ORIGINAL ARTICLE

Egypt. J. Med. Hum. Genet. Vol. 9, No. 2, Nov 2008

Phenotypic variability in patients with isodicentric Y(p11.3). A clinical, cytogenetic and molecular study

Nahla A. Nazmy, Soha F. Kholeif and Amal K. Behery

Human Genetics Department, Medical Research Institute, University of Alexandria

ABSTRACT

Introduction: Isodicentric (idic) chromosomes are the most common Y structural abnormalities and their influence on gonadal and somatic development is extremely variable. The prediction of their phenotypic consequences is often difficult because of the variety of genomic sequences concerned by duplications and deletions, and the variable degrees of mosaicism, 45, X cell line in particular, in various tissues.

The Aim: This study was conducted to provide more information on patients with idic (Yq) allowing a better phenotype-karyotype correlation and understanding the sexual differentiation in these patients .

Patients and Methods: The study included 14 patients referred to the out patient clinic of the Human Genetics Department, Medical Research Institute, University of Alexandria. The reason for referral was genital ambiguity [8 patients], short stature with variable Turner stigmata [4 patients] and primary amenorrhea with normal height [2 patients]. All patients were subjected to clinical examination and chromosome analysis by GTG and CTG-banding techniques. Fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR)were done to determine the structure of the marker chromosomes detected by conventional methods.

Results: Chromosome analysis revealed a 45, X/46, X,idic (Y) (p11.3) in ten patients with variable degree of mosaicism, non mosaic 46, X, idic (Y) (p11.3) in two patients and a predominant 46, XX cell line along with 47, XX, idic (Y) (p11.3) cell line in two other patients .While the patients with an idic (Yq) described in this report were phenotypically different, all are considered as being at increased risk for gonadoblastoma.

The great phenotypic variations seen in patients with an isodicentric Y chromosome greatly limit the genotype – phenotype correlation.

Corresponding Author:

Dr: Nahla A. Nazmy
E-mail: nahlaan@hotmail.com

INTRODUCTION

Isodicentric chromosomes are the most commonly reported aberrations of the human Y chromosome. As they are unstable during cell division, and can generate various types of cell lines, most reported patients are chromosomal mosaics, generally including a 45, X cell line.[1]

Phenotypes depend on the localization of the break points as well as on the proportion of each cell line and vary from male to female or individual with ambiguous genitalia[2,3]. Phenotypic variability is known also to depend on the degree of mosaicism in various tissues. However, clinical expression seems to be related to the genomic capital of the Y chromosome, mainly the Y genes involved in the control of the process of the determination of gonads (Yp) and spermatogenesis (Yq) as well as control of growth and skeletal development (Yp). The clinical features are therefore very variable: 75-80% of patients have short stature and 65-75% have an abnormal or ambiguous sexual development[3,4]. The most likely mechanism of formation of the isodicentric chromosome is by an isochromatid break, followed by a U-type exchange. Breakpoints in the short arm will lead to a duplication of the entire long arm and a part of the short arm (idic(Yq)), while breakpoints in the long arm lead to the duplication of the entire short arm and part of the long arm (idic(Yp)).[4]

The absence of a sex chromosome in conjunction with the presence of a marker chromosome generally implicates a sex chromosome origin for such marker. Identification of marker chromosome is necessary for accurate phenotype – karyotype correlation.[5]

FISH as an adjunct to karyotype analysis provides a sensitive technique to identify sex chromosome mosaicism as well as the nature of marker chromosome in patients with abnormal sex differentiation.[6]

The presence of the pericentromeric Y sequences in patients with gonadal dysgenesis is clinically crucial, since they have an increased risk of developing gonadoblastoma.[7]

The purpose of the present study is to provide more information on patients with isodicentric Yq chromosome, allowing a better phenotype-karyotype correlation and understanding the sexual differentiation in these patients. An accurate diagnosis in these patients is essential not only to their follow up, but also to provide appropriate genetic counseling.

