

X-Y translocation in a retarded phenotypic male

Clinical, cytogenetic, biochemical, and serogenetic studies

RENÉE BERNSTEIN, JOAN WAGNER, JOY ISDALE, G. T. NURSE, A. B. LANE, AND TREFOR JENKINS

From the Department of Human Genetics, School of Pathology, The South African Institute for Medical Research and University of the Witwatersrand, Johannesburg; and the Departments of Paediatrics and Radiology, University of the Witwatersrand, Johannesburg

SUMMARY Cytogenetic studies on a mentally retarded boy revealed an X-Y translocation, karyotype 46,X,t(X;Y)(p22;q11). Only 5 other such cases have been reported and these were all females. The unequivocal male phenotype suggested non-random inactivation of the normal maternally derived X chromosome, and that the non-inactivated X-Y translocation chromosome included the locus for male determination. Confirmation of this was provided by unassociated X and Y chromatin in interphase cells, as well as by reverse banding after BrdU incorporation and autoradiography of metaphase chromosomes. There was anomalous Xg blood group inheritance in the proband, indicating possible localisation of the Xg locus to the terminal portion of the X short arm. Linkage of Xg and a form of X-linked mental retardation is suggested. Close linkage of the Xg locus with the loci for α -galactosidase, phosphoglycerate kinase, G-6-PD, and MPS II was excluded.

Cytologically identifiable translocation of the Y chromosome to the X chromosome has been reported very rarely (Khudr *et al.*, 1973; Borgaonkar *et al.*, 1974; Van den Berghe *et al.*, 1977). In all instances where there was no free-lying Y chromosome, the patients were phenotypic females. Two XX males with presumptive morphological evidence of a Y to X translocation have also been documented (Madan and Walker, 1974; Wachtel *et al.*, 1976).

We wish to report the investigation of a mentally retarded child with a morphologically identified X-Y translocation and an unequivocally male phenotype. This patient afforded a valuable opportunity for studying the pattern of X inactivation in such cases, as well as the location of the male determining genes of the Y chromosome, and the linkage of genes possibly located on the distal portion of the short arm of the X chromosome, including the Xg locus.

Case report

The proband was first referred at the age of 4 years for investigation of severe mental retardation associated

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with skeletal abnormalities and short stature. He weighed 2.3 kg at birth, and was delivered normally at term after a pregnancy uneventful except for a slight show of blood at 16 weeks. The mother gave no history of stillbirths or miscarriages at any time, or of infection, drug ingestion, or irradiation during pregnancy. She had an ovarian cyst removed 3 months before conception. The parents were unrelated and of normal intelligence. The father was aged 26 and the mother 23 years at the time of birth of the proband, who was 3 years younger than his phenotypically normal brother. The family history was non-contributory, except that the father's sister was said to have a son suffering from hyperactivity, slurred speech, and incoordination of eye movements. The father's height was 165 cm and his parents and sister were also short in stature.

Limitation of elbow movements was noted in the proband shortly after birth. His physical and mental development was slow and all his milestones were delayed. He first smiled and lifted his head between 4 and 6 months old, never crawled, presumably because of his upper limb abnormalities, and first walked unassisted when nearly 4 years old. At 5 he still was not

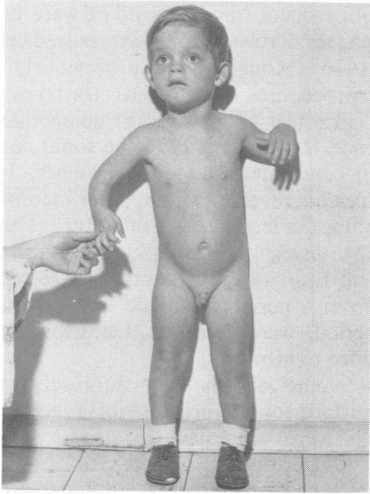


Fig. 1 Appearance of child at 4 years of age.

toilet trained and could not speak intelligibly. His emotional behaviour occasioned great concern; he had uncontrollable temper tantrums, and fits of screaming and 'head-bashing', during which he injured himself.

