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CASE REPORT

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Isodicentric Y chromosome: cytogenetic, molecular and clinical studies and review of the literature

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Abstract Dicentrics are among the most common structural abnormalities of the human Y chromosome. Predicting the phenotypic consequences of different duplications and deletions of dicentric Y chromosomes is usually complicated by varying degrees of mosaicism (45,X cell lines), which may, in some cases, remain undetected. Molecular studies in patients with dicentric Y chromosomes have been few, and only two studies have attempted to determine the presence of SRY (the putative testis-determining factor gene). We report an 18-year-old female with short stature, amenorrhea, hirsutism, hypoplastic labia minora, and clitoromegaly who has a 45,X/46,X,idic(Y)(p11.32)/47,X,idic(Y)(p11.32),idic(Y)(p11.32) karyotype. Southern analysis using Y-specific probes (Y97, 2D6, 1F5, pY3.4) and polymerase chain reaction (PCR) analysis using primers for ZFY and SRY were positive for all loci tested, indicating that almost all of the Y chromosome was present. Our findings and an extensive review of the literature emphasize the importance of molecular analyses 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.

Introduction

Although dicentrics are among the most commonly reported structural abnormalities of the human Y chromosome, relatively few have been studied at the molecular level and only two of these studies (Chen and Culley 1992; Nanko et al. 1993) have included analysis for the presence of SRY (sex-determining region of the Y), a gene located in the Y short arm that is thought to be the testes-determining factor (TDF; Berta et al. 1990; Gubbay et al. 1990; Jäger et al. 1990; Sinclair et al. 1990; Koopman et al. 1991). The presence of this gene within a rearranged Y chromosome would be expected to initiate testicular development. Structurally, some dicentric Ys have the breakpoint in the long arm with duplication of the proximal long arm and the entire short arm, including SRY. Other dicentric Ys result from breakpoints in the short arm and, thus, have the entire long arm and proximal short arm duplicated. These dicentrics may or may not contain SRY.

Most patients with dicentric Y chromosomes present clinically with short stature or various disorders of sexual development. The great majority of reported patients are chromosomal mosaics with two or more cell lines, usually including a cell line lacking the dicentric Y. A comprehensive review of the literature suggests that sexual development in such patients depends on two factors: the structure of the dicentric Y chromosome and the level and distribution of mosaicism present.

We report a patient with short stature, gonadal dysgenesis, and a mosaic 45,X/46,X,idic(Y)(qter→p11.32::p11.32→qter)/47,X,idic(Y)(qter→p11.32::p11.32→qter),idic(Y)(qter→11.32::p11.32→qter) karyotype. Molecular analysis provided evidence for the presence of a number of Y-specific sequences, including SRY, in the isodicentric chromosome of our patient.

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Case report

The patient is an eighteen-year-old black female referred for genetic assessment because of primary amenorrhea and short stature. She was the product of the eighth and last pregnancy to her parents. Other pregnancies had produced a stillborn son, one daughter who died of "jaundice" at 7 months, a son with developmental delay, a son with mental retardation, and three healthy offspring.

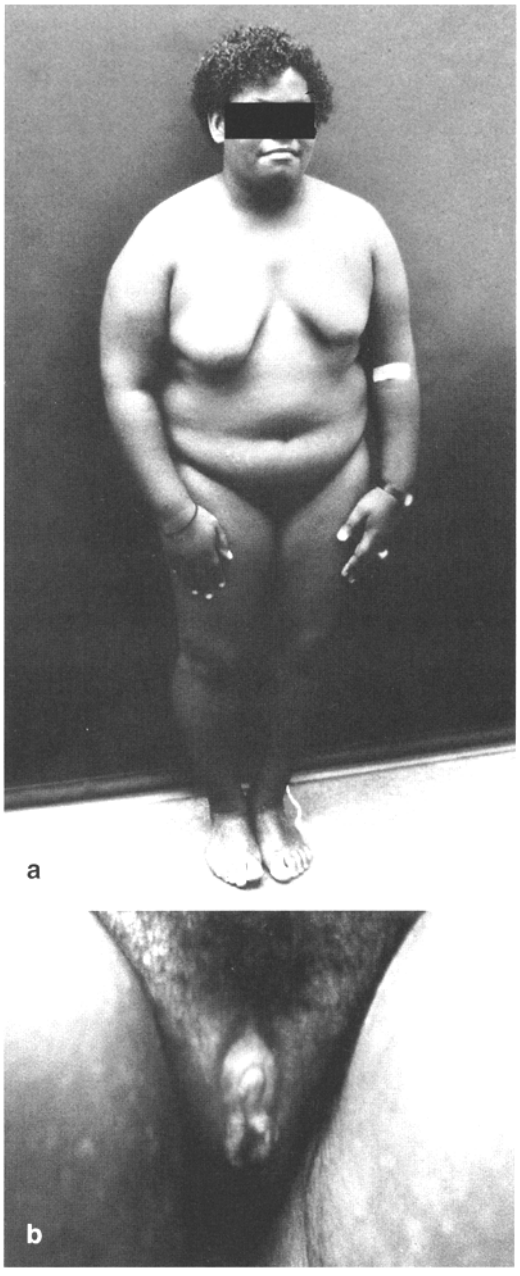

Fig. 1 Front view (**a**) and the external genitalia (**b**) of the patient

At 11 years of age, the patient showed initial breast enlargement and some pubic hair. She developed axillary hair at 16 years of age. She has been sexually active but has never menstruated.