PATIENTS AND METHODS

The study included 14 patients referred to the out patient clinic of the Human Genetics Department, Medical Research Institute, University of Alexandria . The reason for referral was genital ambiguity [8 patients], short stature [4 patients] and primary amenorrhea [2 patients]. They were identified during cytogenetic analysis of 612 patients with abnormal sexual differentiation.

Patients were subjected to pedigree construction, clinical genetic examination with special emphasis on examination of the external genitalia, and chromosome analysis on cultured lymphocytes following trypsin G-banding technique[8]. At least 50-80 metaphases were scored for each patient to determine the propor-

tion of cell line mosaicism, and 6-10 cells were karyotyped. C-banding[9] was performed to all patients to confirm the presence of the heterochromatic region on the distal end of the long arm of the Y chromosome.

Fluorescence in situ hybridization [FISH] was performed to ensure finer characterization of marker chromosomes detected by routine methods and also to extend the number of cells investigated allowing more precise evaluation of the mosaicism. FISH was performed using CEPX /CEPY dual color DNA probe [Vysis , CEPX/Y consists of alpha satellite DNA specific to the centromere region Xp11.1- q11.1 (DXZ1) directly labeled with spectrum green and mixed with probe specific to alpha satellite DNA sequences contained within the centromere region Yp11.1-q11.1 (DYZ3) directly labeled with spectrum orange]. The protocol followed was that provided by the manufacturer. At least 200 interphases were scored as well as metaphases showing good quality signals.

DNA analysis by PCR was done to all patients. DNA samples were analysed for the presence of Y chromosome sequences using the Y specific PCR primers DYZ3 at the centromere and SRY at Yp11.32. Genomic DNA was then isolated from peripheral blood leucocytes by standard methods[10]. The highly repetitive sequence in the Y centromere (DYZ3) was amplified by using a primer set 5'-TGAAAACT-GCAC AGAAGCTG - 3'/5' - ACA-CATCACAAAGAACTATG-3. The whole coding region of the SRY gene was amplified as two overlapping fragments using two primer sets (5'-TTGAGAATGAATACAT TGT-

CAGGG - 3'/5' -GGGTCGCTTCACT CTATCCTG-3' and 5'-CAGTGT-GAAACG GGAGAAAACAGT - 3'/5' - CTTTGCATGT TAATCGTGTT-GACAC-3').[11]

Patients were referred for ultrasound examination, laparotomy and gonadal biopsy when feasible.

RESULTS

Clinical data of the 14 patients included in this study demonstrated that 8 patients had ambiguous genitalia, 4 were phenotypic females with short stature and some Turner stigmata, and two were phenotypic females with primary amenorrhea (Table 1).

As regards the eight patients (8/14) presenting with ambiguous genitalia, the assigned sex was male in 5 cases and female in 3 cases. All cases assigned as males had micropenis, perineoscrotal hypospadius, and undescended testes. Cases assigned as females had enlarged clitoris and abnormalities of labia majora.

Four patients (4/14) were phenotypic females with short stature. They showed variable degrees of Turner stigmata, poorly developed secondary sexual characters (4/4), low posterior hair line (3/4), webbing (2/4), cubitus vulgus (2/4), widely spaced nipple and shield shaped chest in one case.

Two phenotypic female patients (2/14) presented with primary amenorrhea and normal height. One had enlarged clitoris, blind vaginal pouch, bilateral testes in the labia and no uterus. The other one had normal female external genitalia.

