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A Unique Dicentric X;Y Translocation with Xq and Yp Breakpoints: Cytogenetic and Molecular Studies

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SUMMARY

A 32-year-old woman presented with secondary amenorrhea and infertility. She was of normal height and her breasts were well developed, but she had streak gonads; there were no signs of virilization, and she showed no somatic stigmata of Turner syndrome. Chromosome analysis revealed a dicentric X;Y translocation with Xq and Yp breakpoints. Centromeric banding demonstrated a Y centromere and a "suppressed" X centromere. The karyotype of the patient was interpreted as 46,X,t(X;Y)(q22;p11). The Yp breakpoint was confirmed by DNA-hybridization studies with six probes detecting Y-specific sequences. These DNA-hybridization studies were consistent with the presence of the long arm, centromere, and much of the proximal short arm of the Y. The Y-DNA studies of this female also revealed the absence of the distal short arm of the Y chromosome, to which the testis-determining factor has previously been localized.

INTRODUCTION

Cytologically identifiable X;Y translocations that include Yq are very uncommon: fewer than 40 cases, most of them familial, were reviewed by Fryns and van den Berghe (1983) and Bernstein (1985); a few more have since been documented (Cameron et al. 1984; Kelly et al. 1984; Wegner et al. 1984; Ross et al. 1985; Speevak et al. 1985). Interest in these sex-chromosome translocations

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lies not in their rarity but in the information that they have yielded about (1) the localization of genes on the pairing regions of the X and Y short arms and (2) the roles of the X and Y chromosomes in sex determination. All the X;Y translocations so far reported have involved the short arm of the X and the long arm of the Y, with the exception of two definitive cases (Cameron et al. 1984; Kelly et al. 1984) and one doubtful case (Borgaonkar et al. 1974; Koo et al. 1977; Kunkel et al. 1977; Jones et al. 1979) who showed Xq;Yq breakpoints and three cases with Xp and presumptive Yp breakpoints (Bernstein et al. 1978, 1980; Zuffardi et al. 1982).

Cameron et al. (1984) described an oligomenorrheic female of normal height with a 46,X,t(X;Y)(q22;q12) karyotype who was monosomic for region Xq22→Xqter; only the heterochromatic Yq12→Yqter segment was translocated to Xq22. The patient reported by Kelly et al. (1984) had a 46,X,t(X;Y)(q22;q11) karyotype associated with streak gonads.

In the present report, we describe, in an amenorrheic woman of normal stature, a unique dicentric t(X;Y) involving the same Xq22 breakpoint as that found in the patients of Cameron et al. (1984) and Kelly et al. (1984). Our patient differs from the latter two cases by having a translocation breakpoint on Yp and a suppressed X centromere. The t(X;Y) was nonrandomly inactivated. The precise breakpoint on Yp could not be cytogenetically determined, but molecular hybridization with Y-specific DNA probes indicated that much of the Y short arm was present.

CASE REPORT

JN, a 32-year-old black woman, consulted a gynecologist complaining of secondary amenorrhea and infertility. Her menarche was at 16 years, and thereafter she menstruated very infrequently and irregularly (every 4–6 mo), until, at the age of 29 years, her menses ceased. She had unsuccessfully tried to conceive for the previous 5 years, but she was otherwise healthy and there was no relevant history of previous illness. Her parents were unrelated, and she had three brothers and a sister, who were all fertile and had had 15 children among them. (Her father was dead, and her mother and siblings were not available for investigation).

Examination revealed an intelligent, phenotypically normal, obese female. Her height was 170 cm, crown-pubis length was 90 cm, and arm span was 190 cm. She showed none of the somatic stigmata of Turner syndrome, and there was no clitoromegaly. Pubic and axillary hair had a female distribution, but there was slight facial hirsutism; her breasts were large, adipose, and pendulous.