Clinical examination at 5 years 5 months revealed a hyperactive boy, obviously severely retarded mentally (Fig. 1). His height, 95 cm, was considerably below the third centile for his age (average, 111 cm), and his head circumference of 50 cm was exactly on the third centile (average, 53 cm) and could have been normal for a child of such short stature. There was flattening of the head posteriorly and the forehead was prominent. The eyes had a suggestion of ptosis (not evident in the photograph) and mild hypertelorism. The ears were low set, large, simple in shape, and lacking cartilage. The nasal bridge was normal, but the nose was short and 'pug'-shaped. The mouth was rather 'carp-like', with a thin, down-curved upper lip, high-arched palate, and a receding jaw. There was no suggestion of webbing of the neck, which was of normal length, and the anterior and posterior hair lines were normal. Three small naevi were noted on the anterior chest, the left shoulder, and the scalp. The chest was not shield-shaped, but the nipples were low-set and widely spaced.

There was arthrogryposis of the upper extremities, with limitation of extension to 90° in the left elbow and 80° in the right. Elbow flexion and movements around the shoulder, wrist, and finger joints were unimpaired. Both forearms were short, and the hands showed bilateral single palmar creases and short fifth fingers with clinodactyly. In the lower extremities all joints had full movement and the only abnormality noted was bilateral overlapping of the fourth toe by the

fifth. Muscle tone was normal apart from some hypotonicity of the forearm muscles and inability to lift the head when lying prone. There was no evidence of internal abnormalities or of impairment of hearing or vision.

The external genitalia were undeniably male; the penis was of normal size for his age, and the urethral meatus was terminal. Both testes were fairly small and had descended into a normal rugose scrotum. The right one had a diameter of approximately 1.5 cm and was of normally firm consistency, while the left one was about 1 cm in diameter and soft.

Special investigations

X-RAY STUDIES

The first x-ray examination of the proband was carried out when he was 2 years old, before referral. A steep base of skull, dislocated radial heads, short forearm bones, and hip abnormality were reported. Various local and overseas consultants expressed the view that the clinical and radiological features were not diagnostic of any known syndrome, and that the condition was probably unique.

Further x-ray studies at 4 years of age were confined to the limbs (Fig. 2). There was generalised rarefaction of all the bones. The humeri were normal. Bilaterally, the radius and ulna were short in comparison to the length of the humerus (but it should be noted that the father had the abnormally low brachial index of 66.5). The radius, however, was abnormally long in relation to the ulna. There was bilateral dislocation and diastasis of the proximal radioulnar joint and of the elbow joint. The distal radioulnar joint was also diastased and the carpal angle was abnormal. There was delay in the appearance of the carpal ossification centres. At a chronological age of 4 years the skeletal age was 9 months, which is markedly retarded. Clinodactyly was present bilaterally. There was no hypoplasia of the metacarpals. The medial condyles of the tibiae were prominent with widening of the proximal ends of the tibial shafts. The condyles of the femurs were normal.

AGGLUTINATION STUDIES

Agglutination studies for the detection of toxoplasmosis, rubella, and cytomegalovirus antibodies, carried out when the patient was 4 years old, were all negative.

EMI BRAIN SCAN

This did not show any ventricular enlargement, which might be suggestive of hydrocephalus, or any evidence of cerebral atrophy.

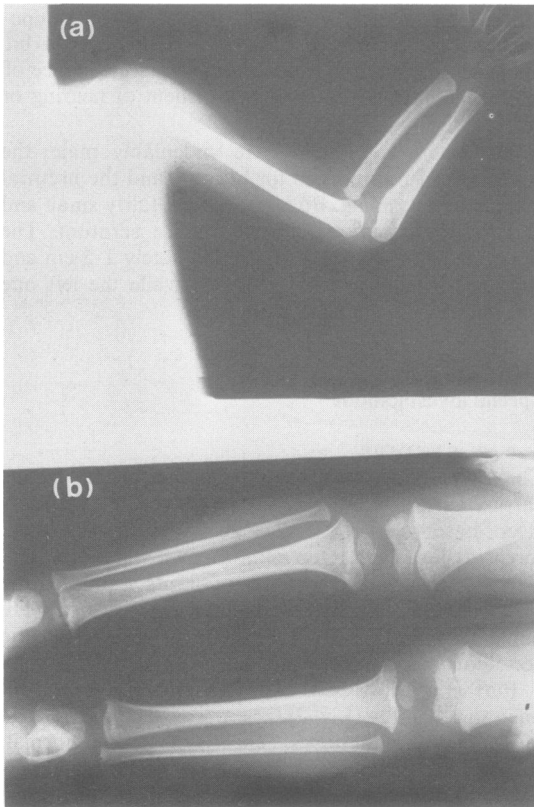


Fig 2 X-ray appearance of (a) left elbow joint, (b) left and right tibiae and knee joints.

