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Short report

# Evidence of a mechanism for isodicentric chromosome Y formation in a 45,X/46,X,idic(Y)(p11.31)/46,X,del(Y)(p11.31) mosaic karyotype

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ABSTRACT

Abnormalities involving sex chromosomes account for approximately 0.5% of live births. The phenotypes of individuals with mosaic cell lines having structural aberrations of the X and Y chromosomes are variable and hard to accurately predict. Phenotypes associated with sex chromosome mosaicism range from Turner syndrome to males with infertility, and often present with ambiguous genitalia. Previous studies of individuals with an 45,X/46,X,idic(Y)(p11) karyotype suggest that the presence of both cell lines should result from an intermediate, 46,XY cell line. Here we report a 2.5 year old female with phenotypic features of Turner syndrome with an isodicentric Y chromosome and a cell line with a deleted Y with a final karyotype of 45,X/46,X,idic(Y)(p11.31)/46,X,del(Y)(p11.31). Fluorescence *in situ* hybridization (FISH) mapping of the Y chromosome breakpoint revealed very low percentages of the deleted Y cells, but suggested a potential mechanism for the formation of the isodicentric Y chromosome. To our knowledge, the 46,X,del(Y) intermediate cell line in our patient has not been previously reported in individuals with mosaic sex chromosome structural abnormalities.

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## 1. Introduction

Abnormalities resulting from sex chromosome mosaicism are associated with a variety of clinical phenotypes [10]. One of the more frequently encountered, small supernumerary marker chromosomes identified in Turner syndrome karyotypes (sSMC(T)) appears to be aberrations of the Y chromosome as an isodicentric chromosome [2,18,4,12,16,5]. Both idic(Y)(p11) and idic(Y)(q11) have been reported, which result in a dicentric chromosome and subsequent deletion and duplication of Y chromosome material [18,4]. While there is some suggestion that the former is less stable than the latter, both have been identified in patients having a 45,X cell line [2,12,16,5,8,9,17]. Hypotheses of postmeiotic and post-zygotic instability suggest that an intermediate cell line should also be present in the form of either 46,XY or 46,X,del(Y)(p11) [6]. We describe a female in whom the "intermediate" cell line was observed, providing evidence for post-meiotic and post-zygotic models of sex chromosome mosaicism.

## 2. Materials and methods

### 2.1. Patient

At 2.8 years old, the female patient was 86.8 cm (15th percentile) and weight of 12.1 kg (25th percentile). Phenotypic features of Turner syndrome included: webbed neck, low posterior hairline, widely spaced nipples, high-arched palate, slightly shortened 4th metacarpals, and cubitus valgus. The history was significant for genital ambiguity at birth described as clitoromegaly and enlarged, rugated, labia. Ultrasound and MRI of the pelvis demonstrated a small uterus, no identified gonads, corpus cavernosa hypertrophy and clitoromegaly. On laparoscopic visualization, two solid structures were observed which were thought to be gonads, although normal testes or ovaries were not evident. A tubular structure was present with the appearance of a vas deferens. Pathology following a bilateral gonadectomy revealed a streak gonad on the right consisting of ovarian-type stroma with an immature testis on the left

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with prominent Sertoli cells and occasional intratubular germ cell. No definitive Leydig cells were identified, although distinct Mullerian (fallopian tubes) and Wolffian (epididymis) structures were seen bilaterally.

### 2.2. Cytogenetic analysis

High resolution GTG-banding was carried out on peripheral blood lymphocytes and gonadal tissue. Thirty metaphase cells were analyzed for each tissue source.

### 2.3. Fluorescence in situ hybridization (FISH) analysis

FISH was carried out with multiple probes for the Y chromosome, including *SRY* (Abbott Molecular Laboratories, Inc., Downers Grove, IL, USA), the heterochromatic satellite III region at Yq12 (*pLAY5.5*), the Y alpha satellite region (*DYZ3*, Abbott Molecular), subtelomeric Xp/Yp (EST Cdy 16c07) and Xq and Yq regions (CDXYS129), and additional BAC DNA probes (RP11-946P8, -808D8, -892B14, -261P4, -74L17, -155F12) from a human BAC library at the Roswell Park Cancer Institute (http://genomics.roswellpark.org/human/overview.html) (Fig. 1). BACs were processed using previously described methods [14] with minor modifications [3]. For each analysis, a minimum of ten metaphase cells and 100 interphase cells were scored. Estimation of the Yp deletion breakpoint was carried out using a control subtelomere Yq probe in combination with BACs centromeric to the *SHOX* locus (see above).