The final karyotypes for all cases are summarized in (Table 1). Standard G-banding on blood lymphocytes, and FISH analysis showed that 10 patients had a 45,X cell line along with the idic (Y)(Figure 1). Two female patients were found to have a non mosaic idic(Y), one with ambiguous genitalia and one with primary amenorrhea. Two other female patients had a predominant 46,XX cell line along with 47, XX, idic (Y) cell line. C–banding confirmed the presence of the heterochromatic region on the long arm of Y chromosome, the abnormal Y chromosome showed a darkly stained band at the end of both arms, indicating the presence of two distal heterochromatic regions (Figure2). With GTG and CBG banding, only one primary constriction was visible in all cells analyzed, probably meaning that the Y chromosome possessed only one active centromere, the other being inactivated. FISH confirmed the origin of Y chromosome. In all patients, a double –hybridization signal was observed in the derivative chromosome for probe DYZ3,corresponding to double centromeric region (Figure 3). PCR analysis confirmed the presence of the Y centromere and the SRY gene in all patients. The presence of testis determining gene (SRY) indicated a breakpoint close to the distal end of Yp at Yp11.3.
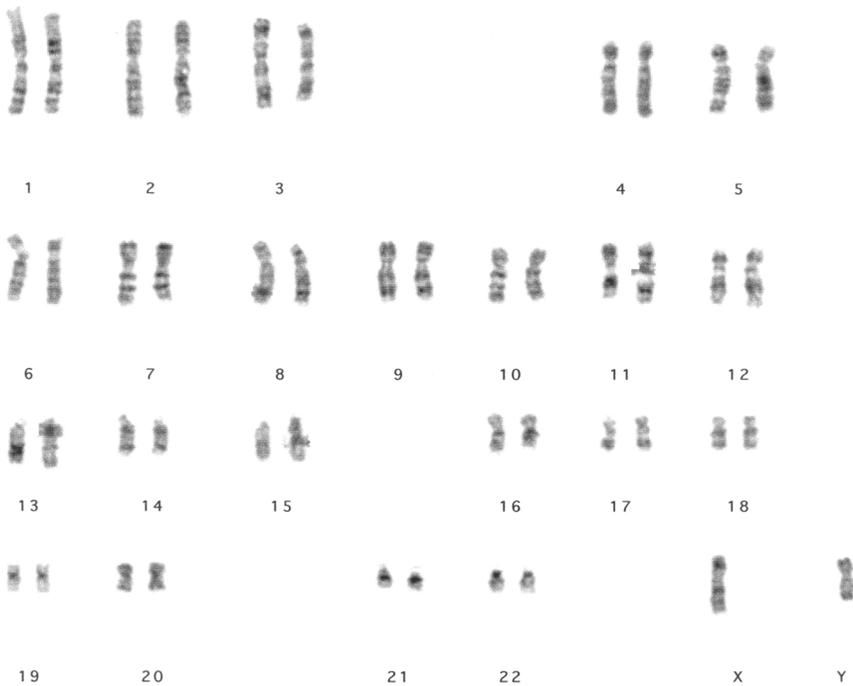

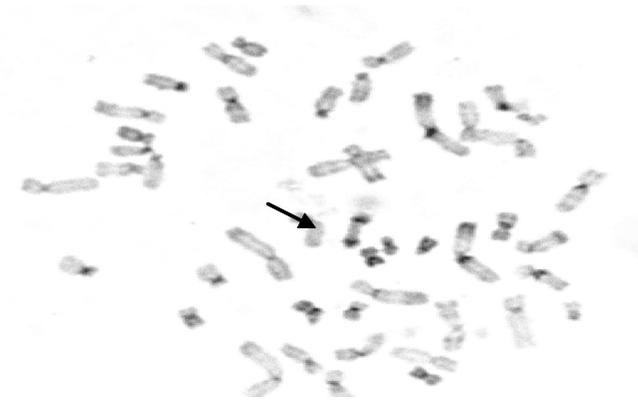**Fig. 1:** G-banded karyotype 46, X,+marker.

