22q11.2 deletion syndrome

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Introduction

This article includes discussion of 22q11.2 deletion syndrome, conotruncal-anomaly-face syndrome, conotruncal anomaly face syndrome, Shprintzen syndrome, DiGeorge syndrome, Sedlackova syndrome, Shprintzen syndrome, and velocardiofacial syndrome. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

DiGeorge and velocardiofacial syndrome (22q11.2 deletion syndrome) is the most common microdeletion disorder in humans and, hence, one of the most common multiple malformation syndromes, with an estimated prevalence of 1 in 2000 to 4000. It is characterized by craniofacial anomalies, conotruncal heart disease, thymic aplasia and hypoplasia, hypocalcemia, and psychiatric illness. In this article, the author reviews the history, clinical features, and genetic basis of this common disorder.

Key points

- DiGeorge and velocardiofacial syndrome (22q11.2 deletion syndrome) is the most common microdeletion disorder in humans and, hence, one of the most common multiple malformation syndromes, with an estimated prevalence of 1 in 2000 to 4000.
- It is characterized by craniofacial anomalies, conotruncal heart disease, thymic aplasia or hypoplasia, hypocalcemia, and psychiatric illness.

Historical note and terminology

In 1968, DiGeorge described congenital absence of the thymus and parathyroid glands in 4 infants with recurrent infections and hypocalcemia (DiGeorge 1968). In 1979, Conley and co-workers broadened the phenotype of DiGeorge syndrome to include conotruncal (outflow tract) defects of the heart as well as characteristic facial features including a bulbous nose, dysplastic ears, and micrognathia (Conley et al 1979).

Strong reported a familial syndrome of right-sided aortic arch, facial dysmorphism, and cognitive and psychiatric dysfunction in 1968 (Strong 1968). Ten years later, Shprintzen and colleagues profiled a series of 12 patients with a combination of cleft palate, congenital heart disease, unique facial features (long face with malar flattening, small palpebral fissures, long nose with bulbous tip, dysplastic ears, and micrognathia), learning disabilities, and short stature and called the condition velocardiofacial syndrome (Shprintzen et al 1978). Conotruncal anomaly face syndrome, originally described in the Japanese literature (Kinouchi et al 1976), comprises clinical features of both DiGeorge syndrome and velocardiofacial syndrome.

With the advent of molecular genetics, DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome were found to have a similar 22q11.2 microdeletion as the basis for their overlapping clinical features (Scambler et al 1991; Scambler et al 1992; Burn et al 1993). This 22q11.2 deletion syndrome is now recognized as one of the most common multiple malformation syndromes. The acronym “CATCH22” (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia) was conceived; however, because this term may be construed as insensitive, it is not universally accepted (Wilson et al 1993; Wulfsberg et al 1996). The compound term “DiGeorge and velocardiofacial syndrome” calls attention to the phenotypic spectrum using historically familiar names (Leana-Cox et al 1996) and is especially applicable when phenotypic features manifest in the absence of the chromosomal deletion (McDonald-McGinn and Sullivan 2011).

Clinical manifestations

Presentation and course

Broad inter- and intrafamilial variability exists in the clinical spectrum of DiGeorge and velocardiofacial syndrome (Holder et al 1993). The phenotype has expanded considerably within the last several years and now includes over 150...
associated findings. The following are the major clinical manifestations:

**Audiologic findings.** Hearing impairment (conductive, sensorineural, or mixed hearing loss) is present in 40% to 60% of patients and seems to be due to cochlear damage (Digilio et al 1999; McDonald-McGinn et al 1999; Van Eynde et al 2016).

**Cardiovascular findings.** Congenital heart disease (conotruncal defects) is present in approximately 68% of individuals to 85% of individuals with DiGeorge and velocardiofacial syndrome (Young et al 1980; Leana-Cox et al 1996). Indeed, the presence of conotruncal defects, especially coupled with psychiatric disorders, is a compelling reason to pursue cyogenetic analysis, even in adults (Vogels et al 2014). The most common anomalies include ventricular septal defect, tetralogy of Fallot, and aortic arch anomalies—for example, interrupted aortic arch and right-sided aortic arch (Young et al 1980; Lindsay et al 1995; Ryan et al 1997; Peyvandi et al 2013). Anomalies of the internal carotid arteries are also reported (Goldberg et al 1993). Non-compaction of the left ventricular myocardium has been reported in this condition (Pignatelli et al 2003; Digilio et al 2013), but the association is not understood and could be coincidental (Stollberger and Finsterer 2011). Vascular anomalies may be encountered in the cervical region (eg, medial deviation of the internal carotid artery) (Stransky et al 2015).