Hormonal studies revealed elevated serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Serum estradiol, progesterone, and testosterone levels were depressed (table 1). Laparotomy, performed prior to cytogenetic studies, revealed a hypoplastic uterus, fallopian tubes, and streak gonads. Normal ovarian or testicular tissue was not visible macroscopically; histological examination of serial sections from a biopsy specimen obtained

TABLE 1

HORMONAL PROFILE OF PATIENT JN

HORMONE	RESULTS	
	JN	Normal Range (Females)
FSH (mIU/ml)	58.7	2–9 (WHO IRP 78/549)
LH (mIU/ml)	54.8	2–16 (WHO IRP 68/40)
Oestradiol-17 beta (E2) (pmol/liter)	<74	<100 (amenorrhea)
Progesterone (nmol/liter)	1.2	.5–5 (preovulatory); 15–65 (postovulatory)
Testosterone (nmol/liter)	.54	.5–4.0
Free androgen index	<1	2.0–9.0
Testosterone-binding globulin (nmol/liter)	27.6	30–90
Prolactin (ng/ml)	8.0	2.15 (NIAMDD RP/11)

NOTE.—WHO IRP = World Health Organization International Reference Preparation; NIAMDD = National Pituitary Agency referenced standard.

from one of the streak gonads revealed only fibrous stromal tissue. No recognizable ovarian or testicular tissue was detected.

METHODS

1. *Cytogenetic Studies*

Peripheral blood metaphases were obtained from routine phytohemagglutinin-stimulated 72-h cultures and from methotrexate-synchronized cultures (Yunis 1976). Fibroblast cultures, established from a skin biopsy, were utilized for chromosome analysis, molecular-hybridization studies, and rodent-human somatic-cell hybrids. Giemsa (GTG), quinacrine (QFQ), and centromeric (CBG) banding were performed by means of standard techniques.

The X-inactivation pattern was studied by means of acridine-orange reverse banding after 5-BrdU incorporation during the last 4–6.5 h prior to terminating peripheral blood cultures (Dutrillaux et al. 1973) and 15 h prior to the termination of a fibroblast culture. Sequential Y- and X-chromatin staining of buccal epithelial nuclei was performed as described elsewhere (Bernstein et al. 1978).

2. *Molecular-Hybridization Studies*

DNA was extracted from cultured fibroblasts and/or peripheral blood leukocytes by means of a modification of the proteinase K–phenol:chloroform: isoamyl alchohol extraction procedure (Gross-Bellard et al. 1973). DNA from the proband and from both a normal male and a normal female was digested with either *Taq*I (Boehringer Mannheim) or *Eco*RI (Anglian) according to the specifications of the manufacturers, electrophoresed in 0.8% agarose, and transferred to nitrocellulose (Southern 1975). By means of nick-translation (Rigby et al. 1977), six Y chromosome–specific DNA probes were radiolabeled with (^{32}P)-dCTP to a specific activity of 3–9 $\times$ 10^7 cpm/μg DNA. The denatured probes were hybridized at 42 or 47 C in 50% formamide for 17–24 h, washed in

