Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes)

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Chromosome 22q11.2 deletion syndrome occurs in approximately 1 of 3000 children. Clinicians have defined the phenotypic features associated with the syndrome and the past 5 years have seen significant progress in determining the frequency of the deletion in specific populations. As a result, caregivers now have a better appreciation of which patients are at risk for having the deletion. Once identified, patients with the deletion can receive appropriate multidisciplinary care. We describe recent advances in understanding the genetic basis for the syndrome, the clinical manifestations of the syndrome, and new information on autoimmune diseases in this syndrome. Curr Opin Pediatr 2002, 14:678–683

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Abbreviations

TOF	tetralogy of Fallot
UFD1L	ubiquitin fusion-degradation protein
VSD	ventricular septal defect

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Overview

Chromosome *22*q11.*2* deletion syndrome is the name given to a heterogeneous group of disorders that share a common genetic basis. Most patients with DiGeorge syndrome and velocardiofacial syndrome have monosomic deletions of chromosome *22*q11.*2* [1,2]. Other syndromes in which a substantial fraction of patients have been determined to have the deletion are conotruncal anomaly face syndrome, Caylor cardiofacial syndrome, and autosomal dominant Opitz-G/BBB syndrome. Complicating the situation further is the fact that not all patients with hemizygous deletions of chromosome *22*q11.*2* have identical deletions. Despite the heterogeneity of both the clinical manifestations and the chromosomal deletions, much progress has been made in the last year in understanding the genetic basis of the chromosome *22*q11.*2* deletion syndromes. Unfortunately, less progress has been made in understanding the genetic bases of the syndromes not caused by chromosome *22*q11.*2* deletions.

When all patients with chromosome *22*q11.*2* deletions are considered together, cardiac malformations, speech delay, and immunodeficiency are the most common characteristics [3,4]. However, no single constellation of features is overwhelmingly associated with the deletion and, thus, caregivers must consider the deletion in any patient with a conotruncal cardiac anomaly, neonatal hypocalcemia, or any of the less common features when seen in association with dysmorphic facial features or in combination. Each year brings new information on the phenotypic spectrum of this syndrome and this past year saw further delineation of the cardiac phenotypes and additional uncommon phenotypic associations.

Management of the immunodeficiency in chromosome *22*q11.*2* deletion syndrome has long been problematic. The spectrum of the immunodeficiency ranges from profound and immediately life threatening to nonexistent. Therefore, no universal approach exists for the treatment of all patients with this syndrome. The use of a fully matched sibling bone marrow transplant or a thymic transplant is required for the profoundly immunodeficient patient [5]. Management of all other patients is not standardized and is probably best approached by stratifying them according to standard laboratory analyses. Recent studies characterizing clinical and laboratory features of the immunodeficiency should aid in the individualized management of these patients.

This review focuses on recent studies characterizing the clinical manifestations and new information on the genetic basis of this complex syndrome. The relevant genes within the deleted region have been further delineated and the *TBX1* gene represents a promising candidate gene. Some of the heterogeneity in this syndrome has been modeled in mice, where the background profoundly affects the phenotype.

Genetic basis of chromosome 22q11.2 deletion syndrome

Phenotypic abnormalities of chromosome 22q11.2 deletion syndrome include thymus and parathyroid hypoplasia or aplasia, cardiac outflow tract abnormalities, cleft palate, velopharyngeal insufficiency, and dysmorphic facial features. The pharyngeal arches and pouches are a common embryonic precursor for the thymus, parathyroid, and conotruncal region of the heart. Defects in these organs can be caused by impaired migration of neural crest cells into pouch endoderm [6•]. Because the phenotype of chromosome 22q11.2 deletion syndrome is so variable and the extent of deletion does not seem to correlate with disease severity, identifying a single gene responsible for all the features of the phenotype has been difficult. The question of whether the manifestations of the syndrome are caused by haploinsufficiency of a single gene or a combination is not purely academic. It has important implications for the development of treatment strategies.