**Craniofacial findings.** Microcephaly is present in approximately 40% of individuals (Goldberg et al 1993), and craniosynostosis has been recognized in a small subset of patients (Al-Hertani et al 2013). Characteristic facial features include a long face with malar flattening, short palpebral fissures, small dysplastic ears, prominent nose with broad nasal root, bulbous tip, and deficiency of the nasal alae, and micrognathia. Dental anomalies include enamel hypoplasia, hypodontia, aberrant tooth shape and delayed tooth eruption (Klingberg et al 2002). The occurrence of cleft palate ranges from 33% (Lindsay et al 1995) to 98% (Goldberg et al 1993). Discrepancies between reported series probably reflect ascertainment bias with higher frequencies of cleft palate in those series originating from craniofacial clinics. The majority of affected individuals, with or without overt cleft palate, typically have hypernasal speech (the result of velopharyngeal insufficiency) complicated by upper airway asymmetry, platybasia, muscle hypotonia, adenoid hypoplasia, and other neuroanatomical abnormalities (Widdershoven et al 2008). Velopharyngeal insufficiency may also predispose to otitis media and conductive hearing loss. Velopharyngeal insufficiency and compromised nasal airway patency may have an impact on olfaction as well (Sobin et al 2006). Anterior glottic webs are found in a minority of individuals with DiGeorge and velocardiofacial syndrome (Miyamoto et al 2004). Speech delay, coupled with learning disability, hearing loss, and dysmorphic facies, is suggestive of the condition and indicates further workup (Vieira et al 2015).

**Endocrinologic findings.** Hypocalcemia is seen in 20% to 63% of patients typically presenting between birth and 3 months of age (Goldberg et al 1993; Lindsay et al 1995; Leana-Cox et al 1996). Approximately 10% of these infants present with hypocalcemic-related seizures (Wilson et al 1993), and Chvostek and Trousseau signs may not be present. Most patients have resolution of hypocalcemia by 1 year of age; however, recurrence of hypocalcemia in later childhood or adulthood, secondary to transient congenital hypoparathyroidism, is reported (Greig et al 1996; Sykes et al 1997). Hypothyroidism, autoimmune hyperthyroidism, and growth hormone deficiency may be seen in these individuals (Goldberg et al 1993; Weinzierl et al 1998; Segni and Zimmerman 2002). In fact, thyroid disease (hyper- or hypothyroidism) has been diagnosed in nearly 10% of patients in 1 study (Shugar et al 2015). Hypercalcemia in early childhood has been reported in a patient with a de novo mutation in AP2S1 (Tenhola et al 2015).

**Genitourinary findings.** Renal anomalies are present in 10% of individuals to 36% of individuals and include absent, dysplastic, or multicystic kidneys, obstructive abnormalities, duplicated kidney and collecting system, and vesicoureteral reflux (Devriendt et al 1996; Ryan et al 1997). Utero-vaginal aplasia (Mayer-Rokitansky-Kuster-Hauser syndrome) has been reported in a few patients (Morcel et al 2011). Cryptorchidism, hypospadias, and imperforate anus are occasionally present (Goldberg et al 1993; Ryan et al 1997; Worthington et al 1997).

**Gastrointestinal findings.** Feeding difficulties are present in approximately one-third of infants, often necessitating gastrostomy tube or nasogastric tube placement (McDonald-McGinn et al 1999). Esophageal abnormalities, Hirschsprung disease, and anteriorly placed anus are less common (Enns et al 1999).

**Immunologic findings.** Defects in T-cell production and function (secondary to thymic aplasia or hypoplasia) are present in 25% to 75% of patients (Ryan et al 1997; Sullivan et al 1998). Infections, thus, pose a substantially increased risk over the general population and may be life-threatening. Secondary humoral deficiencies can occur as well, resulting in a form of variable combined immunodeficiency (Thomas and Graham 1997). In addition,
autoimmunity is not uncommon (Gennery et al 2002). Juvenile rheumatoid arthritis-like polyarthritis is reported in individuals with DiGeorge and velocardiofacial syndrome (Sullivan et al 1997). Idiopathic thrombocytopenic purpura is described in some individuals (Levy et al 1997).

Musculoskeletal findings. Short stature is present in approximately one-third of individuals (Goldberg et al 1993). Cervical spine abnormalities (eg, open or cleft vertebral arch, platybasia, fused vertebrae) are relatively common, and so precautions should be taken during medical treatments and even during the pursuit of ordinary life functions (Hamidi et al 2014; Stransky et al 2015). Other anomalies of the skeletal system include Sprengel anomaly, scoliosis and limb abnormalities, most commonly talipes equinovarus, polydactyly, and syndactyly (Ryan et al 1997; Radio et al 2016). Approximately 60% of individuals have long, slender fingers (Goldberg et al 1993). Inguinal and umbilical hernias are also common.

Neurologic findings. Seizures were reported in approximately 21% of individuals in one large series (Ryan et al 1997). The majority of seizures are associated with hypocalcemia. One case of both hypocalcemia-induced seizure and epilepsy associated with spina bifida has been reported (Kinoshita et al 2010). Hypotonia in infancy and early childhood is present in the majority of patients, resulting in delayed motor milestones. Movement disorders may occur secondary to endocrine diseases or musculoskeletal anomalies; patients may also be susceptible to early-onset Parkinson disease (Boot et al 2015; Oki et al 2016; Pollard et al 2016). Asymmetrical facies and facial nerve palsies are described (Ryan et al 1997). Cognitive impairment is common with mean verbal IQ scores in the borderline range of mental deficiency in both preschool and school age children (Golding-Kushner et al 1985). More severe deficits are noted in receptive language than expressive language (Glaser et al 2002). Verbal IQ scores are generally higher than performance IQ scores (Swillen et al 1997), consistent with a nonverbal learning disability. A specific cognitive profile with impairments in visuospatial, arithmetical, and executive tasks is noted (Zinkstok and van Amelsvoort 2005). Problems in social-emotional functioning and attention and concentration are common.

