Structural aberration of the X chromosome in a patient with gonadal dysgenesis: an approach to karyotype-phenotype correlation

SUMMARY An 18-year-old female with some stigmata of pure gonadal dysgenesis had a chromosome constitution of 46,X,dir dup(X) (pter→q27:q21→qter). The abnormal chromosome was always late replicating. The clinical and cytogenetic picture is compared with that of patients with X;X translocation and some problems of karyotype-phenotype correlation are discussed.

The karyotype-phenotype correlation in patients with an X chromosome rearrangement is a very complex problem deserving special attention, because of the inactivation mechanism of that chromosome.

When only one X (ring, isochromosome, or by deletion) is involved in the rearrangement, or when it is involved in an X;X translocation, the abnormal chromosome is preferentially late replicating and the normal X is active in the somatic cell. However, the patients present several malformations and gonadal dysgenesis is frequently associated with other signs of Turner syndrome. We report a patient with duplication of a segment of a long arm of an X, possibly resulting from an X;X translocation. Mechanisms for explaining the gonadal dysgenesis found in X;X translocation carriers are also discussed.

Case report

The patient, an 18-year-old female, was the third in a sibship of 10. Her mother was 20 and her father 30 years old when she was born and the pregnancy and labour were normal. She had a height of 167 cm, weight 52 kg, span 169 cm, hypertelorism, telecanthus, high palate, slight prognathism, and a broad nasal bridge with stenosis of the right orifice. The mammary glands were poorly developed, the nipples were widely spaced, axillary hair was absent, and pubic hair was sparse (fig 1). Both lower limbs...
Case reports showed genu valgum and there were shallow ulcers on the lower third. The right leg was 1.5 cm shorter than the left. The feet showed an equinovarus deformity. The upper limbs exhibited bilateral cubitus valgus and camptodactyly of third and fourth fingers. The external genitalia were hypoplastic but otherwise normal. The gynaecograms failed to show the outlines of the uterus and ovaries and at exploratory laparotomy the uterus was a small nodule of 2 cm. Bilateral streak gonads were found and microscopical examination showed only connective tissue. There were high levels of LH and FSH with a marked response to LHRH. Thyroid scanning showed hemiagenesis of the gland, the left lobe being absent.

TRH test, T3, T4, and thyroid uptake were normal. Bone age was 17. X-ray of the skull was normal and there was a dorsal kyphoscoliosis. Intravenous pyelogram was normal. Blood analyses were all normal. EEG and ECG showed no abnormalities.

Psychological evaluation showed slight mental retardation.

The mainline dermatoglyphic formulae were 9.7. 5’I-t−Lμ/Lμ.0.0.0.L for both palms. A tibial loop in the hallucal area was present, bilaterally (fig 2).

CYTOGENETIC STUDIES
Chromosome analysis was carried out on peripheral leucocyte cultures. G and C banding and the BrdU

FIG 3 Partial karyotype. (A) GTG bands, (B) CBG bands, and (C) diagrammatical representation of the rearrangement based on the Paris Conference.

FIG 4 Three partial metaphases showing the dup(X) as the late replicating chromosome (BrdU technique).
technique were performed according the methods of Mirzayants and Baranovskaya. X chromatin was studied in buccal smears stained with fuchsins.

A single and apparently normal Barr body was present in 34% of 500 cell nuclei analysed. Chromosome analysis was performed on 100 metaphases and after G and C banding (fig 3) the karyotype of the patient was 46, X, dir dup(X)(pter→q27::q21→qter). The resolution of G banding was not good enough to decide whether the new large dark band in the translocation chromosome was formed by part of Xq21 only or whether it was formed by a segment of Xq27 plus a segment of Xq21.

In all 32 cells studied after BrdU incorporation the abnormal X showed late replication (fig 4).

The patient's parents had normal karyotypes.

Discussion

With the exception of the patient described by Sinha and Nora all known cases of X;X translocations have been unbalanced. In all informative cases the abnormal X showed late replication, and in the great majority of these patients many symptoms of Turner syndrome were observed. In the present case the X chromosome with duplication was also late replicating, but if this chromosome was totally inactivated there would be X monosomy and the patient's phenotype should therefore resemble Turner syndrome, which is not the case. Mirzayants and Baranovskaya tried to explain a similar condition by suggesting that the abnormal X chromosome must have been active at least during embryonic development and that the information provided was sufficient to avoid very deleterious congenital somatic malformations and short stature, but insufficient for normal development of the ovaries.

