Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 2296–2300, April 1989
Genetics

Exchange of terminal portions of X- and Y-chromosomal short arms in human XY females

(sex reversal/human sex chromosomes/Turner suppressing genes/Yp− XY females)

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Communicated by Jean Dausset, December 19, 1988

ABSTRACT **Human Y(+) XX maleness has been shown to result from an abnormal terminal Xp–Yp interchange that can occur during paternal meiosis. To test whether human XY females are produced by the same mechanism, we followed the inheritance of paternal pseudoautosomal loci and Xp22.3-specific loci in two XY female patients. Y-specific sequences and the whole pseudoautosomal region of the Y chromosome of their fathers were absent in these patients. However, the entire pseudoautosomal region and the X-specific part of Xp22.3 distal to the *STS* locus had been inherited from the X chromosome of the respective father. This Xp transfer to Yp was established by *in situ* hybridization experiments showing an Xp22.3-specific locus on Yp in both cases. Such results demonstrate that an abnormal and terminal X–Y interchange generated the rearranged Y chromosome of these two XY females; they appear to be the true countertype of Y(+) XX males. In these patients, who also display some Turner stigmata, the Y gene(s) involved in this phenotype is (are) localized to interval 1 or 2. If the loss of such gene(s) affects fetal viability, their proximity to *TDF* would account for the underrepresentation of interchange 46,XY females compared with Y(+) XX males.**

During male meiosis in humans, the Y chromosome short arm pairs with the distal part of the X chromosome short arm (1, 2). Both sex chromosomes undergo an apparently single recombination event within the most distal part of this pairing segment, the pseudoautosomal region (3–5). Sequences encoding the testis-determining factor TDF have been mapped close and proximal to this region on the Y chromosome (refs. 6–8; see also ref. 9). Candidate DNA sequences for this gene have recently been cloned (10).

An abnormal X–Y interchange initiated proximal to *TDF* has been proposed to cause the two sex reversal syndromes in human—namely, XX maleness and "pure" XY gonadal dysgenesis in females (Swyer syndrome) (11). The X–Y interchange model has been validated for all XX males analyzed; these males possess Y-specific DNA sequences [Y(+) XX males] from a terminal X–Y interchange. Indeed, these individuals have inherited the entire terminal region of their paternal Yp chromosome as a single block and have correspondingly lost the terminal part of their paternal Xp (12, 13). This deletion on the tip of Xp often extends to distal Xp22.3-specific sequences. This loss was first suggested by the loss of expression of the paternal Xg allele (14) and subsequently demonstrated by the deletion of a paternal Xp-specific locus (12). DNA analysis of the X–Y junction of an XX male showed that this chromosomal exchange occurred between homologous sequences (15). Together these data suggest that this abnormal terminal X–Y interchange replaces the normal X–Y crossing over. The reciprocal product of this abnormal terminal X–Y interchange would lose *TDF* from the Y chromosome and proceed to XY gonadal dysgenesis.

XY gonadal dysgenesis is a disorder in which individuals with a 46,XY karyotype are phenotypically females; they are sterile, devoid of secondary sexual characteristics, and strongly predisposed to gonadal neoplasia (see ref. 16). Some familial cases are compatible with an X-linked recessive or a male-limited autosomal recessive inheritance (17–19), but most cases are sporadic.

In contrast to XX males most XY females exhibit no sex chromosome anomaly (ref. 20; G. Scherer, personal communication). The absence of Y-specific sequences has been identified in only a few XY females (20–24). These XY patients are referred to as Yp-deleted XY females hereafter; an abnormal terminal X–Y interchange, which deletes the distal part of Yp including *TDF*, would generate such a rearranged Y chromosome. Reciprocally this model also implies the acquisition of the terminal part at least of the pseudoautosomal region from the paternal X chromosome. If the X breakpoint is located proximal to the pseudoautosomal boundary, the whole paternal X pseudoautosomal region should be present, and therefore two copies of some Xp22.3-specific loci might be seen (one on the maternal X chromosome and one on the paternal rearranged Y chromosome). Similarly, expression of the paternal Xg would be predicted in some XY females; this expression has not yet been reported. Moreover, in the only case analyzed for chromosomal origin of the paternal pseudoautosomal region, no definitive conclusion could be reached (20). To investigate the X–Y interchange model as a cause of Yp-deleted XY gonadal dysgenesis, two sporadic cases of XY females were analyzed. Deletion of Yp could be shown only by DNA analysis. *In situ* chromosomal hybridizations and family analyses using pseudoautosomal and Xp22.3-specific DNA probes confirmed the abnormal terminal X–Y interchange model in both instances.

