

## Isodicentric X chromosome in a moderately tall patient with gonadal dysgenesis: lack of effect of functional centromere on inactivation pattern

**SUMMARY** An isodicentric X chromosome (46, X idic(X)(pter→qter::qter→pter)) with a single functioning centromere was found in all lymphocytes and fibroblasts examined from a female patient 171.5 cm in height presenting with primary amenorrhoea. Replication of the abnormal chromosome was consistently late. In some cells the pattern was asymmetrical but the asymmetry did not appear to relate to the position of the active centromere.

Reports of the phenotypic manifestations of deletions of material from the X chromosome have generated a variety of explanations of the role of particular segments in the control of sexual development and height in females.<sup>1–3</sup> Cases with partial duplications of X chromosome material may have somatic abnormalities which have been accredited to failure of inactivation.<sup>4–6</sup>

Of particular relevance to these discussions is the group of patients in whom terminal or near terminal fusion of two X chromosomes has occurred, resulting in a single large chromosome with minimal loss of material and the apparent loss of function of one centromere. The presence of this inactive centromere has been reported to influence the replication pattern of the contributing chromosomes.<sup>7–9</sup>

Gonadal dysgenesis is a feature of all the reported cases irrespective of which arm of the chromosome is involved in the fusion. Not infrequently the patients are also of short stature, although this is more commonly a feature of those with p arm fusions. Even among patients with q arm fusions interpretation is often complicated by the presence of a 45,X cell line. Only a few cases with terminal or near terminal fusions have been reported without apparent mosaicism.<sup>9–12</sup>

We describe here an investigation of a moderately

tall patient with gonadal dysgenesis in whom we found an isodicentric X chromosome with apparent fusion at qter and no evidence for a 45,X cell line.

### Case report

The patient presented with primary amenorrhoea at the age of 17 years. She worked as a hairdresser and her general health was excellent. She had had no previous hospital admissions.

Her parents were both aged 24 years when she was born. She had three sibs, a sister aged 18 years and two brothers aged 14 and 11, all of whom were of normal development.

On presentation she gave a history of nausea and headaches occurring every 3 to 4 weeks for the last 2 to 3 years, but there had been no vaginal bleeding. She was 171.5 cm tall and of large build. Her weight was 71.7 kg. She had large feet and hands. There was no breast development and only scanty pubic and axillary hair. She had normal female genitalia but the cervix was small and the uterus retroverted with a 6 cm cavity. Laparoscopy showed a streak gonad on the right side but no gonadal tissue was seen on the left. Endocrine studies showed that FSH and LH were raised to post-menopausal levels. Cyclical hormone therapy was started and induced some breast development and regular withdrawal bleeding.

### CYTOGENETIC STUDIES

All cells from phytohaemagglutinin stimulated lymphocyte cultures and from fibroblast cultures derived from a skin biopsy showed the presence of a large chromosome replacing an X. Trypsin/Giemsa<sup>13</sup> and C band<sup>14</sup> staining showed this chromosome to consist of two X chromosomes fused by their long arms but with only one functional centromere (fig 1a, b). Any material which may have been missing from the long arms was too small to be distinguished by these methods.

The chromosome was also examined in preparations made after cultures had been exposed to 200 µg/ml bromodeoxyuridine (BrdU) for the last 5 hours of culture life (fig 1c). The abnormal X chromosome was persistently late replicating and the banding pattern revealed by this technique supported the interpretation that the fusion was terminal. The labelling pattern of the abnormal chromosome was examined in 100 cells and placed in one of the four

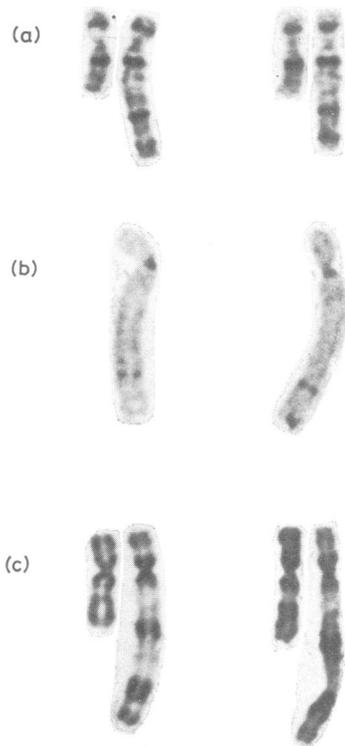


FIG 1 The X chromosomes from the patient showing (a) G bands, (b) C bands (abnormal X only), and (c) late replication pattern after 5 hours in BrdU.

categories illustrated in fig 2. Asymmetrical staining was observed in only 11 cells. In five of these, late synthesis was apparently associated with the functioning centromere and in six it was not.

