

## Chromosome 22q11.2 Deletion Syndrome: DiGeorge Syndrome/ Velocardiofacial Syndrome

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Velocardiofacial syndrome, DiGeorge syndrome, and a variety of other clinical syndromes have a hemizygous deletion of chromosome 22q11.2 as their cause. This deletion syndrome is extremely common, with nearly 1 in 3000 children being affected. This pattern of malformations was recognized as early as 1671, when Nicolai Stensen described a patient with cleft palate and truncus arteriosus. In 1829 L. H. Harrington described a patient with a hypoplastic thymus and hypoplastic parathyroid glands. In the modern era, Eva Sedlackova described a syndrome of velopharyngeal insufficiency and developmental delay, and David Lobdell reported a patient with a hypoplastic thymus and hypoplastic parathyroid glands in 1959. “DiGeorge syndrome” came to be named in 1965 when Angelo DiGeorge described the common embryologic derivation of the heart, thymus and parathyroid glands as the explanation for their joint malformation in patients, and “velocardiofacial syndrome” was named in 1978 by Robert Shprintzen. Despite the extensive history of this disorder, the management of patients remains a challenge. The complex medical care of these patients requires a multidisciplinary approach, and each patient has unique clinical features, requiring a tailored approach. This article focuses on the immune system, but patients require a holistic approach to their needs.

“Chromosome 22q11.2 deletion syndrome” is a term applied to patients who have a hemizygous deletion of chromosome 22q11.2. Approximately 90% of patients carrying the clinical diagnosis of DiGeorge syndrome and 80% of patients carrying the clinical diagnosis of velocardiofacial syndrome

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carry the hemizygous deletion. The deletion also has been demonstrated in additional patients who have coloboma, heart anomaly, choanal atresia, retardation, and genital and ear anomalies (CHARGE syndrome), conotruncal anomaly face syndrome, and cat eye syndrome. There can be confusion in the nomenclature, because there are patients who have the deletion who do not fall into the category of a clinically defined syndrome, and there are patients who have DiGeorge syndrome who do not carry the deletion. The term “DiGeorge syndrome” historically has referred to patients who have a cardiac anomaly, hypocalcemia, and poor T-cell production. In this article, the term “chromosome 22q11.2 deletion syndrome” is used when describing studies of patients known to have the deletion, and specific syndromic nomenclature is used when discussing studies that relied on clinical features.

Chromosome 22q11.2 deletion syndrome is estimated to occur in nearly 1 in 3000 children, and patients typically are born with a conotruncal cardiac anomaly and a mild to moderate immune deficiency (Table 1) [1–11]. Developmental delay, palatal dysfunction, and feeding problems also are seen in most of these infants. A frustrating and as yet incompletely understood aspect of this syndrome is the enormous phenotypic heterogeneity.

## Diagnosis

The deletion arises as a result of an aberrant meiotic exchange event caused by low copy number repeats that bracket the commonly deleted region [12]. Most deletions are spontaneous, and from epidemiologic studies the spontaneous mutation rate is estimated to be between 1 in 4000 and 1 in 6000. The deletion of chromosome 22q11.2 is at least 10-fold more common a spontaneous deletion than the next most frequent human deletion syndrome, suggesting that the low copy number repeats in this region lead to more substantial genomic instability.

The estimate of an incidence of 1 in 3000 births is derived from the spontaneous mutation rate plus the growing number of familial cases. Before the mid-1980s patients who had severe cardiac anomalies did not survive. Now there is a large cohort of adults who have these anomalies, and they are raising their own families. The hemizygous deletion is inherited in an autosomal dominant fashion; thus affected parents have a substantial risk of passing on the deletion to a child.

Identification of an affected infant or an older child in the absence of a family history relies on the recognition of a single feature seen commonly in patients who have the deletion, such as interrupted aortic arch, or a combination of features that individually are not strongly predictive of a deletion but in aggregate raise the suspicion (Table 2).