The patient's physical features at the time of examination included short stature (height 142 cm; < 5th centile), obesity (weight 76 kg; 90th centile), short neck and hirsutism (Fig. 1 a). Examination of the external genitalia revealed clitoromegaly, rudimentary labia minora, hypoplastic labia majora, and a narrow but patent vagina (Fig. 1 b). Her dermatoglyphic traits were noted to be unusual, including 10 ulnar loops, a total finger ridge count (TRC) of 81, an A-B ridge count of 65, and atd angles of 43 (right) and 48 (left). Main line termination on areas 4 (right) and 13 (left) was also noted.

Laboratory findings included prepubertal female levels of estradiol (below 10 pg/ml) and high levels of luteinizing hormone (72 mU/ml with normal of 4–30 mU/ml), follicle-stimulating hormone (53 mU/ml with normal of 4–30 mU/ml) and testosterone (103 ng/dl with normal adult female value of 6.0–86 ng/dl).

Laparoscopic exploration revealed an infantile uterus, a left streak gonad and a right gonadal enlargement. Bilateral salpingo-oophorectomy was performed. Tissue fragments from the right gonad submitted for pathological assessment proved to be ovarian tissue composed of nests of primitive granulosa cells intermingled with variable numbers of germ cells. Rounded hyaline bodies and aggregates of calcium were also features of the lesion (Fig. 2 a). Isolated areas of luteinized cells were identified in the stroma and were devoid of crystalloids of Reinke (Fig. 2 b). These areas, representative of gonadoblastoma, merged with a diffuse germ cell component diagnosed as dysgerminoma (Fig. 2 c). The left fallopian tube was structurally normal (Fig. 2 d). The specimen thought, intraoperatively, to be a left streak ovary proved to consist only of vestigial Wolffian ducts (Fig. 2 e).

Materials and methods

Cytogenetic and fluorescence in situ hybridization (FISH) analyses

Chromosome analysis was performed using methotrexate-synchronized peripheral blood lymphocytes from the patient and her parents (Yunis et al. 1978), and skin fibroblasts and gonadal tissues from the patient. Chromosomes were analyzed using G-banding (Seabright 1971), Q-banding (Caspersson et al. 1971), and C-banding (Sumner 1972).

Lymphocytes from the patient were analyzed by FISH using a biotinylated Y-specific α-satellite probe, DYZ3. The probe and other reagents were purchased from Oncor and used according to manufacturer's instructions. Fluorescence microscopy was performed using a Leitz Orthoplan fluorescence microscope equipped with an H-2 filter for detection of the fluorescein-labeled probe and N-2 filter for the detection of propidium iodide, the counterstain.

DNA analysis

High molecular weight DNA was isolated from peripheral blood of the patient, her parents, and male and female controls. Restriction enzyme digestion, electrophoresis, and Southern blotting were performed essentially as described by Davis et al. (1986). Hybridizations were performed following the method of Sambrook et al. (1989). Radioactive probes labelled with ^{32}P were prepared using the random-primer DNA labeling method of Feinberg and Vogelstein (1983). The following Y-specific DNA probes were used: (1) 2D6, which recognizes a 3.14-kb fragment in *Eco*RI genomic DNA digests (Rasheed et al. 1991), (2) 1F5, which recognizes a 4.1-kb fragment in the *Eco*RI digests (Whisenant et al. 1991); (3) Y97, which recognizes an *Eco*RI 5.5-kb fragment (Wolfe et al. 1985); (4) pY3.4, which recognizes a 3.4-kb fragment in the *Eco*RI digests (Lau et al. 1984).

PCR analysis was used to detect sequences from the SRY gene in peripheral blood, skin, and right and left gonadal tissue from the patient and in blood specimens from her parents and male and female controls. Blood specimens from the same individuals were assayed for the presence of the 340-bp Y-specific zinc finger protein DNA (ZFY; Page et al. 1987). Polymerase chain reaction (PCR) amplification of the 609-bp SRY fragment was accomplished using XES2 and XES7 primers (Berta et al. 1990). PCR amplification of ZFY was performed using ZFY5' and ZFY3' primer sequences (Lau and Chan 1989). For amplification of either ZFY or SRY fragments, the following were added, in order, to 0.2 ml tubes: 13.5 µl dH_2O, 2.5 µl 10 × PCR buffer, 1 µl 100 m*M* $MgCl_2$, 2 µl 20 µ*M* primer 1, 2 µl 20 µ*M* primer 2, 2 µl 2500 µ*M* dNTP, 50–100 ng DNA, and 1 µl 1.25 U/ml *Taq* polymerase. Tubes were run in the Perkin-Elmer DNA thermal cycler (GeneAmp PCR System 9600) under the following parameters: hold at 94° C for 2 min, then 10 s denaturation at 94° C, 1 s annealing at 63° C for ZFY or 1 s annealing at 65° C for SRY, and 10 s extension at 72° C for 30 cycles. Bands were detected by ethidium bromide run on 12% acrylamide gels or 1% agarose gels.

