GENEReviews

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22q11.2 Deletion Syndrome

[*del 22q11.2. Includes: DiGeorge Syndrome (DGS), Velocardiofacial Syndrome (VCFS), Shprintzen Syndrome, Conotruncal Anomaly Face Syndrome (CTAF), Caylor Cardiofacial Syndrome, Autosomal Dominant Opitz G/BBB Syndrome*]

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Summary

Disease characteristics. Individuals with the 22q11.2 deletion syndrome (del 22q11.2) have a range of findings, including congenital heart disease (74% of individuals), particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus); palatal abnormalities (69%), particularly velopharyngeal incompetence (VPI), submucosal cleft palate, and cleft palate; characteristic facial features (present in the majority of Caucasian individuals); and learning difficulties (70-90%). Seventy-seven percent of individuals have an immune deficiency regardless of their clinical presentation. Additional findings include: hypocalcemia (50%), significant feeding problems (30%), renal anomalies (37%), hearing loss (both conductive and sensorineural), laryngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, seizures (without hypocalcemia), and skeletal abnormalities.

Diagnosis/testing. The 22q11.2 deletion syndrome is diagnosed in individuals with a submicroscopic deletion of chromosome 22 detected by fluorescence in situ hybridization (FISH). Fewer than 5% of individuals with clinical symptoms of the 22q11.2 deletion syndrome have normal routine cytogenetic studies and negative FISH testing.

Management. Individuals with 22q11.2 deletion syndrome with congenital heart defects are treated in the usual manner. Low serum calcium concentration is treated with calcium supplementation. Feeding difficulties are addressed by modification of spoon placement when eating, treatment for gastroesophageal reflux with acid blockade, prokinetic agents, and postural therapy. Palatal anomalies are addressed by a craniofacial team; magnetic resonance angiography (MRA) may identify ectopic internal carotid arteries that pose risk during surgical repair in candidates for pharyngeal surgery. Infections are treated aggressively and infants with lymphocyte abnormalities should not be immunized with live vaccines; rarely, prophylactic antibiotics, IVIG therapy, or thymic transplantation are required. Early educational intervention and speech therapy begin at age one year to monitor/treat motor, cognitive, speech, and language delay.

Genetic counseling. The 22q11.2 deletion syndrome is inherited in an autosomal dominant manner. About 93% of probands have a *de novo* deletion of 22q11.2 and 7% have inherited the 22q11.2 deletion from a parent. Offspring of individuals with del 22q11.2 have a 50% chance of inheriting the 22q11.2 deletion. Prenatal testing is available for fetuses determined to be at 50% risk by family history and for fetuses not known by family history to be at increased risk for del 22q11.2 who have findings of congenital heart disease and/or cleft palate detected by ultrasound examination.

Diagnosis

Clinical Diagnosis

The diagnosis of the 22q11.2 deletion syndrome is suspected in individuals with a range of findings that often includes some combination of the following:

- Congenital heart disease (particularly conotruncal malformations)
- Palatal abnormalities [especially velopharyngeal insufficiency (VPI)]
- Hypocalcemia
- Immune deficiency
- Learning difficulties
- Characteristic facial features

Less frequently seen functional differences:

- Severe dysphagia
- Growth hormone deficiency
- Autoimmune disease (thrombocytopenia, juvenile rheumatoid arthritis, Grave's disease, vitiligo, neutropenia, hemolytic anemia)
- Hearing loss (sensorineural and conductive)
- Psychiatric illness

Other structural anomalies:

- Skeletal findings: pre and postaxial polydactyly of the hands and postaxial polydactyly of the feet, supernumerary ribs, hemivertebrae, craniosynostosis
- Genitourinary tract anomalies: renal agenesis, hydronephrosis, multicystic/dysplastic kidneys, duplicated kidney, horseshoe kidney, absent uterus, hypospadias, inguinal hernia, and cryptorchidism
- Laryngotrachealesophageal abnormalities: vascular ring and laryngeal webs
- Ophthalmologic findings: tortuous retinal vessels, ptosis, posterior embryotoxin, scleracornea, coloboma, cataract, and strabismus
- CNS abnormalities: cerebellar atrophy, polymicrogyria, enlarged sylvian fissures, neural tube defects, tethered cord, unprovoked seizures, and asymmetric crying facies
- Gastrointestinal anomalies: anteriorly placed anus or imperforate anus, esophageal atresia, jejunal atresia, accessory spleens, umbilical hernia, diaphragmatic hernia, intestinal malrotation, and Hirshprung disease
- Preauricular tags

Neoplasms:

- Hepatoblastoma, renal cell carcinoma, Wilm's tumor, and neuroblastoma

Testing

Cytogenetic testing. A small percentage (<1%) of individuals with clinical findings of the 22q11.2 deletion syndrome have chromosomal rearrangements involving 22q11.2, such as a translocation between chromosome 22 and another chromosome.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. Deletion of genes in the DiGeorge chromosomal region (DGCR) is the only genetic defect known to be associated with deletion 22q11.2 [Driscoll, Budarf et al 1992; Wilson et al 1992; Desmaze et al 1993; Driscoll et al 1993].

