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The Origin of 45,X Males

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SUMMARY

Maleness in association with the karyotype 45,X is a very rare and hitherto unexplained condition previously described in only four or five patients. This study was carried out to determine whether such males might actually possess Y-chromosomal material. Of the two 45,X males studied, one was found to be a low-grade mosaic with a 46,XY karyotype in less than 3% of fibroblasts; all lymphocytes karyotyped were 45,X. Fibroblast DNA from this individual was found to contain Y-specific repeated sequences in 1%–3% the amount observed in the father, consistent with mosaicism for a 46,XY cell line. No Y-specific repeated sequences were detected in the other patient, in whom all mitoses were 45,X. In neither patient were there detectable amounts of any of the single-copy Y-specific DNA sequences for which we tested. Studies of Xg blood groups and of X-linked restriction fragment length polymorphisms indicated that the single X chromosome was of maternal origin in both 45,X male probands.

In contrast to the situation in XX males, we can exclude paternal X-Y interchange as the etiology in the cases described here. Our findings are compatible with mosaicism being the explanation of at least some "45,X" males.

INTRODUCTION

Most individuals with a 45,X karyotype develop as phenotypic females with Turner syndrome. However, very rare 45,X individuals are sterile males with testes [1–6]. How maleness arises in these individuals is presently unknown.

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Individuals with the karyotype 46,XX who develop testes are referred to as XX males or XX true hermaphrodites [7]. In the past year, it has been shown that many of these patients carry a portion of the Y chromosome [8–11]. It is reasonable to assume that the presence of Y-chromosome-derived DNA in XX males explains their maleness. The aim of the present study was to test whether 45,X males might be explained in the same way.

CLINICAL AND BLOOD GROUP STUDIES

Patient 1

The patient was born at term with a weight of 3,050 g. Congenital malformations included: mild pterygium colli and epicanthic folds, highly arched palate, shield-shaped chest, laterally located mamillae, clinodactyly of the 5th fingers, deep-set nails, and coarctation of the descending arch of the aorta. The penis was short with the urethral meatus opening at its base. The scrotum was empty, and no testes could be palpated. At ages 6 and 7 years, right and left orchiopexy, respectively, was performed. The right testis was histologically normal. Shortly before age 8, the coarctation was corrected.

At age 11, his height was 123.5 cm (< 2nd centile), and weight, 23 kg. The penis measured 5 cm, the urethra opening in the normal place. The left testis was of normal prepubertal size. No testis was found on the right (the testis had been operated on at age 6, and at age 10, a very small testis had been palpated). His mental development was judged to be nearly normal.

At the patient's birth in 1971, his mother was age 26 and his father age 22. A brother was born in 1978. Both parents and brother were healthy. Genealogical studies, extending 4 generations back, did not uncover any consanguinity.

The blood groups (table 1) were compatible with paternity. As the father was Xg(a+) and both mother and proband Xg(a−), the proband's X chromosome is apparently maternal. The proband, parents, and brother all had normal color vision (Ishihara).

Patient 2

The patient was born at term weighing 3,200 g. There was penoscrotal hypospadias. At 5 months, two small testes on the left were biopsied and brought into the scrotum. There was a common vas deferens. Histologically, both testes were normal.

At age 5, laparotomy failed to reveal either ovaries or testes in the abdomen or in the inguinal regions. Correction of the hypospadias was performed. At age 8½, the patient was 110 cm tall (< 2nd centile) and weighed 21 kg. There were no anomalies or other malformations. The penis was of near-normal length, and the result of the plastic

TABLE 1

BLOOD GROUPS

Family		ABO	MN	Ss	P_1	Rh	Lu^a	Kk	Le^aLe^b	Fy^aFy^b	Jk^aJk^b	Xg^a
1	Propositus ...	A_1	M	...	...	...	...	−	...	...	...	−
	Father	A_1	M	...	...	R_2r	...	−	...	...	...	+
	Mother	A_1	M	...	...	R_0	...	−	...	...	...	−
2	Propositus ...	B	M	− +	−	R_1r	−	− +	+	+ +	+ −	−
	Father	A_2	M	+ +	−	R_1r	−	− +	− +	+ +	+ −	+
	Mother	A_1B	M	− +	+	R_1R_2	−	− +	+ −	+ +	+ +	−
	Brother	A_1	M	− +	+	R_1R_1	−	− +	− +	+ −	+ −	−

surgery was good. The scrotum contained two left testes of near-normal size for age. Psychomotor development appeared slightly retarded.