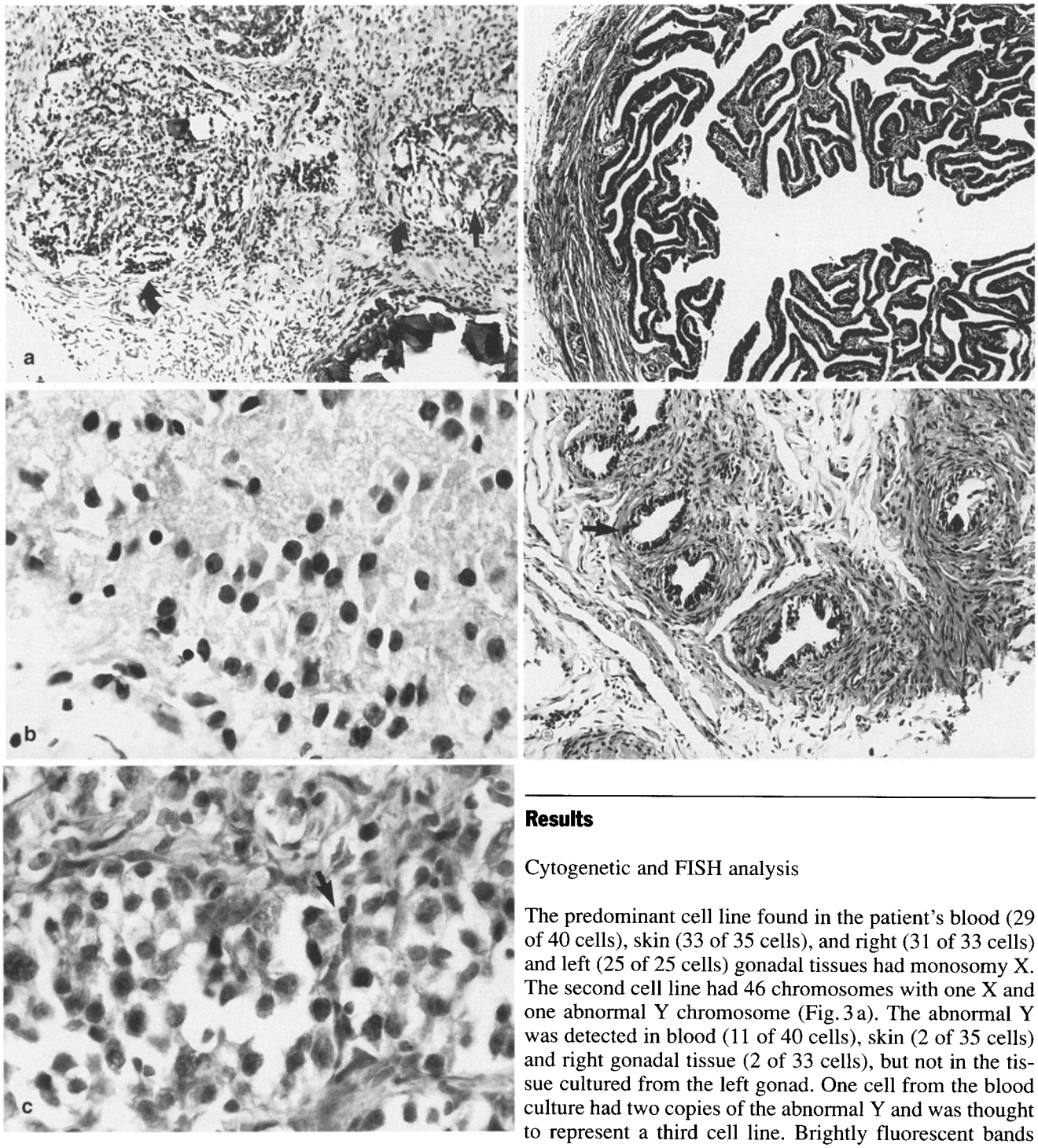

Fig. 2 a–e Histology of the internal genitalia of the patient (hematoxylin and eosin stain): **a** Two nests *(large arrows)* of small dark cells (granulosa cells) contain multiple hyaline bodies *(small arrow)*. Note the area of calcification (× 33). **b** Uniform, round nuclei are surrounded by luteinized cytoplasm; there are no crystalloids of Reinke (× 132). **c** Sheets of germ cells *(arrow)* grow in neoplastic fashion, representing a dysgerminoma (× 132). **d** The left fallopian tube is structurally normal (× 13). **e** Vestigial Wolffian ducts (*arrow*; × 33)

Results

Cytogenetic and FISH analysis

The predominant cell line found in the patient's blood (29 of 40 cells), skin (33 of 35 cells), and right (31 of 33 cells) and left (25 of 25 cells) gonadal tissues had monosomy X. The second cell line had 46 chromosomes with one X and one abnormal Y chromosome (Fig. 3 a). The abnormal Y was detected in blood (11 of 40 cells), skin (2 of 35 cells) and right gonadal tissue (2 of 33 cells), but not in the tissue cultured from the left gonad. One cell from the blood culture had two copies of the abnormal Y and was thought to represent a third cell line. Brightly fluorescent bands were present at the terminus of both arms of the abnormal chromosome by Q-banding (Fig. 3 b), which stained darkly by C-banding. C-banding also demonstrated the presence of two internal regions of centromeric heterochromatin, only one of which was constricted, separated by a small intervening segment of euchromatic material (Fig. 3 c). The abnormal chromosome was interpreted to be a dicentric isochromosome composed of two copies of the long arm, centromere, and proximal portion of the short arm of the Y chromosome. Both parents were karyotypically normal.

