

Non-mosaic Tetrasomy Yp by Complex Isodicentric Rearrangement of the Y Chromosome: Prenatal Diagnosis with Cordocentesis in a Fetus with Abnormal Obstetric Ultrasound

Salvatrice A. Lauricella¹, Martina Busè², Valeria T. Consiglio³, Hellenia C. Cuttaia¹, Valentina Cigna⁴, Giovanna Schillaci⁴ and Maria Piccione^{2*}

¹Laboratory of Citogenetica Medica, AOOR Villa Sofia- Cervello, Palermo, Sicily

²Department of Science per la PROMOZIONE della Salute e Materno-Infantile "Giuseppe D'Alessandro," Università degli Studi di Palermo, Palermo, Sicily

³CRR Malattie rare, AOOR Villa Sofia-Cervello, Palermo, Sicily

⁴UOS Medicina Fetale e Diagnosi Prenatale, AOOR Villa Sofia-Cervello, Palermo, Sicily

Abstract

Tetrasomy Y is a very rare event, especially when it is present in a complete form. It is determined by complex rearrangement of the Y chromosome. Clinical features include psychomotor delay, skeletal abnormalities and facial dysmorphism.

We report on a case of prenatal diagnosis of non-mosaic tetrasomy Yp, performed by karyotype and fluorescence in situ hybridization (FISH) on fetal blood. These analyses showed the presence of two isodicentric Y, with two copies of SRY and one copy of DXZ1 (XCEN) in each one. Karyotype was characterized as 47; X, Isodicentric (Y) (pter→q12::q12→pter) x2 (SRYx4). Cytogenetic studies were performed after detection of abnormal prenatal ultrasound, showing severe intrauterine growth restriction (symmetric IUGR), hydropic placenta, mild cerebellar hypoplasia, microretrognathia, hyperechogenic bowel with slight distension, dilation of recto-sigmoid tract, ambiguous genitalia, clinodactyly of the right fifth finger, suspected polydactyly. It was not possible to make a clear genotype-phenotype correlation because a pregnancy interruption was performed.

Keywords: Isodicentric Y; Tetrasomy Y; Prenatal diagnosis; FISH

Introduction

Isodicentric chromosomes are considered the most frequent structural abnormalities of Y chromosome [1]. Because of their instability during cell division, the loss of a Y isodicentric chromosome seems mainly lead to the origin of mosaics with a 45, X cell line [1-3].

Y isodicentric chromosomes are often associated with severe sex-related phenotypes, ranging from Turner syndrome to normal male phenotypes to patients with ambiguous genitalia to infertile males with hypospadias [4-7]. Phenotypic variability is provided by percentage of 45, X cells distributed in various tissues and the presence or absence of the SRY gene. So the localization of the breaking point of the Y chromosome is key in the determination and differentiation of the gonads. Furthermore, it seems that the percentage of cells with Yp is crucial to have a male or female phenotype. In particular, mosaicism with 20 to 100% cells with idic Yp seem to have a male phenotype [8].

Our case, diagnosed with karyotype and FISH on fetal blood, revealed a tetrasomy Yp by complex isodicentric rearrangement of the Y chromosome. The rearranged chromosome was present in two copies.

Tetrasomy Y is a very rare event, especially when it is present in a complete form. There has only been one previous report of non-mosaic tetrasomy Y with 47 chromosomes, which describes two Y isochromosomes: short arm and long arm isochromosomes respectively [9].

Genuardi et al. [10] describe a 16-year-old female patient, with normal mental development, normal stature, primary amenorrhea and ambiguous genitalia, with a 46, X, dic (Y) (pter-q11.21::q11.21-pter) karyotype.

Neas et al. [11] report a case of non-mosaic isodicentric Yp. They describe a 4-year-old boy with mild developmental delay, normal

genitalia and normal stature, who has a 46 chromosomes karyotype with an isodicentric Yp, so SRY region in two copies.

The phenotype, described in literature, includes speech delay, short stature, brachycephaly, facial asymmetry, large ears, epicanthus, hypertelorism, micrognathia, delayed dentition, radio-ulnar synostosis, clinodactyly of the fifth finger, behavioral disorders. All patients with Y chromosome tetrasomy show different degrees of mental retardation, various skeletal abnormalities and facial dysmorphism [12].

Materials and Methods

Clinical report

A cytogenetic prenatal diagnosis on fetal blood was performed because of the detection of abnormal prenatal ultrasound.

It was first pregnancy of non-consanguineous partners. Family history was negative for both partners. No risk factor has been reported for both partners during pregnancy.