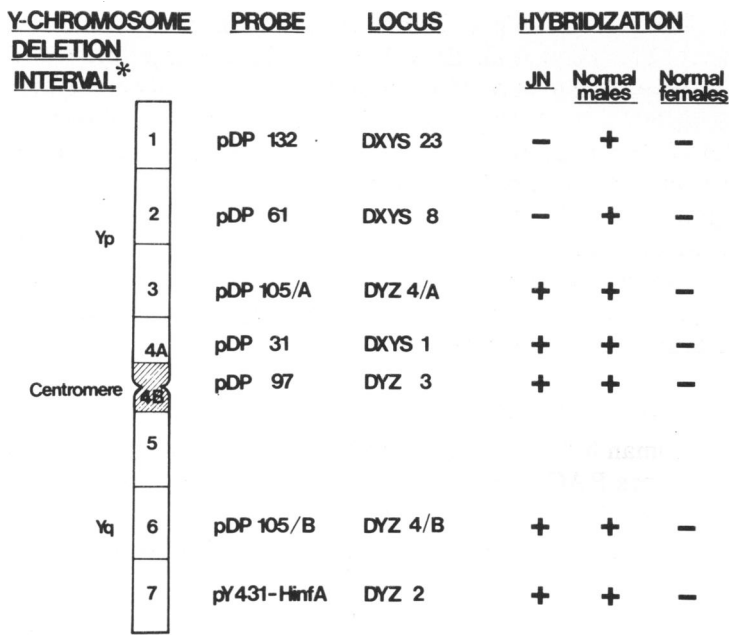

FIG. 1.—DNA-hybridization probes used to test for the presence (+) or absence (−) of Y-specific restriction fragments (see fig. 4). The deletion intervals to which these loci have been assigned are numbered 1–7. No implication as to cytologic distances is intended.
*According to Page 1986; Vergnaud et al. 1986.

0.1 × standard saline citrate (SSC), 0.1% sodium dodecyl sulfate at temperatures of 55–70 C, and autoradiographed with 3M X-ray film, type XD.

The probes described below have been assigned to a deletion map initially published by Vergnaud et al. (1986) and recently updated (Page 1986); a schematic representation of this deletion map is shown in figure 1.

Probe pDP132 (D. C. Page, unpublished data) detects highly homologous sequences on the X and Y chromosomes (locus *DXYS23*). At high stringency, pDP132 detects a Y-specific *Taq*I fragment of 4.4 kb, a marker for deletion interval 1 on the short arm of the Y chromosome.

Probe pDP61 (D. C. Page, unpublished data) is a subclone derived from plasmid 115 (Geldwerth et al. 1985), and it detects highly homologous sequences on the X and Y chromosomes (*DXYS8*). At high stringency, pDP61 detects a Y-specific *Taq*I fragment of 2.1 or 2.6 kb, a marker for interval 2 on the short arm of the Y chromosome.

Probe pDP105 (D. C. Page, unpublished data) defines multiple Y-specific loci (*DYZ4*). At low stringency, pDP105 detects many Y-specific *Taq*I fragments. We scored for the presence or absence of *Taq*I fragments of 2.5 kb (pDP105/A) and 5.2 kb (pDP105/B). Fragment pDP105/A is a marker for interval 3, on the short arm, whereas pDP105/B is a marker for interval 6, on the long arm of the Y chromosome.

Probe pDP31 detects highly homologous sequences on the X and Y chromosomes (*DXYS1*) (Page et al. 1982, 1984). At high stringency, pDP31 detects a Y-specific *Taq*I fragment of 15 kb, a marker for interval 4A, on the short arm.

Probe pDP97 (D. C. Page, unpublished data) is a subclone derived from cosmid Y97 (Wolfe et al. 1985). At high stringency, it detects a repeated Y-specific *Eco*RI fragment of 5.5 kb (*DYZ3*), a marker for the centromere of the Y chromosome and for interval 4B (D. C. Page, unpublished data).

Probe pY431-*Hinf*A (K. Smith, personal communication) detects highly repeated, Y-specific sequences (*DYZ2*). We scored for the presence, at low stringency, of Y-specific fragments on *Eco*RI digests, a marker for interval 7 on the long arm of the Y chromosome.

3. *Somatic-Cell Hybridization*

Rodent-human hybrids were constructed from JN's fibroblasts and from the rodent cell lines RAG(HGPRT−), Cl.ID(TK−), and B82(TK−). Fusion was achieved with 50% polyethylene glycol (PEG; mol. wt. 1,500). Fused hybrids were maintained in hypoxanthine-aminopterin-thymidine (HAT) medium for 1–2 days after fusion, until hybrid colonies were isolated. Unfused human fibroblasts were eliminated with ouabain. Five of 11 clones isolated from the RAG-human cross (JNR) were continuously maintained in HAT medium for retention of the X chromosome.