DERMATOGLYPHIC INVESTIGATION

This showed a double loop whorl on the thumb, small central pocket whorls on the 2nd, 3rd, and 4th digits, and a whorl on the 5th digit of the left hand. The right hand had an ulnar loop on the thumb and 3rd digit, a central pocket whorl on the 4th digit, and small whorls on the 2nd and 5th digits. The total ridge count was only 46. The average total finger ridge count for normal males was reported by Penrose (1967) as 145 (SE 1.74, $n = 825$). The palmar triradius was in the t'' position on the left hand and the t' position on the right hand, with abnormally obtuse *atd* angles of 82° and 67° , respectively. The palmar thenar spaces were open on both hands. There was an ulnar loop in the left hypothenar space and a vestigial pattern in the right. The left III and right IV interdigital spaces had a distal loop. The total *a-b* ridge count was 88.

Methods

CYTOGENETIC STUDIES

Peripheral blood cultures were established initially according to the usual whole blood microculture tech-

niques. Subsequent banding studies were carried out on metaphases derived from synchronised cell cultures (Yunis, 1976). Modifications of previously described banding procedures were used: (i) trypsin-Giemsa banding (Priest *et al.*, 1975); (ii) quinacrine mustard fluorescence (J. Rowley, 1976, personal communication); (iii) centromeric banding (Sumner, 1972); (iv) acridine-orange reverse banding after incorporation of BrdU during the last 6 hours of culture (Dutrillaux *et al.*, 1973), using the photographic techniques of Verma and Lubs (1975). A total of 278 metaphases, derived from 6 peripheral blood cultures over an 18-month period, were screened. Unfortunately, a skin biopsy failed to grow.

Buccal epithelial cells were fluoresced with quinacrine mustard for the presence of Y bodies, and the same cells were subsequently relocated and stained with a klinger-thionine stain for X chromatin. Peripheral blood neutrophils were fluoresced to show drumsticks and Y bodies. Autoradiographic studies were performed by incorporation of tritiated thymidine ($1.0 \mu\text{C}/\text{ml}$ culture medium) during the last 6 hours of culture, and exposure in K-2 emulsion for 17 days.

BIOCHEMICAL INVESTIGATION

Biochemical investigation of the case consisted of testing for the presence of 4 enzymes, whose structural genes are situated on the X chromosome, according to established methods for these procedures: (i) red cell glucose-6-phosphate dehydrogenase (World Health Organization, 1967); (ii) red cell phosphoglycerate kinase (Shonk and Boxer, 1964); and (iii) white cell lysosomal α -galactosidase (Kolodny and Mumford, 1976). In addition, evidence for the presence of the enzyme L-iduronic acid 4-sulphate sulphatase (absent in mucopolysaccharidosis type II) was obtained by testing the proband's urine for abnormal amounts of glycosaminoglycans, using the cetylpyridinium chloride precipitation method (Pennock, 1969), and by the alcian blue spot test (Pennock *et al.*, 1970).

GENE MARKER STUDIES

The unlikely possibility that parentage might not be as stated was explored by gene marker studies on the proband and both his parents. The ABO, MNSs, Rhesus, Kell, and Duffy blood groups were investigated with commercially available anti-A, -B, -AB, -M, -N, -S, -s, -D, -C, -c, -E, -e, -K, -k, -Fy(a), and -Fy(b) sera, using methods recommended by Race and Sanger (1975). The erythrocyte enzyme polymorphisms, 6-phosphogluconate dehydrogenase, adenosine deaminase, first locus phosphoglucomutase, acid phosphatase, and adenylate kinase were analysed by techniques described by Giblett (1969), as well as esterase D (Hopkinson *et al.*, 1973) and glutamic-pyruvate transaminase (Chen *et al.*, 1972). Xg studies

were carried out on the brother and maternal grandparents of the proband, as well as on himself and his parents (Race and Sanger, 1975).