Fig. 2: C-banded metaphase showing the presence of two heterochromatic region on the long arm of isodicentricY chromosome.
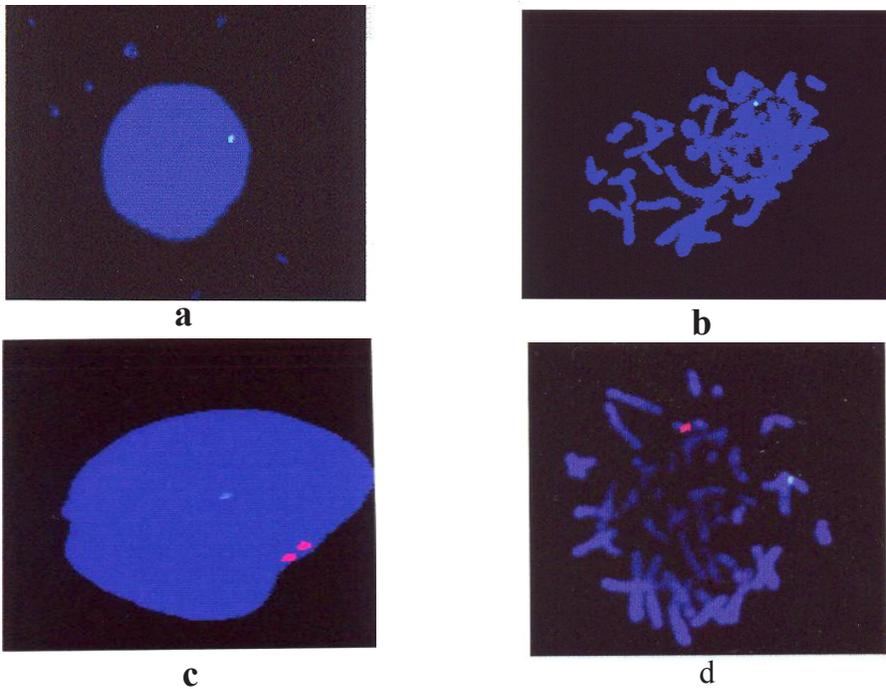

Fig. 3: FISH probes for centromeric X (CEPX,spectrum green hybridizes to the centromere of human X chromosome) and for centromeric Y sequence DYZ3 (CEPY, spectrum orange hybridizes to the centromere of human chromosome Y):

a- Interphase cell showing one green signal of the X chromosome and no red signals of the Y chromosome.

b- Metaphase showing one green signal of the X chromosome and no red signals of the Y chromosome (45, X).

c- Interphase cell one green signal of the X chromosome and two red signals of the Y chromosome.

d- Metaphase showing one green signal of the X chromosome and two red signals of the Y chromosome(46, X, idicY).

Table 1: Clinical data of patients with isodicentric Y (p11.3).

Pat. No.	Age in years	Assigned sex	Presenting symptom	External genitalia
1	16	Female	Primary Amenorrhea	N.female
2	3	Female	AG	Enlarged clitoris, hypoplastic labia
3	1/12	Female	AG Dysmorphic features	Enlarged clitoris, fused labia
4	23	Female	SS(153cm) Primary amenorrhea	N.female
5	17	Male	AG	Micopenis, perineoscrotal hypospadias, undesc testis
6	13	Female	SS (119cm)	N.female
7	7/12	Male	AG	Micopenis, perineoscrotal hypospadias, undesc testis
8	7/12	Male	AG	Micopenis, perineoscrotal hypospadias, undesc testis
9	3	Male	AG	Micopenis, perineoscrotal hypospadias, undesc testis[rt]
10	19	Female	SS(120cm) Primary amenorrhea	N female
11	1	Male	AG	Empty scrotum, perineoscrotal hypospadias , enlarged phallus
12	15	Female	SS(139cm) Primary amenorrhea	N. female
13	12	Female	AG	Enlarged phallus, hypertrophied labia,no vaginal opening
14	19	Female	Primary Amenorrhea	Enlarged clitoris, blind vagina

AG:ambiguous genitalia; SS: short stature; N:normal; rt :right; abd testis: abdominal testis; low HL: low