Buccal smears showed a large Barr body and in some cells this appeared bipartite (fig 3).

Blood from the patient's parents was also examined. No anomaly on trypsin/Giemsa or BrdU

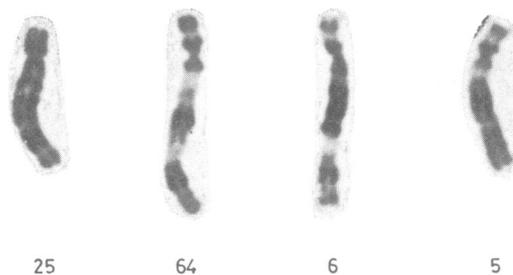


FIG 2 Representative examples of inactivation patterns found after BrdU labelling with number of cells with each pattern found.

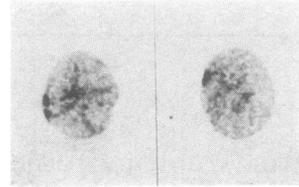


FIG 3 Nuclei of cells from a buccal smear showing sex chromatin.

late labelled cells could be distinguished. Xg blood groups were uninformative; the patient, her mother, and father were all Xg<sup>a</sup> positive.

### Discussion

Difficulties have arisen in interpreting the effect of large isodicentric X chromosomes because of the frequently observed presence of a 45,X cell line and the possibility that such a line exists undetected in others. Our case, in whom no 45,X cell line has been demonstrated, is tall and, apart from gonadal dysgenesis, shows none of the features of Turner's syndrome. Similarly, the three other patients reported with q arm fusions and no evidence of mosaicism were 175 cm,<sup>11</sup> 175 cm,<sup>12</sup> and 182 cm<sup>10</sup> tall. This is perhaps not surprising if the relevant genes are located on the p arm although the patient reported by Sarto and Therman<sup>9</sup> with p arm fusion was without the stigmata of Turner's syndrome. All adult patients with terminal fusions of X so far reported have had primary amenorrhoea, which has usually been shown to be associated with gonadal dysgenesis irrespective of which end of the chromosome is involved. However, these cases have all presented because of clinical features resulting from failure of gonadal development. In contrast, no reproductive abnormality was shown by the carrier of a recombinant X chromosome presumed to be missing some p terminal material found by Buckton *et al*<sup>15</sup> through an investigation of a family with an inversion X.

The derivation of the abnormal chromosome in our case is uncertain. The absence of informative data from the Xg blood grouping does not allow us to determine the parent from whom the chromosome was derived. We have examined the parental X chromosomes very carefully for any evidence of anomaly but a small paracentric inversion of the end of the q arm would not be detectable.

The question does arise as to why the phenotypic expression differs from that of the triple X female or from female carriers of partial X duplications.<sup>4,5</sup> As far as we are able to determine no material is missing from the ends of the fused X chromosome and, anyway, persons with simple deletions of the

long arm have presented with secondary amenorrhoea only.<sup>16 17</sup>

Phenotypically normal persons with partial duplication of the X chromosome have shown preferential inactivation of the abnormal X,<sup>4 5</sup> but this is also true of the large isodicentric chromosomes. In circumstances in which excess X chromosome material does not appear to be inactivated various congenital abnormalities are present.<sup>4-6</sup> We have looked at the X inactivation pattern in our patient. Five hours after the introduction of BrdU about 25% of the mitoses showed no BrdU incorporation on either X chromosome, 64% showed symmetrical incorporation on both parts of the abnormal chromosome, and the remaining 11% showed incorporation on only one half of the abnormal X chromosome. However, unlike the cases reported by Sarto and Therman<sup>9</sup> and Maraschio *et al*<sup>7</sup> with p arm fusion, and a case of q arm fusion,<sup>8</sup> the later replicating portion of the chromosome would appear to be unrelated to the position of the functioning centromere. It seems improbable that these findings indicate that half the chromosome remains active, but reflects more the time of exposure to BrdU; X chromatin in the interphase cells was uniformly large and often bipartite. It does suggest that the onset of replication is separately determined in the two parts of the abnormal chromosome.

The explanation of the clinical effect of this chromosomal abnormality thus remains obscure. One possibility is that the large dicentric chromosome presents pairing problems at meiosis which leads to failure of the female gonad.

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## Recurrent spontaneous abortions due to a homologous Robertsonian translocation (14q14q)

**SUMMARY** A female with a history of recurrent spontaneous abortions was shown to carry a balanced Robertsonian translocation involving the No 14 homologues. One abortus had trisomy 14 with a 46,XX, -14, +t(14q14q)mat karyotype.

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