Results

Preliminary chromosome analysis of unbanded metaphases disclosed a karyotype of 46,XX,-C,+A. The apparent extra A group chromosome was a large metacentric, the size of a number 3, substituting for a C group chromosome. There was no identifiable Y chromosome. Giemsa banding of elongated early metaphase chromosomes from a synchronised cell culture showed that the 2 arms of the abnormal X were not identical. There was extra chromatin attached to the distal end of the short arm, with banding patterns consistent with, but not diagnostic of, a Y chromosome. There was no detectable loss of the pale distal p22 band of the translocation X (Fig. 3). Quinacrine mustard banding showed the typical brilliant distal fluorescence of the long arm of a Y chromosome at the tip of the translocated material. Centromeric banding confirmed the presence of darkly staining heterochromatin, normally present on the distal segment of the Y long arm. On reverse banding, the telomeric p22 positively staining band of the translocation X chromosome was consistently broader and more prominent than its normal homologue. This strongly suggests that the fusion point between the X short arm and the Y involves this band, but it has not

been possible to determine cytologically whether any portion of the affected chromosomes had been deleted (Fig. 4). In 11 suitably reverse banded metaphases photographed with colour film, the normal X showed a dull orange fluorescence associated with a late replicating X chromosome, as opposed to the translocation X which was brightly fluorescent.

Further identification of the late replicating, and hence inactivated, X chromosome was carried out on buccal smears, peripheral blood smears, and metaphases labelled with tritiated thymidine. Buccal epithelial cells displayed a fluorescent Y body in 83%, and an X chromatin (Barr) body in 37%, of 300 cells screened. Subsequent karyotyping did not reveal any fluorescent satellite or other variants capable of being interpreted as a Y body and the Barr body was of normal size in all cells. In none of the 48 cells in which both X and Y bodies were visualised by sequential staining were they in association with each other. In 17 of the 500 peripheral blood neutrophils screened, a normal sized drumstick was detected, and a Y body unassociated with the drumstick was seen in 10 of these (Fig. 5). Autoradiographic studies on 17 informative metaphases showed a late labelling C group chromosome, whereas the translocation chromosome was relatively unlabelled, indicating that the normal X chromosome was probably non-randomly late labelling (Fig. 6).

Chromosomal analysis of peripheral blood metaphases of both parents disclosed normal karyotypes

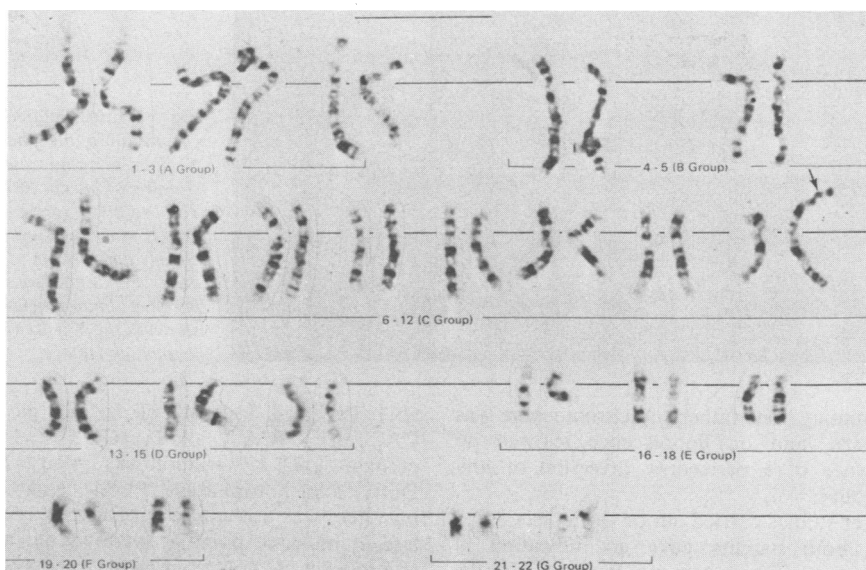


Fig. 3 Trypsin-Giemsa banded karyotype of an early metaphase, showing a translocation onto the distal portion of the short arm of one X chromosome (arrowed).