RESULTS

1. *Cytogenetic Studies*

Peripheral blood chromosome analysis of G-banded metaphases revealed a normal autosomal complement and an abnormal X chromosome in 122 of 127 cells analyzed [46,Xmar(X)] (fig. 2). A 45,X karyotype was found in five (3.9%) of the 127 cells. All 58 fibroblast metaphases analyzed had a 46,X,mar(X) karyotype. The abnormal X was noticeably shorter than its normal homologue, and the G-banding pattern of the mar(X) did not match that of the normal X. However, when the mar(X) was inverted, the G-bands on the abnormal Xq corresponded to those on the normal Xp. A faint band on the mar(X), usually visible as two chromatid dots, corresponded to the position of the normal X centromere but could not be clearly identified as centromeric heterochromatin by means of G-banding. The G-band-negative region between bands Xp21 and Xq21 on the mar(X) was consistently shorter than that on the normal X, possibly owing to the presence of a suppressed X centromere (figs. 2, 3*a*).

On the distal portion of the abnormal Xp, adjacent to the primary centromeric constriction, Q-banding showed the brilliant fluorescence characteristic of Yq12→qter. The mar(X) was thus identified as a t(X;Y), and the primary centromeric constriction corresponded to that of a Y-chromosome centromere (fig. 3*c*).

C-banding confirmed both the presence of distal Yq heterochromatin and that the primary centromeric constriction belonged to the Y chromosome. Another, unconstricted, dark C-band (not clearly visible on G-banding) was

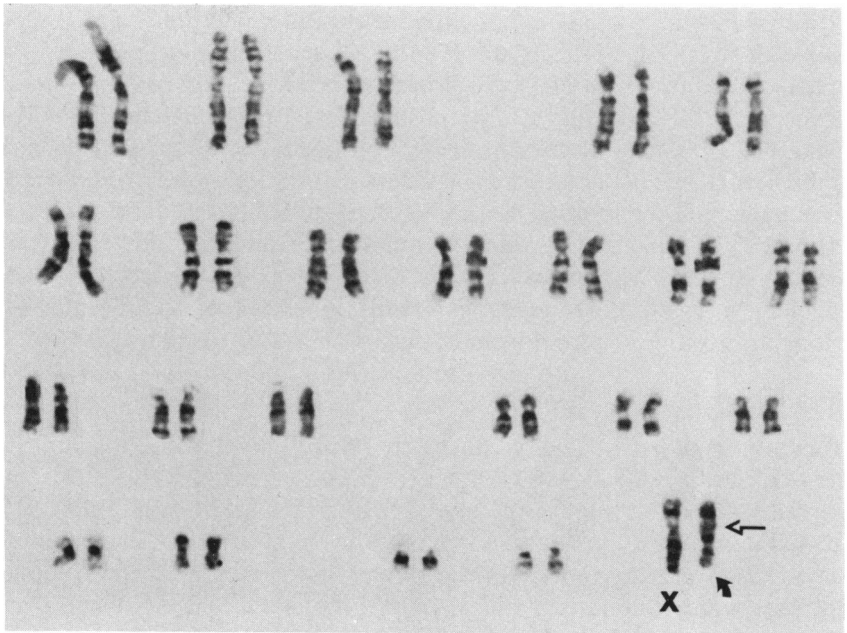

FIG. 2.—Giemsa-banded karyotype of the proband, 46,X(mar)X. The abnormal X (solid arrow) is inverted to show the correspondence of bands Xp21 on the normal and abnormal X chromosomes. A faint band, representing a suppressed X centromere, is indicated by the open-head arrow.

seen on the midportion of the t(X;Y) long arm, corresponding to the position of the normal X centromere. This C-band was therefore interpreted as an inactivated (suppressed) X centromere (fig. 3*b*), similar to the C-banding pattern of other dicentric chromosomes described by Therman et al. (1986).

The final interpretation of the karyotype, as based on G-, Q-, and C-banding, was 46,X,t(X;Y)(q22;p11) or (Xpter→Xq22::Yp11→Yqter). JN therefore had a dicentric chromosome with effective loss of Xq22→Xqter and presence of Y-chromosomal material that presumably included at least the proximal portion of Yp, based on the identification of a Y centromere.

