Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes

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Introduction
The nomenclature of the velocardiofacial syndrome, known as chromosome 22q11.2 deletion syndrome, has become confusing because many clinical syndromes are associated with a hemizygous deletion of chromosome 22q11.2. 35–90% of patients clinically diagnosed with DiGeorge syndrome (cardiac anomalies, hypoparathyroidism, immunodeficiency) and 80–100% with velocardiofacial syndrome (pharyngeal dysfunction, cardiac anomaly, dysmorphic facies) have the hemizygous deletion.1,4 Additionally, some patients with CHARGE (coloboma, heart, atresia, retardation of growth, genitourinary problems, ear abnormalities) and conotruncal anomaly face syndromes have the deletion. The reason for the confused nomenclature is the enormous phenotypic heterogeneity of this syndrome (table 1). Here, the term chromosome 22q11.2 deletion syndrome is used when referring to patients who have the deletion, and specific syndromic nomenclature is used when the resource data rely on clinical features.

Chromosome 22q11.2 deletion syndrome is seen in one in 3900 to one in 9700 children,1,5–8 and babies are born typically with a conotruncal cardiac anomaly and mild-to-moderate immune deficiency. Developmental delay, facial dysmorphism, palatal dysfunction, and feeding difficulties are also seen in most infants with the syndrome. Other clinical features (table 1) are noted less consistently. Despite the diversity of clinical features, nearly all patients will benefit from coordinated multidisciplinary care. Here, we address some of the most common medical issues of velocardiofacial syndrome and review recent insights into its pathophysiology.

Epidemiology and genetics
Population-based estimates of the incidence and prevalence of chromosome 22q11.2 deletion syndrome are very different. One of the most-widely cited estimates is that of Wilson and colleagues,6 who calculated a minimum prevalence rate of one in 4000 livebirths on the basis of the presence of the deletion in 5% of patients with congenital cardiac defects. Most estimates come from surveys of one institution or clinic. Goodship and colleagues6,7 examined 207 infants with congenital heart defects other than small ventricular septal defect, who were diagnosed between 1994 and 1995 in Newcastle, UK. Of the 170 infants who were ultimately examined, five had the deletion. Two other children were diagnosed 4 years later, making the final estimate of prevalence of one in 3900 livebirths. Because not all patients have cardiac anomalies, this represents a minimum estimate.

Search strategy and selection criteria
A comprehensive investigation was undertaken by searching Medline and PubMed for English language publications. The search included papers published up to Sept 30, 2006. The search terms included “epidemiology”, “thymus”, “immune deficiency”, “velocardiofacial syndrome”, “DiGeorge syndrome”, “chromosome 22”, and “TBX1”. Combinations of search terms were also used. To limit the number of references, only a subset of relevant articles were selected.
These numbers are much higher than those of Katzman and colleagues, who reported that 16 of 297 (5%) patients referred for examination because of developmental delays were positive for the deletion. Screening of this population might not accurately indicate the general population or the population with the highest risk of having the deletion. The largest study of birth prevalence of chromosome 22q11.2 deletion syndrome used a registry of birth defects with active surveillance in the Atlanta metropolitan area, USA, and patients identified through a screening programme of infants with congenital heart disease, and positive FISH tests done by a regional genetics laboratory. 45 patients were identified between 1994 and 1999. The overall prevalence was one in 5950 births. This is the only study that measured the prevalence in different races, showing that it was similar in white, black, and Asian people (one in 6000 to one in 6500), but higher in Hispanic people (one in 3800).

All these studies probably underestimated the true incidence and prevalence of this disorder. The clinical phenotype is variable, and often patients without a congenital heart defect are diagnosed with a delay of several years. Almost all studies are dependent on clinical referral, and therefore patients with atypical or minimal phenotype might be missed. The deletion can be inherited in an autosomal dominant fashion; however, it is mostly a de novo mutation. Only a few studies have tested asymptomatic parents for the presence of the mutation; estimates that mutations are inherited from a parent are between 8% and 28%. Symptomatic parents frequently have a much milder phenotype than their offspring, with a lower frequency of congenital heart defects. This low frequency of heart defects might be related to poor survival of patients with cardiac anomalies before the availability of cardiac bypass machines in the middle of the 1980s. Genetic counselling is crucial in families with an affected parent because the recurrence risk is 50%, and offspring are often more severely affected.

