11DS patients of all ages with hypocalcemia; the dose should be the recommended daily allowance or as indicated therapeutically.[32]

Recurrent infections, particularly otitis media, might be an important problem during this period, and hearing loss might occur. Children should be treated appropriately for infections and followed carefully for potential hearing problems. Unrecognized hearing loss might contribute to delayed speech and cognitive development.[31,32,43,49]

Reconstituting the immune system is essential for patients with complete DGS, which can be accomplished by two methods: thymus tissue transplantation and a fully matched peripheral blood T-cell transplantation. Patients with complete DGS need to be protected from infections and blood products. Antifungal, antiviral, and antipneumocystis prophylaxis, and immunoglobulin replacement therapy should be commenced in these patients. Blood products could induce graft-versus-host disease when T-cells are absent. If necessary, patients should receive cytomegalovirus-negative and irradiated blood products. In addition, live viral vaccines should be avoided in patients with severe immunodeficiency.[43,49] Adverse events following live immunizations are typically minor and self-limited, suggesting that live vaccines could be considered in patients with mild-to-moderate immunosuppression.[62] As mentioned above, hypogammaglobulinemia might develop in patients with 22q11DS. For example, severe antibody deficiencies that are associated with lower respiratory tract infections and autoimmune conditions might occur. Therefore, patients should be screened for potential antibody deficiency.[49] Importantly, the degree of immunodeficiency cannot be predicted based on other phenotypic features and must be assessed individually in each patient with 22q11DS.[63]

Patients with 22q11DS have high death rates. Most deaths occur during the first year of life, and are associated with the presence of congenital heart diseases, particularly severe cardiac defects.[64] Right-sided heart failure, which is related to pulmonary vascular resistance, is a common complication of these anomalies, and was proposed to be an important contributor to mortality.[64] Surgical treatment is necessary for many of the cardiac problems in patients with 22q11DS. Nevertheless, individualized surgical approaches are needed according to the underlying cardiac lesion in each patient.[65] Laryngeal abnormalities are not rare and are important to recognize, particularly if cardiac surgery is planned. Therefore, complete ear, nose, and throat examinations and airway evaluations should be performed before any surgical procedure.[66]

Speech during childhood should be given careful attention, and speech therapy might be necessary in 22q11DS patients. Submucosal cleft palate can be detected easily using careful physical examinations, and can be corrected using surgery. Patients with velopharyngeal insufficiency should be followed up and treated by an experienced team. Surgery is often necessary and useful to correct velopharyngeal insufficiency with or without palatal defect. Adenoidectomy might worsen speech articulation; therefore, it should be avoided as much as possible. In addition, head-and-neck vascular anomalies are common in patients with 22q11DS, and there is an increased risk of carotid artery injury because of medical displacement during pharyngeal surgery. This possibility should be considered before and during relevant operations.[19,67,68] Finally, the risk of obstructive sleep apnea is increased in patients with 22q11DS after velopharyngeal insufficiency surgery.[69]

Preschool and school-aged children with 22q11DS should be screened for neurocognitive and psychiatric problems. These patients should be followed carefully because early support and treatment are vital in these individuals. Adjusting the child's school environment might also maximize learning. Behavioral issues and psychiatric illnesses are likely to become more problematic with increasing age. Although psychotic disorders are chronic in most cases, they can also be transient. Anxiety disorders are a major risk factor for psychosis in patients with 22q11DS. As such, accurate psychiatric management should start in childhood and continue throughout adulthood in these individuals.[45,46]

As mentioned above, 22q11DS might affect many systems, and urinary ultrasonography should be performed after diagnosis. Children with 22q11DS should be screened for scoliosis, and surgical treatment might be necessary to correct this condition. Symmetric leg pain is seen frequently in 22q11DS patients during childhood, whereas asymmetric leg pain suggests other pathologies. Patients should also be screened for thyroid function and if necessary, thyroid morphology. Vomiting is common with 22q11DS, and can indicate a problem in the gastrointestinal system such as reflux or malrotation. If indicated clinically, patients should also be screened for autoimmune disorders such as Celiac disease. Subjects should also be screened for strabismus and refractive errors at 2 years or 3 years of age.[31,32]

Children with 22q11DS should be followed up using the specialized growth charts available for this syndrome.

If growth problems are detected, an endocrinologist could be consulted.[53,70]

The optimal management of patients with 22q11DS requires a comprehensive team approach, including specialists in genetics, pediatrics, endocrinology, plastic surgeons, immunologists, otolaryngologists, and speech therapists. 22q11DS is not a rare syndrome, and there is a need to form a local specialist team to ensure optimal management of affected patients. Appropriate guidelines for the management of patients are available in the literature, which contain useful information for physicians interested in 22q11DS syndrome.[31,32,71] 22q11DS might be difficult to recognize and diagnose in some patients, although the clinical findings for early diagnosis are known. Early diagnosis provides the best opportunity for modifying the course of the illness and optimizing patient outcome.

Disclosure

The authors report no conflicts of interest in this review.

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