The diagnosis currently relies on the fluorescence in situ hybridization (FISH) method, which is extremely accurate but time-consuming and expensive. Efforts to develop a rapid polymerase chain reaction–based method are underway and soon may yield a commercial test [13–15]. Certain patients

Table 1  
Clinical findings in patients who have chromosome 22q11.2 deletion syndrome

Finding	Percentage of patients affected
Cardiac anomalies	49–83
Tetralogy of Fallot	17–22
Interrupted aortic arch	14–15
Ventriculoseptal defect	13–14
Truncus arteriosus	7–9
Hypocalcemia	17–60
Growth hormone deficiency	4
Palatal anomalies	69–100
Cleft palate	9–11
Submucous cleft palate	5–16
Velopharyngeal insufficiency	27–32
Bifid uvula	5
Renal anomalies	36–37
Absent/dysplastic	17
Obstruction	10
Reflux	4
Ophthalmologic abnormalities	7–70
Tortuous retinal vessels	58
Posterior embryotoxon (anterior segment dysgenesis)	69
Neurologic	8
Cerebral atrophy	1
Cerebellar hypoplasia	0.4
Dental: delayed eruption, enamel hypoplasia	2.5
Skeletal abnormalities	17–19
Cervical spine anomalies	40–50
Vertebral anomalies	19
Lower extremity anomalies	15
Speech delay	79–84
Developmental delay in infancy	75
Developmental delay in childhood	45
Behavior/psychiatric problems	9–50
Attention deficit hyperactivity disorder	25
Schizophrenia	6–30

*Data from [1–11].*

who have classic features but no evidence of a deletion by FISH can represent a diagnostic dilemma. Point mutations in the T-box 1 gene (*TBX1*) [16,17], a very small deletion not detected by standard FISH, or a non-chromosome 22 basis could account for the clinical features. In particular, deletions of chromosome 10, mutations in the chromodomain helicase DNA-binding protein gene *CHD7*, and prenatal exposure to teratogens such as isotretinoin or glucose should be sought as potential explanations [18–22]. In spite of best efforts, no clear etiologic basis currently can be found in some patients who have a clinical picture of DiGeorge syndrome. This issue is a clinically significant, because the risk of recurrence in these kindreds is not known.

Table 2  
The frequency of the chromosome 22q11.2 deletion in various patient populations

Phenotypic feature	Frequency of deletion (%)
Any cardiac lesion	1.1
Conotruncal cardiac anomaly	7–50
Interrupted aortic arch	50–60
Pulmonary atresia	33–45
Aberrant subclavian	25
Tetralogy of Fallot	11–17
Velopharyngeal insufficiency	64
Velopharyngeal insufficiency postadenoidectomy	37
Neonatal hypocalcemia	74
Schizophrenia	0.3–6.4

### The genetic basis of the phenotype

Within the commonly deleted region of chromosome 22q11.2, there are more than 35 genes. A continuing question is which of the genes within the deleted region contribute to the phenotype. A series of clever *LoxP* Cre deletions were made in mice mimicking the deletions in humans and uncovered the transcription factor *TBX1* as the most likely gene contributing to the cardiac phenotype [23–26]. The murine models have revealed two surprising features. All embryos with a deletion show abnormalities of the branchial arch, which is the precursor to the heart and thymus, but only a subset of mice have cardiac anomalies at birth. This ability to recover from the early branchial arch artery defect is intriguing and raises the question of whether an in utero intervention could be developed to mitigate the effects of the deletion. The second surprise was the magnitude of the effect of the background genes [27]. A parathyroid or thymus phenotype was not seen initially. When the deletion mice were backcrossed onto other strains, the parathyroid and thymic phenotypes were more obvious. Data on background gene effects are difficult to identify in humans. Series of patients from the United States and Europe agree largely on the phenotypic manifestations, but patient cohorts from Chile and China have slightly different profiles that could represent ascertainment bias or true phenotypic differences related to background gene effects [28,29]. Studies of multiplex kindreds, in which background gene effects would be expected to be minimized, show significant phenotypic heterogeneity, suggesting that background genes contribute to the phenotype. Other factors, however, are probably substantial source of variability.

