

- ⁶ Littlefield JW. Genes, chromosomes and cancer. *J Pediatr* 1984;**104**:489-94.
- ⁷ Faulkner KW, Holmes LB, Steinfeld A, Abrams IF. A child with 18q- syndrome and cerebellar astrocytoma. *J Pediatr* 1983;**103**:600-2.
- ⁸ Yunis JJ, Ramsay N. Retinoblastoma and subband deletion of chromosome 13. *Am J Dis Child* 1978;**132**:161-3.
- ⁹ Riccardi VM, Sujansky E, Smith AC, Francke V. Chromosomal imbalance in the aniridia-Wilms' tumor association: 11p interstitial deletion. *Pediatrics* 1978;**61**:604-10.
- ¹⁰ Cohen AJ, Pi FP, Berg S, *et al.* Hereditary renal cell carcinoma associated with a chromosomal translocation. *N Engl J Med* 1979;**301**:592-5.
- ¹¹ Hecht F, Kaiser-McCaw B. Chromosomes in familial neuroblastoma. *J Pediatr* 1981;**98**:334.
- ¹² Robinson MG, McCorquodale MM. Trisomy 18 and neurogenetic neoplasia. *J Pediatr* 1983;**103**:600-2.
- ¹³ Moedjono SJ, Funderburk SJ, Sparkes RS. 18p- syndrome resulting from translocation (13q;18q) in a mildly affected adult male. *J Med Genet* 1979;**16**:399-402.
- ¹⁴ Soule EH, Newton W, Moon TE, Tefft M. Extraskelatal Ewing's sarcoma. A preliminary review of 26 cases encountered in the intergroup rhabdomyosarcoma study. *Cancer* 1978;**42**:259-64.

Correspondence and requests for reprints to Dr J M Garcia-Sagredo, Servicio de Genética Médica, CIBER, Ramón y Cajal, 28034 Madrid, Spain.

An isodicentric X chromosome with short arm fusion in a woman without somatic features of Turner's syndrome

I C S BARNES*, D J CURTIS*, AND S L B DUNCAN†

*Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN; and †Jessop Hospital for Women, Leavygreave Road, Sheffield.

SUMMARY A 25 year old woman with gonadal dysgenesis but no other somatic features of Turner's syndrome was found to have a 45,X/46,XidicX(p22.3) karyotype. It is postulated that because her stature is within the normal range there has been no loss of genetic material in the fusion of the two Xs. Her mother, who also had a history of menstrual problems, was found to be a 46,XX/47,XXX mosaic.

Isodicentric X chromosomes, formed by fusion of two X chromosomes, have been widely described.¹ The phenotypic effects of this X chromosome abnormality are variable and depend on the amount of material deleted and whether the chromosomes are fused by the short or the long arms. Despite the variable presence of a 45,X cell line, they do, in general, form two distinct groups. Those joined by the short arms exhibit shorter than average stature with gonadal dysgenesis, while those attached by the long arms exhibit normal or taller than average stature with gonadal dysgenesis. Other Turner stigmata can occasionally be present in both groups, but are more frequently associated with short arm fusions.

The present case describes a 25 year old woman with gonadal dysgenesis and normal stature whose karyotype is 45,X/46,Xidic(X)(p22.3). Her mother,

who also had a history of menstrual problems, had a 46,XX/47,XXX karyotype.

Case report

The female proband (born 8.5.59) presented in July 1981 with a desired, but unconfirmed, pregnancy (LMP April 1981). Clinical examination did not confirm pregnancy. Enquiry into her menstrual history was inconsistent on different occasions. She described her first period as a flowing blood loss following a fight when she was kicked in the stomach. This could have been at about 15 years of age. Menstruation had been very irregular and scanty; between 1977 and 1980 she had been prescribed various courses of the contraceptive pill. During these times she had fairly regular withdrawal bleeding. She stopped the pill in 1980 to try to become pregnant. After the amenorrhoeic episode in 1981 she had a period in February 1982. On review in 1982 because of oligomenorrhoea and infertility she was found to be on the tall side of the normal range (170.75 cm) and underweight (52.25 kg): ponderal index=18. She had a dependent and childish personality and was poorly integrated with her life situation. Neck and carrying angle were unremarkable. Breast development was stage 3 and pubic hair was stage 4 in distribution, but rather scanty. The vulva and vagina were normal and there was a small, anteverted uterus. Tomography of the skull was normal and the bone age showed epiphyseal fusion.

