Case reports

Journal of Medical Genetics, 1982, 19, 222–236

Inherited partial X chromosome duplication in a mentally retarded male

SUMMARY A mentally retarded male patient with a structurally abnormal X chromosome is reported (karyotype 46,dir dup(X)(p11.2→p21.2)Y). In the normal mother a similar X chromosome duplication was found, which was preferentially inactivated. Xg blood groups were studied in the family. The findings indicated that recombination took place at maternal meiosis, as both karyotypically normal sons and the proband were Xg(a−), the mother being Xg(a+). Functional X chromosome disomy may explain clinical abnormalities in reported patients with X duplication and a normal Y chromosome.

A number of structural X chromosome aberrations have been reported, only a few of which represent structural X chromosome abnormalities in a male karyotype. Recently, partial duplications of the X chromosome and male karyotype associated with developmental abnormalities have been reported. We report here a mentally retarded male with duplication of short arm material of the X chromosome (karyotype 46,dir dup(X)(p11.2→p21.2)Y) inherited from the mother.

Case report

The proband was born in 1951. He was the third in a sibship of four. The mother had two further miscarriages. The mother's age at birth was 33 and the father's 35. Pregnancy was normal with delivery at home. Birthweight was 3000 g and length 49 cm. At birth severe asphyxia was present for several minutes. A small umbilical hernia was present.

Development was retarded. IQ at 13 years was 45 (Binet-Simon). He was operated on for bilateral talipes equinovarus at the age of 10, at which time he was admitted to an institution for the mentally retarded. He was then reported to be of very short stature (13 cm below average) and obese; head circumference was 54 cm. Physical examination at the age of 26 (figs 1, 2) showed a small fat male with a large head, height 141 cm, weight 66 kg, head circumference 60 cm. The facial features were coarse and the ears were rather small with attached lobes. Hearing and sight were normal. The fingers and toes were short and plump with tapering finger ends and some retroflexion of the distal phalanges. Severe thoracic kyphosis was present, as well as generalised hypotonia. The external genitalia were normal. EEG was moderately abnormal and x-ray of the skull was normal. He died at the age of 27 from pneumonia and cardiac failure, secondary to chronic respiratory failure. Necropsy showed an enlarged and dilated heart with right ventricular...
hypertrophy and consolidation of the lungs. Liver, spleen, kidneys, and adrenals were normal on macroscopic examination, as were the large vessels, intestinal tract, gallbladder, pancreas, and testes. The brain weighed 1460 g. Symmetrical hemispheres were seen and no dilation of the ventricular system was present. Slight atrophy was noted.

**CYTOGENETIC FINDINGS**

Chromosome analysis was carried out after QFQ and RBA banding of chromosomes from peripheral blood cultures.

The proband's karyotype showed 46 chromosomes with a normal Y and an abnormal X chromosome. The abnormal X had extra material on the short arm which was interpreted as a direct duplication of bands p11.2→p21.2.

One of the X chromosomes in the mother was similar to that seen in the proband. BrdU incorporation studies showed preferential inactivation of the abnormal X in 25 metaphases examined. In the proband, BrdU incorporation studies did not suggest inactivated parts of short arm material on the X chromosome. Partial karyotypes are shown in fig 3. The father, two brothers, and one sister had normal karyotypes.

**TABLE Blood group studies**

<table>
<thead>
<tr>
<th>Proband, born in 1951</th>
<th>Blood groups</th>
<th>Xg (a)</th>
<th>ABO</th>
<th>MN</th>
<th>Rh</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>46, dir dup(X) (p11.2→p21.2)Y</td>
<td>–</td>
<td>A₂</td>
<td>N</td>
<td>R₃r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Mother, born in 1918</td>
<td>–</td>
<td>A₁</td>
<td>N</td>
<td>R₂r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>46,X, dir dup(X) (p11.2→p21.2)</td>
<td>+</td>
<td>A₂</td>
<td>N</td>
<td>R₁r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Father, born in 1916</td>
<td>+</td>
<td>A₁</td>
<td>N</td>
<td>r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sister, born in 1947</td>
<td>+</td>
<td>A₂</td>
<td>N</td>
<td>R₂r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>46,XX</td>
<td>–</td>
<td>A₁</td>
<td>N</td>
<td>r</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Brother, born in 1949</td>
<td>–</td>
<td>A₂</td>
<td>N</td>
<td>R₁R₂</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

