Monosomy 18p and pure trisomy 18p in a family with translocation (7;18)

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SUMMARY A three generation pedigree is described in which there are two carriers of translocation $t(7;18)$. Two members of the family have trisomy 18p and a stillborn child had monosomy 18p and holoprosencephaly. Another stillborn child probably had holoprosencephaly; the karyotype was not analysed. Based on this observation, the occasional occurrence of holoprosencephaly in monosomy 18p (10% of previously reported cases) may not be the result of the expression of a recessive mutant gene in the hemizygous state, as assumed up to now.

Two thirds of cases of 18p— chromosome have been found to have originated from de novo deletions and a few cases from de novo translocations. Familial transmission by translocation or inversion has been recorded in fewer than 10% of cases.¹ Phenotypically monosomy 18p is known to cause a relatively discrete retardation syndrome, but there is a small distinct group (10%) exhibiting various degrees of holoprosencephaly.

We present a family with translocation $t(7q+; 18p-)$ in which two female carriers of the balanced translocation have transmitted holoprosencephaly (one with proven monosomy 18p) and pure trisomy 18p to their offspring.

Case reports

The male proband (III.2, fig 1) was stillborn in the 32nd week of pregnancy. Antenatal diagnosis by

FIG 2 Proband (III.2) stillborn with holoprosencephaly owing to monosomy 18p.

FIG 1 Family pedigree including years of birth.

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sonography showed microcephaly with an intracerebral defect. The proband's phenotype showed holoprosencephaly (fig 2). Neuropathological examination revealed holoprosencephaly of the semilobar type. Unilateral agenesis of the diaphragm was the only additional malformation. Both parents were 26 years old, healthy, and non-consanguineous.

The only living child (III.1) of II.1 and II.2, a 4-year-old female, is moderately retarded in her psychomotor development. Her walking is clumsy with adducted legs, genu recurvatum, and flat feet. Phenotypically there are only slight stigmata, such as broad eyebrows, thick curly eyelashes, receding chin, low hairline at the nape, widely spaced hypoplastic nipples, and hyperextensible cubitus valgus

(fig 3). Her height and weight corresponded to her age (103 cm, 15 kg). *X*-ray examination of her hips revealed small femoral heads and short and broad femoral necks, coxa valga.

One of the mother's three sibs (II.3), a male, was stillborn. From the report given by the maternal grandfather there is every reason to believe this child also had holoprosencephaly.

The mother's 21-year-old brother (II.4) is mentally handicapped. He has only been able to attend a sheltered workshop and his speech development has remained very poor.

He has difficulty in standing and walking as the

FIG 3 The 4-year-old sister (III.1) of the proband with pure trisomy 18p.

FIG 4 The 21-year-old brother (II.4) of the proband's mother with pure trisomy 18p.

result of severe flexion and extension defects of the hip joints and a fixed equinus deformity of the feet. His phenotype is similar to that of his niece (III.1): a long, thin face, broad eyebrows, narrow and concave nasal bridge, tapering nasal tip, long philtrum, high palate, receding chin, fleshy neck with low hairline, and widely spaced nipples (fig 4). His height, weight, and head circumference are normal (183 cm, 72 kg, 56 cm). *X*-ray examination of his hips revealed small femoral heads and short, very broad femoral necks, coxa valga.

CYTOGENETIC STUDIES

In the proband (III.2) a post mortem fibroblast culture led to the detection of a nearly total loss of the short arm of chromosome 18, karyotype 46,XY, del(18)qter→p11·1: (fig 5); pachytene diagram: AD CD (fig 6).

FIG 5 Partial karyotypes of chromosomes 7 and 18 showing balanced translocation $t(7q+;18p-)$ in the carrier mother (II.2) (middle), monosomy 18p in the proband (III.2) (above), and trisomy 18p in the proband's sister (III.1) (below). G banding.

FIG 6 Pachytene diagram showing the two adjacent segregational types of the balanced 7;18 translocation resulting either in monosomy 18p (AD CD) or in trisomy 18p (AB CB).

The proband's mother (II.2) and his maternal grandmother (I.2) had a balanced translocation of almost the entire short arm of chromosome 18 onto the telomere of the long arm of one chromosome 7, karyotype 46,XX,t(7;18)(7pter→qter:118p11.1→pter;18qter→p11.1:) (fig 5); pachytene diagram: ABCD (fig 6).

The proband's sister (III.1) and his uncle (II.4) were trisomic for 18p, karyotype 46,XX(XY),der(7),t(7;18)(qter;p11.1)mat (fig 5); pachytene diagram: AB CB (fig 6). The karyotypes of II.1, I.1, and II.5 were normal.

Discussion

In this family with two balanced translocation $t(7q+;18p-)$ carriers, segregation resulted in unbalanced offspring having either monosomy or trisomy for nearly the whole of 18p.

The occurrence of two probable cases of holoprosencephaly (one with proven monosomy 18p) sheds no light on the hypothesis of Gorlin *et al*² that the association between 18p- and holoprosencephaly could be the result of the expression of a recessive mutant gene on the intact chromosome 18. We believe holoprosencephaly is the maximal degree of craniofacial expression of monosomy 18p.

Patients with pure trisomy 18p are very rare. Most of the cases described showed the trisomy 18p to be associated with a partial trisomy of a proximal segment of 18q³ or with an additional part of another

autosome.⁴ A recombinant chromosome resulting from a parental pericentric inversion includes a deficiency and a duplication.^{5,6} Patients with an additional isochromosome 18p must be considered to have tetrasomy 18p.⁷ For this reason a direct comparison between these cases may not be justified.

The facial appearance presented by Serville *et al*⁴ seems to be very similar to that of our patients. Of the main clinical features of trisomy 18p described by Turleau *et al*³ we can only confirm the 'pinched nose'. The band 18q11³ or the region above the sub-band 18q12.2⁸ is thought to be crucial for the full phenotype of Edwards's syndrome. The motor defects in our patients are suggestive of the similar but more pronounced symptoms in complete trisomy 18.

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