



## Mosaic Isodicentric Y Chromosome in a Patient with Mixed Gonadal Dysgenesis

CASE REPORT

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ABSTRACT

Here, we report a male with mixed gonadal dysgenesis and a mosaic karyotype, 45,X[49]/47,X, idic(Y)(q11.2)x2[4]/46,X, idic(Y)(q11.2)[47]. We used fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) to determine the structural rearrangement and genetic content of the Y chromosome. Our findings emphasize the importance of the use of a combination of cytogenetic and molecular genetics techniques during characterization of a patient with a derivative Y chromosome before any general conclusions can be reached concerning the relative effects of the Y chromosome abnormality and mosaicism on sexual differentiation.

Keywords: Isodicentric Y, mixed gonadal dysgenesis, mosaicism, SRY

### INTRODUCTION

Dicentric chromosomes are the most frequently observed structural abnormalities of the Y chromosome. Dicentric aberrations are unstable during cell division and can generate various types of cell lines (1). Most reported patients are chromosomal mosaics, generally including a 45,X cell line. Among the cases, a wide range of variations in phenotype, external genitalia, histology of the gonad, and chromosomal findings have been observed (1). There is phenotypic variability among patients with 45,X/46,X, idic(Y) mosaics, which was attributed to variable locations of the breakpoints and to the proportion of 45,X cells distributed over different tissues (2-4). Nonetheless, the highly variable nature of mosaicism makes the phenotype-genotype correlation difficult (5).

Mixed gonadal dysgenesis (MGD) is a developmental anomaly in which most of the patients have dysgenetic testes, a contralateral streak gonad, and a 45,X/46,XY karyotype (6). The pathogenesis of MGD is probably related to a disturbed network of gene expression that controls testicular differentiation (7). The Y chromosome contains crucial loci for normal male sexual development. SRY, a transcription factor-coding gene on the short arm of the Y chromosome, has a critical role in switch, leading to testis development. In addition, genes on the long arm of the Y chromosome (Yq11) are required for normal spermatogenesis. Isodicentric Y (idicY) is one of the most common structural abnormalities described for the Y chromosome and usually results in the 45,X/46,X, idic(Y) mosaic karyotype. Most 45,X/46,XY mosaic patients with MGD have a structural abnormality on the Y chromosome. In one study, 25% of patients with MGD were mosaic for 45,X and a cell line with a dicentric Y chromosome (8).

Here, we report a patient with ambiguous genitalia and mixed gonadal dysgenesis who had a phallus, with one gonad palpated in the labioscrotal fold and the urethral meatus opening into the perineum with a mosaic karyotype 45,X [49]/47,X, idic(Y)(q11.2)x2[4]/46,X, idic(Y)(q11.2)[47].

### CASE REPORT

A peripheral blood sample of 10-month-old infant with undefined sexuality due to ambiguous genitalia was admitted to our laboratory for cytogenetic analysis. The birth weight was 3200 g after an uneventful pregnancy period. The infant was the first offspring of a non-consanguineous marriage. The mother was a healthy 21-year-old female without drug abuse during pregnancy. The father was healthy 24-year-old male. No similar case in the family was reported.

On physical examination, the case was a well-developed infant with a weight of 9300 g (25<sup>th</sup>-50<sup>th</sup> percentile) and height of 70 cm (10<sup>th</sup> percentile). The phallus was 3 cm in length with one urethral meatus opening into the perineum. The right gonad was palpated in the labioscrotal fold, but the left gonad could not be palpated. Other systemic findings were normal. Laboratory examination revealed FSH: 0.58 mLU/mL, LH: 0.54 mLU/mL, estradiol: 15 pg/mL, testosterone: 0 ng/dL, DHEA-SO4: 6.5 µg/dL, ACTH: 9.89 pg/mL, cortisol: 8.27 µg/dL, and

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AMH: 100 ng/mL. Imaging studies were carried out to observe the internal genitalia and gonads. Pelvic ultrasonography showed gonads; the right gonad was 10.3x5.5 mm in the scrotum and the left gonad was 8.9x5.1 mm at the inguinal area, but no Müllerian structures were observed. Although gonad biopsy from the right gonad revealed normal testis tissue and epididymal cyst, gonadal tissue was not observed on the left side; instead, the persistence of Müllerian duct structures, including a fallopian tube, was observed.

#### CYTOGENETICS AND FLUORESCENT IN SITU HYBRIDIZATION (FISH) ANALYSIS

Cytogenetic analysis was performed on peripheral blood lymphocytes on GTG- and CBG-banded metaphases after written informed consent form was obtained. One hundred metaphase cells were analyzed; the karyotyping was reported according to the International System for Human Cytogenetic Nomenclature (ISCN, 2009) (9). Chromosome analysis demonstrated a mosaic karyotype, 45, X[49]/47, X, idic(Y)(q11.2)x2[4]/46, X, idic(Y)(q11.2) [47], by GTG banding (Figure 1). We showed the absence of a heterochromatin region at the q arm of the derivative Y chromosome, but centromeric heterochromatin staining was not evaluated exactly by CBG banding (Figure 2).

