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Isodicentric Y Mosaicism Involving a 46, XX Cell Line: Implications for Management

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Abstract

Carriers of isodicentric Y (idicY) mosaicism exhibit a wide range of clinical features, including short stature, gonadal abnormalities, and external genital anomalies. However, the phenotypic spectrum for individuals carrying an idicY and a 46, XX cell line is less clearly defined. A more complete description of the phenotype related to idicY is thus essential to guide management related to pubertal development, fertility, and gonadoblastoma risk in mosaic carriers. Findings from the evaluation of twin females with an abnormal karyotype, 48, XX, +idic(Yq)x2/47, XX, +idic(Yq)/46, XX, are presented to highlight the importance of interdisciplinary care in the management of multifaceted disorders of sex development.

Keywords

Isodicentric Y; Disorders of Sex Development; Gonadoblastoma; Mosaicism; Interdisciplinary Care

INTRODUCTION

Isodicentric Y (idicY) is recognized as the most common structural abnormality of the Y chromosome [Hsu, 1994; Tuck-Muller et al., 1995]. Isodicentric Y structures are thought to arise from a double strand break, with subsequent repair by homologous crossing over

between sister chromatids to yield a dicentric structure with symmetrical arms [Hsu, 1994; Lange et al., 2013, 2009].

Multiple factors limit the ability to delineate clear correlations between idicY and observed phenotypes. First, the high frequency of idicY mosaicism makes phenotypic associations challenging [Hsu, 1994; Lange et al., 2009]. IdicY mosaicism is thought to result from instability of the dicentric structure during mitosis, leading to loss of the isodicentric Y and subsequent aneuploid cell lines [Hsu, 1994; Lange et al., 2009]. Ninety-one to 95% of idicY carriers are mosaic for a 45, X cell line [Hsu, 1994]. The high frequency of a monosomy X cell line among individuals carrying an isodicentric Y is suspected to contribute to the phenotypic correlations with short stature and Turner syndrome findings that are commonly reported in the literature [Hsu, 1994]. Additional reports of idicY in conjunction with other complex cytogenetic irregularities suggest a wide range of clinical characteristics including short stature, infertility (e.g. azoospermia), gonadal abnormalities (e.g., gonadal dysgenesis), and atypical genitalia (e.g., clitoromegaly, hypospadias). Depending on the portion of the Y that is present, idicY can be associated with either a male or female phenotype [Schellberg et al., 2002; Lange et al., 2009; Nazmy et al., 2008; Fernandez and Pasaro, 2006]. The variability in the type and extent of mosaicism, as well as varying breakpoints on the isodicentric Y across patients, create significant difficulties when attempting to ascertain phenotype etiology [Tuck-Muller et al., 1995]. In addition, attempts to delineate karyotype-phenotype correlations have been hindered by ascertainment bias in this population, as many individuals with idicY are identified postnatally following evaluation for Turner syndrome, genital ambiguity, or findings of primary amenorrhea or male infertility [Hsu, 1994; Lange et al., 2009]. Thus, previous patient reports have provided little guidance regarding clinical implications and management for individuals incidentally identified and without the signs or symptoms classically associated with isodicentric Y.

These gaps in knowledge pose a unique challenge in caring for this patient population, particularly with regard to ascertaining risk for gonadoblastoma. Estimation of this risk for idicY carriers is difficult due to limited molecular studies and the high degree of mosaic variation in reported individuals [Tuck-Muller et al., 1995]. Review suggests a gonadoblastoma prevalence of 10-24%, though the unique contribution of the isodicentric Y to this risk, versus the contribution from additional mosaic cell lines, is unclear [Tuck-Muller et al., 1995]. Recent studies suggest this risk may be associated with dysregulation of the *TSPY* tandem repeat region, a known tumor suppressor within the *GBY* locus of the Y chromosome [Cools et al., 2006; Lau et al., 2009; Looijenga et al., 2010; Tsuchiya et al., 1995]. *TSPY* is located in the pericentromeric region of the p arm; however, the mechanism of action is not well understood and clinical testing for the presence or expression of *TSPY* is unavailable [Lau et al., 2009]. Without complete characterization of genotype and associated phenotype, gonadoblastoma risk will remain unclear, leading to uninformed decision making regarding gonadectomy and cancer screening for idicY carriers.