MATERIALS AND METHODS

Patients. The two young XY female subjects of this study (patients LAG092 and PAR097) are unrelated; each is the only child of nonconsanguinous parents. At birth both had marked lymphedema of the extremities and increased nuchal skinfolds indicating Turner syndrome. Their weights and sizes were normal, and no renal or cardiac anomalies were noted. The external genital organs were normal female, and pelvic echography revealed a normal uterus but the absence of gonads in each case. The peripheral lymphedema progressively decreased but was still visible on the feet at 15 mo.

Karyotypic Analysis. The absence of mosaicism was shown by karyotypic analysis of >100 metaphases from peripheral lymphocytes of both subjects and also from fibroblasts of

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Abbreviation: RFLP, restriction fragment length polymorphism.

subject LAG092. Prometaphase banding failed to reveal any deletion of the Y chromosome.

***In Situ* Hybridization.** Probes were radiolabeled with [^{3}H]dCTP and [^{3}H]dTTP by the random-priming technique (25) to a specific activity >3 × 10^7 dpm/μg. *In situ* hybridizations to metaphase chromosomes were done as described by Mattei *et al.* (26).

Probes and Southern Blot Analyses. Y-specific sequences from Yp or Yq were analyzed by probes 27a (*DYS104*), 47a and 47z (*DXYS5Y*), 13d (*DXYS7Y*), 7b (*DXYS2Y*), 16 (*DXYS6Y*), 115 (*DXYS8Y*), 52d (*DYS3*), 1 (*DXYS4Y*), 50f2 (*DYS7*), 52d (*DYS3*), 118 (*DYS8*), and pDP34 (*DXYS1Y*) (refs. 6, 27–30).

X-specific loci mapping between Xp22.3 and Xpter were analyzed by probes 38j (*DXS283*), J15 (*DXS284*), J21 (*DXS277*), J502 (*DXS285*), IP402, and IP147. All these newly isolated probes have been mapped distal to *STS* and *DXS278* using other X chromosome anomalies (C.P., J.L., M. C. Simmler, F. Rouyer, and J.W., unpublished work). The probes used for loci *DXS31*, *DXS278*, and *STS*, which map to the same Xp22.3 region, were M1A (29), CRI-S232 (31), and STb14 (32), respectively.

Pseudoautosomal loci were analyzed with probes 29C1 (*DXYS14*), 362A (*DXYS20*), U7A (*DXYS60*), 113D (*DXYS15*), 601 (*DXYS17*), and 19B (*MIC2*) (refs. 3, 4, 33–35).

The order of X- and Y-specific loci has been determined elsewhere (refs. 6 and 36; see also ref. 9) and is shown in Fig. 1. The chromosomal origin of the paternal pseudoautosomal loci inherited by the young XY females was determined by a three-generation DNA analysis of both paternal grandparents (case LAG092) or paternal grandmother only (case PAR097).

For Southern blot hybridization analysis, genomic DNA was digested by *Taq* I, *Msp* I, and *Pvu* II, according to the manufacturer's recommendations. Samples were electrophoresed on 0.8% agarose gels, transferred to a nylon membrane (GeneScreen, NEN), and hybridized as described (36). DNA inserts used as probes were labeled with [α-^{32}P]dCTP by the random-priming technique (25). Membranes were washed under the conditions indicated in the references for the relevant probe. Probes 38j, J21, J502, J15, IP402, and IP147 were washed at 68°C with 2× SSC (1× SSC = 0.15 M sodium chloride/0.015 M sodium citrate, pH 7) and 0.1% SDS.