Ocular findings. Blood-vessel anomalies (such as tortuous retinal vessels), colobomas, posterior embryotoxon, and strabismus may be associated with DiGeorge and velocardiofacial syndrome (Goldberg et al 1993; McDonald-McGinn et al 1999). Additional findings include abnormalities of the orbits, eyelids, or eyes (hooding, narrow palpebral fissures, narrow or widened interorbital space, sparse and thin eyebrows and eyelashes, blepharitis, distichiasis), posterior embryotoxon, and tortuous retinal vessels; refractive errors, iris remnants, and strabismus are recognized as well (Gokturk et al 2016).

Psychiatric findings. Individuals with DiGeorge and velocardiofacial syndrome are at risk to develop a range of psychiatric illnesses, most often appearing late in adolescence or early adulthood (Goldberg et al 1993; Pulver et al 1994; Karayiorgou et al 1995; Hooper et al 2013). This risk has been estimated at 25 times that of the general population (Shprintzen 2008). These conditions frequently include pronounced separation anxiety and night terrors in childhood, and attention deficit hyperactivity disorder, wide mood swings, and obsessive-compulsive disorder in adolescence. Preadolescent and young adolescent children studied longitudinally show slowed growth in attention regulation and subclinical symptoms of schizophrenia; lower academic achievement and neurocognition, with increased social and behavioral difficulties, are reported (Hooper et al 2013). Social cognitive training has proven effective in a small group of adolescents (Shashi et al 2015). Some suggest that the predominantly affective symptoms seen in early childhood and adolescence may evolve into schizophrenia or schizoaffective disorder in adulthood (Murphy et al 1999). The deletion carries the third highest recognized risk for schizophrenia (Prasad et al 2008), which may develop in 20% to 25% of patients (Philip and Bassett 2011). Catatonia may be more common that previously recognized, especially in patients with psychiatric symptoms that are refractory to treatment (Faiedda et al 2015). Intercital schizophrenia-like psychosis has been reported in an adult who had experienced childhood-onset epilepsy (Tastuzawa et al 2015). In addition, reports describe a spectrum of bipolar disorders, including bipolar I, bipolar II (ultracyclers), cyclothymic, and schizoaffective (manic) disorders in these individuals with onset in late childhood or early adolescence (mean age of onset is 12 years) (Paplos et al 1996). Chronic mania has been reported (Praharaj et al 2010), but it is not clear if behavior remains stable during the patient's lifetime (Antshel et al 2008). In 1 study, autism spectrum disorders are present in approximately 50% of children with DiGeorge and velocardiofacial syndrome (Vorstman et al 2006a). The severity of behavioral and psychiatric disorders is such that a majority of caregivers believe they are the most challenging aspect of this disorder (Karas et al 2014).

Prognosis and complications

Prognosis in the neonatal period is usually dependent on the severity of the cardiac malformation, if present, and
immune function. Cardiac surgery may be complicated by depressed immune status, neonatal hypocalcemia, pulmonary vascular reactivity and increased airway bleeding, and a number of airway anomalies, including bronchomalacia, bronchospasm, and malpositioned bronchus; anomalies of the larynx include laryngeal (glottic) web, subglottic stenosis, laryngeal paralysis, vocal nodule, and laryngomalacia (Carotti et al 2008; Leopold et al 2012). Not surprisingly, hospital stays are longer and require more resources (O'Byrne et al 2014). The vast majority of individuals will have some degree of developmental delay and learning disabilities (Goldberg et al 1993); however, a great degree of variability exists between and within families (Lindsay et al 1995; Leona-Cox et al 1996). Obesity with hyperphagia in a small subset of patients may have a psychiatric basis (Bassett et al 2016). Intellectual development can be moderately, severely, or profoundly affected (Evers et al 2009). Children are challenged by cognitive, social, and emotional issues, but these can be counterbalanced by strengths such as kindness, humor, persistence, and enthusiasm; in quality-of-life testing, boys score significantly lower than girls (Looman et al 2010). These attributes may stem from the observation that patients' verbal skills outweigh performance IQ and visuospatial memory (Furniss et al 2011). Such deficits in spatial and temporal processing, whereby individuals cannot remember the positions of objects, in turn influence performance of patients' working memory (Wong et al 2014). Disruption in the neural circuitry critical to working memory may be suggestive of a psychotic disorder (Montojo et al 2014). Patients have difficulty focusing, planning, and executing specific acts (Furniss et al 2011). Depressive, defiant, and anxiety disorders may be predictive of later psychosis (Antshel et al 2010). Psychosis has also been correlated with progressive intellectual decline (Evers et al 2014). Approximately 10% to 30% of individuals will develop psychiatric illness ranging from mild depression to frank psychosis (Goldberg et al 1993; Pulver et al 1994). Diffusion tensor MRI has identified white matter abnormalities, with apparent lower axonal integrity, in these patients (Bakker et al 2016). These cognitive and behavioral issues play a very significant role in determining quality of life (Maessen et al 2010). The precise nature of the cytogenetic abnormality may also have a bearing on prognosis. One woman with apparent "genetic dosage compensation," ie, deletion of 1 copy of 22q11.2 and reciprocal duplication of the other copy, was phenotypically normal (Alkalay et al 2011). Early-onset Parkinson disease is an indication for genetic workup (Pollard et al 2016). Adults are at risk for sudden death. Mechanisms are probably multiple and may include fatal arrhythmia. Again, mechanisms are unclear; in one study of 5 patients, for example, sympathetic activity was normal (Verschure et al 2016).