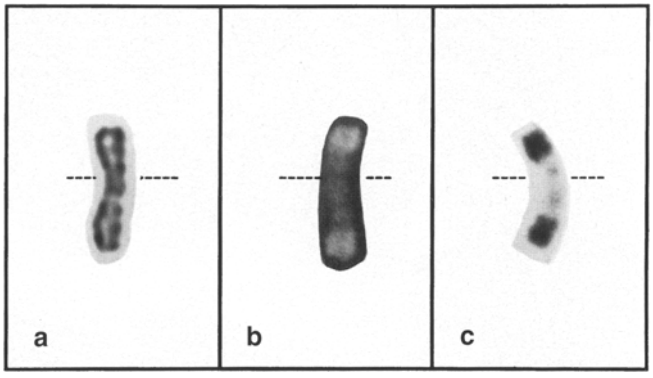

Fig. 3 Appearance of the isodicentric Y chromosome from the patient by G-banding (**a**), Q-banding (**b**), and C-banding (**c**)

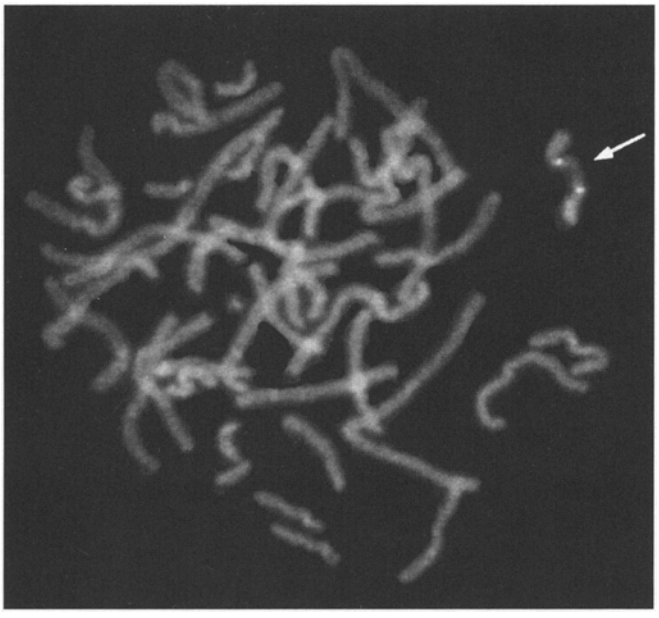

Fig. 4 Fluorescence in situ hybridization (FISH) analysis using the DYZ3 probe (Y-specific α-satellite). Metaphase showing two hybridization sites in the dicentric Y *(arrow)*

The cytogenetic interpretation was supported by FISH analysis. The Y-specific α-satellite probe hybridized to the two centromeric regions of the abnormal chromosome. The hybridization signals appeared to be separated by the combined lengths of most of two Y chromosome short arms (Fig. 4). FISH also confirmed the presence of the third cell line; 2 of 100 lymphocytes examined contained two copies of the abnormal Y.

DNA analysis

Analysis of genomic DNA from the patient indicated that sequences derived from the short arm, centromere, and the middle and terminal portions of the long arm of the Y chromosome were present (Table 1). The Y-specific sequences were present in the DNA from the patient's father and the male control but not in DNA from her mother or the female control.

Table 1 Results of molecular analysis(+, hybridization of probe or amplification with primer; –, lack of hybridization of probe or amplification with primer)

Probe or primer	Map position	Patient	Father	Mother	Controls	
					Male	Female
SRY	Yp11.32	+	+	–	+	–
ZFY	Yp11.32	+	+	–	+	–
Y97	Ycentromere	+	+	–	+	–
2D6	Yq11	+	+	–	+	–
1F5	Yq11.2	+	+	–	+	–
pY3.4	Yq12	+	+	–	+	–

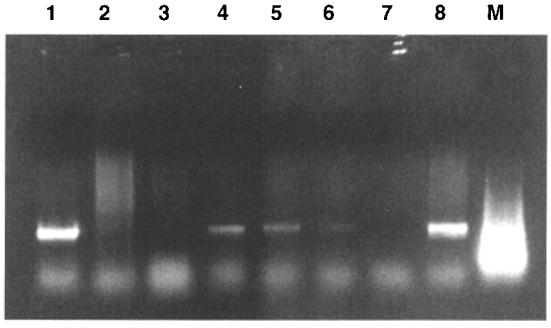

Fig. 5 Amplified SRY fragment (609 bp) was present in blood *(lane 6)*, skin *(lane 5)*, and right gonad *(lane 4)* but absent in the left gonad of the patient *(lane 3)*. *Lane 1* patient's father; *lane 2* patient's mother; *lane 7* female control; *lane 8* male control; *M* standard marker PBR322, *Msp*I digest

With ZFY primers, amplification of DNAs from the male control, the patient, and her father resulted in a band at 340 bp, whereas no band was produced with DNAs from the female control or the patient's mother (data not shown). Amplification of DNAs from the blood of the male control, the patient, and her father using SRY primers produced a 609-bp band, while amplification of DNAs from the female control and the patient's mother did not result in the band. SRY sequences were also detected in skin and tissue from the right gonad of the patient but not in left gonadal tissue (Fig. 5), confirming the tissue distribution of the dicentric Y determined by cytogenetic analysis.

