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Clinical manifestations of Deletion 22q11.2 syndrome (DiGeorge/Velo-Cardio-Facial syndrome)

MC Digilio,[1] B Marino,[2] R Capolino,[1] and B Dallapiccola[3]

[1] *Medical Genetics, Bambino Gesù Hospital, Rome, Italy*

[2] *Pediatric Cardiology, Institute of Pediatrics, University "La Sapienza", Rome, Italy*

[3] *Experimental Medicine and Pathology, University "La Sapienza", and CSS-Mendel Institute, Rome, Italy*

Contact information: Dr. Maria Cristina Digilio, Medical Genetics, Bambino Gesù Hospital, Piazza S. Onofrio 4, 00165, Rome, Italy Phone: +39-06-68592227 +39-06-68592227 Fax: +39-06-68592101 ; Email: digilio@opbg.net

Abstract

Deletion 22q11.2 syndrome (Del22) (DiGeorge/Velo-Cardio-Facial syndrome) is characterized by congenital heart defect (CHD), palatal anomalies, facial dysmorphisms, neonatal hypocalcemia, immune deficit, speech and learning disabilities. CHD is present in 75% of patients with Del22. The most frequently seen cardiac malformations are "conotruncal" defects, including tetralogy of Fallot (TF), pulmonary atresia with ventricular septal defect (PA-VSD), truncus arteriosus (TA), interrupted aortic arch (IAA), and ventricular septal defect (VSD). The study of the specific "cardiac phenotype" in patients with Del22 shows that a particular cardiac anatomy can be identied in these subjects. In addition to CHD, various organ systems can be involved, so that a multidisciplinary approach is needed in the evaluation of patients with Del22.

MeSH: Deletion 22q11, DiGeorge syndrome, Velo-Cardio-Facial syndrome, Heart defects, congenital

Introduction

DiGeorge and Velo-Cardio-facial syndromes are genetic conditions with overlapping features, including congenital heart defect (CHD), facial anomalies, hypoplastic thymus with immune deficit, palatal anomalies, neonatal hypocalcemia, speech and learning disabilities.[1,3] Cytogenetic and molecular studies have demonstrated that microdeletion of chromosome 22q11.2 (del22) is detectable in the majority of patients with DiGeorge/Velo-cardio-facial syndrome.[4,5] Del22 syndrome is considered to be developmentally related to neural crest anomalies, influencing the differentiation of the branchial arches.[6,7] It is estimated that del22 syndrome occurs in 1 in 4000-6000 live births, making this disorder a significant health concern in general population.[8]

Clinical features

The variability in the clinical expression of del22 syndrome is extremely wide.[9] Classical features of del22 syndrome include CHD, velopharyngeal insufficiency or cleft palate, facial anomalies, speech and learning disabilities, neonatal hypocalcemia, and T-cell immune deficit. Nevertheless, the spectrum of anomalies associated with del22 is becoming wider and wider.[2] Inter-individual variability in del22 phenotype is characteristic, since subjects with full-blown clinical expression of the syndrome as well as mildly affected individuals can be found. The main clinical features of Del22 syndrome and their occurrence in our series of 165 patients are listed in Table 1.

Table 1 Main clinical features of Del22 syndrome and their occurrence in this series

Clinical finding	Affected individuals	%
Facial anomalies	165/165	100%
Congenital heart defect	136/165	82%
Speech / Learning difficulties	132/165	80%
Neonatal hypocalcemia	121/165	73%
T-cell deficiency	97/141	69%
Skeletal anomalies	52/165	32%
Palatal anomalies	51/165	31%
Asymmetric crying face	35/165	21%
Renal malformations	25/165	15%
Genital anomalies	19/165	11%

Facial anomalies

Accurate phenotypical evaluation of patients with Del22 demonstrates that facial anomalies, severely or mildly expressed, are detectable in all subjects. Characteristic facial features include periorbital fulness, narrow upslanted palpebral fissures, prominent nose with large tip and hypoplastic nares, small mouth with everted upper lip and small dysmorphic ears (Figures 1,2). Many children, particularly in neonatal age, may have only a “subtle” facial phenotype. The experience of physicians caring with children affected by del22 is fundamental in recognizing mild facial anomalies associated with the syndrome.

