47,XXX chromosome constitution in a male

SUMMARY An 18-year-old boy with a male phenotype was examined because of testicular hypoplasia. Chromosome analysis using Q- and R-banding techniques and BUdR treatment showed a 47,XXX karyotype, in both lymphocytes and fibroblasts.

Cytogenetic problems raised by this case are discussed in relation to data from previous published reports.

Case report

The patient was born in 1959, when the father was 31 and the mother 34 years old. He was the last of five children. The first child, a female with spina bifida, died at 3 months. A second pregnancy ended with a spontaneous abortion during the first trimester. The patient has three living sisters, aged 19, 22, and 23, respectively. Two of these are married, and one has a child with a normal phenotype.

Since the age of 12 the patient has been treated with androgen substitutive therapy for testicular hypoplasia. Satisfactory pubertal physical development was achieved, but no effect on sexual behaviour, which continued to show prepubertal features, was observed.

At the age of 17 a testicular biopsy was performed. Histological examination showed a thickening of all basement membranes and marked atrophy of germinal cells.

On physical examination the patient had normal body proportions; his height was 177 cm, his weight 66 kg. His face was expressionless. Body and pubic hair were normally distributed and on his face he had sparse hair and acne. Gynaecomastia was not present. The penis was of normal size and both testes were small and soft (fig 1).

Hormonal studies showed plasma levels of testosterone, LH, and FSH to be similar to those found in patients with Klinefelter's syndrome. Endocrinological findings are described in another report (Borghi *et al*, in preparation).

The subject first came to our hospital at the age of 18.

CYTOGENETIC STUDIES

In a buccal smear 20% X chromatin-positive nuclei were found and some cells showed a double X chromatin body. All the nuclei observed were negative for Y fluorescence.

Cytogenetic analysis carried out on peripheral

FIG 1 Probant at age of 18 years.

blood cultures showed a modal number of 47 chromosomes. The use of the Q-banding technique enabled the karyotype of the patient to be identified as trisomy X, while Y fluorescence could not be detected in any of the metaphases examined (fig 2). A bright fluorescence on the short arm of chromosome 13 was found. In the father's karyotype, where a normal Y chromosome was present, chromosome 13 also showed a similar Q-banding pattern. This makes the hypothesis that Y material had been translocated onto 13p unlikely. On these grounds, we are inclined to interpret this finding as a Q-intensity variant of the 13p region (fig 3). The 47,XXX chromosome constitution in the patient's cells was also confirmed by the observation, in all scored mitoses, of two inactive X chromosomes, using BUdR treatment followed by acridine orange staining (fig 4).¹

As the patient declined to submit to another testicular biopsy, it was not possible to examine fibroblasts from the testes. Chromosome analysis was also performed on fibroblast cultures obtained from the skin, and the 47,XXX karyotype was again observed.

Cytogenetic data obtained from lymphocytes and fibroblasts are summarised in the table. The mitoses with less than 47 chromosomes show a random loss of one or more chromosomes. No abnormalities were found in the chromosome constitution of the mother.

TABLE Cytogenetic data from lymphocytes and fibroblasts

	No of chromosomes				Total mitoses
	<45	45	46	47	
Peripheral blood	11	6	16	207	240
Skin fibroblasts	1	0	2	53	56

As the patient and both his parents showed an (a+) phenotype for the Xg group, it was not possible to establish the origin of the non-disjunction.

Discussion

A 46,XX karyotype in a male was first reported by

de la Chapelle *et al.*² Since then, nearly 60 cases of male patients with an XX sex chromosome constitution have been described. The present case appears to be the first example of 47,XXX karyotype associated with a male phenotype. Several hypotheses have been advanced to justify the presence of a male phenotype without any apparent Y material.

As in 46,XX males, many pathological symptoms of Klinefelter's syndrome were also present in the patient we examined. This might suggest that these patients were originally XXY, or as in the present case, XXXY. After testicular differentiation is triggered, mitotic non-disjunction may produce two stem-lines, one containing the Y chromosome.

2 Q-banded karyotype of the patient.

FIG 3 Chromosome 13 of (a) the patient and (b) his father showing Q-intensity variant of the short arm.

