Am. J. Hum. Genet. 52:463-471, 1993

Deletion (X)(q26.1→q28) in a Proband and Her Mother: Molecular Characterization and Phenotypic-Karyotypic Deductions

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Summary

During a routine prenatal diagnosis we detected a female fetus with an apparent terminal deletion of an X chromosome with a karyotype 46,X,del(X)(q25); the mother, who later underwent premature ovarian failure, had the same Xq deletion. To further delineate this familial X deletion and to determine whether the deletion was truly terminal or, rather, interstitial (retaining a portion of the terminal Xq28), we used a combination of fluorescence in situ hybridization (FISH) and Southern analyses. RFLP analyses and dosage estimation by densitometry were performed with a panel of nine probes (DXS3, DXS17, DXS11, DXS42, DXS86, DXS144E, DXS105, DXS304, and DXS52) that span the region Xq21 to subtelomeric Xq28. We detected a deletion involving the five probes spanning Xq26-Xq28. FISH with a cosmid probe (CLH 128) that defined Xq28 provided further evidence of a deletion in that region. Analysis with the X chromosome–specific cocktail probes spanning Xpter-qter showed hybridization signal all along the abnormal X, excluding the possibility of a cryptic translocation. However, sequential FISH with the X α-satellite probe DXZ1 and a probe for total human telomeres showed the presence of telomeres on both the normal and deleted X chromosomes. From the molecular and FISH analyses we interpret the deletion in this family as 46,X,del(X)(pter→q26::qter). In light of previous phenotypic-karyotypic correlations, it can be deduced that this region contains a locus responsible for ovarian maintenance.

Introduction

Phenotype-karyotype correlations by deletion mapping of females with structural abnormalities of the X chromosome have enabled the tentative localization of regions responsible for normal ovarian function and maintenance. The two most important regions appear to be Xp11 and Xq13 (Simpson 1987), as individuals with terminal deletions originating at these regions usually show complete ovarian failure. In addition, individuals with terminal deletions originating at both Xp21 and Xq24 show less severe perturbations of ovarian function. These patients have tended to manifest premature rather than complete ovarian failure, suggesting that either loss of a smaller portion of Xq or perturbation of a different region of Xq can reduce, but not necessarily obliterate, reproductive capacity (de Grouchy et al. 1981; Fitch et al. 1982; Fryns et al. 1982; Taysi 1983; Trunca et al. 1984; Krauss et al. 1987; Schwartz et al. 1987; Naguib et al. 1988; Veneman et al. 1991).

On the basis of the study of one family with an interstitial deletion of Xq (Krauss et al. 1987), a premature ovarian failure gene (POF1) has been tentatively localized to the Xq21.3-Xq27 region (Davies et al. 1991, p. 903). In all other cases involving deletions of Xq, the

Received July 13, 1992; final revision received November 18, 1992.

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0002-9297/93/5203-0003$02.00

cytogenetic interpretations have, to date, been considered to be terminal deletions. However, the difficulties involved in accurately determining the specific breakpoints by cytogenetics alone are well known.

In the present report we have studied a familial distal Xq deletion originally interpreted, on cytogenetic analysis, as terminal. Using Southern blot analysis with a series of DNA probes spanning the distal long arm of (X)(q21→qter), fluorescence in situ hybridizations (FISH) with total human telomere probe, and a probe cocktail that spans the entire length of the X chromosome, we more precisely determined the karyotype in the proband and her mother as 46,X,del(X)(pter→q26::qter). Our report also supports the tentative localization of the POF1 gene to distal Xq.

Subjects, Material, and Methods

Clinical Assessment of the Patients

The proband was detected when genetic amniocentesis was performed in the first pregnancy of a 36-year-old woman. At that time her spouse was 41 years old. The family history was unremarkable for birth defects, neonatal deaths, or spontaneous fetal loss. No other family members were available for investigations. The proband's grandparents had expired. The proband's maternal aunt had two children while in her third decade; a hysterectomy was performed after the birth of the second child, for reasons that are unknown. This woman refused to participate in our investigation.