Figure 1 Facial appearance of patient with Del22 syndrome

Figure 2 Facial appearance of patient with Del22 syndrome

Congenital heart defects

75% of patients with Del22 have symptomatic CHD.[2] The most frequently seen cardiac malformations are "conotruncal" defects, including tetralogy of Fallot (TF), pulmonary atresia with ventricular septal defect (PA-VSD), truncus arteriosus (TA), and interrupted aortic arch (IAA).[2,10–15] VSD, as well as asymptomatic aortic arch malformations are increasingly been diagnosed in patients with Del22 (Table 2).[16]

Table 2 Cardiac anomalies in this series.

Cardiac defect	Affected individuals	%
Tetralogy of Fallot	36/136	26%
Pulmonary atresia and ventricular septal defect	33/136	24%
Ventricular septal defect	26/136	19%
Interrupted aortic arch	14/136	10%
Truncus arteriosus	13/136	10%
Double outlet right ventricle	4/136	3%
Double aortic arch	3/136	2%
Atrial septal defect	3/136	2%
Other	4/136	3%

The study of the specific "cardiac phenotype" in patients with Del22 shows that a particular cardiac anatomy can be identified.[15] In fact, patients with conotruncal heart defect and Del22 have often additional CHDs as a distinctive recognizable pattern.

Tetralogy of Fallot: Additional cardiac defects are found in the half of the patients with this TF and Del22.[17,18] The associated cardiac defects include: 1) right or cervical aortic arch with or without aberrant left subclavian artery; 2) hypoplasia or absence of the infundibular septum; 3) absence of the pulmonary valve; 4) discontinuity and diffuse hypoplasia of the pulmonary arteries.

Pulmonary atresia with ventricular septal defect: Considering the pattern of pulmonary blood supply, among children with pulmonary atresia with ventricular septal defect two major groups of patients can be recognized: 1) children with a single ductus arteriosus that usually presents confluent and well formed pulmonary arteries (also called tetralogy of Fallot with pulmonary atresia), and 2) children with major aortopulmonary collateral arteries (MAPCA) frequently associated with discontinuity, hypoplasia or absence of the central pulmonary arteries. In children with pulmonary atresia with ventricular septal defect and Del22 the pattern of pulmonary blood supply provided by the MAPCA is prevalent.[19–22] Additionally, a high prevalence of right aortic arch and of discontinuity and defects of arborization of the pulmonary arteries can be found.

Truncus arteriosus: Del22 is prevalent in patients with TA with nonconfluent pulmonary arteries (Type 3 of van Praagh), in which the right pulmonary artery arises

from the TA near to the truncal valve, and the left pulmonary artery is supplied by the ductus arteriosus.[23–25] Additional CHDs to TA are: 1) interruption or right aortic arch; 2) discontinuity, stenosis, or crossing of the pulmonary arteries; 3) severe dysplasia of the truncal valve; 4) origin of the TA from the right ventricle.
Interrupted aortic arch: Del 22 is particularly common in patients with IAA type B.[26–30] In these cases the infundibular septum is often hypoplastic or absent and is deviated posteriorly and to the left; the VSD results in a subarterial position doubly committed with the pulmonary and aortic valves.
Ventricular septal defect: The type of VSD in patients with Del22 is prevalently subarterial doubly committed.[16,31] Right or cervical aortic arch may be associated.

Palatal anomalies

Two thirds of the patients with Del22 are found to have palatal anomalies, and the spectrum of malformations is wide.[2,3,40] The majority have velopharyngeal insufficiency in the absence of cleft palate, but overt clefts, bifid uvula and cleft lip may also be present. Palatal function plays an important role in the development of speech.