Yamagishi et al (1999) suggested that the gene responsible for the features of the 22q11.2 deletion syndrome was *UFD1L*, a gene originally described by Pizzuti et al (1997); however, attention has now shifted to *TBX1*. Mutations in *TBX1* have been found in individuals with DiGeorge syndrome who do not have a deletion [Gong et al 2001, Yagi et al 2003]; at least one of these mutations affects function [Stoller & Epstein 2005]. It is still uncertain what other genes must be deleted since mutations in *TBX1* do not account for the CNS manifestations of deletion 22q11.2 syndrome. Furthermore, some individuals with features of 22q11.2 deletion syndrome, including typical conotruncal cardiac anomalies, have not had either an identifiable deletion by FISH analysis or a *TBX1* mutation.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

- **FISH.** The two probes commercially available for 22q11.2 FISH analysis are TUPLE1 and N25. The detection rate of FISH analysis using either probe is thought to be equivalent; however, FISH using either one of these probes is not sensitive enough to detect small deletions (<40 kb) within 22q11.2.

  Note: The probe ARSA, which hybridizes to chromosomal locus 22q13.3, may also be used in testing, but only for control purposes.

Molecular genetic testing: Research A few individuals with findings of the 22q11.2 deletion syndrome have normal routine cytogenetic studies and no deletion by FISH testing using the commercially available probes, but have variant deletions of the DGCR detected with probes that are available on a research basis only. A multiplex ligation-dependent probe amplification (MLPA) assay has been developed to detect deletions of 22q11.2. MLPA is a quantitative multiplex PCR approach for determining relative copy number of a genomic target sequence. It has been shown to be successful in diagnosis of deletions of 22q11.2 [Fernandez et al 2005]. A commercially available MLPA kit (SALSA P023; MRC-Holland, Amsterdam) holds promise for rapid and more comprehensive deletion detection.

Other diagnostic approaches include array CGH (comparative genomic hybridization) [Mantripragada et al 2004] and quantitative PCR [Kariyazono et al 2001].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1: Testing Used in the 22q11.2 Deletion Syndrome

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
FISH	Deletion of 22q11.2 DGCR	>95%	Clinical Testing
Direct DNA [1]	Smaller 22q11 deletion or point mutation	<5%	Research only

1. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with this disorder.

Testing Strategy for a Proband

When a deletion 22q11.2 is suspected, it is recommended that routine cytogenetic analysis be performed at the time of FISH testing because a small percentage (<1%) of individuals with clinical findings of the 22q11.2 deletion syndrome have chromosomal rearrangements involving 22q11.2, such as a translocation between chromosome 22 and another chromosome.

Genetically Related Disorders

No other phenotypes are associated with deletion of 22q11.2.

Clinical Description

Natural History

Findings in 250 individuals (48% male; 52% female) with 22q11.2 deletion syndrome are summarized below [McDonald-McGinn, Kirschner, Goldmuntz, Sullivan et al 1999]. In unpublished data on 600 individuals, the percentages for the following findings remain the same [author, unpublished data 2005].

Thirty-three percent of individuals were five years of age or younger. Marked inter- and intrafamilial variability is observed.

Heart. Congenital heart defects are present in 74% of affected individuals and are the major cause of mortality (>90% of all deaths) in this diagnosis [McDonald-McGinn et al 2001] (Table 2).

Table 2: Cardiac Findings in 222 Individuals with 22q11.2 Deletion Syndrome

Cardiac Finding	% of Affected Individuals
Tetralogy of Fallot (TOF)	22%
Interrupted aortic arch (IAA)	15%
Ventricular septal defect (VSD)	13%
Truncus arteriosus (TA)	7%
Vascular ring	5%
Atrial septal defect	3%
Aortic arch anomaly	3%
VSD; ASD	4%
Other [1]	4%
Normal	26%

From McDonald-McGinn, Kirschner, Goldmuntz, Sullivan et al 1999

1. Hypoplastic left heart syndrome; pulmonary valve stenosis; double outlet right ventricle/interrupted aortic arch; bicuspid aortic valve; heterotaxy/A-V canal/interrupted aortic arch

Palate. Sixty-nine percent of individuals with deletion 22q11.2 have a palatal abnormality (Table 3). The most common, velopharyngeal incompetence (VPI), may be a structural problem (short palate), a functional problem (hypotonia of the velophayrngeal musculature), or a combination of the two. Often children initially diagnosed with deletion 22q11.2 because of a cardiac defect are subsequently found to have unrecognized but clinically significant VPI [McDonald-McGinn, LaRossa et al 1997]. About 17% of persons have no palatal involvement.

