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Velocardiofacial syndrome (VCFS): an important syndrome to recognize, caused by a microdeletion of chromosome 22q11

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Abstract. The phenotypic heterogeneity of the velocardiofacial syndrome (VCFS) or Shprintzen syndrome caused by a chromosomal 22q11 deletion will be discussed. The acronym 'CATCH22' (Cardiac defects – Abnormal facies – Thymic hypoplasia – Cleft palate – Hypocalcaemia) has been suggested to indicate the associated phenotype. The variable clinical phenotype was previously recognized as DiGeorge syndrome and Shprintzen syndrome, but both are caused by a microdeletion of chromosome 22q11. However, most patients show only partial expression with mild clinical features. Through a sensitive genetic investigation called FISH (Fluorescence in situ hybridization) a diagnostic test of VCFS has become routinely possible, leading to an increased number of patients that are diagnosed. Early diagnosis is very important to recognize associated problems, to initiate adequate treatment and to provide necessary genetic counselling.

Key words: 22q11 deletion, CATCH22, velocardiofacial syndrome (VCFS).

Introduction

Deletions of the long arm of chromosome 22 were initially described in children with DiGeorge syndrome (DGS). This syndrome is characterized by a variable facial dysmorphism, congenital heart defect, cleft palate, thymic and parathyroid hypo-/aplasia. In a few patients, small deletions were found involving chromosome band '1.1' of the long arm of chromosome 22 (del22q11) (GREENBERG 1993) (Fig. 1). Recently the same deletion was

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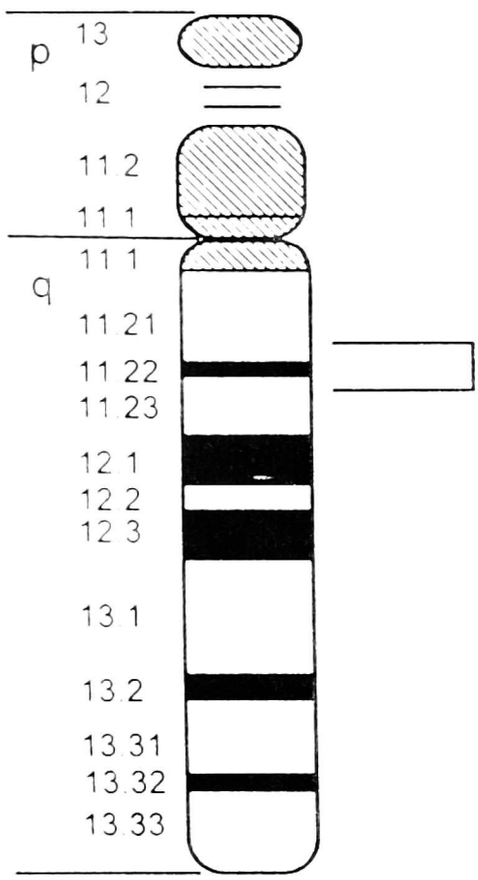


Fig. 1. Schematic presentation of chromosome 22. The chromosomal 22q11 region (on the long arm of chromosome 22) is indicated.

demonstrated in patients with Shprintzen syndrome (VCFS). Typical patients with this syndrome have a characteristic facial dysmorphism, cleft palate, a congenital heart malformation and learning disabilities (SCAMBLER et al. 1992). In time, it became evident that the clinical phenotype of patients with a 22q11 deletion is variable, leading to a broadening of the phenotypic spectrum. Most patients show clinical features of both DGS and VCFS. Often, only partial expression of the phenotype, with minimal clinical features is found (GOLDBERG et al. 1993, GOLDMUNZ et al. 1993, SWILLEN et al. 1993, LIPSON et al. 1994). Because of this variable phenotypic spectrum in patients with del22q11 (including DGS and Shprintzen syndrome (VCFS)) the acronym 'CATCH22' (Cardiac defects – Abnormal facies – Thymic hypoplasia – Cleft palate – Hypocalcaemia) has been suggested (WILSON et al. 1993). Since 'CATCH22' is also the title of a book in Anglo-Saxon literature about front soldiers in the Vietnam-war, we prefer the term VCFS in this article. Most patients with a del22q11 show the characteristic clinical features of VCFS. The patients with DGS (with del22q11) could be seen as an extreme presentation of VCFS. Generally, patients with the DGS have a less favourable prognosis in comparison with VCFS, which is related to the severe congenital cardiac malformation, mental retardation and immune deficiency. It could therefore still be useful to distinguish DGS and Shprintzen syndrome.

VCFS is a frequent syndrome. Its incidence is probably underestimated, since most patients (especially those with mild expression) are still not diagnosed. The estimated prevalence is around 1:5000. Given this high prevalence and variable clinical manifestations of VCFS, it can be expected that most physicians will be confronted with this (relatively unknown) disorder.

In this article the embryogenesis, clinical manifestation, diagnostic technics and inheritance of VCFS will be discussed.

Embryogenesis of VCFS

Errors in early embryological development have been recognized as a possible etiology of VCFS. However, how to match the development of the face, parathyroid, thymus and heart? The answer is found in experimental animal work, involving ablation of the premigratory cranial neural crest during embryological development. These experiments result in conotruncal and thymic abnormalities as seen in DGS (KIRBY 1987, HALFORD et al. 1993a).