Immune deficit

The immunodeficiency in Del22 syndrome is due to poor formation of thymic tissue and impaired production of T-cells. The most common immunologic abnormality is low number of T-cell, and functional T-cell deficiency is found in a minority of all patients.[41] Nevertheless, the spectrum of immunocompromise in the Del22 patient population is broad. Children with Del22 have a significant risk of infection due to anatomical effects such as CHD and cleft palate. The additional risk associated with immunodeficiency may represent a critical factor in the management of these patients. Fortunately, the T-cell number usually increases by time and the cell function is not altered. Usually, patients with del22 are at most risk for repeated infections in the first years of life, but older children and adults do generally not have recurrent infections.

Hypocalcemia

Neonatal hypocalcemia is recognized in most of children with Del22.[2] This symptom is related to hypoparathyroidism due to absence or underdevelopment of parathyroid glands, which leads to low blood calcium levels.[42,43] Hypocalcemia may cause tremors, seizures, and arrhythmia. Calcium supplementation leads to normalization of blood calcium levels. The development of hypoparathyroidism later in life is rarer.

Speech / Learning impairment

Developmental delays can be present in children with del22, including delays in the motor, linguistic and cognitive domains.[44,45] Delayed motor development is mainly attributed to the hypotonia present in more than half of the patients with del22. Psychomotor therapy is therefore recommended from an early age. Difficulties in expressive language are generally evident in preschooler children. This delayed speech development is prevalently due to the concomitance of velopharyngeal insufficiency and developmental delay. Speech difficulties related to velo-palatal abnormalities may become clearly manifest late, particularly when speech has fully developed. During childhood, the majority of the children has learning problems, especially in the area of reading comprehension, arithmetic and problem-solving. Common problems seen in these patients are impulsivity, distractibility, perseveration, and hyperactivity. Several common behavioural and temperamental features have been observed in children and adolescents with del22, including a predisposition to show a withdrawn behavior, depression, anxiety and a tendency to engage in obsessive and/or compulsive behaviours. Therefore, good monitoring and follow up of the socio-emotional development is important in all ages.

Skeletal anomalies

Skeletal anomalies and deformations have been detected in patients with del22.[46–48] In the first reports, a variety of hand malformations and clubfoot have been described. Thereafter, scoliosis and vertebral maformations, including butterfly vertebrae and vertebral coronal cleft, have been added to the list. As characteristic diagnostic marker, most of del22 patients have long tapered fingers (Figure 3).

Figure 3 Long tapering fingers characteristics of Del22 syndrome

Asymmetric crying face

Unilateral partial facial palsy due to hypoplasia of the depressor anguli oris muscle (DAOM) results in asymmetry of the lower lip, especially evident in smiling and crying. The eye on the affected side usually closes normally. DAOM can be detected in about 20% of neonates with del22.[49]

Audiological anomalies

Hearing impairment is documented in 60% of patients with del22.[2,50] Hearing loss is conductive in the majority of the cases, probably related to chronic otitis media with effusion and upper respiratory tract infections. Nevertheless, congenital sensorineural deafness is also diagnosed in some cases. Audiological evaluation is recommended in Del22 children, in order to reduce the risk of speech deficit.