Within the last year, elegant studies using chromosome-engineering techniques in mice have led to the proposal of several candidate genes. Several different deletions were generated within a region of mouse chromosome 16, a region syntenic to the human chromosome 22q11.2 region, and tested for expression of the phenotypes seen in patients [7–9•,10,11,12••,13•]. From these extensive studies in mouse models, one candidate gene appears most promising, *TBX1*. The *TBX1* gene belongs to a family of transcription factors that contain a DNA binding domain called "T-box." Homozygous deletion of the *TBX1* gene in mice was lethal in late gestation; however, the known features of chromosome 22q11.2 deletion syndrome, including cleft palate, abnormal facial features, thymic and parathyroid hypoplasia, and cardiac outflow tract abnormalities, were apparent in the embryos [9•,13•]. Absent or reduced fourth pharyngeal arches and cardiac outflow tract defects were seen in embryos that were haploinsufficient for the *TBX1* gene [8,9•,13•]. Cardiac features were seen in isolation when the deletion carrying *TBX1* was bred onto certain mouse strains, whereas thymic and parathyroid phenotypes were seen more frequently in other mouse strains [12••], which suggests that the manifestations of *TBX1* haplosufficiency may be dependent on the genetic background. However, the *TBX1* locus is not always found within the deleted region of 22q11.2, and clear loss of function mutations in *TBX1* have not yet been found in humans with the 22q11.2 deletion syndrome phenotype. An ambitious study evaluated 105 patients with features of DiGeorge syndrome but who did not have a demonstrable deletion of chromosome 22q11.2. Seven patients had mutations or rare variants of *TBX1*; however, in many cases, the same gene defects were seen in unaffected family members [14•]. This could reflect the heterogeneity of the syndrome or could suggest that *TBX1* mutations are not responsible for the full phenotype.

Two other genes have been considered as credible candidate genes: (1) The *CRKOL* gene is highly expressed in derivatives of the neural crest, and codes for an adaptor protein involved in the response to growth factors and focal adhesion signaling. Deletion of both copies of *CRKOL* gene resulted in gestational deaths in mice that also had many of the abnormalities associated with 22q11.2 deletion syndrome, including defects of the cardiac outflow tract and thymus as well as dysmorphic facial features [15]. Mice hemizygous for the deletion did not express a similar phenotype. (2) The ubiquitin fusion-degradation protein (UFD1L) encodes a protein important for ubiquitin-dependent protein turnover [16]. The ubiquitin fusion-degradation protein is expressed in a pattern consistent with the features of chromosome 22q11.2 deletion syndrome (*ie*, branchial arches) [17]. Further studies have not confirmed a role for this gene in the phenotype [18], and no recent studies have appeared. Thus, *TBX1* is the leading candidate gene. Indeed, it seems likely to play a substantial role in the phenotype. Certain caveats should be considered. Not all patients with compatible clinical features have a deletion that includes the *TBX1* gene. Other genes within the deleted region may modify or mold the phenotype. For example, the platelet glycoprotein gene, *GP1b*, may be implicated in the mild thrombocytopenia seen in a number of patients. Genes other than *TBX1* may play a role in behavioral aspects of the syndrome [10,19].

Cardiac features

Cardiac anomalies, immunodeficiency, and speech delay appear to be the most frequent phenotypic manifestations of chromosome 22q11.2 deletion syndrome. The cardiac anomalies are often described as conotruncal anomalies; however, various outflow tract anomalies are also seen. Interrupted aortic arch, isolated ventricular septal defect (VSD), and tetralogy of Fallot (TOF) are the most common anomalies. Pulmonary atresia with VSD and truncus arteriosus are nearly as common. The remainder of the cardiac defects spans an enormous spectrum, ranging from hypoplastic left ventricle to vascular rings. Only 20% of patients with the deletion have a normal heart and great vessels [3,4,20•].

Tetralogy of Fallot with pulmonary atresia is particularly strongly associated with the deletion, and TOF has been

used as a model to identify the gene(s) critical to the development of cardiac defects in the deletion. Fourteen patients with TOF had deletion mapping performed to identify the region of overlap between the patients. The shortest region, which was deleted in all patients, is relatively proximal to the centromere [21]. This is a region that contains the *TBX1* gene, which may explain the finding. It is also similar to the region described in an interesting consanguineous kindred in which three of four members homozygous for a region of chromosome 22q11.2 proximal to the *COMT* gene had clinical features consistent with DiGeorge syndrome. The authors hypothesize that a mild mutation within that region becomes clinically significant when homozygous [22].