The neural crest originates from the neuro-ectoderm, which is initially found at the dorsal side of the embryo. Cranial neural crest cells are involved in the development of connective tissue and muscles of the face and connective tissue and skeleton of the pharyngeal arches. The thymus and parathyroid glands develop from the third and fourth pharyngeal pouches. The neural crest cells from the left fourth pharyngeal pouch give rise to the aortic arch and its outflow tracts. These cells form the aorticopulmonary septum and populate the truncal folds. The (conotruncal) cardiac malformations found in VCFS are thus specific developmental abnormalities.

Abnormalities found in VCFS can therefore be seen as an error caused by an abnormal neural crest cell migration and/or differentiation during embryological development. Deletions of chromosome 22q11 indicate that this is a constitutional disorder. Most likely, one or more genes located in this chromosomal band region play a crucial role in cranial neural crest differentiation. Several candidate-genes have already been isolated, but it is still not clear whether the phenotype results from the deletion of a single critical gene or from more genes in this 22q11 region (AUBRY et al. 1993, HALFORD et al. 1993a, b). Studies reported so far show that the severity of clinical features seen in VCFS, is not correlated with the size of the deleted region of chromosome 22q11 (DESMAZE et al. 1993, DRISCOLL et al. 1993).

Clinical manifestation

The phenotypic expression in patients with microdeletion 22q11 is variable. Patients with the same del22q11 can have the full-blown picture of clinical features (as seen in DGS) or only minimal clinical signs of VCFS. Associated findings can also vary. Incidence figures are difficult to interpret because most reported studies are biased, e.g. if only patients with cleft palate or cardiac malformations were studied. For example, Dr. Shprintzen being attached to a craniofacial clinic, found 98% of the patients with VCFS having a cleft palate (GOLDBERG et al. 1993). The broad spectrum of clinical features in patients

with VCFS will be further discussed and a few illustrative histories will be given.

Clinical features of VCFS

1. Cardiac anomalies

Characteristic cardiac anomalies in patients with VCFS are of conotruncal origin and typically include tetralogy of Fallot (TOF), ventriculoseptal defect (VSD) and right-sided aortic arch (Table 1). Other less frequent anomalies are based on development disorders of the pharyngeal pouch arteries (MOERMAN et al. 1980, KIRBY 1987, GOLDBERG et al. 1993). The most severe congenital heart defects have been described in DGS and include interrupted aortic arch or truncus arteriosus. As one can notice, a high degree of variability in cardiac anomalies exists and many patients with VCFS have no congenital heart defects. GOLDMUNZ et al. (1993) reported that 30% of the patients with an isolated conotruncal heart defect had the 22q11 deletion. Retrospectively, these patients also had other features of VCFS which had not been recognised. In half of the families with familial conotruncal heart disease, a del22q11 was found (WILSON et al. 1992). In a small study of patients with isolated TOF, 2 out of 40 patients (5%) had a del22q11 (WILSON et al. 1992). In patients with an isolated conotruncal heart defect, FISH analysis for a del22q11 can therefore be indicated. On the other hand, for patients with another type of cardiac malformation, such as the atriumseptal defect, the diagnosis of VCFS is less likely.

Table 1. Congenital cardiac malformations in VCFS

Conotruncal heart defects
Truncus arteriosus
Fallot's tetralogy (TOF)
Ventricle septum defect (VSD)
Double outlet right ventricle
Pulmonary stenosis or atresia
Aortic arch anomalies
Right-sided aortic arch
Interrupted aortic arch
Open ductus botalli/ persistent ductus arteriosus
Aberrant left subclavian artery

In the past, most children with severe cardiac malformations died at a young age. Nowadays, their prognosis is much better, and therefore the associated developmental delay and speech disorders have become more important.

2. Dysmorphic features

Facial dysmorfism in VCFS is not always obvious. Characteristic facial features exist, such as a small mandible (retrognathia), a small mouth, small palpebral fissures, low-set ears with auricular malformations (generally small auricles with helical thickening or auricular protrusion). Patients with VCFS typically have a long nose with a prominent nasal bridge, a broad/squared nasal root with narrow alveolar base and deficient alae. This typical nose is especially found in somewhat older children with VCFS (Fig. 2). Other features include: a small stature, narrow hands with long tapering fingers (Fig. 3) and mild (relative) microcephaly (SHPRINTZEN et al. 1978, GOLDBERG et al. 1993, WILSON et al. 1993). Again, none of the facial features are obligatory in VCFS.

3. Velopharyngeal insufficiency

Patients with VCFS show a spectrum of palate malformations including cleft palate, bifid uvula, short palate, submucous cleft palate (the cleft palate is covered by intact mucosa) or only incompetence of the velopharyngeal muscles. The diagnosis of these malformations often requires a specialist ear/nose/throat-examination. The clinical presentation of velopharyngeal insufficiency varies with age. Newborns often have a history of feeding problems. They suffer from nasal regurgitation of feedings (often misdiagnosed as oesophageal reflux), or long lasting feedings. Later on, recurrent middle ear infections occur, caused by dysfunction of the Eustachian tube. This can sometimes lead to deafness in adolescence or adulthood. The most important problem in children and adults with VCFS are speech disorders. Most patients have a (severe) hypernasal speech. Varying degrees of articulatory impairment related to velopharyngeal muscle incompetence can be noticed. Hypernasal speech is found in most patients and therefore represent a reliable symptom to diagnose patients with VCFS. Patients with an isolated cleft palate (no cleft lip) require special attention, since 8% had VCFS (with a del22q11) (GOLDBERG et al. 1993).