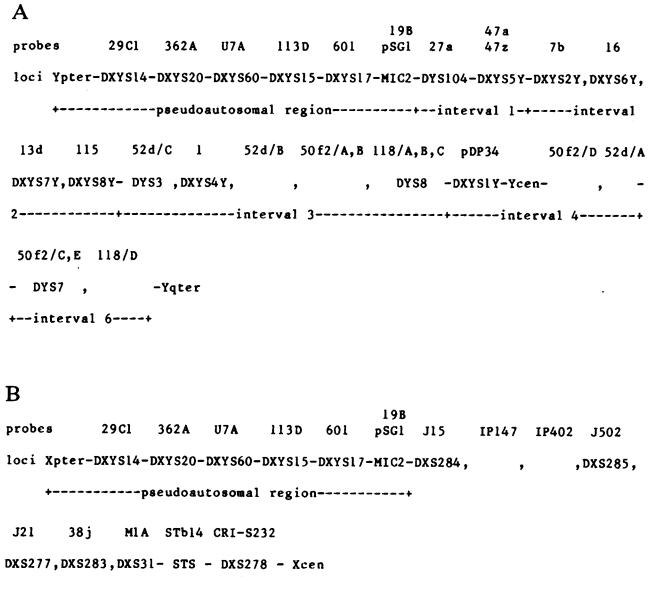

FIG. 1. Order of loci detected by the probes used in this study. Probe numbers are indicated on the upper line above the line with loci names. (*A*) Order of Y chromosome loci; intervals numbered according to Vergnaud *et al.* (6) are indicated on the lower lines. (*B*) Order of loci from Xp22.3.

Hybridization patterns were visualized by autoradiography of the filters by use of Kodak XAR-5 film at −70°C and intensifying screens.

RESULTS

Deletion of Y-Specific Sequences. Karyotypic analysis demonstrated that 45,X mosaicism did not cause the phenotype of the two patients and failed to detect any deletion from their Y chromosomes. Southern blot analysis was also used to investigate Yp deletions. Genomic DNAs from the patients and their fathers were digested with suitable restriction enzymes and probed for Y-specific DNA fragments belonging to one of the intervals 1, 2, 3, 4, and 6 as defined by Vergnaud *et al.* (6) (Fig. 1). Probes 27a, 47a, 47z, 7b, 13d, 115, and 16 failed to detect any Y-specific DNA sequences in either patient. Conversely, Y sequences recognized by probes 118, 1, 52d, 50f2, and pDP34 were revealed in both patients (Fig. 2 and Table 1). No deletion of Y-specific DNA sequences was detected with any of the probes in the fathers of the patients.

Chromosomal Origin of the Paternal Pseudoautosomal Loci. The inheritance of the restriction fragment length polymorphism (RFLP) alleles of six pseudoautosomal loci—*DXYS14*, *DXYS20*, *DXYS60*, *DXYS15*, *DXYS17*, and *MIC2*—was analyzed in the two families by Southern blot analysis. RFLPs provided direct evidence for the presence of one paternal and one maternal allele for all six pseudoautosomal loci in patient LAG092 and for loci *DXYS14* and *DXYS20* in patient PAR097. Loci *DXYS14* and *DXYS20* usually hybridized complexly. The presence of one copy of these loci from each parent was based on detection of some but not all paternal and maternal bands in each subject. In other instances some bands of the Southern blot autoradiographs were of double intensity; this was assumed to be due to two copies of that locus in the subject. Two copies were observed for both heterozygous loci (*DXYS60*, *DXYS15*, *DXYS17*, and *MIC2* in subject LAG092 and *DXYS17* in subject PAR097) and homozygous loci (*DXYS60*, *DXYS15*, *DXYS17*, and *MIC2* in subject PAR097). Parental phase was assessed by three-generation analyses. As shown in Table 2 and illustrated in Fig. 3, in all informative cases both XY girls had inherited one

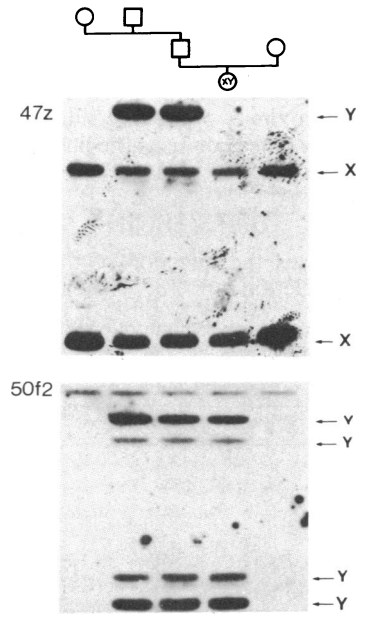

FIG. 2. Southern blot analysis of *Taq* I-digested genomic DNAs from young XY female of the LAG092 family hybridized with probes 47z and 50f2. Arrows indicate X- and Y-specific bands.