Between first presenting in 1981 and 1984, gonadotrophin levels on several occasions were raised and oestrogen levels were low (table 1). Prolactin was normal (148 mU/l). She was not taking hormones at these times. A five day course of clomiphene showed no increase in urinary oestrogens. Laparotomy showed small pelvic organs in the normal anatomical relationships. The right ovary was a 3 cm streak gonad merging with the ovarian ligament. The left ovary was more rounded (2×1×1 cm). Histological examination of biopsies from both ovaries showed no primordial germ cells or follicles.

Her mother (born 13.4.27) reported a rather similar menstrual history. She had a late menarche at 19 years. Her three liveborn children were conceived when she was between 27 and 32 years and following the third birth (our patient) she had no further menstruation. She recalled two or three 'miscarriages' during her fertile years. Her second child (male) was killed in a road accident. Her elder daughter experienced 11 years of infertility, but conceived after investigation and treatment with clomiphene citrate. Her child is normal. Both mother and elder daughter are of short stature.

CYTOGENETIC STUDIES

Chromosome investigations were performed on cultured lymphocytes and on fibroblasts cultured from both gonads and a skin biopsy. The results are set out in table 2. The percentage of 45,X cells was highest in fibroblasts cultured from the right gonad and completely absent in fibroblasts grown from the skin biopsy.

In cells with 46 chromosomes there was one normal X chromosome and a large chromosome formed by two Xs joined by their short arms (fig 1a). G banding (fig 1b) showed that little, if any, material had been deleted as a result of the fusion, and so the

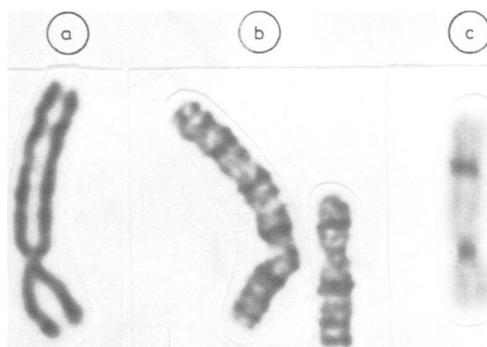


FIG 1 Isodicentric X chromosome (a) solid stain, (b) G banded, (c) C banded.

breakpoints were interpreted as being terminal (p22.3). This chromosome showed only one centromeric constriction, but C banding showed two areas of centromeric heterochromatin (fig 1c). The karyotype was, therefore, 45,X/46,XidicX(p22.3). Replication studies using the BrdU-Hoescht-Giemsas technique showed that the abnormal X chromosome was late replicating in all cells studied from both fibroblasts and lymphocytes (fig 2).

Sex chromatin bodies were observed in 35% of buccal mucosa cells and in 44% of fibroblasts. They appeared as single, double, or bipartite bodies (fig 3).

Chromosome analysis of lymphocytes from the proband's sister showed a normal female karyotype while those analysed from their mother showed two cell lines, 85% of which were 47,XXX while the remaining 15% were 46,XX.

Discussion

Cases of isodicentric X chromosomes which are fused by the short arms generally exhibit gonadal dysgenesis, short stature, and occasionally Turner stigmata. One reported exception is a 25 year old woman with secondary amenorrhea and normal stature (163 cm).² The present report describes a similar case in which the stature was within the normal range (170.75 cm).

It has been known for some time that there are genes controlling stature and other somatic features of Turner's syndrome on the short arm of the X chromosome.^{3,4} The occurrence of Turner stigmata is more often associated with larger deletions of Xp, whereas reduction in stature appears to be a consequence of even very small terminal deletions. Thus, short stature in Xp:Xp fusion chromosomes is thought to be attributable either to real Xp monosomy caused by loss of chromosome material at the

TABLE 1 Plasma levels of gonadotrophins and oestradiol.

Date	FSH (IU/l)	LH (IU/l)	Oestradiol (pmol/l)
9.12.81	39	76	55
24.6.82	47	53	104
22.2.83	29	40	176
4.10.84	60	66	90

TABLE 2 Cytogenetic studies.