Based on the murine studies, haplosufficiency for *TBX1* seems to be the major determinant of cardiac, thymus, and parathyroid phenotypes, probably because of the role *TBX1* plays in the development of branchial arch structures. *TBX1* contributes to the endodermal proliferation in the branchial arches, with haplosufficiency leading to compromised formation,

particularly of the arch arteries. Secondary effects are seen because *TBX1* drives the expression of fibroblast growth factors that contribute to the growth of surrounding cells and also regulates the expression of myogenic growth factors that are important for branchiomic muscle development. Thus, haplosufficiency for the transcription factor *TBX1* leads to direct compromise of branchial arch structures and has a wealth of secondary effects. Patients who have chromosome 22q11.2 deletion syndrome also have a variety of malformations that do not map to branchial arch structures. Central nervous system changes such as developmental delay and psychiatric problems are common, and skeletal anomalies and renal anomalies are seen also—features that are difficult to attribute to dysfunction in branchial arch development. *TBX1* is expressed somewhat in the developing brain mesoderm and in the sclerotome that gives rise to various structures in the spinal column [30]. Although its role in these sites is not understood, haplosufficiency in these regions may contribute to the other phenotypic features. Confirming the importance of *TBX1* in brain development, patients who have a mutation in *TBX1* have the same developmental delay phenotype as patients who have the deletion [16].

Because the role of *TBX1* primarily involves embryologic development, interventions directed at preventing or treating the biologic effects of haplosufficiency probably would need to be instituted in utero. Recent advances in understanding the regulation of *TBX1* have led to the possibility of regulating its expression through the retinoic acid pathway. Isotretinoin exposure causes a syndrome with similarities to chromosome 22q11.2 deletion syndrome [31]. Retinoic acid is known to be a repressor of *TBX1* expression [32]. Manipulation of this pathway could normalize levels of *TBX1* in haplosufficient babies if detected early enough. There also is intense interest in identifying modifier genes, either within the deleted region or in background genes, with the hope that these genes could provide a framework for developing meaningful interventions [33,34]. Recently vascular endothelial growth factor was identified as a modifier of the cardiac phenotype [34].

### **Management—overview**

There are few prospective studies to support a specific management style for patients who have chromosome 22q11.2 deletion syndrome. A coordinated approach to the many subspecialty needs and a recognition that patient phenotypes and outcomes vary tremendously are essential. Most patients receive their diagnosis shortly after birth because of the presence of a cardiac anomaly. In infants, an approach to identify medical problems such as cardiac anomalies, hypocalcemia, severe immunodeficiency, or intestinal malrotation, which could lead to severe morbidity, should be instituted as soon as possible. Feeding problems can compromise development, and frank nutritional compromise delays healing and contributes to defects in

host defense [35]. The toddler years require attention to development and speech; the school-age years require additional attention to cognitive development and growth. Behavioral issues are more likely to become a problem with increasing age, and frank psychiatric disorders are seen in teenagers and adults. Fig. 1 gives a sense of the dynamic nature of the needs of patients who have chromosome 22q11.2 deletion syndrome. Education of parents regarding the future potential requirements of the patient is difficult because of the variations among patients and the current inability to predict psychiatric needs of patients.

**Management—neonatal**

Cardiac anomalies are seen in approximately 75% of all patients who have chromosome 22q11.2 deletion syndrome and are the major cause of death. An early initial echocardiographic evaluation is important for infants diagnosed shortly after birth, because not all cardiac anomalies are obvious. For patients who require early cardiac surgery, there are several questions regarding management from the immunologist’s perspective. Low T-cell numbers are seen in 75% to 80% of infants who have chromosome 22q11.2 deletion syndrome. In most cases this decrement is mild or moderate and does not impact the procedure. It is not known whether postoperative infections are increased in this population. Less than 1% of patients who have the deletion lack T cells, but these patients represent a special category at the time of cardiac surgery [5]. These patients require protection from infection and blood products. Blood products can induce graft-versus-host disease in patients without T cells, and graft-versus-host disease from transfusions almost always is fatal. Definitive therapy for patients lacking T cells is discussed later.