Table 3: Palatal Findings with 22q11.2 Deletion Syndrome

Palatal Finding	% of Affected Individuals
Velopharyngeal incompetence (VPI)	27%
Submucosal cleft palate (SMCP)	16%
Overt cleft palate	11%
Bifid uvula	5%
Cleft lip/cleft lip and palate [1]	2%
Infantile VPI [2]	8%
Need follow-up [3]	14%
Normal	17%

From McDonald-McGinn, Kirschner, Goldmuntz, Sullivan et al 1999

1. Either unilateral or bilateral
2. "Infantile VPI" or occult submucosal cleft palate diagnosed by history (nasal regurgitation and frequent otitis media), physical examination, or nasendoscopy (incomplete closure of the velopharyngeal mechanism during crying and swallowing) in children too young to provide an adequate speech sample for definitive diagnosis
3. No overt abnormality, but children too young to provide an adequate speech sample

Feeding. About 30% of children have feeding difficulties, often severe dysphagia requiring nasogastric tube feedings and/or gastrostomy tube placement. Feeding difficulties are independent of cardiac defects and palatal anomalies. Further evaluation of such children may reveal a preponderance of nasopharyngeal reflux, prominence of the cricopharyngeal muscle, abnormal cricopharyngeal closure, and/or diverticulum. Thus, the underlying feeding problem in many children appears to be dysmotility in the pharyngoesophageal area, which is derived from the third and fourth pharyngeal pouches [Eicher et al 2000].

Immune function. Immunodeficiency occurs as a result of thymic hypoplasia. Because the role of the thymus is to support the maturation of functional T cells, impaired T-cell production is the primary defect. T-cell functional defects and antibody defects are less common and are secondary to the T-cell production abnormality [Sullivan 2004].

Compared to control individuals without the deletion, newborns with the 22q11.2 deletion syndrome have significantly fewer cells of thymic lineage; however, improvement in T-cell production occurs over time. In one study, children with the most significant deficiencies in T-cell production improved most in the first year of life [Sullivan et al 1999]. In a study of immune function in 60 affected children over the age of six months, 77% were considered to be immunodeficient regardless of their clinical presentation. Sixty-seven percent had impaired T-cell production, 19% had impaired T-cell function, 23% had humoral defects, and 13% had IgA deficiency [Smith et al 1998, Sullivan et al 1998].

Additional phenotypic features associated with 22q11.2 deletion syndrome such as aspiration pneumonia, palatal dysfunction, and gastroesophageal reflux can all contribute to recurrent infection, especially true in persons with congenital heart disease. Furthermore, dysphagia can lead to poor nutrition which further impairs cellular immunity. Despite these issues, very few school-aged children require active management for their immunodeficiency [Sullivan 2004].

Parathyroid function. Hypocalcemia is present in 17-60% of persons with deletion 22q11.2 and is typically most serious in the neonatal period. Calcium homeostasis typically normalizes with age, although recurrence of hypocalcemia in later childhood has been reported during illness and/or puberty. In some instances, children receiving ongoing care for infantile hypocalcemia may not be diagnosed with the 22q11.2 deletion syndrome until school age; while at least one otherwise asymptomatic adult came to attention following onset of hypoparathroidism in the fourth decade [M Eagen, personal communication].

Craniofacial. Craniofacial findings include auricular abnormalities, nasal abnormalities, "hooded eyelids," ocular hypertelorism, cleft lip and palate, asymmetric crying facies, and craniosynostosis [McDonald-McGinn, Gripp et al 2005]. However, the presence of these features as well as other facial findings, such as a long face and malar flatness, is variable. In fact, some individuals offer no clues to their underlying diagnosis based on their facial features, especially persons of African-American heritage [McDonald-McGinn et al 1996; McDonald-McGinn, Minugh-Purvis et al 2005].

Eyes. A prospective evaluation for ocular abnormalities in 33 individuals revealed hooding of the upper lids (41%), ptosis (9%), hooding of the lower lids (6%), epicanthal folds (3%), and distichiasis (3%). Other findings included posterior embryotoxon (69%), isolated corneal nerves (3%), sclerocornea (3%), deep iris crypts (10%), tortuous retinal vessels (58%), small optic nerves (7%), and tilted discs (3%). Strabismus was observed in 13% and amblyopia in 6%. While posterior embryotoxon was observed in 12-32% of controls, the incidence in individuals with the 22q11.2 deletion syndrome was almost as high as that seen in Alagille syndrome (89%) [Krantz et al 1997]. The incidence of astigmatism, myopia, and hyperopia was comparable to that in the general population. A small number of persons have cataracts and colobomas.

Ear, nose, and throat. Ear abnormalities include overfolded or squared off helices; cupped, microtic, and protuberant ears; preauricular pits or tags, and narrow external auditory meati. A prominent nasal root, bulbous nasal tip, hypoplastic alae nasae, and a nasal dimple/bifid nasal tip are common [Gripp et al 1997]. Stridor resulting from vascular ring, laryngomalacia, and laryngeal webs can occur. Chronic otitis media and chronic sinusitis are common. Both sensorineural and conductive hearing loss have been reported.

Central nervous system. Although the majority of individuals with the 22q11.2 deletion syndrome have a history of hypotonia in infancy and learning disabilities [Moss et al 1995], specific neurologic manifestations are uncommon. Seizures are seen in some individuals and are most often, but not always, associated with hypocalcemia. In one study, 7% (27/383) of persons with deletion 22q11.2 had unprovoked seizures [Kao et al 2004].

Several individuals have asymmetric crying facies [Cayler 1969, Levin et al 1982, Silengo et al 1986, Sanklecha et al 1992, Giannotti et al 1994].

Rarely, ataxia and atrophy of the cerebellum are observed [Lynch et al 1995].