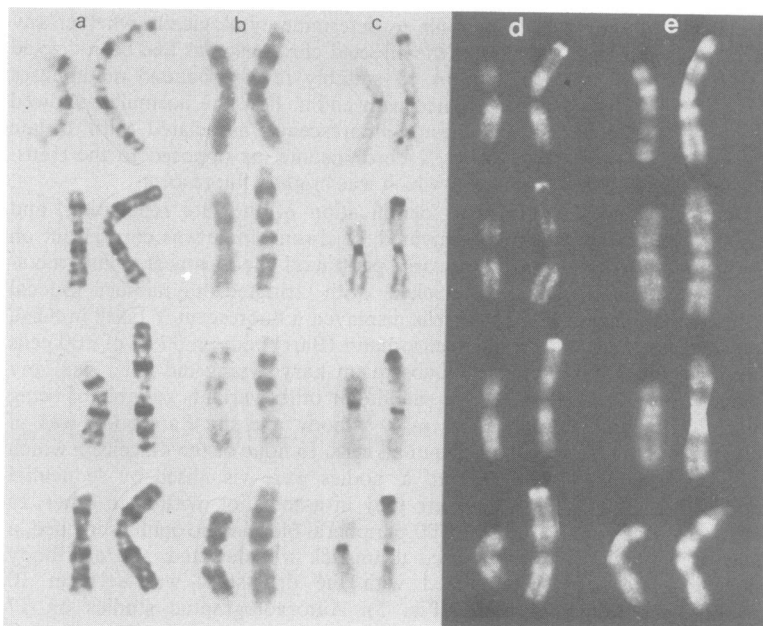


Fig. 4 Morphology of the normal X chromosome (left column) and abnormal $t(X;Y)$ chromosome (right column). (a) G-banding, (b) reverse A-O banding (printed in black and white from a colour transparency), (c) C-banding, (d) Q-M banding, (e) reverse A-O banding (photographed with black and white film).

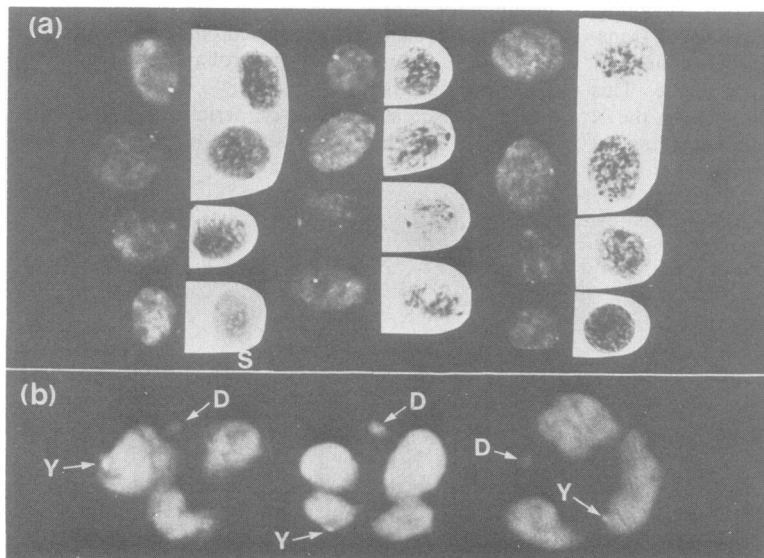


Fig. 5 Unassociated X and Y chromatin in interphase nuclei. (a) Sequential quinacrine and klinger staining of buccal epithelial nuclei. The brightly fluorescent Y body and darkly staining Barr body are clearly apparent in most of the cells. (b) Quinacrine staining of peripheral blood neutrophils showing the Y body (Y) and drumstick (D).

on Giemsa banding. The father's Y chromosome was of average size, and on fluorescence showed no obvious evidence of a pericentric inversion or any other abnormality.

Gene marker studies carried out on the index case, a brother, and both parents gave no indication of parental exclusion. There was no variation in the following systems: ABO and Rhesus, all individuals O R₁/r; G6PD, all B; 6PGD, all A; ADA, all 1; PGM₂,

all 1; PepA, all 1; PepD, all 1; EsD, all 1; AK, all 1; CA_I, all 1; CA_{II}, all 1; ICD, all 1; glutathione peroxidase, all 1. Variation was found in the MNSs, P, Duffy, acid phosphatase, PGM₁, and GPT systems, but there was nothing to suggest exclusion. Nevertheless, it must be pointed out that the father had the commonest phenotype in most of the systems and the probability of finding, at random among South African Caucasians, a man who would be compatible

