

EDMOND CHIU

JOHN LLOYD

Department of Psychiatry,
The Royal Melbourne Hospital, PO Box 3050,
Melbourne, Victoria, Australia

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- 2 World Federation of Neurology: Research Committee Research Group. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J Neurol Sci* 1989;94:327-32.
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Heterotaxia syndromes and 22q11 deletion

In a recent issue of your journal we read with interest the very accurate review by Penman Splitt *et al*¹ 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 DiGeorge²⁻⁴ and velocardiofacial syndromes. In the paper of Penman Splitt *et al*¹ 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,⁵⁻⁷ 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 DiGeorge 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.

BRUNO MARINO

MARIA CRISTINA DIGILIO

ALDO GIANNOTTI

Pediatric Cardiology and Medical Genetics,
Bambino Gesù Hospital, Piazzas S Onofrio 4,
00165 Rome, Italy

BRUNO DALLAPICCOLA

Human Genetics, Tor Vergata University,
00133 Rome, Italy

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- 2 Scambler PJ, Carey AH, Wyse RKH, *et al*. Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome. *Genomics* 1991;10:201-6.
- 3 Wilson DI, Cross IE, Goodship JA, *et al*. A prospective cytogenetic study of 36 cases of DiGeorge syndrome. *Am J Hum Genet* 1992;51:957-63.
- 4 Scambler PJ, Kelly D, Lindsay E, *et al*. Velocardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* 1992;339:1138-9.
- 5 Melchionda S, Digilio MC, Mingarelli R, *et al*. Transposition of the great arteries associated with deletion of chromosome 22q11. *Am J Cardiol* 1995;75:95-8.
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This letter was shown to Dr Penman Splitt, 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.

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→A¹ 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 content of sweat, and pancreatic insufficiency (PI).² About 15% of patients display pancreatic sufficiency (PS).³

The isolation of the CFTR gene⁴⁻⁶ has made it possible to identify the main disease causing mutation, ΔF508, accounting for about 70% of molecular defects in the world population,⁴ and over 600 rarer presumptive mutations (CF Genetic Analysis Consortium). Among these, the 1717-1G→A mutation is a splice site alteration 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 origin¹ and since then it has been detected in other populations, having an overall frequency of 1.1%.⁷

To date, a clinical correlation for this mutation has been defined only in patients who are compound heterozygotes for ΔF508, who display a similar pancreatic and pulmonary phenotype to that of homozygotes for ΔF508.⁸

In this report we describe the first three patients found to be homozygous for the 1717-1G→A mutation. They showed early pancreatic insufficiency (one meconium ileus) and two of them had early onset of respiratory symptoms, but with subsequent minimal lung involvement progression. These findings suggest that this mutation might predispose to a milder respiratory course.

Two patients (cases A and B) regularly attend 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 at term (birth weight 3550 g) to healthy, non-consanguineous parents. At birth, she presented with meconium ileus, which was sur-

gically treated with a 10 cm ileal resection. She had a high immune reactive trypsinogen (IRT) value at 5 days of life (173 ng/ml, normal value <40 ng/ml) and CF was confirmed by a positive pilocarpine iontophoresis sweat test (112 mmol/l chloride).⁹ Global treatment for CF was started at 2 months with pancreatic enzyme supplementation (Pancrease^R) and chest physiotherapy (positive expiratory pressure technique). At the latest clinical visit, aged 2 years 4 months, she was normal on examination, weight was 14 kg (75th centile), height 94 cm (97th centile). Good nutritional status was obtained with a low dose of pancreatic enzyme (1785 U/kg/day of pancrelipase) associated with a high fat content diet. A chest x ray showed only minimal thickening of the bronchial walls in the lower lobes. *Staphylococcus aureus* was intermittently isolated from bronchial secretions. She needed only one therapeutic antibiotic course for upper respiratory tract infection, and had had no admission to hospital since the diagnosis. No alterations in hepatic or nutritional indices were ever noted. Liver ultrasound was in the normal range.

The second patient, case B, a male, was born at term (birth weight 2850 g) to healthy, non-consanguineous parents. CF presented with malabsorption and bronchiolitis, requiring four hospital admissions in the first months of life. CF was confirmed by a positive pilocarpine iontophoresis sweat test (80, 105 mmol/l chloride). Regular follow up at our specialised CF Centre and adequate treatment were started at 6 months, with pancreatic enzymes (Pancrease^R), mucolytic and bronchodilator aerosol, and physiotherapy. He grew impressively after the start of therapy, body weight reaching the 50th centile at 2 years, and developing along the 97th centile from 5 years. At the last clinical visit, he was asymptomatic, not clubbed, his weight was 38 kg and height 139 cm. Steatorrhea was absent and fat absorption coefficient was 93%, with 1061 U/kg/day of pancrelipase and a high fat content diet. A chest x ray showed only basal bronchial wall thickening. *Staphylococcus aureus* was chronically isolated from sputum samples. He needed only one therapeutic antibiotic course per year for upper respiratory tract infection and the clinical course was mild, with no further hospital admission, after starting treatment at our Centre following diagnosis. Lung function tests were always in the normal range. As compliance with chest physiotherapy was poor, daily sporting activities were encouraged. No alterations in nutritional indices were ever noted. Liver function tests were normal until July 1995, when serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and glutamyltransferase (GT) were slightly increased (42 U/l, 47 U/l, and 53 U/l, with normal values less than 37 U/l, 41 U/l, and 49 U/l). Ultrasound liver examination showed early signs of liver disease, so ursodeoxycholic acid therapy was prescribed.

The third patient, case C, a female, was born to healthy, non-consanguineous parents. Both paternal and maternal ancestors came from the same small city near Naples. Cystic fibrosis presented early with failure to thrive, malabsorption, and bronchiolitis, and she had atelectasis in the upper left lobe, leading to hospital admissions at 1 and 3 months of age. CF was confirmed by a positive pilocarpine iontophoresis sweat test (93 mmol/l chloride). Regular follow up at the CF Centre and treatment was started with pancreatic enzyme