Additional CNS abnormalities include multicystic white matter lesions of unknown significance and perisylvian dysplasia [Bingham et al 1997], hypoplastic pituitary gland, and polymicrogyria (see Polymicrogyria Overview).

Recent investigations utilizing functional MRI scans revealed significantly reduced posterior brain volumes relative to age- and sex-matched controls with more significant white matter loss in the left occipital and left parietal regions than in the frontal lobes [Barnea-Goraly et al 2003, Bearden et al 2004, Bish et al 2004, Kates et al 2004]. Many of these changes in brain structure can be postulated to relate to the specific cognitive deficits exhibited in the area of working memory, executive function, visuospatial skill, language, and math performance.

Overall, the pattern of CNS abnormalities is broad and overlaps with that seen in some cases of Opitz G/BBB syndrome [Neri et al 1987, Guion-Almeida & Richieri-Costa 1992, MacDonald et al 1993].

Psychosocial development and cognitive function. In general, young children with the 22q11.2 deletion syndrome have delays in motor milestones (mean age at walking of 18 months), delay in emergence of language (many are nonverbal at age 2-3 years), and autism/autistic spectrum disorders in approximately 20% [Fine et al 2005].

Specifically, in a study of 28 toddlers assessed with standardized tests, mental development was average in 21%, mildly delayed in 32%, and significantly delayed in 46%; in motor development, 8% were average, 13% were mildly delayed, and 79% were significantly delayed.

In a group of 12 preschoolers assessed using the WPPSI-R, the full scale IQ was 78±11, the mean performance IQ was 78±14, and the mean verbal IQ was 82±15. In total language, 16% were average, 44% were mildly delayed, and 40% were significantly delayed [Solot et al 1998].

Older individuals with 22q11.2 deletion syndrome generally have an atypical neuropsychologic profile across multiple domains, the most striking aspect of which is a significantly higher verbal IQ score than performance IQ score. Moss et al (1995) observed a mean split between the verbal IQ and performance IQ in 66% of 80 school-age children consistent with a nonverbal learning disability that is rare in the general population [Wang et al 1998]. Because the full scale IQ score alone does not accurately represent the abilities of many individuals with 22q11.2 deletion syndrome, verbal and performance IQ scores need to be considered separately.In addition, affected individuals exhibit relative strengths in the areas of rote verbal learning and memory, reading decoding, and spelling. Deficits are found in the areas of nonverbal processing, visual-spatial skills, complex verbal memory, attention, working memory, visual-spatial memory, and mathematics. This evidence of stronger verbal than visual memory skills and stronger reading than math skills also supports the presence of a nonverbal learning disorder that requires specific cognitive remediation, behavior management, and parental counseling.

In a group of 80 school-aged children assessed with the age-appropriate Weschler IQ test, the mean IQ score was 76, whereas, 18% attained full scale IQ scores in the average range, 20% in the low-average range, 32% in the borderline range, and 30% in the retarded range.

Psychiatric illness. Behavior and temperament observed in some individuals with the 22q11.2 deletion syndrome include disinhibition and impulsiveness on the one hand and shyness and withdrawal on the other [Swillen et al 1999]. Attention deficit, anxiety, perseveration, and difficulty with social interactions are also common, along with autism and autistic spectrum disorders [Swillen et al 1999; Niklasson et al 2001; Vorstman, personal communication].

The incidence of psychiatric disorders, including schizophrenia, bipolar disorder, anxiety, and depression, is increased. The prevalence and exact nature of these psychiatric disorders are still being investigated [Shprintzen et al 1992, Chow et al 1994, Bassett et al 1998, Yan et al 1998, Murphy et al 1999, Baker & Skuse 2005, Bassett et al 2005, Oskarsdottir et al 2005]

Growth. Most adults with the 22q11.2 deletion syndrome are of normal stature; however, in 95 children between the ages of one and 15 years, 41% were below the fifth centile in height. Of these, four were significantly below the fifth centile; all had low levels of growth factors IGF1 and IGFBP3. Three had evidence of growth hormone deficiency; three had a small pituitary gland on MRI; and two responded to human growth hormone therapy [Weinzimer et al 1998].

Autoimmune disease. Polyarticular juvenile rheumatoid arthritis (JRA) occurs in children with the 22q11.2 deletion syndrome at a frequency 20 times that of the general population rate. The age of onset of JRA ranges from 17 months to five years. HLA types permissive for the development of JRA are observed [Sullivan et al 1997, Keenan et al 1997]. Other autoimmune disorders associated with 22q11.2 deletion syndrome include: idiopathic thrombocytopenia purpura (ITP), hyperthyroidism (Grave's disease), hypothyroidism, vitiligo, hemolytic anemia, autoimmune neutropenia, aplastic anemia, and celiac disease. ITP is seen 200 times more frequently in individuals with deletion 22q11.2 than in the general population [Sullivan et al 1997, Jawad et al 2001, Kawame et al 2001].

Musculoskeletal system. Of 108 individuals evaluated for skeletal abnormalities, 6% had upper-extremity anomalies, including pre- and postaxial polydactyly, and 15% had lower-extremity anomalies including postaxial polydactyly, club foot, overfolded toes, and syndactyly of toes 2 and 3 [Ming et al 1997].

