Segregation of an X ring chromosome in two generations

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SUMMARY A 45,X/46,X,r(X) mosaicism was found in a mother and daughter. Characterisation of the ring by banding studies showed that breakpoints had occurred at bands Xp13 and Xq27. It is confirmed that women heterozygotes for partial deficiencies of the short arm of an X chromosome are fertile. Although the mother developed secondary amenorrhoea at the age of 29, it is suggested that fertility per se may not be affected by deficiencies of the distal part of Xq.

About 5% of patients with gonadal dysgenesis have a 45,X/46,X,r(X) chromosome constitution. Most of these females have primary amenorrhoea, short stature, infantile secondary sexual characteristics, and some minor dysmorphisms often encountered in Turner's syndrome.

One case of fertility has been reported in one of these patients, in whom the only pregnancy resulted in miscarriage.¹ Priest *et al*² have described X chromosome defects in three generations of a family. Both the mother and grandmother of a 45,X/46,X,i(Xq) patient were themselves mosaics for 45,X/46,XX/46,X,r(X). It has been suggested that isochromosome formation, as well as ring formation and mosaicism, were secondary to a familial predisposition to X chromosome abnormality.

We report the first observation of an X ring chromosome segregating in two generations of a family.

Case reports

CASE 1

This patient was the only daughter born to a 24-year-old mother and a 29-year-old father. Birthweight was 2200 g. The neonatal period was unremarkable but from the first year of life the patient was under medical control because of growth retardation. At the age of 12 years she was referred to the Department of Paediatric Endocrinology, University of Rome. At that time the following data were recorded: height 116 cm (−4 SD), weight 22 kg (−3.6 SD). On clinical examination the most striking features were a high, narrow palate, cubitus

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valgus, many pigmented naevi, and narrow hyperconvex nails. The total ridge count of the ten digits was 156 (mean value in females 126). The bone age was slightly retarded (9/12).

The first spontaneous menstruation occurred at the age of 12 years 4 months, when the patient was 121 cm tall.

CASE 2

She was the mother of case 1. She was born in 1941 as the second child of a 40-year-old mother and a 47-year-old father. Birthweight was 3000 g. The only clinical finding recorded during childhood was short stature. First menstruation occurred at 13 years and she married at 22 years. The only pregnancy at the age of 23 was unremarkable with delivery at term. Secondary amenorrhoea started at the age of 29. She was then treated for 6 years with oestrogens and progesterones. At the age of 38 the following data were recorded: height 136 cm, weight 51 kg, well developed secondary sexual characteristics, and short fourth metacarpals. The total ridge count on the fingertips was 152.

Cytogenetic studies

Chromosome analyses were performed in both patients on short term peripheral blood cultures and on cultured skin fibroblasts. The results of the cytogenetic studies are summarised in the table. A 45,X/46,X,r(X) mosaicism was demonstrated in both tissues of the patients. The 45,X cell line was present in about 30% of lymphocytes in case 1 and in about 15% in case 2. The proportion of 45,X cells was about 55% in skin fibroblasts of mother and daughter.

TABLE Cytogenetic studies on the patients

Patients	Tissue examined	Karyotype	Total No of cells	Mean (%)
Case 1	Blood	45,X	306	70.18
		46,X,r(X)	130	29.82
	Skin	45,X	34	54.83
		46,X,r(X)	28	45.17
Case 2	Blood	45,X	366	84.92
		46,X,r(X)	63	14.62
	Skin	47,X,r(X),r(X)	2	0.46
		45,X	23	54.76
		46,X,r(X)	19	45.17

The frequency of sex chromatin positive cells from buccal smears was within the normal range of our laboratory (18% and 20% respectively). A total of 250 lymphocyte metaphases from case 1 and 285 metaphases from case 2 were scored by RBA bands. In all cells examined the X ring chromosome was late replicating. Two rings were observed only in 0.46% of maternal cells, but not in preparations obtained from the daughter. The ring structure was rather unstable, appearing to be duplicated in 5 to 10% of metaphases (fig 1).