Therman et al presented data which strongly suggested the existence of an active segment in the inactivated X chromosome, probably located in the region Xp11. The activity of this segment in all the extra inactivated chromosomes in poly-X patients could explain the malformations presented by these subjects. The findings of our patient do not fit this hypothesis since, in spite of some similarities in clinical appearance with the poly-X syndrome, she possesses the possibly active segment in duplicate.

Sarto et al presented two hypotheses to explain gonadal dysgenesis in some patients with balanced X;autosome translocations. The first of these explained the problem of gonadal development on the basis of the selective inactivation of the same X chromosome in all or almost all cells, which could result in an effective hemizygosity for a recessive gene, with a frequency estimated by those authors of about 0.02. A second explanation was the existence of a critical region in the X chromosome, the continuity of which would be extremely important for normal sexual development, demonstrating a position effect. This region should be between Xq13 and Xq26.

All patients described with X;X translocations have gonadal dysgenesis and many of them signs of Turner syndrome. Mirzayants and Baranovskaya suggested that in those subjects with an X;X translocation the pure gonadal dysgenesis is determined by Xq27→qter monosomy, since this is the only region which differs between the generally normal XXX and the isodicentric patients. The case we report does not support this hypothesis as the patient had gonadal dysgenesis in spite of this region being absolutely intact in both chromosomes.

It is our opinion that gonadal dysgenesis in cases of translocations involving the long arm of the X chromosome associated with an autosome or another X would be better explained by the hypothesis of effect suggested by Sarto et al or by a change in the nature or time of X inactivation, which would be determined by the abnormal structure of the chromosome independently of the type of the abnormality.

The inactivation centre of the human X chromosome appears to be located in Xq13. The patient did not have a duplication of this region in the rearranged inactivated X chromosome, and she should therefore not have a bipartite Barr body which in fact she does not. Another possibility, suggested by de la Chapelle et al to explain the occurrence of bipartite X chromatin takes into account the size of the inactivated X and not the existence of a centre of inactivation. However, despite the length of the inactivated rearranged X chromosome, bipartite chromatin was not found.

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Partial trisomy 6p: 46,XX,−10, der(10),t(6;10) (p22;q26)pat and HLA localisation

SUMMARY A child with multiple facial anomalies showed partial trisomy 6p, 46,XX,−10,der(10), t(6;10)(p22;q26)pat. Family studies suggested that the HLA complex is probably between 6p22.4 and 6p21.05.

The HLA system had previously been localised between 6p21 and 23 and more precisely located by Berger et al\(^4\) above 6p21.05. We have studied the clinical presentation and the HLA system of the family of a child with partial trisomy 6p derived from a paternal translocation.

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Since Breuning et al\(^4\) collected and studied the first six known cases of trisomy 6p, 12 cases have been found with similar clinical manifestations, varying in the breakpoint and the part of 6p which was triplicated. Independent of the classification of the clinical manifestations of new syndromes, the importance of duplication-deficiency chromosomal abnormalities is determined by the localisation of gene loci. The HLA system was localised between 6p21 and 23 in 1979,\(^2\) and more precisely by Berger et al\(^3\) at above 6p21.05. Our results suggest that the HLA system is below 6p22.4, the breakpoint found in the balanced translocation 6p22:10q26 of the father which produced the partial trisomy 6p22−pter of the proband.

Case report

The proband, born 6.4.75, is the second child of healthy unrelated parents with no relevant family history. The father is 37 and the mother 30. The older child is a normal 7-year-old boy. The mother has had no other pregnancies and this one was at term with a normal delivery.

At birth the child weighed 2200 g. Physical examination revealed high forehead, blepharoptosis of the left eye, bilateral blepharophimosis, convergent strabismus, high arched palate, grooved tip nose, low set ears, small mouth with thin lips, short frenula tying the tongue, bilateral clinodactyly of the 5th fingers, kyphosis, and psychomotor retardation. When she was brought to us 3 years later (fig 1), she weighed 10 kg (3rd centile) and was 79-3 cm tall (3rd centile). X-ray examination showed bilateral brachymesophalangy of digits 2 and 5 and an ulnar reduction of 5 mm. Bone age was 6 months retarded for her age. Blood and urine tests, aminoacids, and mucopolysaccharides were all normal. No proteinuria was detected.

**FIG 1** Face of the proband.