### Table 1: Clinical findings in patients with chromosome 22q11.2 deletion syndrome

<table>
<thead>
<tr>
<th>Frequency of finding</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Cardiac anomalies</td>
<td>49–83%</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>17–22%</td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>14–15%</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>13–14%</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>7–9%</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>17–60%</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>4%</td>
</tr>
<tr>
<td>Palatal anomalies</td>
<td>69–100%</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>9–11%</td>
</tr>
<tr>
<td>Submucous cleft palate</td>
<td>5–16%</td>
</tr>
<tr>
<td>Velopharyngeal insufficiency</td>
<td>27–92%</td>
</tr>
<tr>
<td>Bifid uvula</td>
<td>5%</td>
</tr>
<tr>
<td>Renal anomalies</td>
<td>36–37%</td>
</tr>
<tr>
<td>Absent or dysplastic</td>
<td>37%</td>
</tr>
<tr>
<td>Obstruction</td>
<td>10%</td>
</tr>
<tr>
<td>Reflux</td>
<td>4%</td>
</tr>
<tr>
<td>Ophthalmological abnormalities</td>
<td>7–70%</td>
</tr>
<tr>
<td>Tortuous retinal vessels</td>
<td>58%</td>
</tr>
<tr>
<td>Posterior embryotoxon (anterior segment dysgenesis)</td>
<td>69%</td>
</tr>
<tr>
<td>Neurological</td>
<td>8%</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>1%</td>
</tr>
<tr>
<td>Cerebellar hypoplasia</td>
<td>0.4%</td>
</tr>
<tr>
<td>Dental</td>
<td></td>
</tr>
<tr>
<td>Delayed eruption, enamel hypoplasia</td>
<td>2.5%</td>
</tr>
<tr>
<td>Skeletal abnormalities</td>
<td>17–19%</td>
</tr>
<tr>
<td>Cervical spine anomalies</td>
<td>40–50%</td>
</tr>
<tr>
<td>Vertebral anomalies</td>
<td>19%</td>
</tr>
<tr>
<td>Lower limb anomalies</td>
<td>35%</td>
</tr>
<tr>
<td>Speech delay</td>
<td>79–84%</td>
</tr>
<tr>
<td>Developmental delay in infancy</td>
<td>75%</td>
</tr>
<tr>
<td>Developmental delay in childhood</td>
<td>45%</td>
</tr>
<tr>
<td>Behaviour or psychiatric problems</td>
<td>9–50%</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>25%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>6–30%</td>
</tr>
</tbody>
</table>

Data were taken from references 16, 18, 112–114, 131–136.

**Diagnosis**

Diagnosis is generally straightforward. Most patients with a clinical phenotype of velocardiofacial syndrome or DiGeorge syndrome have a hemizygous deletion of chromosome 22q11.2. The FISH method is accurate, but often takes 2–3 days and is expensive. Efforts to develop a rapid PCR-based method are underway and might result in a commercial test soon. Diagnosis becomes more confused when a patient with classic features of velocardiofacial syndrome has no evidence of deletion by FISH. A point mutation, which has been described in a few patients, might be present in T-box 1 (TBX1). This mutation, or a deletion that is too small to be detected by standard FISH, or a non-chromosome 22 cause can all be associated with the same clinical manifestations as in chromosome 22q11.2 deletion syndrome. Patients with features of velocardiofacial syndrome or DiGeorge syndrome who have deletions of chromosome 10, or mutations in chromodomain helicase DNA binding protein 7 (CHD7), and patients with prenatal exposure to isotretinoin or high glucose have been described. Several patients with the clinical phenotype of velocardiofacial syndrome or DiGeorge syndrome have no known cause; this is an important issue because the risk of recurrence is not known.