FISH was carried out with multiple probes for the Y chromosome (Abbot Molecular Laboratories, INC, Downers Grove, Chicago, IL, USA), including SRY (LSI SRY spectrum orange/CEP X spectrum green), the Y alpha satellite region (DYZ3), and whole chromosome Y (WCP-Y) probes. For each analysis, a minimum of 10 metaphase cells and 100 interphase cells were scored. FISH analyses revealed double signals for SRY (Figure 3) and CEPY regions on the chromosome, suggesting idic(Yp). The whole-chromosome probe hybridized with only the derivative chromosome, excluding the presence of a translocation including the Y chromosome (Figure 4). The proportion of mosaicism of cell lines was similar with the cytogenetic analysis results.

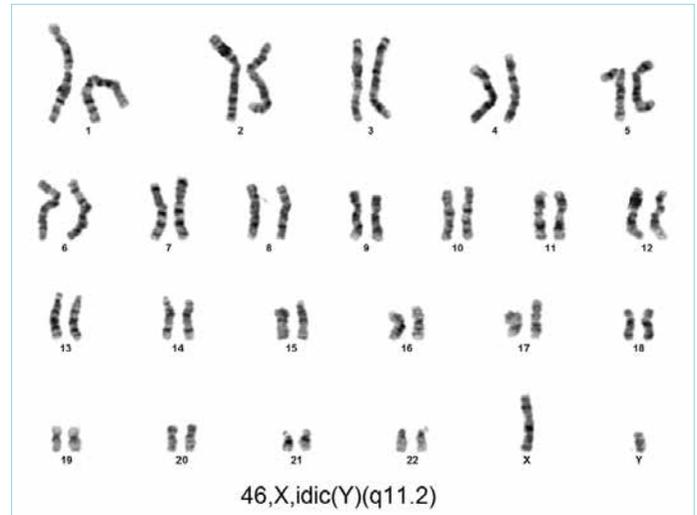
#### MOLECULAR ANALYSIS

Genomic DNA was extracted from peripheral blood using standard procedures and amplified in multiplex polymerase chain reactions. We tested 14 Y-DNA loci via a sequence-tagged site (STS), including the SRY (sY14), ZFY (sY238), AZFa (sY84, sY86), AZFb (sY127, sY131, sY134, sY143, sY164), AZFc (sY254, sY255, sY277, sY283) and AZFd (sY152,) regions. According to the PCR results, the patient had amplified SRY and ZFY regions, whereas a total deletion of AZFa, b, c and d STS marker regions was detected.

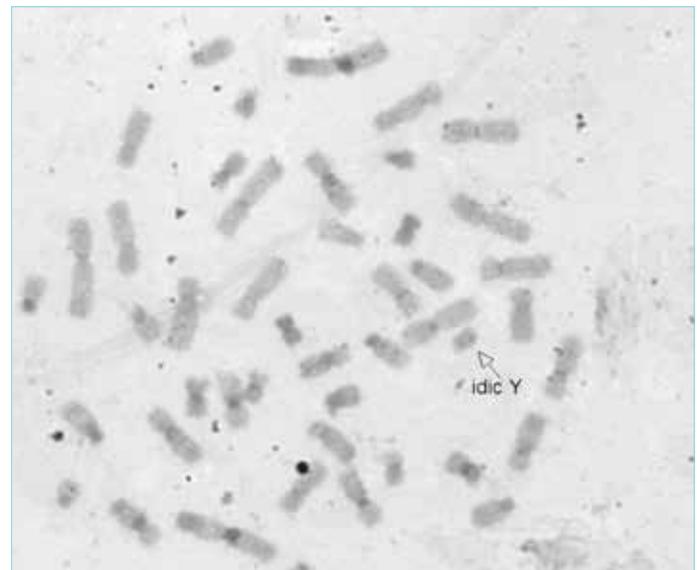
The parents were informed about the results of the cytogenetic and molecular genetics investigations during the nondirective genetic counseling session, including characteristics, prognosis, management, and current and possible future treatment options of the abnormalities.