Internal genitalia	Gonads	Turner stigmata	karyotype [G-banding&FISH]
N.uterus	Small ovaries	-	46,XX[64%]/ 47,XX,idic(Y)[36%]
N uterus	small ovaries	-	46,XX[80%]/ 47,XX,idic(Y)[20%]
N.uterus	Small ovaries	-	45,X[54%]/ 46,XX[24%]/ 46,X,idic(Y)[22%]
Hypoplastic uterus	Streak gonads	Poor 2ry sexual characters, cubitus vulgus	45,X[12%]/ 46,X,idic(Y)[88%]
Hypoplastic uterus	Streak gonads	–	45,X[62%]/ 46,X,idic(Y)[38%]
Hypoplastic uterus	Streak gonads	Low HL, poor 2ry sexual characters, cubitus vulgus	45,X[73%]/ 46,Xidic(Y) [27%]
-	Abd. testis	-	45,X[68%]/ 46,X,idic(Y)[30%]/ 47,XY,idic(Y)[2%]
-	Abd. testis	-	45,X[55%]/ 46,X,idic(Y)[45%]
	Testis at the pubic tubercle[rt]	-	45,X[64%]/ 46,X,idic(Y)[26%]
hypoplastic uterus	Streak gonads	Webbing, low HL, widely spaced nipple, no development of 2ry sex characters	45,X[58%]/ 46,X,idic(Y)[42%]
-	Abd. testis	-	45,X[30%]/ 46,X,idic(Y)[70%]
Hypoplastic uterus	Streak gonads	Webbing, low HL, poor 2ry sex characters	45,X[82%]/ 46,X,idic(Y)[18%]
No uterus	Bilateral testes in labia	-	46,Xidic(Y)
No uterus	Bilateral testes in labia	-	46,X,idic(Y)

hair line; undesc testis:undescended testis.

DISCUSSION

Due to instability of isodicentric chromosomes during cell division, several types of cell lines are found in the great majority of patients with an idic (Y), all presumably descendants of a progenitor and unstable idic (Y) chromosome[12]. Such mosaic patients exhibit a phenotype ranging from female with features of Turner syndrome and streak gonads (~50%), males with azoospermia, hypospadias and small/abnormal testes (~30%), to individuals with sexual ambiguity and gonadal dysgenesis (~20%)[2,4,13]. Short stature is also a common finding,with no regard to the sexual differentiation of the patient[15]. Predicting the phenotypic consequences of different duplications and deletions of dicentric Y chromosomes is usually complicated by varying degrees of mosaicism (45, X cell line), which may, in some cases, remain undetected.[14]

Mosaicism as well as phenotypic variability were features present in our patients. Ten of the patients (10/14) in the present study had a 45, X cell line along with the idic (Yq). Six presented with ambiguous genitalia and 4 with short stature and some Turner stigmata Similarly Tuck-Muller et al.[13], Bergendi et al.[15], and Robinson et al.[16] showed the presence of virtually all euchromatin, including SRY in patients with features of Turner syndrome and an isodicentric (Yq) chromosome Nonomura et al.[17] reported monochorionic monozygotic twins with discordant sexual phenotype due to different ratios of mosaicism 47, X, idic (Y), idic (Y) /46, X, idic (Y) /45, X.Two other female patients (2/14) in the present study had 46, XX cell line along with 47, XX, idic (Y) (one had normal female phenotype and primary amenorrhea, and the other had clitoral enlargement). Similar types of mosaicism was previously reported[18-20]. As pointed out by Hsu[4], Tuck-Muller et al.[13] and Bouayed Abdelmoula and Amouri[14] in their respective reviews of idic (Y) cases, the sexual differentiation of patients probably depends on the distribution of the 45, X cell line in various tissues, including the gonads.It has been proposed that the predominance of XO or XY cells determines gonadal differentiation into a streak gonad or a testis[3,21]. However, studies on gonadal tissue are hindered by the fact that it is rarely available for analysis, and a more easily-accessible tissue is usually studied.[22]