A practical issue for clinicians is to decide which patients should be tested. Scarce prospective data exist on this topic; however, substantial efforts have been made to define the appropriate patient populations for testing (table 2). Of 251 infants with conotruncal defects who were examined prospectively, 45 (18%) had the deletion. The frequency of the deletion varied with the nature of the cardiac defect.
The findings in other centres vary widely, from 7% to 50% of patients with conotruncal heart defects who were FISH positive. In infants with a congenital heart defect and no syndromic features, the frequency of chromosome 22q11.2 deletion syndrome was reported to be very low (0–1%). The most difficult population to identify consists of patients with chromosome 22q11.2 deletion syndrome and mild facial features, and developmental delay or speech delay. A study showed that physicians who have been trained to recognise facial features (figure 1) are more likely to identify patients correctly; however, most primary-care clinicians would have only one or two patients with chromosome 22q11.2 deletion syndrome under their care, suggesting that special outreach efforts would need to be made to improve diagnosis.

**Pathophysiology**

The disease mechanisms of chromosome 22q11.2 deletion syndrome can be seen from two perspectives. One is the mechanism that underlies the deletion, and the other is the mechanism by which the deletion leads to the clinical phenotype. Since 1993, the deletion has been linked to low copy number repeats (LCRs). Four discrete blocks of LCRs are present in this region, and every block consists of several modules of repeats that have various lengths and orientations within a block. These blocks have been named LCR A–D, with A being the most proximal (figure 2). These LCRs are seen only in primates and are, therefore, a recent evolutional acquisition. Support for the hypothesis that unequal meiotic exchange is the dominant mechanism of deletion comes from the identification of asynchronous replication at the site of the deletion. Asynchronous replication has been postulated to enhance mispairing of LCRs.

In the largest study so far that addressed the mechanism of the deletion, no intrachromosomal rearrangements were seen. Instead, the deletion was attributable to an aberrant meiotic exchange event. The characteristic deletion of chromosome 22q11.2 deletion syndrome is at least ten times more common than is the next most frequent human deletion syndrome. LCRs on chromosome 22q11.2 are larger, more complex, and have higher homology than any other LCRs in the genome associated with human chromosomal deletion syndromes.

More than 35 genes are present within the commonly deleted region of chromosome 22q11.2. Chromosome 22 was fully sequenced in 1999, and within 2 years the gene mainly responsible for the phenotypic features of velocardiofacial syndrome was identified as TBX1. Some Cre–loxP deletions in mice mimicked the effect of the deletions in man, and showed that TBX1 is the dominant gene contributing to the cardiac phenotype. The development of a Tbx1-knockout mouse supported the importance of this gene in cardiac development, and tracked the aberrant cardiac development to impaired formation of the fourth branchial arch artery, a precursor to the right ventricle and outflow tract. Murine models have been instructive and revealed two surprising features. Although the phenotype of early embryonic fourth branchial arch defect is fully penetrant, only some mice have cardiac lesions at birth. The ability to recover from the early branchial arch artery defect is very intriguing, and raises the question of whether an intervention in utero could be developed to counter the effects of the deletion, if identified prenatally. Also the magnitude of the background modifier effect was unexpected. Initially, the mice carrying the deletion did not have a substantial parathyroid or thymus phenotype. However, when the deletion was bred into other strains, the parathyroid and thymic phenotypes were more obvious. In human beings, few data support the existence of a background effect. Many patients from the USA and Europe are generally similar in terms of phenotypic manifestations. However, patients from Chile and China have some

![Table 2: Frequency of the chromosome 22q11.2 deletion](image)

<table>
<thead>
<tr>
<th>Frequency of deletion</th>
<th>Any cardiac lesion</th>
<th>1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conotruncal cardiac anomaly</td>
<td>7–50%</td>
<td></td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>50–60%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>33–45%</td>
<td></td>
</tr>
<tr>
<td>Aberrant subclavian</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>11–17%</td>
<td></td>
</tr>
<tr>
<td>Velopharyngeal insufficiency</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Velopharyngeal insufficiency post-adenoidectomy</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Neonatal hypocalcaemia</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0–6%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Frequency of the chromosome 22q11.2 deletion**

In this patient, a slightly bulbous nose tip and hooded eyes are the primary features.