Of 63 individuals on whom chest films were examined, 19% had vertebral anomalies including butterfly vertebrae, hemivertebrae, and coronal clefts; 19% had rib anomalies, most commonly supernumerary or absent ribs. Hypoplastic scapulae were seen in 1.5% [Ming et al 1997]. Significant cervical spine abnormalities observed in 50% of 79 persons studied prospectively included posterior block vertebrae of C2-C3 without block vertebrae in 21%, hypoplastic/anomalous C1 in 75%, dysmorphic C2 in 59%, and posterior element fusion with block vertebrae of C2-C3 in 13% [Ricchetti et al 2004]. In addition, 56% of persons with cervical spine anomalies had instability on flexion and extension radiographs; 33% had increased motion at more than one vertebral level; of these, four children had abnormalities including increased C2-C3 segmental motion with anterior and posterior narrowing of the spinal canal on further examination with cervical CT scan and/or MRI. Two of the four had surgical stabilization; one of the two required an emergency procedure following onset of symptoms of spinal cord compression.

Kidneys. A prospective evaluation using renal ultrasonography in 80 individuals with the 22q11.2 deletion syndrome who had no prior history of uropathy revealed renal or other GU abnormalities in 31% [Wu et al 2002]. These included single kidney, echogenic kidney,

multicystic dysplastic kidney/small kidneys, calculi, bladder wall thickening, horseshoe kidney, duplicated collecting system, renal tubular acidosis, and hydronephrosis (5%), and enuresis. The high incidence of renal abnormalities is similar to that reported by Devriendt et al (1996). In addition, hypospadias, undescended testes [McDonald-McGinn et al 1995] and absent uterus have also been observed [Huff, personal communication].

Other. Other findings observed in individuals with the 22q11.2 deletion syndrome include: abnormal lung lobation, significant constipation, imperforate anus, intestinal malrotation/nonrotation, Hirshsprung disease, diaphragmatic hernia (including late presentation), umbilical and inguinal hernia, leg pain, and craniosynostosis [McDonald-McGinn et al 1995; McDonald-McGinn, Kirschner et al 1999; McDonald-McGinn, Maisenbacher et al 2004; McDonald-McGinn, Gripp et al 2005].

Bernard-Soulier syndrome (BSS) [Budarf et al 1995], an autosomal recessive disorder of thrombocytopenia and giant platelets, is caused by a mutation in one of four genes, one of which *(GP1BB*) maps to 22q11.2. BSS is associated with the 22q11.2 deletion syndrome in persons whose non-deleted chromosome 22 has a mutation in *GP1BB*. Individuals with both 22q11.2 deletion syndrome and BSS are particularly susceptible to bleeding secondary to surgical procedures.

Despite recent reports of neoplasia in individuals with deletion 22q11.2, it is unclear if deletion 22q11.2 predisposes to cancer. Malignancies reported include: hepatoblastoma [Patrone et al 1990; Scattone et al 2003; Adam, personal communication 2004]; renal cell carcinoma [Scattone et al 2003]; Wilms tumor [Wallgren-Pettersson, personal communication]; and neuroblastoma [Chatten et al 1991]. Based on these reports a causal relationship between 22q11.2 deletion syndrome and hepatoblastoma seems likely as the population incidence of hepatoblastoma is 1/1,000,000.

Genotype-Phenotype Correlations

The majority of individuals have the same large deletion of the DGCR. Of note, the size of the deletion remains unchanged with parent-to-child transmission. The great inter- and intrafamilial clinical variability makes genotype-phenotype correlations difficult [Driscoll et al 1995, McDonald-McGinn et al 2001]. Anecdotally, developmental delays appear to be more significant in familial cases; however, this may reflect socioeconomic rather than genetic factors.

Penetrance

Penetrance is complete in individuals with deletion 22q112 detected by FISH; variability is marked.

Anticipation

To date, anticipation has not been observed.

Nomenclature

It is now recognized that the 22q11.2 deletion syndrome encompasses the phenotypes previously called DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS) (Shprintzen syndrome), conotruncal anomaly face syndrome (CTAF) [Matsuoka et al 1994], many cases of the autosomal dominant Opitz G/BBB syndrome [McDonald-McGinn et al 1995, Fryburg et al 1996, LaCassie & Arriaza 1996], and Cayler cardiofacial syndrome (asymmetric crying facies) [Giannotti et al 1994]. The clinical descriptions of DGS, VCFS, and CTAF resulted from an ascertainment bias.

DGS was originally described as a developmental field defect of the third and fourth pharyngeal pouches with a conotruncal cardiac anomaly and aplasia or hypoplasia of the thymus gland and parathyroid glands. Later, congenital heart disease was added. The majority of individuals with DGS were identified in the neonatal period with a major congenital heart defect, hypocalcemia, and immunodeficiency.

VCFS, also called Shprintzen syndrome, was originally described as the combination of velopharyngeal incompetence (VPI), congenital heart disease (usually a ventricular septal defect or tetralogy of Fallot), characteristic facial features, and developmental delay or learning difficulties. Children with VCFS tended to be diagnosed in cleft palate clinics or craniofacial centers when they reached school age and speech and learning difficulties became evident [Wilson et al 1993; Wulfsberg et al 1996; McDonald-McGinn, Zackai et al 1997, Thomas & Graham 1997].