At the patient's birth in 1974, his mother was age 31 and his father age 32. Both parents were healthy, and genealogical studies extending 4 generations back showed that they were not consanguineous. One brother, born in 1971, had pigmented nevi covering about one-third of his body, but was otherwise normal.

Blood groups (table 1) were compatible with paternity. The father was Xg(a+) but all other relatives Xg(a−). Hence, the patient's X appears to be of maternal origin. The patient's color vision was judged normal at age 5 (Boström and Kugelberg color plates). His father and brother were given the same test, and both had normal color vision but his mother was shown to have severe myopia, subnormal visual acuity, defects of the visual fields, and defective color vision. These defects were due to hypoplasia of both optic nerves. There were so-called tilted discs in both eyes. These findings did not suggest any of the common forms of X-linked color blindness, consistent with the fact that she had two sons with normal color vision.

CYTOGENETIC STUDIES

Patient 1

Both parents were cytogenetically normal as shown by lymphocyte and skin fibroblast mitotic studies (table 2). The father's Y chromosome was longer than average and normally fluorescent. The proband was studied repeatedly. Four blood cultures and one fibroblast culture tested between 1971 and 1979 showed 45,X mitoses only. Several hundred mitoses and 1,000 interphase nuclei from the 1979 blood culture were screened by quinacrine fluorescence for the presence of a Y chromosome or a Y chromatin body, but neither was found.

In 1971, a buccal mucosa smear had shown 15/1,000 cells with a fluorescent spot judged at the time to be a possible Y chromosome. Again in 1977, some 5% of buccal mucosa cells appeared to be Y-chromatin-positive.

Skin fibroblast studies in 1982 showed that although most mitoses (179/186) were 45,X, five of 186 cells were clearly 46,XY as seen in GTG- and QFQ-banding. The QFQ-banding indicated that the Y chromosome was structurally normal with a brightly fluorescent band Yq12 and that it was the same length (longer than average) as the father's. Moreover, 34/1,000 of interphase nuclei from the same culture had a Y-chromatin body corresponding in size to the Y chromosome. In 1984, a frozen aliquot of the same fibroblast culture was thawed and the chromosome studies repeated. Of a total of 434 mitoses studied by quinacrine fluorescence, five had the karyotype 46,XY while all others had less than 46 chromosomes and no Y chromosome. Moreover, 8/1,000 interphase nuclei had a Y-chromatin body. The DNAs used for the detection of Y-chromosome-specific DNA sequences were prepared from these 1982 and 1984 fibroblast cultures.

Patient 2

Both parents and the brother were cytogenetically normal (table 2). Only 45,X cells were detected in the propositus, in blood cultures (on two occasions), and skin fibroblast cultures (on three occasions). In addition, 1,000 interphase nuclei from the 1975 blood culture, 1,000 nuclei from a buccal smear, and 100 mitoses and 1,000 interphase nuclei from the blood culture made in 1979 were screened by quinacrine fluorescence for the presence of Y-chromatin or a Y chromosome, but none was found. Thus, there was no indication of the presence of any Y chromosome in this patient.

DNA STUDIES

Human genomic DNAs were analyzed by restriction digestion, agarose electrophoresis, gel transfer, and hybridization with radiolabeled cloned DNA probes as described [10, 12].

