Female phenotype and multiple abnormalities in sibs with a Y chromosome and partial X chromosome duplication: H–Y antigen and Xg blood group findings

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SUMMARY A mentally retarded female child with multiple congenital abnormalities had an abnormal X chromosome and a Y chromosome; the karyotype was interpreted as 46,dup(X)(p21→pter)Y. Prenatal chromosome studies in a later pregnancy indicated the same chromosomal abnormality in the fetus. The fetus and proband had normal female genitalia and ovarian tissue. H–Y antigen was virtually absent in both sibs, a finding consistent with the view that testis-determining genes of the Y chromosome may be suppressed by regulatory elements of the X.

The abnormal X chromosome was present in the mother, the maternal grandmother, and a female sib: all were phenotypically normal and showed the karyotype 46,Xdup(X)(p21→pter) with non-random inactivation of the abnormal X. Anomalous segregation of the Xgα allele suggests that the Xg locus was involved in the inactivation process or that crossing-over at meiosis occurred.

In 1902, the biologist McClung described an 'accessory chromosome' in half the spermatozoa of certain insects and suggested that this chromosome influenced the sex of the developing larva. His observations led to similar discoveries in other species, and eventually to the well established dictum that, among mammals, the Y chromosome is responsible for testicular differentiation of the primordial gonad, and that in the absence of the Y, the gonad becomes an ovary.

Evidence for a testis-determining locus on the Y chromosome comes from the serological detection of H–Y antigen, a cell surface component determined by phylogenetically conserved genes normally situated in the pericentric region of the human Y. Not only is H–Y antigen found in the heterogametic sex (XY) of all vertebrate species examined so far, but its presence is associated with differentiation of the mammalian testis or ovotestis regardless of apparent karyotype (reviewed in Wachtel and Ohno). In vitro, H–Y antigen specifically induces testicular architecture in XX gonads of the fetal calf and newborn rat, whereas H–Y antibody specifically blocks testicular reaggregation in dispersed XY Sertoli cells of the newborn mouse and rat. Thus, H–Y serology affords a useful measure of presence and activity of testis-determining genes in mammals generally and in man in particular.

Many examples of phenotypic sex at variance with chromosomal or gonadal sex or both point to the occurrence of other genes, not on the Y chromosome, that may exert a regulatory effect on testis-determining H–Y genes. For example, the XY wood-lemming condition associated with the H–Y negative (H–Y−) phenotype is inherited as an X linked trait; there is evidence that a similar condition occurs in man (reviewed in Wachtel and Ohno). Here we report the investigation of two related H–Y negative 46,XY females both with duplication of a portion of the X short arm, thereby
providing further evidence for the existence of regulatory elements of the X and further elucidation of the effects of disomy of the X short arm.\textsuperscript{14}

**Case report**

A 3-year-old girl (fig 1, III.2) was referred for investigation of congenital abnormalities associated with profound mental retardation. The second of four children, she was born at term when her mother was 23 and her father 25 years old. Pregnancy and delivery were normal and she weighed 1.76 kg. A ventricular septal defect and cleft palate were noted. The mother's first pregnancy (III.1) was complicated by toxaemia and oligohydramnios resulting in the birth of a 2.27 kg term distressed female with 'malrotation of the gut' and other abnormalities, the details of which are not available. The infant died 24 hours after birth but no necropsy was performed. The third pregnancy was complicated by tonsillitis and recurrent kidney infection but resulted in the birth of a term phenotypically normal girl weighing 2.44 kg (III.3). A nephrectomy was later performed on the mother for pyelonephritis of the left kidney. A fourth pregnancy (III.4) was monitored by amniocentesis and was terminated at 20 weeks' gestation, after finding the same karyotypic abnormality in cultured amniotic cells as in the proband.

The proband's mother (II.2), who was phenotypically normal, had been adopted as a young girl and very little is known of her natural family. Her eldest sib was a male who died at 3 years of age of undetermined cause (II.1) and her mother's third pregnancy resulted in a premature female stillbirth (III.3). The proband's father (II.4) and his younger brother (II.5) were subject to psychotic episodes but other relatives were phenotypically normal.

When assessed at 3 years of age, the proband's younger sister (III.3) was phenotypically normal, but her speech was limited. Her other milestones had been normal. There were no physical abnormalities apart from a convergent squint which was also present in her father.