A more complete understanding of the phenotype related to isodicentric Y is thus essential to guide management related to pubertal development, fertility, and tumor risk in mosaic carriers. Given the multisystem effects of idicY, as well as the extreme phenotypic heterogeneity, we argue that care should involve an interdisciplinary approach, with

contributions from genetics, gynecology, urology, endocrinology, surgery, and psychology. Here we highlight the role of our interdisciplinary team in the risk assessment, clinical evaluation, and management of twin females presenting with a rare mosaic karyotype containing both an isodicentric Y and a normal female, 46, XX cell line.

CLINICAL REPORT

The patients are 18-year-old female twins referred to our Disorders of Sex Development (DSD) Program after an abnormal karyotype was identified at an outside hospital. The twins' evaluation in the DSD Program included an interdisciplinary approach involving adolescent gynecology, pediatric endocrinology, genetics specialties, and psychology.

The twins were the product of a preterm vaginal delivery at 33-weeks' gestation to a 22-year-old primagravida mother. Birth weights were 1506 grams (approximately 10th centile) and 1723 grams (approximately 25th centile) for twin A and B, respectively. No genital ambiguity was noted at birth. Prenatal exposures were denied with the exception of prescription steroids given at the time of premature labor. Both twins exhibited delayed milestones, walking at 2 years and speaking their first words around preschool age. Despite parallels in early development, the twins showed differences in levels of cognitive impairment. Twin A was enrolled in self-contained special education classes, while twin B attended mainstream classes with some additional assistance. Additional past medical history reported from the referring institution included failure to thrive, joint hypermobility, and short stature with delayed bone age.

Previous gynecological evaluation from the referring hospital included a pelvic ultrasound for twin A, showing a uterus measuring $6.9 \times 2.8 \times 3.4$ cm with a 6mm endometrial lining, and right and left ovary around $2 \times 2 \times 1.9$ cm with normal appearance. For Twin B, the uterus measured $6.3 \times 2.3 \times 3.7$ cm with an 8 mm lining and both ovaries around $2 \times 2 \times 1$ cm with a normal appearance. Menarche occurred at age 15 for twin A and she reported regular light periods for the first year. She was started on combined oral contraceptives for birth control due to pregnancy risk concerns and was changed to depot medroxyprogesterone acetate (DMPA) injections, on which she became amenorrheic. She stopped the injections when she turned 18 and has not restarted her menstruation. Twin B had menarche at age 13 and reported frequent heavy periods with significant dysmenorrhea. After one year on combined oral contraceptives, she was started on DMPA and was amenorrheic for a year on the progesterone implant. Initial pediatric endocrinology evaluation, completed at age 17, included testosterone, estradiol, FSH, LH, Alpha Fetoprotein and β -hCG levels, all found to be within normal limits. AMH level was assessed at age 18 (Table I).

Family history was unremarkable for birth defects, menstrual or pubertal irregularities, and other hormonal concerns. The twins' mother obtained a high school diploma with some learning delays. Their father attended school until the 8th grade with some additional career-focused training. Cytogenetic analysis for the twins' mother was normal. Cytogenetic analyses on the twins' father could not be obtained as he died at age 27 after a motor vehicle accident. Parental height was reported to be 157.5cm (20th centile) and 177.8cm (60th

centile) for the twins' mother and father, respectively, yielding a mid-parental height of 161.0cm (37th centile). Parental head circumference was not assessed.

Physical exam at age 17 revealed that twin A weighed 40.6kg (<3rd centile) and was 155.1cm tall (11th centile). Twin B weighed 50.9kg (25th centile) and was 155.7cm tall (13th centile). Head circumference was not obtained. Despite outside records indicating short stature, evaluation of their final adult height is within their predicted female mid-parental height range. Twin A had upslanted palpebral fissures and a high palate. Twin B had upslanted palpebral fissures. Both had generalized joint hypermobility. Neither twin had physical findings associated with Turner syndrome. Both had Tanner IV breast and pubic hair development with normal appearing female genitalia and no evidence of clitoromegaly.