Subsequently, the Y line is probably eliminated during the following cell divisions.^{3 4 5}

As the genetic information for male differentiation is located in a very small portion of the juxta-centromeric region of the Y chromosome,^{6 7} the hypothesis that non-fluorescent material might have been translocated from the Y to an autosome or to an X chromosome must also be considered. XX males with increased length of the short arm of one of the Xs have been reported by Madan⁸ and by Wachtel *et al.*⁹ The authors suggested that an X-Y interchange had occurred in these patients, according to the hypothesis of Ferguson-Smith.¹⁰ No appreciable difference in length of the short arms of the X chromosomes was found in our case, either in lymphocyte or fibroblast banded mitoses. However, the possibility of a very small Y segment being translocated onto Xp cannot be ruled out.

A rare mutant gene able to induce testicular differentiation and male sex development both in XX³ and XXX subjects is another possible explanation. Two factors suggest that this gene mutation is dominant.

Firstly, consanguinity among parents of XX males has not been observed in any of the cases reported. Secondly, although a higher frequency among

sibs, cousins, or uncles of the probands would be expected, familial recurrence of XX males is extremely rare.¹¹

The possibility of failed inactivation of the male-determining genes, presumably located on the X chromosome, has also been suggested by some authors.^{5 12}

Finally, the presence of mosaicism, with an extremely circumscribed Y cell line, must be considered.^{13 14 15} Pawlowitzki *et al.*¹⁶ reported an XX male in whom the Y body was detected only in Sertoli cells. Although in our investigation the analysis was performed on a large number of mitoses from two different types of tissue, the possibility of mosaicism cannot be excluded.

U BIGOZZI,* G SIMONI,† E MONTALI,*
L DALPRÀ,† F ROSSELLA,†

M PIAZZINI,* AND A BORGHI,†

*Cattedra di Genetica Medica, Università di Firenze;

†Istituto di Biologia Generale, Facoltà di Medicina, Università di Milano; and

‡Cattedra di Endocrinologia e Medicina Costituzionale, Università di Firenze, Italy

FIG 4 R-banded chromosomes of the patient obtained using BUdR and acridine orange. Arrows indicate two late replicating X chromosomes.

References

- ¹ Dutrillaux B, Laurent C, Couturier J, Lejeune J. Coloration par l'acridine orange de chromosomes préalablement traités par le 5-bromodeoxyuridine (BrdU). *C R Acad Sci (Paris)* 1973;**276**:3179-81.
- ² de la Chapelle A, Hortalting H, Niemi M, Wemistrom J. XX sex chromosomes in a human male: first case. *Acta Med Scand* 1964;**412**:25-38.
- ³ de la Chapelle A. Nature and origin of males with XX sex chromosomes. *Am J Hum Genet* 1972;**24**:71-105.
- ⁴ de la Chapelle A. The aetiology of human XX males. In: *V International Congress of Human Genetics, Mexico*. Amsterdam: Excerpta Medica, 1976. International Congress Series, No 397.
- ⁵ Rios ME, Kaufman RL, Sekhon GS, Bucy JC, Bauman JE, Jacobs LS. An XX male: cytogenetic and endocrine studies. *Clin Genet* 1975;**7**:155-62.
- ⁶ Krmpotik E, Szego K, Modestas R, Molabola G. Localization of male determining factors on short arm of Y chromosome. *Clin Genet* 1972;**3**:381-7.
- ⁷ Tiepolo L, Zuffardi O. Localization of factors controlling spermatogenesis in the non-fluorescent portion of the human Y chromosome long arm. *Hum Genet* 1976;**34**:119-24.
- ⁸ Madan K. Chromosome measurement of an XXp+ male. *Hum Genet* 1976;**32**:141-2.
- ⁹ Wachtel SS, Koo GC, Breg WR, et al. Serologic detection of a Y-linked gene in XX males and XX true hermaphrodites. *N Engl J Med* 1976;**295**:750-4.
- ¹⁰ Ferguson-Smith MA. X-Y chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. *Lancet* 1966;**2**:475-6.
- ¹¹ de la Chapelle A, Schröder J, Murros J, Tallqvist G. Two XX males in one family and additional observations