**BLOOD GROUP FINDINGS**

Blood group studies including Xg blood grouping are shown in the table. Segregation of ABO, MN, Rh, and K showed no inconsistencies. The proband had inherited the mother's normal X and was Xga(–), so the Xgα allele was thought to be carried on the mother's normal X chromosome. Subsequent findings in the two karyotypically normal brothers showed them also to be Xgα(–). As the Xg locus escapes inactivation, the findings may suggest that the Xgα allele was carried on the mother's abnormal X with recombination in the proband, or, alternatively, the Xgα allele was on the normal X with recombination in the two normal brothers.

**Discussion**

On the basis of the Q and R banding pattern we interpreted the abnormal X chromosome as a direct duplication of bands p11.2→p21.2, although a small insertional X;autosome translocation cannot be ruled out.

X: X translocations generally show late replication, whereas X;autosome translocations may show a variable inactivation pattern between persons and between cells. The patient's mother showed preferential inactivation of the abnormal X, which is as expected of a dup(X). The phenotype of the mother was reportedly normal and apparently her fertility was not significantly impaired.

Functional disomy of active X chromosome material may be responsible for mental and physical retardation and congenital malformations. The case reported by Steinbach et al. had a partial duplication of long arm material Xq13→Xq22, and the clinical features included hypotonia, growth retardation, and minor congenital malformations, including hypoplastic genitalia.

A female phenotype with multiple malformations
associated with a male karyotype including an abnormal X chromosome was reported by Bernstein et al. The abnormal X was interpreted as a duplication of p21→pter. In addition to sex reversal, H-Y antigen was found to be virtually absent. This finding was interpreted as interference with a putative regulatory element on the X chromosome.

The recent tentative localisation of the H-Y antigen suppressor gene distal to Xp22 would perhaps explain why the sexual development in Bernstein's patient with a distal duplication was severely affected, while our patient, with a more proximal duplication, had a male phenotype; however, unfortunately, H-Y antigen studies were not carried out in our patient.

Anomalous segregation of the Xg* allele in Bernstein's patient might suggest that the Xg locus was involved in the inactivation process, but recombination at meiosis was also a possibility. Since both our proband and his brothers were Xg(a−) and the mother was Xg(a+), the findings in our patient do not seem to help in elucidating this problem. Furthermore, there was no evidence from BrdU incorporation for inactivation of short arm material on the X chromosome in the proband.

We thank Dr Ruth Sanger and the staff of the MRC Blood Group Unit, London, for performing the Xg blood group studies, and Mrs Birthe Jespersen for expert technical assistance.

KAREN BRØNDUM NIELSEN* AND FINN LANGKJÆR†
*The John F Kennedy Institute, DK 2600 Glostrup; and †Andersvange, Institution for the Mentally Retarded, DK 4200 Slagelse, Denmark

References

A complex chromosome rearrangement resulting in trisomy 15q22→qter

SUMMARY A black infant with malformations was found to have trisomy 15q22→qter. The mother had a complex chromosomal rearrangement involving three chromosomes (5, 13, and 15). A comparison with previously published cases of trisomy for distal 15q suggests a pattern of clinical findings including retardation in growth and development, microcephaly, asymmetrical faces, prominent occiput, antimongoloid slant of the palpebral fissures, micrognathia, prominent nose, and congenital heart disease.

Partial trisomy for the distal third to half of the long arm of chromosome 15 has been observed rarely. In the four previously reported families,1–4 the affected children were the result of maternal malsegregation of balanced translocations involving two chromosomes. We report an affected child resulting from the maternal malsegregation of a complex chromosome rearrangement involving three chromosomes, 5, 13, and 15.

Case report

The proband, a newborn black male, was the 1820 g product of an uncomplicated term pregnancy. He was born to a 28-year-old gravida 3, para 0, abortis 2 mother. There was no history of smoking nor alcohol or drug abuse. Labour was spontaneous and delivery was vaginal with mid-forceps assistance. The infant was meconium-stained and subsequently received...