Review of outside records revealed genetics evaluation initiated in twin A due to a significant history of developmental delay and gastrointestinal issues, including irritable bowel syndrome and constipation. Cytogenetic analysis revealed a complex mosaic karyotype, 48, XX, +idic(Yq) x2 [3]/47, XX, +idic(Yq) [3]/46, XX [14]. Follow-up studies obtained in twin B revealed the same mosaic chromosomal complement, 48, XX, +idic(Yq) x2 [3]/47, XX, +idic(Yq) [7]/46, XX [10]. Fluorescence in situ hybridization (FISH) was negative for *SRY* located at Yp11.3 and positive for two copies of the centromeric probe *DYZ3*, confirming the dicentric structure (Figure 1A). A SNP Microarray (Illumina cytoSNP 850K platform) was performed on twin A at the University of Michigan Medical Genetics Laboratory with a focus on further delineating Y chromosome breakpoints to determine gonadoblastoma risk. A 39.3 Mb gain of material from region Yq11.222-q12 (20105854-59357887)(GRCh37/hg19) was identified, with no detection of genomic material from Yp or the pericentromeric region of Yq extending to Yq11.221, suggesting a final isodicentric Yq structure with incomplete duplication of the q arm (Figure 1B). No additional copy number variants or large regions of homozygosity were detected. All cytogenetic and molecular analyses were performed on peripheral blood samples. No other tissue samples were provided for analysis.

As part of their evaluation, the twins and available family members underwent psychosocial counseling and evaluation with a clinical psychologist. Evaluation was focused on preexisting risk and resilience factors in family adaptation, understanding of the genetic diagnosis, and sources of family social support.

DISCUSSION

The twin patients described here provide a novel look at the phenotype associated with mosaic isodicentric Y in conjunction with a 46, XX cell line. Several studies investigated the correlation between isodicentric Y mosaicism and sex development, however, the clinical picture is complicated by the high frequency of 45, X cell line mosaicism [Hsu, 1994; Cools et al., 2011; Kim et al., 2012; Mekki et al., 2012; Tuck-Muller et al., 1995; DesGroseilliers et al., 2006; Lange et al., 2009]. Only two individuals with a 46, XX female chromosomal complement and a mosaic isodicentric Y cell line have been reported [Nazmy et al., 2008]. Cytogenetic analyses in both individuals showed a 46, XX/47, XX idic(Y) karyotype with FISH indicating the presence of *SRY*. This is in contrast to our patients who

do not have the *SRY* region. The first individual was reported to have typical external female genitalia with small ovaries and primary amenorrhea, while the second had an enlarged clitoris, hypoplastic labia, and small ovaries [Nazmy et al., 2008]. Clinical comparisons, however, are limited as these phenotypes are likely the result of contributions from Yp and *SRY*. Query of the Databases of genomic variation and Phenotype in Humans using Ensembl Resources (*DECIPHER*) (<https://decipher.sanger.ac.uk/>) did not identify additional patients with similar cytogenetic findings. Although one patient was identified in the ClinGen database (<http://clinicalgenome.org/>) with a similar duplication of the Y chromosome (nssv579309), only limited phenotypic information, including female gender and developmental delay and/or other significant developmental or morphological phenotypes, was reported. Findings from clinical evaluation of both twin A and B suggest that idic(Yq) (-*SRY*) in the presence of a 46, XX cell line may result in typical female sex development with partial or intact ovarian function. Furthermore, the probable mitotic instability of the idicYq likely resulted in a relatively higher proportion of cells with only the 46, XX cell line in both [Lange et al., 2009].

The deletion of Yp and corresponding absence of *SRY* in the twins described in this report is consistent with their female phenotype [Lange et al., 2009]. The karyotype findings may provide an explanation for their learning difficulties and cognitive impairment, as studies have identified intellectual disabilities in 17% of individuals with Yp breakpoints [Tuck-Muller et al., 1995; Nazmy et al., 2008]. However, we cannot exclude that learning difficulties inherited from the mother are a contributing factor [Samango-Sprouse et al., 2014]. Although short stature has been associated with idicY, both twins had height within two inches of their female mid-parental height and are thus of normal height [Tuck-Muller et al., 1995; Nazmy et al., 2008]. There are currently no reported associations of idicY with the hypermobility identified in both patients, although benign joint hypermobility is common in the general population. Twin A's history of gastrointestinal issues and failure to thrive is not consistent with reported isodicentric Y phenotypes and thus raises concern for additional genetic contributions. These findings could have an environmental or epigenetic etiology given the absence of similar findings in her identical twin sister. CMA did not detect additional copy number variations outside the Y chromosome in twin A, reducing concern for an underlying microdeletion or duplication syndrome. At this time, the reason for the differences in the twins' phenotypes is not apparent, although one possibility is that they have differences in the level of idicY mosaicism in different tissues due to the mitotic instability of the idicY [Lange et al., 2009]. Further genetic evaluation is being considered.