Obstetric ultrasound, performed at 22.2 weeks of gestation, showed: severe intrauterine growth restriction (symmetric IUGR), hydropic placenta, mild cerebellar hypoplasia, microretrognathia, hyperechogenic bowel with slight distension, dilation of recto-sigmoid

*Corresponding author: Maria Piccione, via Alfonso Giordano, 390127 Palermo (PA), Sicily, Tel: 00 33 14838895; E-mail: piccionemaria@libero.it

Received May 25, 2015; Accepted June 15, 2015; Published June 22, 2015

Citation: Lauricella SA, Busè M, Consiglio VT, Cuttaia HC, Cigna V, et al. (2015) Non-mosaic Tetrasomy Yp by Complex Isodicentric Rearrangement of the Y Chromosome: Prenatal Diagnosis with Cordocentesis in a Fetus with Abnormal Obstetric Ultrasound. Gynecol Obstet (Sunnyvale) 5: 298. doi:10.4172/2161-0932.1000298

Copyright: © 2015 Lauricella SA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

tract, ambiguous genitalia, clinodactyly of the right fifth finger, suspected polydactyly.

Cytogenetic study and FISH

Fetal lymphocytes obtained by cordocentesis were cultured in RPMI 1640. After fixation, the chromosome preparation were G and C Banded (GTG and CBG) according to the classic protocols [13,14].

Fluorescent in situ hybridization (FISH) was performed with the Y chromosome a-satellite (Poseidon, Kreotech Diagnostics) and SRY-DNA probe (Vysis). Slides were counterstained with 4',6-diamino-2-phenylindole (DAPI) (200ng/mL) and evaluated using a fluorescence microscope Olympus BX70 equipped with a cooled CCD Video Camera Image Point, Photometrics (Olympus, Center Valley, USA). Images analysis was carried out with Cytovision software version 3.93.2 (Applied Imaging/PSI, Santa Clara, USA).

Results

Karyotype on fetal lymphocytes obtained by cordocentesis revealed two rearranged Y chromosomes. CBG-banding showed two isodicentric Y: the thick C-band in the middle of the rearranged chromosomes allowed us to understand that the breakpoint occurred near the telomeric tract of Y long arm. Rearranged Y chromosomes were isodicentric, with short arms and centromere duplication, and deletion of long arms proximal tract. Karyotype was defined as 47, X, idic (Y) (q12) x2 (Figure 1A).

We performed dual color FISH analysis to verify the presence of abnormal Y chromosomes. FISH analysis showed two copies of SRY (Yp11.3) and one copy of DXZ1 (XCEN) in each isodicentric chromosome, leading to the karyotype 47; X, ish idic (Y) (pter → q12::q12 → pter) x2 (SRYx4) (Figure 1B and 1C).

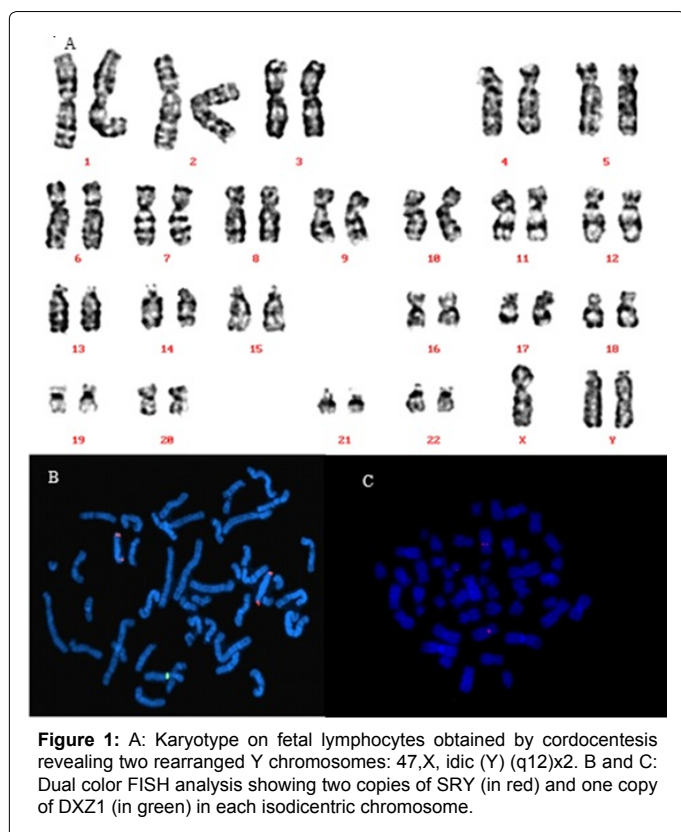


Figure 1: A: Karyotype on fetal lymphocytes obtained by cordocentesis revealing two rearranged Y chromosomes: 47, X, idic (Y) (q12)x2. B and C: Dual color FISH analysis showing two copies of SRY (in red) and one copy of DXZ1 (in green) in each isodicentric chromosome.

FISH confirmed the presence of tetrasomy Yp (Yp11.3).

Chromosome analysis of the parents revealed normal male and female karyotype, so the rearrangement was *de novo*.

Discussion

The rarity of our case is the presence of a double isodicentric (Yp) non-mosaic, even though the isodicentric rearrangement of Y chromosome is frequent because of the palindromic sequences at the ends heterochromatic Yq12, site of recombination [15]. Moreover, this distal portion is full of fragile sites characterized by AT sequences interspaced by Alu repetitive sequences.