Prevalence

Estimates of prevalence vary from one in 4000 [Wilson et al 1994] to one in 6395 [Devriendt et al 1998]. Given the variable expression of the deletion 22q11.2, the incidence is probably much higher than previously estimated. In a population-based study in Sweden, the mean annual incidence was 14.1 per 100,000 live births [Oskarsdottir et al 2004, Oskarsdottir, Belfrage et al 2005, Oskarsdottir, Persson et al 2005]. A U.S. population-based study conducted by the Centers for Disease Control (CDC) found an overall prevalence of about one in 6000 in whites, blacks, and Asians, and one in 3800 in Hispanics [Botto et al 2003].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Each of the anomalies seen in the 22q11.2 deletion syndrome can be found as an isolated anomaly in an otherwise normal individual.

Up to 8% of individuals with an isolated palatal cleft, including submucosal cleft, may have deletion 22q11.2, making this the most common genetic syndrome associated with palatal clefts. Conversely, the 22q11.2 deletion syndrome is the most common genetic basis of congenital velopharyngeal incompetence.

Disorders with overlapping features:

- Smith-Lemli-Opitz syndrome (when polydactyly and cleft palate are present). Smith-Lemli-Opitz syndrome is associated with elevated serum concentration of 7-dehydrocholesterol (7-DHC) or an elevated 7-dehydrocholesterol:cholesterol ratio. Molecular genetic testing for mutations of the *DHCR7* gene is available.
- Alagille syndrome (when butterfly vertebrae, congenital heart disease, and posterior embryotoxon are present). Sequence analysis of the *JAG1* gene detects mutations in more than 70% of individuals who meet clinical diagnostic criteria. FISH detects a microdeletion of 20p12, including the entire *JAG1* gene, in approximately 5-7% of affected individuals.
- VATER syndrome (when heart disease, vertebral, renal, and limb anomalies are present)
- Oculo-auriculo vertebral (Goldenhar) syndrome (when ear anomalies, vertebral defects, heart disease, renal anomalies are present)

Individuals suspected of having the 22q11.2 deletion syndrome but having normal FISH studies may have a chromosome abnormality involving some other chromosomal region, including deletion 10p13-p14.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

In the neonatal period:

- Measurement of serum ionized calcium concentration to assess for hypoparathyroidism, followed by a formal endocrinology evaluation if abnormal
- Measurement of absolute lymphocyte count; a low absolute lymphocyte count necessitates evaluation of T- and B-cell subsets and referral to an immunologist.
- Evalution of humoral immune response
- Renal ultrasound examination to evaluate for structural renal defects
- Chest x-ray to evaluate for thoracic vertebral anomalies
- A baseline cardiac evaluation by a cardiologist that includes a chest x-ray, ECG and echocardiogram; if a vascular ring is suspected, a chest MRI may be required.

In infancy:

- Assessment for possible feeding problems such as significant gastroesophageal reflux; difficulty with sucking/swallowing, advancing feeds, addition of textured foods; vomiting and constipation
- Speech and language assessment by age one year given that almost all affected children have delay in emergence of language and would benefit from early intervention strategies. In addition, such an evaluation aids in the diagnosis of a palatal abnormality/VPI.

After age four:

- Cervical spine films (five views: flexion, extension, AP, lateral, open mouth) in all individuals over age four years, the age that the cervical spine becomes ossified

As needed:

- Evaluation of children with short stature (height below the 2nd centile) by an endocrinologist for possible growth hormone deficiency
- Evaluation in any person with evidence of anxiety, mood disorder, behavioral differences, or frank pyschoses
- Evaluation by a hematologist of any person with a history of a bleeding disorder

Treatment of Manifestations

- Depending on the age and presenting problems of the individual with the 22q11.2 deletion syndrome, a multidisciplinary evaluation involving healthcare providers from the following specialties is often necessary: medical genetics, plastic surgery, speech pathology, otolaryngology, audiology, dentistry, cardiology, immunology, child development, child psychology, neurology, and general pediatrics.
- Low serum calcium concentration warrants calcium supplementation in a standard manner and, when possible, referral to an endocrinologist because of the increased risk of renal calculi in individuals on long-term calcium supplementation.

- Feeding difficulties should be evaluated by a gastroenterologist to assess for possible structural abnormalities such as intestinal malrotation/nonrotation, Hirschprung disease, and late-onset diaphragmatic hernia [McDonald-McGinn et al 2004].
- Strategies for addressing feeding difficulties include: modification of spoon placement when eating; treatment for gastroesophageal reflux with acid blockade, prokinetic agents, postural therapy; and medication to treat gastrointestinal dysmotility and to facilitate bowel evacuation [Dinulos & Graf 1998, Eicher et al 2000].
- Educational intervention and speech therapy should be instituted at age one year because of the high risk for motor, cognitive, speech, and language delay.
- Growth hormone deficiency, if present, should be treated as in the general population.
- Immune deficiency generally requires no specific intervention except treating infections aggressively. Rarely, prophylactic antibiotics, IVIG therapy, or thymic transplantation are required.
- Early diagnosis and early intervention for psychiatric illnesses improve long-term prognosis in individuals with schizophrenia and bipolar disorder [Clark & O'Callaghan 2003] and other disorders including autism and ADHD/ADD.