Cultured tissue	45,X	46,XidicX	Total	% XO line
Lymphocytes	4	46	50	8
Right gonad	4	16	20	20
Left gonad	1	19	20	5
Skin	0	30	30	0

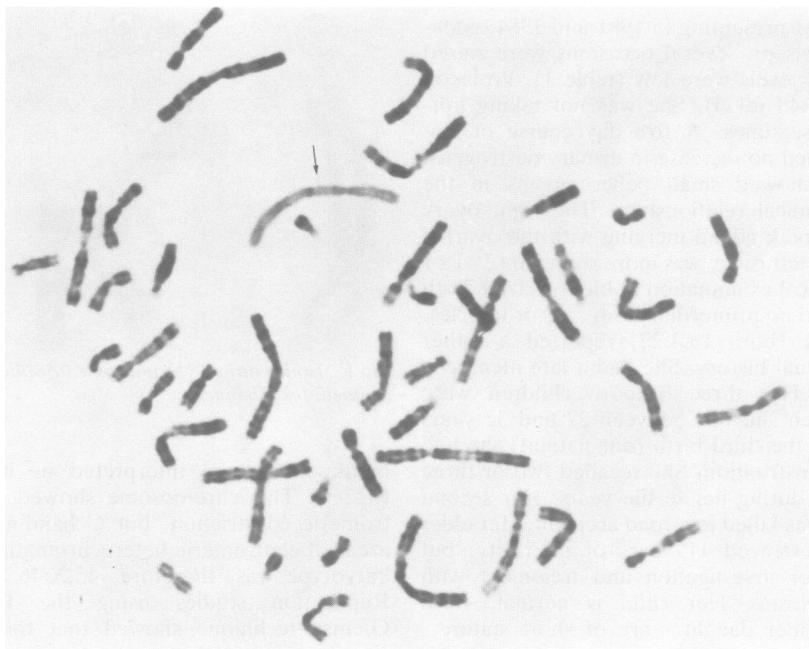


FIG 2 RBG banded cell showing the late replicating isodicentric X chromosome.

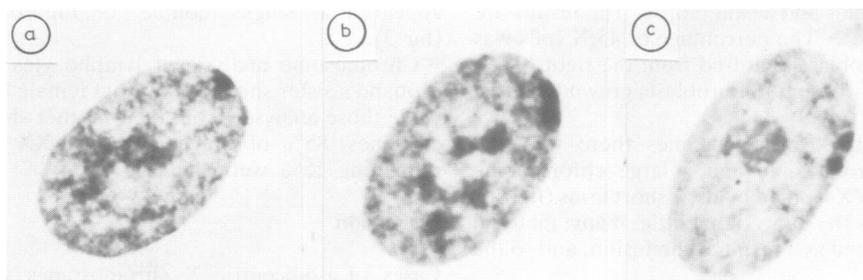


FIG 3 Sex chromatin in fibroblasts showing (a) single, (b) bipartite, and (c) double bodies.

site of attachment, or functional monosomy due to modification of the area Xp22.3 which usually remains active on the inactive X. In these two cases where the stature is within the normal range, it would appear that there had been no loss of genetic material and any modification of Xp22.3 which had occurred had not affected the stature.

Rivera *et al*⁵ have suggested that fusion chromosomes can arise without loss of genetic material following impaired telomeric replication. In the case of the X chromosomes, fusion could occur between sister chromatids in the maternal or paternal germ cells or at an early stage in the zygote. Fusion

between homologous X chromosomes could occur during prophase of the first meiotic division in the mother. The 45,X cell line which is often associated with isodicentric X chromosomes is usually assumed to be a postzygotic effect of mitotic instability. The absence of a 46,XX cell line in all cases described so far indicates that if the formation of the isodicentric X were postzygotic, it would have had to occur at the one cell stage.

The fact that the mother of the proband is 46,XX/47,XXX mosaic could be coincidental, but might also indicate that the X:X fusion had occurred in her germ cells. It has been suggested that these

particular mosaics have an increased risk of abnormal offspring.⁶ It has also been suggested that the increased risk of single organ malformations in the progeny of Turner and triple X women may be related to their premature ovarian ageing.⁷ In the present case, the mother had two or three miscarriages during her fertile years and following the birth of the proband she suffered premature menopause.