Chromosome analysis from cultured amniotic fluid cells showed an apparent Xq terminal deletion, 46,X,del(X)(q25). The father had a 46,XY chromosome complement, whereas the mother showed the same deletion that the fetus had. The parents elected to continue the pregnancy. Delivery at 40-wk gestation resulted in a 2,520-g infant. Apgar scores were 8 at 1 min and 9 at 10 min. During a routine clinic visit at 5 mo of age, mild edema of the dorsum of both hands and feet and hypoplastic, hyperconvex fingernails and toenails were noted. These features were still present at age 9 years. However, the proband's growth and developmental milestones were normal. She sat without support at age 5 mo and took her first steps at age 10 mo. Menarche occurred at age 11 years. She continues to have menses at regular intervals to the present age of 16 years. She is an A student in school and is in good health.

The proband's mother experienced menarche at age 13 years. By age 21 years she manifested oligomenorrhea and did not menstruate for a year. Thereafter, her cycles resumed, with the intermenstrual interval ranging from 2 wk to 4 mo. Two years after the birth of the proband the mother had a second pregnancy, which terminated in a first-trimester spontaneous abortion. No fetal tissues could be obtained for cytogenetic analysis. Despite the patient being in apparent good health, menopause occurred at age 39 years. She showed no signs of autoimmune disease, adrenal abnormalities, central nervous system dysfunction, weight extremes, or other known causes of premature ovarian failure. Follicle stimulating hormone was 78.4 mIU/ml, and luteinizing hormone was 61.0 mIU/ml. At age 51 years she is still in good health.

Conventional Cytogenetics

Chromosome analyses of peripheral blood of the proband and her mother were performed for various reasons on five different occasions, and cultured skin fibroblasts from both the subjects were also studied. Extensive investigations, by GTG and QFQ techniques, of over 300 metaphases (150 each) showed the ostensible terminal deletion in both subjects. Analyses of 200 cells (100 each) by RFA- and RHG-banding techniques showed selective inactivation of the deleted X chromosome. No evidence of mosaicism for a 45,X cell line was seen in the proband or in her mother.

Molecular Cytogenetics: FISH

Three different FISH approaches were used to characterize the deleted X chromosome. First, the X α-satellite DNA probe for DXZ1 (Oncor, Gaithersburg, MD) and total human telomere probe (Oncor) were sequentially hybridized as follows: Denatured chromosomal DNA was incubated overnight with the DXZ1 probe. The slides were sequentially washed at 43°C in 65% formamide and 2 × SSC. Denatured telomere probe mixture was then added to the same slide; a cover glass was applied, and the container was sealed and reincubated overnight. The slides were washed at 43°C in 50% formamide, and the signals of both hybridizations were detected with fluorescein isothiocyanide (FITC)-labeled avidin and were amplified with anti-avidin antibody. This allowed the identification of telomeres at the end of the deleted long arm of the X chromosome. Second, an X chromosome–specific cocktail mixture of probes that traverse the entire length (Oncor) was used to determine whether any non-X chromosome–specific segment was present on the deleted X chromosome.

Third, the probe for DXZ1 and a cosmid (CLH 128; C. Lavedan and C. Schwartz, unpublished data), the

Table 1

Information on Probes Used for Southern Hybridization

Chromosome Location	Locus	Probe	Cloning Information	Restriction Enzyme	Allele Size (kb)
Xq21.3	DXS3	p19-2	pBR322/*Eco*RI	*Msp*I	4.4, 12
Xq22	DXS17	S21/9	gtWES/*Eco*RI	*Taq*I	2.2, 2.0
Xq24-q25	DXS11	p22-33	pBR322/*Hin*dIII	*Taq*I	11, 20
Xq25	DXS42	p43-15	pBR322/*Bgl*II	*Bgl*II	6.0, 9.5
Xq26.1	DXS86	St1	pBR329/*Eco*RI	*Bgl*II	12, 7.2/4.8
Xq26.2	DXS144E	c11	pBR322/*Pst*I	*Taq*I	4.3, 3.0
Xq27.1–27.2	DXS105	cX55.7	pAT153/*Eco*RI	*Taq*I	3.2, 4.5
Xq28	DXS304	U6.2	pBR322/*Hin*dIII	*Taq*I	7.0, 3.3
Xq28	DXS52	St14-1	pBR322/*Eco*RI	*Taq*I	many
4pter-q26	D4S12	A1	pSP64/*Eco*RI	*Hae*III	1.4, 1.0

