Cardiol Young 2005; 15: 229–231

ISSN 1047-9511

Brief Report

Duplication of the 22q11.2 region associated with congenital cardiac disease

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Abstract The DiGeorge, or velocardiofacial, syndrome has been aetiologically linked to heterozygous deletion of the q11.2 region of chromosome 22. It is the most common of the microdeletion syndromes, and is associated with malformations involving the ventricular outflow tracts. Duplication of the 22q11.2 region has also been reported, adding to a growing list of syndromes involving genomic deletion or duplication that cause disease by decreasing or increasing the gene dosage. We report two cases of congenital cardiac disease associated with microduplications of 22q11.2, and discuss the evidence to date for the potential clinical significance of this genetic defect.

Keywords: Velocardiofacial syndrome; tetralogy of Fallot; hypoplastic left heart; genetics

The DiGeorge, or velocardiofacial, syndrome includes characteristic facial features, neurodevelopmental disabilities, facial and palatal clefting, deficiencies of the endocrine and immune system, and structural disease of the heart, particularly involving the ventricular outflow tracts. Cardiac defects are present in three-quarters of patients, and are the major cause of morbidity and mortality associated with the syndrome.[1] The most frequent cardiac anomaly is tetralogy of Fallot, which occurs in about one-fifth of all patients. Other common defects, in order of decreasing frequency, include interruption of the aortic arch, ventricular septal defect, common arterial trunk, vascular ring, atrial septal defect, and other malformations of the aortic arch.

The link between velocardiofacial syndrome and heterozygous deletion of the q11.2 region of chromosome 22 was first reported by Driscoll et al.[2] in 1992. With an incidence of 1 in 5,000 live births, it is the most common of the microdeletion syndromes not detectable by standard cytogenetics. Greater than nineteenth-twentieths of these submicroscopic deletions can be detected by fluorescence in situ hybridization studies using probes of deoxyribonucleic acid that target the 22q11.2 region.

The velocardiofacial syndrome critical region is thought to be predisposed to rearrangement by the presence of repetitive segments of deoxyribonucleic acid called low-copy repeats.[3] During chromosomal pairing in gametogenesis, misalignment followed by recombination at the site of these repeats can lead to either loss or duplication of a chromosomal segment. In theory, these events should occur with equal frequency. Until recently, however, there were no reports of patients with such duplications. The reasons for this may include the absence of a defined phenotype, mild and variable anomalies, and technical issues which make it more difficult to detect extra than missing copies of a region. We report here two cases of congenital cardiac disease associated with microduplication of 22q11.2, identified when screening for microdeletion of the same region.

Case reports

Our first infant, a female, was born at 36 weeks gestation. Fetal ultrasonography at a regional centre

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Accepted for publication 10 December 2004

during the second trimester had identified a possible congenital cardiac malformation. Fetal echocardiography was not performed.

With the exception of a small chin and broad nasal root, the infant was not dysmorphic, and had no visible congenital anomalies. She was tachypneic at birth, and subsequently developed cyanotic spells. Clinical examination and investigations, including echocardiography, were consistent with tetralogy of Fallot and a right-sided aortic arch. Non-cardiac issues identified in the neonatal period included mild central hypotonia, seizures, and impairment of hearing. Renal ultrasound was normal.

Peripheral blood was sent for karyotyping and fluorescence in situ hybridization analysis. G-banded chromosome analysis showed a normal female karyotype. Fluorescence in situ hybridization using a commercial probe set (Vysis) identified three signals for the TUPLE1 (22q11.2) probe on interphase nuclei, compared with two signals for the ARSA (22q13) control probe. This duplication was not evident using metaphase chromosomes, with each chromosome 22 showing one signal. Parental studies revealed the same genetic defect in the father, who was healthy but had a history of learning difficulties.

The second patient, a male infant, was born at 40 weeks gestation. No dysmorphic features were identified. Respiratory distress, cyanosis, and metabolic acidosis developed shortly after birth. Physical findings and echocardiography revealed typical hypoplasia of the left heart. Other problems identified included esotropia, hyperopia, and difficulties with feeding. Auditory tests, and renal ultrasound, were normal. Fluorescence in situ hybridization studies of the interphase revealed microduplication of 22q11.2. The same analysis of the interphase of the parental karyotypes was normal, suggesting a new chromosomal rearrangement.

Discussion

We have described two patients having cyanotic congenital cardiac disease, in whom a normal karyotype was found on routine chromosome analysis, but in whom submicroscopic partial trisomy for the 22q11.2 region became evident when using interphase fluorescence in situ hybridization. We did not attempt further to characterize the extent of the duplication. One of the individuals had tetralogy of Fallot, while the other had hypoplastic left heart syndrome. To the best of our knowledge, there are only two previous cases reported to date with congenital cardiac disease and this genetic rearrangement. Our report, we submit, adds to the growing literature on duplication or deletion syndromes that are proposed to cause disease via increased or decreased genetic dosage.

In December 2003, Ensenauer et al.reported on 13 patients with 22q11.2 microduplications, identified from a cohort of 653 individuals referred to rule out such microdeletions.[4] Congenital cardiac disease was found in 2 of these patients, 1 having tetralogy of Fallot, and the other had hypoplastic left heart syndrome and interrupted aortic arch. Although their numbers were small, the authors speculated that the 22q11.2 microduplication may be under-diagnosed, and could represent a new syndrome with variable features including developmental delay, seizures, renal malformations, hearing loss, and dysmorphic facies. They also noted that routine chromosomal analysis, and metaphase fluorescence in situ hybridization, are inadequate to rule out duplications, and that technical expertise with interphase chromosomes is necessary for accurate diagnosis. Retrospective review of our samples did reveal a slightly brighter signal from the 22q11.2 probe on one of the metaphase chromosome 22 locations, albeit that this was not easily or consistently detected.

Recently, in May 2004, Hassed et al. reported a case of 22q11.2 microduplication with cleft palate, hydronephrosis, and minor dysmorphic features.[5] There was no cardiac disease. Screening of the family members of the index case revealed the same genetic rearrangement in the father and both siblings, consistent with autosomal dominant transmission.

Reports to date, including ours, have identified 22q11.2 microduplications in patients selected on the basis of clinical features suggestive of velocardiofacial syndrome. Consequently, the group is inherently biased toward features which overlap with this syndrome. It is possible that the phenotype of the 22q11.2 microduplication syndrome may be much more variable. The prevalence and importance of congenital cardiac disease in this population also remain to be seen.

The identification of patients with complex congenital cardiac malformations and microduplication of 22q11.2 is another step toward understanding the embryological and molecular genetic basis for both normal cardiac development and congenital cardiac disease. Further delineation of the phenotypic spectrum associated with this genetic rearrangement will necessitate the collection of more cases, and screening for this duplication in large populations of patients with congenital cardiac malformations. Determination of the prevalence and description of the features will hopefully lead to the development of appropriate clinical criterions to justify testing.

Acknowledgment

We express our appreciation to Francois Bernier, who provided valuable input to the writing of our report.

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https://doi.org/10.1017/S1047951105000466 Published online by Cambridge University Press