Treatment of velopharyngeal insufficiency is difficult. Early speech therapy is indicated. Excellent results after velopharyngeal flap surgery are reported in young patients (LIPSON et al. 1991). Adenoidectomy should be avoided, since the hypernasal speech and articulatory impairment may get worse (MOSS et al. 1990). In few patients with VCFS, an ectopic course of the internal carotid arteries has been reported, which may pose additional risks during surgery. Therefore, magnetic resonance angiography (MRA) is indicated before surgery in patients with VCFS (MACKENZIE STEPNER et al. 1987).

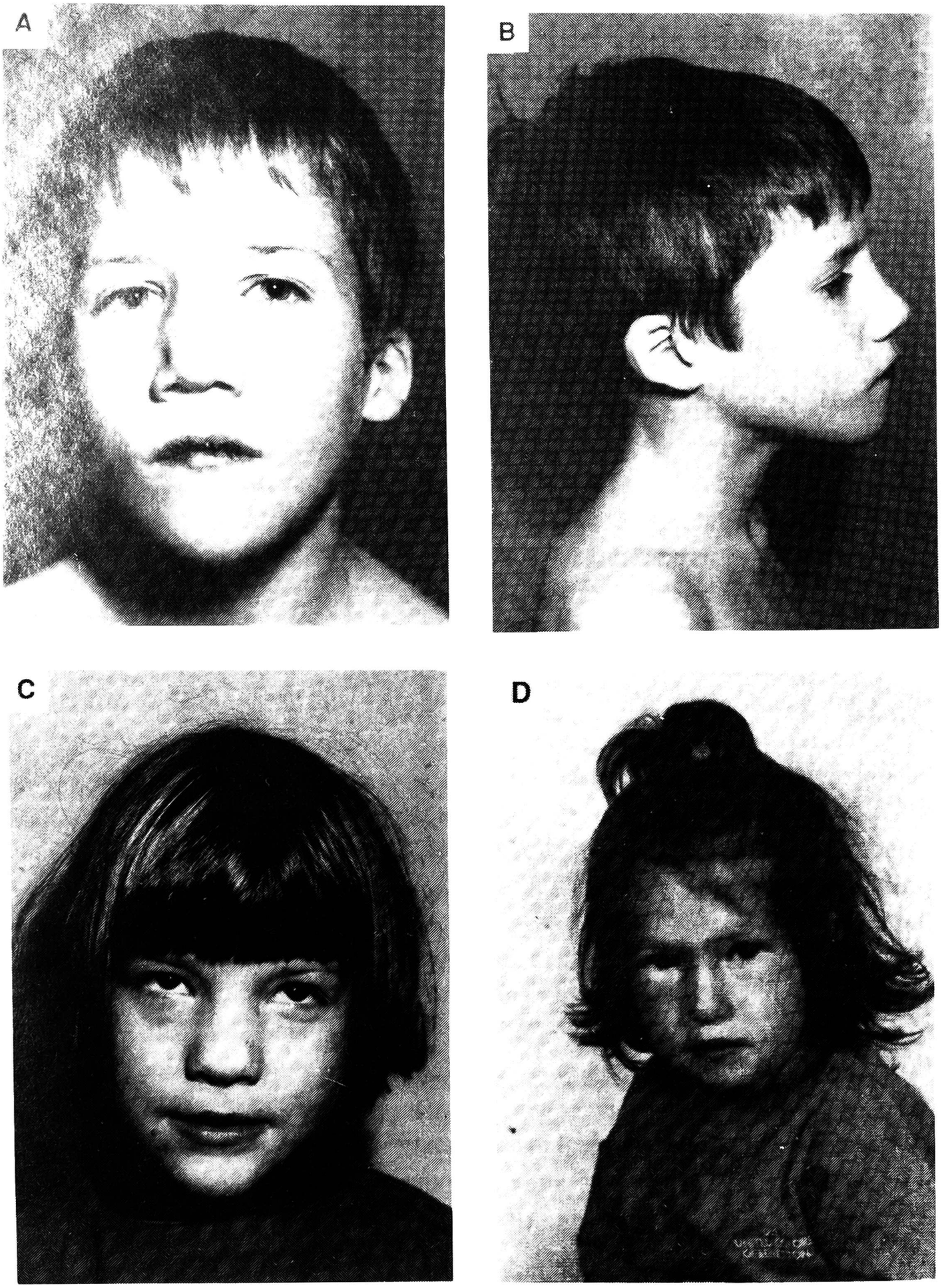


Fig. 2. (A,B,C,D). Facial features of VCFS (Shprintzen syndrome). Characteristic facial features are: small palpebral fissures, small mandible with a small mouth and lowset (slightly) malformed ears. The nose is long and prominent with a broad nasal bridge.