Characterisation of the ring chromosome by RBA bands indicated that the breakpoints were at bands Xp13 and Xq27 (fig 2).

Discussion

The present observations may be evidence of X ring chromosome segregation, rather than an example of

FIG 2 Diagrams of normal X and X ring chromosomes, and partial karyotype of X chromosomes from case 2 (RBA bands).

FIG 1 Morphological variability of X ring chromosome in selected metaphase plates from the patients (RBA bands).

familial predisposition to X chromosome abnormality. Cytogenetic analyses have shown no evidence of a 46,XX cell line: therefore, we suggest that in both patients the 45,X/46,X,r(X) mosaicism originated in 46,X,r(X) embryos. Ring chromosomes, because of their structure, may behave in an unstable manner in cell division. The increased rate of cell division in the 45,X, compared to that in the euploid population,³ could account for the prevalence of the 45,X cell line in the 46,X,r(X) population and for the differences in the proportion of cells with an X ring in the mother and in the daughter, 24 years younger.

In the absence of a 46,XX cell line in the tissues examined, our observation adds to the evidence for fertility in females carrying partial X chromosome deficiencies. Available evidence suggests that the idea that two normal Xs are necessary for the normal maturation and development of oocytes should be reconsidered.

Fraccaro *et al*⁴ described three sisters, carrying an Xp— abnormality, who menstruated and, at least in two cases, were fertile. After reviewing other similar published observations, the conclusion was reached that a short arm deletion of the X chromosome above band p11 would not cause gonadal dysgenesis. The location of the breakpoint in Xp in our two patients does not contradict this idea. The maintenance of ovarian function in Xp— females has been interpreted either as non-involvement of the 'never-inactivated' part of the short arm or, according to the Hoo model,⁵ as deletion of the part of the X chromosome which is present in quadruplicate in the female sex chromosomes, being the distal region of Xp originally homologous to the medial segment of Xq. Thus, there are on record more than 15 women heterozygous for a partial deficiency of the short arm of an X chromosome who either had children or had the ability to produce gametes. However, we are not aware of any report of a fertile Xq— female.

The two patients identified in our study are also heterozygous for a partial deficiency of the X region distal to band q27. Although the mother developed secondary amenorrhoea at the age of 29, she became pregnant once, proving that fertility per se may not be affected by deficiencies of the distal part of Xq.

Therefore, the evidence from Xp— females and from the present observation indicates that the distal regions of Xp and Xq may be lost without affecting fertility. Thus, the model of Hoo,⁵ suggesting that gonadal dysgenesis is caused by deletion of the distal bands of the Xq arm, cannot be correct.

However, the possibility must be considered that fertility in our case 2 is related to the presence, at least in gonadal tissues, of a 46,XX cell line, originating through non-disjunction. A similar unusual cytological mechanism is found both in XY female lemmings and in the X monosomic females of *Microtus oregoni*, in which oocytes and possibly the entire germ line acquire two X chromosomes, presumably through non-disjunction.⁶

Rather than assuming the presence in the patient of a complex mosaicism, including a 46,XX cell population, we favour the hypothesis that loss of the two distal bands of Xq does not necessarily affect fertility. After reviewing all cases of balanced X;autosome translocations involving the long arm of an X chromosome in humans, we came to the conclusion that the 'integrity' of the region included between interband Xq13–21 and bands Xq24–26 is critical for normal post-puberal gonadal function.⁷ According to our model, loss of integrity in this region results in an increased rate of oocyte depletion, possibly by means of a position effect. Therefore, the assumption that deficiency of the distal segment of Xq could not be responsible for infertility does not contradict data derived from studies of females with balanced Xq;autosome translocations. It is possible that in the index case secondary amenorrhoea resulted from the prevalence of the 45,X cell line, as a consequence of its increased rate of division.

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