![Figure 1: Facial dysmorphia in chromosome 22q11.2 deletion syndrome](image)
have various deletions with one breakpoint in an LCR. There have been no consistent phenotypic differences when distant low copy number repeats (LCRs). 8% of patients have a 1·5 Mb deletion, and the remainder of patients have various deletions with one breakpoint in an LCR. There have been no consistent phenotypic differences when different deletions have been compared.

**Figure 2:** Genes in the commonly deleted region of chromosome 22

The most common deletion, which is 3 Mb, is seen in about 90% of patients and occurs between the two most distant low copy number repeats (LCRs). 8% of patients have a 1·5 Mb deletion, and the remainder of patients have various deletions with one breakpoint in an LCR. There have been no consistent phenotypic differences when different deletions have been compared.

**Figure 3:** Transcription factors regulating thymus and parathyroid development

TBX1 regulates the expression of several growth factors and transcription factors. Knockout mice for those genes have a phenotype (indicated in parentheses) that in part reproduces that seen in chromosome 22q11.2 deletion syndrome. EYA1 and HOXA3 induce expression of GCM2, which is needed for thymus and parathyroid development. AHF=anterior heart field. P arch=pharyngeal arch. ISL1=islet-1. SHH=sonic hedgehog homologue. FOXA=forkhead box A. FGF=fibroblast growth factor. PAX9=paired box gene 9. GCM2=gastrointestinal brain homeobox 2. GCM2=glial cells missing homologue 2. EYA1=eyes absent homologue 1. HOXA3=homeobox A3. Retinoic acid

Important differences that might be ascertainment bias or true phenotypic differences related to distinct modifier genes. Polymorphisms of the vascular endothelial growth factor might modify the phenotype in some circumstances.

In mice, TBX1 is expressed in the pharyngeal mesenchyme and endodermal pouch. Pharyngeal pouches are the initial segmentation for structures of the face and upper thorax, and are temporary structures. The third (endodermal) pouch gives rise to the parathyroid and thymus. Haplosufficiency for TBX1 leads to smaller parathyroid and thymus, and TBX1 is an early requirement (figure 3). Additionally, TBX1 directly activates fibroblast growth factor 8 (FGF8), FGF10, myogenic factor 5 (MYF5), and myogenic differentiation 1 (MYOD1). FGF8 and FGF10 are thought to promote growth of surrounding cells and might also have a role in neural crest migration. MYF5 and MYOD1 regulate development of the branchiomeric muscles. Aberrant development of these muscles might explain the swallowing and feeding difficulties that are common in infancy.

TBX1 is also expressed in the secondary heart field, which gives rise to the cardiac outflow tract and the right ventricle, and the mesenchyme of the brain. Cells of the secondary heart field are derived from the pharyngeal mesoderm. The primary heart field gives rise to the primitive linear tube and is not dependent on TBX1. Several studies of cell-fate mapping revealed that TBX1 is expressed by a small set of cells in the anterior heart field that become cardiomyocytes in the outflow tract (figure 4). These cells might mark a path for the subsequent migration of neural crest cells or they might be themselves essential to form the structures. The cascade of transcription factors is not as well described for the heart as for the parathyroid and thymus. Nevertheless, the pattern seems similar to that in the neck structures, with islet-1 (ISL1) regulating sonic hedgehog homolog (SHH). SHH in turn activates the expression of several forkhead box (FOX) family members: FOXA2 in the neck structures, and FOXA2, FOXC1, and FOXC2 in the secondary heart field. The FOX family members bind to tissue-specific enhancers in the TBX1 gene, leading to two well described events. TBX1 drives the expression of FGF8 and FGF10, which are important for survival, proliferation, and migration of neural crest cells. TBX1 also regulates the expression of paired-like homodomain transcription factor 2 (PITX2). This transcription factor is important for body closure, craniofacial development, and left–right asymmetry for heart development.

Patients with chromosome 22q11.2 deletion syndrome have various malformations that do not map to branchial arch structures. Behavioural, cognitive, and psychiatric disturbances are very common, whereas distal skeletal, vertebral, and renal anomalies are seen in a few patients only. TBX1 is expressed in the developing brain mesoderm and in the sclerotome, which gives rise to various structures in the spinal column. Although the role of TBX1 in these sites is not well understood, its expression pattern gives a framework for understanding the non-branchial arch phenotypes.