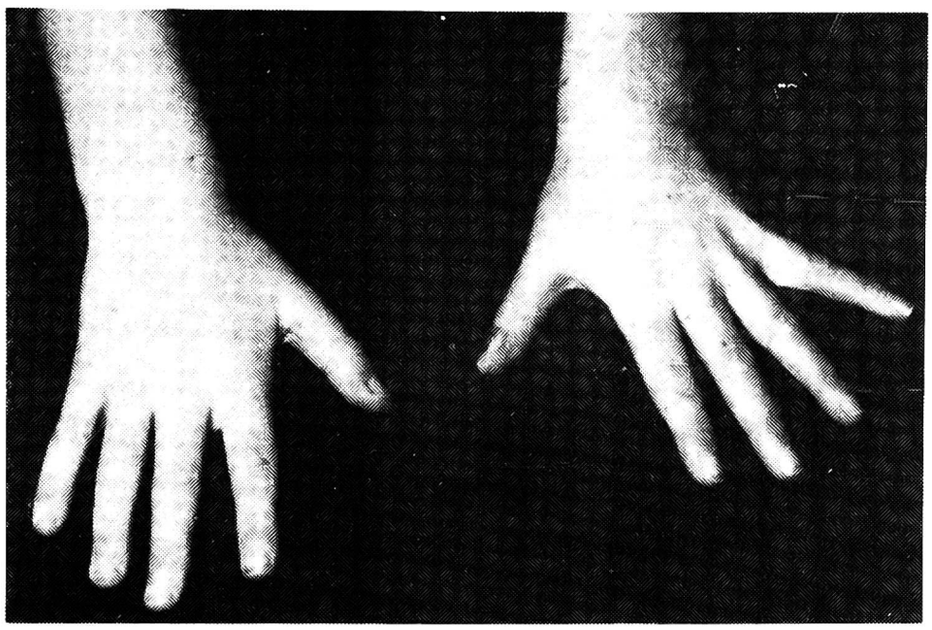


Fig. 3. The typical hands seen in VCFS. The hands of a 5-year-old girl with VCFS. Note the long, tapering fingers.

4. Mental development and psychiatric disorders

Forty to fifty percent of the patients with VCFS show mild to moderate mental retardation (MR) (SHPRINTZEN et al. 1978, 1981, GOLDING-KUSHNER et al. 1985). Severe MR is rare. Patients with DGS are more at risk to have severe MR. WILSON et al. (1993) reported that at least half of the patients with DGS have severe MR. An explanation is thusfar unknown; there is no evidence that this maybe related to a higher morbidity of children with DGS (e.g. more severe heart defect, immune disorder). Most patients with VCFS have a normal to borderline intelligence. In a present study of 37 patients with VCFS (with del22q11), we confirm that one of the main clinical features of this syndrome are learning disabilities and/or MR. Mental retardation (defined as IQ < 70 or > –2 S.D. below the mean) was found in 45%. In the majority, the MR was mild (38%) and only 2 patients had a moderate MR. Severe MR seems to be rare in VCFS. Only one child was severely retarded with a familial deletion and cerebellar hypoplasia on MRI-scan. Already in their initial description of the syndrome, SHPRINTZEN et al. (1978) recognized the presence of learning disabilities in all patients. Since then, learning difficulties were reported in 82% to 100%, of the patients with VCFS (SHPRINTZEN et al. 1978, 1981, LIPSON et al. 1991). Mental retardation (not specifically defined) seems to be present in 40% (GOLDBERG et al. 1993) to 46% (SHPRINTZEN et al. 1981, GOLDBERG et al. 1993). The reason for the learning problems is caused by a poor visuo-spatial insight, weak abstractive thinking and poor development

of numerical concepts. This is demonstrated by a disharmonic profile within the intelligence test. Therefore, most patients need remedial teaching or attend special schools. Children with VCFS can have behavioural problems. Often, they can have problems with social integration and have a withdrawn character. Their behaviour can show extremes, from withdrawn and shy to uninhibited and hyperactive behaviour (SHPRINTZEN et al. 1981).

In about 10% of the adolescent and adult patients with VCFS psychiatric disorders occur (SHPRINTZEN et al. 1978, GREENBERG et al. 1993). In typical cases we find psychotic disorders (schizophrenia) in adolescents and young adults. Also children can present psychiatric problems. Several children with a 22q11 deletion were referred to our genetic centre by a child-psychiatrist.

The pathogenesis of mental retardation and psychiatric problems in VCFS is not known. Biological factors can play a role, as brain anomalies are described in VCFS. The exact meaning of the reported brain anomalies (small vermis, a small posterior fossa or the small cysts adjacent to the anterior horns) remains unclear (MITNICK et al. 1994). Interestingly is that in the 22q11 region a gene maps, coding for Catechol-O-Methyltransferase (COMT). This enzyme is important in the degradation of neurotransmitters such as (nor)adrenaline and dopamine. The gene is probably involved in some patients in the 22q11 deletion, though the significance of this is still unclear (DUNHAM et al. 1992).

On the other hand, there is evidence that behavioural and psychiatric problems can be influenced by the language problems. This is obvious in children who cannot express themselves and therefore have difficulties in social interactions. But, whether or not language problems can lead to psychiatric disorders is less obvious. A comparative study between patients with VCFS and patients with an isolated cleft palate could clarify this issue. An early recognition of behavioural and psychiatric problems is important, as well as an early start of speech therapy.

5. Immune disorders

Hypoplasia or aplasia of the thymus can lead to a lowered number of mature T-cells. This may cause immunodeficiency and potentially fatal infections in VCFS. Fortunately, this is a problem seen only in a few patients with DGS. Usually, low T-cell numbers lead only to frequent common infections in early childhood (SWILLEN et al. 1993). Most patients have a good outcome because of a tendency towards spontaneous remission. Prognostic parameters for T-cell immunity, such as the size of the thymus on X-ray or on ultrasound, and thymic appearance during cardiac-surgery are not reliable. Only in 3 out of 14 patients with DGS a thymus was found during cardiac-surgery, though all 14 patients

had a normal immune status (BASTIAN et al. 1989). In these cases the thymus is probably present but has not descended into the mediastinum during embryological development. The most discriminating tests for the prediction of persistent immunodeficiency are the number of (total) CD4+ cells (cut off point 400 total CD4+ cells/mm^3), and a disturbed T lymphocyte proliferation test after stimulation with phytohemagglutinin (BASTIAN et al. 1989, WILSON et al. 1993).

Patients with T-cell deficiency can develop a graft-versus-host reaction after (blood) transfusion, for example after exploration or correction of the heart defect. Transfusion with lymphocyte-free blood is recommended until the immune status is known (WILSON et al. 1992, 1993).

