

## Electronic letter

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### DiGeorge syndrome with discordant phenotype in monozygotic twins

EDITOR—In a recent issue of this journal, Goodship *et al*<sup>1</sup> reported monozygotic twins with a deletion in chromosome region 22q11 and a discordant phenotype. They concluded that phenotypic variability in this syndrome cannot be explained on the basis of genotypic differences alone.

Here we report another case of monozygotic twins with an identical deletion in 22q11 but with discordant manifestation of heart disease. The Turkish twins who were born 4 weeks preterm presented with typical symptoms of DiGeorge syndrome. Both boys had characteristic dysmorphic features, including short palpebral fissures, square nasal tip, small mouth, and prominent forehead. Both had hypoplasia of the thymus with markedly decreased levels of CD3 positive lymphocytes (50 and 39% of the total, respectively). Hypocalcaemia owing to low levels of parathyroid hormone (0.76 and 0.7 pmol/l, respectively) was found in both infants, leading to hypocalcaemic seizures in twin 1. Now, at 12 months of age, both infants show significant developmental delay. They are both rather quiet and display a general lack of activity. The second twin's coordination and motor skills are at a 6-8 month level and twin 1 is doing slightly better. Neither of them can stand alone or has started walking yet.

In contrast to the previously mentioned manifestations, the cardiac defects of the two children were significantly different. Twin 1 only had a small atrial septal defect with spontaneous closure at 9 months of age, whereas the other twin had complex heart disease consisting of an atrial septal defect, a large ventricular septal defect, a patent ductus arteriosus, and an interrupted aortic arch distal to the origin of the left carotid artery (type 1b) necessitating cardiac surgery on the second day of life.

Zygosity studies were carried out by typing for red cell antigens (ABO, rhesus, MNSs, Kell) and plasma proteins (haptoglobin, plasminogen,  $\alpha$ 1-antitrypsin, group specific component, complement c3, transferrin, properdin factor B) and erythrocyte enzymes (phosphoglucomutase, erythrocyte acid phosphatase). Additionally, Southern blot analysis of restricted DNA fragments (RFLP) with single locus probes for hypervariable DNA polymorphisms MS1, MS31, MS43a, MS205, YNH24, and G3 was performed as well as PCR analysis of short tandem repeat systems (VWA, TH01, FES). All tests showed an identical genotype in both twins; thus the probability that they are not monozygotic can be calculated to be  $<4.8 \times 10^{-7}$ . Cytogenetic analysis of 20 G banded metaphases of each twin showed a male karyotype without numerical or gross structural aberrations in either patient. However, fluorescence in situ hybridisation (FISH) with a probe for locus D22S75 (Oncor, Heidelberg, Germany) and the more distally located probe TUPLE1 (Vysis, Bergisch-Gladbach, Germany) detected a microdeletion in the region 22q11.2 in both twins. Thus, both twins have a karyotype 46,XY,ish del(22)(q11.2 q11.2)(D22S75-, TUPLE-). There was no evidence for a deletion or any other alteration of the chromosomal region 22q11 nor for other structural or numerical chromosomal changes in either parent by both cytogenetic and FISH analysis.

This case draws attention to the possibility that non-genetic factors contribute to the phenotype of patients with microdeletion in 22q11. In this respect, it is interesting that Ryan *et al*<sup>2</sup> also discussed such mechanisms when reporting on a European collaborative study of 556 patients with deletions in 22q11. Among them, there were 12 families with more than one sib affected. Comparison of sibs of the same family showed a significant degree of variation of symptoms, particularly in heart abnormalities. In their report, Goodship *et al*<sup>1</sup> discussed the possibility of non-genetic influences that could result in different manifestation of defects. Monozygosity on its own has been shown to account for a higher incidence of a wide spectrum of heart malformations; however, the defect seen in our patient is quite characteristic for DiGeorge syndrome and hence should be discussed in relation to the microdeletion. Goodship *et al*<sup>1</sup> hypothesised that a deletion in 22q11 only predisposed twins to malformations, while the twinning process itself with factors such as growth disadvantage, disturbance of laterality, and possible placental vascular anastomoses with twin-twin transfusion provides an additive effect which then results in manifestation of the defect in only one of the twins.

The relevance of non-genetic factors as discussed above is difficult to evaluate, but they may certainly play a role. Another possible reason for discordance in phenotype could be an additional acquired change of genetic information in only one twin. This could affect the region of 22q11, for example by point mutations, a small deletion resulting in loss of hemizygosity, or alterations of imprinting, but could also affect other chromosomal regions. Such a second, somatic mutation would have to occur locally, for example in embryonic tissue involved in organogenesis of the heart. Even within 22q11, several genes have been suggested as possible candidates for DiGeorge syndrome. This will probably make proving this hypothesis a difficult task.

In summary, we report a second pair of monozygotic twins with a microdeletion in 22q11 with significantly discordant manifestation of heart disease. This observation provides further evidence that the variability of clinical symptoms in patients with microdeletions in 22q11 cannot be explained by the deletion itself nor by an effect resulting simply from interaction with other genes. It underlines that exogenous factors that either do or do not affect other genes contribute to the manifestation of clinical symptoms in 22q11 microdeletion syndromes.

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- 1 Goodship J, Cross I, Scambler P, Burn J. Monozygotic twins with chromosome 22q11 deletion and discordant phenotype *J Med Genet* 1995;32:746-8.
- 2 Ryan AK, Goodship JA, Wilson, DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C, Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green JA, Winter RM, Brueton L, Brøndum-Nielsen L, Stewart F, Van Essen T, Patton M, Paterson J, Scambler PJ. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 1997;34:798-804.