Prevention of Secondary Complications

Infants with lymphocyte abnormalities should not be immunized with live vaccines (i.e., oral polio, MMR). Their immune status should be re-evaluated in childhood before receiving live vaccines. In addition, antibody studies to assess results of immunizations are warranted.

Surveillance

Affected individuals require follow-up as needed on a "system by system" basis.

Regular developmental assessments benefit the child and assist the school in providing appropriate remediation.

Periodic re-evaluation by a medical geneticist can apprise the family of new developments and/or recommendations.

Therapies Under Investigation

Search Clinical Trials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The 22q11.2 deletion syndrome is a contiguous deletion syndrome inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 93% of probands have a *de novo* deletion of 22q11.2.
- Seven percent have inherited the deletion from a parent.
- Recommendations for the evaluation of parents of a proband include FISH testing because mildly affected adults, as well as normal adults with somatic mosaicism, have been identified [McDonald-McGinn et al 2001].

Sibs of a proband

- The risk to the sibs of a proband depends upon the status of the parents.
- If the parents of an individual with the 22q11.2 deletion syndrome have normal FISH studies, the risk to sibs is low, but greater than that of the general population because parents with germline mosaicism or low-level somatic mosaicism have been identified.
- If a parent is also found to have the 22q11.2 deletion syndrome, the risk to each sib is 50%.

Offspring of a proband. Offspring of individuals with the 22q11.2 deletion syndrome have a 50% chance of inheriting deletion 22q11.2.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to have the deletion, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancies. Prenatal testing using FISH analysis is available.

- Chromosome preparations from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or CVS at 10-12 weeks' gestation can be analyzed using FISH in the same manner described in Molecular Genetic Testing.
- Fetuses at increased risk may be evaluated between 18 and 22 weeks' gestation by high-resolution ultrasound examination for palatal and other associated anomalies and by echocardiography for cardiac anomalies.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-risk pregnancies. In some fetuses not known by family history to be at increased risk for the 22q11.2 deletion syndrome, findings of congenital heart disease and/or cleft palate detected by routine ultrasound examination may suggest the diagnosis, in particular in those individuals with conotruncal cardiac anomalies such as interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, and ventricular septal defect. Chromosome preparations obtained from fetal cells can be analyzed using FISH. Establishing the diagnosis of the 22q11.2 deletion syndrome even late in gestation can be useful for perinatal management.

Preimplantation genetic diagnosis (PGD) is available for families in which the diagnosis of the 22q11.2 deletion syndrome has been established in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of 22q11.2 Deletion Syndrome

Critical Region	Chromosomal Locus	Protein Name
DGCR	22q11.2	Unknown

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for 22q11.2 Deletion Syndrome

188400	DIGEORGE SYNDROME; DGS
192430	VELOCARDIOFACIAL SYNDROME
600594	DIGEORGE SYNDROME CRITICAL REGION GENE 2; DGCR2
601279	DIGEORGE SYNDROME CRITICAL REGION GENE 6; DGCR6
601755	DIGEORGE SYNDROME CRITICAL REGION GENE 14; DGCR14
609030	DIGEORGE SYNDROME CRITICAL REGION GENE 8; DGCR8

Table C. Genomic Databases for 22q11.2 Deletion Syndrome

Critical Region	Entrez Gene
DGCR	6899 (MIM No. 188400)

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Tbx1 was inactivated in the mouse by gene targeting approaches to assess its role in embryonic development [Jerome & Papaoiannou 2001, Lindsay et al 2001, Merscher et al 2001]. Mice heterozygous for the null mutation survived in normal Mendelian ratios and were mildly affected with defects consistent with the 22q11.2 deletion syndrome. Phenotypic studies of *Tbx1*-null mouse mutants have substantiated the role of *Tbx1* in the etiology of all of the physical anomalies in the 22q11 deletion syndrome [Liao et al 2004]. The full range of malformations in the 22q11 deletion syndrome was elicited by varying the dosage of *Tbx1* [Liao et al 2004]. All the pharyngeal arch derived malformations increased as the dosage became more extreme, suggesting that similar pathogenic mechanisms are responsible.

Normal allelic variants: A number of genes have been mapped within the DGCR (DiGeorge chromosomal region) on 22q11.2 (see Table 4).

Pathologic allelic variants: More than 85% of individuals with deletion 22q11.2 have deletions in the same approximately 3-Mb region; the remainder have either variant deletion endpoints or recurrent, atypical shorter deleted segments nested within the large typically deleted region (TDR) [Levy et al 1995, Kurahashi et al 1996, O'Donnell et al 1997, McQuade et al 1999]. A small 20-kb deletion within the typically deleted region was reported in an individual with a classic VCFS/DGS phenotype [Yamagishi et al 1999]. This smaller deletion disrupts the *UFD1L* and *CDC45L* genes. In several additional affected individuals, the deletions do not overlap the typically deleted region in that they begin distal to it and extend toward the telomere. The location of duplicated sequence blocks in the vicinity of the 22q11.2 deletion endpoints strongly implicates them in the events leading to the typical and atypical deletions.