In our case we found two isodicentric Y, resulting from breakage in the terminal heterochromatic region and “mirror” duplication. These isodicentric Y are probably derived from nondisjunction during second meiotic division; we hypothesize that because we did not found any normal cells lines. The rearrangement was *de novo*, so risk of recurrence is extremely low.

This complex rearrangement determines a tetrasomy Yp, with the deletion of the PAR2 gene SYBL1 and the presence of SRY in four copies.

SYBL1 codes for a member of the synaptobrevin family, a group of proteins involved in membrane transport. This gene is located in the pseudoautosomal region 2 (PAR2) of X and Y chromosomes (Xq28 and Yq12). Mutations in SYBL1 have been associated with bipolar affective disorder [16,17].

For what concerns SRY, as it is known, it is one of the main genes involved in sexual development. So we could simply argue that the presence of four copies of SRY is responsible for ambiguous genitalia, detected by prenatal ultrasounds.

In conclusion, due to the limited number of cases of non-mosaic tetrasomy Y reported in the literature, to date it is not yet possible to make a clear genotype-phenotype correlation. From a comparison with the described cases, three clinical features are more common: psychomotor retardation, skeletal abnormalities, facial dysmorphism. Psychomotor delay is variable and ranges from speech delay to severe mental retardation. In our case, obstetric ultrasound showed: severe intrauterine growth restriction, hydropic placenta, mild cerebellar hypoplasia, microretrognathia, hyperechogenic bowel with slight distension, dilation of recto-sigmoid tract, ambiguous genitalia, clinodactyly of the right fifth finger, suspected polydactyly. A pregnancy interruption was performed, so we could not observe the evolution of the phenotype.

References

1. Hsu LY (1994) Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. *Am J Med Genet* 53: 108-140.
2. Tuck-Muller CM, Chen H, Martínez JE, Shen CC, Li S, et al. (1995) Isodicentric Y chromosome: cytogenetic, molecular and clinical studies and review of the literature. *Hum Genet* 96: 119-129.
3. Bouayed Abdelmoula N, Amouri A (2005) [Dicentric Y chromosomes. First part: cytogenetic and molecular aspects]. *Ann Biol Clin (Paris)* 63: 263-278.
4. Willis MJ, Bird LM, Dell'aquila M, Jones MC (2006) Natural history of prenatally diagnosed 46,X,isodicentric Y. *Prenat Diagn* 26: 134-137.
5. Beaulieu Bergeron M, Brochu P, Lemyre E, Lemieux N (2011) Correlation of intercentromeric distance, mosaicism, and sexual phenotype: molecular localization of breakpoints in isodicentric Y chromosomes. *Am J Med Genet A* 155A: 2705-2712.
6. Cui YX, Wang WP, Li TF, Li WW, Wu QY, et al. (2015) Clinical and cytogenomic

- studies in a case of infertility associated with a nonmosaic dicentric Y chromosome. *Andrologia* 47: 477-481.
7. Lee J, Park JK, Kim DS, Lee HS, Choi SI, et al. (2015) Detailed analysis of isodicentric Y in a case with azoospermia and 45,x/46,x, idic(Y) mosaicism. *Ann Clin Lab Sci* 45: 206-208.
 8. Xu J, Siu VM (2010) Is there a correlation between the proportion of cells with isodicentric Yp at amniocentesis and phenotypic sex? *Prenat Diagn* 30: 839-844.
 9. Pasantes JJ, Wimmer R, Knebel S, Münch C, Kelbova C, et al. (2012) 47,X, idic(Y), inv dup(Y): a non-mosaic case of a phenotypically normal boy with two different Y isochromosomes and neocentromere formation. *Cytogenet Genome Res* 136: 157-162.
 10. Genuardi M, Bardoni B, Florida G, Chiurazzi P, Scarano G, et al. (1995) Dicentric chromosome Y associated with Leydig cell agenesis and sex reversal. *Clin Genet* 47: 38-41.
 11. Neas KR, Yip MY, James C, Kirk EP (2005) Patient with a non-mosaic isodicentric Yp and mild developmental delay. *Am J Med Genet A* 137: 223-224.
 12. DesGroseilliers M, Lemyre E, Dallaire L, Lemieux N (2002) Tetrasomy Y by structural rearrangement: clinical report. *Am J Med Genet* 111: 401-404.
 13. Seabright M (1971) A rapid banding technique for human chromosomes. *Lancet* 2: 971-972.
 14. Sumner AT (1972) A simple technique for demonstrating centromeric heterochromatin. *Exp Cell Res* 75: 304-306.
 15. Lange J, Skaletsky H, van Daalen SK, Embry SL, Korver CM, et al. (2009) Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. *Cell* 138: 855-869.
 16. Saito T, Parsia S, Papolos DF, Lachman HM (2000) Analysis of the pseudoautosomal X-linked gene SYBL1 in bipolar affective disorder: description of a new candidate allele for psychiatric disorders. *Am J Med Genet* 96: 317-323.
 17. Müller DJ, Schulze TG, Jahnes E, Cichon S, Krauss H, et al. (2002) Association between a polymorphism in the pseudoautosomal X-linked gene SYBL1 and bipolar affective disorder. *Am J Med Genet* 114: 74-78.