6. Hypocalcaemia

Hypoplasia or aplasia of the parathyroid glands can cause parathormone deficiency, resulting in hypocalcaemia. In the past, hypocalcaemia was an important diagnostic parameter in DGS (this explains why most patients with DGS had hypocalcaemia in previously reported studies). Symptoms and time of onset of the hypocalcaemia can vary. Patients with DGS can present hypocalcaemia during the first weeks of life and sometimes convulsions are the first symptoms. Some patients never had hypocalcaemia or only after several years. The response to treatment is good and in more than half of the patients the hypocalcaemia is transitory (WILSON et al. 1993). Monitoring the calcaemia during neonatal care is very important, e.g. in the case of a patient with a typical cardiac defect as seen in VCFS. On the other hand when convulsions occur in a patient with VCFS, hypocalcaemia has to be excluded.

7. Other features

Most patients with VCFS (and with a del(22q11)) have additional features (GOLDBERG et al. 1993, WILSON et al. 1993). Frequent findings include short stature, hypotonia and urological malformations. In some patients with the CHARGE association (Coloboma, Heart anomaly, choanal Atresia or stenosis, grow or developmental Retardation, Genital hypoplasia and "Ear" deformations), a 22q11 deletion could be demonstrated (GOLDBERG et al. 1993, personal observation). The CTAFS or conotruncal anomaly face syndrome, first described in Japanese patients, is also caused by a 22q11 deletion (MATSUOKA et al. 1994). The del(22q11) is also reported in the Cayler cardiofacial syndrome: the association between cardiac abnormalities and hypoplasia of

the musculi depressor anguli oris (GIANNOTTI et al. 1994). Some patients with initial diagnosis of Opitz syndrome, happened to have a 22q11 deletion (FRYBURG et al. 1996).

Clinical illustrations

1. Variable expression of the 22q11 deletion within one family

In this family triplets were born. The triplets showed a similar phenotype, with retrognathia, small palpebral fissures and small dysplastic ears. The first child had a truncus arteriosus, hypocalcaemia with parathormone deficiency and a non-detectable thymus during cardiac surgery. The second child had also a truncus arteriosus, no thymus was demonstrated on X-ray and ultrasound investigation, but the calcium level in blood was found to be normal. The clinical diagnosis in both children is DGS. The third child had no heart malformation, no hypocalcaemia, although the thymus could not be visualized. He had long tapering fingers and suffered from nasal regurgitation of feedings. The father of these children had learning problems and recurrent middle ear infections during childhood. He has a hypernasal speech and showed hearing loss. Clinical diagnosis in the third child and the father is VCFS. The four patients were shown to have a 22q11 deletion.

2. Mental retardation as an important clinical problem

P. is the youngest of five children. She lived with her foster parents since the age of 1.5 years. As a child, she had frequent middle ear and recurrent upper respiratory tract infections. Her psychomotor development was retarded. Formal IQ tests showed a moderate MR, with a discrepancy between verbal and performal intelligence. She has articulation problems and hypernasal speech. No other clinical manifestations were found except for high myopia. No evident facial dysmorfism was seen, although she has long tapering fingers. The diagnosis of VCFS was suspected and proven by the finding of a 22q11 deletion. Cardiac investigation showed no heart defect. Family history learned that a brother died shortly after birth from a severe heart malformation. Another brother with mental retardation and immune deficiency also has a del22q11. The deletion was inherited from their mother, who has a hypernasal speech and mild mental retardation.

3. Associated psychiatric disorders

A girl, the elder of two daughters, has a history of delayed speech development. Motor milestones were normal. She went to a nursery school but soon

speech problems and behavioural problems were noticed. As a young child, she was restless, sometimes aggressive and she had tantrums. At the age of 3 she received speech therapy because of persistent hypernasal speech, but little progress was noted. At the age of 6, a pharyngoplasty was performed. Because of behavioural problems, she was admitted to a residential child-psychiatric unit. She was subsequently referred to the Clinical Genetic Centre because of her special facial appearance. Facial dysmorfism included a broad nasal bridge, hypertelorism and malformed ears with an auricular tag on the right side. Full scale IQ was 80. The diagnosis of Shprintzen syndrome (VCFS) was made based on her characteristic facial appearance, hypernasal speech, typical behavioural problems and this was confirmed by FISH, showing a chromosomal 22q11 deletion. Cardiac investigations were normal.

4. Feeding problems

C. is the second-born child of healthy parents. She was born preterm at 29 gestational weeks. Birth weight, length and head circumference were all at 25th centile. The neonatal period was complicated by IRDS grade 4. She had no other problems. During the first months of life, she had important feeding problems, caused by a cleft palate. Further investigations revealed a right sided aortic arch, with a non-obstructive impression of the oesophagus (possibly an aberrant left subclavian artery). Gavage-drip-feeding was necessary. After surgical correction of the cleft palate at the age of 9 months, no improvement in feeding occurred. She refused to drink and had nasal regurgitation of feedings. At the age of 14 months a gastrostomy was placed. She showed mild facial dysmorfism: small mouth, small mandible, narrow palpebral fissures and small ears were noticed. She had long, tapering fingers. Psychomotor development was mildly retarded; she had delayed speech development. Chromosomal investigations showed a 22q11 deletion.

