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Clinical Report

Unique Mosaic X/Y Translocation/Insertion in Infant 45,X Male

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We report on a 45,X male with hydrocephaly, lobar holoprosencephaly and ichthyosis. In situ hybridization and molecular analysis have demonstrated the presence of a mosaic SRY-bearing derivative X chromosome that included Yp and heterochromatic Yq fragments.

Key words: 45,X male; ichthyosis; mosaicism; SRY gene; X/Y translocation

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INTRODUCTION

A number of 45,X male patients have been previously reported in the literature [de la Chapelle et al., 1986]. Most of these cases have resulted from Y/autosomal translocations or insertions [Kellermayer et al., 2005]. The patients' phenotypes are generally dependent on the autosomal locus involved and the Y chromosome loss. These individuals have male phenotype, infertility and some of the clinical features of Turner syndrome. Some patients have demonstrated congenital malformations, hypogonadism and mental retardation.

CLINICAL REPORT

The patient was a 48-day-old infant male born to a 25-year-old Moldavian woman from a second pregnancy. No information about propositus' father was available. Apgar scores were 4 and 7 at 1 and 5 minutes; birth weight 3,160 g (25th centile), height was 48 cm (10th centile). He had prominent progressive hydrocephaly (cranial circumference 40 cm, 97th centile), major and minor fonticuli (5×5 cm and 3×3 cm, respectively), ichthyosis and male developed external genitalia without sexual ambiguity (Fig. 1). The left testis was in the scrotum, the right testis had homolateral localization in the inguinal canal. The patient had slightly short upper and lower extremities, as well as a number of micro-abnormalities: short neck, saddle nose, low-set ears, elongated nail-bones, palmar transverse folds, pigmented nevus in right infrascapular region. The ultrasound encephalography has depicted lobar holoprosencephaly, agenesis of the corpus callosum, absence of the cavum septum pellucidum and cistern dilatation. The cortical sulci were not visualized. No abnormalities were found during abdominal ultrasonography and X-ray examination of cortical bones and thorax.

MATERIALS AND METHODS

Chromosome analysis was performed on cultured PHA-stimulated peripheral blood lymphocytes with GTG-, C- and QFH-staining in accordance with standard techniques. FISH analysis was performed on metaphase chromosomes and interphase nuclei using standard protocols with the following DNA probes: DXZ1, DYZ1, DYZ3, WCPX, WCPY, and LSI SRY (Vysis[Q3]). Signals were visualized under a DMRXA (Leica[Q4]) and Axio Imager (Zeiss[Q5]) micro-

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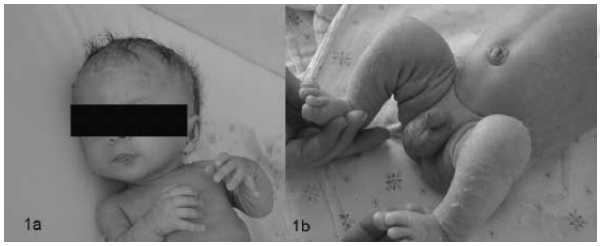

FIG. 1. Patient's photos. The hydrocephaly, facial abnormalities (**a**) and ichthyosis manifestations are prominent (**b**).

scopes equipped with color filters. Images were analyzed using QFISH (Leica) and Isis (MetaSystems[Q6]) software.

DNA was extracted from peripheral leukocytes by a standard method. Molecular analysis was performed using multiplex PCR amplifications of SRY, AMELX/AMELY, ZFY/ZFX loci, and 22 Y-specific STSs. The markers and primers sequences have been chosen from Laboratory guidelines for molecular diagnosis of Y chromosomal microdeletions [Simoni et al., 1999] and the NCBI (www.ncbi.nlm.nih.gov) database. X chromosome heterozygosity has been evaluated by analysis of CAG-repeats in exon 1 of the androgen receptor gene and six additional markers (DXS1062, DXS1192, STR44, STR45, STR49, and STR50).