**Clinical vignette**

A 15-year-old boy with mild mental retardation and unusual facial features began to experience behavioral changes, which were first interpreted as isolation and depression. He soon developed auditory and visual hallucinations as well as delusions. His past medical history is significant for "failure to thrive" during infancy due to difficulty breast-feeding and recurrent nasal regurgitation. Developmental milestones were delayed; he began to walk at 17 months and first spoke single words around 18 months of age. He had recurrent otitis media with persistent conductive hearing loss and had tympanostomy tubes placed at 18 months of age. An inguinal hernia was repaired at 4 years of age. A neurodevelopmental evaluation at 9 years of age noted hypernasal speech and estimated cognitive abilities in the borderline to mild range of mental deficiency.

He was hospitalized and evaluated by psychiatry and neurology services. He was noted to have unique facial features, which included a relatively long face with malar flattening, long nose with a bulbous nasal tip, short palpebral fissures, small ears with thickened helices, long slender fingers, flat affect, tremor, and a slow, awkward gait. Repeat neuropsychological testing revealed a 30-point decline in his full-scale IQ. EEG and head CT scan were normal. A fluorescence in situ hybridization test for DiGeorge and velocardiofacial syndrome showed a 22q11.2 deletion. Echocardiogram and renal ultrasound were normal. Parental fluorescence in-situ hybridization studies were normal.

**Biological basis**

**Etiology and pathogenesis**

Approximately 76% of individuals to 90% of individuals with DiGeorge and velocardiofacial syndrome have a chromosome 22q11.2 microdeletion recognizable by fluorescence in-situ hybridization (Driscoll et al 1993; Lindsay et al 1995). Approximately 10% to 25% are inherited in an autosomal dominant fashion (Hall 1993), whereas the remainder are thought to represent de novo events. Other chromosomal rearrangements, including an interstitial deletion at 10p13, are reported in individuals with the DiGeorge syndrome phenotype (Dasouki et al 1997).

**Cytogenetics.** The initial evidence for involvement of genes on chromosome 22 in the etiology of DiGeorge syndrome inclusion.
included a family with a chromosome 2;22 translocation. Family members with an unbalanced rearrangement that resulted in monosomy 22q11.2 had clinical features of DiGeorge syndrome (de la Chapelle et al 1981). Subsequently, cytogenetically visible interstitial deletions of 22q11 were detected in approximately 25% of DiGeorge syndrome patients (Scambler et al 1991). Southern blotting and DNA dosage analysis revealed microdeletions within 22q11 in DiGeorge syndrome patients (Fibison et al 1990). The finding of several velocardiofacial syndrome patients with a deletion 22q11.2 using fluorescence in-situ hybridization suggested that DiGeorge syndrome and velocardiofacial syndrome were related disorders (Scambler et al 1992). It is now evident that the overlapping features of DiGeorge syndrome and velocardiofacial syndrome presumably result from haploinsufficiency for the same genes (Kelly et al 1993).

Approximately 76% of patients to 90% of patients with DiGeorge and velocardiofacial syndrome have a 1.5 Mb to 3 Mb microdeletion within chromosome 22q11 referred to as the “typically deleted region.” The typically deleted region is subdivided into 5 intervals, encompassing some 50 genes (Swillen and McDonald-McGinn 2015). To date, no significant correlation exists between the size of the deletion and the severity of the phenotype (Carlson et al 1997). Furthermore, considerable variability occurs in the phenotype observed within individual families, indicating that the phenotype is not solely related to the size of the deletion (Demczuk et al 1995b; Lindsay et al 1995; Carlson et al 1997). Both deletions and reciprocal duplications have been identified in patients with varying phenotypes by chromosomal microarray analysis (Leite et al 2016). Genetic factors play a major role in the phenotypic variability of a mouse model of DiGeorge syndrome (Taddei et al 2001).