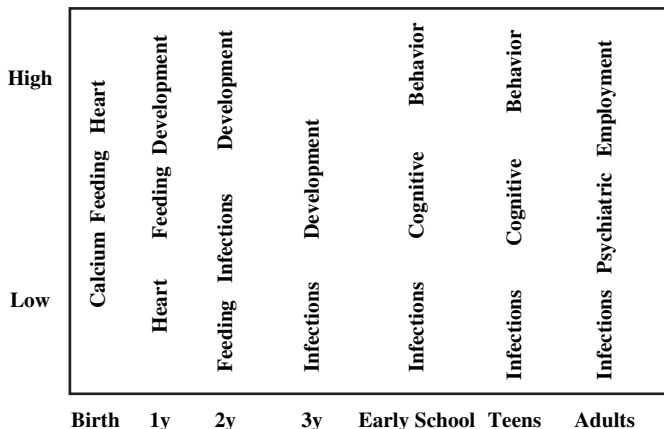


Fig. 1. Changing needs of patients who have chromosome 22q11.2 deletion syndrome. The y-axis indicates the level of attention.

Often patients require cardiac surgery before definitive information regarding the immune system is available. Many large centers in the United States irradiate all blood products provided to infants less than 1 year of age to prevent graft-versus-host disease. Another strategy is to stratify risk according to the absolute lymphocyte count as a surrogate for a T-cell count, but this strategy lacks both specificity and sensitivity.

Hypocalcemia often presents in the neonatal period and is exacerbated by cardiac surgery. Calcium supplementation typically is sufficient in the immediate postoperative period. Persisting hypocalcemia requires management by an endocrinologist to balance vitamin D requirements, calcium, and phosphorus. Oversupplementation leads to nephrocalcinosis, and a balance is required. Most children do not require prolonged calcium supplementation, although rare cases of late onset or recurrence of hypocalcemia have been described.

Feeding issues can be extremely difficult for parents in early infancy. Feeding and swallowing problems seem to arise from poor coordination of the pharyngeal muscles, tongue, and esophageal muscles [35]. Patients who have cardiac defects also might have shortness of breath, leading to poor feeding, and breastfeeding is known to be difficult for patients who have palatal clefting. Thus, many variables may contribute to poor feeding.

### **Management—development**

Speech is one of the most troubling aspects for most parents, because communication is fundamental to bonding. Defects in phonation, language development, and comprehension are fairly common [36]. Phonation problems can be caused by laryngeal webs, velopharyngeal insufficiency, or vocal cord paralysis. Surgery can correct these abnormalities, but phonation typically remains problematic [37,38]. Speech is more delayed than receptive skills, and social language skills typically are even more delayed. Early receptive language skills seem to correlate with overall function [39]. This pattern of skills and weaknesses is almost unique to patients who have chromosome 22q11.2 deletion syndrome [40]. Optimal management for speech delay is not known. Advocates of sign language believe that the ability to communicate is critical and that signing allows the child to progress developmentally [40,41]. Advocates of speech therapy believe that signing delays language acquisition [36]. There have been no direct comparisons of the two methods, and parents who have used both strategies report satisfaction with the method. Most patients learn to speak and communicate effectively.

The mean full-scale IQ is approximately 70, with a range from normal to moderately disabled [1,4,7,42]. Visuo perceptual abilities and planning tend to be the weakest areas [4,43]. This pattern of nonverbal learning disability is not unique to chromosome 22q11.2 deletion syndrome and is seen in other syndromes that involve developmental delay. In fact, learning disability

occasionally is the only manifestation of chromosome 22q11.2 deletion syndrome [44]. Successful school-based interventions have been developed for children who have nonverbal learning disabilities and typically are used for patients who have chromosome 22q11.2 deletion syndrome, although no interventions targeted for this specific group of patients have been developed.