The absence or mutation of SRY on the isodicentric Y chromosome is another factor that adds diversity to the phenotype[23]. Six cases presented here have cells containing SRY but exhibit a female phenotype. Previous cytogenetic studies demonstrated that about 4–6.2% of patients with Y chromosome mosaicism are phenotypically females regardless of the presence of SRY[16,24,25]. It is thought that the development of a male phenotype is initiated early in development by action of the SRY gene product in the cells of the developing gonadal ridge. It appears that in patients exhibit a female habitus, absent or insufficient SRY transcript to specify a male phenotype was present in this tissue at the appropriate time during development[26], Robinson et al.[16] concluded that the majority of structurally abnormal Y chromosomes found in Turner syndrome patients contain two copies of virtually all the Y euchromatin, but although all patients with a Y isodicentric carried the testis determining factor gene SRY, the mosaic nature of their karyotypes rendered this insufficient to induce a male phenotype. The

degree and distribution of the 45, X cell line seem to be decisive factors in phenotype determination.

Two patients (2/14) in the present study had a non-mosaic karyotype in blood lymphocytes with idic (Yq) chromosome containing SRY, but still had female phenotype with bilateral testes in the labia majora DesGroseilliers et al.[1] reported similar non mosaic cases. In such cases, it is possible that the isodicentric Ychromosome was stabilized early on during gametogenesis in the father, through inactivation or synergic action of the centromeres[4,27]. Ulder et al.[28] concluded that they must be cryptic mosaics with an unidentified 45, X or other cell line lacking SRY. It is also possible that they carry a point mutation in SRY inhibiting its action[29]. The various degrees of mosaicism seen in patients could thus reflect the instability of the idic (Y) and the variable moment of its stabilization during embryogenesis.[27]

Some indication as to the origin of Y isodicentrics can be deduced from the fact that a normal 46, XY cell line was absent from all cases. However, the absence of a detectable 46, XY cell line in all 13 isodicentric cases described by Robinson et al.[16] and in 99 of the 102 described by Hsu et al.[4] strongly suggests that such errors are more likely to occur during gametogenesis before the spermatid stage, or during the first division after fertilization. This suggests that the abnormal Y chromosome was either (1) present in the sperm before fertilisation and resulted from an error during gametogenesis before the spermatid stage because two chromatids are required to generate these rearrangements, or (2) arose from an error in the first zygotic division. Errors occurring after the first zygotic division would result in mosaicism including a normal cell line. It can be argued that if the error occurred at a very early stage in development such mosaicism would be in many cases undetectable.

Because women with gonadal dysgenesis and Y material are at higher risk (15-20%) of developing gonadoblastoma[30], all our female patients were referred for surgical removal of their gonads The putative gonadoblastoma locus (GBY) hypothesized by Page is thought to correspond to the TSPY gene (testis-specific protein Y-encoded)[31], which has clusters in several loci on both the short and the long arm of the Y chromosome[32,33]. The fact that there may be multiple GBY loci on the Y chromosome could explain why such tumors have been reported in both idicY with breakpoints in the long and short arms.[3,4]

CONCLUSION

The great phenotypic variations seen in patients with an isodicentric Yq chromosome greatly limit the genotype – phenotype correlation. This variability is explained by the degree of mosaicim in different tissues. To improve the genotype-phenotype correlation, it is useful to analyze more than one tissue, as significantly different proportions of various cell lines can be found and to perform histological studies of the gonads. Molecular definition of the breakpoints will also provide more information, allowing for a better genetic counseling.

FISH analysis is a powerful tool in defining the Y rearrangement, and extending the number of cells investigated allowing a more precise evaluation of the

mosaicism. Molecular study by PCR technique is also needed to better characterize the chromosomal breakpoints and the deletion intervals.

Our findings and an extensive review of the literature emphasize the importance of detailed molecular analysis of abnormal Y chromosomes before any general conclusions can be reached concerning the relative effects of the Y chromosome abnormality and mosaicism on sexual differentiation.