The following table lists some of the DiGeorge and velocardiofacial syndrome candidate genes within the typically deleted region. TBX1 is currently the most likely of the candidate genes and is located in the 22q11 region most often deleted (Huh and Ornitz 2010). Mutations in TBX1 have also been identified in non-deleted patients and are thought to be causal based on functional and experimental data (Stoller and Epstein 2005; Aggarwal and Morrow 2008). Other genes remain under investigation.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Reference</th>
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<tbody>
<tr>
<td>CLTD</td>
<td>Encodes a protein with homology to human clathrin heavy-chain</td>
<td>(Gong et al 1996)</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase: a CNS enzyme involved in the metabolic degradation of dopamine and norepinephrine; increased prefrontal dopamine may affect cognition and contribute to psychosis in patients.</td>
<td>(Grossman et al 1992; Gothelf et al 2008)</td>
</tr>
<tr>
<td>CRKL</td>
<td>Encodes an SH2-SH3-SH3 adaptor protein</td>
<td>(Guris et al 2001)</td>
</tr>
<tr>
<td>CTP</td>
<td>Mitochondrial citrate transport protein</td>
<td>(Goldmuntz et al 1996)</td>
</tr>
<tr>
<td>DGCR2 or LAN or IDD</td>
<td>Encodes a potential adhesion receptor protein</td>
<td>(Demczuk et al 1995a; Wadey et al 1995)</td>
</tr>
<tr>
<td>DGCR6</td>
<td>Encodes a putative protein that has homology to the human laminin gamma-1 chain and Drosophila gonadal protein</td>
<td>(Demczuk et al 1996)</td>
</tr>
<tr>
<td>DGCR8</td>
<td>Encodes a protein containing one WW motif and two DSRM motifs</td>
<td>(Shiohama et al 2003)</td>
</tr>
<tr>
<td>GNB1L</td>
<td>Encodes a G-protein beta-subunit-like polypeptide</td>
<td>(Gong et al 2000)</td>
</tr>
<tr>
<td>GSCL</td>
<td>Homology to the homeodomain family of transcription factors (goosecoid-like homeobox gene)</td>
<td>(Gottlieb et al 1997)</td>
</tr>
<tr>
<td>HIRA</td>
<td>Human homologue of the <em>S cerevisiae</em> HIR1 and HIR2 transcriptional repressors</td>
<td>(Lamour et al 1995)</td>
</tr>
</tbody>
</table>
**PCQAP**
Encodes a protein subunit of the multiprotein complex PC2

**RanBP1**
Binding partner of the Ras-related nuclear protein Ran/TC4

**TBX1**
T-box transcription factor

**TMVCF**
Encodes a transmembrane protein

**TUPLE1**
A putative transcription factor

**UFD1L**
Encodes a protein involved in degradation of ubiquitinated proteins

**ZNF74**
A putative transcription factor

Central nervous system findings. Neuroanatomic anomalies may be seen on CT and MRI scans in a minority of individuals with DiGeorge and velocardiofacial syndrome. Findings include cerebral atrophy, hypoplasia of the cerebellar vermis, small posterior fossa, small cysts adjacent to the anterior horns, gray matter heterotopias consistent with abnormal neuronal migration, hippocampal hypoplasia, Chiari malformation, focal white matter signal hyperintensities, enlargement of the corpus callosum, and polymicrogyria (Ryan et al 1997; Antshel et al 2005). A study of cortical architecture revealed cortical dysplasia in an affected patient; this form of arrested maturation was evident in all lobes of the cortex and probably represents persistence of the normal radial columnar architecture of the neocortical plate in the first half of gestation (Sarnat and Flores-Sarnat 2013). Quantitative volumetric neuroimaging studies show reduced tissue volumes in the nonfrontal lobar regions of the brain, consistent with the neurocognitive profile of DiGeorge and velocardiofacial syndrome (Kates et al 2001). High-resolution imaging studies show a significant reduction in frontal deep white matter, suggesting frontostriatal dysfunction, a finding noted in individuals with schizophrenia (Kates et al 2004). Diffusion tensor imaging has demonstrated altered integrity of white matter in the superior and inferior longitudinal fasciuli and thalamic to frontal tracts, which may contribute to behavioral abnormalities or deficits in visual-spatial memory in patients (Kikinis et al 2013; Villalon-Reina et al 2013). It has been hypothesized that the psychiatric and cognitive deficits may be due to disordered structural and functional connectivity, as well as abnormalities in association pathways and midline structures (eg, corpus callosum, cingulate gyrus) (Scariati et al 2016).

Congenital heart disease, craniofacial malformations, endocrinopathies, and immunodeficiencies. During the fourth week of embryonic development, neural crest cells migrate into the pharyngeal arches and participate in the formation of the craniofacial region, aortic arches and conotruncus, thymus, and parathyroid glands (Bockman and Kirby 1984). It is likely that the recognizable features in DiGeorge and velocardiofacial syndrome patients (unique facial features, congenital heart disease, thymus hypoplasia, parathyroid hypoplasia) result from either aberrant neural crest cell migration or from a disorder of cell interaction with pharyngeal pouch endoderm from which the affected structures are derived (Bockman and Kirby 1984).

DiGeorge and velocardiofacial syndrome studies suggest a role for TBX1 in mediating epithelial-mesenchymal signaling in regions of the developing face of the mouse (Zoupa et al 2006). The transcription factor encoded by TBX1 is important to cardiac development and is often deleted in patients (Stoller et al 2010). It is also required for the elongation and elevation of palatal shelves (Goudy et al 2010).