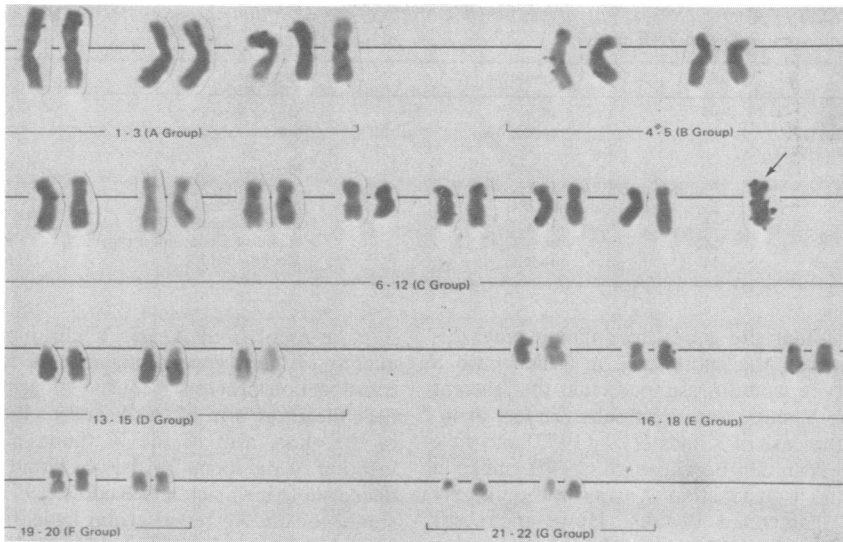


Fig. 6 Autoradiography showing the late labelling normal X chromosome (arrowed). The translocation X chromosome is placed with the A3 group.

with being the father of the index case, assuming the mother to be the mother, is as high as 0.25, or 1 in 4.

Studies of the Xg(a) antigen revealed that the mother, father, and brother of the proband were all Xg(a+); since the mother's mother was Xg(a+) and her father Xg(a-), she herself is an obligate Xg^a/Xg heterozygote. All these positive reactions showed strong agglutination. The proband himself was repeatedly found to be Xg(a-) when tested in this laboratory, but confirmatory testing of the whole family by Miss Phyllis Moores of the Natal Provincial Blood Transfusion Service, Durban, indicated that he was, in fact, very weakly Xg(a+), whereas the reactions of the rest of the family were the same as our findings.

None of the biochemical tests revealed any abnormality. There was no evidence of mucopolysacchariduria, and the glucose-6-phosphate dehydrogenase, phosphoglycerate kinase, and α -galactosidase levels were within normal limits.

Discussion

Translocations involving the Y chromosome appear to be extremely rare, though improved methods for detecting it may show that this is not actually the case. Until Zech (1969) discovered that the distal segment of the long arm of the human Y chromosome fluoresced brilliantly under ultraviolet light, and Arrighi and Hsu (1971) showed the constitutive heterochromatic nature of this segment, the only means of identifying

the Y chromosome positively was morphological. It is now accepted that this heterochromatic region is probably not phenotypically expressed, and it is conceivable that many hitherto unexplained cases of male differentiation in the presence of a female karyotype could be due to undetectable X-Y or Y-autosomal translocations, involving the genetically active non-fluorescent portion of the Y.

Khudr *et al.* (1973) have postulated 3 mechanisms which might give rise to an X-Y translocation. (1) A break near the centromere of the Y, with deletion of the centromere and short arm, could, during end-to-end meiotic pairing with the X chromosome, lead to fusion, particularly if there had been some deletion of the terminal euchromatin of Xp. (2) A postmeiotic break in an XXY zygote, and the shedding of the centric fragment of the Y, could have a similar result, though this seems unlikely since it would require 2 abnormal events, non-disjunction followed by translocation. Nevertheless, Van den Berghe *et al.* (1977) described just such a case. (3) Pericentric inversion of the Y could lead to fusion of the X and the inverted Y segment at meiosis. If the breakage is equidistant from the Y centromere, this would not be detected by present banding techniques. Khudr *et al.* (1973) and Van den Berghe *et al.* (1977) favour the third of these mechanisms, but the first explanation appears equally likely for the cases they and Borgaonkar *et al.* (1974) report, if the male determining genes are located on the short arm. Observations of Y chromosome abnormalities and their resultant phenotype by Jacobs

Table Correlation of phenotypic sex, karyotype, possible origin of translocation chromosome, and X inactivation pattern in the present and previously reported cases

Authors	Sex	Karyotype	Origin of X_t	X inactivation
Khudr <i>et al.</i> (1973)	F	46,XX _t	Meiotic,?inv(Y)	Non-random X _t
Borgaonkar <i>et al.</i> (1974)	F	46,XX _t	Meiotic,?inv(Y)	?
Van den Berghe <i>et al.</i> (1977)				
Case 1	F	46,XX _t	Meiotic,?inv(Y)	Random X and X _t
Case 4	F	46,XX _t	Meiotic,?inv(Y)	? Non-random X _t
Case 5	F	46,XX _t	Inherited (mat)	? Non-random X _t
Case 3	M	46,X _t Y	Inherited (mat)	—
Case 2	M	46,XX _t /47,XXY	Non-disjunction → post zygotic X _t	Random X and X _t
Present case	M	46,XX _t	Meiotic,?inv(Y)	Non-random X

