Towards earlier diagnosis of 22q11 deletions

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Abstract

Over a 7 year period, 551 patients were investigated for the presence of a chromosome 22q11 deletion by fluorescence in situ hybridisation. Analysis of the presenting features of the 67 individuals with this chromosome deletion permitted us to devise guidelines to facilitate early diagnosis.
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Deletion of chromosome 22 is the most common chromosome deletion, affecting approximately one in 4000 live births, and is a significant cause of cardiac, craniofacial, and developmental abnormalities.[1] Interstitial chromosomal deletions at 22q11 are found in 83% of individuals with velocardiofacial syndrome[2] and in 94% of those with DiGeorge syndrome.[3] Early diagnosis of the chromosome 22 deletion is important because of its diverse medical complications, its associated learning difficulties, and its possible hereditary implications for close relatives. However, the specific fluorescence in situ hybridisation (FISH) test for this chromosome deletion is only requested after a clinical suspicion is raised. The classic presenting triad of congenital cardiac defect, palatal insufficiency or cleft, and hypocalcaemia is easy to recall but diagnosis is delayed in many cases because individuals have atypical findings. Here, we analyse the presenting details of 67 patients with chromosome 22 deletions and summarise the clinical clues that facilitate diagnosis.

Patients

A total of 551 patients were investigated for the presence of a 22q11 deletion over a seven year period (1992–8). Most diagnostic FISH tests (66%) were requested by a clinical geneticist, in nearly one third of cases the investigation was requested by a paediatrician, and the remaining requests were made by a paediatric pathologist after postmortem examination.

Methods

Metaphase chromosome spreads were prepared from phytohaemagglutinin stimulated lymphocyte cultures by standard methods before FISH analysis using labelled cosmid probes specific for the 22q11.2 region. Clinical details of affected patients were obtained from examination of hospital records.

Results

Deletions at 22q11.2 were detected in 67 of the 551 patients tested. Notably, only 12% of these deletions were visible by conventional cytogenetic banding studies. The clinical scenarios in which these individuals presented are shown in table 1.

Information regarding the various systems involved was not available for all 67 patients. Details regarding cardiac status were known for 55, facial appearance for 58, palate for 41, development for 43, thymus gland for 34, and serum calcium for 39 patients. Cardiac defects were detected in 46 patients, including ventricular septum defect (26 patients), Fallot's tetralogy (10), atrial septum defect (eight), and interrupted aortic arch (seven). Dysmorphic facies (unusually shaped ears, long nose with broad bridge, microstomia, micrognathia and upslanting, short palpebral fissures) were noted in 50 patients. Thymic hypoplasia or aplasia was detected in 16 individuals and hypocalcaemia was documented in 21. Abnormalities of the palate (such as cleft, slack, or high palate) were seen in 24 patients, and learning difficulties or developmental delay were noted in 32. The observation of long or tapering fingers was specifically recorded in 13 of the 67 patients.

Table 1 Modes of presentation of 67 patients found to have 22q11 deletions and differential diagnoses where 22q11 deletion might be considered

Diagnostic period	*Proportion of cases*	*Presentations leading to diagnosis in our study*	*Differential diagnoses*
Prenatal	6%	Prenatal growth retardation and cardiac abnormality	Maternal diabetes (suggested by renal agenesis)
		Polyhydramnios	Other chromosomal disorder (suggested by polyhydramnios and heart defect)
		Family history of congenital heart disease	
Neonate to age 2 years	39%	*Usual presentation (35%)*	Fetal alcohol syndrome
		Full or partial DiGeorge phenotype	CHARGE association
		Characteristic facies (see text for description)	Opitz syndrome
		Unusual presentation (5%)	Waardenburg syndrome
		Prominent atypical major malformation (such as renal agenesis, choanal atresia, anorectal malformation)	Cranio-cerebello-cardiac syndrome
		Dysmorphism alone + parent recently diagnosed	
Children aged ≥2 years	41%	*Usual presentation (18%)*	Myopathy with mild mental handicap (fig 1)
		2 of the following 3 features: congenital cardiac defect, palatal insufficiency/cleft, hypocalcaemia	
		Unusual presentation (23%)	
		For example, cardiac anomalies only + family history of cardiac abnormalities	
Adults	14%	Learning difficulties and past history of core features	Psychosis + learning disability
		Asymptomatic parent of affected child	

CHARGE, colobomata, heart defects, atresia choanae, retarded growth and development, genital anomalies, ear anomalies.