Interest in the identification of specific functions of TBX1 is related to the possibility of finding an intervention that might ameliorate the effects of haplosufficiency for TBX1. Advances in the knowledge of the regulation of TBX1 have led to the possibility of controlling its expression through the retinoic-acid pathway. Fetal isotretinoin exposure has long been known to cause a syndrome with remarkable similarity to chromosome 22q11.2 deletion syndrome. Retinoic acid is a repressor of TBX1 expres-
Manipulation of this pathway might make its expression return to normal in haplosufficient babies, if detected early enough. The identification of modifier genes, either within the deleted region or in background genes, is also of great interest because they might offer the basis for the development of meaningful interventions.

Although data indicating that TBX1 has a role in the phenotype of chromosome 22q11.2 deletion syndrome are convincing, data showing that other genes within the deleted region are contributing to the phenotype exist. Haplosufficiency for glycoprotein Ibβ might contribute to the mild thrombocytopenia seen in patients, and haplosufficiency for catechol-O-methyl transferase was implicated by some studies in the behavioural and psychiatric disturbances, and might be related to the mild increase in malignant disease.

Management

The management of patients with chromosome 22q11.2 deletion syndrome is highly dependent on age and phenotype (figure 5). Few prospective studies support a specific management style. Here, we describe common strategies for each organ system. Patients with the chromosome 22q11.2 deletion syndrome might present at any age, although most patients receive their diagnosis shortly after birth because of the presence of a cardiac anomaly. In newborn babies, a thorough physical and radiographic examination should seek medical problems that are likely to need immediate intervention, such as cardiac anomalies, hypocalcaemia, severe immunodeficiency, or intestinal malrotation. Feeding difficulty can be very distressing for parents of babies with chromosome 22q11.2 deletion syndrome, but it is typically revealed after the patient is back at home. Development and speech during childhood need careful attention, whereas additional consideration to cognitive development and growth is needed during school years. Behavioural issues are likely to become more problematic with increasing age, and psychiatric disorders are seen in teenagers and adults (figure 5).

The range of cardiovascular anomalies is wide, although conotruncal defects are the most frequent ones. Slight variations might dictate a different surgical intervention. Two-dimensional and colour-Doppler echocardiography is essential to define the anatomy; additionally, the thymus might be visualised in this way. Cardiac catheterisation is not always needed but can provide helpful information. Cardiac anomalies are seen in about 75% of all patients with chromosome 22q11.2 deletion syndrome and are the major causes of death.

Surgical implications of chromosome 22q11.2 deletion syndrome are not fully known. Surgical risk is low in most patients. Many patients who need bypass surgery have minor residual cognitive issues. Whether this event is more frequent in those with chromosome 22q11.2 deletion syndrome is not known. The two issues that affect clinical care before surgery are monitoring of serum calcium concentration and identification of a serious immunodeficiency. Low numbers of T cells are seen in 75–80% of infants with chromosome 22q11.2 deletion syndrome. In most infants, a mild-to-moderate decrement of T-cell numbers occurs, and needs no specific attention during surgery or recovery from surgery. Less than 1% of patients with the deletion are thought to have no T cells. These patients are rare but need protection from infection and blood products. Blood products that contain lymphocytes can induce graft-versus-host disease in patients without T cells, which is almost always fatal, indicating that care should be taken. Care of patients without T cells is discussed below.