Gonadal dysgenesis is a constant feature of all X fusion chromosomes regardless of whether they are attached by the long or the short arms, or whether there is a 45,X cell line present. In the present case it is impossible to be certain whether she had truly completed pubertal development and had a menarche, or whether the menstrual losses and secondary sex characteristics had been entirely produced by exogenous hormones. However, by the time of investigation the girl had ovarian failure associated with dysgenetic ovaries. If, as indicated by the normal stature, there had been no loss of genetic material, this finding would confirm the belief that gonadal malfunction in Xp fusions cannot be explained solely on the basis of Xp deletion.⁸ This had previously been inferred from the finding that females with a deletion of the terminal portion of Xp are fertile.^{9,10} There was a 45,X cell line in the lymphocytes and fibroblasts from gonadal tissue in this patient which could have influenced the development of the gonads, but in other cases of Xp fusions without evidence of mosaicism gonadal malfunction still occurs. It is possible that the actual size of the abnormal chromosome leads to problems in pairing at meiosis, so that the primary oocytes which rest in the first prophase of meiotic division until puberty are unstable and consequently become atretic. This would be a similar situation to that of

the male where regular pairing of the X and Y chromosomes as a bivalent is a prerequisite for normal sperm formation.¹¹

References

- Zakharov AF, Baranovskaya LI. X-X chromosome translocations and their karyotype-phenotype correlations. In: Sandberg AA, ed. *Cytogenetics of the mammalian X chromosome*. Part B. New York: Alan R Liss, 1983.
- Sarto GE, Therman E. Replication and inactivation of a dicentric X formed by telomeric fusion. *Am Obstet Gynecol* 1980;136:904-8.
- Ferguson-Smith MA. Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. *J Med Genet* 1965;2:142-55.
- Jacobs PA. Structural abnormalities of the sex chromosomes. *Br Med Bull* 1969;25:94-9.
- Rivera H, Sole MT, Garcia-Cruz D, et al. On telomere replication and fusion in eukaryotes: a propos of a case of 45,X/46,X,ter rea(X:X)(p223;p223). *Cytogenet Cell Genet* 1984;38:23-8.
- Dewhurst J. Fertility in 47,XXX and 45,X patients. *J Med Genet* 1978;15:132-5.
- Fryns JP, Kleczkowska A, Petit P, et al. X-chromosome polysomy in the female: personal experience and review of the literature. *Clin Genet* 1983;23:341-9.
- Ferraro M, De Capoa A, Mostacci C, et al. Cytogenetic and clinical studies in gonadal dysgenesis with 46,X,Xt (qter→p221::p223→qter) karyotype: review and phenotype/karyotype correlations. *J Med Genet* 1980;17:457-63.
- Fraccaro M, Maraschio P, Pasquali F, et al. Women heterozygous for deficiency of the (p21→pter) region of the X chromosome are fertile. *Hum Genet* 1977;39:283-92.
- Fryns JP, Kleczkowska A, Petit P, et al. Fertility in patients with X chromosome deletions. *Clin Genet* 1982;22:76-9.
- Miklos GLG. Sex chromosome pairing and male infertility. *Cytogenet Cell Genet* 1974;13:558-77.

Correspondence and requests for reprints to Mrs I C S Barnes, Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN.

Translocation X;13 in a patient with retinoblastoma

G PONZIO*, E SAVIN*, G CATTANEO†, M P GHIOTTI†, A MARRA†, O ZUFFARDI‡, AND C DANESINO‡

*Istituto di Genetica Medica, Università di Torino; †Ospedale di Santa Croce, Divisione di Pediatria, Moncalieri; and ‡Istituto di Biologia Generale e Genetica Medica, Università di Pavia, Italy.

SUMMARY We describe the clinical and cytogenetic findings in a child with retinoblastoma and a translocation between chromosomes X and 13. The X;13 translocation in this patient does not involve band 13q14, the assigned locus for retinoblastoma.

Retinoblastoma (Rb) is a childhood retinal cancer with an incidence of 1 in 20 000 births¹ that occurs as a sporadic or a hereditary disease, the latter being a highly penetrant (95%) autosomal dominant trait. About 5% of retinoblastoma patients have a chromosome aberration.² This is usually an interstitial deletion of the region 13q14, but balanced translocations³ with breakpoints in this region have been reported, and the locus for Rb has been