## 3. Results

Blood chromosome analysis demonstrated a mosaic karyotype, with a 45,X cell line and an isodicentric Yp (45,X[16]/46,X,idic(Y)(p11.31)[20]) (Fig. 2A). FISH revealed the presence of two copies of the *SRY* gene on the isodicentric Y (Fig. 2B), and one metaphase with an apparently normal Y chromosome (Fig. 2C). Analysis with BAC probes indicated that RP11-74L17 was deleted at Yp, but that RP11-155F12 was present with only one signal, suggesting that the breakpoint in our patient was either within RP11-155F12 or just proximal to it, distal to *SRY* (Fig. 1). Both gonadal and non-gonadal tissues failed to reveal the del(Y)(p11.31) chromosome. However, FISH studies of non-gonadal tissue showed the majority of cells to have signals consistent with a 45,X cell line compared to blood, followed by the idic(Y)(p11.31), with a small percentage of cells containing the del(Y)(p11.31) (Table 1). Taken together, the results suggested a mosaic 45,X/46,X,idic(Y)(p11.31)/46,X,del(Y)(p11.31). nuc ish idic(Y)(p11.31)(*ESTCdy16c07-, RP11-946P8-,RP11-808D8-, RP11-892B14-,RP11-261P4-,RP11-74L17-,RP11-155F12+,SRY++, DYZ3++,DYZ1++,CDXYS129++*),del(Y)(p11.31p11.31)(*ESTCdy16c07-, RP11-946P8-,RP11-808D8-,RP11-892B14-,RP11-261P4-,RP11-74L17-,RP11-155F12+,SRY+,DYZ3+,DYZ1+,CDXYS129+*) karyotype.

## 4. Discussion

Mosaic postnatal cases of idic(Y)(p11) are associated with broad phenotypes, including: Turner syndrome, ambiguous genitalia, craniofacial abnormalities, short stature, incomplete masculinization, male infertility with or without short stature, and less often, male mental retardation [1]. This heterogeneity is largely attributed to the ratio of clones in different tissues, and the presence or absence of *SRY* [10,1,15]. Thus, a direct correlation between phenotype and percent mosaicism is difficult. Nonetheless, the presence of an intact or structurally abnormal Y chromosome is clinically significant, due its association with an increased risk for gonadoblastoma [8,13,7,19].

Recent studies by Lange et al. (2009) demonstrated several mechanisms by which isodicentric Y chromosomes may occur: homology mediated crossing over between palindromic sequences along sister chromatids, recombination between a Yq palindrome on one chromatid with similar sequences closer to the centromere within the heterochromatin on the other chromatid, or recombination limited to within heterochromatic regions. While the majority of breakpoints in idic(Yp) occurred within Yq palindromes just distal to the chromosome Y centromere (Fig. 1), other individuals frequently revealed breakpoints resulting from recombination within heterochromatin. However, the deletion breakpoint in our patient appears to be proximal to *SRY,* and as such, does not overlap with palindromic or heterochromatic regions. Aside from a single metaphase cell observed in the peripheral blood, our inability to detect metaphase cells with the deleted Y chromosome is puzzling. By interphase analysis of stimulated blood, the del(Y)(p11.31) pattern was observed in ~14–26% of interphase cells (depending on the DNA probe), whereas skin contained the del(Y)(p11.31) in ~4–14% of cells. Fertilization of a normal egg with an idic(Y)(p11.31) sperm followed by a break due to an active dicentric chromosome being pulled toward different spindle poles could lead to mosaicism for the idic(Y)(p11.31) and del(Y)(p11.31) cells; further missegregation would be required for the 45,X cells. If the latter occurred, a higher proportion of cells with del(Y)(p11.31) would be expected. In fact, a very low percentage of cells with the del(Y)(p11.31) was observed, as shown by the absence of the Yp telomere signal and the presence of only one Y chromosome centromere signal. This suggests that loss of the Yp telomere occurred first, perhaps during spermatogenesis. The deleted Y cell then fertilized an egg, resulting in 46,X,del(Y)(p11.31). Selection against the deleted Y could have occurred early in embryogenesis, leading to subsequent nondisjunction of the del(Y) chromosome and the presence of both idic(Yp) and 45,X cells. The mechanism of mosaic cell line formation in our patient appears to be consistent with those proposed by Fryns [6], in that cells mosaic for Y chromosome alterations are postzygotic events that can occur via chromosome breakage (in our case, formation of the idic(Yp) due to attempted repair of earlier Yp deletion); non-disjunction

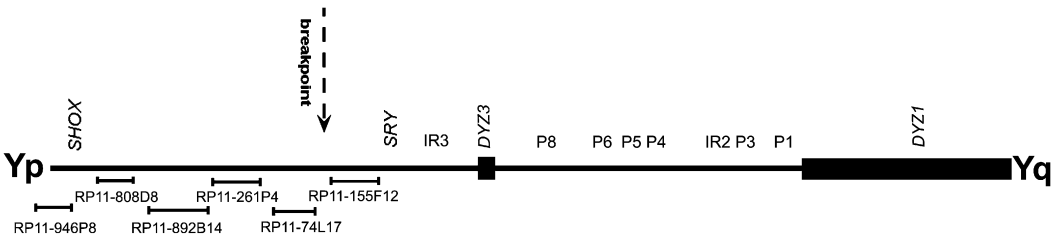


**Fig. 1.** Regions corresponding to BAC probes used to map the Yp deletion and isochromosome Y breakpoints. BACs to the right of the breakpoint are retained and duplicated on the isochromosome Yp. Additional regions between *SRY, DYZ3* and *DYZ1* were adapted from Lange et al. (2009) and represent palindromic sequences (P) within the long arm of chromosome Y or inverted repeat segments, (IR).

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