Some patients with the chromosome 22q11.2 deletion syndrome might need cardiac surgery before obtaining definitive information regarding the status of their immune system. However, in these patients several strategies have been devised to reduce the risks. In many large centres in the USA, all blood products given to infants less than 1 year old are irradiated. Another strategy is to stratify risk in accord with the absolute lymphocyte count from a complete blood count. When the number of T cells is reduced, typically the absolute lymphocyte count is low. However, this strategy is not specific or sensitive. In the absence of prospective data, many physicians choose irradiation of blood products; however, this is a cumbersome
Although the rate of decline of T-cell numbers in patients with chromosome 22q11.2 deletion syndrome is slower than that of controls, the T-cell population is smaller than that of healthy controls throughout childhood.77,78,82

Most studies show little effect of thymic hypoplasia on humoral immunity. Humoral immunity refers to the ability of B cells to produce antigen-specific antibodies. Serum IgG and IgM concentrations, and specific IgG against diphtheria and tetanus toxins are usually normal. The number of patients with IgA deficiency seems to be higher than that in the general population, with estimates ranging from 2% to 30%.73,82,85-87 Selective IgA deficiency is thought to arise in one in 700 individuals in the general population (0-0.001%). Defects in cellular immunity might result in impaired antibody production to some antigens, such as measles or pneumococcal polysaccharides.85,86,89

The mechanism underlying these defects might be reduction of the repertoire of T-cell receptor families.90 The genetic diversity of T-cell receptors enables T cells to recognise many specific antigens. Another possible consequence of restricted T-cell receptor families is an increased frequency of infections, in addition to an increased frequency of autoimmune diseases. Some autoimmune diseases, such as juvenile rheumatoid arthritis, immune thrombocytopenia, and Raynaud’s phenomenon are more frequent in patients with chromosome 22q11.2 deletion syndrome than in the general population.91,95,96 The increased frequency of autoimmune diseases might be secondary to decreased numbers of T regulatory (CD4+CD25+) cells, which prevent organ-specific autoimmunity,93 or might be due to compensatory homeostatic expansion of T cells.94

Thymic aplasia with absence of peripheral T cells is a devastating disorder that should be addressed immediately. Infants with thymic aplasia are at risk of developing graft-versus-host disease after transfusion of non-irradiated blood products, and are at risk for opportunistic infections such as Pneumocystis jiroveci and Cytomegalovirus. Furthermore, infants with substantial thymic defects, and very low T-cell numbers or impaired T-cell function should not be treated with live viral vaccines because of the risk of developing disseminated disease from attenuated viral strains. By contrast, patients with mild thymic defects, whose CD4+ T-cell counts are greater than 400, can safely receive the measles–mumps–rubella live attenuated vaccine.95-97 Treatment for patients with absent T cells aims to restore T-cell function either through transplantation of mature T cells,98-99 through transplantation of thymus tissue.100 Mini transplant protocols have been successfully used, and combined thymus–parathyroid transplantations have been done.100,101 This field is rapidly advancing.

Speech, hearing, and vision issues are typically addressed during infancy. Although tortuous retinal vessels are seen in a third of patients and posterior embryotoxon is seen sporadically, vision is typically normal or close to normal in patients with chromosome 22q11.2 deletion syndrome.102 Accommodation and convergence difficulties might indicate a generalised hypotonia, and refractive errors are

Figure 5: Change in health concerns with age
common but do not threaten vision. Hearing is important for the acquisition of language, and about 10% of patients with chromosome 22q11.2 deletion syndrome have sensorineural hearing loss, and 45% have conductive loss. These difficulties are important to address; however, speech delay in velocardiofacial syndrome is different from that in patients with congenital deafness. Hearing difficulties are a minor contributor to language delay in most patients.

Speech delay is one of the most distressing aspects for most parents of children with chromosome 22q11.2 deletion syndrome. Speech difficulties include defects in phonation, in language acquisition, and in comprehension. Phonation can be abnormal because of anatomical issues, including laryngeal webs, velopharyngeal insufficiency, or vocal cord paralysis. Hoarseness and hypernasality partly respond to surgical intervention, but phonation remains abnormal in many patients. Expressive language and speech skills are usually more delayed than are receptive skills, and expressive language skills are less evolved than expected on the basis of cognitive development. Social language skills are typically even more delayed. This pattern of skill weaknesses is almost unique to patients with chromosome 22q11.2 deletion syndrome. Management of speech delay is very controversial. Experts of sign language think that the ability to communicate and develop the grammar of language is of paramount importance, and sign language enables the child to progress developmentally. An alternative approach is based on the belief that sign language delays language acquisition and uses intensive speech therapy. There have been no direct comparisons of the two approaches, and parents seem to be satisfied with both sign language and intensive speech therapy. Ultimately most patients learn to speak and communicate effectively. The major obstacles for adults and teenagers are not speech or phonation, but the ability to reason and integrate information from verbal communication.

