PROBABLE INVERTED TANDEM DUPLICATION OF Xp IN A 46,Xp+Y BOY

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Summary A mentally retarded 16-month-old boy with subnormal stature, strabismus, anteverted nares and deformed ears was found to have a *de novo* structural rearrangement of the X chromosome (46,Xp+Y). The banding patterns of the abnormal X chromosome were interpreted to be an inverted tandem duplication of the segment Xp22.1→Xp22.3. Several other possibilities were considered but thought less likely. DNA replication studies with BrdU incorporation revealed the replication pattern of the duplicated segment to be similar to the equivalent portion of the X chromosome.

INTRODUCTION

Various structural rearrangements of the X chromosome have been described in a number of women with gonadal dysgenesis. They include isochromosomes for the long and short arms, deletions of the long and short arms, ring formations and pericentric inversions of the X chromosome, and X-autosome, X-X and X-Y translocations. Structural aberrations of the X chromosome in men, on the other hand, have been reported much less frequently. We would like to describe a boy with a *de novo* mirror duplication of the distal portion of Xp, a hitherto unreported aberration.

CASE REPORT

The patient, a boy, was born at term on July 9, 1976 in the second uncomplicated pregnancy. His parents were unrelated. The first pregnancy had resulted in an early spontaneous abortion. No family history indicating congenital defects or mental retardation was present. The mother was 24 years old and the father 26 when the patient was born. The delivery was induced uneventfully. The birth weight was 3,100 g. During the first 3 months of life, the infant was always a poor feeder and failed to thrive. Delayed development was noticed at 5 months of age.

Fig. 1. The patient at 16 months of age. Note right internal strabismus, anteverted nares, and a carp-shaped mouth.

Upon physical examination at 16 months of age, the body weight was 7,240 g, the height 72.3 cm, and the head circumference 43.0 cm; all the figures were less than the 3rd percentile. He could not stand unsupported or say any meaningful words. He had anteverted nares, right internal strabismus, a carp-shaped mouth, and deformed ears with folded helix and prominent antihelix (Fig. 1). Otherwise, no major malformations were observed, including genital organs. Dermatoglyphic patterns of the patient consisted of 5 loops, 3 arches and 2 whorls on the fingertips, a total finger ridge count of 27, a transitional simian crease on the right palm, and a radial loop pattern in the left thenar area.

CYTOGENETIC FINDINGS

Cytogenetic studies of the patient and his parents were performed using cultured peripheral blood lymphocytes. Conventional chromosome preparations from the patient revealed a 46,Xp+Y karyotype. Based on G-, R-, Q- and C-banding pattern of the early metaphases, the X chromosome abnormality was interpreted as an inverted tandem duplication of region Xp22.1→Xp22.3 (Fig. 2). The karyotype was designated as 46, Y, inv dup (X) (pter→p22.3::p22.1→p22.3::p22.3→qter).

DNA replication studies with BrdU incorporation and acridine orange staining (Dutrillaux *et al.*, 1973) revealed a similarity between the replication pattern of the extra Xp segment and the equivalent portion of the X chromosome (Fig. 3). This indicates that the extra segment was early replicating and thus genetically active,

Fig. 2. G-banding patterns in normal (Xn) and abnormal (Xp+) X chromosomes.

Fig. 3. DNA replication patterns in the Xp+ and Y chromosomes. BrdU incorporation followed by acridine-orange staining.

and further supports the interpretation of inverted tandem duplication. The X-chromatin test in the buccal epithelial cells was negative. Both parents had normal G-banded chromosomes.

DISCUSSION

The X chromosome abnormality in our case was interpreted as inverted tandem duplication of the distal portion of Xp. Other interpretations, such as direct tandem duplication and X-autosome or X-X translocation, were possible but seemed less likely. The interpretation of inverted tandem duplication, however, is not conclusive in view of the paucity of bands in the chromosome segment involved and also due to the lack of supportive clinical evidence. Inverted tandem duplications have been previously described in various autosomes but not in the X chro-

Table 1. Translocations involving the X chromosome in the males in the literature.

Types	Case No.	Karyotypes	Clinical features	Reference
Balanced X-autosomal translocation	1	46,Y,t(Xp-;14q+)mat	Reduced fertility	Buckton <i>et al.</i> , 1971
	2	46,Y,t(1q-;Xq+)mat	Azoospermia	Dutrillaux <i>et al.</i> , 1972
	3	46,Y,t(Xq-;5q+)	Azoospermia and Klinefelter's stigmata	Stengel-Rutkowski <i>et al.</i> , 1976
	4	46,Y,t(4q-;Xq+)mat	Normal phenotype (child)	Cervenka <i>et al.</i> , 1976
	5	46,Y,t(Xp-;17q+)mat	Normal phenotype (child)	Hagemeyer <i>et al.</i> , 1977
Unbalanced X-autosomal translocation	6	47,Y,Xq-,+2t(14q+;Xq-)mat	Klinefelter's syndrome	Allderice <i>et al.</i> , 1978
	7	47,XY,+der(X),t(Xp-;17q+)mat	Mental retardation and congenital anomalies	Hagemeyer <i>et al.</i> , 1977
	8	46,XY,-22,+t(Xq22q)mat	Hypogonadism, intellectual defect and behavior disorder	Jenkins <i>et al.</i> , 1974
	9	46,XY,-21,+der(X),t(X;21)(q22;q22)mat	Multiple congenital anomalies	Cann <i>et al.</i> , 1975
Unbalanced X-X translocation	10	47,XY,+der(XX)mat	Behavior disorder	Laurent <i>et al.</i> , 1975
Unbalanced X-Y translocation	11	46,XtY/47,XXY	Klinefelter's syndrome	van den Berghe <i>et al.</i> , 1977
	12	46,XtY	Craniofacial dysmorphism	<i>ibid.</i>
	13	46,Y,t(X;Y)(Xqter→Xp22.2;:Yq11→Yqter)mat	Craniofacial dysmorphism and hypogonadism	Tiepolo <i>et al.</i> , 1977
Insertional translocation	14	46,Y,ins(X;?)(q13;?)	Multiple congenital anomalies	Sparkes <i>et al.</i> , 1977

mosome (*cf.* Taylor *et al.*, 1977, for reference). All the inverted tandem duplication reported up to the present have been sporadic, a fact also in support of our interpretation.

Fourteen instances of structural aberrations of the X chromosome in males have been described in the literature. They can be classified into five groups: (1) balanced X-autosome translocations (5 cases), (2) unbalanced X-autosome translocations (4 cases), (3) an unbalanced X-X translocation, (4) unbalanced X-Y translocations (3 cases), and (5) an insertional translocation of the X chromosome (Table 1). It seems that the presence of the material from at least one entire X chromosome, with the possible exception of the terminal portion of Xp, is essential for survival. Cases 12 and 13 in Table 1 with an unbalanced X-Y translocation, in spite of nullisomy for the terminal segment of Xp, were life sustaining and showed few physical abnormalities. This would indicate the localization of few vital genes in this segment. Case 14 had a small chromosome segment of unknown origin inserted into the long arm of the X chromosome. The banding patterns of the X chromosome are also consistent with the interpretation of direct duplication of the segment Xq13→Xq24. All the abnormalities, except in Case 14, were inherited.

BrdU-acridine-orange staining in our case provided evidence that the extra chromosome segment is early replicating and therefore genetically active. It is tempting to try to relate the activity of the duplicated X segment with the phenotype of the patient.

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