X-inactivation studies showed that the t(X;Y) was inactivated in all 80 peripheral blood metaphases (fig. 3*d*). (Unfortunately, X-inactivation studies on fibroblast metaphases were unsuccessful.) An X-chromatin (Barr) body was observed in 26% and a Y-chromatin body in 71% of 300 buccal nuclei. Sequential staining for X chromatin in Y chromatin–positive cells showed X-chromatin bodies in the same position as the Y chromatin in 24 informative buccal nuclei (fig. 3*e*), again indicating preferential inactivation of the t(X;Y).

Further indirect confirmation of the nonrandom inactivation of the t(X;Y) was obtained from five clones derived from the cross JNR, which were continuously maintained in HAT medium to specifically select for the X chromosome. Of these five HGPRT-dependant clones, three died (presumably owing to loss of the normal X), and two retained only the normal X chromosome. None of the other fusions yielded clones that retained the t(X;Y).

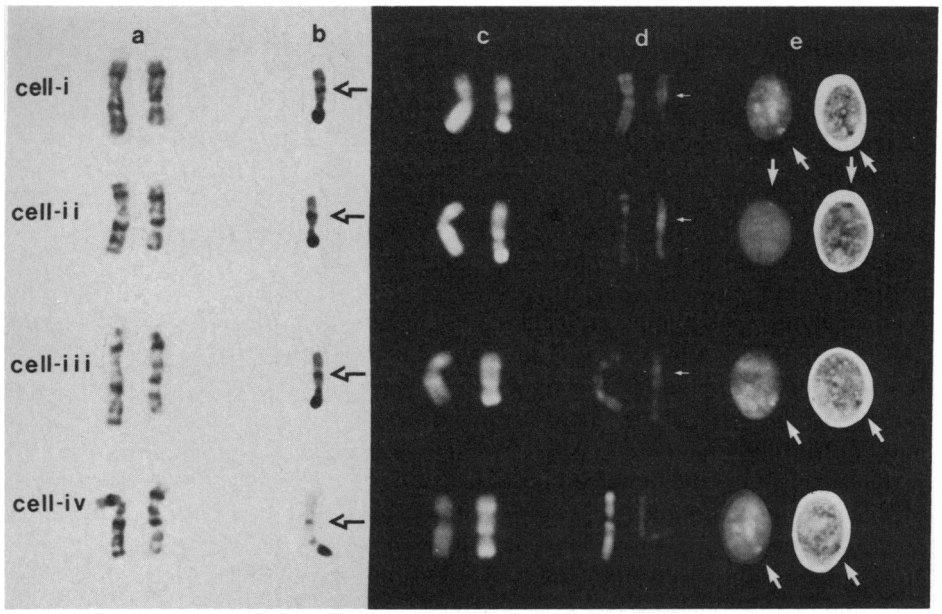

FIG. 3.—*a*, Giemsa-banded partial karyotypes of the normal X (left) and the t(X;Y) (right). *b*, Centromeric banding pattern of the t(X;Y), showing dark Yq12 heterochromatin, the primary centromeric constriction of the Y centromere, and the dark band of the suppressed X centromere (arrowed). *c*, Quinacrine-banded partial karyotypes of the normal X and the t(X;Y), showing the brilliant fluorescence of Yq12. *d*, Acridine-orange reverse banding after 5-BrdU incorporation during the late S-phase; the whole t(X;Y) is inactivated except for two fluorescent pericentric bands adjacent to the suppressed X centromere in cells i–iii (arrowed). *e*, Sequential quinacrine and cresyl-violet staining of buccal epithelial nuclei, showing associated X- and Y-chromatin bodies (arrowed).

2. *Molecular-Hybridization Studies*

Southern blot analysis was performed using each of the six probes described above. The results are shown in figures 1 and 4. Probes pDP105, pDP31, pDP97, and pY431-*Hinf*A showed a normal XY male pattern in the proband, but the Y-specific fragments detected by pDP61 (2.1 kb) and pDP132 (4.4 kb) were absent.

