Short reports

Interstitial deletion of chromosome 4, del(4)(q12q21.1), in a child with multiple congenital abnormalities

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Deletions of the distal region of the long arm of chromosome 4 are well documented and characterised, whereas deletions of the proximal region are apparently rare. We report another child with a proximal interstitial deletion of chromosome 4, del(4)(q12q21.1), and multiple congenital anomalies, including bilateral colobomata, which has not previously been described in patients with similar deletions.

The proband was the second child of a 22 year old mother and 47 year old father who were healthy and unrelated. He has three sibs and five half sibs, all phenotypically normal. Delivery was at 41 weeks after an unremarkable pregnancy. There was fetal distress during the second stage, but a spontaneous vaginal delivery occurred before obstetric intervention could be arranged. Apgar scores were 9 and 10 at one and five minutes respectively. Birth weight was 3240 g (10th centile), length 52 cm (50th centile), and head circumference 35.5 cm (50th centile).

The baby was referred for cytogenetic investigation on day 14 because of abnormal facial appearance, poor feeding, and an apnoeic episode. He was noted to be hypotonic and to have bilateral iris colobomata. Further ophthalmic examination showed right microphthalmia with a coloboma involving the optic disc and macula. The coloboma on the left involved part of the optic disc with sparing of the macula. Additional dysmorphic features were a high arched palate and

widely spaced nipples. He had a transient heart murmur. Skull and spinal x rays, CT scan, and ultrasound examination of the head showed no further abnormalities.

His growth and development have been delayed and on re-examination at 3 years 10 months his head circumference and weight had fallen below the 3rd centile. His head was an unusual shape with bitemporal narrowing and sparse hair (fig 1). He sat with support but had developed a scoliosis. He had a persistent nasal discharge although there was no evidence of choanal atresia. He had bilateral deafness but responded to loud low notes.

Cytogenetic analysis of a peripheral blood sample using GTG and RBG banding indicated an interstitial deletion of the proximal region of the long arm of chromosome 4 (fig 2). The karyotype was interpreted as 46,XY,del(4)(pter→q12::q21.1→qter). Parental karyotypes were normal.

Figure 1 The proband at 3 years 10 months.

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There are numerous reports of distal 4q deletions and recognisable syndromes resulting from del(4)(q31) and del(4)(q33) are well defined,¹ but only seven

Figure 2 (a) Partial karyotype, GTG banding (right) and RBG banding (left). The deleted chromosome is on the right in each pair. (b) Diagram of chromosome 4 showing location of the deleted segment.

children with proximal deletions involving bands 4q12 to 4q21 have been described.^{1,2} Our patient shows a number of features in common with those previously reported, notably mental retardation, developmental delay, feeding difficulties, poor growth and small size, hypotonia, abnormal facies, and unusually shaped head with domed forehead and abnormal ears. In addition, he has bilateral colobomata, which has not been previously documented. He did not, however, have the disproportionately small hands and feet, depressed nasal bridge, seizures, or pigmentary changes that have been described elsewhere.

Clinical variation between people with proximal 4q deletions including bands 4q12 to 4q21 is most likely attributable to the patients having slightly different deletions involving overlapping sets of genes. Molecular analysis of the deletions, which will more precisely define the breakpoints, should enable more accurate phenotype-deletion correlation.

- 1 Lin AE, Garver KL, Diggans G, *et al*. Interstitial and terminal deletions of the long arm of chromosome 4: further delineation of phenotypes. *Am J Med Genet* 1988;31:533-48.
- 2 Beall MH, Falk RE, Ying K-L. A patient with an interstitial deletion of the proximal portion of the long arm of chromosome 4. *Am J Med Genet* 1988;31:553-7.

Application of a new DNA sequence polymorphism as a genetic marker in prenatal diagnosis of phenylketonuria

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Classical phenylketonuria (PKU), a severe inborn error of amino acid metabolism with an incidence of about 1 in 16 000 Chinese births, is caused by absence of hepatic phenylalanine hydroxylase (PAH). DNA analysis has been used to detect mutations at the PAH locus and to provide prenatal diagnosis for fetuses at risk for PKU.^{1,2} Recently, an A→T substitution at

codon 398 of the PAH gene in the Chinese has been found and described as a new DNA sequence polymorphism (S Z Huang *et al*, unpublished data). Here we report the use of this sequence polymorphism as a genetic marker for prenatal diagnosis of PKU by DNA amplification with PCR and oligonucleotide hybridisation.

A young couple, who already had one child with PKU, consulted us and asked for prenatal diagnosis during the eighth week of gestation (figure). RFLP analysis in this family showed no heterozygosity apart from the *EcoRI* polymorphic site, and the father, mother, the child with PKU, and the fetus all had both the 17 kb and 11 kb *EcoRI* fragments. Accordingly, the fetus had a 50% chance of being normal and

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