Partial trisomy 3q causing mild Cornelia de Lange phenotype

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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.

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The Cornelia de Lange syndrome is a well recognised dysmorphic syndrome first described by Brachmann in 1916¹ and later by Cornelia de Lange,² after whom the condition was named. Typical features include intra-uterine growth retardation, short stature, microcephaly, mental retardation, hirsutism, limb anomalies, and distinct facial features. Usually it occurs as a sporadic event and is therefore considered to result from a new dominant mutation or microdeletion. However, occasional families have been reported with recurrence in sibs, suggesting autosomal recessive inheritance,³⁻⁵ and a milder phenotype has been described occurring in successive generations, consistent with autosomal dominant inheritance.^{6,7}

Occasional chromosomal abnormalities have been reported in association with the Cornelia de Lange syndrome, including a de novo reciprocal translocation with breakpoints at 3q26 and 17q23.⁸ A similar facial phenotype has been reported in children with duplication of 3q,^{9,10} although birth weight is usually within normal limits and upper limb reduction defects are rarely a feature.¹¹ However, in view of the phenotypic overlap and the number of reports involving abnormalities of chromosome 3q, it is considered likely that the gene(s) responsible for the Cornelia de Lange syndrome map to this area.⁸ A family reported with duplication of 3q22.1-q24 appears to have a different phenotype,¹¹ and the precise localisation of a "critical region" on 3q, causing the Cornelia de Lange phenotype, remains to be determined. Current mapping studies are concentrating on the region 3q26-27 (M Ireland, personal communication), trisomy of which is essential in the production of the dup(3q) phenotype,^{10,12} and disruption of which has occurred in the de novo translocation reported by Ireland *et al.*⁸

Insertions are rare chromosomal aberrations, involving three breakpoints.¹³ 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.

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

Figure 1 The proband aged 1 year.

Figure 2 The proband aged 18 months.

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Figure 3 Brother of the proband aged 16 months.

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. The philtrum was long and prominent, with a thin upper lip and wide mouth. The hands and feet were normal, apart from mild fifth finger clinodactyly.

The younger brother of the proband (fig 3) was born at term, weighing 3700 g. Generally, his development is thought to be better than that of his sister; he sat at 7 months, crawled at 1 year, and has more words than the proband at the same age. However, when seen at 16 months of age, he was not yet walking. On examination, he too had arched eyebrows, epicanthic folds, a flat nasal bridge, 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.

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, Gaithersburg, 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-

Figure 4 Chromosome preparation showing (A) the normal chromosome 3 homologues and ins(10) identified in the proband; (B) the balanced insertion identified in the father.

Figure 5 Fluorescence in situ hybridisation of the father's chromosome 3 using a chromosome 3 paint.

ditions have been mapped following such descriptions. Recent attention has focused on 3q as the localisation of the Cornelia de Lange gene,⁸ although it is unclear whether the full phenotype is the result of a submicroscopic chromosomal duplication, deletion of a single gene, or a contiguous gene syndrome. The convincing case reported by Ireland *et al*⁸ would suggest that disruption of a gene(s) on either 3q or 17q is sufficient to produce the Cornelia de Lange phenotype. The two sibs we have reported have facial features reminiscent of the Cornelia de Lange syndrome and are trisomic for the region 3q25.1-q26.2. They lack the severe mental retardation, growth retardation, and limb abnormalities present in most of the sporadic cases described to date. Their father, who carries a balanced insertion of 3q25.1-3q26.2 into 10q21.2, does not have features of the Cornelia de Lange syndrome, which might be expected if only gene disruption by the insertion breakpoints was the cause

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*⁸ (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.

- 1 Brachmann E. Ein Fall von symmetrischer Monodaktylie durch Ulnadefekt, mit symmetrischer Flughautbildung in den Ellenbogen sowie anderen Abnormalitäten. *Jb Kinderheilkd Phys Erzieh* 1916;84:225-35.
- 2 de Lange C. Sur un type nouveau de generation (typus Amstelodamensis). *Arch Med Enf* 1933;36:713.
- 3 Beratis NG, Hsu LYF, Hirschhorn K. Familial de Lange syndrome. Report of three cases in a sibship. *Clin Genet* 1971;2:170-6.
- 4 Naguib KK, Teebi AS, Al-Awadi SA, Marafie MJ. Brachmann de Lange syndrome in sibs. *J Med Genet* 1987;24:627-31.
- 5 Fryns JP, Dereymaeker AM, Hoefnagels M, D'Hondt F, Mertens G, van den Berghe H. The Brachmann-de Lange syndrome in two siblings of normal parents. *Clin Genet* 1987;31:413-15.
- 6 Robinson LK, Wolfsberg E, Jones KL. Brachmann-de Lange syndrome: evidence for autosomal dominant inheritance. *Am J Med Genet* 1985;22:109-16.
- 7 Bankier A, Haan E, Birrell R. Familial occurrence of Brachmann-de Lange syndrome. *Am J Med Genet* 1986;25:163-5.
- 8 Ireland M, English C, Cross I, Houlby WT, Burn J. A de novo translocation t(3;17)(q26.3;q23.1) in a child with Cornelia de Lange syndrome. *J Med Genet* 1991;28:639-40.
- 9 Wilson GN, Hieber VC, Schmickel RD. The association of chromosome 3 duplication and the Cornelia de Lange syndrome. *J Pediatr* 1978;93:783.
- 10 Steinbech P, Adkins WW, Caspar H, *et al*. The dup(3q) syndrome: report of eight cases and review of the literature. *Am J Med Genet* 1981;10:159-77.
- 11 van Essen AJ, Kok K, van den Berg A, *et al*. Partial 3q duplication syndrome and assignment of D3S5 to 3q25-3q28. *Hum Genet* 1991;87:151-4.
- 12 Williamson RA, Donlan MA, Dolan CR, Thuline HC, Harrison MT, Hall JG. Familial insertional translocation of a portion of region 3q22.1-q24 in different offspring. *Am J Med Genet* 1981;9:105-11.
- 13 Gardner RJM, Sutherland GR. *Chromosomal abnormalities and genetic counselling*. Oxford: Oxford University Press 1989:80-8.

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.