As an infant, the proband failed to thrive and was admitted to hospital on several occasions. At 11 months of age she had a transient purpuric episode of unknown aetiology. Head circumference of 42 cm, height of 67 cm, and weight of 5.4 kg were all below the 3rd centile. Chest x-ray showed right ventricular enlargement with a probable left to right intra-cardiac shunt. Myoclonic jerks were observed.

At 3 years of age she was admitted for investigation of jaundice of two months' duration. Intravenous cholangiogram showed multiple stones in the gall bladder and two stones in the common bile duct. Liver function tests were abnormal and there was a marked unexplained hypercholesterolaemia. Neither parent showed evidence of disturbed

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**FIG 1** Family pedigree showing sex chromosomes and segregation of the Xp\textsuperscript{+} abnormality and and Xg blood group.

- \(\text{\textbullet\ }\text{Normal karyotype}\)
- \(\text{\textbullet\ }\text{Proband}\)
- \(\text{\textbullet\ }\text{Spontaneous abortion}\)
- \(\text{\textbullet\ }\text{Dead - not investigated}\)
- \(\text{\textbullet\ }\text{Female stillbirth or neonatal death}\)
- \(\text{\textbullet\ }\text{Karyotype 46, Xp+}\)
- \(\text{\textbullet\ }\text{Karyotype 46, Xp+Y}\)
- \(\text{\textbullet\ }\text{Karyotype 46, Xp+}\)

III.4 Electively aborted after prenatal diagnosis
lipid metabolism. Cholesterol and bilirubin levels subsided spontaneously.

On examination, she was hypotonic and unable to sit unaided, had no head control, no comprehension or intelligible speech, and was very irritable. She responded to auditory and visual stimuli. Head circumference was 47 cm, height 83 cm, and weight 10 kg (all well below the 3rd centile). The skin was transparent, the face and skull were asymmetrical, the forehead was prominent and bossed, and the occiput was small and flattened (fig 2). There was mild hypertelorism, the eyes were deep set and slanted downwards, and she had a bilateral convergent squint. The nose was short with a depressed nasal bridge, the lips were narrow, and the mouth ‘carp-shaped’. There was a cleft of the hard and soft palates, the teeth were malaligned, and the dentition was abnormal. The jaw was prognathic and the ears were fairly large and low set. The chest was asymmetrical, with a convexity of the anterior right chest wall, and the nipples were low set and widely spaced. The liver was enlarged 1 cm below the costal margin, but the spleen was not palpable. The external genitalia were those of a normal prepubertal female. No gonads were palpable in the inguinal region or labiae and there was no clitoral hypertrophy. The fingers and toes were long and tapering, apart from the fifth fingers which were shortened and showed clinodactyly; transverse palmar creases of both hands were normal. The feet were maintained in a hyperextended position and the heels were prominent. The third and fourth toes were overlapped by the second and fifth toes, respectively. At 5 years of age she was able to sit unassisted, but had otherwise made no further progress. Her head circumference was 48.5 cm. At 5 years 3 months she developed acute gastroenteritis and pneumonia which caused her death.

Necropsy examination showed a clefted hard and soft palate, a healed ventricular septal defect, acute suppurative bronchopneumonia, marked fatty changes of the liver, and a fibrotic gall bladder with several cholesterol stones. The brain weighed 1080 g. There was asymmetrical bulging of the left parieto-occipital region and the skull was deformed in the same contour. The posterior left hemisphere was larger than the right and the lateral ventricles were moderately enlarged. Areas of increased gliosis consistent with changes secondary to epilepsy or anoxia were noted. Internal examination of the pelvic area showed a normal vagina and cervix and hypoplastic uterus and fallopian tubes (fig 3a). Histological examination showed tubular structures adjacent to the fallopian tubes resembling immature epididymis. No gonads were identified macroscopically, but a small area of ovarian stroma with scant early primordial follicle formation, many

![Image of the proband at 5 years of age.](image)

![Image of necropsy findings.](image)

**Fig 2** Appearance of proband at 5 years of age.

**Fig 3** Necropsy findings on the proband. (a) Macroscopic appearance of the female internal genitalia; (b) histological appearance of the gonad (original magnification, × 100); (c) histological appearance of the gonad (original magnification, × 400) showing ovarian stroma and scattered degenerating primordial follicles.
showing degenerative changes, was found microscopically on sectioning the uterine adnexae (fig 3b, c). No testicular tissue was detected in any of the sections from the entire area.