Table 2 Combinations of clinical features that should lead to consideration of FISH analysis for a possible 22q11 deletion

Column A	*Column B*	*Column C*
The presence of one of the following	*Two or more of the following core features*	*One core feature plus one of these associated features*
Conotruncal cardiac anomaly (such as Fallot's tetralogy, interrupted aortic arch, truncus arteriosus, or major aorto-pulmonary collateral arteries)	Characteristic facial abnormalities (see text) (86%)	Long slender fingers and hands
	Non-conotruncal congenital cardiac defect	Short stature
	Learning difficulties/developmental delay (74%)	Hypotonia
Parent of an affected child	Cleft palate, velopharyngeal insufficiency, or swallowing difficulty (59%)	Renal abnormalities or Potter sequence
	Hypocalcaemia (54%)	Psychiatric (especially bipolar) disorders
	Immunodeficiency or thymic hypoplasia (47%)	Family history of congenital cardiac defects

Figures indicated in column B are frequencies of individual features ascertained in our series of affected cases.
FISH, fluorescent in situ hybridisation.

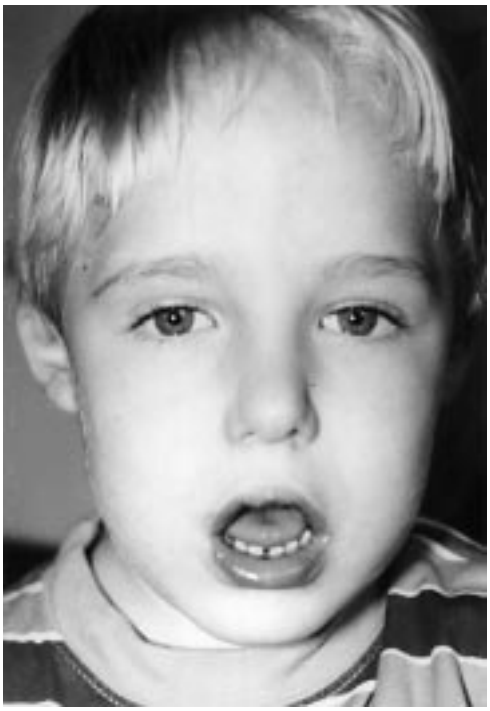

Figure 1 Typical myopathic facial appearance in a boy with a chromosome 22q11 deletion. (Photograph reproduced with permission of the patient's parents.)

Of the 40 affected children whose parents had been tested, nine were found to have inherited the deleted chromosome, usually from the mother (eight patients).

Discussion

In our series, patients had similar frequencies of congenital heart disease, hypocalcaemia, and palatal abnormalities to those reported in two recent studies,[4 5] but we discovered that the main diagnostic problem is pronounced clinical variability, which causes the true diagnosis to be overlooked or delayed considerably.

Retrospective examination of our clinical data revealed useful guidelines for prospective clinical diagnosis (table 2) that should permit the diagnosis of the condition in most individuals. We suggest that FISH 22 deletion analysis should be performed on patients who meet one of the criteria in column A. Thus, any patient with a conotruncal congenital cardiac anomaly, even in isolation, should be investigated for the presence of the deletion, because this problem occurs so frequently in 22q11 deleted individuals,[4] and can be the only manifestation.[6] Alternatively, the possession or history of two features in column B, or one feature in column B in addition to one in column C, are regarded as sufficient to merit investigation. These guidelines were devised with the aim of achieving a high sensitivity in the initial detection of patients for whom the FISH analysis should be considered. Retrospectively, the use of table 2 alone would have permitted the detection of our 67 patients with deletions with 100% sensitivity, but the available data do not permit an accurate determination of the specificity or positive predictive value of the guidelines.

Typical presenting features are also determined by the age of the individual. In the perinatal period, the presence of any cardiac or palatal anomaly or of hypocalcaemia should prompt close examination for other dysmorphic features. In childhood, suspicious findings are velopharyngeal insufficiency (perhaps indicated by hypernasal speech or recurrent otitis media), myopathic looking facies (fig 1), short stature, and mild learning difficulties. In adults, however, clues to diagnosis are often more subtle, including hypernasal speech, psychiatric symptoms, mildly dysmorphic facies, and long slender fingers, but close examination of the childhood medical and educational histories nearly always pays dividends.

To summarise, the diagnosis in a large proportion of our patients was delayed either because there was no pathognomonic clinical feature or there was erroneous clinical diagnosis of an unprovable rare condition (table 1). Chromosome 22q11 deletion is a relatively common condition and is a readily diagnosed cause of serious congenital malformations and puzzling dysmorphic syndromes.

We are indebted to the large number of clinicians who referred these patients to our department.

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