Partial trisomy 3q causing mild Cornelia de Lange phenotype

S E Holder, L M Grimsley, R W Palmer, L J Butler, M Baraitser

Abstract
A brother and sister are reported with developmental delay and facial features suggestive of the Cornelia de Lange syndrome. Cytogenetic analysis showed them to be trisomic for the region 3q25.1-26.2 because of the inheritance of an unbalanced interchromosomal insertion from their father, who was a balanced insertion carrier.

The clinical phenotype and cytogenetic analysis (including chromosome painting studies) in relation to the possible localisation of the Cornelia de Lange gene are discussed.

Case report
The proband (figs 1 and 2) was the first child of healthy, unrelated parents. She was born at term after a normal pregnancy, birth weight 3300 g. There were no immediate concerns, but her early developmental milestones were delayed; she sat at 8 months, walked at 20 months, and, when seen aged 4 years, was only just starting to form short sentences and become toilet trained. She also had behavioural problems and was being assessed for a special school. On examination, her height was on the 50th centile, and her weight was

Insertions are rare chromosomal aberrations, involving three breakpoints. Carriers of balanced interchromosomal insertions are at risk of having unbalanced offspring, although the resulting imbalance will lead to either pure trisomy or pure monosomy for the inserted segment, rather than the mixed trisomy/monosomy caused by reciprocal translocations and inversions.

In this report the combination of an unbalanced karyotype, resulting from a chromosomal insertion, and a distinct dysmorphic appearance with possible relevance for gene mapping studies is described.
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between the 25th and 50th centile. Her head circumference was on the 3rd centile for her age. She had a round face, narrow arched eyebrows, mild synophrys, epicanthic folds, flat nasal bridge, and a small upturned nose, long philtrum, and thin upper lip. His hands and feet were unremarkable. Height and weight are on the 50th centile for age and his head circumference is on the 25th centile.

Figure 3  Brother of the proband aged 16 months.

CYTOGENETIC STUDIES
Cytogenetic studies were performed on PHA stimulated synchronised lymphocyte cultures prepared for high resolution studies. Initial analysis of the proband showed the presence of an abnormal chromosome 10. There was an extra dark band in the proximal part of the q arm. All other chromosomes were normal.

High resolution banding studies were carried out on her parents' chromosomes. Her mother had a normal karyotype, but her father was found to have the same abnormal chromosome 10, and an abnormal chromosome 3, with an interstitial deletion of 3q35.1 to 3q26.2. The father therefore carried a balanced insertion with the karyotype: 46,XY,del(3)(q25.1q26.2), ins(10;3)(q21.2;q25.1q26.2) (fig 4B).

The proband was the result of an unbalanced meiotic segregation of this insertion making her trisomic for the region 3q25.1 to 3q26.2: 46,XX,ins(10;3)(q21.2;q25.1q26.2) (fig 4A).

The proband's brother was found to have the same unbalanced insertion. Family studies have not identified other relatives who are insertion carriers, although it has not been possible to test both paternal grandparents.

The use of a chromosome 3 paint (CAM-BIO, Cambridge, UK) and fluorescence in situ hybridisation (ONCOR Inc, Gaithersberg, USA) confirmed the presence of chromosome 3 material inserted into a C group chromosome (fig 5).

Discussion
Chromosomal aberrations associated with a distinct phenotype often provide valuable clues to gene localisation, and numerous con-
of their dysmorphism (the mental retardation being caused by their partial trisomy of 3q).

The fact that, once again, this chromosomal region is associated with the Cornelia de Lange phenotype lends further support to the suggestion that this is the likely localisation of the gene(s) responsible for this important mental retardation syndrome. The breakpoints of the insertion reported here (3q25.1 and 3q26.2), and their proximity to the breakpoint identified in the case reported by Ireland et al. (3q26.3), suggest that the “critical region” for the Cornelia de Lange syndrome is between 3q25.1 and 3q26.3 and further mapping work should concentrate on this region of distal 3q.

A cell line is in preparation: contact Dr M Ireland, Genetic Advisory Service, 19 Claremont Place, Newcastle upon Tyne NE2 4AA.

Note added in proof

Additional work on samples from this family has been carried out (M Ireland, personal communication). Using a cosmid probe mapping to 3q26.3, it would appear that the breakpoints of the translocated insertion are 3q26.2–3q27, and not 3q25.1–3q26.2 as stated in the paper. These results will be published in the form of a letter in a future edition of the journal.
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