The mother embarked on a fourth pregnancy and amniocentesis at 16 weeks showed an α-fetoprotein of <16 μg/ml but the same karyotypic abnormality as in the proband. The pregnancy was terminated at 20 weeks’ gestation and the fetus was unequivocally female. Hypertelorism, micrognathia, and very low set, large ears were noted and a large midline posterior cleft palate was present. There was a single palmar crease on the left hand, the heels were prominent and the fifth toes overlapped the fourth toes, bilaterally. Evagination of the left diaphragm resulted in herniation of the spleen and bowel into the left thoracic cavity. The left lung was hypoplastic and the heart showed a ventricular septal defect. Examination of the genitalia (fig 4a) showed a vagina, cervix, uterus, and fallopian tubes. Normal fetal ovarian tissue was present with ovarian stroma and numerous early primordial follicles (fig 4b, c). The entire gonads were sectioned and examination of all the sections showed no evidence of any testicular tissue.

**Materials and methods**

**CYTOGENETIC STUDIES**

Synchronised peripheral blood cultures were established by modification of a technique described by Yunis.\(^1^6\) Amniotic cell metaphases were obtained by a standard ‘closed system’ culture technique. Fibroblast cultures were established from both proband and aborted fetus for chromosome analysis and serological studies.

Chromosome banding procedures were performed by minor modification of the following previously described banding procedures: (a) trypsin Giemsa banding\(^1^6\); (b) quinacrine-mustard banding\(^1^7\); (c) centromeric banding\(^1^8\); (d) reverse banding after 5-BrdU incorporation during the last 6 hours of culture,\(^1^9\) using photographic techniques described by Verma and Lubs\(^1^0\); and (e) videodensitometry was done on selected metaphases by the method of Dewald et al.\(^2^1\)

Autoradiographic studies were carried out by incorporation of tritiated thymidine in a final concentration of 1·0 μC/ml of culture 6 hours before culture termination and exposure of labelled slides in K-2 emulsion for 17 days. Buccal smears were stained with Klinger-thionine stain for X chromatin screening and with quinacrine mustard for detection of a fluorescent Y body.

**SEROLOGICAL STUDIES**

H-Y antibodies were generated in highly inbred C57BL/6 (B6) female mice by weekly injections of spleen cells from B6 males. The females were bled and the sera separated and stored frozen until use. The H-Y phenotype of human cells was determined by using the protein-A assay of Koo and Goldberg.\(^2^2\) The technique is founded on the observation that the protein-A component of the cell wall of Staphylococcus aureus binds immunoglobulins.\(^2^3\) This reaction allows labelling of target cells with a visual marker such as sheep red blood cells (SRBC).

For the present study, SRBC were coated with protein-A according to the method of Goding.\(^2^4\) Target cells were exposed to H-Y antibodies (comprising both IgG and IgM molecules) and then exposed to PA-SRBC. H-Y+ target cells, which had already bound H-Y antibodies, now bound the PA-SRBC thus forming ‘rosettes’.

In the ‘direct’ test, PA-SRBC were reacted with fibroblasts and blood leucocytes from the proband. H-Y phenotype was determined by comparing the number of rosettes formed by cells of the proband with the number formed by cells of a normal male (H-Y+) and normal female (H-Y−).

In the ‘indirect’ test, H-Y antisera were divided into equal portions and these were absorbed with
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fibroblasts of the proband and fetus and with corresponding cells of normal male and female controls, respectively. Absorbing cells were discarded and the sera were reacted with mouse sperm. The sperm were exposed to PA-SRBC as above. In this test, positive absorption reduced the titre of antibodies thereby limiting the reactivity of H–Y antiserum for H–Y+ target cells (sperm); this signified that the absorbing cells contained H–Y antigen on their surfaces.

Gene marker studies
These were carried out on red cells and serum using standard techniques: blood groups according to Race and Sanger,25 red cell enzymes according to Harris and Hopkinson,26 and haptoglobins and transferrins according to Giblett.27

Results
Cytogenetic studies
Giemsa banded metaphases from the proband showed 46 chromosomes with a single structurally abnormal X chromosome and a Y chromosome. Two extra bands, morphologically resembling the Xp21 and Xp22 bands, were attached to the distal portion of Xp and the karyotype was interpreted as 46,dup(X)(p21→pter)Y (fig 5). Quinacrine banding confirmed the presence of a fluorescent Y chromosome. There was no detectable evidence of a pericentric inversion of the Y or Y short arm deletion (fig 6a, b i). Centromeric banding again confirmed the presence of a Y chromosome, but centromeric, quinacrine, and reverse banding did not further elucidate the origin of the extra bands on Xp. There was no evidence of mosaicism in 115 peripheral blood and skin fibroblast metaphases analysed.