REFERENCES

1. DesGroseilliers M, Beaulieu Bergeron M, Brochu P, Lemyre E, Lemieux N. Phenotypic variability in isodicentric Y patients: Study of nine cases. Clin. Genet. 2006; 70 (2): 145-50.

2. Abdelmoula NB, Amouri A. Les chromosomes Y dicentriques - Deuxieme partie: Correlation phenotype - genotype Dicentric Y chromosome - Second part: Phenotype-genotype correlations. Ann.Biol.Clin.(Paris) 2005; 63 (4): 363-75.

3. Alvarez Nava F, Soto M, Martinez MC, Prieto M, Alvarez Z. FISH and PCR analyses in three patients with 45, X/46, X, idic (Y) karyotype: Clinical and pathologic spectrum. Ann. Genet. 2003; 46 (4): 443-8.

4. Hsu LY. Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. Am.J.Med.Genet. 1994 1; 53(2): 108-40.

5. Gray BA, Bent Williams A, Wolff DJ, Zori RT. A non-sex chromosome marker in a patient with an atypical Ullrich-Turner phenotype and mosaicism of 46, X, mar/46, XX. Clin. Genet. 2001; 60(1):73-6.

6. Wiktor AE, Van Dyke DL. Detection of low level sex chromosome mosaicism in Ullrich-Turner syndrome patients. Am.J.Med.Genet. 2005 15; 138 (3): 259-61.

7. Page DC. Hypothesis: A Y-chromosomal gene causes gonadoblastoma in dysgenetic gonads. Development 1987;101 Suppl:151-5.

8. Seabright M. A rapid banding technique for human chromosomes. Lancet 1971 30; 2 (7731): 971-2.

9. Sumner AT. A simple technique for demonstrating centromeric heterochromatin. Exp.Cell Res. 1972; 75 (1): 304-6.

10. Sambrook J, Fritsch EF, Maniatis T. Molecular cloning: A laboratory manual. 2nd ed.: Cold Spring Harbor Laboratory Press; 1989.

11. Yorifuji T, Muroi J, Mamada M, Uematsu A, Kawai M, Momoi T, et al. Analysis of the SRY gene in Turner syndrome patients with Y chromosomal material. J.Med.Genet. 2001; 38 (11): E41.

12. Kohn B, Kleyman SM, Conte RA, Macera MJ, Glassberg K, Verma RS. Characterization of an isodicentric Y-chromosome for the long arm in a newborn with mixed gonadal dysgenesis. Ann.Genet. 1997; 40 (1): 10-3.

13. Tuck Muller CM, Chen H, Martinez JE, Shen CC, Li S, Kusyk C, et al. Isodicentric Y chromosome: Cyto-

genetic, molecular and clinical studies and review of the literature. Hum. Genet. 1995; 96 (1): 119-29.

14. Bouayed Abdelmoula N, Amouri A. Les chromosomes Y dicentriques. [Dicentric Y chromosomes. First part: Cytogenetic and molecular aspects]. Ann. Biol.Clin.(Paris) 2005; 63 (3): 263-78.

15. Bergendi E, Plochl E, Vlasak I, Rittinger O, Muss W. A Turner-like phenotype in a girl with an isodicentric fluorescent Y chromosome mosaicism. Klin.Padiatr. 1997; 209 (3): 133-6.

16. Robinson DO, Dalton P, Jacobs PA, Mosse K, Power MM, Skuse DH, et al. A molecular and FISH analysis of structurally abnormal Y chromosomes in patients with Turner syndrome. J. Med. Genet. 1999; 36 (4): 279-84.

17. Nonomura K, Kakizaki H, Fukuzawa N, Fujieda K, Harada N, Niikawa N, et al. Monozygotic twins with discordant sexual phenotypes due to different ratios of mosaicism of 47, X, idic (Y), idic (Y)/46, X, idic (Y)/4, X.Endocr.J. 2002; 49 (4): 497-501.