Discussion

Although a considerable number of cases with dicentric Y chromosomes have been reported (Appendices 1, 2), only 13 have been studied at the molecular level (Müller et al. 1986; Disteche et al. 1986a; Magenis et al. 1987; Stalvey et al. 1988; Guttenbach et al. 1990; Haaf and Schmid 1990; Batstone et al. 1991; Cooper et al. 1991; Taniuchi et al. 1991; Bernstein et al. 1992; Chen and Culley 1992; De Arce et al. 1992; Savary et al. 1992; Nanko et al. 1993;

Table 2 Isodicentric Y chromosomes with short arm vs long arm breakpoints: comparison of cases

	Short-arm breakpoints	Long-arm breakpoints
Mental retardation	04/23 = 17%	03/20 = 15%
Short stature	29/39 = 74%	31/40 = 78%
Genitalia:		
Ambiguous	14/45 = 31%	05/46 = 11%
Female	20/45 = 44%	21/46 = 46%
Male	11/45 = 24%	20/46 = 43%
Hypospadias	0/11 males = 0%	9/20 males = 45%
Gonadoblastoma	09/37 = 24%	04/39 = 10%
Turner stigmata	12/36 = 33%	17/42 = 40%

Takihara et al. 1993). Only two of these studies included analysis for the presence of SRY, which was present in a schizophrenic man (Nanko et al. 1993) and absent in an 11-year-old girl with gonadal dysgenesis (Chen and Culley 1992).

Molecular analysis of our patient's DNA confirmed that sequences from the long arm and most of the short arm of the Y chromosome are present. ZFY and SRY, which map near the pseudoautosomal boundary, are both present, placing at least one breakpoint in Yp11.32. Although we have interpreted this chromosome as an isodicentric, we were unable to prove the duplication of short-arm sequences. Quantitative hybridization analysis to address this question was not attempted due to anticipated difficulties in interpretation of the data when mosaicism is present. In situ hybridization with a probe for SRY may be informative in this regard and will be pursued in the future to demonstrate the duplication. Since no Y sequences were shown to be deleted, the abnormal chromosome could be the result of a telomeric fusion or a Y;Y translocation with one breakpoint distal to SRY and the second breakpoint more proximal to the centromere. However, at least one breakpoint is likely to be within the pseudoautosomal region because of the proximity of SRY to the pseudoautosomal boundary (approximately 5 kb) (Rappold 1993).

The great majority (82 of 90 or 91%) of patients with dicentric Y chromosomes have mosaic karyotypes, most including a 45,X cell line. The importance of the 45,X cell line in the sexual development of these patients is clear from inspection of Appendix 2. Patients with dicentric Ys with long-arm breakpoints should have two copies of TDF in the duplicated short arm. However, among the 86% of these patients who are mosaic, almost half had female external genitalia, and hypospadias was common among the phenotypically male patients. Y chromosome aneuploidy with a 45,X cell line has been reviewed recently by Hsu (1994) who concluded that the 45,X cell line is apparently more influential in sex determination and sexual development than is the presence of Y chromosome material. The importance of mosaicism in determining phenotypic outcome is underscored by the report of Fujimoto et al. (1991) who described monozygotic twins, discordant for sex, but both with the same 45,X/46,X,idic(Y)(p11) karyotype. The effect of a 45,X cell line is further demonstrated by our patient, who is female although SRY is present in a percentage of her cells.

Table 2 presents a comparison of short and long arm breakpoint cases drawn from the data in Appendices 1 and 2. Short stature and other features of Turner syndrome are common in both groups and mental retardation is infrequent. Ambiguous genitalia are significantly more frequent among patients with short-arm breakpoints ($\chi^2 = 5.64$, $P < 0.025$). Hypospadias, which was found in 9 of 20 phenotypic males with long-arm breakpoints (45%), was not reported in the 11 males in the short-arm breakpoint group ($\chi^2 = 6.98$, $P < 0.01$).

Our patient had gonadal dysgenesis and a right gonadoblastoma. The increased incidence of malignancy in intra-abdominal gonads of patients with Y-derived chromosomes is an important clinical consideration. Gonadoblastoma is less frequently reported among patients with long-arm breakpoints (3 of 38) than among patients with short-arm breakpoints (9 of 37) although the difference failed to reach statistical significance. A gene (GBY) distinct from TDF has been hypothesized to be responsible for gonadal neoplasia (Page 1987) and several studies have supported this hypothesis (Disteche et al. 1986b; Magenis et al. 1987; Petrovic et al. 1992). GBY is presumed to lie near the centromere or in the proximal long arm of the Y (Page 1987). If GBY maps to the Y long arm, then some patients with long-arm breakpoints may be lacking this gene.

Bias of ascertainment is a significant problem in the interpretation of these data. The literature on postnatally diagnosed dicentric Y cases indicates a high rate of phenotypic abnormality. Few prenatally diagnosed cases have been reported (Polani et al. 1979; Bernstein et al. 1992). However, comparison with prenatally diagnosed cases of 45,X/46,XY mosaicism leads to the expectation that many patients with dicentric Y chromosomes go unreported. The vast majority of 45,X/46,XY individuals are born as normal males (Chang et al. 1990), although a significant number (27%) had abnormal gonadal histology at birth and none were followed after birth.

Because of the wide phenotypic variation found among patients with dicentric Y chromosomes, correlations between karyotype and phenotype have been difficult to draw. This presents a problem in cases of prenatal or neonatal detection of a dicentric Y. Issues of sexual development and risk of gonadoblastoma are of major concern. The roles of mosaicism and genes such as TDF and GBY in determining phenotypic outcome are not clear. Molecular study of more patients with abnormal Y chromosomes may make it possible to determine the relative importance of mosaicism in the phenotypic development of individuals with dicentrics and other abnormalities of the Y chromosome.