FIG 5  G banded karyotype of the proband showing the abnormal Xp+ and normal Y chromosome.

FIG 6  (a) Q banded metaphase of the proband showing the Xp+ and Y chromosomes; (b) the Xp+ and Y from two cells of (i) the proband, and (ii) the fetus, and (iii) the normal XY of their father.
Screening of buccal epithelial cells showed a large Y fluorescent body in the majority of interphase nuclei and no X chromatin body was detected.

Amniotic, fetal blood, and skin metaphases showed the same karyotypic abnormality as in the proband (fig 6b ii).

The abnormal X was inherited from the proband's mother and maternal grandmother. They and the proband's younger sister were 46,Xdup(X) (p21→pter). There was no evidence to suggest an autosomal origin for the extra bands on Xp (fig 7).

Uniformly large X chromatin bodies in buccal epithelial nuclei (fig 8a), late labelling of the anomalous metacentric C chromosome after tritiated thymidine incorporation during late synthesis (fig 8b), and dull acridine orange fluorescence of the abnormal X chromosome after 5-BrdU incorporation during late synthesis (fig 8c), indicated non-random inactivation of the abnormal X chromosome in the proband's grandmother, mother, and sister. Giemsa and quinacrine banded metaphases of the proband's father, paternal uncle, and paternal grandparents showed a normal karyotype. The size and banding characteristics of the Y chromosome were the same in the proband and the male paternal family members. There was no morphologically detectable evidence of any structural abnormality of the Y chromosome (fig 6b iii).

**Videodensitometric studies (fig 9)**

Four abnormal X chromosomes ranged in length from 7·67 µ to 9·47 µ and the centromere index from 50·7 to 51·7. The mean and SD for the length of normal X chromosomes of similar contraction is 5·9 ± 0·6 µ and for the centromere index is 62·3 ± 2·97. Thus, the abnormal X chromosome was somewhat longer and more metacentric than normal.

**FIG 8** Non-random inactivation of the Xp+ chromosome in family members with a 46,XXp+ abnormality.

(a) Uniformly large buccal X chromatin bodies; 
(b) late-labelling of the anomalous metacentric X chromosome after tritiated thymidine incorporation; 
(c) dull reverse banded A-O fluorescence of the Xp+ chromosome after 5-BrdU incorporation.

**FIG 7** G banded karyotype of the proband's mother showing the Xp+ chromosome and normal X chromosome.
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with most of the Xp arm. No part of the density profile of the abnormal X resembled any part of the Y chromosome from the same metaphase.

**SEROLOGICAL STUDIES**

Data from our direct PA-SRBC assays are summarised in table 1. In three tests, $10 \times 10^6$ blood leucocytes from normal XY males produced more rosettes than the same number of blood leucocytes from normal XX females or from the XY female proband ($p=0.05$), and in a similar series of six tests, $1 \times 10^6$ fibroblasts from normal XY males produced more rosettes than the same number of fibroblasts from the XY female proband ($p=0.008$).

In a series of four indirect tests (shown in table 2), significantly fewer (sperm) rosettes were formed using serum absorbed with $1 \times 10^6$ fibroblasts from normal XY males than were formed using unabsorbed H-Y antiserum or H-Y antiserum absorbed with $1 \times 10^6$ fibroblasts from normal XX females ($p=0.014$).

In contrast, the percentage of rosettes formed after absorption of H-Y antiserum with cells from the XY female proband did not differ significantly from the percentage formed after absorption with the same number of female or male cells ($p=0.343$ and $p=0.171$, respectively). Indirect PA-SRBC tests using fibroblasts from the XY female fetus, and from normal male and female controls, are shown in

**TABLE 1** Direct PA-SRBC tests showing reaction of mouse H-Y antiserum with cells from normal XY males, normal XX females, and XY female proband

<table>
<thead>
<tr>
<th>Blood leucocytes</th>
<th>Fibroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>XY M</td>
<td>45%</td>
</tr>
<tr>
<td>XX F</td>
<td>29</td>
</tr>
<tr>
<td>XY F</td>
<td>24</td>
</tr>
</tbody>
</table>

*Average number of rosettes per 100 target cells. Each number represents an average of scores from 3 separate tests (leucocytes) or from 6 separate tests (fibroblasts) using different batches of H-Y antiserum. The averages shown were derived from the formula: number of rosettes per number of rosettes + free target cells (leucocytes or fibroblasts). Any target cell to which $\geq 3$ SRBC were adsorbed was counted as a 'rosette'. Suspicions were scored as coded samples.