Diagnosis of VCFS made by genetic investigations

The 22q11 deletion found in VCFS is usually too small to be detected on routine karyotyping. The technique of choice to demonstrate a 22q11 deletion is FISH (Fluorescence In Situ Hybridisation). FISH is a fast and relatively easy genetic investigation and can be performed on the same cells (blood, amnio-, chorion villi cells, (skin) fibroblasts or EBV-cell-line) used for normal karyotyping. A small DNA-fragment in the 22q11 region is fluorescently

labelled and is hybridized to a chromosomal spread. In normal persons, two fluorescent signals in the 22q11 region on both chromosomes 22 can be demonstrated. Patients with VCFS (who have the deletion) show signals on only one of the chromosomes 22 (Fig. 4). One of the current limitations is that some patients with typical clinical features of VCFS or DGS do not have a detectable 22q11 deletion, with the above described technique. The deletion is found in 90% of the patients with DGS, and in 76% to 100% of the patients with VCFS (CAREY et al. 1992, DRISCOLL et al. 1993). More 22q11 deletions are probably found if the diagnostic criteria are more strictly applied. Possible explanation for the false-negative results with the FISH-technique in patients with typical VCFS features is the possibility of another mutation in the 22q11 region, e.g. without a deletion of this region.

Interestingly, the phenotypical features as seen in DGS can also be found in chromosome 10p deletions, maternal diabetes, fetal alcohol syndrome or in retinoic-acid malformation syndrome. Therefore the term DiGeorge sequence is probably more appropriate.

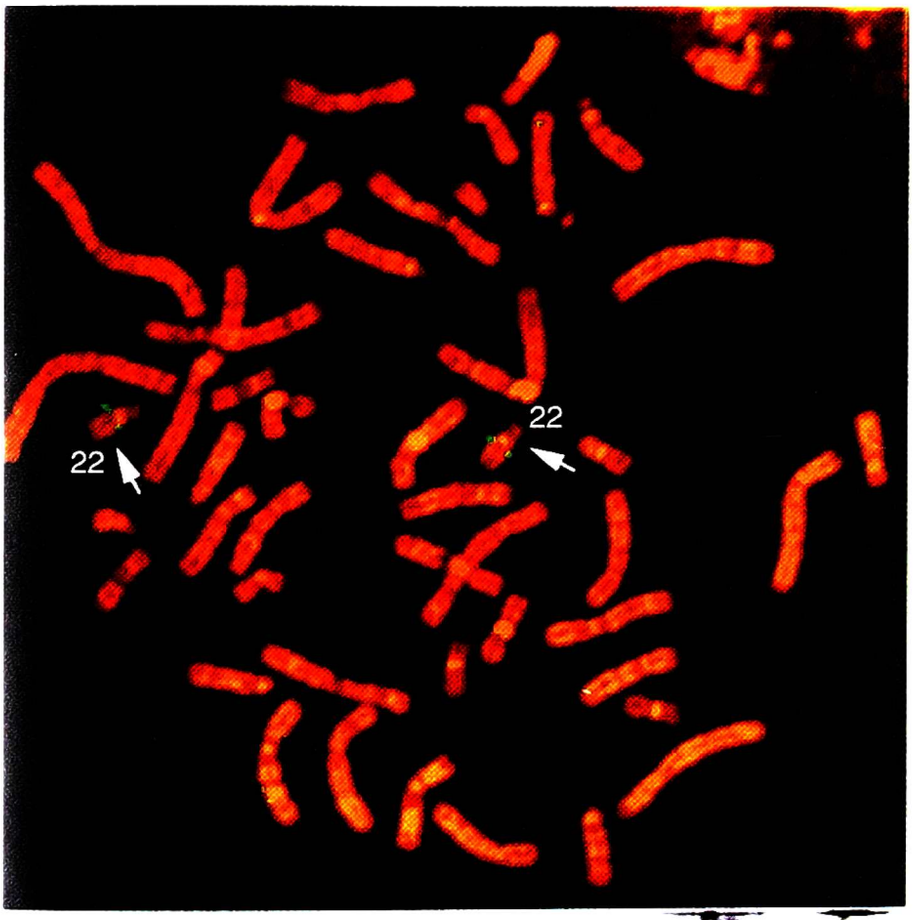
Genetic counselling in VCFS

Autosomal dominant inheritance in VCFS

Children of patients with VCFS (with the 22q11 deletion) have a 50% chance of inheriting the same deletion. As in other autosomal dominant inherited disorders, one has to consider the variable expression and the occurrence of *de novo* mutations.

1. Variable expression in VCFS

The clinical expression in VCFS is extremely variable. The expression ranges from a multiple congenital anomaly – mental retardation syndrome to an almost normal phenotype (e.g. patients presenting with hypernasal speech and psychiatric disorder in adulthood). Until now, no reliable factors exist to predict the severity of the phenotype. For example: no correlation is found between the severity of the syndrome and the size of the 22q11 deletion. Possible explanations of the variability are the influences of other genes, environmental or chance factors. At present, there is no evidence for genomic imprinting or dynamic mutations.