The DNA hybridization probes used detect X-linked restriction fragment length polymorphisms (RFLPs) and/or Y-specific restriction fragments. In the case of probes detecting X-linked RFLPs, we list below only the sizes of the allelic restriction fragments. In the case of probes detecting Y-specific DNA sequences, we list only the Y-specific restriction fragments for which we scored; as described in the references, many of these probes also detect autosomal or X-chromosomal restriction fragments. The probes used are as follows: (1) RC8 [13] detects X-linked, allelic *Taq*I fragments of 3.0, 3.4, and 5.7 kilobases (kb). (2) D2 [14] detects X-linked, allelic *Pvu*II fragments of 6.0 and 6.6 kb. (3) L1.28 [15] detects X-linked, allelic *Taq*I fragments of 10 and 12 kb. (4) pDP34 [12, 16] detects X-linked, allelic *Taq*I fragments of 11 and 12 kb as well as a Y-specific 15-kb fragment. (5) 19-2 [14] detects X-linked, allelic *Msp*I fragments of 4.4 and 12 kb. (6) S21 [17] detects X-linked, allelic *Taq*I fragments of 2.5 and 2.7 kb. (7) 22-33 [14] detects X-linked, allelic *Taq*I fragments of 10 and 17 kb. (8) 43-15 [14] detects X-linked, allelic *Bgl*II fragments of 6 and 9 kb. (9) 47c [18] detects Y-specific *Taq*I fragments of 3 and 4.3 kb. (10) 115 [18] detects a Y-specific *Taq*I fragment of either 2.1 or 2.6 kb (D. C. Page and J. Weissenbach, unpublished results, 1985). (11) 50f2 [9] detects multiple Y-specific loci on *Eco*RI or *Taq*I digests. (12) 52d [9] detects multiple Y-specific loci on *Eco*RI or *Taq*I digests. (13) A 1.8-kb *Pst*I fragment purified from plasmid 71-7A [19] detects multiple Y-specific *Taq*I fragments. (14) pY431-HinfA (K. Smith, personal communication, 1985), detects a highly repeated Y-specific *Hae*III fragment of 2.1 kb. (15) pY3.4 [20] detects a highly repeated Y-specific *Hae*III fragment of 3.4 kb.

To determine the parental origin of the single X chromosome in the two 45,X males, both families were typed for as many as eight X-linked RFLPs. The results are shown in table 3. These X-linked RFLPs provide information as to the parental origin of the X chromosome only when, by chance, the propositus is hemizygous for an allele present in one but not both parents. Such is the case in family 1 when analyzed with probe S21: the propositus is hemizygous for the 2.5-kb allele, for which the mother is homozygous, while the father is hemizygous for the 2.7-kb allele. Thus, the propositus' single X chromosome derives from his mother. In family 2, the X-linked RFLPs detected by probes RC8, D2, and 19-2 are all informative, and again, the propositus' single X chromosome is demonstrated to be maternal in origin.

Using hybridization probes derived from the human Y chromosome, DNAs from the two 45,X males and their relatives were tested for the presence of a number of Y-specific sequences. The results of these tests for Y-specific DNA are summarized in table 4. Six of the hybridization probes we used detect single-copy, Y-specific sequences. Three of these six—50f2, 52d, and 71-7A—detect multiple Y-specific restriction fragments. Certain of these single-copy, Y-specific DNA sequences are present in many 46,XX males [9–11]. Hybridization probes pY431-HinfA and pY3.4 detect Y-specific repeated sequences. In families 1 and 2, the three normal 46,XY males (the fathers and, in family 2, the brother) exhibit all of the Y-specific sequences found in unrelated control males. The mothers, with normal 46,XX karyotypes, exhibit none of these Y-specific sequences. In neither of the 45,X males did we detect any of the single-copy, Y-specific sequences for which we tested. In the 45,X male of family 1, we did detect the highly repeated, Y-specific 2.1-kb and 3.4-kb *Hae*III fragments homologous to, respectively, probes pY431-HinfA and pY3.4 (table 4, fig. 1). However, these Y-specific repeated sequences were present in greatly reduced amounts compared to those observed in the father in family 1 (or in unrelated control males; results not shown). To quantitate the reduction in these repeated sequences, we compared the intensity of the hybridizing 2.1- and 3.4-kb *Hae*III fragments in that 45,X male with the corresponding intensities obtained using equal or reduced (10-fold, 100-fold, 1,000-fold, and 10,000-fold) amounts of paternal DNA. The intensity of the 2.1-kb *Hae*III band in the 45,X male is somewhat greater than that observed with paternal DNA in 100-fold reduced amount (fig. 1). We observed a similar reduction in the intensity of the 3.4-kb *Hae*III band in this 45,X male. In the 45,X male of family 1, the Y-specific 2.1- and 3.4-kb *Hae*III fragments are both present in approximately 1%–3% the amount (per microgram genomic DNA) present in the father. These results are consistent with 1%–3% mosaicism for a Y-containing cell line. In contrast,