Table 1. Y-specific sequences present in XY females

Case	Y-specific fragments																
	27a	47a	47z	13d	7b	16	115	52d/C	1	52d/B	50f2/A,B	118/A,B,C	pDP34	50f2/D	52d/A	50f2/C,E	118/D
LAG092	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+
PAR097	−	−	−	−	ND	ND	−	+	+	+	+	+	+	+	+	+	+

Summary of DNA analyses of young XY females LAG092 and PAR097 with Y-specific sequences. Probes 50f2, 52d, and 118 detect several bands (A, B, C, etc.) corresponding to distinct locations mapped by Vergnaud *et al.* (6). ND, not done.

allele from the paternal grandmother, demonstrating that they had inherited the paternal X allele. Conversely the absence of a Y allele could be either directly observed (case LAG092) or inferred (case PAR097). These results show that both young XY females inherited the whole pseudoautosomal region from the paternal X chromosome and lost the entire pseudoautosomal region from the paternal Y chromosome. Because the gene *MIC2* maps close to the proximal boundary of the pseudoautosomal region, the subjects could have acquired some very distal X-specific loci from the paternal X chromosome, a possibility we further investigated.

A Double Dose of X-Specific Loci. Genomic DNA from both Yp-deleted XY females was analyzed with probes M1A (locus *DXS31*), STb14 (locus *STS*), CRI-S232 (locus *DXS278*), and six other recently isolated probes: 38j, J15, J21, J502, IP402, and IP147; all probes detect X-specific loci mapping to Xp22.3 (see *Materials and Methods*). Because no informative RFLPs could be found in the two families, the presence or absence of a second copy of these loci was determined by dosage indicated by band intensity in Southern blot autoradiographs. In both XY females, probes M1A, 38j, J15, J21, J502, IP402, and IP147 display a hybridizing signal comparable to normal females (Fig. 4). Thus each female has inherited two copies of all these loci, most probably one from each parent. STb14, the probe for the *STS* locus, gave banding intensities expected in males (data not shown), and therefore only one copy of the locus is present in each subject. Furthermore, a single maternal and no paternal allele of locus *DXS278* (probe CRI-S232) were observed in both subjects (data not shown).

X–Y Interchange. Both inheritance of the terminal portion of the paternal Xp and loss of the terminal portion of Yp strongly suggest that the terminal portion of Xp has been transferred to Yp. Direct evidence for such a transfer was provided by *in situ* hybridization using X-specific probe 38j and pseudoautosomal probes 362A and 113D. Grains obtained with these three probes were essentially clustered at the tips of Xp and Yp, as shown in Fig. 5 for the X-specific probe. The close proximity of the three loci to the tips of the patients' Y chromosomes confirms the paternal origin of the second copy of the *DXS283* locus.

DISCUSSION

This study addresses the question of the etiology of XY females with a deletion on Yp. This anomaly has been proposed to be caused by an abnormal X–Y interchange (11)—possibly involving the terminal parts of the short arms of both sex chromosomes, as has been demonstrated for (Y+) XX maleness (12, 13). In both XY females analyzed here Y-specific DNA sequences from intervals 3 and 4 but not intervals 1 or 2 were detected. The deletion thus involves the distal part of the Y chromosome short arm. This localization is consistent with the mapping of *TDF* to the distal part of interval 1 (6, 10). Segregation analysis of the pseudoautosomal alleles in the two families established that none of the Y-linked alleles of the paternal pseudoautosomal loci have been transmitted to the patients. Thus, all the terminal part of the short arm of the Y chromosome distal to interval 3 is deleted as a single block. Conversely, we observed the acquisition of the paternal X-linked alleles for all informative pseudoautosomal loci and the additional mobilization of seven X-specific loci mapping to Xp22.3. *In situ* hybridization established that X-specific loci were located on the Yp in both subjects. Thus, the family studies in conjunction with *in situ* hybridization show that the entire terminal part of the short arm of the paternal X chromosome has been transferred onto the Y chromosome. Our data establish that Yp-deleted XY females, like Y(+) XX males, can result from an abnormal terminal Xp–Yp interchange (see Fig. 6).

