Partial disomy of Xp and the presence of SRY in a phenotypic female

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Abstract

We present a study of a mentally retarded and mildly dysmorphic female in whom initial cytogenetic studies identified the karyotype 46, X,+mar. Further characterisation of the structurally abnormal chromosome by fluorescence in situ hybridisation (FISH) showed that it is composed of both X and Y chromosome material with a centromere originating from the Y chromosome. The presence of the DMD gene and the absence of the XIST gene was shown by FISH using locus specific probes. The Y segment included the SRY and ZFY genes. Based on these findings, the karyotype was defined as 46, X,der(Y)(t(X;Y)(p21.1;q11)). This case illustrates male to female sex reversal owing to a partial duplication of the short arm of the X chromosome in the presence of SRY.

Partial duplication of the short arm of the X chromosome combined with an intact SRY gene is uncommon with only 20 cases reported. In contrast, all 47, XXY subjects, who have two intact but only one active X chromosome, are phenotypically male. Furthermore, only 10% of the women with XY gonadal dysgenesis have deletions or intragenic mutations of the SRY gene. This indicates that most of these cases are attributable to mutations in the SRY promoter, or alterations of genes downstream in the testis determining pathway. In support of this hypothesis, a locus critical for sex reversal was recently mapped to Xp21.

We present a study of a retarded and mildly dysmorphic infant with a structurally abnormal chromosome which was shown to consist of both X and Y material. In spite of the presence of the SRY and ZFY genes, the external genitalia were female suggesting that sex reversal is caused by the presence of two active copies of Xp21.

Case report

The proband was the first child of healthy, unrelated, white parents. She was born at term after an uneventful pregnancy. Her birth weight was 2500 g (<10th centile for 39 weeks), birth length 52 cm (50th centile), and head circumference 34 cm (10th–50th centile). The infant had a peculiar appearance with a small anterior fontanelle, a carp shaped mouth, abnormal helices of the right ear, bitemporal narrowing, and high arched palate. The external genitalia were female. There was no family history of malformations, repeated spontaneous abortions, or mental or growth retardation.

Subsequent clinical and laboratory investigations showed a mild ventricular septal defect and severe gastro-oesophageal reflux. Ultrasonography of the brain and the urinary tract was normal, as were skeletal arrays. Neurological and ophthalmological examinations did not show any pathological findings. Following the preliminary cytogenetic results, ultrasonography of the pelvis was performed. The gonads could not be identified, whereas the uterus and vagina appeared normal.

The child was re-evaluated at the age of 18 months. Her weight was 8 kg (<3rd centile), length 80 cm (25th–50th centile), and head circumference 46 cm (5th centile). She had good head control, but could not sit unsupported. Her mental development was 9 months below her chronological age.

Methods

CYTOGENETIC STUDIES

Metaphase chromosomes were prepared from phytohaemagglutinin (PHA) stimulated lymphocyte cultures using standard procedures. Cytogenetic analyses included GTG, QFQ, AgNOR, and C banding and were performed according to standard procedures. Nuclei from buccal epithelial cells were used for X and Y chromatin analyses.

FLUORESCENCE IN SITU HYBRIDISATION

Chromosome slides were prepared from lymphocyte cultures as previously described. Whole chromosome painting was performed using chromosome specific libraries for the X and Y chromosomes. They were amplified and labelled by PCR with biotin-16-dUTP (Boehringer Mannheim) and digoxigenin-11-dUTP (Boehringer Mannheim), respectively. Centromere specific hybridisation was performed using probes specific for the X (DXZ1, Oncor) and the Y (DYZ3, Oncor) centromeres. FISH against the DMD locus was performed by pooling the cDNA probes cMDM1–2a, cDMD 2b–3, cDMD 4–5a, cDMD 5b–7, and cDMD...
Results

Cytogenetic analysis of 300 cells from the proband showed the abnormal karyotype 46, X, +mar (figure A). The size and shape of the marker corresponded to a G group chromosome although it was AgNOR negative. Since the only identified gonosome was a normal X chromosome, we suspected that the marker was a gonosome derivative. X chromatin (Barr body) was present in only 2% of the 300 buccal nuclei analysed. No Y chromatin was observed (not shown). The parental karyotypes were normal.

