Familial pericentric inversion (13) detected by antenatal diagnosis

EDNA L MALTBY

Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN.

SUMMARY A recombinant rec (13), dup q chromosome was diagnosed in a 17-week fetus following amniocentesis. Subsequently, a familial pericentric inversion of chromosome 13 was seen to be segregating in the family and the same recombinant 13 was present in a mentally retarded aunt of the fetus. The clinical features of the carriers of the inversion product are discussed with reference to previous cases.

Most cases of familial pericentric inversions are detected following the birth of an abnormal child, owing to an unbalanced recombinant chromosome forming after crossing over in a meiotic inversion loop. A family is presented in which an inverted 13 had been segregating for at least three generations before a routine amniocentesis carried out for an unrelated problem showed an abnormal fetal chromosome complement.

Case report

Amniocentesis was performed upon a 24 year old primigravida at 16⅓ weeks gestation as she had spina bifida occulta and was anxious. The fetal chromosome complement was 46,XX,13p+. Chromosome analysis of the parents' blood revealed the mother to be carrying a pericentric inversion of chromosome 13, inv(13)(p13q22) and the father's karyotype to be normal. The fetal karyotype was interpreted as 46,XX,rec(13),dup q.inv(13)(p13q22) and the pregnancy was terminated at 22 weeks. At necropsy, the fetus was shown to have hexadactyly on all four limbs, bilateral clefts in the upper lip and palate, eyes of normal size, a fusion of the antero-inferior aspects of the cerebral hemisphere, absence of olfactory bulbs and nerves, and a Meckel diverticulum in the gastrointestinal tract.

When the parents were seen for genetic counselling, it was discovered that there was a family history of miscarriage and children with polydactyly (fig 1). The mother's 18 year old sister (III.7) was mentally retarded and had phenotypic abnormalities. Trigonocephaly, combined with mild micrognathia, microphthalmia, epicantthic folds, a long philtrum, poor teeth, heavy eyebrows, and long thick eyelashes led to a distinct facial appearance (fig 2). There were accessory auricles on the right ear, capillary haemangiomata on the back of the neck, and a highly arched palate. She displayed delayed physical and mental development and was said to be irritable. Hexadactyly on all four limbs had been repaired while she was a child. Gene marker studies on esterase D (EsD), an enzyme marker associated with the region 13q14, showed normal levels and served only to confirm that the breakpoint of the inversion was distal to 13q14, or that EsD is proximal to 13q22.

Chromosome preparations from lymphocyte cultures were G banded and silver stained to identify NOR regions. These techniques confirmed the
breakpoints (p13q22) of the familial inversion accurately and indicated that the NOR region was incorporated into the inversion. The NOR region was also shown to be present within the recombinant chromosome (fig 3). Both the inverted 13 and the recombinant 13 associated with acrocentric chromosomes. The family study indicated that the inversion had been present for at least three generations.

Discussion

The clinical features associated with duplication of the region 13q22→qter in the two affected cases reported here are in agreement with those described from seven cases of distal 13q duplication resulting from parental inv(13) summarised by Wenger and Steele. The syndrome has also been described in carriers of unbalanced translocation products resulting in trisomy distal 13q. Published photographs of older affected subjects underline the characteristic facial appearance resulting from the combination of trigonocephaly, long upcurved eyelashes, thick eyebrows, short broad nose over elongated philtrum, and poor teeth. In addition to these features, microphthalmia was present in our patient III.7, although the review of cases by Wenger and Steel indicates that it is linked with duplication of band q21. This may be the result of a multifactorial effect in which the expression is controlled in part by genes in band q22. A similar explanation may pertain to the finding in the affected fetus (IV.1) of cleft lip and palate, which, in trisomies of chromosome 13, has been linked with duplication of band q14. The highly arched palate of patient III.7 may be a less severe expression of the same effect. The polydactyly exhibited by both carriers, and the haemangiomas and accessory auricles of patient III.7, are all typical features. Behavioural irritability is also a fairly consistent finding.

All the phenotype abnormalities resulting from the unbalanced recombinant chromosome are
assumed to be the result of the trisomy of the distal long arm, as deletion of the terminal p13 region will have minimal effect. The meiotic mechanism whereby crossing over in an inversion loop leads to unbalanced recombinants has been discussed in a previous case. In only one family has a pericentric inversion of 13 produced both possible unbalanced recombinants, but one of the two examples of the trisomy p recombinant died at 6 weeks and the second was terminated after diagnosis following amniocentesis. The family described here has a history of perinatal deaths as well as miscarriage but at least one of the stillbirths was said to have polydactyly, indicating the trisomy q recombinant. A segregation analysis of 60 parents in which one of the parents was a carrier of inv(13) has shown a significant predominance of males among the viable offspring. This suggests a possible selection against female offspring, but most offspring of this family for three known generations have been female.

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References


Correspondence and requests for reprints to Ms E L Maltby, Centre for Human Genetics, University of Sheffield, Langhill, 117 Manchester Road, Sheffield S10 5DN.

Trisomy 18 phenotype in a patient with an isopseudodicentric 18 chromosome*

ERIC A WULFESBERG, ROBERT S SPARKES, IVANA J KLISAK, AND AUDREY TENG

Division of Medical Genetics, Departments of Medicine, Pediatrics, and Psychiatry, UCLA School of Medicine, Los Angeles, California, USA.

Summary We report a female patient with a typical trisomy 18 phenotype who has a 46,XX, −18, +isopseudodic(18)(p11) karyotype. The lack of features of the 18p− syndrome suggests that a significant amount of short arm material is present and that the Turner-like features associated with 18p− may be determined by monosomy for 18p11. The phenotype-genotype correlations in abnormalities affecting chromosome 18 are reviewed.

A variety of structural abnormalities affecting chromosome 18 has been described including monosomy, trisomy, and tetrasomy for 18p, as well as partial monosomy and trisomy for 18q. We report a patient with a typical trisomy 18 phenotype who had an isopseudodicentric chromosome 18.

Case report

The proband was the 2·4 kg product of a 42 week gestation to a 20 year old G1 mother and her 21 year old husband. Breech presentation prompted a caesarean section delivery. At birth, an omphalocele and multiple dysmorphic features were noted. Examination (fig 1) in the nursery showed the weight and length (42 cm) to be below the 3rd centile for age. Examination of the head showed a circumference of 33 cm (5th centile), a prominent occiput, and low set, poorly formed ears. The face had a short nose, short palpebral fissures (1·75 cm), and micrognathia. Abnormalities of the chest and

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E L Maltby

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