Probe pDP31, which detects X-linked allelic fragments of either 11 or 12 kb, showed double intensity of the 11-kb fragment when compared with the 15-kb Y-specific fragment in the proband. Similarly, when hybridized to the proband's DNA, probe pDP61 detected the 2.8-kb X-specific band at an intensity equal to that in normal females.

DISCUSSION

The phenotypic sex of 46,X,t(X;Y) individuals is determined by the interaction of several factors, the first of which is the physical presence or absence of testis determining–factor (TDF) genes on their t(X;Y) chromosome. The localization of a TDF or of factors on Yp (and possibly on proximal Yq) was

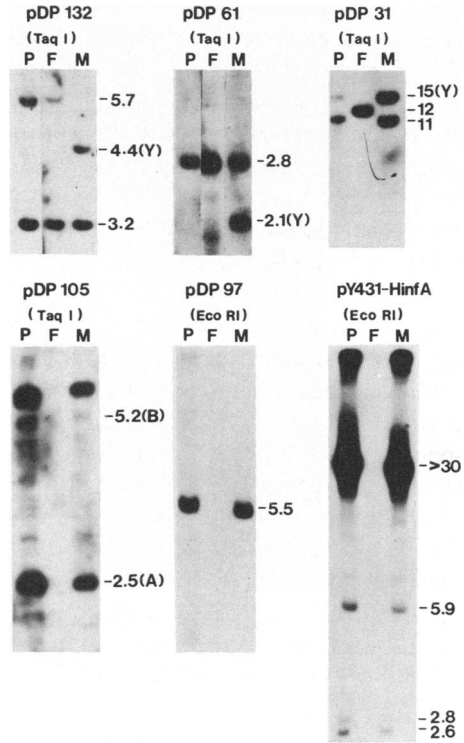

FIG. 4.—Autoradiographs showing hybridization of *Taq*I or *Eco*RI digests of the proband's DNA (P), as well as those of a normal female (F) and a normal male (M), to six DNA probes (all fragment sizes are in kilobases). The Y-specific DNA fragments detected by X-Y-specific probes pDP132, pDP61, and pDP31 are indicated by (Y). The fragments detected by pDP105 A and B, pDP97, and pY431-*Hinf*A are all Y specific.

originally deduced from the sexual phenotypes of patients with structural abnormalities of the Y chromosome (Buhler 1980; Davis 1981). The male phenotype of three cases of 46,X,t(X;Y) with a presumptive Yp breakpoint (as based on C-banding indicative of a suppressed Y centromere) was consistent with this assignment (Bernstein 1985). Two of these males were postpubertal and had features of XX males (Bernstein et al. 1980; Zuffardi et al. 1982). The most convincing cytogenetic evidence that distal Yp is the site of testicular determinants was (1) the demonstration of Yp material attached to distal Xp in four XX males (Magenis et al. 1982, 1985) and (2) loss of distal Yp in a phenotypic female with gonadal dysgenesis (Magenis et al. 1984). The isolation and cloning of single-copy Y-specific and X-Y-specific DNA probes (reviewed by Goodfellow et al. [1985]) was soon followed by the molecular demonstration of Yp DNA in the majority of XX males investigated (Guellaen et al. 1984; Andersson et al. 1986; Vergnaud et al. 1986). A seven-interval deletion map of the human Y chromosome was constructed on the basis of Y DNA–hybridization studies

(Page 1986; Vergnaud et al. 1986). The presence of certain Yp DNA sequences in most XX males (Vergnaud et al. 1986) and the absence of the same Yp sequences in some XY females (Disteche et al., in press) provided strong evidence that TDF was located in deletion interval 1 of Yp (Page 1986).

In the present case, Y chromosome–specific DNA probes, some of which have been detected in XX males, were hybridized to the DNA of the proband in an attempt to show the extent of Yp-specific DNA sequences in the X;Y translocation. Four of these probes detect sequences on Yp, one (pDP105) detects sequences on Yp and Yq, and pY431-*Hinf*A detects highly repeated sequences on the distal portion of Yq.