**TABLE 2** Indirect PA-SRBC tests showing reaction of mouse H-Y antiserum with mouse sperm after absorption with cultured skin fibroblasts from normal males and females and from the XY female proband

<table>
<thead>
<tr>
<th>Unabs</th>
<th>Abs F</th>
<th>Abs M</th>
<th>Abs XY F</th>
</tr>
</thead>
<tbody>
<tr>
<td>34*</td>
<td>35</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

Unabs denotes unabsorbed antiserum: Abs denotes absorption with cells of the indicated sex. Each number is an average of readings from 4 separate tests using different batches of antiserum.

*Average number of rosettes per 100 sperm cells. Any sperm cell to which $\geq 3$ SRBC were adsorbed was counted as a 'rosette'. Suspicions were scored as coded samples.

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**FIG 9** Videodensitometric analyses of 4 different abnormal X chromosomes and two Y chromosomes.

The density profile beneath each chromosome is determined by computer processing of a digitised video image of the chromosome and then plotted by a computer-controlled plotting device (Calcomp). Vertical lines subdividing the density profiles are the computer-determined edges of each band. The bands have been numbered, beginning with the p arm telomere (Tp) and ending with the q arm telomere (Tq). The computer-determined centromere position is indicated by the dashed line. The computer-determined total lengths and arm lengths, expressed in microns ($\mu$), are shown below the density profiles.

normal. The density profile and band pattern of each q arm was normal. However, in each case the density profile of p arm bands 3 and 4 were similar in width and staining intensity to one another and so were 4 and 6. This may suggest a direct duplication...
TABLE 3  Indirect PA-SRBC tests showing reaction of mouse H-Y antiserum with mouse sperm after absorption with cultured skin fibroblasts from normal males and females and from XY female fetus

<table>
<thead>
<tr>
<th></th>
<th>Abs F</th>
<th>Abs M</th>
<th>Abs XY F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unabs</td>
<td>54</td>
<td>41</td>
<td>61</td>
</tr>
</tbody>
</table>

Numbers represent readings from single test. Suspensions were scored as coded samples.

*Average number of ‘rosettes’ per 100 sperm cells.

The absorption of H-Y antiserum with $1 \times 10^6$ fibroblasts of the fetus did not reduce the percentage of rosette formation in comparison with the percentage formed after absorption with the same number of fibroblasts from normal female controls.

The foregoing data indicate, generally, the absence of H-Y in blood and cultured skin fibroblasts of the XY female proband and skin fibroblasts of the XY female fetus.

In as much as absorption may be a more sensitive indicator of antigenicity in serological systems, however, we are alerted to the possibility of expression of some H-Y antigen in the tissues of both proband and fetus. Thus, the data presented in table 2 may indicate ‘leakage’ of some H-Y genes in a system of multiple H-Y genes, the majority of which are suppressed. Function of a subcritical portion of H-Y genes is perfectly consistent with normal ovarian differentiation: evidently in polled goats and in man H-Y genes may be transmitted by both parents, thereby generating a recessive mode of male sex determination.

G E N E  M A R K E R  S T U D I E S

There was no variation in the following systems (all subjects possessing the common alleles): Kell, Kidd, G6PD, ADA, peptidase A, B, C, and D, EsD, CA1, CA11, PGM2, and transferrin. Variation was encountered in a number of systems but no anomalous segregation was evident in them: ABO, Rhesus, MNSs, P, Duffy, 6PGD, acid phosphatase, adenylyl kinase, PGM1, GPT, GLOI, and haptoglobin. The results of Xg blood group typing are shown in table 4.

<table>
<thead>
<tr>
<th>Family member</th>
<th>Xg a</th>
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<tbody>
<tr>
<td>I.2</td>
<td>+</td>
</tr>
<tr>
<td>I.3</td>
<td>+</td>
</tr>
<tr>
<td>I.4</td>
<td>+</td>
</tr>
<tr>
<td>II.2</td>
<td>+</td>
</tr>
<tr>
<td>II.4</td>
<td>-</td>
</tr>
<tr>
<td>II.5</td>
<td>-</td>
</tr>
<tr>
<td>III.2</td>
<td>+</td>
</tr>
<tr>
<td>III.3</td>
<td>-</td>
</tr>
</tbody>
</table>

Discussion

The most striking features in these two cases of probable 46, dup(X)(p21→pter)Y were (1) a female phenotypic and gonadal sex in the presence of a morphologically normal Y chromosome, and (2) multiple somatic developmental abnormalities associated with a single active abnormal X chromosome. Absence of H-Y antigen in the proband and fetus could explain the absence of testicular differentiation and the resultant female phenotype. This is borne out in vitro by the observation that dispersed XY Sertoli cells of the neonatal testis reaggregate to form ovarian follicles in the presence of H-Y antibody.