SOURCES.—Wyman and White (1980); Aldridge et al. (1984); Bruns et al. (1984); Drayna et al. (1984); Gilliam et al. (1984); Hanauer et al. (1985); Kunkel et al. (1985); Scambler et al. (1985); Goonewardena et al. (1986); Hofker et al. (1987); Oberle et al. (1987); Rekila et al. (1988); and Dahl et al. (1989).

latter localized to Xq28, were cohybridized to verify the ostensible absence of region Xq28 in the deleted X chromosome. The cosmid was nick-translated in the presence of biotin-labeled nucleotides by using kits (S-4089-Kit and S1390-Kit; Oncor). The nick-translated and purified probe was precipitated, redissolved in hybridization buffer, denatured at 75°C for 10 min, and allowed to reanneal for 1 h. The cosmid probe was then combined with denatured X α-satellite probe and placed on denatured chromosomes on the slide and incubated overnight. The slides were washed (65% formamide and 2 × SSC), hybridization was detected with FITC-avidin, and signals were amplified with anti-avidin antibody.

Preparation of DNA and Southern Blot Hybridization

Genomic DNA was isolated from peripheral blood samples collected from the mother and the daughter. DNA from four chromosomally normal males and four chromosomally normal females served as controls. The genomic DNA samples were digested to completion and fractionated by agarose gel electrophoresis on 0.7% gels (Cavenee et al. 1984). Southern transfers of the restriction fragments were carried out in the presence of 0.025 M $NaPO_4$ (pH 6.6) as described elsewhere (Schwartz et al. 1986). The DNA probes listed in table 1 were labeled by random priming (Amersham, Arlington Heights) to a specific activity of at least 1 $\times 10^8$ cpm/μg (Feinberg and Vogelstein 1983). Hybridization, washing, and autoradiography were performed as described elsewhere (Schwartz et al. 1986). The presence or absence of each of the DNA probes on the deleted X chromosome (table 1) was sought on the basis of familial pattern of RFLP analysis when possible.

Densitometry

Whenever familial patterns were noninformative for a given RFLP, densitometric analysis was performed.