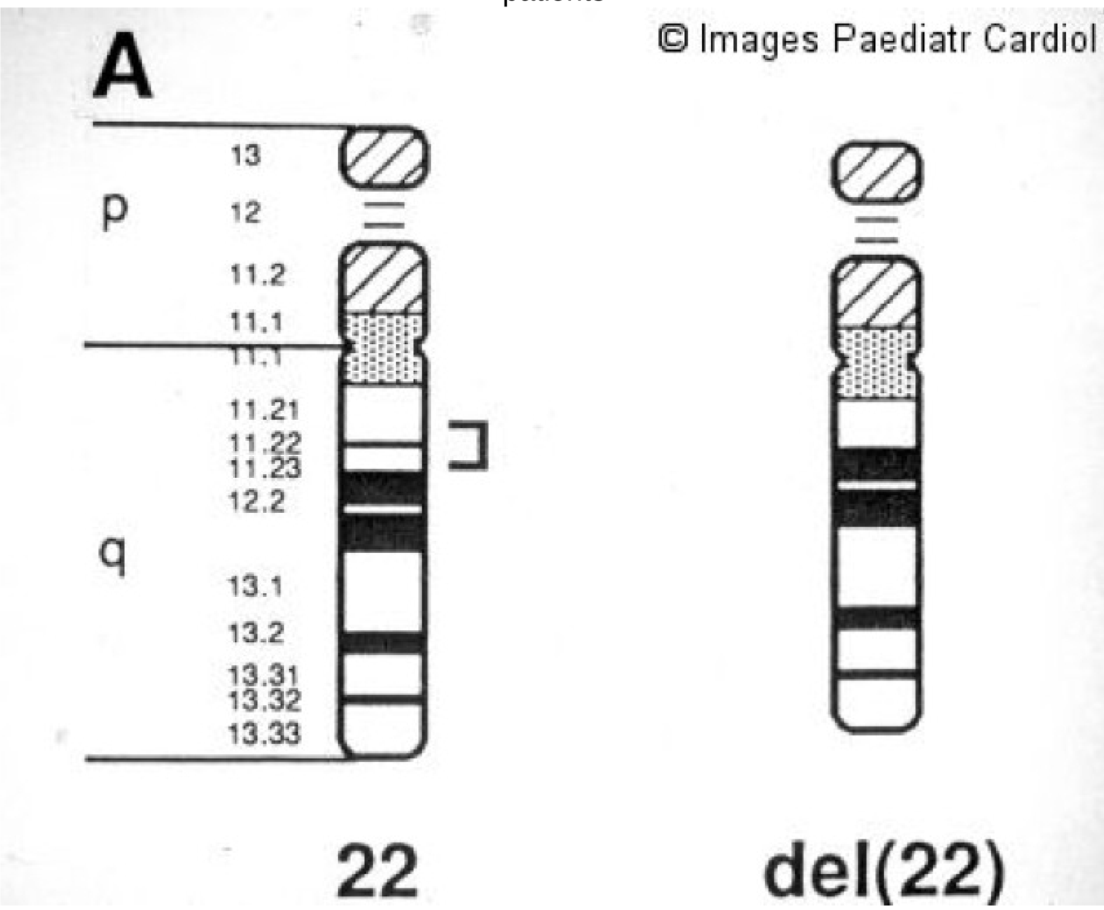
Growth

A specific pattern of growth is identifiable in patients with Del22.[51] Weight deficiency is frequent in the first years of age, being prevalently related to feeding difficulties. The growth in weight improves with time leading to overweight and obesity in adolescence. On the contrary, short stature is present in a minority of the patients. In fact, adolescent patients have prevalently normal height, with a small group of patients showing a constitutional delay in height growth.

Genetics

In 1992, a microdeletion of chromosome 22 at the q11.2 band was reported.[52] The critical region has been subsequently defined (Figure 4).