Neurochemical or neuropsychiatric disorders. The catechol-O-methyltransferase gene is located within the region typically deleted in DiGeorge and velocardiofacial syndrome (Grossman et al 1992). The gene encodes an enzyme that inactivates catecholamines such as dopamine, norepinephrine, and epinephrine (Dunham et al 1992). Presence of catechol-O-methyltransferase (COMT) activity may serve as a functional barrier for catecholamines in the brain (Kaplan et al 1980) and placenta (Barnea et al 1988). Catechol-O-methyltransferase occurs in soluble and membrane-bound forms, but resides predominantly in the cytoplasm. The soluble form has high and low activity alleles. Low catechol--methyltransferase activity has been reported in women with primary affective disorder (Cohn et al 1970).

Individuals hemizygous for the catechol-O-methyltransferase gene (such as those with a 22q11.2 deletion) and carrying a low activity allele on their nondeleted chromosome may be predisposed to the development of psychotic features (Lachman et al 1996). This could occur either due to decreased inactivation of catecholamines in the brain,
increased placental transfer of catecholamines, or both. The specific catabolic clearance of dopamine has been implicated as well (Armando et al 2012). Approximately 23% of a randomly selected population was classified as "low" metabolizers (Weinshilboum and Raymond 1977); therefore, the frequency of the low activity allele in the DiGeorge and velocardiofacial syndrome population may be of significance. This functional COMT polymorphism may have a gender-moderated effect on the neuroanatomic phenotype in individuals with DiGeorge and velocardiofacial syndrome (Kates et al 2006).

Expression studies performed in mice and humans show that the majority of 22q11.2 genes are expressed in the brain during multiple stages of development (Maynard et al 2003). Thus, the neuropsychiatric findings in individuals with DiGeorge and velocardiofacial syndrome may be the result of the deletion of multiple 22q11.2 genes.

Renal anomalies. Urologic malformations associated with 22q11.2 deletions may represent variable expression of an embryologic defect of the lower or upper ureteral bud (Devriendt et al 1996). Anorectal anomalies may be related to a defect in mesenchyme cell migration, an abnormality of the cell matrix, or defect in programming (Worthington et al 1997).

Epidemiology

DiGeorge and velocardiofacial syndrome is one of the most common multiple malformation syndromes. It is the most common microdeletion disorder in humans (Aggarwal and Morrow 2008). The combined incidence of DiGeorge and velocardiofacial syndrome has been estimated to be approximately 1 in 2000 (Shprintzen 2008) to 1 in 4000 (McDonald-McGinn and Sullivan 2011). Males and females are affected equally, with no apparent differences among ethnic groups (McDonald-McGinn and Sullivan 2011).

Differential diagnosis

The 22q11.2 deletion syndrome can occur in combination with other conditions, thus complicating diagnosis. Differential diagnosis may include autosomal dominant Opitz GBBB syndrome (vascular ring and cardiovascular defects, developmental delay, cleft palate), CHARGE association (cardiovascular defects, growth deficiency, developmental delay, cleft palate, cranial nerve abnormalities, renal anomalies), and Kabuki syndrome (cardiovascular defects, renal abnormalities, developmental delay, growth deficiency, cleft palate). Care must be taken to distinguish hypocalcemic seizures from epilepsy (Tsai et al 2009); distal deletion of 22q11.2 is clinically different from more proximal deletions of 22q11.2 (Madan et al 2011).

Diagnostic workup

A prenatal screening panel that includes 22q11.2 deletion syndrome is being tested (Vora and O'Brien 2014). The efficacy of cell-free DNA screening is under scrutiny as well (Hui 2016). The finding of a conotruncal anomaly by prenatal ultrasound or other diagnostic workup should compel caretakers to search for this deletion. The condition can be encountered in undiagnosed adults as well (Vogels et al 2014).

Fluorescence in situ hybridization is the most widely used method for the detection of 22q11.2 deletions in DiGeorge and velocardiofacial syndrome patients. Approximately 76% to 90% of individuals with the DiGeorge and velocardiofacial syndrome phenotype will have a demonstrable 22q11.2 deletion by fluorescence in-situ hybridization (Driscoll et al 1993). This may reflect genetic heterogeneity (the possibility of another locus for DiGeorge and velocardiofacial syndrome), a smaller deletion than is detectable by the probe, or a point mutation in “fluorescence in-situ hybridization negative” individuals. To date, there has been no genotype-phenotype correlation between the size of the deletion and the severity of the phenotype (Carlson et al 1997).

Parental fluorescence in situ hybridization analysis is recommended in those cases with a documented 22q11.2 deletion due to the phenotypic variability seen in this disorder.

Microarray-based comparative genomic hybridization (array-CGH) is an alternative methodology for the detection of 22q11.2 deletions. Proponents claim higher resolution and efficiency with array-CGH compared to fluorescent in situ hybridization (Mantripragada et al 2004). Multiplex ligation-dependent probe amplification is a highly sensitive and economic alternative to currently used methods (Vorstman et al 2006b). Quantitative fluorescent PCR has been used with success as well (Stofanko et al 2013).
The routine blood count predicts the 22q11.2 deletion (specificity 89.7%) when the mean platelet volume is greater than 10fL (Naqvi et al 2011).

