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Human Genetics

The Etiology of Maleness in XX Men

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Summary. Information relating to the etiology of human XX males is reviewed. The lesser body height and smaller tooth size in comparison with control males and first-degree male relatives could imply that the patients never had any Y chromosome. Neither reports of occasional mitoses with a Y chromosome, nor of the occurrence of Y chromatin in Sertoli cells are convincing enough to support the idea that low-grade or circumscribed mosaicism is a common etiologic factor. Reports of an increase in length of one of the X chromosomes in XX males are few and some are conflicting. Nor is there any evidence to support the idea of loss of material. However, absence of visible cytogenetic alteration does not rule out the possibility of translocations, exchanges or deletions.

A few familial cases are known. Mendelian gene mutations may account for a number of instances of XX males, similar genes being well known in several animal species. The existing geographical differences in the prevalence of human XX males could be explained by differences in gene frequency. But if gene mutation were a common cause of XX maleness there would be more familial cases.

Any hypothesis explaining the etiology of XX males should take into account the following facts. There are at least 4 examples of XX males who have inherited the Xg allele carried by their fathers, and at least 9 of such males who have not. The frequency of the Xg phenotype among XX males is far closer to that of males than to that of females, while the absence of any color-blind XX males (among 40 tested) resembles the distribution in females. Furthermore, H-Y antigen is present in XX males, often at a strength intermediate between that in normal males and females. Finally, in a pedigree comprising three independently ascertained XX males, the mothers of all three are H-Y antigen-positive, and the pattern of inheritance of the antigen in two of them precludes X-chromosomal transmission.

Many of the data are consistent with the hypothesis that XX males arise through interchange of the testis-determining gene on the Y chromosome and a portion of the X chromosome containing the Xg gene. However, actual evidence in favor of this hypothesis is still lacking, and the H-Y antigen data are not easy to explain. In contrast, if recent hypotheses on the mechanisms controlling the expression of H-Y antigen are confirmed, a gene exerting negative control on testis determination would be located near the end of of the short arm of the X chromosome. This putative gene is believed not to be inactivated in normal females, for at least two other genes located in the same region, i.e. *Xg* and *steroid sulfatase*, are not. Deletion or inactivation of these loci would explain how XX males arise and would be consistent with most, but not all, the facts.

There is yet no single hypothesis that by itself can explain all the facts accumulated about XX males. While mosaicism appears very unlikely in most cases, Mendelian gene mutation, translocation, X-Y interchange, a minute deletion or preferential inactivation of an X chromosome, or part thereof, remain possible. The etiology of XX maleness may well be heterogeneous.

Clinical Features

General

Apart from height and tooth size the clinical features will not be dealt with in detail. XX males resemble individuals with Klinefelter's syndrome in their general masculine appearance (Fig. 1) and male psychosexual orientation, normal to weak secondary sexual characteristics, small testes (Fig. 2), abnormal testicular histology with azoospermia (Fig. 3) and normal to low androgen

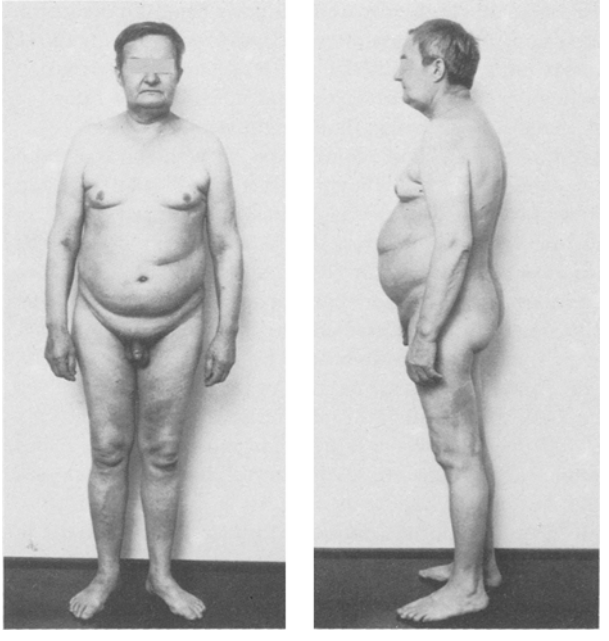

Fig. 1. A 58-year-old man with the karyotype 46,XX. The patient was karyotyped because small testes were noted when he was hospitalized for malignant lymphoma

