ELECTRONIC LETTER

Chromosome 10p13-14 and 22q11 deletion screening in 100 patients with isolated and syndromic conotruncal heart defects

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Heart defects are among the most common congenital anomalies, occurring in approximately 1% of newborn populations.¹ Conotruncal heart defects (CTHD), which account for 50-60% of all congenital heart malformations, are known to have a strong genetic component. They occur either as an isolated malformation or in association with extracardiac anomalies. In particular, CTHD constitute a cardinal component of branchial arch syndromes, such as DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), and conotruncal anomaly-face syndrome (CTAFS). The wide phenotypic spectrum includes cardiac defects, abnormal facies, thymic hypoplasia or aplasia, cleft palate, and hypoparathyroidism.^{2,3} The presence of a characteristic 3 Mb microdeletion on chromosome 22q11 in 70-90% of these patients indicates a common genetic aetiology.^{4,5} Haploinsufficiency for the *Tbx1* transcription factor in the critical region appears to be responsible for the aortic arch defects in these disorders.⁶ 22q deletions also occur in a high percentage (10-40%) of syndromic cases (CTHD associated with at least one extracardiac anomaly)⁷⁻¹¹ and in non-syndromic familial cases.¹²⁻¹⁴ Although 22q11 microdeletions in a few patients with isolated CTHD have been reported,^{9,15} their exact prevalence remains unknown. In most studies,^{7,8,10,11,16} no 22q11 deletions were found in isolated cases. One possible explanation may be that variant deletions occur in >10% of 22q11 deletion patients¹⁷ and the detection rate of different probes used for microdeletion screening may vary. On the other hand, 22q11 deletion patients who were originally diagnosed as isolated may have been classified retrospectively as syndromic, because of subtle (facial and other) dysmorphism upon re-examination.⁹ A second critical region for CTHD exists on chromosome 10p13-14.^{18,19} However, the incidence of 10p13-14 deletions in DGS/VCFS patients is much lower than that of the classical 22q11 deletion.²⁰ That the few patients with 10p13-14 deletions described so far were all severely affected may be an ascertainment bias, as the underlying deletions were relatively large. For these reasons, we decided to study prospectively the presence of 22q11 (DGS1) and 10q13-14 (DGS2) microdeletions in 100 patients with isolated and syndromic CTHD.

SUBJECTS AND METHODS

Each patient admitted to the German Heart Centre in Berlin for conotruncal heart malformation was carefully examined by an experienced clinician before cardiac catheterisation. One hundred patients (age range 4 days to 58 years, mean 6.1 years), 81 with isolated CTHD and 19 syndromic cases, were included in this study (table 1). Of the syndromic patients, only one presented classical DGS, one VCFS, one Down syndrome, and two had a positive family history for cardiac defects. Peripheral blood lymphocyte chromosomes were analysed by fluorescence in situ hybridisation. Cosmids Sc11.1a (D22S427), 443 (D22S941/D22S942), 100c10 (COMT), and

Table 1 Frequency of 22q11 deletion in 100 CTHD patients

Primary diagnosis	Isolated conotruncal defects		Syndromic conotruncal defects	
	Number non-deleted	Number deleted	Number non-deleted	Number deleted
TA	4	0	0	1
DORV	8	0	2	0
TGA	22	0	4	0
TOF	28	2	6	1
PA	14	0	3	0
PS	3	0	2	0
Total	79	2 (2.5%)	17	2 (10.5%)

TA, truncus arteriosus; DORV, double outlet right ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; PA, pulmonary atresia; PS, pulmonary stenosis.

YAC 966a8 (TUPLE1) all map to the commonly deleted region on chromosome 22q11.^{14,21} PACs PI14-323N1 (D10S585) and PI04-204F19 (WI-2389) are from the DGS2 critical region on 10p13-14.^{18,19} To detect hemizyosity for 10p13-14 and 22q11, at least 20 metaphases were analysed with each probe for each patient.

RESULTS

Altogether, 22q11 deletions were found in two patients with isolated tetralogy of Fallot (TOF), one patient with TOF and congenital malformation of the thumb, and one patient with truncus arteriosus and thymus aplasia (table 1). In one isolated and the two syndromic cases, cosmids Sc11.1a and 443 were deleted, whereas cos110c10 was present (deletion of proximal DGS1 region). In the second isolated TOF case, cosSc11.1a was present and cos443 and cos100c10 were absent (distal deletion). This is consistent with earlier observations that both deletion size¹⁷ and clinical phenotype are variable.³ There is no correlation between the severity of the phenotype and the size of the deletion.^{14,21} We did not find a 10p13-14 deletion in the 100 patients studied.

CONCLUSION

Our results suggest that 22q11 microdeletions occur in approximately 2% of patients with isolated CTHD. The incidence of 10p13-14 deletions in patients with isolated and syndromic CTHD appears to be extremely low.

Abbreviations: CTHD; conotruncal heart defects; VCFS, velocardiofacial syndrome; DGS, DiGeorge syndrome; CTAFS, conotruncal anomaly-face syndrome; TOF, tetralogy of Fallot

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