Diagnosis may be overlooked for many years, as evidenced by highly diverse cases: in one boy, a hypocalcemic seizure occurred at 8 years of age and led to the diagnosis (Simao et al 2013); in another, adult-onset hypoparathyroidism was diagnosed in a 71-year-old psychiatric patient (Passeri et al 2010).

Management

Initial laboratory evaluations in the neonatal period should include serum calcium measurements and absolute lymphocyte count determination. Low calcium warrants calcium supplementation. Calcium homeostasis typically normalizes with age, although recurrence of hypocalcemia in later childhood and adulthood has been reported (Greig et al 1996; Sykes et al 1997). Therefore, periodic serum calcium screening is recommended (Taylor et al 2003). A low absolute lymphocyte count necessitates evaluation of T-cell and B-cell subsets and immunology referral. Partial immunodeficiency is a cause of recurrent sinus and pulmonary infection in childhood (Gennery 2012). Infants with severe immunocompromise should not receive live vaccines (oral polio or measles, mumps, rubella vaccine) and should be re-evaluated before receiving a live vaccine during childhood. Likewise, patients need to receive irradiated blood products to avoid the serious complication of transfusion-associated graft-versus-host disease (Naqvi et al 2011). Severe immune deficiency may require bone marrow transplantation (Lee et al 2008). Transplantation of T cells or cultured thymus tissue has proven successful, eliminating the need for prophylactic antibiotics and immunoglobulin therapy (Markert et al 2010; McDonald-McGinn and Sullivan 2011; Gennery 2012). Infusion of HLA-matched sibling donor T lymphocytes has proven successful in combating severe adenovirus infection (Iw et al 2013).

Renal ultrasound is recommended due to the increased incidence (approximately 30%) of structural renal abnormalities in these individuals that are not readily detectable by other means (Devriendt et al 1996).

Children with short stature should be evaluated by an endocrinologist for growth hormone deficiency as they may be at increased risk for pituitary abnormalities (Weinzimer et al 1998). Reduced growth appears to be related to the syndrome itself, perhaps a genetic effect, rather than a cardiovascular deficiency (Matthiesen et al 2016). In addition, hypoparathyroidism and hypocalcemia can lead to reduced mineralization of bone and can require monitoring of bone metabolism and bone mineral density (Ficcadenti et al 2015).

Early educational intervention is suggested. Speech and language assessment may aid in diagnosis of a palatal abnormality, with subsequent referral to a craniofacial team for appropriate management. Cephalometry (ie, measurement of cranial base angle, nasopharyngeal depth, velum and velopharyngeal length, and other dimensions) may be helpful in assessing the severity of velopharyngeal dysfunction (Veerapandiyam et al 2011). Candidates for pharyngeal flap correction of velopharyngeal insufficiency should have an MRA to identify ectopic internal carotid arteries that may pose a risk for surgery (Oppenheimer et al 2010). In one study, pharyngoplasty proved more efficacious than palatoplasty alone, which may require additional surgery (Spruijt et al 2012a). Velopharyngoplasty results in normal voice resonance in about one-half of patients, although this may take up to 5 years to develop following surgery; the remainder may manifest residual hypernasality or require further surgery (Spruijt et al 2012b). Superiorly based pharyngeal flap surgery has led to improvement in hypernasality, audible nasal emission, and speech intelligibility in a group of 12 patients (Filip et al 2013).

The use of methylphenidate for ADHD in this population is routinely avoided due to concerns about psychotic exacerbation. However, an open-label study notes that methylphenidate is both a safe and effective treatment for ADHD in children with DiGeorge and velocardiofacial syndrome (Gotthelf et al 2003). S-adenosyl-L-methionine (SAMe) is thought to enhance the COMT enzyme and has proven to be effective in the treatment of patients with depression with or without psychotic symptoms, though no improvement in ADHD symptoms was apparent (Green et al 2012).

The risk of psychiatric illness is present at birth, of course, and early diagnosis and treatment may lead to improved outcomes. In this arena, genetic counselors play an integral but also challenging role (Martin et al 2012) and should realize that parents use the Internet for their main source of information about the syndrome (van den Bree et al 2013). Treatment of the psychiatric illness of patients with DiGeorge and velocardiofacial syndrome is challenging, and many patients do not respond to traditional neuroleptic therapy. The potential use of alphamethyldopa in this population is noted in a single case of the successful treatment of a woman with psychosis (O'Hanlon et al 2003).
Special considerations

Pregnancy

Prenatal diagnosis is available utilizing fluorescence in-situ hybridization analysis on amniocytes, chorionic villi, or fetal lymphocytes (percutaneous umbilical cord sampling). Although definitive, such testing is invasive, and noninvasive screening of cell free DNA in maternal serum is becoming more common (Gross et al 2015; Wapner et al 2015). Referral to a perinatal genetics center is suggested in order that the parents receive appropriate genetic counseling. As affected individuals become able to reproduce, the prevalence of the disorder is likely to rise; at present, an estimated 6% to 10% of cases are familial (McDonald-McGinn and Sullivan 2011).