The etiology of the twins' idicY mosaicism is unclear. Previous work suggests that isodicentric Y chromosomes arise from double strand break and repair through homologous recombination of sister chromatids [Lange et al., 2009, 2013]. However, the loss of genomic material from Yq11.1-q11.21 in the isodicentric Y structure suggests a more complex mechanism. It could be hypothesized that the final structure of the isodicentric Y arose through an initial pericentric inversion with breakpoints in the pericentromeric region of Yp and Yq11.221, with subsequent sister chromatid formation, double strand break, and repair by homologous recombination (Figure 3). With regards to the inheritance of the isodicentric Y, the mother had a normal karyotype making it unlikely to be maternally inherited. The father is not available for cytogenetic analysis. Given that Y chromosome pericentric

inversions are estimated to occur in 1 in 1000 males [Friedrich and Nielsen, 1973], we cannot rule out the possibility that the father carried a pericentric inversion of the Y chromosome and that isodicentric Y formation occurred as a subsequent event during paternal meiosis. This seems most likely given that both twins carry the same isodicentric Y structure. However, given that the father cannot be tested, this cannot be confirmed, and we cannot exclude the possibility that he carried the idicYq himself. If he did carry the isodicentric Y, it would be assumed that he had a second, intact Y chromosome given his reported normal sexual development and fertility. The presence of the 46, XX cell line, in addition to the idicY, most likely occurred as a result of nondisjunction, although it is impossible to determine whether this occurred during maternal or paternal meiosis.

The goals of the University of Michigan Disorders of Sex Development Program were to separately assess the twins for gonadal function, fertility potential, and risk for gonadoblastoma. In terms of gonadal function and fertility potential, both started pubertal development, have normal tanner stage IV breasts, started menstruation at age 15 and 13, and have had a normal endocrine evaluation. These findings suggest ovarian function and thus potential fertility. AMH levels, which reflect ovarian reserve [van Rooij et al., 2002; Visser et al., 2013], show a low value in twin A and a normal level in twin B. Knowledge regarding fertility in isodicentric Y carriers has been limited to studies of infertile males with q arm breakpoints (resulting in loss of sequence associated with spermatogenesis) [Lehmann et al., 2012], thus highlighting the need to investigate fertility potential in those with different isodicentric Y breakpoints and/or varying mosaic chromosomal complements. The twins have been on complete ovarian suppression for the last few years, and thus further hormonal and ovulatory assessments cannot be performed at this time. Twin A has chosen to discontinue hormonal suppression, providing the opportunity to assess the return of her cycles.

In evaluating the twins' risk for malignancy, the possible presence of Y material in ovarian tissue raised concern for gonadoblastoma. The family presented to our program to discuss the benefits and limitations of ovarian biopsy to identify pathological variations indicative of gonadal dysgenesis and gonadoblastoma risk. The risk of gonadoblastoma has been estimated to be as high as 15% in mosaic 45,X/46,XY individuals [Cools et al., 2011], and a comparison of cases with idicY with short arm or long arm breakpoints reported a risk of 24% and 10%, respectively [Tuck-Muller et al., 1995]. Results from SNP microarray suggest complete absence of Yp, and thus absence of the *TSPY* repeat region implicated in tumorigenesis in the gonadal tissues of isodicentric Y carriers [Cools et al., 2006; Lau et al., 2009; Looijenga et al., 2010]. In addition, the twins have a predominant 46, XX cell line and presumed partial or intact ovarian function, reducing the concern for a dysgenetic gonad and thus the associated gonadoblastoma risk. When comparing to other populations, males with 47,XXY and 48,XXYY karyotypes do not have an increased risk of germ cell tumors, however, this is due to their germ cells undergoing apoptosis at an early age [Cools et al., 2011; Looijenga et al., 2010]. Based on this information, we estimate gonadoblastoma risk to be greatly reduced. However, whether the risk is reduced due to the absence of the *TSPY* region or the presence of two X chromosomes cannot be determined with certainty.