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Table 1. Permanent tooth size comparisons between four XX males and their relatives. The table indicates direction and the sums of the results of mean size or single comparisons. Adapted from Alvesalo and de la Chapelle (1979)

	46,XX males		
	Smaller	Equal	Larger
In comparison with			
Fathers ($N = 3$)	21	1	2
Fathers and brothers ($N = 6$)	25	2	1
Mothers ($N = 3$)	3	4	16

levels. Mild mental retardation, a common feature of Klinefelter's syndrome, is not typical in XX males. The commonest reasons for referral are the same in the two syndromes: infertility, small testes or an abnormality of the secondary sexual characteristics.

Body Height and Tooth Size

That XX males are shorter (168.2 ± 1.52 cm) than normal XY males (173.5 cm) (de la Chapelle 1972) has been taken to indicate that the Y chromosome contains gene(s) that control height. This view is supported by evidence from the comparative heights of other groups of individuals with different sex chromosome complements. For instance, XY females are taller than XX females, and XYY males are taller than XY males. That similar genes reside in the X chromosome is suggested by the fact that XX females are taller than X females, XXX females are taller than XX females and XXY males are taller than XY males. However, height is influenced not only by genetic, but also by nutritional and hormonal factors. The size of the crowns of the deciduous and permanent teeth is a useful measure of body size, because it is determined very early in life. Tooth germs are already present at about the time when the sex determination of the gonad occurs (7–8 weeks). Determination of the size of several permanent tooth crowns apparently begins in early fetal life and is complete 3 years after birth (Moorrees et al. 1963). Hence, as parameters of body size, tooth sizes show less variation due to environmental influences and so probably reflect a primary genetic effect better than height does.

Regarding the Y chromosome it has been shown that both deciduous and permanent teeth are larger in XYY males than in XY males (Alvesalo et al. 1975; Alvesalo and Kari 1977).

Data on XX males support the idea that they lack the Y-chromosomal gene(s) affecting tooth size. Permanent teeth in four XX males were smaller than those of male controls and similar in size to those of female controls. The teeth of the XX males were smaller than those of their first-degree male relatives and of the same size as those of three of their mothers (Table 1). That the small size was not a simple familial trait is shown by the finding that the teeth of the fathers and mothers of XX males were similar in size to those of control males and females (Alvesalo and de la Chapelle 1979).

Let us now consider the data on tooth size in relation to the etiology of XX maleness. It could be argued that XX males originally had a Y chromosome, which existed late enough to initiate male determination of the gonads, but was lost too early to affect tooth size. This explanation appears unlikely in view of the close proximity in the timing of these events, but the evidence would be stronger if derived from data on the size of deciduous rather than permanent teeth. Furthermore, if maleness is caused by the translocation of the testis-determining gene(s) from the Y to another chromosome, the gene(s) affecting tooth size are not involved.

The latter idea is supported by recent results of tooth measurements in two males with deletions in different parts of the proximal band (Yq11) of the long arm of the Y chromosome (Alvesalo and de la Chapelle 1981). The patient with the more proximal break had, and the patient with the more distal break did not have, smaller teeth than their male relatives, indicating that the postulated gene for tooth size is in the band Yq11. Since both patients had testes, these findings confirm that the testis-determining gene (which is believed to be in Yp) and the gene for large teeth (probably in Yq11) are not identical (cf. Bühler 1980).

The study of tooth size in XX males has reinforced the previously held notion that the shortness of stature of XX males is primarily due to genetic factors.

Incidence

As in other rare conditions lacking an unambiguous diagnostic clinical sign, the incidence of XX males can be determined only by the screening of large unselected populations. Identification of XX males does not require banding of metaphase chromosomes, so earler studies on unbanded chromosomes are informative. Also, screening by X chromatin followed by karyotyping will reveal the condition.