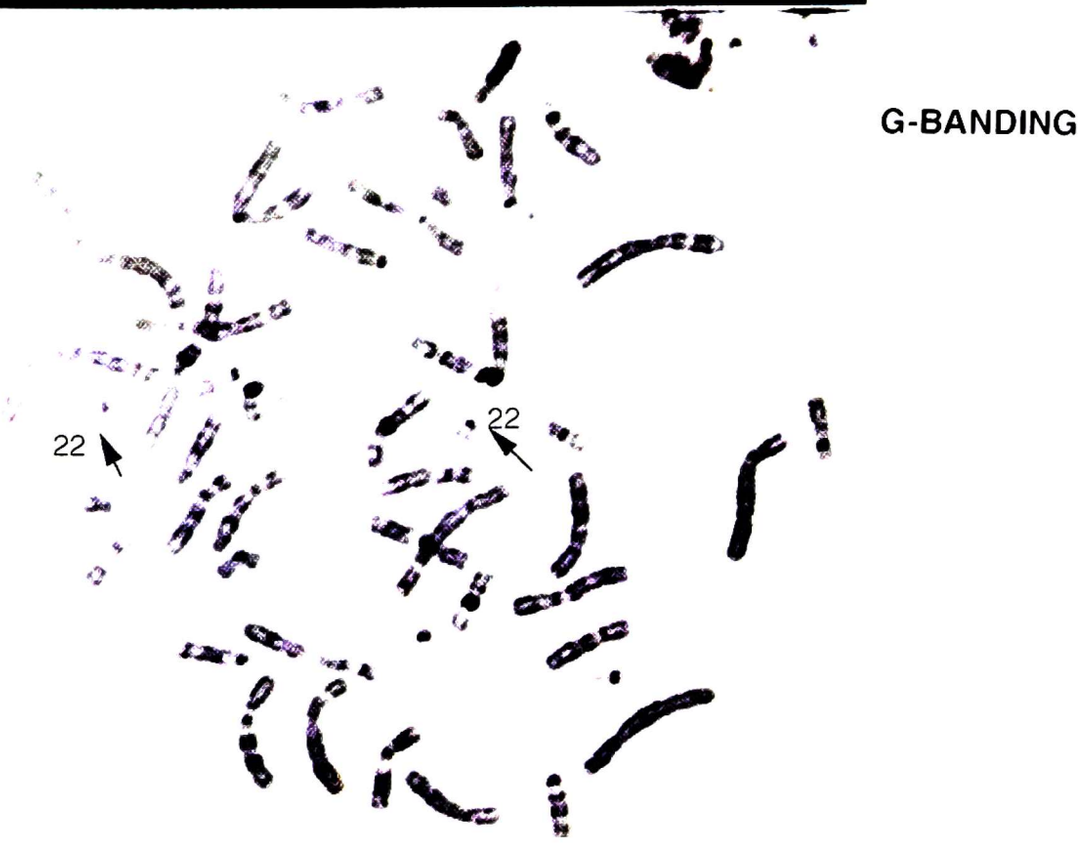
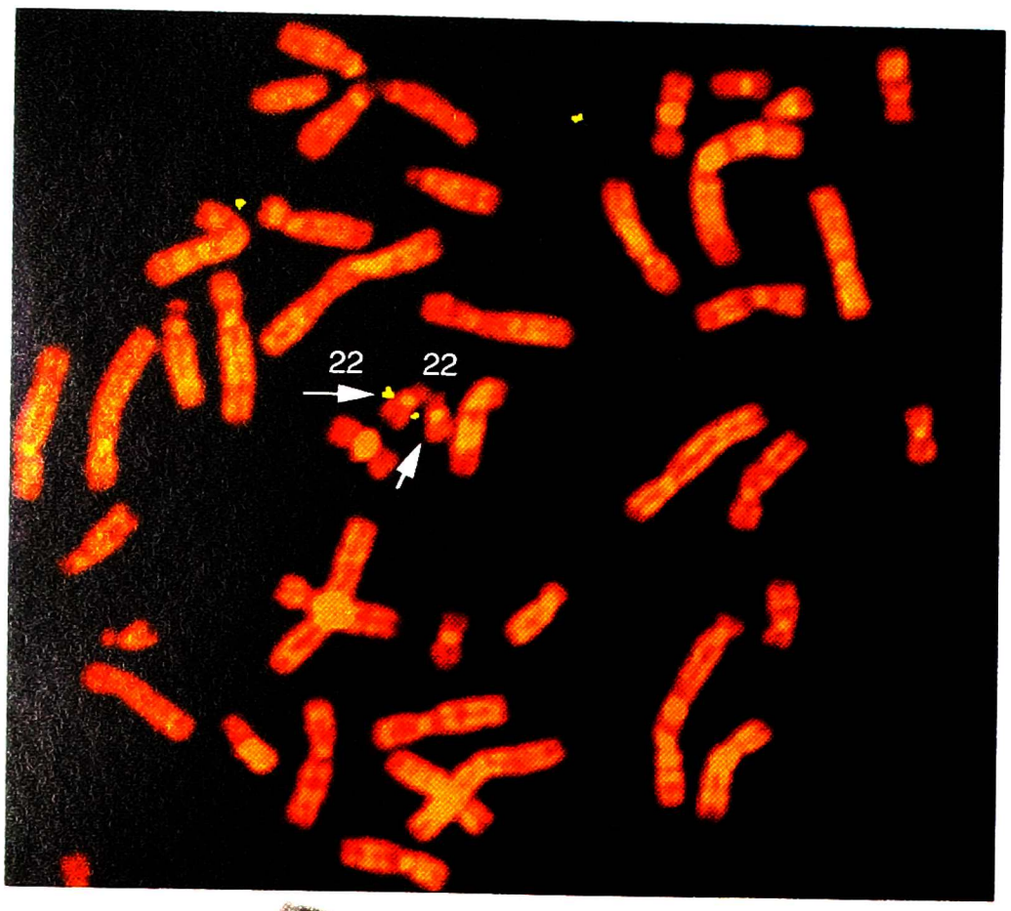