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Appendix 1 Phenotypic variation in patients with dicentric Y chromosomes with short-arm breakpoints. Only cases studied with chromosome banding are included (*NR* not reported, *MR* mental retardation)

Karyotype	IQ	Age	Short stature	External genitalia	Gonadal differentiation	Turner stigmata	Reference
45,X/46,X,dic(Y)(p11.32)	normal	18 years	+	ambiguous	left streak, right gonadoblastoma	+	Present case
46,X,dic(Y)	NR	NR	+	female	NR	NR	Bühler et al. (1971)
45,X/46,XYdic/47,XYYdic/47, XYdicYdic	normal	6 years	–	ambiguous	ovotestes	–	Ying and Ives (1971)
46,XYdic	MR	16 years	+	female	bilateral streaks, gonadoblastoma	+	Armendares et al. (1972)
45,X/46,X,dic(Yq)	low normal	11 years	borderline	female	left ovotestis, right streak	+	Cohen et al. (1973)
45,X/46,X,Yqdic	NR	12 years	+	female	bilateral streaks	NR	Frey et al. (1975)
45,X/46,X,dic(Yq)	NR	15 years	+	ambiguous	left streak, right abdominal testis and gonadoblastoma	NR	Hayek and Yunis (1975)
45,X/46,X,dic(Y)(p11)/46,X, del(dicY)/47,X,dic(Y),dic(Y)/47, dic(Y),del(dicY)/47,X,del(dicY), del(dicY)	normal	4 years	+	ambiguous	testes	–	Buchanan et al. (1976)
45,X/46,X,dic(Y)/47,XY,dic(Y)/47, X,dic(Y),dic(Y)	NR	15 years	–	male	NR	NR	Kulikov et al. (1976)
45,X,t(1;14)(q31;q31)/46,X,dic(Y), t(1;14)(q31;q31)	NR	2 years	–	female	NR	NR	Kulikov et al. (1976)
45,X/46,XYqdic	NR	17 years	+	ambiguous	left abdominal testis and gonadoblastoma, no gonadal tissue on right	–	Tuncbilek et al. (1976)
45,X/46,X,dic(Yq)	normal	4 years	+	ambiguous	left testis, right streak and fallopian tube	–	Armandares et al. (1977)
45,X/46,X,dic(Y)(p11)	NR	12 years	+	ambiguous	left abdominal testis, right streak	–	Giraud et al. (1977) case 1
45,X/46,X,dic(Y)(p11)/47,X, dic(Y),dic(Y)/47,XY,dic(Y)/47, XYY/48,XYY,dic(Y)	MR	18 years	+	infantile female	bilateral streaks	+	Giraud et al. (1977) case 2
45,X/46,X,dic(Y)(p11)	NR	28 years	+	male	testes, oligospermia	–	Giraud et al. (1977) case 3
45,X/46,X,terrea(Y;Y)(pter;pter) /47,XYY	normal	8 months	NR	ambiguous	abdominal testes, gonadoblastoma	–	Roubin et al. (1977)
45,X/46,X,dic i(Yq)/47,X,i(Yq), i(Yq)/47,XYY	normal	20 months	+	ambiguous	left testis, right dysgenetic testis	–	Alexander et al. (1978)
45,X/46,X,dic(Y)	NR	Infant	+	ambiguous	left ovary, right testis	–	Fass et al. (1978)
45,X/46,X,idic(Yq)	NR	18 years	+	female	ovaries with streak tissue, Leydig and Sertoli cells and gonadoblastoma	–	King and Cook (1978)
46,XYqi/47,XYqiYqi	low normal	6 years	+	female	NR	+	Schmid and D'Apuzzo (1978)
45,X/46,X,dic(Y)(p11)/46,XX/ 47,XX,dic(Y)(p11)	NR	12 years	+	female, clitoral hypertrophy	NR	–	Chieri and Hirschhorn (1979)