RESULTS

Cytogenetic examination has revealed 45 chromosomes in all analyzed metaphases. Two abnormal cell lines, each with 45 chromosomes, have been

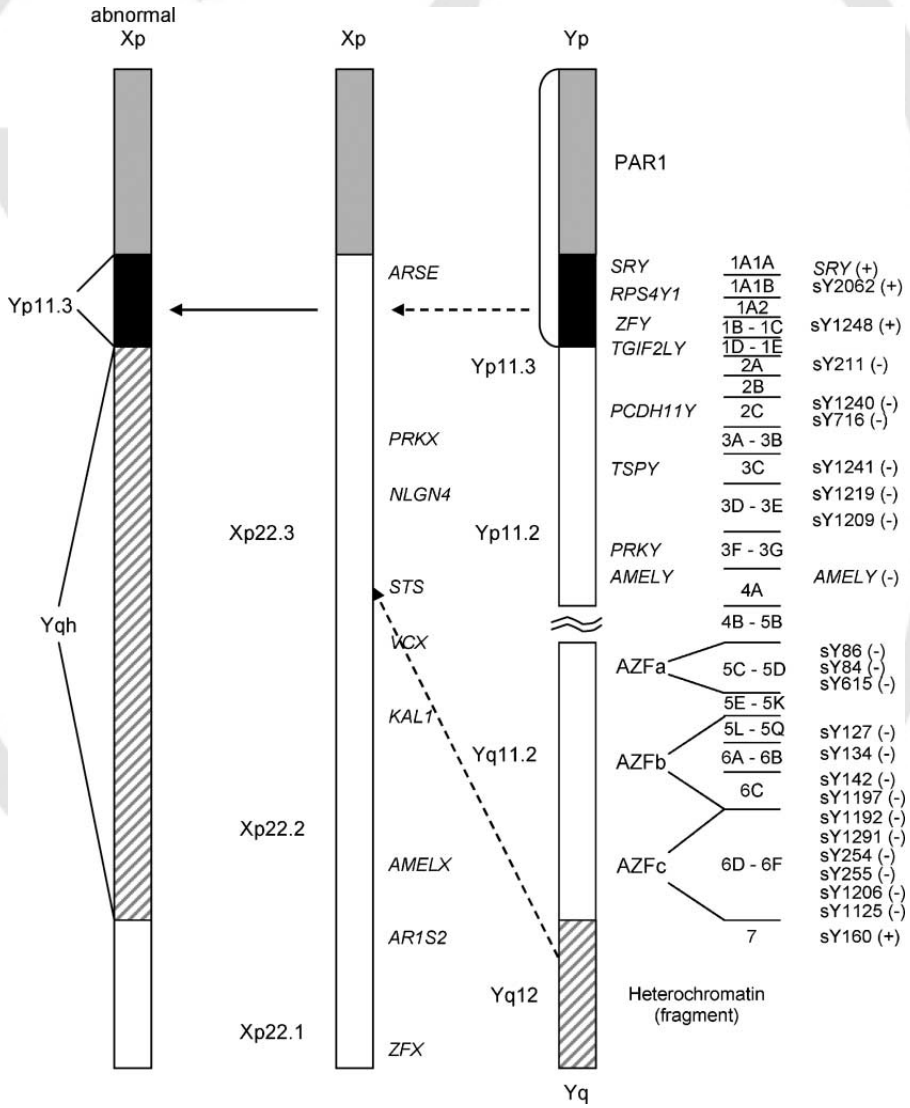

FIG. 2. Schematic representation of the X/Y rearrangement. Grey color indicates the Pseudoautosomal Region 1 (PAR1), black color shows MSY fragment of the Yp11.3, heterochromatic region of Yq12 (Yqh) is shaded diagonally. The localization of some loci and genes on the X and Y chromosomes, and the Y chromosome deletion intervals are indicated. Analyzed STSs are shown at the right. Pluses (+) indicate confirmed presence of STSs and minuses (−) indicate confirmed absence of markers.

