Chromosome 22q11 microdeletions in tetralogy of Fallot

A H Trainer, N Morrison, A Dunlop, N Wilson, J Tolmie

Abstract

Chromosome 22q11 fluorescence in situ hybridisation (FISH) studies were performed on 33 consecutive individuals attending a paediatric cardiology clinic with tetralogy of Fallot. Seven children had 22q11 microdeletions but only four had other clinical features associated with the newly recognised chromosome 22 deletion syndrome (CATCH 22). Chromosome 22q11 FISH studies should therefore be performed on all patients with tetralogy of Fallot.

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Tetralogy of Fallot is the commonest cyanotic congenital cardiac defect and may occur either as an isolated abnormality or in association with other non-cardiac malformations.¹ Recognisable syndromes associated with tetralogy of Fallot include DiGeorge syndrome and velocardiofacial syndrome both of which may arise from microdeletion of chromosome 22q11.² This very small chromosome aberration is best identified by specialised molecular cytogenetic studies employing the fluorescence in situ hybridisation (FISH) technique. Chromosome 22q11 microdeletions have recently been documented in patients with tetralogy of Fallot alone,³ and it is not clear what percentage of all patients with this condition have an underlying submicroscopic or cryptic chromosome 22 abnormality. In individual cases this information will alter the risk of recurrence after one affected child which is normally derived from empiric data.⁴ We therefore performed 22q11 FISH studies on 33 sequential patients attending a paediatric cardiology clinic with a diagnosis of tetralogy of Fallot in order to investigate the prevalence of 22q11 deletions in this population and identify families with familial and sporadic 22q11 microdeletions.

Subjects and methods

We approached 40 consecutive families attending the cardiology clinic with a child with tetralogy of Fallot. A three generation family tree was drawn and the child evaluated for clinical features suggestive of an underlying syndrome diagnosis. Blood was taken for routine chromosome banding studies and specialised FISH studies using cosmids sc11.1, E0472, sc4.1, and D0832 all of which map to 22q11. In children with a chromosome

abnormality, its origin was investigated through examination of parental blood samples.

Results

Seven families from the 40 who were approached refused a blood sample. The remaining 18 males and 15 females included two children with trisomy 21 Down's syndrome.

Routine chromosome preparations were normal in 30 patients and one was noted to have a coincidental familial chromosome 13 paracentric inversion.

Seven patients had microdeletions at 22q11 detected by FISH. Three of these patients were clinically diagnosed as having velocardiofacial syndrome, one in the course of this study and two while attending the cleft palate clinic. In two of these families one parent was not available and both parents in the third family, neither of whom had clinical features, refused to give blood samples, although they had two daughters with velocardiofacial syndrome and 22q11 microdeletion.

The fourth patient with a chromosome 22q11 microdeletion, which was not present in either parent, had a previous clinical diagnosis

Royal Hospital For Sick Children,
Glasgow, Duncan
Guthrie Institute of Medical Genetics
A H Trainer
N Morrison
A Dunlop
J Tolmie

Department of Cardiology
N Wilson

Correspondence to:
Dr A H Trainer, Duncan
Guthrie Institute of Medical
Genetics, Yorkhill Hospital
NHS Trust, Glasgow
G3 8SJ.

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Girl with isolated tetralogy of Fallot associated with a chromosome 22q11 microdeletion.

of partial DiGeorge syndrome. The remaining three patients with chromosome 22 microdeletions had isolated tetralogy of Fallot with no other clinical features to suggest this underlying chromosome abnormality. In these three, the chromosome deletions were not familial.

Discussion

In this study we identified three patients (11%) who have tetralogy of Fallot as the only clinical feature of an underlying chromosome 22q11 microdeletion. Recently, this chromosome abnormality has been associated with diverse abnormalities signified by the acronym CATCH 22 (cardiac defects, abnormal facies, thymic aplasia/hypoplasia, cleft palate, hypoparathyroidism, and microdeletion of 22q11).⁵ While another study of 22q11 deletions in tetralogy of Fallot⁶ confirmed the presence of deletions in the majority of cases associated with velocardiofacial syndrome and DiGeorge syndrome, no deletions were identified in otherwise non-dysmorphic individuals. In fact, the authors of this study admitted that, in some of their cases, suggestive dysmorphic features were only identified *after* the chromosome abnormality was detected. In our experience, some patients with chromosome 22q11 microdeletion have either no dysmorphic features or very subtle features which are easily overlooked (figure).

In an epidemiological study of tetralogy of Fallot,¹ non-cardiac malformations were found

in only 27% of patients, made up of 8% with a clinically recognisable syndrome, 8% with chromosome aneuploidy, and 11% with no underlying diagnosis. Therefore, the important implication of our small study is that FISH analysis should be routinely performed in patients where tetralogy of Fallot occurs as an isolated malformation. Identification of this chromosome deletion highlights the possibility of other associated problems, such as immunological disorders or learning disabilities, also known to be associated with 22q11 microdeletion. From the parents' perspective, identifying the chromosome deletion clarifies the sibling recurrence risk and facilitates genetic counselling for the affected child who may ask for advice in the future.

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