A paracentric inversion of 7q illustrating a possible interchromosomal effect

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SUMMARY A family is described in which the proband has a rearranged X chromosome involving monosomy Xp and trisomy Xq, while the mother has a paracentric inversion of chromosome 7. It is suggested that the phenomenon of interchromosomal effect may link these observations. A brief review of the published and computer catalogued data on paracentric inversion in man is included.

Paracentric inversions have been infrequently reported since the first verification in man.¹ A recent review² gives details of 50 persons or kindreds with a paracentric inversion in publications and a computer search adds 37 unpublished cases from the Repository database (D Borgaonkar, 1984, personal communication). We are aware of one further very recent report³ which, together with the present case, makes 89 families in all.

This report describes a child with a rearranged X chromosome, whose mother carries a paracentric inversion of chromosome 7. The possibility of an interchromosomal effect linking these observations is considered. The term interchromosomal effect was coined by Lejeune⁴ and can be defined as the influence that a chromosome abnormality has on the meiotic behaviour of other chromosomes.

Case report

The proband, an 8 month old girl, had undergone extensive tests for jaundice and liver malfunction. She was the first child of healthy unrelated parents, with no history of spontaneous abortion. The pregnancy and birth were normal. She was shown to have a conjugated hyperbilirubinaemia (maximum SBR 254 $\mu\text{mol/l}$, direct bilirubin 98 $\mu\text{mol/l}$) with accompanying abnormal liver function tests (AspAT 1044 units/l, alkaline phosphatase 686 units/l, GT 59 units/l). The following disorders were excluded: biliary atresia, galactosaemia, α_1 -antitrypsin deficiency, cystic fibrosis, aminoacidopathy, mucopolysaccharidosis, and viral infection (including

intrauterine). Liver biopsy revealed a giant cell hepatitis.

The liver function tests slowly returned to normal and she recovered spontaneously. Cytogenetic investigations were requested when a slight developmental delay was noted at 6 months with weight on the 3rd centile and length and head circumference on the 10th centile.

Materials and methods

Venous blood samples from the child and both parents were cultured and harvested by standard methods and the resulting cytogenetic preparations were G banded and sequentially C banded. Late labelling studies were performed on the child's chromosomes using bromodeoxyuridine for the last four to six hours of culture.

Results

The child was found to have a female karyotype of 46 chromosomes with a large rearranged X chromosome (fig 1a, b), having an almost complete extra dose of Xq attached to Xp. The child was therefore monosomic for a tiny piece of Xp (Xp22→pter) and trisomic for Xq (Xq11→qter). C banding showed that the marker was monocentric (fig 1c, d). The abnormal X was consistently found to be late labelling and it is of incidental interest to note that there was often a synchronous pattern of band replication in the two large areas of Xq homology (fig 2a), although asynchronous replication was sometimes present (fig 2b).

The father had an apparently normal 46,XY male

FIG 1 (a) *G* banded karyotype from proband showing rearranged X ($Xp+$). (b) Partial karyotype showing Xs and 7s. (c), (d) *G* and sequential C banded partial metaphase showing that $Xp+$ is monocentric.

mitotic karyotype. The mother had a paracentric inversion of chromosome 7(q22q34) (fig 3a, b).

Discussion

The chromosome abnormality in the proband can be expected to have a negligible effect on the child's

phenotype since the monosomy of Xp is very small, and women with a deletion of the distal segment of Xp usually show no, or very mild, Turner stigmata.⁵ The large trisomy of Xq is unlikely to cause problems because complete trisomy X is usually compatible with a healthy, fertile, female phenotype. The fact that the abnormal X is consistently

FIG 2 Bromodeoxyuridine late labelling of Xp+ with homologous Xq regions showing (a) synchrony and (b) asynchrony.

FIG 3 Partial metaphase from mother showing paracentric 7 (46,XX,inv(7)(q22q34). (a) Mid metaphase, (b) early metaphase.

late labelling should further reduce any possible effects on sexual development, IQ, and fertility. The parents have therefore been given optimistic but cautious genetic counselling regarding the child's prognosis.

Classical genetic theory predicts that a heterozygous paracentric inversion is likely to form a loop at meiosis. The full implications of crossover within the 'loop' and 'interstitial' segments during meiosis in

paracentric carriers have been discussed by Madan *et al.*² The reproductive outcome of a paracentric carrier has been shown to include offspring with a dicentric chromosome,⁶ a broken dicentric,⁷ a small interstitial deletion,^{8,9} and duplication.¹⁰

The present report of a paracentric inversion in the mother and apparently unrelated duplicated X in the child describes what may be yet another type of reproductive problem for the paracentric inver-

sion carrier, namely that of an interchromosomal effect. Many of the reported families with a paracentric inversion have a second unrelated chromosome anomaly either in the same person or in a close relative.¹¹⁻¹⁵ Several families have been described in which a balanced abnormality is combined with aneuploidy for unrelated chromosomes.¹⁶⁻¹⁸

The evidence for the existence of interchromosomal effects is largely incidental, and the selection of published cases is heavily influenced by both ascertainment and publication bias. However, although formal proof of interchromosomal effects is still lacking, the associations seem too frequent to be explained by chance alone.

To summarise the types of meiotic mishap that can occur in a paracentric inversion then, the following categories of abnormal offspring have been reported. (1) True dicentric recombinants.⁶ (2) 'Recombinants' resulting from a broken dicentric.⁷ (3) 'Recombinants' resulting from unequal crossing over.⁸⁻¹⁰ (4) Interchromosomal effects.

While these categories of 'reproductive error' collectively appear to be high in the known cases of inversion, it is impossible to estimate the reproductive risk in paracentric carriers because of the low numbers and obvious sampling bias. Madan *et al*² conclude that the vast majority of paracentric inversions are harmless, but risks increase in families where recurrent abortion or abnormal children or both are found. We have recently completed prenatal diagnosis on the paracentric inversion carrier in this report, and detailed banded analysis has revealed a 46,XY,inv(7) male karyotype. However, since category (3) above is the most frequent type of abnormality reported, and duplications and deletions may conceivably be very tiny, we thought it wise to qualify our 'apparently normal' report. Madan *et al*² further emphasise the need for caution in the interpretation of fetal chromosome analysis. We await the outcome of the pregnancy.

Note

We should like to draw attention to the erroneous table in the eighth listing of the *Repository of chromosomal variants and anomalies in man* suggesting that 144 paracentrics were known. These errors have since been corrected (D Borgaonkar, 1984, personal communication).

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