It is not clear how H-Y genes are suppressed in XY female wood lemmings,29 46,XY human females with pure gonadal dysgenesis,13 and the 46,XY females of the present family. A regulatory gene on the X chromosome has been postulated22 33 and presumably mutation of this gene could cause suppression of the testis-determining segment of the Y chromosome. In the absence of H-Y antigen, cells of the fetal gonad would organise an ovary; in these absence of two X chromosomes (which are required for survival of the human oocyte) the ovary would degenerate, to be represented later by an undifferentiated gonad containing ovarian stroma but lacking follicles.34

The extra bands on the abnormal X chromosome resembled normal distal p21 and p22 bands on light microscopy, and videodensitometric analysis favours the view that these extra bands represent a duplication, rather than a translocation of an autosomal segment to Xp. The slight possibility of an insertional autosomal translocation cannot, however, be excluded by techniques available at present. Those females who had two X chromosomes were phenotypically normal, presumably through preferential inactivation of the duplicated X.

If the abnormal bands in the present study do represent a duplicated portion of Xp, then suppression of testis-determining H-Y genes could be explained as a position effect, that is, interference with normal regulatory (or structural) function by insertion of adjacent material.

If, for example, the putative regulatory element acted under normal circumstances as an inhibitor of (excess) H-Y synthesis, duplication might reduce synthesis of H-Y below a certain critical threshold and the result would be failure of testicular differentiation. Herbst et al35 discovered two morphological types of X chromosome in the wood lemming, one of which is present in XY females.

The previously reported cases of 46,XY females...
with multiple congenital abnormalities\textsuperscript{36} (RH Lindenbaum, 1979, personal communication) all had gonads with testicular histology. These cases differ from ours in that testicular differentiation had occurred with failure of male differentiation after testicular dysgenesis, perhaps because of a receptor failure\textsuperscript{39} which could have been part of the associated generalised dysmorphogenesis.

The cause of the proband’s profound mental retardation and the multiple abnormalities present in both proband and fetus is not clear. These defects could be the result of disomy of a portion of the X short arm as a result of the duplication of bands p21 and p22. Theran and Patua\textsuperscript{14} have postulated the existence of an X inactivation centre on the proximal long arm, which must be intact for inactivation to occur. They maintain that an isochromosome of the X short arm is never seen in liveborn infants because such an abnormality would have no inactivation centre and hence would lead to disomy of the short arm and inviability. Another child with a complex (X;15) translocation investigated by us\textsuperscript{37} showed incomplete inactivation of the X short arm in at least 50% of her cells and many of the abnormalities observed were found in the present case. These included the peculiar postural hip flexion (fig 2), cleft palate, long tapering fingers, large low set ears, and profound mental retardation. These features are, however, non-specific, and the 46,XY females with MCA quoted above also had features in common with the proband and fetus. Silengo’s case\textsuperscript{38} had an asymmetrical skull, ‘carp-shaped’ mouth, partial cleft palate, depressed nasal bridge, and downward slanting eyes, all features shared by our patient. Lindenbaum’s patients (1979, personal communication) had a cleft palate, low set ears, microcephaly, and a VSD in one case, in common with our patient. However, the postaxial polydactyly noted in his three patients was absent in the proband and fetus.

Available evidence suggests that the Xg blood group locus is situated on the short arm of the X chromosome\textsuperscript{36,38} and is not normally subject to inactivation.\textsuperscript{39} It would appear from the present study that the Xg\textsuperscript{a} allele which is situated on the abnormal non-randomly inactivated X is, in fact, inactivated. The proband (III.2) is Xg(a+), while her sister (III.3), in spite of the fact that she possesses the same abnormal X chromosome and hence the Xg\textsuperscript{a} allele, is Xg(a−). The possibility, however, of cross-over between the abnormal X and its normal homologue in the mother (II.2) at meiosis, cannot be discounted.

Unfortunately the father of the proband’s mother (I.1) is dead, so it is not possible to determine whether she (II.2) is heterozygous at the Xg locus. There is nothing in the gene marker studies to suggest that the stated father is not the actual father.

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