A small number of individuals have the deletion as the result of unbalanced translocations that delete the 22pter ↓q11 region. (For more information, see Genomic Databases table above.)

Normal gene product: Several of the gene products from within the deletion have been identified and are being further characterized. See Table 4 for a list of genes and their relevant gene products.

Abnormal gene product: Unknown

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

The 22q11 Group
PO Box 1302
MK13 0LZ, United Kingdom
Milton Keynes
Phone: (+44) 1908 320 852
Email: 22q11@melcom.cix.co.uk
www.vcfs.net

The International 22q11.2 Deletion Syndrome Foundation, Inc.
1874 E. Route 70, Suite 3
Cherry Hill, NJ 08003
Phone: 877-739-1849
Email: mabissi@22q.org
www.22q.org

International DiGeorge/VCF Support Network
c/o Family Voices of New York
46 1/2 Clinton Avenue
Cortland, NY 13045
Phone: 607-753-1621 (day); 607-753-1250 (eve)
Fax: 607-758-7420

Max Appeal
Landsowne House
Wollaston, Stourbridge

West Midlands, UK
DY8 1049
Phone: (+44) 0 138-482-1227
Email: info@maxappeal.org.uk
www.maxappeal.org.uk

National Library of Medicine Genetics Home Reference
22q11.2 deletion syndrome

NCBI Genes and Disease
DiGeorge syndrome

Velo-Cardio-Facial Syndrome Education Foundation
PO Box 874
Milltown, NJ 08850
Phone: 866-VCFSEF5 (866-823-7335); 732-238-8803
Email: info@vcfsed.org
www.vcfsef.org

Chromosome 22 Central
237 Kent Avenue
Timmins, ON
Canada P4N 3C2
Phone: 705-268-3099
Email: a815@c22c.org
www.c22c.org

Chromosome Deletion Outreach, Inc
PO Box 724
Boca Raton, FL 33429-0724
Phone: 888-CDO-6880 (888-236-6680); 561-395-4252 (family helpline)
Email: info@chromodisorder.org
www.chromodisorder.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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Table 4. Genes within the DiGeorge Chromosomal Region (Centromere to Telomere)

Gene	Function/Homology	Expression	Reference
DGCR6	Similarity to lamin g-.chain & Drosophila gonadal protein	Widely expressed	*Demczuk et al 1996*
LAN/DGCR2/IDD	Similarity to LDL-receptor & C-type lectin	Widely expressed	*Budarf et al 1995*, *Wadey et al 1995*, *Demczuk et al 1995*
TSK2 (serine/threonine kinase)	Serine/threonine kinase	Testis	*Gong et al 1996*, *Goldmuntz et al 1997*
DGSI/ES2	Similarity to protein of unknown function *C.elegans*	Widely expressed	*Gong et al 1996*, *1997*, *Rizzu et al 1996*
GSCL (goosecoid-like)	Homeobox protein of paired-like class	Testis; brain	*Gottlieb et al 1997*
CTP (citrate transport protein)	Mitochondrial inner membrane-electroneutral exchange	Widely expressed	*Heisterkamp et al 1995*, *Goldmuntz et al 1996*
CLTCL (clathrin heavy chain-like)	Similarity clathrin-heavy chain	Most abundant sk. muscle	*Gong et al 1996*, *Kedra et al 1996*, *Sirotkin et al 1996*, *Holmes et al 1997*
HIRA	Homology to yeast HIR1 and HIR2	Widely expressed	*Halford, Wilson, et al 1993*, *Lorain et al 1996*
NLVCF	Unknown	Widely expressed	*Funke et al 1998*
UFD1L	Similarity to yeast ubiquitin fusion degradation 1 protein	Widely expressed	*Pizzuti et al 1997*
CDC45L	Similarity to other CDC45 proteins	Widely expressed	*McKie et al 1998*, *Saha et al 1998*, *Shaikh et al 1999*
TMVCF	Similarity to rat protein of unknown function	Widely expressed; highest in lung	*Sirotkin, Odonnell, et al 1997*
hCDCrel-1 (human cdc-related)	Similarity GTP-binding proteins	Unknown	*Zieger et al 1997*
GP1BB (glycoprotein Ibβ)	Subunit of platelet receptor von Willebrand factor	Platelets	*Budarf et al 1995*
TBX-1	Member of T box DNA family of transcription factors	Adult sk. muscle & testis; fetal tissues	*Chieffo et al 1997*
COMT (Catechol-O-methyltransferase)	Catecholamine metabolism	Widely expressed	*Grossman et al 1992*
ARVCF	Novel member of catenin subfamily	Widely expressed	*Sirotkin, Morrow, et al 1997*
T10	Unknown	Widely expressed	*Halford, Wadey, et al 1993*
N41 cDNA	Unknown	Widely expressed	*Emanuel et al 1993*
LZTR-1	Similarity to leucine upper-like domain	Widely expressed	*Kurahashi et al 1995*
ZNF74	RNA binding protein	Widely expressed	*Aubry et al 1993*, *Grondin et al 1996*

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