This past year has been notable for a more comprehensive delineation of the cardiac phenotype. The murine deletion models emphasize the importance of the great vessels and additional studies of humans have confirmed that many cardiac anomalies are seen in association with great vessel anomalies [23]. Large studies of the cardiac phenotypes demonstrated that the deletion was seldom found in patients with an isolated cardiac defect and no other syndromic features [20,24]. Another significant finding was that the cardiac anomalies were often compound. Valvular anomalies and defects in arborization of the pulmonary vessels were seen. The defects varied in the extent to which the anatomic site was involved [20]. The difficulty of classifying compound defects, their ability to predict the presence of the deletion, and the difficulties they pose with surgical treatment are well described in another series from the same institution [24].

Immune system

The immune system is demonstrably affected in 80% of children with chromosome 22q11.2 deletion syndrome. As a consequence of thymic hypoplasia, patients typically have diminished T-cell numbers. The function is preserved except for the rare cases (<0.5%) that have absent T cells. Antibody production is generally normal [25], although IgA deficiency is increased in patients with the deletion [26•]. Clinical consequences of the T-cell production defect are predictable. Patients suffer from prolonged viral infections and have frequent bacterial superinfections of the upper and lower respiratory tract. About 20% of the patients have a normal immune system as defined by normal T-cell numbers. The infections are also seen in this population with normal T-cell numbers, suggesting that anatomy, reflux, allergies, cardiac disease, and poor nutrition contribute to the recurrent infections. Of the patients who have a mild to moderate decrement in T-cell production, the absolute T-cell numbers are not predictive of infections. Interestingly, among the few known adults, approximately 25% have recurrent infections.

Recurrent infections are predictable, based on the known immunodeficiency. Another consequence is autoimmune disease, which is seen in approximately 9% of all patients with the deletion [26•]. No one specific autoimmune disease is seen in this syndrome, rather the risk of all autoimmune diseases seems to be increased. Diabetes has been described [27], as has autoimmune thyroid disease in a substantial subset of patients [28]. Juvenile rheumatoid arthritis is statistically the most common autoimmune disease in children with the deletion [29•]. It appears to be more frequent in the subset of patients who have IgA deficiency.

Hypocalcemia

Hypoplastic parathyroid glands reflect the abnormal development of the third and fourth branchial arches. Neonatal hypocalcemia is one of the strongest predictors of a chromosome 22q11.2 deletion because there are few other causes. It is seen in 17% to 60% of patients with the deletion, depending on the definition used. It generally improves over the first year of life as the parathyroid glands hypertrophy. Few older patients require ongoing calcium supplementation. Despite this, it has become increasingly clear that hypocalcemia can develop in older patients. Three recent reports describe new onset tetany or seizures caused by hypocalcemia in adults with previously undiagnosed disease. Previously, hypocalcemia was unmasked in adults who were stressed because of acute medical conditions or trauma. Three recent reports describe patients who were well at the time of presentation [30–32]. This suggests that primary hypocalcemia at any age should be considered a risk factor for the deletion.

Neurologic and developmental or behavioral issues

Speech delay is an extremely common finding in patients with the deletion. It may be the most consistent feature in this syndrome when carefully analyzed. The characteristics of speech delay are distinctive and different from the speech delay seen in other chromosome syndromes (*eg*, Down syndrome) [33,34]. This careful characterization has not translated into outcomes-based research on specific interventions. Speech and cognitive intervention have been advocated at an early age. Also some advocate sign language as a bridge to language development. No data support one strategy over another. It is of interest that, in late childhood, verbal skills are a particular strength of these patients. Patients with the deletion are usually characterized as having a nonverbal learning disability in their later school-aged years [35]. Various subtle central nervous system abnormalities have been described in patients with the deletion, but it has been difficult to correlate the structural findings with developmental analyses. An elegant study attempted to identify structural correlates related to difficulties with abstract reasoning [36]. Eight patients and eight controls

were asked to perform increasingly difficult computations. Brain activity was analyzed by functional magnetic resonance imaging. The patients exhibited increased activity in the left supramarginal gyrus compared with controls. Abstract and conceptual reasoning are often impaired in patients and mathematics is typically difficult for them. This study suggests that subtle defects may exist in the neural processing that manifest as impaired abstract reasoning.