TABLE 2

CYTOGENETIC STUDIES

FAMILY	INDIVIDUAL	DATE		TISSUE	CHROMOSOME COUNTS							STAINING METHOD	KARYOTYPE
		Mo	Yr		< 44	44	45	46	47	> 47	Total		
1	Propositus	8	71	B	...	...	24	1*	...	...	25	G	45,X
		9	71	B	...	...	61	1†	...	...	62	G	45,X
		12	71	B	...	...	49	1‡	...	...	50	G	45,X
		12	71	F	...	...	50	...	...	...	50	G	45,X
		1	79	B	1	1	48	...	...	...	50	G, GTG	45,X
		1	79	B	...	2	98	...	...	...	100	QFQ	45,X
		7	82	F	2	...	179	5§	...	...	186	GTG, QFQ	45,X/46,XY
		11	84	F	2	6	421	5§	...	...	434	QFQ	45,X/46,XY
	Father	9	71	B	...	...	...	20	...	...	20	G	46,XY
		12	71	B	...	...	1	19	...	...	20	G	46,XY
		7	82	F	...	...	1	19	...	...	20	GTG, QFQ	46,XY
	Mother	9	71	B	...	...	1	22	...	...	23	G	46,XX
		12	71	B	...	...	...	22	...	...	22	G	46,XX
		7	82	F	...	...	...	20	...	...	20	GTG, QFQ	46.XX

2	Propositus	3	75	B	...	1	79	...	...	...	80	GTG	45,X
		3	75	B	1	1	198	...	...	...	200	QFQ	45,X
		3	75	F	...	...	58	1†	...	...	59	GTG	45,X
		3	75	F	3	1	96	...	...	...	100	QFQ	45,X
		4	79	B	1	...	24	...	...	...	25	GTG	45,X
		4	79	B	1	1	23	...	...	...	25	QFQ	45,X
		4	79	F	2	1	47	...	...	...	50	GTG, QFQ	45,X
		10	82	F	...	...	36	3*	...	...	39	GTG, QFQ	45,X
	Father	3	75	B	...	...	1	49	...	...	50	GTG, QFQ	46,XY
		4	79	B	2	...	1	47	...	...	50	GTG, QFQ	46,XY
		10	82	F	1	...	1	18	...	...	20	GTG, QFQ	46,XY
	Mother	3	75	B	...	1	1	18	...	...	20	GTG, QFQ	46,XX
		4	79	B	...	...	...	21	...	...	21	GTG	46,XX
		10	82	F	...	...	...	20	...	...	20	QFQ	46,XX
	Brother	3	75	B	...	...	1	19	...	...	20	GTG, QFQ	46,XY
		10	82	F	...	2	1	17	...	...	20	GTG, QFQ	46,XY

NOTE: B = 3-day culture of lymphocytes from peripheral blood, F = long-term culture of fibroblasts from a skin biopsy, G = Giemsa staining (no banding), GTG = G-banding by trypsin, QFQ = Q-banding by quinacrine fluorescence.

* Karyotype 46,X, + mar.

† Karyotype 46,X, + C.

‡ Karyotype 46,X, − C, + D, + E.

§ Karyotype 46,XY.

These studies were carried out on the fibroblast culture initiated and studied in 1982, then frozen, thawed, and recultured in 1984.