The central nervous system manifestations of chromosome 22q11.2 deletion include structural defects such as microcephaly and functional aspects such as attention deficit hyperactivity disorder, poor social interaction skills, impulsivity, and bland affects [45–48]. Ten percent to 30% of older patients experience bipolar disorder, autistic spectrum disorder, or schizophrenia/schizoaffective disorder. Psychiatric disorders are common in all patients who have developmental delay, but there is a significant increase in psychiatric disturbances in this syndrome.

### **Management—immunodeficiency**

Most patients who have chromosome 22q11.2 deletion syndrome have diminished T-cell numbers as a consequence of thymic hypoplasia. Approximately 20% of the patients have no evidence of diminished T cells [49], and less than 1% have true thymic aplasia requiring a transplant [5]. Most patients have mildly or moderately diminished circulating T cells. The next two subsections describe management for both the common patients who have a mild or moderate decrement in T-cell numbers and the rare patient who has complete thymic aplasia.

#### *Management—mild or moderate immune deficiency*

Children who have chromosome 22q11.2 deletion syndrome and a mild to moderate decrement in the T-cell count have largely normal immunoglobulin levels and T-cell proliferative responses [49,50]. T-cell numbers decline with age in all children, but the decline in patients who have chromosome 22q11.2 deletion syndrome seems to be slower. In fact, adults who have chromosome 22q11.2 deletion syndrome have normal T-cell numbers for the most part. The slower age-determined decline in T-cell numbers in patients compared with controls is caused by the homeostatic proliferation of existing T cells. The initial clue that homeostatic expansion occurs was a study describing the differences in naive and memory T cells in an early childhood population [51]. Early changes in the T-cell repertoire also were seen, and, although mild, they indicated that the T-cell compartment was altered by the early lymphopenia. A study of adults confirmed that the changes in naive and memory T cells progress further with aging, as do the defects in repertoire (deletions, oligoclonality) [52,53]. Telomere length was found to be shorter even within the naive T-cell population in patients [53]. Based on these findings, compromise in T-cell function would be expected in adult patients. A compromised repertoire would restrict the ability



of the T cells to respond to pathogens, and shortened telomeres would be expected to compromise the proliferative ability of T cells in response to infection. There are few data from adult patients addressing this issue, but modest defects in function have been seen in children. The T-cell receptor rearrangement excision circles (TREC) count, a marker of proliferative history, was found to correlate with proliferation of memory T cells, suggesting that extensive shortening of telomeres compromises T-cell function as measured by proliferation [54]. Supportive of the studies documenting compromised proliferative ability in at least a subset of cells is the finding that spontaneous apoptosis is increased in patients compared with controls [55]. Because cells with short telomeres undergo spontaneous apoptosis, this finding may reflect the inherent limitations of the T cells. Despite these findings, cytokine production is normal, and global proliferative ability is intact in children [54,56].

The humoral immune system has been examined in several studies. Although the humoral immune system is largely intact in patients who have chromosome 22q11.2 deletion syndrome, as one would expect for a defect in thymic development [57], there are data demonstrating infrequent humoral dysfunction. It is an uncommon finding in the patients who have the deletion, but the frequency is clearly greater than in the general population. IgA deficiency, impaired responses to vaccines, and frank hypogammaglobulinemia have been described [58–60]. A pattern of more severe infection correlated with immunoglobulin abnormalities [58,59].