(1969) suggest that the genes determining male differentiation are on the short arm, in which case a female phenotype would presuppose that the relevant segment of the Y short arm must either be lost or inactivated. In the case of Khudr *et al.* (1973) and case 4 described by Van den Berghe *et al.* (1977), unlike in our patient, the translocation X was non-randomly preferentially inactivated (Table). However, recent studies on H-Y antigen (Wachtel, 1977) indicate that the male determining genes could be located on the proximal portion of Yq as well as Yp. The morphological appearance of the translocated X chromosome in our patient is similar to that described by Khudr *et al.* (1973), and the first patient of Van den Berghe *et al.* (1977), and does not further elucidate the exact localisation of the gene or genes controlling male differentiation on the Y chromosome.

Regardless of whether the male determining genes are located on the proximal long arm or short arm of the Y chromosome, the presence of H-Y antigenic activity in XX males and XX true hermaphrodites with no detectable mosaicism (Wachtel *et al.*, 1976), and reports of aberrant segregation of the Xg blood group in normal and XX males (Ferguson-Smith, 1966; Sanger *et al.*, 1971), have provided supporting evidence for an X-Y genetic interchange at meiosis, resulting in the transfer of male determining genes from the Y to the X chromosome (Ferguson-Smith, 1966). Our male patient with a morphologically visible X-Y translocation lends further support to this hypothesis. Of course, the possibility exists that our patient had an undetected mosaicism with a 47,XXY cell line (cf. Case 2, Van den Berghe *et al.*, 1977) which is sufficient to confer a male phenotype, but examination of 278 peripheral blood metaphases did not reveal any such mosaicism.

Pearson and Bobrow (1970) showed conclusively that it is the short arm of the Y that associates with the X chromosome during first spermatogenic meiosis. In the morphologically proved cases (Khudr *et al.*, 1973; Borgaonkar *et al.*, 1974; Van den Berghe *et al.*, 1977), the present one, and 2 presumptive cases of X-Y translocation (Madan and Walker, 1974; Wachtel *et al.*, 1976), the mitotic association has been between the

short arms of both X and Y chromosomes. Consequently, if any genetic material is lost during the translocation process, it must be lost from the region near the short arm of the Y and/or the distal portion of the short arm of the X (band p22). The exact location of the locus for the Xg blood group remains uncertain (McKusick and Ruddle, 1977), but previous studies of the Xg blood group have indicated that its locus lies on the short arm of the X chromosome, and possibly very distally (Race and Sanger, 1975). In our proband and his family we find some evidence to confirm this. His father, heterozygous mother, and brother are Xg(a+), yet the proband has a negative to weakly positive reaction.

The mass of evidence on the Xg locus, which has accumulated since its discovery in 1962, indicates that when it is situated on a normal X chromosome it is not subject to inactivation, but that when it is carried on a deleted X it probably is (Race and Sanger, 1975). There appear to be no data on the activity of the locus on an abnormal, translocated X. In our case, the evidence suggests that the normal X chromosome is non-randomly inactivated and, since the other X carries the Y translocation, the normal X is probably maternally derived. As it is normal, and hence the Xg locus on it is presumably not inactivated, it would therefore be the mother's Xg^{a-} bearing chromosome. However, the paternal X chromosome, to which the Y is attached, would be expected to carry Xg^a, and yet the proband's red cells reacted only very weakly with one anti-Xg(a) serum and not at all with another. This would seem to indicate that the translocation itself involved either the partial deletion or the suppression of the activity of the Xg locus, which must consequently be situated either in, or closely adjacent to, the p22 band of the X chromosome.

The question of partial deletion of the Xg locus may be dismissed at once. It is inconceivable that breakage occurring through a locus could result not in the total suppression of the normal gene product, but in its partial expression, particularly when such expression happens to be immunologically detectable. An only slightly more acceptable possibility is that not one, but two, closely linked loci may be responsible for the

Xg blood group. This is a hypothesis that might perhaps be explored in the context of earlier reports of anomalous expression of Xg. Rather more attractive, perhaps, is the alternative hypothesis that the Y linked material, translocated to a situation adjacent to the Xg locus, may exert a suppressor effect upon it. We hesitate to advance any of these hypotheses with any assurance, and are content to claim merely that the site of the translocation does furnish new presumptive evidence of the possible position of the Xg locus on the X chromosome.