References cited


Gross SJ, Ryan A, Benn P. Noninvasive prenatal testing for 22q11.2 deletion syndrome: deeper sequencing increases


Huh SH, Ornitz DM. Beta-catenin deficiency causes DiGeorge syndrome-like phenotypes through regulation of Tbx1. Development 2010;137(7):1137-47. PMID 20215350

Hui L. Cell-free DNA testing for 22q11.2 deletion syndrome: appraising the viability, effectiveness and appropriateness of screening. Ultrasound Obstet Gynecol 2016;47(2):137-41. PMID 26833636


Kaplan GP, Hartman BK, Creveling CR. Localization of 4 catechol-O-methyltransferase in the leptomeninges, choroid plexus and ciliary epithelium: implications for the separation of central and peripheral catechols. Brain Res 1980;204:353-60. PMID 7006735


Kikinis Z, Makris N, Finn CT, et al. Genetic contributions to changes of fiber tracts of ventral visual stream in 22q11.2


Maynard TM, Haskell GT, Bhasin N, et al. RanBP1, a velo-cardiofacial/DiGeorge syndrome candidate gene, is expressed
at sites of mesenchymal/epithelial induction. Mech Dev 2002;111(1-2):177-80. PMID 11804793


Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry 1999;56:940-5. PMID 10530637


O'Byrne ML, Yang W, Mercer-Rosa L, et al. 22q11.2 deletion syndrome is associated with increased perioperative events and more complicated postoperative course in infants undergoing infant operative correction of truncus arteriosus communis or interrupted aortic arch. J Thorac Cardiovasc Surg 2014;148(4):1597-605. PMID 24629220


Prasad SE, Howley S, Murphy KC. Candidate genes and the behavioral phenotype in 22q11.2 deletion syndrome. Dev Disabil Rev 2008;14:26-34. PMID 18636634


Sarnat HB, Flores-Sarnat L. Radial micro-columnar cortical architecture: maturational arrest or focal cortical dysplasia. Pediatr Neurol 2013;48:259-70. PMID 23498558


Scariati E, Padula MC, Schaer M, Eliez S. Long-range dysconnectivity in frontal and midline structures is associated to psychosis in 22q11.2 deletion syndrome. J Neural Transm (Vienna) 2016. [Epub ahead of print] PMID 27094177


Shprintzen RJ. Velo-cardio-facial syndrome: 30 years of study. Dev Disabil Rev 2008;14:3-10. PMID 18636631


Spruijt NE, Reijmanhinze J, Hens G, Vander Poorten V, Mink van der Molen AB. In search of the optimal surgical


Stoller JZ, Epstein JA. Identification of a novel nuclear localization signal in Tbx1 that is deleted in DiGeorge syndrome patients harboring the 1223delC mutation. Hum Mol Genet 2005;14(7):885-92. PMID 15703190


Taddei I, Morishima M, Huynh T, Lindsay EA. Genetic factors are major determinants of phenotypic variability in a mouse model of DiGeorge/del22q11 syndromes. Proc Natl Acad Sci 2001;98(20):11428-31. PMID 11562466


Tenhola S, Hendy GN, Valta H, et al. Cinacalcet treatment in an adolescent with concurrent 22q11.2 deletion syndrome and Familial Hypocalciuric Hypercalcemia Type 3 caused by AP2S1 mutation. J Clin Endocrinol Metab 2015;100(7):2515-8. PMID 25993639


Tsai PL, Lian LM, Chen WH. Hypocalcemic seizure mistaken for idiopathic epilepsy in two cases of DiGeorge syndrome (chromosome 22q11 deletion syndrome). Acta Neurol Taiwan 2009;18(4):272-5. PMID 20329596


Villalon-Reina J, Jahanshad N, Beaton E, Toga AW, Thompson PM, Simon TJ. White matter microstructural abnormalities in girls with chromosome 22q11.2 deletion syndrome, Fragile X or Turner syndrome as evidenced by diffusion tensor imaging. Neuroimage 2013;81:441-54. PMID 23602925


Widdershoven JC, Beemer FA, Kon M, Dejonckere PH, Mink van der Molen AB. Possible mechanisms and gene involvement in speech problems in the 22q11.2 deletion syndrome. J Plast Reconstr Aesthet Surg 2008;61:1016-23. PMID 18554997


**References especially recommended by the author or editor for general reading.**

Former authors

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
DiGeorge syndrome: 279.11

ICD-10:
DiGeorge syndrome: D82.1

**OMIM numbers**

Velocardiofacial syndrome: #192430
DiGeorge syndrome: #188400

**Profile**

**Age range of presentation**

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

male=female

**Family history**

family history typical
family history may be obtained

**Heredity**

heredity typical
heredity may be a factor
autosomal dominant

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
autosomal dominant Opitz GBBB syndrome
CHARGE association
Kabuki syndrome

Other topics to consider
Cavum septi pellucidi and cavum vergae
Developmental language disorder
Intravenous immune globulin
Microcephaly
Myopathies associated with parathyroid disorders
Polymicrogyria