If XY females with a Yp deletion and Y(+) XX males are caused by the same process, the rearranged Y chromosome of Y-deleted XY females should be the exact reciprocal

Table 2. X or Y chromosomal origin of each paternal pseudoautosomal locus

Case	Paternal pseudoautosomal locus					
	DXYS14	*DXYS20*	*DXYS60*	*DXYS15*	*DXY17*	*MIC2*
LAG092						
X	+	+	+	+	+	+
Y	−	−	−	−	−	−
PAR097						
X	+	NI	NI	NI	NI	+
Y	−	NI	NI	NI	NI	−

Chromosomal origin of *DXYS14, DXYS20, DXYS60, DXYS15, DXYS17,* and *MIC2* as determined by hybridization of *Taq* I and/or *Msp* I DNA digests with probes 29C1, 362A, U7A, 113D, 601, and 19B, respectively. NI, not informative.

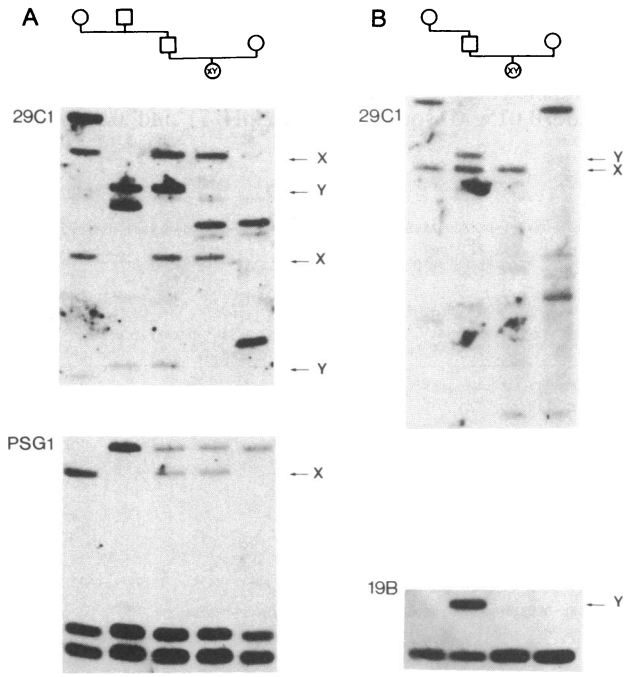

FIG. 3. Southern blot analysis of DNAs from the family of young XY female LAG092 hybridized with probe 29C1 (locus *DXYS14*) (*Taq* I digestion, *Top*) and pSG1 (gene *MIC2*) (*Msp* I digestion, *Bottom*) (*A*), and *Taq* I-digested DNAs from the family of young XY female PAR097 hybridized with probes 29C1 (*Top*) and 19B (gene *MIC2*) (*Bottom*) (*B*). Arrows indicate X or Y chromosomal origin of the paternal alleles inherited by the young XY females.

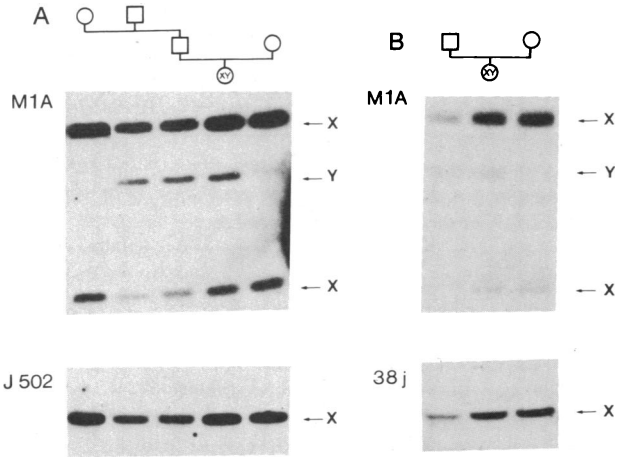

FIG. 4. Southern blot analysis of *Taq* I-digested genomic DNAs from the family of young XY female LAG092 hybridized with probes M1A (locus *DXS31*) and J502 (locus *DXS285*) (*A*) and from the family of young XY female PAR097 hybridized with probes M1A (locus *DXS31*) and 38j (locus *DXS283*) (*B*). Hybridization of the same filters with probe 50f2, which detects an autosomal band, was used as an internal control of the amount of DNA present in each lane.

