DiGeorge syndrome with discordant phenotype in monozygotic twins

Editor—In a recent issue of this journal, Goodship et al 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 sit 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, MNs, Kell) and plasma proteins (chaptoglobin, plasminogen, α1-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 monozygotic can be calculated to be <4.8 x 10^-5.

Cyto genetic 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.
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