#### DISCUSSION

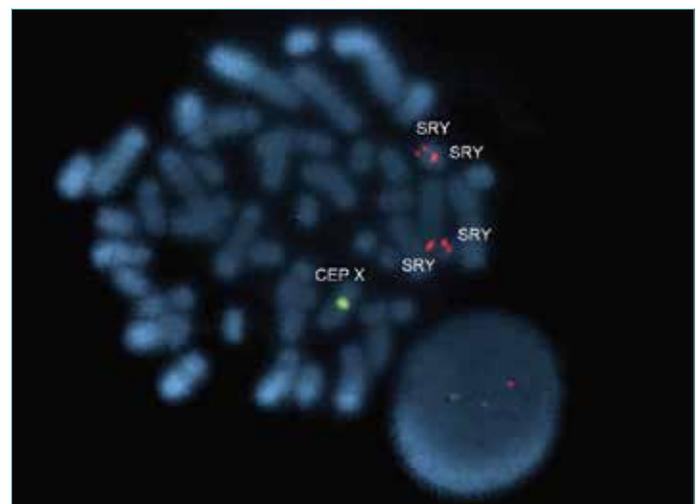
Idic (Y) is the most common detectable aberration of the Y chromosome detected cytogenetically. It can sometimes be mistaken for a normal Y chromosome by routine Giemsa staining procedure because of its similarity in size compared to the normal Y chromosome (1, 5). In our patient, the derivative chromosome was observed similarly as a normal Y chromosome by GTG banding, but



**Figure 1.** The karyotype of the patient after GTG banding with one idic (Y) chromosome



**Figure 2.** The CBG-banded metaphase of the patient



**Figure 3.** FISH examination by probes for the SRY region revealed that the derivative chromosome has two SRY signals



**Figure 4.** FISH examination after hybridization with the whole chromosome Y probe revealed that the derivative chromosome is a Y chromosome, without translocation

a heterochromatic region on Yq was not observed by CBG banding. FISH examination by probes for the SRY region and whole chromosome Y revealed that the derivative chromosome is a Y chromosome, and one SRY signal was present at the top of both arms of this chromosome. Thus, the derivative Y chromosome was described as idic(Yp). The breakpoint in our patient, as in most patients with idic(Y), is on the long arm of chromosome Y, which results in duplication of the entire short arm and centromere and a deletion of distal Yq, including the heterochromatic region of the chromosome.

Isodicentric chromosomes have two centromeres, but usually, one centromere is inactive. Centromeric activity at the dicentric situation is responsible for chromosomal stability. If each of the centromeres remains active, the dicentric Y chromosome may be broken apart during chromosome segregation, leading to its damage or loss (10). Conversely, if a dicentric chromosome has one active centromere, segregation of the chromosome is free of meiotic problems (11). In our patient, the karyotype revealed mosaic idic(Y) with 45,X cells; therefore, he might have cells with idic(Y), including both one and two active centromeres at the beginning. If idic(Y) individuals are mosaics without a 46,XY cell line, this indicates that gametogenic or early post-zygotic origins are the most frequent reason (1). Our patient was also mosaic without a normal cell line, as impressed in previous reports (1, 12); his first cell probably had an idic(Y) chromosome.

The phenotypic effect of idic(Y) is likely to depend on the presence or absence of important loci, such as the SRY and special genes that are responsible for spermatogenesis. The idic(Yp) chromosome has usually two short arms, which include SRY and Yq in variable sizes according to the breakpoints. Although there is a wide range of variation in phenotype, the male phenotype is observed in most cases with idic(Yp) (1, 6, 12). Our patients' breakpoint was on Y(q11.2), and we demonstrated SRY on both arms of idic(Y) by FISH exami-

nation. He had a phenotype with ambiguous genitalia, mixed gonadal dysgenesis, a phallus, one gonad palpated in the labioscrotal fold, and the urethral meatus opening into the perineum.

Y microdeletions, generally resulting from intrachromosomal recombination events between large homologous repetitive sequence blocks in Yq11, are the most frequent known genetic cause of non-obstructive severe oligozoospermia or azoospermia, with a frequency ranging from 10% to 15% (13). Since large structural rearrangements of the Y chromosome are commonly associated with 45,X/46,XY chromosomal mosaicism, they result in Y chromosome instability (14). We also observed a large deletion including the AZF a, b, c, and d regions in our patient, and this finding supports the previous reports (1, 5, 14).

The incidence of gonadoblastoma has been reported to be 20%, associated with the presence of X/XY karyotypes in cases with MGS (15). The development of gonadoblastoma is thought to be less common in patients with idic(Y)(q11.2); however, gonadectomy is usually recommended (16). We believe that our patient also has a risk for gonadoblastoma because of the 45,X/ 47,X, idic(Y)(q11.2)x2/ 46,X,idic(Y)(q11.2) mosaic karyotype.

Our findings and earlier reports emphasize the importance of the use of a combination of cytogenetic and molecular genetics techniques during characterization of a patient with a derivative Y chromosome before any general conclusions can be reached concerning the relative effects of the Y chromosome abnormality and mosaicism on sexual differentiation.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Authors' contributions:** Conceived and designed the experiments or case: ZY, BY, ÖÖ, FİŞ. Performed the experiments or case: ZY, BY, ÖÖ, FİŞ. Analyzed the data: ZY, BY, ÖÖ, FİŞ. Wrote the paper: ZY. All authors read and approved the final manuscript.

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