found: one with just an apparently normal X chromosome and the other with just one abnormal X chromosome. In 41 of 50 analyzed metaphases the QFH- and C-banding analyses have shown the presence of a heterochromatic fragment in the terminal portion of Xp. In situ hybridization demonstrated that Yqh material was inserted into the Xp22 region in 80% metaphases. FISH analysis with the DYZ3 probe yielded negative results. In situ hybridization with a LSI SRY probe demonstrated a cryptic translocation of Yp11-Ypter to the terminal portion of short arm of abnormal X chromosome; otherwise an apparently normal X chromosome was intact. However an unexpectedly negative result was observed for the WCPY probe which has been interpreted as insufficient hybridization sensitivity for this probe. FISH analysis with WCPX probe has demonstrated an absence of hybridization in the subtelomeric region of the short arm of the X derivative chromosome, but a signal has been observed in the terminal portion of Xp. Ultimately the patient's karyotype has been considered as mos 45,add(X)(p22).ish der(X)t(X;Y)(p22;p11.3)ins(-X;Y)(p22;q12)(SRY+,DYZ1+,DXZ1+,DYZ3-)[80]/45,X.ish (SRY-, DYZ1-, DXZ1+, DYZ3-)[20].

Molecular analysis has detected the presence of SRY, AMELX, ZFX, ZFY, sY2062, sY1248, and sY160 loci. The Yp breakpoint has been mapped between sY1248 and sY211 (Fig. 2). The male specific region of the human Y chromosome (MSY) covering about 1 Mb including SRY, RPS4Y1, ZFY genes and possibly TGIF2LY gene has been retained. PCR amplifications were negative for all of the analyzed Yq specific STSs excluding sY160. This indicates that the Yq breakpoint is localized distal to the AZFc region. None of analyzed X chromosome markers has displayed heterozygosity. PCR amplifications were positive for AMELX and ZFX, but presence or absence of these loci on X derivate could not be interpreted correctly because of normal X chromosome.

DISCUSSION

Only two 45,X males with X/Y translocations have been previously reported in the literature [Weil et al., 1993; Stuppia et al., 1999]. In both patients the chromosome abnormality has been considered as a result of the combination of two meiotic mutations: the loss of maternal X chromosome and the formation of an X/Y translocation in the father's spermatogenesis. An ectopic recombination between Yp11.2 and Xp22.3 loci has been determined to take place in both cases. The origin of the chromosome abnormality in this patient is difficult to understand. Undoubtedly it is the result of at least three gonosomal mutations. Intriguingly that molecular analysis has not shown X chromosome heterozygosity despite of a mosaicism. Unfortunately the patient's parents were not available for genetic examination and no information about propositus' father was available.

A number of genes responsible for different diseases have been mapped to Xp22. X-linked ichthyosis, recessive chondrodisplasia punctata X-linked 1, X-linked mental retardation and Kallmann syndrome are resulting from deletions and/or mutations of *STS*, *ARSE*, *FACL4*, and *KALIG* genes, respectively. Various combinations of the above-mentioned diseases are referred to as contiguous gene deletions and can be caused by translocations, interstitial or terminal Xp deletions [Ballabio et al., 1989]. Besides the ichthyosis; progressive hydrocephaly, lobar holoprosencephaly, mild facial dysmorphism, and severe psychomotor retardation are also seen in this patient. The X-linked mental retardation associated with calcifications of basal ganglia, hydrocephaly and mild facial dysmorphism (MRX21), as seen in this patient, and previously described as Fried syndrome [Strain et al., 1997] have been mapped within the interval DXS7109-DXS7593 in Xp22.2 and the *AP1S2* gene mutations have been found in all affected male subjects [Saillour et al., 2007]. In this patient it is an attractive supposition that the hydrocephaly and/or SNC anomalies have resulted from the complex mosaic X chromosome rearrangement in the Xp22 region.

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