Heterotaxia syndromes and 22q11 deletion

In a recent issue of your journal we read with interest the very accurate review by Penman Split et al on defects of left-right asymmetry. The authors correctly reported that in patients with heterotaxia (asplenia and polysplenia syndromes), conotruncal defects are one of the more frequent heart malformations. It is well known that 22q11 deletion has been described in a subgroup of patients with conotruncal anomalies in the setting of Di-George syndrome and velocardiofacial syndromes. In the paper of Penman Split et al it was reported (personal communication to the authors) that the same microdeletion has been found in two patients, one with dextrocardia and one with left isomerism (polysplenia syndrome).

Since 1993 we have performed clinical and molecular evaluation of all patients with conotruncal anomalies observed at our hospital, including 20 cases with heterotaxia. Fifteen had asplenia syndrome and five polysplenia. All patients underwent phenotypic and cardiac examinations. Fluorescent in situ hybridisation was used for detecting 22q11 deletion.

No patients had phenotypic features of Di-George or velocardiofacial syndromes, and the genetic study did not show 22q11 deletion in any case. Our experience suggests that the conotruncal anomalies in the setting of heterotaxy syndromes are not related to 22q11 deletion, and are probably secondary to distortion of cardiac looping or to the anomaly of the situs itself. Different gene(s) and different developmental mechanisms may be involved in the pathogenesis of conotruncal anomalies in patients with situs solitus and in those with laterality defects.

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First report of three cystic fibrosis patients homozygous for the 1717-1G→A mutation

We report the identification for the first time of three cystic fibrosis (CF) patients homozygous for the 1717-1G→A mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The clinical presentation of CF varies widely, the most common characteristics being chronic obstructive lung disease, raised electrolyte levels and pancreatic insufficiency (PI). About 15% of patients display pancreatic insufficiency (PS).

The isolation of the CFTR gene has made it possible to identify the main disease causing mutation, AF508, accounting for about 70% of molecular defects in the world population, and over 600 rarer presumptive mutations (CF Genetic Analysis Consortium). Among these, the 1717-1G→A mutation is implicated in causing a G→A base change at the 3' end of the consensus sequence of intron 10. It was first reported in a patient of Celtic origin and since then it has been detected in other populations, having an overall frequency of 1.1%.

To date, a clinical correlation for this mutation has been defined only in patients who are compound heterozygotes for AF508, who display a similar pancreatic and pulmonary phenotype to that of homoygotes for AF508. In this report we describe the first three patients found to be homozygous for the 1717-1G→A mutation. They showed early pancreatic insufficiency (output below 100 in basal bronchial wall), and had other symptoms, but with subsequent minimal lung involvement progression. The isolated findings suggest that this mutation might pre-dispose to a milder respiratory course.

Two patients (cases A and B) regularly attended the Milan CF Centre at the Department of Pediatrics, University of Milan; the third patient (case C) is followed at the Naples CF Centre, Pediatrics Department, II University of Naples.

The three 1717-1G→A homozygous patients include: case A, a female, born in 1986 (birth weight 2850 g); case B, a male, born in 1986 (weight 2900 g, height 52 cm); case C, a female, born in 1989 (birth weight 2900 g, height 54 cm).

This letter was shown to Dr Penman Split, who replies as follows.

We entirely agree with Marino et al that the conotruncal anomalies seen in patients with heterotaxy are likely to be secondary to distortion of cardiac looping and thus the mechanism is different from that seen in cases of 22q11 deletion. Their observations confirm our impression that 22q11 deletions are rare in patients with heterotaxy. While the two cases that we referred to are exceptional, they show the extreme phenotypic diversity associated with deletions of 22q11.