TABLE 3

SEGREGATION OF X-LINKED RFLPs

FAMILY	INDIVIDUAL	DNA PROBE (RESTRICTION ENZYME)							
		RC8 (*Taq*I)	D2 (*Pvu*II)	L1.28 (*Taq*I)	pDP34 (*Taq*I)	19-2 (*Msp*I)	S21 (*Taq*I)	22-33 (*Taq*I)	43-15 (*Bgl*II)
1	Propositus	3.4	...	13	12	...	2.5	10	...
	Father	3.4	...	13	12	...	2.7	10	...
	Mother	3.4	...	10, 13	12	...	2.5	10	...
2	Propositus	3.4	6	10	11	12	2.5	10	6
	Father	5.7	6.6	10	11	4.4	2.5	10	6
	Mother	3.4	6	10	11	12	2.5, 2.7	10	6
	Brother	3.4	6	10	11	12	2.5	10	6

NOTE: Only the X-linked allelic fragments detected are given. For example, probe pDP34 detects a Y-specific 15-kb *Taq*I fragment in addition to the X-linked allelic fragments indicated. (...), not tested.

we did not detect any trace of these Y-specific repeated sequences in the 45,X male of family 2. This is the case even using conditions (e.g., exposure of autoradiograms for 10 days) where we can detect the presence of normal male DNA in 10,000-fold reduced amount (results not shown).

DISCUSSION

The hypotheses put forward to account for 46,XX males [21] could possibly be used to explain testicular differentiation in 45,X males. However, the situation is different in several important respects. Here, we review and discuss briefly the mosaicism and X-Y interchange hypotheses.

Mosaicism

45,X males might be 45,X/46,XY mosaics in whom the XY line is rare or has been eliminated altogether, at least in some tissues. Our patient 1 appears to be an example of such circumscribed mosaicism; the 46,XY cell line was detected in only one fibroblast culture out of a total of six (four lymphocyte, two fibroblast) cultures. This fibroblast culture was cytogenetically studied on two occasions. In 1982, there were 2.7%, and in 1984, 1.2% 46,XY mitoses. The presence of repetitive, Y-specific DNA sequences in reduced amount (fig. 1) was also consistent with 1%–3% mosaicism for an XY cell line.

Cytogenetic studies of patient 1 indicated that the Y chromosome present in less than 3% of fibroblasts was structurally normal. The DNA hybridization results were consistent with such low-grade mosaicism for a structurally normal Y chromosome. First, the Y-specific repeated sequences were present in 1%–3% the amount observed in the father (fig. 1). Second, our ability to reliably detect mosaicism for single-copy Y-specific sequences currently extends only to about 5%–10% mosaicism (our unpublished results, 1985). Thus, our failure to detect even reduced amounts of single-copy Y-specific sequences in patient 1 (table 4) is consistent with the observed low-grade mosaicism for a normal Y chromosome.

TABLE 4

Y-SPECIFIC DNA STUDIES

FAMILY	INDIVIDUAL	DNA PROBE (RESTRICTION ENZYME)							
		SINGLE-COPY						REPEATED	
		47c (*Taq*I)	115 (*Taq*I)	50f2 (*Taq*I)	52d (*Taq*I)	pDP34 (*Taq*I)	71-7A (*Taq*I)	pY431-HinfA (*Hae*III)	pY3.4 (*Hae*III)
1	Propositus	–	–	–	–	–	–	+*	+*
	Father	+	+	+	+	+	+	+	+
	Mother	–	–	–	–	–	–	–	–
2	Propositus	–	–	–	–	–	–	–	–
	Father	+	+	+	+	+	+	+	...
	Mother	–	–	–	–	–	–	–	...
	Brother	+	+	+	+	+	+	+	...
Normal males		+	+	+	+	+	+	+	+
Normal females		–	–	–	–	–	–	–	–

NOTE: Individuals were scored for the presence or absence of Y-specific DNA restriction fragments detected by the probes. (...), not tested.

* This propositus' DNA showed a 2.1-kb *Hae*III band (detected by probe pY431-HinfA) of about 1%–3% the intensity seen in his father's DNA (fig. 1). This propositus' DNA also showed a 3.4-kb *Hae*III band (detected by probe pY3.4) similarly reduced relative to that seen in his father's DNA.