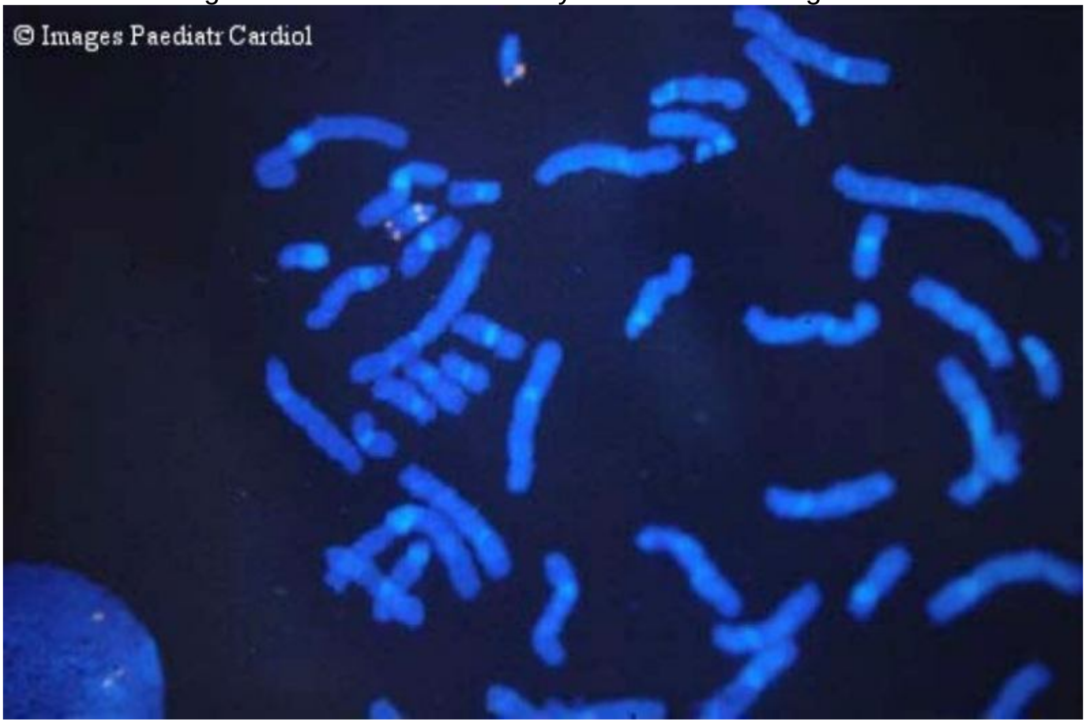
Figure 4 The 22q11 critical region commonly deleted in DiGeorge/velocardiofacial patients



The majority of the patients carry a common 3 Mb deletion, but smaller deletions have also been found. To date, the size of the deletion has not been correlated with the phenotypical expression of the syndrome. Fluorescent in situ hybridization (FISH) is used as genetic laboratory test for 22q11.2 microdeletion detection (Figure 5).

At least 30 genes have been mapped in the typical deleted region. Among genes located in the "critical" chromosomal region, TUPLE1, UFD1L and TBX1 have been particularly studied.[53–55] Although TBX1 mutations have been recently detected in rare patients with clinical features of DiGeorge/Velo-Cardio-Facial syndrome without an identifiable Del22,[56] it remains unclear whether several genes must be haploinsufficient to cause a clinical phenotype or whether a single locus predominates.

Figure 5 Fluorescent in situ hybridization showing Del22



Familial transmission

The Del22 is a "de novo" occurrence in the family in most of the cases. Nevertheless, inheritance of the microdeletions from one of the parents is possible, the frequency varying from 6% to 28% in different series.[2,9,57–59] The affected parent often demonstrates a milder phenotype. Various genetic and non-genetic factors, including modifier genes, mosaicism, unstable mutations, allelic variations chance and environmental interactions, can be hypothesized to be involved in variable clinical expression of the syndrome in the same family.

Non-syndromic conotruncal heart defects

Several observations suggesting that del22 could be associated with "non-syndromic" CHDs can be found in the previous literature on this argument.[32,33] However, 80% of these patients, reported as apparently "isolated" CHD, had in fact extracardiac features fitting within the del22 syndrome phenotype. Other investigations have shown that Del22 is virtually never found in non-syndromic patients with conotruncal CHDs.[34–38] In a personal series of 305 patients with true non-syndromic CHD, we detected only one deleted patient.[14] Thus, we believe that, in clinical practice, genetic tests searching for del22 are not indicated in all patients with conotruncal CHDs, but only in subjects with clinical anomalies of del22 syndrome. Classic or subtle facial anomalies are fundamental useful tools for selecting children who should be tested for Del22.[14,39] In this regard, also patients with distinct anatomic conotruncal defect subtypes must be included.[14,39]

Conclusions

Clinical expression of Del22 syndrome can be extremely variable and the degree of various organ systems involved is wide. Early recognition of the deletion is important, so that the treatment of involved organ anomalies can be initiated, screening for associated malformations performed and prevention of neuropsychological problems provided. In fact, as occurrs in several multiple system clinical conditions, the care of patients with Del 22 can be very complex. A multidisciplinary approach is fundamental to ensure that the patient will be able to attain his or her maximal potential.

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