Chromosome painting showed that the abnormal chromosome consists of material from both the X and Y chromosome. Furthermore, using the Y specific library, cross hybridisation to the pseudoautosomal region on the X chromosome indicated involvement of the short arm of the X chromosome (figure B). Using centromere specific probes we showed that the marker is a Y chromosome derivative (figure C, D). Moreover, gene spe-
cific probes showed that the DMD locus at Xp21.2–21.3 is present on the marker chromosome, while the XIST locus (Xq13) is not (figure C and D, respectively). Thus, the origin of the X chromosome material included band p21.2–21.3–pter.

Isolated DNA from the patient was found to contain the SRY gene as determined by PCR$^7$ and Southern blotting using the probe pDP1327 (data not shown). In addition, the probe pDP1007, which detects the ZFY gene, hybridised to a 2.7 kb fragment and cross-hybridised to a 2.1 kb fragment, known to be the ZFX gene on the X chromosome (not shown).

Discussion

We report a female infant with a structurally abnormal chromosome consisting of X and Y chromosome material. Parental karyotypes were normal, indicating a de novo reciprocal translocation during the premeiotic cell divisions or meiosis I, at the time of spermatogenesis. The DMD locus, which is shown to be on the marker chromosome, is physically close to the dosage sensitive sex reversal (DSS) locus,$^{10}$ which makes the presence of this locus highly likely also. Because the marker chromosome does not include the XIST locus for X chromosome inactivation, it is conceivable that genes on the rearranged chromosome are expressed, including the SRY locus.

A number of studies have shown the importance of the SRY gene for testicular formation.$^{11,18}$ Transgenic insertions of the gene cause testicular development in XX embryos of the mouse,$^{17}$ and sex reversed XY females in the human have been shown to carry mutations in the SRY gene.$^{19,20}$ However, there are a number of reports of male to female sex reversal, in spite of a normal SRY gene.$^{10,12}$ In these cases, the sex reversal has been associated with a duplication of the distal part of the short arm of the X chromosome. The fact that two active copies of chromosomal region Xp21.1–22.11 cause sex reversal was initially reported by Arn et al.$^8$ and was referred to as the sex reversed X-like region (SRXV). Shortly after, Bardoni et al.$^{10}$ limited the sex reversal region to Xp21 and named it the dosage sensitive sex reversal (DSS) locus. The size of the duplicated region did not seem to be related to the degree of variability of sexual differentiation, suggesting that additional genes on Xp are not involved in sex reversal.

Nevertheless, some sex reversed females show neither mutations in the SRY gene nor linkage to the X chromosome.$^{21}$ These findings have led to the suggestion that there may be other loci that permit or inhibit the development of the testis. Indeed, autosomal loci that could be involved in sex reversal have been identified. In campomelic dysplasia (CMPD1), where patients with an XY karyotype are often phenotypically female, an autosomal sex reversal locus (SRA1) has recently been localised to 17q24.2–25.1.$^{22}$ Other autosomal regions that have been associated with sex reversal are deletions of 9q$^7$ and 10q.$^{23}$ Detailed molecular analysis of these patients may show new genes that are crucial for sex determination.

The patient reported in this study has a normal X chromosome, along with a chromosome derived from an unbalanced XY translocation, which makes her partially disomic for Xp21.1–pter and nullisomic for Yq11–pter. This is an uncommon event with approximately 10 cases reported.$^{8,10}$ These patients have in common a number of characteristics such as mental retardation, psychomotor delay, and dysmorphic features. Since these abnormalities are not usually associated with Yq deletions,$^{24}$ the phenotype of these patients is most likely attributable to the presence of two active copies, and thereby double dosage, of expressed Xp linked genes.

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