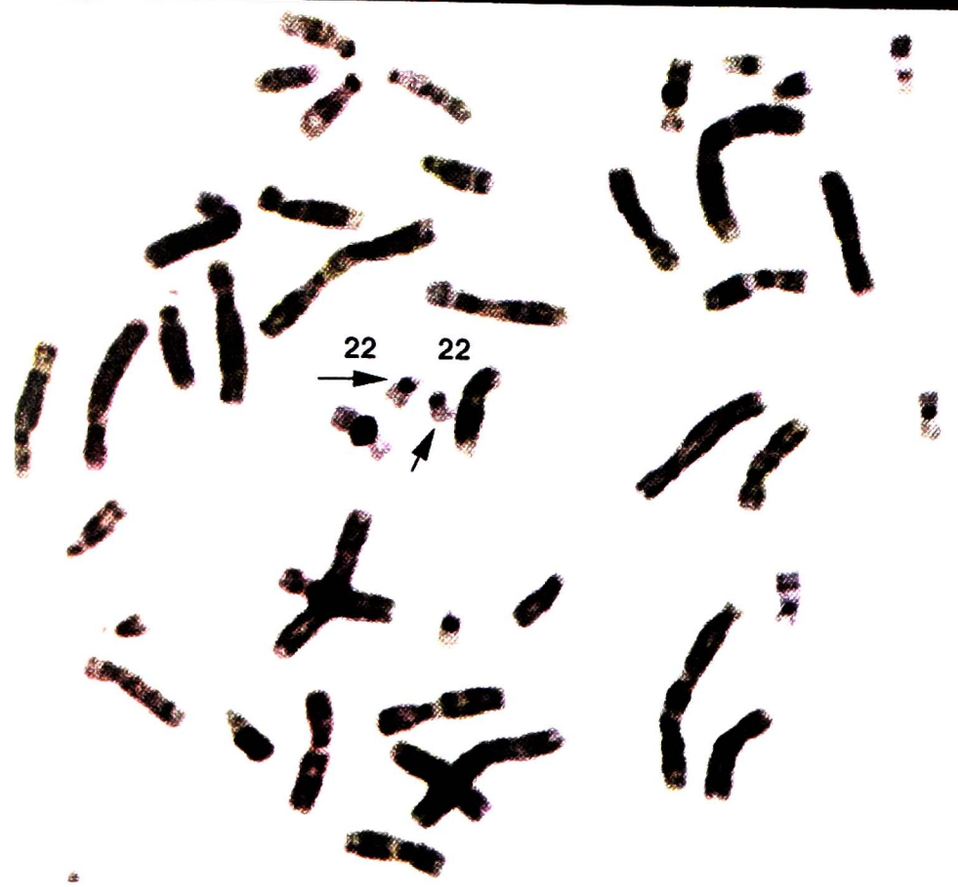
Fig. 4A. Detection of a chromosomal 22q11 deletion by FISH technique

FISH results with the DO832 probe, showing two hybridization sites (on metaphase chromosomes of white blood cells) on the long arm of chromosome 22 in the 22q11 region (two arrows; two fluorescent labelled spots per chromosome, since every chromosome has two sister chromatides)



FISH 22Q11 PROBE DO832

DEL 22Q11



G-BANDING

Fig. 4B. Detection of a chromosomal 22q11 deletion by FISH technique

FISH result with the DO832 probe, showing only one hybridization site (on metaphase chromosomes of white bloodcells) on the long arm of chromosome 22 in the 22q11 region (two arrows; one chromosome has two spots and the other chromosome 22 has no spots) of a patient with VCFS

2. New mutations

As in other autosomal dominantly inherited disorders, the 22q11 deletion can occur *de novo*. The parents are than normal and no deletion can be demonstrated.

Guidelines for genetic counselling

1. Family investigations in the case of a child with VCFS

When the diagnosis of VCFS (with a 22q11 deletion) is made in a patient, the parents should be investigated. Clinical examination and history can already yield the answer, but detection of the 22q11 deletion is more accurate.
– If the parents do not have the 22q11 deletion, the recurrence risk in the next pregnancy is very low. Nevertheless germline mosaicism for a del22q11 in parents has been reported recently (SITCH et al. 1996).
– If one of the parents has the 22q11 deletion, the recurrence risk is 50% for every pregnancy. Further investigations are indicated in other relatives. Prenatal investigations may be indicated.

2. Prenatal diagnosis

Prenatal diagnosis of a del22q11 is technically possible on chorion villi or cells obtained by amniocentesis. Prenatal diagnosis of VCFS is still a difficult issue, since the phenotypic expression is extremely variable, even within one family. An expert ultrasound investigation can detect important malformations, such as the cardiac malformations and the cleft palate. However, the degree of mental retardation cannot be predicted.

3. VCFS without the 22q11 deletion

The parents of patients with a clinical diagnosis of VCFS or DGS, but without the 22q11 deletion have to be examined carefully. Recurrence risks are probably the same as autosomal dominant inheritance (see above), if one of the parents has typical features of VCFS.

Conclusion

Patients with VCFS show an extremely variable expression in phenotype. These patients are at risk for medical complications, mental retardation and psychiatric disorders. The recurrence risk is high (50%) in familial cases. Early diagnosis is thus very important and taking VCFS in consideration is important,

whenever one of the characteristic clinical features is present. Sensitive genetic investigations (like FISH) can confirm the diagnosis of VCFS.

Further fundamental research will certainly result in the isolation of the genes, responsible for the phenotypic features in VCFS and give an insight in their pathogenesis. On the other hand, systematical follow-up of patients with VCFS will give a better understanding of the clinical manifestation and this certainly will result in a better treatment and possibly prevention of associated disorders.

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