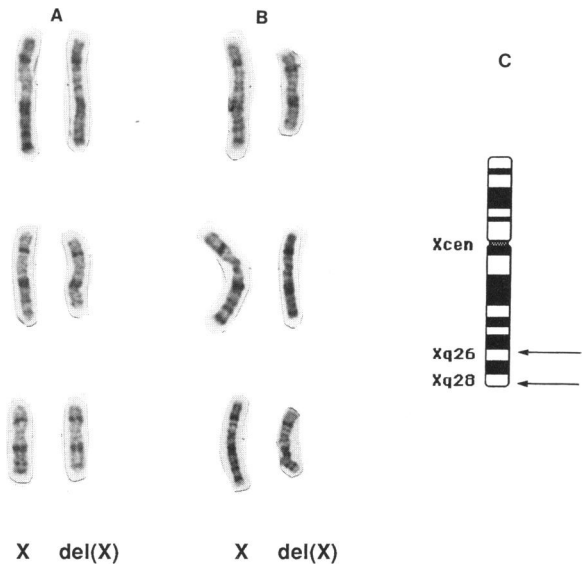
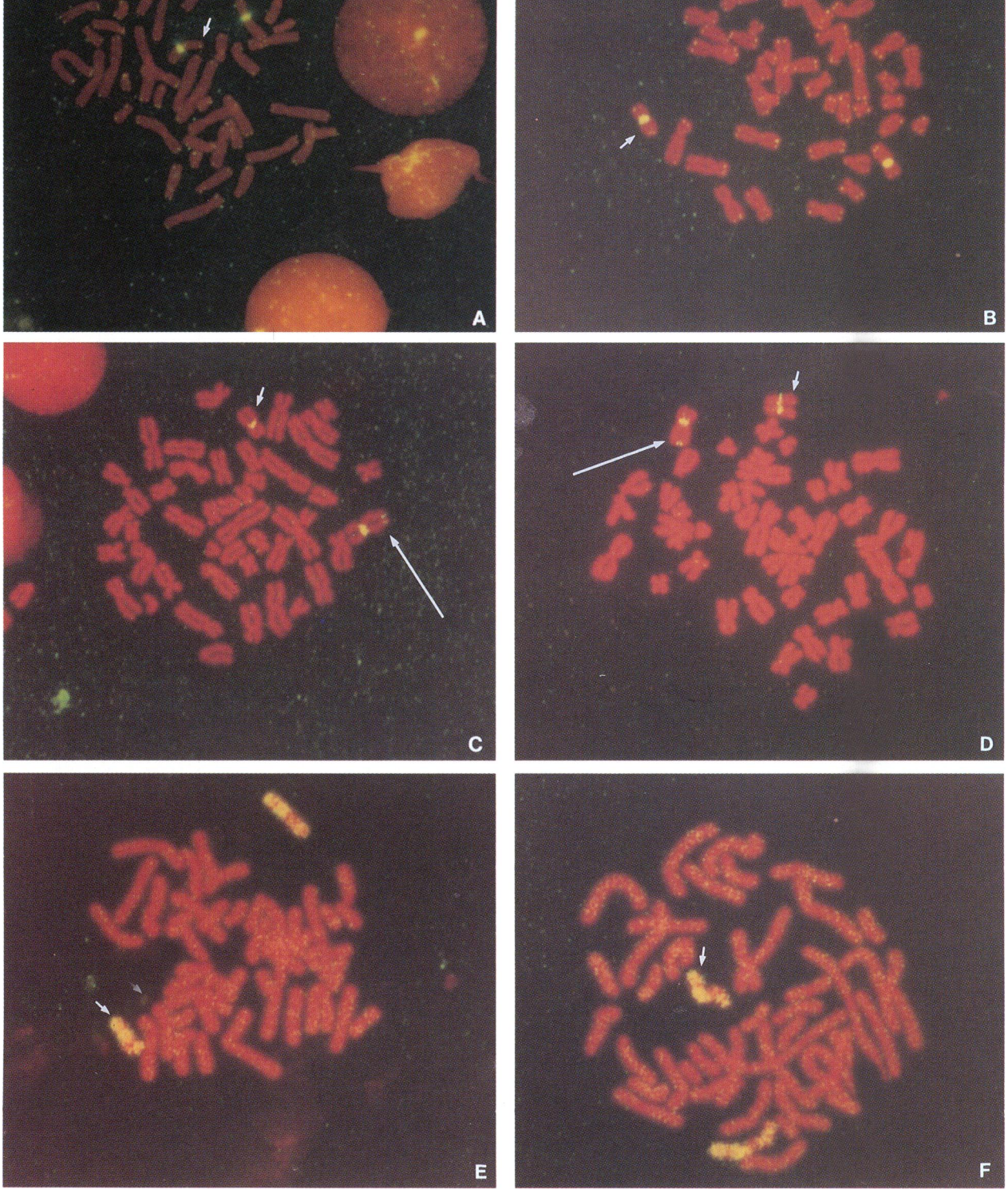


Figure 1 GTG-banded partial karyotype of X chromosomes from the proband (*A*) and her mother (*B*). *C*, Diagram of X chromosome showing the deleted region (Xq26→q28).


A
B
C
D
E
F

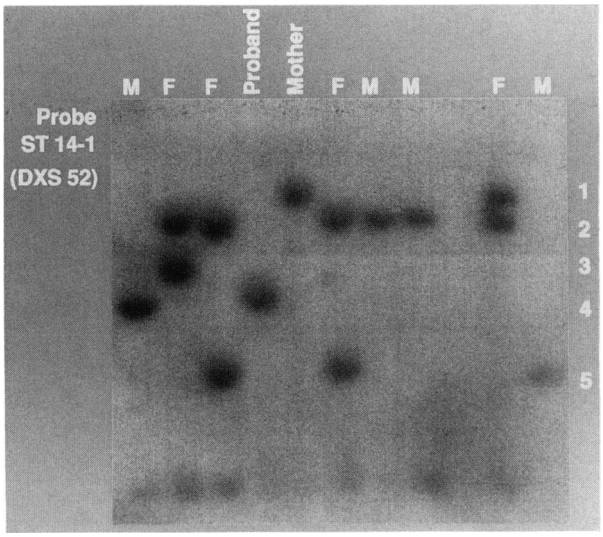


Figure 3 Autoradiograph using St14–1 (DXS52) probe. DNA samples from four normal males (lanes M), four normal females (lanes F), the proband (lane Proband), and her mother (lane Mother) were subjected to Southern blot analysis with the Xq28 probe, St14-1. The allele numbers for this particular set of samples are listed on the right. The unlabeled lane is a blank. The proband and her mother exhibited only a single allele each. Yet the single allele differs between the two individuals. We interpret that the proband inherited from her father the normal X chromosome with the St14–1 allele 4 and inherited from her mother the deleted X; the mother's single X chromosome carries another St14–1 allele 1.