The probes used have been ordered on the Y chromosome by means of deletion mapping (Page 1986; Vergnaud et al. 1986). They represent a means of independently determining, albeit at a gross level, those portions of the Y chromosome present or absent from the patient's genome. Probe pDP132, which detects a Y-specific DNA sequence commonly present in XX males, (interval 1 as defined by Vergnaud et al. [1986] and Page [1986]) was not present in the proband. The Y-specific sequence detected by probe pDP61, a sequence that is also present in many XX males (interval 2), was also absent in the proband, indicating that the distal portion of Yp, containing probes pDP132 and pDP61, is deleted. Probes pDP105, pDP31, and pDP97, which are also present in some XX males, all showed the typical Y-specific DNA fragments. As expected, pY431-*Hinf*A gave the usual Y-specific DNA fragments after digestion with *Eco*RI. Thus, independently of the chromosome-banding studies, the DNA studies suggest the presence of the long arm, centromere, and proximal short arm (intervals 3–7) and the absence of the distal short arm (intervals 1 and 2). Given the female phenotype of JN, these DNA studies are consistent with the presence of TDF in interval 1 of Yp (Page 1986; Vergnaud et al. 1986).

X-specific dosage effects were seen with X-Y probes pDP31 and pDP61. The X-specific fragment detected by pDP31, a fragment that has been localized to Xq13-q21 (Page et al. 1984), was present at double the intensity of the Y-specific fragment, confirming the cytogenetic observation that Xq13-q21 had not been deleted in the translocation event. Probe pDP61 shows an X-specific band equal in intensity to that of normal females, indicating that the X-specific sequence is not located on Xq22→Xqter, the portion of Xq deleted in JN.

Because only one streak gonad was biopsied, it was not possible to establish whether the other streak gonad contained any primitive testicular tissue. The importance of removing both streaks was stressed to JN, because of the increased risk of malignancy in her dysgenetic gonads.

Screening of more than 300 cells yielded no cytogenetic evidence of mosaicism for an intact Y chromosome. The phenotype could have been modified by 45,X mosaicism, but only a minority of peripheral blood cells and not a single fibroblast metaphase showed loss of the t(X;Y). The percentage of 45,X cells in other tissues, especially the gonads, is unknown.

The Xq22 breakpoint of this translocation is also of interest. The phenotype of JN—and of the patients of Cameron et al. (1984) and Kelly et al. (1984), patients who also had an Xq22 breakpoint—differs from that of previously

described females with a 46,X,t(X;Y) karyotype and Xp;Yq breakpoints (Bernstein 1985). All three women had a stature >150 cm, and two of them had normal breast development, associated with oligomenorrhea in Cameron et al.'s (1984) 17-year-old patient and with oligomenorrhea followed by secondary amenorrhea in 32-year-old JN. The 17-year-old female described by Kelly et al. (1984) had primary amenorrhea and no breast development. Deletions, inversions, or translocations affecting the critical region Xq13→Xq27 are almost always associated with varying degrees of gonadal dysgenesis, but stature is usually normal and somatic features of Turner syndrome are minimal (Therman 1983). These patients' normal height contrasts with the short stature that is both associated with Xp deletions and found to be a characteristic feature of all t(X;Y) cases involving Xp (Bernstein 1985).

The t(X;Y) in JN is unique, in that the clear cytological demonstration of a Y centromere indicates that at least the proximal portion of Yp must be present; but, unlike the three males previously reported (Bernstein et al. 1978, 1980; Zuffardi et al. 1982) as having a 46,X,t(X;Y)(p22;p11) karyotype, she had a female phenotype. On the basis of cytogenetic studies alone, one could not have excluded the possibility that TDF genes were, in fact, present but nonrandomly inactivated. However, the molecular studies show that Y-chromosome interval 1, which contains TDF (Page 1986; Vergnaud et al. 1986), is in fact deleted.

The findings in JN illustrate the complex nature of sex determination and emphasize the need for a multidisciplinary approach in the investigation of unusual chromosome abnormalities, if the phenotype-genotype interrelationships are to be understood.

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