18. Schellberg R, Schwanitz G, Schweikert HU, Raff R. Chromosome mosaicism in patients with normal and abnormal Y-chromosome. Int.J.Hum.Genet. 2002; 2 (4): 213-21.

19. Bashamboo A, Rahman MM, Prasad A, Chandy SP, Ahmad J, Ali S. Fate of SRY, PABY, DYS1, DYZ3 and DYZ1 loci in Indian patients harbouring sex chromosomal anomalies. Mol.Hum. Reprod. 2005; 11 (2): 117-27.

20. Fernandez R, Pasaro E. Molecular analysis of an idic (Y) (qter -->p11.32: p11.32-->qter) chromosome from a fe-

male patient with a complex karyotype. Genet.Mol.Res. 2006; 5 (2): 399-406.

21. Bergada C, Coco R, Santamarina A, Chemes H. Variants of sexual differentiation in relation to sex chromosomal aberrations. Acta Endocrinol.Suppl. (Copenh) 1986; 279:183-7.

22. Gole LA, Lim J, Crolla JA, Loke KY. Gonadal mosaicism 45,X/46,X,psu dic (Y) (q11.2) resulting in a Turner phenotype with mixed gonadal dysgenesis. Singapore Med.J. 2008; 49 (4): 349-51.

23. Wu HH, Lee TH, Chen CD, Yeh KT, Chen M. Delineation of an isodicentric Y chromosome in a mosaic 45,X/46,X,idic(Y)(qter-p11.3::p11.3-qter) fetus by SRY sequencing, G-banding, FISH, SKY and study of distribution in different tissues. J.Formos. Med.Assoc. 2007; 106 (5): 403-10.

24. Kelly TE, Franko JB, Rogol A, Golden WL. Discordant phenotypes and 45,X/46,X,idic(Y). J.Med. Genet. 1998; 35 (10): 862-4.

25. Quilter CR, Nathwani N, Conway GS, Stanhope R, Ralph D, Bahadur G, et al. A comparative study between infertile males and patients with Turner syndrome to determine the influence of sex chromosome mosaicism and the breakpoints of structurally abnormal Y chromosomes on phenotypic sex. J. Med. Genet. 2002; 39 (12): e80.

26. Lovell Badge R, Hacker A. The molecular genetics of SRY and its role in mammalian sex determination. Philos. Trans.R.Soc.Lond.B.Biol.Sci.1995 29; 350 (1333): 205-14.

27. Kohler MR, Vogt PH. Interstitial dele-

tions of repetitive DNA blocks in dicentric human Y chromosomes. Chromosoma 1994; 103 (5): 324-30.

28. Udler Y, Kauschansky A, Yeshaya J, Freedman J, Barkai U, Tobar A, et al. Phenotypic expression of tissue mosaicism in a 45,X/46,X,dicY(q11.2) female. Am.J.Med.Genet. 2001 1;102 (4): 318-23.

29. Fernandez R, Marchal JA, Sanchez A, Pasaro E. A point mutation, R59G, within the HMG-SRY box in a female 45, X/46, X, psu dic (Y)(pter-->q11:q11-->pter). Hum.Genet. 2002; 111 (3): 242-6.

30. Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia. Cancer Genet.Cytogenet. 1987; 25 (2): 191-218.

31. Lau YF, Lau HW, Komuves LG. Expression pattern of a gonadoblastoma candidate gene suggests a role of the Y chromosome in prostate cancer. Cytogenet.Genome Res. 2003;101 (3-4): 250-60.

32. Tsuchiya K, Reijo R, Page DC, Disteche CM. Gonadoblastoma: Molecular definition of the susceptibility region on the Y chromosome. Am.J.Hum.Genet. 1995; 57 (6): 1400-7.

33. Rottger S, Yen PH, Schempp W. A fiber-FISH contig spanning the non-recombining region of the human Y chromosome. Chromosome Res. 2002; 10 (8): 621-35.