Ovarian biopsy has been used previously in patients with 45, X mosaicism and Y chromosomal material to identify gonads with testicular and dysgenetic features [Cools et al., 2011; Wünsch et al., 2012]. Though biopsy can provide some information regarding the presence of unusual elements in the ovarian structure, clinical utility is limited as focal tissue may not be representative of the complete gonad [Wünsch et al., 2012]. Based on the findings from the DSD team evaluation and comprehensive discussion with the family, ovarian biopsy was rejected. Given that information on gonadoblastoma risk in mosaic isodicentric Y carriers with a 46, XX cell line is limited, the family and clinical team elected to pursue screening with yearly pelvic ultrasound and gonadal tumor markers. Their one year follow-up revealed normal imaging of the ovaries and negative markers for germ cell tumors. The necessity of continued screening will be re-evaluated based on findings from future clinical evaluation of the twins and as additional information on the pathogenesis of gonadoblastoma in idicY carriers becomes available.

The findings presented in this report demarcate the current limitations in knowledge surrounding management of individuals with idicY mosaicism in conjunction with a 46, XX cell line. The presence of this normal cell line raises questions of future gonadoblastoma risk and fertility potential. Given the multifaceted needs of these patients, an interdisciplinary approach is warranted to ensure comprehensive care. Involvement of the University of Michigan Interdisciplinary DSD team allowed for integration of expertise across multiple medical specialties, including genetics, endocrinology, gynecology, and psychology. This collaboration is essential for the complete assessment of ovarian structure, function, gonadoblastoma risk, and psychosocial adjustment- information necessary for patient education, psychosocial support, as well as evidence-based and shared decision making regarding care. In light of limited evidence, no practice guidelines, and uncertain prognostic information, team discussions allowed for the development of a shared management plan that supported the needs and expectations of the patients and their family.

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Figure 1.

A. Fluorescence in situ hybridization analysis indicating hybridization of two copies of the *DYZ3Y* chromosome centromeric probe (shown in aqua) in twin A, confirming the dicentric structure of the Y. The above image illustrates the 48, XX, +idic(Yq) x2 mosaic cell line, originally identified on karyotype for twin A. **B.** SNP array data for twin A indicating a gain of genomic material from Yq11.222-q12 with absence of material from Yp and Yq11.1-11.221.

Figure 2.

A. Ideogram indicating the normal structure of the Y chromosome. **B.** Pericentric inversion involving the pericentromeric region of the p arm and proximal region of Yq results in rearrangement of the proximal q arm to the p arm. **C.** Sister chromatid formation during gametogenesis. **D.** Double strand break of the Y chromosome with subsequent homologous recombination between sister chromatids results in isodicentric Yq structure with loss of proximal q arm and entire p arm. Y chromosome ideogram adapted from the University of Washington Department of Pathology (<http://www.pathology.washington.edu/research/cytopages/idiograms/human/>).

TABLE I

Clinical Data obtained at age 17 years

	Reference Range	Twin A	Twin B
Testosterone (ng/mL)	0.10-0.90	0.31	0.24
Estradiol (pg/mL)	21-85 *	79	38
FSH (mIU/mL)	1.5-11.7 *	4.8	6.7
LH (mIU/mL)	0.4-11.7 *	0.6	2.4
AFP-Tumor Marker (ng/mL)	0.0-7.9	<2.0	<2.0
Beta HcG Subunit (mIU/mL)	0-5	<2	<2
AMH (ng/mL) (Taken at 1 year follow-up)	0.9-9.5	1.0	3.0

FSH=Follicle- Stimulating Hormone, LH=Lutenizing Hormone, AFP=Alpha Fetoprotein, HcG=Human Chorionic Gonadotropin, AMH=Anti-Mullerian Hormone.

* Reference range for Tanner Stage IV pubertal development per Esoterix Inc Laboratory Services (Calabasas Hills, CA).