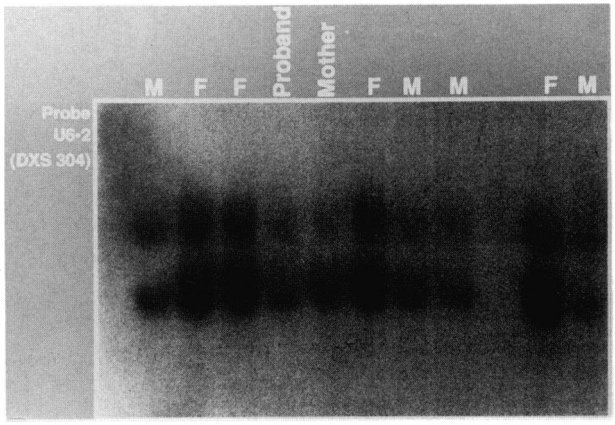


Figure 4 Southern hybridization to the DXS304 locus (U6.2). DNA samples from four normal males (lanes M), four normal females (lanes F), the proband (lane Proband), and her mother (lane Mother) were analyzed. The unlabeled lane is a blank. All individuals have two nonpolymorphic bands. Densitometric analysis was performed to distinguish between a single copy and two copies of this gene. When compared with the normal females, the proband and her mother show only half the signal.

Here the hybridization signals were measured and quantified by using a densitometer (Model 300A; Molecular Dynamics). The autosomal probe D4S12 (table 1) was hybridized to each filter to control for differences in sample concentrations. We then assessed the ratio of signals unique to X chromosome probes to the signals unique to the reference probe on chromosome 4. Comparisons were made between the controls (males and females) and our two subjects with the Xq deletion.

Results

The apparent chromosome complement as evident from traditional karyotype analysis was 46,X,del(X)(q25) in both the proband and her mother (fig. 1*a* and *b*). This impression held even after high-resolution chromosome analysis at about the 650-band level. Chromosome analyses involving over 300 cells from each subject in our study showed no evidence of mosaicism. Replication studies (RFA and RHG) utilizing 5-bromodeoxyuridine incorporation showed the abnormal X chromosome to be inactivated in 175 of the 200 cells scanned. In the remaining 25 cells the results were inconclusive.

With the more recent availability of FISH techniques and a telomere-specific probe, this interpretation was somewhat altered. When an X α-satellite DNA probe, DXZ1, was used in conjunction with the telomere probe, the X chromosome telomeres were readily identified on the long arms of both the normal and the deleted X. This suggested that the deletion was not truly terminal but was apparently interstitial (fig. 2*a* and *b*). Cohybridization (i.e., FISH) with the cosmid CLH 128 localizes to Xq28, and an X α-satellite probe failed to show the cosmid signal on the deleted X chromosome (fig. 2*c* and *d*). FISH with X-specific cocktail

Figure 2 *A* and *B*, Sequential FISH with X α-satellite and human telomere probe. Arrows indicate the deleted chromosome, which shows the telomeres. *C* and *D*, Cohybridization with X α-satellite and cosmid CLH 128 (localized to Xq28). Short arrows show the lack of hybridization on the deleted X chromosomes, whereas the long arrows denote hybridization on the normal X chromosomes. *E* and *F*, Chromosome painting with X-specific paint probe. Arrows point to the long arms of the deleted X chromosomes, clearly showing only the X chromosome–derived chromatin. Photographs *A*, *C*, and *E* are of samples from the proband; and photographs *B*, *D*, and *F* are of samples from her mother.

Table 2

Results of RFLP, Densitometry, and FISH Analyses

Locus	Probe	Chromosome Location	Proband	Mother
DXS3	p19-2	Xq21.3	Homozygous	Homozygous
DXS17	S21/9	Xq22	Homozygous	Homozygous
DXS11	p22-23	Xq24-25	Homozygous	Homozygous
DXS42	p43-15	Xq25	Homozygous	Homozygous
DXS86	St1	Xq26.1	Hemizygous	Hemizygous
DXS144E	c11	Xq26.2	Hemizygous	Hemizygous
DXS105	cX55.7	Xq27.1–q27.2	Hemizygous	Hemizygous
DXS304	U6.2	Xq28	Hemizygous	Hemizygous
DXS52	St14-1	Xq28	Hemizygous	Hemizygous

NOTE.—"Homozygous" denotes the presence of a locus on both X chromosomes, and "hemizygous" denotes deletion of the locus from one X chromosome. For FISH analysis results, refer to the text.

probes failed to show any non-X chromosome–derived area on the X chromosomes, in either the proband or her mother. Thus, the deleted X chromosome did not contain segments translocated from an autosome (fig. 2*e* and *f*).