Organs of the abdominal cavity are infrequently affected in a way that needs medical intervention. Renal agenesis, duplicated kidneys, dysplastic kidneys, duplicated ureters, and other minor malformations are seen in about a third of patients with chromosome 22q11.2 deletion syndrome. These dysfunctions generally need no intervention. Nephrocalcinosis is not a congenital anomaly of the kidney, but arises often as a consequence of excessive calcium replacement for hypocalcaemia. Genitalia, liver, and spleen are not typically affected in this syndrome; however, the gastrointestinal tract is a source of concern. Malrotation of the intestines is not a common feature, but it can be very serious if not diagnosed. Feeding and swallowing difficulties seem to arise from poor coordination of the pharyngeal muscles, tongue, and oesophageal muscles. Patients with cardiac defects might also have shortness of breath as a factor that leads to poor feeding, and breastfeeding is known to be difficult for infants with palatal clefting. Thus, many dysfunctions can contribute to poor feeding. Because feeding is one of the most intimate parts of parenting, feeding difficulties of infants can be very frustrating for parents. Constipation is very common, as is gastroesophageal reflux. The mechanisms underlying constipation and reflux are not known, although hypotonia is a frequent cofactor.

Speech delay profoundly affects the quality of life of the patient, but most aspects of development are somewhat affected. The mean full-scale intelligence quotient is about 70, indicating a range from normal-to-moderately disabled. Cognitive skills are not all affected in the same way, and most patients have reasonable skills related to comprehension and social rules. Visuo-perceptual abilities and planning tend to be the weakest cognitive skills. This pattern of non-verbal learning disability is not unique to chromosome 22q11.2 deletion syndrome and is seen in other syndromes with developmental delay. Indeed, learning disability is occasionally the only manifestation of chromosome 22q11.2 deletion syndrome. School-based interventions have been successfully developed for children with non-verbal learning disabilities. These interventions are thought to be suitable for children with chromosome 22q11.2 deletion syndrome, although no studies have attempted to define the best possible learning strategy.

Nearly 50% of patients have microcephaly. The parietal lobe is typically affected and has important roles in memory retrieval, which is crucial for any learning process. Functional MRI studies have shown that the patterns of brain use during mathematical tasks are different in patients with the chromosome 22q11.2 deletion syndrome compared with those in controls. Other anatomical findings might elucidate the pathophysiological changes of some cognitive features seen in patients with chromosome 22q11.2 deletion syndrome. For example, a small vermis is seen in such patients and in those with autistic spectrum disorder. The posterior vermis seems to control social drive, and this anomaly might explain the social awkwardness in some patients with the chromosome 22q11.2 deletion syndrome.

The behavioural aspects of chromosome 22q11.2 deletion include attention deficit hyperactivity disorder, poor social interaction skills, impulsivity, and blunted affect. Bipolar disorder, autistic spectrum disorder, and schizophrenia or schizoaffective disorder are reported in 10–30% of teenagers and adults. Psychiatric disorders are common in all patients with developmental delay; however, the association is stronger in patients with chromosome 22q11.2 deletion. Schizophrenia is associated specifically with aberrant brain structure. Insight into the mechanism underlying the association of psychiatric diseases and chromosome 22q11.2 deletions might come from murine models. Mice carrying the Cre–LoxP deletion showed abnormal prepulse inhibition. The prepulse inhibition test measures the startle response to various stimuli. Patients with schizophrenia have impaired prepulse inhibition as do mice with the deletion. This result proved to be due to haplosufficiency for TBX1 and guanine
nucleotide binding protein (G protein), β polypeptide 1-like (GNB1L). Up to now, patients with behavioural difficulties and frank psychiatric disturbances have been treated with conventional modalities. Whether this finding will enable tailored inventions for patients with the chromosome 22q11.2 deletion syndrome remains to be seen.

**Conflict of interest statement**

We declare that we have no conflict of interest.

**References**