Data on karyotype screening of the newborn are available from seven major centers in different parts of the world. As summarized by Nielsen and Sillesen (1975), there were 2 males with the karyotype 46,XX among 34,379 boys karyotyped. In another series X-chromatin screening of 61,742 newborn boys revealed 2 males with 46,XX (de la Chapelle 1972). These data are summarized in Table 2. The finding of 4 individuals among 96,121 boys screened points to an incidence of one XX male in approximately 24,000 newborn boys. In such a rare condition, however, even these large surveys do not suffice to yield wholly reliable estimates of the true incidence, and geographical variations cannot be evaluated.

There is one way in which XX males detected in clinical practice can be used to estimate their incidence and their relative frequency in different populations. The symptomatology of XX males being very similar to that of XXY males, the modes of ascertainment are likewise similar. For instance, in the great majority of XX males and XXY males detected in clinical practice the reason for karyotyping is either infertility, small testes or an abnormality of the secondary sexual characteristics, e.g. gynecomastia. With ascertainment being similar it becomes relevant to determine the relative frequencies of XX males and

Table 2. Incidence of 46,XX and 47,XXY males in surveys of newborn boys. Adapted from de la Chapelle (1972) and Nielsen and Sillesen (1975)

No. of newborn boys studied	Method	Number found	
		46,XX	47,XXY[a]
34,379	Karyotype	2	33
61,742	X-chromatin	2	n.a.
Total 96,121		4	

[a] Excluding mosaics; n.a., not available

XXY males detected in any one sample from, say, one country, one district, or even one laboratory.

Such data are assembled in Table 3. In these series the relative frequencies of XX males and XXY males show some degree of uniformity in five laboratories (XX male : XXY ratios of 1 in 14, 1 in 18, 1 in 18, 1 in 19, and 1 in 26, respectively). But in Leuven, Belgium, the corresponding ratio is 1 in 153. Interpretations are offered as follows.

Firstly, the differences might be due to artifacts stemming from differences in methodology or in the practices or habits relating to the referral of patients for karyotyping. But since no evidence of such differences is available, it is justifiable to assume that the frequencies truly reflect the actual incidences. If this were so, a gene causing maleness in XX embryos must be considered, since gene frequencies do differ between countries or regions, recessive genes especially varying greatly in frequency.

Secondly, the incidence of XXY Klinefelter's syndrome is known to be close to 1 in 1000 newborn boys, and the data in Table 2 support this figure. If the XX male : XXY ratios from Finland, Sweden, France, and Scotland only are considered, the ratio is 50 in 994 or 1 in 20. This mode of calculation indicates an incidence of one XX male in 20,000 males, a figure that is in reasonably close agreement with the estimate of 1 in 24,000 drawn from Table 2.

I conclude that the bulk of the evidence indicates an incidence of the order of one XX male in every 20,000–25,000 newborn males, but there appear to be regional differences.

The literature contains descriptions of some 135 males with 46,XX (references available on request). A further 20 patients from several different countries are known to me through correspondence (personal communications from Drs. J. Geraedts, C. B. van der Hagen, F. Lošan, C. San Roman, H. B. Wong 1980), and many more have undoubtedly been diagnosed. It appears that XX males are diagnosed with a frequency that well matches the above approximation of their incidence.

Table 3. Number of 46,XX males and non-mosaic 47,XXY males detected in six cytogenetic diagnostic laboratories

City and reference[a]	Approximate no. of individuals karyotyped[b]	No. of patients found		Ratio
		XX♂	XXY	XX♂ : XXY
Helsinki [1]	9,000[c]	9	126	1 : 14
Stockholm [2]	12,000	8	140	1 : 18
Chambéry [3]	15,000	7	129	1 : 18
Paris [4]	11,000	11	207	1 : 19
Edinburgh [5]	52,000[d]	15	392[e]	1 : 26
Leuven [6]	33,000[c]	2	305	1 : 153

[a] The data were made available by the following (personal communications 1980): [1] A. de la Chapelle, [2] J. Lindsten, [3] B. Noel, [4] J. de Grouchy and C. Turleau, [5] K. E. Buckton, [6] H. van den Berghe

[b] Males and females

[c] Includes a large proportion of patients studied for acquired hematological disorders

[d] Includes figures from large surveys of normal individuals

[e] Includes cases not originally karyotyped in Edinburgh (referrals)

Cytogenetic Features

X Chromosome

In the great majority of XX males described in the literature, the two X chromosomes are reported as structurally normal and indistinguishable from each other. The following are exceptions to this rule.