Appendix 1 Continue

Karyotype	IQ	Age	Short stature	External genitalia	Gonadal differentiation	Turner stigmata	Reference
45,X/46,X,dic(Yq)	MR	14 years	+	male	testes	+	Hermier et al. (1979)
45,X/46,X,idic(Y)(p11.3)	normal	38 years	+	infantile female	bilateral streaks	–	Daniel et al. (1980)
45,X/46,XY/46,X,tan dic(Y)	normal	22 years	+	female	right streak, bilateral gonadoblastoma	–	Herva et al. (1980)
45,X/46,XdicY	MR	24 years	+	female, clitoral hypertrophy	bilateral streaks	+	Plauchu et al. (1981) case 1
45,X/46,XdicY	normal	21 years	–	female	bilateral streaks, right gonadoblastoma	–	Plauchu et al. (1981) case 2
45,X/46,X,dic(Y)/ 47,X,dic(Y),dic(Y)	NR	38 years	+	ambiguous, hypospadias	no gonadal tissue on left, right streak	–	Ponzio et al. (1981)
46,X,dic i(Yq)	normal	43 years	–	male	testes, azoospermia	–	Ataya et al. (1983)
45,X/46,XY/46,X,dic(Y)(p11)/47, XY,dic(Y)(p11)	normal	24 years	+	female	left streak, right ovotestis	–	Sloan et al. (1984)
45,X/46,X,idic(Yq)/46,XY/46,X, i(Yp)/47,XYY/47,XY,idic(Yq)	NR	infant	NR	ambiguous	NR	NR	Magenis et al. (1985) case 17
45,X/46,X,idic(Yq)/47,X,idic(Yq), idic(Yq)	NR	19 years	+	female	bilateral streaks with gonadoblastoma	–	Magenis et al. (1985) case 18
46,X,dic(Y)(p11.2)	NR	11 years	NR	female	gonadal dysgenesis	NR	Müller et al. (1986) Chen and Culley (1992)
46,X,dic(Yq)	NR	NR	–	female	dysgenetic abdominal testes	NR	Kovaleva and Yakovlev (1986)
45,X/46,XY/46,X,del(Yq)/46,X, monoc(Yq)/46,X,dic(Yq)/47, XY,dic(Yq)/47,X,monoc(Yq), monoc(Yq)	normal	13 years	+	male	testes	–	Fryns et al. (1987) case 1
45,X/46,XY/46,X,del(Yq)/46,X, monoc(Yq)/46,X,dic(Yq)/47, X,del(Yq),del(Yq)/47,XY, monoc(Yq)/47,X,monoc(Yq), dic(Yq)/47,XYY	normal	12 years	border-line	male	testes	–	Fryns et al. (1987) case 2
45,X/46,X,idic(Y)	NR	NR	NR	ambiguous	left ovotestis, right streak	NR	Stalvey et al. (1988)
45,X/46,X,idic(Y)(p11)	NR	infant	NR	ambiguous	left ovotestis, right streak	+	Weckworth et al. (1988) case 2
45,X/46,X,idic(Y)(p11)	NR	14 years	NR	female	left streak, right dysgenetic testis	+	Weckworth et al. (1988) case 4
45,X/46,X,dic(Y) (qter→p?::p?→qter)	NR	26 years	+	male	NR	+	Dennis et al. (1990)
46,X,i(Yq)/45,XO/46,XY/47, XYY/47,XY,i(Yq)/47,X, i(Yq),i(Yq)	normal	26 years	–	male	testes, azoospermia	–	Haaf and Schmid (1990); Guttenbach et al. (1990)
45,X/46,X,dic(Yq)	normal	34 years	+	male	testes, azoospermia	–	Mićić et al. (1990) case 1
45,X/46,X,idic(Y)(p11)	normal	15 months	+	female MZ twin	NR	+	Fujimoto et al. (1991)
45,X/46,X,idic(Y)(p11)	normal	15 months	+	male MZ twin	testes	–	Fujimoto et al. (1991)
45,X/46,X,idic(Yq)	NR	11 years	+	female	bilateral streaks	+	Seifer et al. (1991)
45,X/46,X,psu dic(Y)(p11.32)	NR	55 years	–	male	testes, azoospermia	–	Savary et al. (1992)

Appendix 2 Phenotypic variation in patients with dicentric Y chromosomes with long-arm breakpoints. Only cases studied with chromosome banding are included (*NR* not reported, *MR* mental retardation)

Karyotype	IQ	Age	Short stature	External genitalia	Gonadal differentiation	Turner stigmata	Reference
45,X/46,XY/46,XYdic/46,XYq-	normal	22 years	+	male, cryptorchidism	ovotestes, left gonadoblastoma	+	Morillo-Cucci and German (1971) patient 2
45,X/46,XY/46,XYdic/47,XYYdic	normal	49 years	+	female, clitoral hypertrophy	abdominal dysgenetic testes	+	Morillo-Cucci and German (1971) patient 3
45,X/46,XY/46,XYdic[a]	normal	18 years	–	infantile female	left spherical gonad with Leydig cells and tubular structures, right streak	+	Stevenson et al. (1971)
45,X/46,X,i(Yp)	normal	20 years	+	infantile female	bilateral streaks	+	Siebers et al. (1973)
45,X/46,X,dic(Y)(q1:2)/46,X, del(dic Y)/47,X,dic Y,dicY/47, X,dicY,del(dic Y)/47,X, del(dicY)del(dicY)	normal	24 years	+	infantile female	no gonadal tissue on left, right streak	+	Johnston et al. (1974)
45,X/46,X,dic(Y) (pter→q12::q12→pter)/46, X,del(Y)(q12)	normal	19 years	+	infantile female	bilateral streaks with gonadoblastoma	–	Málková et al. (1974)
45,X/46,X,dic(Y)(q12)	NR	14 years	+	infantile female	bilateral streaks	+	Giraud et al. (1977) case 4
45,X/46,X,dic(Y) (pter→q11::q11→pter)	normal	14 years	+	infantile female	left streak with gonadoblastoma, right mucinous cystadenoma	+	Ying et al. (1977)
45,X/46,X,idic(Y)(q11.2)	NR	17 years	+	infantile female	NR	+	Daniel et al. (1980) case 1
45,X/46,X,psu dic(Yp)	normal	16 years	+	female	NR	–	Magenis et al. (1985) case 4
45,X/46,X,psu dic(Yp)	NR	17 years	+	female	bilateral streaks	+	Magenis et al. (1985) case 5
45,X/46,X,psu dic(Yp)	NR	39 years	–	female	bilateral streaks	–	Magenis et al. (1985) case 6
45,X/46,X,psu dic(Yp)	NR	infant	NR	ambiguous	NR	–	Magenis et al. (1985) case 7
45,X/46,X,psu dic(Yp)/47,X, psu dic(Yp),+psu dic(Yp)	NR	infant	NR	ambiguous	NR	–	Magenis et al. (1985)case 8
45,X/46,X,psu dic(Yp)	NR	2.5 years	–	ambiguous	NR	–	Magenis et al. (1985) case 9
45,X/46,X,psu dic(Yp)	NR	6 days	–	male, bifid scrotum	testes	–	Magenis et al. (1985) case 10
45,X/46,X,psu dic(Yp)	normal	2 years	–	male, hypospadias	testes, cryptorchidism	–	Magenis et al. (1985) case 11
45,X/46,X,psu dic(Yp)	MR	14 years	–	male	testes	+	Magenis et al. (1985) case 12
45,X/47,X,psu dic(Yp), +psu dic(Yp)	NR	16 years	+	ambiguous	right testis, no gonadal tissue on left	+	Magenis et al. (1985)case 13
45,X/46,X,psu dic(Yp)	normal	15 years	–	male	testes, delayed puberty	–	Magenis et al. (1985) case 14; Magenis et al. (1987)
46,X,psu dic(Yp)	normal	50 years	+	male, hypospadias	testes	–	Magenis et al. (1985) case 15
45,X/46,X,psu dic(Yp)	NR	10 years	+	female	left streak, no gonadal tissue on right	+	Magenis et al. (1985) case 16
45,X/46,X,dicYp(pter→q11.23: :q11.23→pter)	NR	15 years	+	female, clitoral hypertrophy	left abnormal testis; right streak	+	de Almeida et al. (1986) case 1
45,X/46,X,dicYp(pter→q11.23: :q11.23→pter)	NR	15 years	+	male, hypospadias	testes, bilateral fallopian tubes	–	de Almeida et al. (1986) case 2