- bearing on the etiology of XX males. *Clin Genet* 1977; **11**:91-106.
- ¹² Powers HO, Neu RL, Smulyan H, Gardner LI. An adult phenotypic male with a 46,XX chromosome complement. *J Clin Endocrinol Metab* 1970;**31**:576-9.
 - ¹³ Bartsch-Sandhoff M, Schade H, Wiegelmann W, Solbach H, Scholz W. Ein Beitrag zur Geneses von XX-Männer. *Humangenetik* 1974;**21**:245-53.
 - ¹⁴ Dosik H, Wachtel SS, Khan F, Spergel G, Koo GC. Y-chromosomal genes in a phenotypic male with a 46,XX karyotype. *JAMA* 1976;**236**:2505-8.
 - ¹⁵ Mirò R, Caballin MR, Marina S, Egozcue J. Mosaicism in XX males. *Hum Genet* 1978;**45**:103-6.
 - ¹⁶ Pawlowitzki JH, Holzgreve W, Kövary M, Niermann H, Scholz W. Testing mosaicism in a XX male. *Ann Genet* 1978;**21**:152-6.

Requests for reprints to Dr U Bigozzi, Cattedra di Genetica Medica, Viale Morgagni 85, Firenze, Italy.

Complex chromosomal rearrangement leading to partial trisomy 22

SUMMARY We have examined a boy with a peculiar facial appearance and mental retardation. Cytogenetic studies showed 47,XY, monosomy 22, + two marker chromosomes, M1 and M2. The karyotype is interpreted as functionally partial trisomy 22. Chromosome analyses of both parents and three sibs were normal.

Several cases of trisomy 22 (non-mongoloid trisomy G) have been described.¹⁻⁵ There is a wide variation in the phenotypic appearance of these cases. However, there are many similarities which allow the description of a specific syndrome. It has been suggested by Zellweger *et al*⁵ that trisomy 22 syndrome (T22), cat eye syndrome (CES), which is a partial trisomy 22, and cases with symptoms of both T22 and CES, the so-called intermediate cases, are variants of the same disorder. The main feature(s) of T22, cleft palate, and of CES, coloboma of the iris and imperforate anus, are absent in our patient. He has, however, some of the characteristics of T22 or CES or both, suggesting an intermediate case. The purpose of this report is to describe the clinical picture and the concomitant chromosomal aberrations.

Case report

The proband (fig 1) was born in January 1975 after an uneventful pregnancy; the mother was 24 and the

FIG 1 Front and side view of proband.

father 30 years old. The mother has two daughters born in 1972 and 1978, and one son born in 1973, all of whom are normal. The parents are unrelated. The boy was small (birthweight 2780 g, height 48 cm, head circumference 34.5 cm). He was hypotonic and cyanotic after birth, needing oxygen for 6 hours. Apgar score at 1 minute was 8. Physical examination showed right-sided cryptorchidism. He had a peculiar facial appearance and poorly formed ears. Routine laboratory tests were normal.

He was admitted to the paediatric ward twice at the age of 2 and 4½ months because of continued vomiting, seborrhoeic dermatitis, and episodes of coughing and wheezing. He was thin and his peculiar appearance was now more marked with hypertelorism, antimongoloid slanting of the eyes, eyelid folds, epicanthus, and mild bilateral ptosis. He had micrognathia, large, low-set ears with an indentation on each ear lobe, and small bilateral preauricular sinuses. There was frontal bossing, his nose was broad with a depressed nasal bridge, and the mouth was downturned. He had low-set, widely spaced nipples, moderate cubitus valgus, and short lower extremities. His motor development was normal, but his mental milestones were delayed. The back of his head was flat and asymmetrical. Laboratory investigations, including urinary mucopolysaccharides, liver function tests, thyroid function test, repeated urinary amino-acid screening, and malabsorption tests, were normal. IgG, IgA, and IgM were normal, but IgE was raised (120 U/ml). Radiological allergen sorbent test for egg albumin was positive. The leucocyte count was variable (35 000 to 7400) with marked and prolonged leucocytosis, but a bone marrow puncture was normal. Intravenous pyelogram, electroencephalogram, and chest x-ray were normal. A barium meal showed massive regurgitation into the oesophagus when the patient was