Madan and Walker (1974) studied an XX male in whom one of the X chromosomes had a longer short arm than the other. The feature was visible in the microscope and on microphotographs and could be corroborated by measurements (Madan 1976). There did not appear to be any alteration in the banding pattern, the increase in length affecting the terminal band (p22). Family studies could not be done.

Wachtel et al. (1976) reported an XX male in whom the short arm of one X was longer than its homolog and carried an extra minute near-terminal band. The father's karyotype was normal; the mother could not be studied.

The question of the length and morphology of the X chromosomes was dealt with in an extensive study involving chromosome measurements in twelve XX males and various controls by Evans et al. (1979). The conclusion was that there was a signifi-

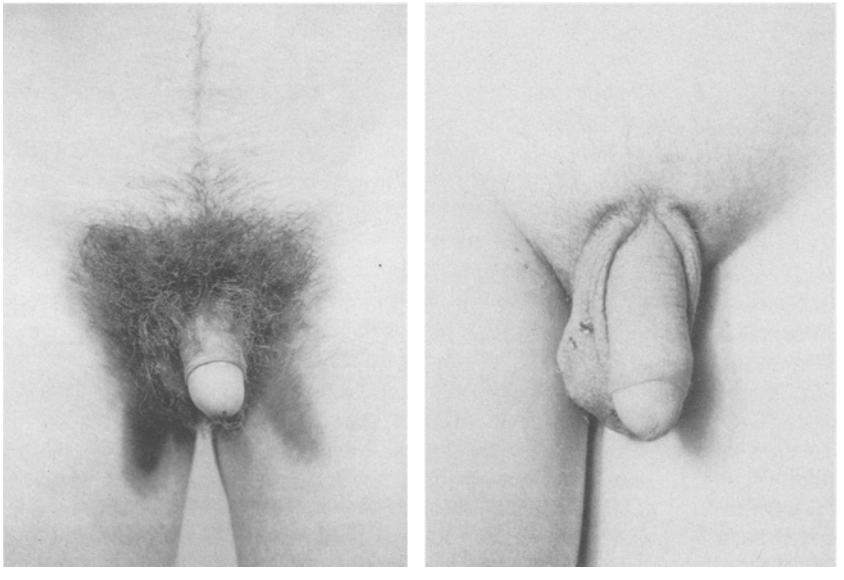

Fig. 2. External genitalia of two males with the karyotype 46,XX showing normal appearance apart from small testicular size. The hair had been shaved before the picture on the right was taken