product of the rearranged X chromosome of Y(+) XX males. In particular, X and Y breakpoints in Yp-deleted XY females are expected to have locations similar to those found in Y(+) XX males. Indeed, these breakpoints on the Y chromosome might correspond to those separating intervals 2 and 3 in Y(+) XX males (6). Mapping data for X breakpoints in XX males is poor, but cases have been reported with breakpoints in the pseudoautosomal region (13, 15) or elsewhere in Xp22.3 (12), sometimes even proximal to *STS* (37, 38). In both XY females in this study the X breakpoints are distal to the *STS* locus and map in the distal X-specific part of Xp22.3—i.e., within the region where breakpoints also occur in XX males. The Y chromosome of these XY females can thus be regarded as the reciprocal product of the terminal X–Y interchange producing the rearranged X chromosomes of Y(+) XX males. As already noted in XX males, this interchange probably replaces the normal XY crossing-over because both young XY females show inheritance of paternal X-linked alleles for all tested pseudoautosomal loci.

XXp− females frequently display some stigmata of the Turner syndrome, which has been associated with a partially deleted Y chromosome. Development of marked lymphedema of the extremities is seen in this condition neonatally. Definition of the portion of the Y chromosome carrying the corresponding "edema-suppressing" gene(s) should be possible. According to a simple "symmetrical" hypothesis the edema-suppressing gene(s) should be encoded by X and Y homologous loci (39). Pseudoautosomal loci are candidates for "Turner-suppressing" genes (39) because karyotypic anomalies indicated that Turner-suppressing genes are located on Xp (40). However, in 46,Y,t(X;Y) (Xp22;Yq11) and in 46,X,t(X;Y) (Xp22;Yq11) with Xp terminal deletions including *STS*, the peripheral lymphedema is not seen (see ref. 41), and Turner stigmata have been described in an XYp− female with a deletion proximal to *MIC2* (20), suggesting that the pseudoautosomal region is not involved. Similarly, in the subjects of our study, deletion of the Y pseudoautosomal region is compensated by transposition of the entire pseudoautosomal region from the X chromosome, excluding a pseudoautosomal location of edema-suppressing gene(s). The deletion of Y-specific sequences seen in young XY females PAR097 and LAG092 are, to our knowledge, the smallest reported to date; these results map the Y gene(s) controlling development of lymphedema characteristic of