Compared with an HIV population with similar T-cell counts, patients who have the deletion have much better immunologic function. Opportunistic infections are very infrequent [5], the most common infection being an upper respiratory tract infection. The frequency of these infections does not correlate with T-cell counts, suggesting anatomy may be the major contributor to upper respiratory tract infections [61]. Nevertheless, there are long-term clinical consequences of thymic hypoplasia. Autoimmune disease is significantly increased, with juvenile rheumatoid arthritis and hematologic autoimmune diseases being the most common [49,62–64]. Idiopathic thrombocytopenia purpura is the most common of the autoimmune diseases, although platelet size and number are slightly aberrant at baseline in most patients who have the deletion [33]. Celiac disease was recently described in 1 of 48 patients who had chromosome 22q11.2 deletion, which seems to be increased over the frequency in the general population [65]. The mechanism underlying the susceptibility to autoimmune disease is not well established, but homeostatic expansion selects for self-reactive or low-affinity T cells. A decrease in regulatory T cells also has been seen [66] and could contribute to the predisposition to autoimmunity. An increase in allergic diseases also is seen in chromosome 22q11.2 deletion syndrome, contributing to the infection pattern, and this predisposition to allergy also may be related to the homeostatic expansion because T-helper type 2 differentiation seems to be the default pathway in homeostatic proliferation in mice [67].

Clinical studies show that most patients do not demonstrate a susceptibility to opportunistic infections. Concordantly, the risk of using live viral vaccines in infants seems to be low except for patients who have thymic aplasia and/or very low T-cell counts [68]. Both the measles, mumps, rubella and the varicella vaccine were found to be safe and efficacious in children who had the deletion and who had mild to moderate T-cell compromise [69,70]. It would not be appropriate to give live viral vaccines to patients who have severe T-cell compromise.

### *Management—thymic aplasia*

Patients who have true thymic aplasia and absent T cells represent a very specific group. The genetic etiologies are slightly different, with chromosome 22q11.2 deletion found in approximately half of these patients [71]. A spectrum of T-cell counts is seen in thymic aplasia, ranging from a T-cell count of zero to a normal T-cell count (see discussion below). These features may make it difficult to identify patients who require a transplant.

A thymus transplant, fully matched peripheral blood transplant, or donor lymphocyte infusions are required for patients who have thymic aplasia. It is not always clear at which point a thymus transplant or a fully matched T-cell transplant would be appropriate. An evaluation of the naive T-cell count in early infancy can be used to estimate the potential for thymic production of T cells, but the counts can change substantially over a few months. The two interventions with data to support them are a thymic transplant and a fully matched transplant of T cells (so that thymic education is not required) [72,73]. For a thymus transplant, the donor thymic tissue is harvested and cultured to ensure that mature T cells capable of causing graft-versus-host disease have been eliminated [74]. Thin slices of the cultured thymus are implanted in the quadriceps muscle. Although partial HLA matching is desirable, it is not necessary [75]. Functional T cells appear approximately 3 to 4 months after transplantation, and the T-cell repertoire after transplantation is normal initially, suggesting that the graft is capable of supporting normal T-cell development [76]. The implanted thymus involutes rapidly and does not sustain prolonged production of T cells, but sufficient numbers are produced to provide adequate host defense, and patients do well clinically [71]. Follow-up studies will define the long-term fate of the patients who have undergone transplantation.

Approximately one third of infants who have thymic aplasia caused by DiGeorge syndrome or chromosome 22q11.2 deletion syndrome have a dramatic oligoclonal expansion of a few founding T cells [77]. In this setting, the T-cell counts do not reflect the adequacy of the T-cell compartment because they are expanded from a very small number of functional T cells. Fortunately, there are several clues to this phenomenon. Often the infants have erythroderma, similar to that seen in Omenn's syndrome. The T cells are predominantly or almost exclusively of a memory phenotype (CD4/CD45RO

or TREC negative), and the repertoire is oligoclonal [77,78]. Repertoire and TREC studies are not widely available, but the combination of an almost exclusively memory T-cell phenotype and erythroderma should lead to the suspicion of either Omenn's syndrome or oligoclonal expansion in the setting of thymic aplasia.

## Summary

The immunologist typically is the care coordinator for patients who have DiGeorge syndrome or chromosome 22q11.2 deletion syndrome. If not the coordinator, the immunologist often is one of the first clinicians to discuss the syndrome with the family. A clear understanding of the multidisciplinary needs as well as a strategy to prioritize urgent needs is valuable in the infancy period, when many issues may arise. Anticipatory guidance is valuable for the family, and a comprehensive approach to the consequences of the immune deficit can improve the quality of life markedly.

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