Appendix 2 Continue

Karyotype	IQ	Age	Short stature	External genitalia	Gonadal differentiation	Turner stig-mata	Reference
45,X/46,X,dicYp(pter→q11.23: :q11.23→pter)	NR	18 years	+	infantile female	bilateral streaks	+	de Almeida et al. (1986) case 3
45,X/46,X,dicYp(pter→q11.22: :q11.22→pter)	NR	10 years	+	ambiguous, hypospadias	no gonadal tissue on left, right testis	–	de Almeida et al. (1986) case 4
45,X/46,X,dic(Y)(q11)/46, X,del(Y)(q11)	normal	24 years	+	male	testes, azoospermia	–	Chandley et al. (1986)
45,X/46,X,dic(Y)(q11)	NR	NR	+	female	bilateral streaks with gonadoblastomas	+	Disteche et al. (1986a)
45,X/46,X,dic(Y)(q11.2)	NR	5 years	NR	male, hypospadias	testes	NR	Drummond-Borg et al. (1988) patient 1
45,X/46,X,dic(Y)(q11.2)	NR	10 years	+	male, hypospadias	testes	NR	Drummond-Borg et al. (1988) patient 2
45,X/46,X,dic(Y)(q11.2)/47, X,dic(Y),dic(Y)	NR	6 months	NR	male, hypospadias	partially descended testes	NR	Drummond-Borg et al. (1988) patient 3
45,X/46,X,idic(Yp)	normal	2 years	+	male, hypospadias	left testis, no gonadal tissue on right	–	Kosztolanyi (1988) case 2
45,X/46,X,idic(Y)(q11)	NR	3 years	NR	female	benign mucinous fibroadenoma, left testicular streak	+	Weckworth et al. (1988) case 1
45,X/46,X,idic(Y)(q11)	NR	3 years	NR	male, hypospadias	left ovotestis in scrotum, right streak	–	Weckworth et al. (1988) case 3
45,X/46,X,i(Y)(pter→q12: :q12→pter)	NR	14 years	+	female	bilateral streaks	NR	Maraschio et al. (1990) case 1
45,X/46,X,+idic(Y)	NR	18 years	+	female	NR	–	Speleman et al. (1990) case 1
45,X/46,X,+idic(Y)	NR	2 years	+	female	NR	–	Speleman et al. (1990) case 2
45,X/46,Xdic(Y) (pter→q12::q12→qter)	NR	14 years	+	male	testes	+	Batstone et al. (1991)
46,X,idic(Y)(pter→q11.21: :q11.21→pter)	MR	3 years	–	male	testes	–	Blackman et al. (1991)
45,X/46,X,dic(Y)(q11.22)	NR	25 years	+	male, hypospadias	left cryptorchidism, right hypotrophic testis	–	Proto et al. (1991)
45,X/46,X,psu dic(Y)(q11.2)	normal	33 years	+	male	testes, no germinal tissue, azoospermia	–	Taniuchi et al. (1991)
45,X/46,X,dic(Y)	NR	9 years	+	female	no gonadal tissue	–	Cooper et al. (1991) case 2
45,X/46,X,idicY(nf)	normal	14 years	+	infantile female	bilateral streaks	–	De Arce et al. (1992)
46,X,dic(Y)(q11)	MR	46 years	+	male	testes	–	Nanko et al. (1993)
45,X/46,X,psu idic(Y)	normal	32 years	–	male	testes, no germinal tissue, azoospermia	–	Takihara et al. (1993) patient 1
46,X,psu idic(Y)	normal	41 years	+	male	testes, no germinal tissue, azoospermia	–	Takihara et al. (1993) patient 2

[a] Originally interpreted as 45,X/46,XXq-/46,XXq-dic