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Distal monosomy 14 not associated with ring formation

SUMMARY A 12-year-old boy with congenital heart disease, short stature, mildly dysmorphic facies, and mild intellectual impairment was found to have a de novo terminal deletion (14)(q32·3). Although his phenotype resembles that of six reported patients with a similar breakpoint, his CNS involvement is milder. He appears to be the first reported case of a terminal deletion of chromosome 14 not associated with ring 14 formation. Advanced parental ages and maternal origin of the chromosome with the deletion are noted.

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There are ten previously reported cases of terminal monosomy of chromosome 14q not associated with partial duplication of another chromosome. In nine, the loss was associated with ring formation,[1–5] and in one[6] with mosaicism for a complex inversion. We report the first case where the loss was the result of a simple de novo deletion.

Case report

The patient was a 12-year-old white male admitted for evaluation of congenital heart disease. He was born at term to 35-year-old unrelated parents, after an uncomplicated pregnancy, with a birth weight of 3250 g. Except for the heart disease, he has remained in good physical health. A heart murmur was first detected when he was 2 years old and was followed with annual examinations. The present admission was prompted by decreasing exercise tolerance of 2 years' duration. Cardiac catheterisation showed an atrial septal defect and a partial anomalous venous return that have now been surgically corrected. His psychomotor development was delayed in comparison to his older sibs. In school he is two grade levels behind chronological age. Formal psychometric testing (WISC-R) showed low average intelligence (full scale IQ 85), but with significant verbal-performance discrepancy (verbal IQ 94, performance 78). There is no history of seizures or other neurological symptoms and an EEG was not performed. There is no family history of consanguinity, congenital malformations, or mental retardation. Both parents, an older brother, and three older sisters are in good health, of average height, and at least average intelligence.

On physical examination, the patient was a mildly dysmorphic child (fig 1). Weight was at the 5th centile and head circumference at the 50th centile, while the height was below the 3rd centile and at the

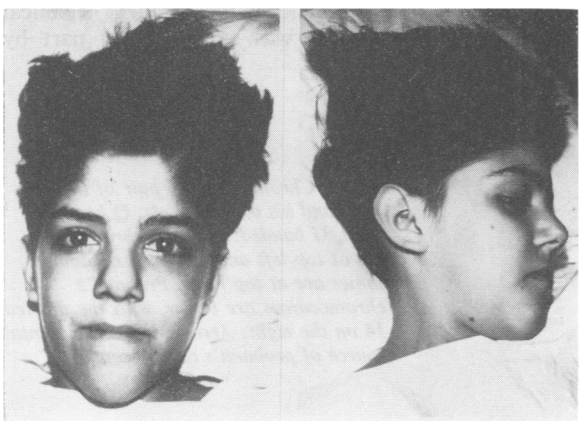

FIG 1 *The proband at 12 years. Note high forehead, low anterior hairline, broad nasal bridge, broad philtrum, and simple helix.*

50th centile for a 9-year-old. The dysmorphic features included a high forehead with a low anterior hairline; high arched palate with a marked maxillary overbite giving the appearance of micrognathia; a broad nasal bridge; broad philtrum; normally set ears, but with poor helix formation; and increased carrying angle of the elbows. Eye examination was normal with no ptosis present. The chest was without deformities, with normally spaced nipples. No organomegaly was present. The genitals were normal, with Tanner stage II sexual development. Neurological examination was normal, including muscle tone and tendon reflexes.

Chromosome analysis using G and R banding techniques showed the breakpoint to be 14q32·3 (fig 2). Six of the ten previous cases have also had a breakpoint within band 14q32. Banded karyotypes of both parents were normal. Satellite polymorphisms using G and Q banding showed the deleted chromosome 14 to be maternal in origin (fig 3).

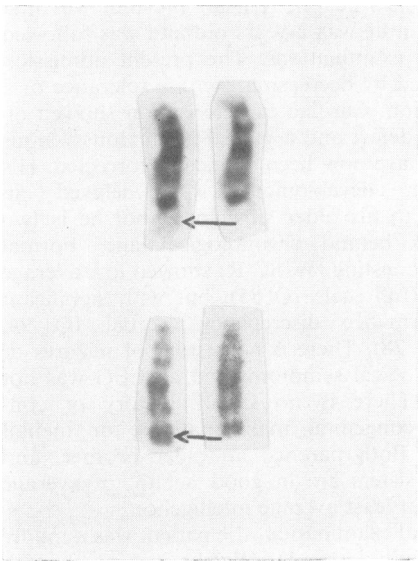

FIG 2 *Chromosome 14 pair from two cells of the proband. Top cell, G banded; bottom cell, RBA banded. Left chromosome of each pair is the normal 14, the right is the deleted 14. Arrow indicates breakpoint at 14q32·3.*

Discussion

Our patient shows many of the dysmorphic features shown by the six cases which share a similar breakpoint, including high forehead, broad nasal bridge, high arched palate, ear abnormalities, and short stature. He has milder CNS involvement; the absence of seizures is of note because they are considered a consistent feature of ring 14 syndrome.[1 3] His intellectual status, although clearly lower than that of other family members, is in the normal range. Head size and muscle tone are normal. The most severe finding in our patient, congenital heart disease, was present in only two of the other six cases; both of these had pulmonary stenosis.

An interesting cytogenetic observation is the preponderance of rings among previously reported cases with terminal deletions of chromosome 14. The same is true for chromosome 13.[7] This may reflect over-reporting of ring chromosomes or under-detection of simple, small, terminal deletions which are difficult to visualise in comparison to rings.

The mean maternal age at birth of a child with 14q− in the nine cases (ours included) where data were available is 28·2 years, about 2 years higher than expected.[8] Advanced maternal age may therefore be a factor in the occurrence of de novo deletions. It would be useful if studies of such cases would, in the future, include determination of the parental origin of the deletion.

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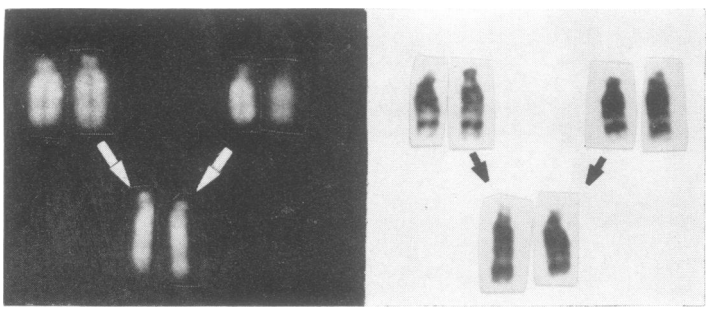

FIG 3 *Chromosome 14 pair of the proband and his parents. Left, Q banded; right, G banded. Paternal chromosomes are at top left and maternal chromosomes are at top right. Proband's chromosomes are below, with the deleted 14 on the right. Arrows indicate parental source of proband's chromosomes.*

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