RFLP Analysis

In defining the breakpoints in this deletion, more precisely than is possible by cytogenetic means, DNA hybridization analyses were performed using nine probes spanning the region Xq21→Xqter (table 1). Informative probes included c11 (DXS144E), which localizes to band Xq26.2, and probe St14–1 (DXS52), which is localized to band Xq28. Figure 3 illustrates our study with St14–1. Because this probe detects many different alleles in the population, females generally have two different alleles, as seen in all of our female controls. However, the proband and her mother exhibited only a single allele each. Yet the single allele differs between the two subjects. Our interpretation is that the proband inherited from her father the normal X chromosome with St14–1 allele 4 and inherited from her mother the deleted X; the mother's single normal X chromosome carries St14–1 allele 1. The other seven probes in table 1 were not informative for RFLP analysis.

Densitometric Analysis

For the seven probes that were uninformative by RFLP analysis, densitometric analysis was employed to quantitate the presence of one versus two copies of the single allele in question. A single-copy probe from chromosome 4 (A1) was used as a control to normalize the hybridization signals observed. Figure 4 shows a Southern blot hybridization with U6.2 (DXS304), a probe derived from Xq28. All individuals predictably exhibited the same alleles, but the intensity of the signals in normal females is approximately twice that in control males. The proband and her mother show bands with an intensity equal to that in the males, indicating only one copy at this locus. Table 2 summarizes both data obtained using the nine DNA probes from the X chromosome and the results of three FISH investigations.

Discussion

Telomeres define the end of a chromosome arm and confer stability. FISH studies in this family clearly showed the presence of a telomere at the distal terminus of the long arm of the deleted X chromosome. It could be argued that the presence of telomeres on chromosomes with terminal deletions provides evidence for regeneration of the telomeres subsequent to the event that led to its deletion. Indeed, evidence supporting telomere regeneration was gathered by Morin (1991), who reported alpha-thalassemia associated with an apparent terminal deletion of 16p. Telomere repeats (TTAGGG) were added, presumably by telomerase activity. This concept is further supported by the work of Wilkie et al. (1990) and Greider (1991). However, if such a scenario were common, then one would expect the telomeres to be regenerated in all deletions, so as to prevent the formation of ring chromosomes and iso-X chromosomes; otherwise, these may be exceptional chromosome abnormalities where telomere regeneration is somehow prevented.

A second possibility is that the deletion we studied actually represents a cryptic reciprocal translocation in this family, with subsequent unbalanced segregation during meiosis. Cryptic translocations involving telomeres or subtelomeric areas and resulting in clinical conditions have been summarized recently (Ledbetter 1992). In such a case, the translocation could have resulted in the contribution of the telomere of another chromosome in exchange for the segment of the X chromosome deleted in our patient. In view of the fact that cryptic translocations do exist and that there are no telomere probes unique for the long arm of X chromosome for FISH, this possibility cannot be categorically refuted. However, the probe cocktail for the entire span of the X chromosome failed to show any nonhybridizing region on the terminal area of the deleted X chromosome, implying the absence of autosomal material. The lack of mental retardation or somatic malformations in our patients also argues against the possibility that autosomal genes were translocated to the distal terminal of the X chromosome through cryptic translocation, for partial autosomal trisomy would produce an abnormal phenotype.

A third possibility is unequal meiotic crossing-over involving the long arms of two X chromosomes in one of the ancestral females. This seems to be the most likely cytogenetic explanation for the interstitial deletion in our subjects. Such an event would result in one X chromosome having a tandem duplication of distal Xq; the other X chromosome would show deletion for the same region. Fertilization involving both an ovum with the deleted X chromosome and a sperm bearing a normal X would result in a 46,X,del(Xq) complement. Hu and Worton (1992) convincingly reviewed evidence of unequal crossing-over or homologous recombination as the cause for some tandem duplications and deletions. If, from one of the homologous X chromosomes, the telomere region was transferred to Xq26.1 in exchange for Xq26.1→qter, then one derivative chromosome would show interstitial deletion and the other would show duplication. We favor this argument as the most likely explanation for the formation of the deleted X chromosome in this family. This karyotype would be designated 46,X,del(X)(pter→q26::qter).