The mechanism determining which of the X chromosomes is inactivated in an unbalanced X autosome translocation is uncertain, but appears to conform to selection of the more viable genotype (Leisti *et al.*, 1974). Therman and Patau (1974), in an extensive review of X autosomal translocations, found that in nearly all cases of balanced X autosomal translocations the normal X is inactivated. However, in most unbalanced X autosomal translocations, the translocation X is inactivated completely if the translocated segment is attached to Xp, and limited to the X portion if the autosomal segment is attached to Xq. It is nevertheless well established that a structurally deleted X chromosome not involved in a translocation is invariably non-randomly inactivated (Brown and Chandra, 1973). The inactivation of X-Y translocation chromosomes has varied. In the case of Khudr *et al.* (1973), and 2 of the 3 46,XX_t cases quoted by Van den Berghe *et al.* (1977), the translocation X was non-randomly inactivated, while in the third, inactivation appeared to be random. The lack of association between X and Y bodies in buccal epithelial and peripheral blood neutrophil nuclei, BrdU reverse banding, and autoradiographic studies confirms the initial supposition, based on the male phenotype, that in the present patient the translocation chromosome represents the active X (Table).

Although banding patterns did not show any obvious deletion of any part of the X short arm, the Xg findings, the marked mental retardation, combined with some of the features found in Turner's syndrome, suggest some loss of X chromosomal material. Our patient was almost certainly nullisomic for the terminal portion of the short arm of his non-inactivated X chromosome. Linkage between the Xg locus and that for a form of mental retardation, with or without hydrocephalus, has been shown by Fried and Sanger (1973) probably to be close, though their findings were not conclusive. Our patient had no hydrocephalus, and his clinical features were not similar to those of the patients described by Edwards (1961) and Fried (1972). X-linked mental retardation may, however, present with a wide range of expression within families, and variability between families, suggesting that there may be a number of possible alleles

at the locus, or more than one locus on the X chromosome governing mental retardation (Fried, 1972). We would suggest that the form of retardation manifested by our patient could represent deletion of a locus near the Xg locus.

The somatic features of Turner's syndrome have been attributed to the loss of the short arm of an X chromosome (Jacobs, 1969). Some of these somatic features, such as short stature and skeletal deformities, were present in our patient. However, these features, together with mental retardation and abnormal dermatoglyphic patterns are non-specific and compatible with a variety of chromosome disorders. The dermatoglyphic patterns observed in this child are quite different from those described in Turner's syndrome and other sex chromosome abnormalities (Borgaonkar and Mules, 1970). The distal axial triradii with increased *atd* angles, bilateral single palmar creases, and very low ridge count are, in fact, more in keeping with an autosomal chromosome abnormality (Alter, 1966; Uchida, 1966).

In Turner's syndrome, radiological abnormalities in early childhood are minimal and non-specific. Retardation of skeletal maturation and slight generalised rarefaction of the bones may be the only abnormalities seen on x-ray, and these may be present from birth (Baker *et al.*, 1967; Caffey, 1967; Sutton, 1969). Cubitus valgus and widening of the proximal ends of the tibial shafts become more prominent as the child grows older. The coarse reticular pattern of the carpals, metacarpals, and phalanges is only apparent after 7 years of age (Bercu *et al.*, 1976). In this child, the marked retardation of skeletal age, generalised rarefaction of the skeleton, widened tibial shafts, and prominent medial tibial condyles were present. The diastasis of the proximal radioulnar joints could be an extreme variant of the cubitus valgus deformity seen in patients with Turner's syndrome. All these radiological abnormalities, however, are non-specific and occur in patients with other congenital abnormalities.

The p22 region of the X chromosome appears from this and previous studies to contain at least one, and possibly more, loci essential to the normal functioning of the individual. The differences between our patient and those previously described with X-Y translocations indicate that, even in the absence of disparities of chromosome morphology among them, cases with this kind of translocation can provide new genetic information. Such cases are, however, rare, and the information they yield is likely to be more frequently applicable to the investigation of the more common problems of XX males and true hermaphrodites with an XX karyotype.

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Requests for reprints to Dr R. Bernstein, Department of Human Genetics, South African Institute for Medical Research, PO Box 1038, Johannesburg 2000, South Africa.