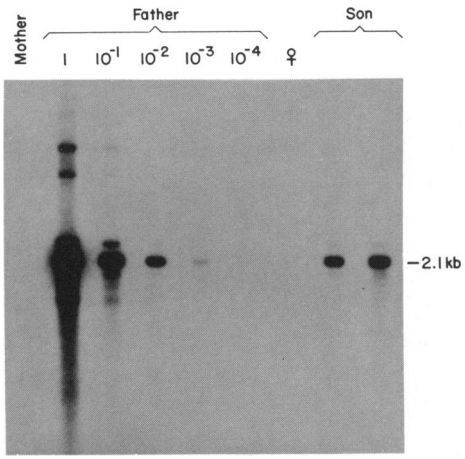

FIG. 1.—Hybridization of *Hae*III-digested DNAs from Family 1 with probe pY431-HinfA. Probe pY431-HinfA detects a Y-specific 2.1-kb *Hae*III fragment. *Each lane* contains 5 μg of *Hae*III-digested human DNA. *From left to right:* mother, father (undiluted, then 10-fold, 100-fold, 1,000-fold, and 10,000-fold dilutions into control female DNA), control female, and 45,X/46,XY son (*at left,* from 7/82 fibroblast culture; *at right,* from 11/84 fibroblast culture). The intensities of the autoradiographic bands suggest that, per microgram of genomic DNA, there are 1%–3% as many copies of the Y-specific 2.1-kb *Hae*III fragment in the son as in the father.

In patient 2, extensive cytogenetic and DNA studies produced no evidence of Y-chromosomal material, even in a minority of cells. Using DNA hybridization probes for Y-specific repeated sequences, we can detect the presence of normal male DNA in 10,000-fold reduced amount, and thus we should be able to detect the presence of a normal Y chromosome in as few as 1 in 10,000 cells. However, these repeated *Hae*III fragments are located principally if not exclusively in distal Yq [22–24] and, thus, would be of little use in detecting mosaicism involving an abnormal Y chromosome lacking that region. The DNA hybridization studies alone, then, cannot argue against low-grade mosaicism for a structurally abnormal Y chromosome in patient 2. Similarly, cytogenetic methods based on detection of the quinacrine-bright distal portion of Yq cannot argue against such mosaicism. There also remains the possibility that a Y-bearing cell line exists in tissues other than those we sampled or existed in fetal life but was later eliminated.

The X-Y Interchange Hypothesis

At least 10 families are known in which a 46,XX male was Xg(a−) even though his father was Xg(a+) [7, 8]. Such anomalous inheritance of this dominant, X-linked marker led Ferguson-Smith [25] to propose that maleness in XX men was brought about by an interchange of genetic material between the X and the Y chromosome at paternal meiosis. According to this hypothesis, the Xg-bearing portion of the father's X chromosome was replaced by a testis-determining portion of his Y chromosome. Recent blood group and DNA studies of XX males are consistent with this model [8, 9, 12]. Indeed, certain single-

copy Y-specific DNA sequences have been detected in 12 of 19 XX males tested [11]. Thus, it would seem that X-Y interchange can account for many cases of XX maleness.

If 45,X males were also the result of a paternal X-Y interchange, then they should have a paternally derived X that had acquired the male-determining portion of the Y. This is an awkward hypothesis requiring the coincidence of two abnormal events: first, X-Y interchange during or prior to paternal meiosis, and second, nondisjunction either during meiosis in the mother or mitosis in the proband. There are strong reasons to discard this hypothesis in the present cases. Both Xg and X-linked RFLP studies indicate that, in each of the probands, the single X chromosome is of maternal origin. In case 1, the presence of a 46,XY cell line suggests that the zygote was also 46,XY and that the 45,X cell line is the result of mitotic nondisjunction. In case 2, we did not detect certain single-copy Y DNA sequences present in many 46,XX males and therefore assumed to be near the male determinant(s) on the Y (sequences detected by probes 47c, 115, 50f2, and 52d [11]). This result argues against but does not exclude the presence of a male-determining portion of the Y chromosome in the 45,X cells of case 2.

Other Hypotheses

Do some apparently 45,X males carry a small male-determining portion of the Y either translocated to an autosome [6, 26] or segregating independently as a cytogenetically undetected mini-chromosome? This is clearly not the situation in our case 1, a 45,X/46,XY mosaic. Again, in case 2, the absence of certain single-copy Y DNA sequences argues against but cannot exclude the presence of the testis-determining portion of the Y.

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