Krauss et al. (1987) reported a similar family. Four women in two generations had terminal deletion of one of their X chromosomes. Three of these four women also had premature ovarian failure, which occurred between the ages of 24 and 37 years. Extensive DNA hybridization studies later showed the deletion in this family to be interstitial, encompassing region Xq21.3-q27. The investigations of Krauss et al. (1987) were used to localize a region (i.e., POF1) responsible for premature ovarian failure, tentatively assigned to Xq22→q27 (Davies et al. 1991, p. 903). In the family that we studied, Southern blot hybridization analysis of DNA from the proband and from her mother showed deletion of loci localized to proximal Xq26 (probes St1 and c11), Xq27 (probe cX55.7), and Xq28 (probes U6.2 and St14–1). RFLP analysis was sufficiently informative to allow direct assessment of c11 and St14–1; deletion of DNA sequences at the other three loci was determined through densitometric analysis. By contrast, probe p22–33 (DXS11), which is localized to Xq24→25, was clearly not deleted (table 2). Thus, our molecular analysis may further localize POF1 on Xq to Xq26.1→q27, the region common to both the deletion reported by us and that reported by Krauss et al. (1987).

A number of other apparent terminal deletions involving distal Xq have been associated with premature ovarian failure (Simpson 1987). In general, deletion originating at Xq13 invariably causes complete ovarian failure, with over 90% of such cases having this phenotype. Thus, two distinct regions on Xq can be deduced as necessary for ovarian function. At least 18 individuals have been reported with apparent terminal deletions of the distal long arm of the X chromosome, typically Xq25 or 26→qter (de Grouchy et al. 1981; Fitch et al. 1982; Fryns et al. 1982; Taysi 1983; Trunca et al. 1984; Krauss et al. 1987; Schwartz et al. 1987; Naguib et al. 1988; Veneman et al. 1991). The onset of menarche in female patients with the Xq deletion (from our report as well as those reported elsewhere) was not said to be delayed, with a range of 11–14 years of age. However, in adult patients where information is available, menopause usually occurred prematurely. In fact, reproductive span of the mother of our proband was relatively long (menopause age 39 years). In all of the cases discussed above, except for the family studied by Taysi (1983), the index patients came to medical attention because of menstrual irregularities or premature ovarian failure. By contrast, the family that we studied was ascertained through prenatal diagnosis for advanced maternal age, an ascertainment that is unbiased with respect to endocrine function. It follows that terminal or interstitial deletions involving Xq25-q26 may be relatively more frequent than reported, since they may go undetected because of the lack of striking phenotypic effect. Indeed, transmission of the deleted Xq chromo-

some through several generations from the mothers to their otherwise normal daughters has been recorded on several occasions (Trunca et al. 1984; Krauss et al. 1987; Naguib et al. 1988; Veneman et al. 1991). In one family, a daughter with Down syndrome inherited the deleted X chromosome (Taysi 1983). In two other families, the mothers transmitted their normal X chromosome to a daughter (de Grouchy et al. 1981) and a son (Fitch et al. 1982, patient 2). The karyotypes of two other infants born to mothers with Xq deletion are unknown (Fitch et al. 1982, patient 3; Naguib et al. 1988).

In summary, using FISH and Southern blot analyses, we have defined the breakpoints in a mother and her daughter with distal deletion of one of the X chromosomes of each. On the basis of the presence of telomeres, the familial deletion reported here may be interstitial rather than terminal. Further, we argue that all stable chromosomes with ostensible terminal deletions may contain a telomere sequence, and, as such, it can be argued that they represent interstitial deletions.

Acknowledgments

This research was supported in part by the visiting scholar program of the Southeastern Region Genetics Group (grant MCJ-131002), by the Genetics Program Contract, State of Tennessee Department of Health and Environment, and by a University of Tennessee Chair of Excellence (to J.L.S). We thank Dr. V. G. Dev for reconfirming the late-replication studies. Molecular analysis was performed at the Greenwood Genetics Center during a visiting assignment (A.T.T).

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