Other neurologic findings suggest that the central nervous system is a major target for the chromosome deletion. Although the findings are often subtle, many patients have one or more neurologic features (Table 1). Seizures are typically seen as a consequence of hypocalcemia, however, two reports from this past year clearly describe seizures in patients with the deletion in the absence of hypocalcemia [37,38].

Schizophrenia is a known association with chromosome 22q11.2 deletion. Considerable debate occurs about whether this is a primary association or whether it is secondary to the developmental delay that itself is a risk factor for schizophrenia. Two studies suggest that the association is primary. Limited studies have looked at the frequency of the deletion in nonselected patients with schizophrenia [39,40]. A recent study found that the frequency of chromosome 22q11.2 deletion in a Japanese population with schizophrenia is low [40]. This is consistent with what has been seen previously. This particular study is of interest because the single patient identified had no other features suggestive of having the deletion. It is, thus, difficult to argue in this case that the schizophrenia resulted from developmental delay. Supporting this is a finding that patients with the deletion have small temporal lobe and hippocampus volumes, a finding seen in patients with schizophrenia who do not have the deletion [41]. Although there can never be a murine model for schizophrenia, a murine model of chromosome 22q11.2 deletion shows defects in memory, learning, and sensorimotor gating [19,41]. Patients with schizophrenia exhibit similar defects in sensorimotor gating.

New phenotypic associations

No review would be complete without an update on the phenotypic manifestations in the syndrome. Two Web sites are updated with new findings and they serve as excellent resources for families and caregivers (www.vcfsef.org, http://www.cbil.upenn.edu/VCFS/22qandyou/). Additional Web sites run by individuals provide support and information for families. A synopsis of the clinical features is given in Table 1. It will probably be impossible to compile a completely comprehensive list of phenotypic associations; however, it is important to realize the enormous spectrum of features that are seen. For example, lung aplasia was recently described in a patient

Table 1. Features associated with chromosome 22q11.2 deletion syndrome

Craniofacial	Eye	Vascular	Genitourinary/abdominal	Endocrine	Musculoskeletal
Velopharyngeal insufficiency	Tortuous retinal vessels	Medial carotid arteries	Renal anomalies	Hypocalcemia	Polydactyly
Overt or occult cleft palate	Posterior embryotoxon	Tortuous vertebral arteries	Malrotation	Hypothyroidism	Scoliosis
Dental anomalies	Iris nodules	Raynaud phenomenon	Hernias	Growth hormone deficiency	Vertebral anomalies
Retrognathia	Small optic disks	Circle of Willis anomalies	Hypospadius		Sprengel deformity
Asymmetric crying face	Strabismus		Reflux		Club foot
Microcephaly	Coloboma				Joint laxity

with chromosome 22q11.2 deletion syndrome [42], which had not been previously described. Many variations on the cardiac conotruncal or outflow tract anomalies have been described. The tremendous, if not infinite, variations are highlighted by two reports of unusual cardiac malformations. In one case, a right ductus arteriosus from a right aortic arch was the presenting manifestation of the deletion [43]. In the second case, the innominate artery arose aberrantly from the right pulmonary artery [23]. A VSD was also present. The most common anomalies seen in this deletion syndrome are cardiac defects, speech delay, and diminished T-cell numbers. A high index of suspicion is warranted for children presenting with the classic manifestations but is also warranted for patients with a single common manifestation and one or more uncommon manifestations.

Conclusions

Much of the new information on chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes) has focused on the genetics. In that regard, it has been an exciting year. A credible candidate gene has been identified and mouse models have demonstrated a possible explanation for the phenotypic diversity in this syndrome. An important study from Chile documents that the human phenotype may be somewhat distinctive in different populations [44•]. In this series, immunodeficiency and laryngeal web were more common than in the European and American series. Caregivers should be aware of the phenotypic heterogeneity. Coordinated, multidisciplinary care provides these children the best opportunity for full lives.

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