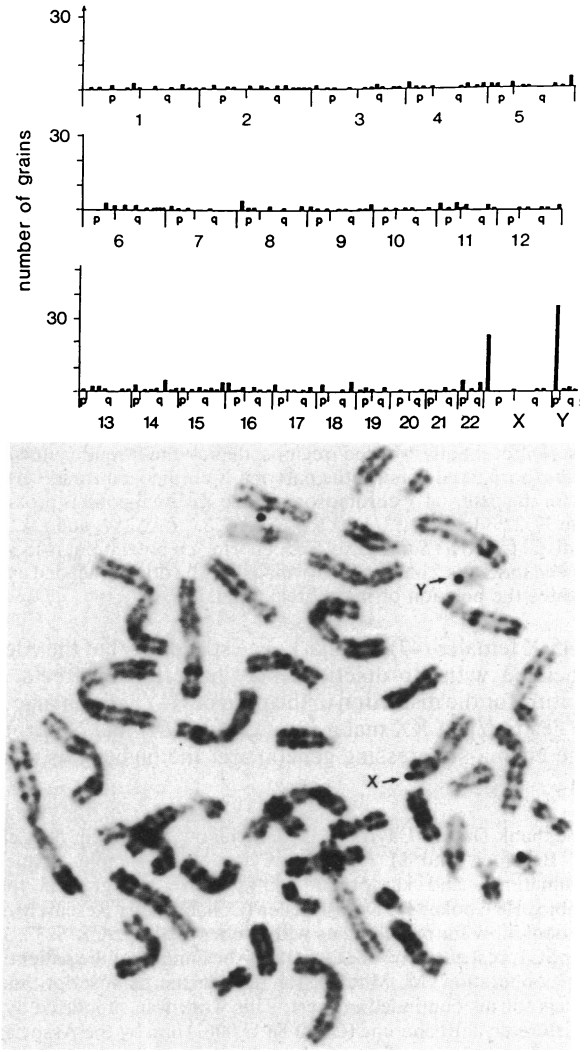

FIG. 5. Histograms of the grain distribution and *in situ* hybridization of metaphase chromosomes: probe 38j (locus *DX283*) with young XY female LAG092. Silver grains are clustered at the tips of both Xp and Yp (arrows).

Turner syndrome to interval(s) 1 and/or 2 (6). This location raises the issue of homology between the X and Y Turner-suppressing genes. If expression of these genes continues after X inactivation, these genes escape this inactivation, at least partially. The above data map the X chromosome Turner-suppressing gene(s) proximal to the loci transferred onto the Y chromosome. According to the current view of the spread of X chromosome inactivation, this gene would be predicted to lie distal to the DNA polymerase α gene, which is not expressed on the inactive X chromosome and is located in Xp22.1–Xp21.3 (ref. 42; and see ref. 9). A more proximal position of the X chromosome Turner-suppressing gene(s) would mean that resistance to inactivation is not confined to the region of Xp22.3.

The relative infrequency of XY females with a deletion on Yp compared with the number of Y(+) XX males is intriguing. Only seven other cases of Yp-deleted XY females, possibly resulting from an abnormal X–Y interchange, have been reported (20–24), whereas most other XY females show no Y chromosome anomaly after cytogenetic and DNA analyses (ref. 20; and G. Scherer, personal communication). Turner stigmata have been reported for six of these seven Yp-deleted XY females but not for other XY females (see refs. 10 and 20). A high incidence of mortality during fetal life is reported for the Turner syndrome, affecting up to 99% of

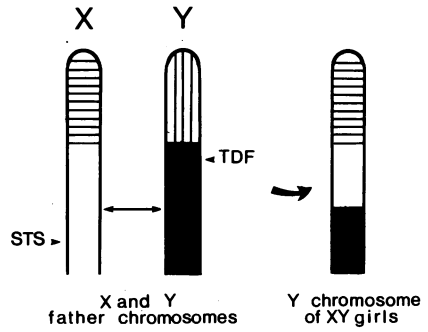

FIG. 6. Genesis of the Y chromosome lacking *TDF* in both XY females by an abnormal terminal Xp–Yp interchange during paternal meiosis. The black region represents the Y-specific part, and the white region represents the X-specific part of the chromosome short arms. Differentially shaded regions depict the pseudoautosomal regions (horizontal bars for the paternal X chromosome and vertical bars for the paternal Y chromosome). The Xp breakpoint is proximal to the Xp22.3 loci *DXS31*, *DXS277*, *DXS283*, *DXS284*, and *DXS285* and distal to the *STS* and *DXS278* loci. The Yp breakpoint is located between intervals 2 and 3 of the Y map (6). The double-headed arrow indicates the position of these breakpoints.

the 45,X females (43). Similarly, we speculate that the edema associated with Yp deletions may have lethal effects, accounting for the distortion in the ratio of X–Y interchange XY females to Y(+) XX males. The closer *TDF* and Y chromosome edema-suppressing gene(s) are, the higher this distortion.

We thank Drs. P. Cayroche, P. Czernikow, D. Julien, N. Leporrier, B. Noel, and M. O. Réthoré for blood samples, patients' examinations, and karyotypic analysis. We are grateful to A. Balabio, H. Cooke, H. Donis-Keller (Collaborative Research), and P. Goodfellow for providing us with probes Stb14, 29C1, S232, 19B, and pSG1, respectively. We also thank the families of the patients for their cooperation, M. Mitchell for reading the manuscript, and P. Tiollais for his continued interest. This work was supported by the Ministère de la Recherche (Grant 88.C.0061) and by the Association Française des Myopathes.

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