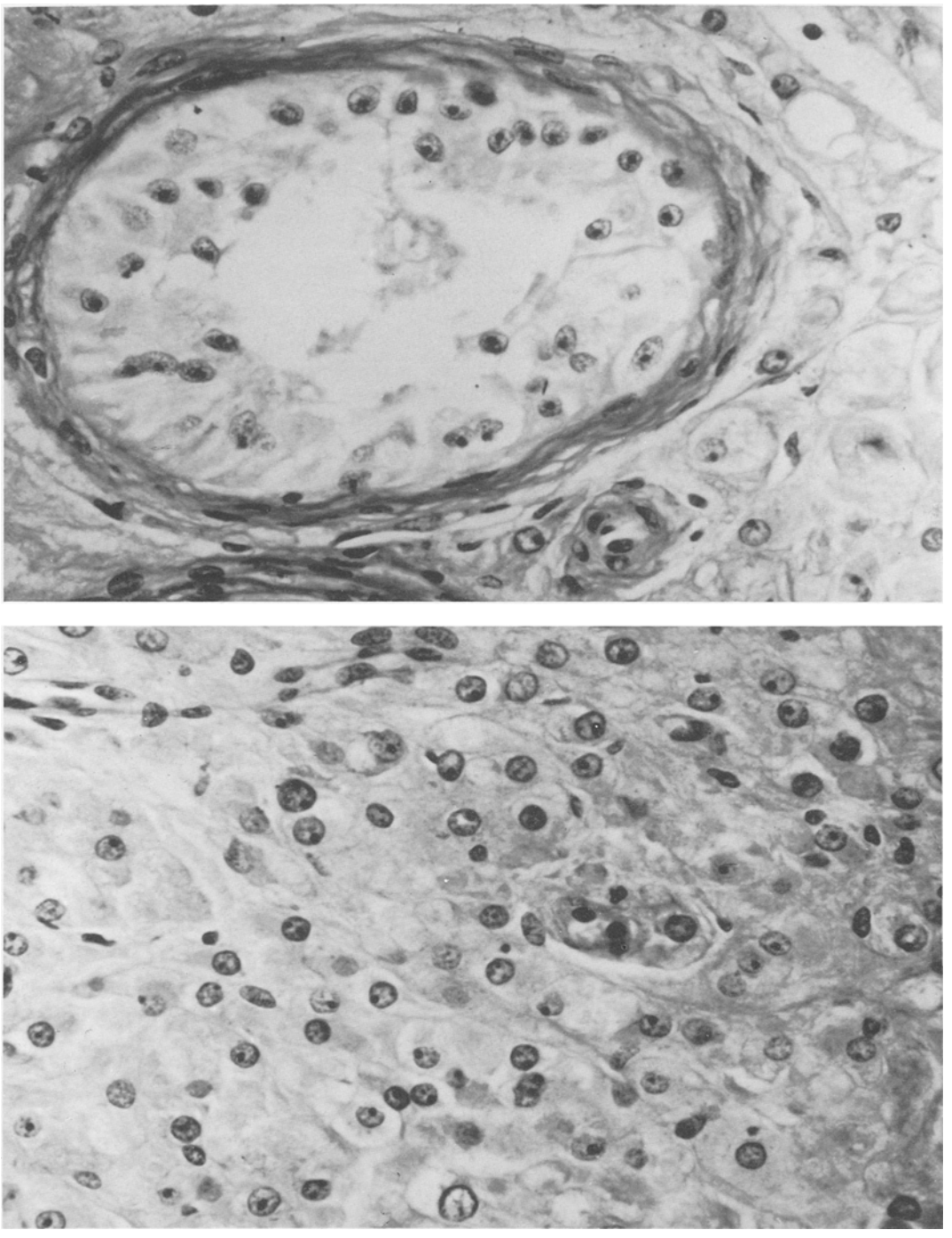

Fig. 3. Testicular histology from an XX male. *Upper part,* section of seminiferous tubule showing thickening of basement membrane and tubule containing only Sertoli cells and no germinal cells. *Lower part,* abundance of Leydig cells in interstitial tissue

cant increase (0.4% to 22.9%) in the size of the short arm of one X chromosome in 8, and no such increase in 4 of the 12 patients. From these results and various other considerations the authors concluded that in around 70% of XX males, maleness is a consequence of the inheritance of a paternal X-Y interchange product. In a study designed to try to confirm the work by Evans et al. (1979), measurements failed to indicate any Xp+ phenomenon, even though visual inspection of microphotographs suggested a possible Xp+ in 2 of 5 males with XX and none of 5 control females (de la Chapelle et al. 1979). But measurements gave clear-cut evidence that the lengths of the arms of the two X chromosomes did not differ significantly from each other or from various control X chromosomes (Fig. 4). The existence of an Xp− phenomenon in XX males could also be excluded.

In an experiment carried out by J. P. M. Geraedts and M. J. Addink (personal communication 1980) DNA cytophotometry and electronic measurements of the lengths of the X chromosomes of three XX males were compared with those of control females. Neither heteromorphism between the two X chromosomes of any individual, nor any differences between XX males and XX female controls were found.

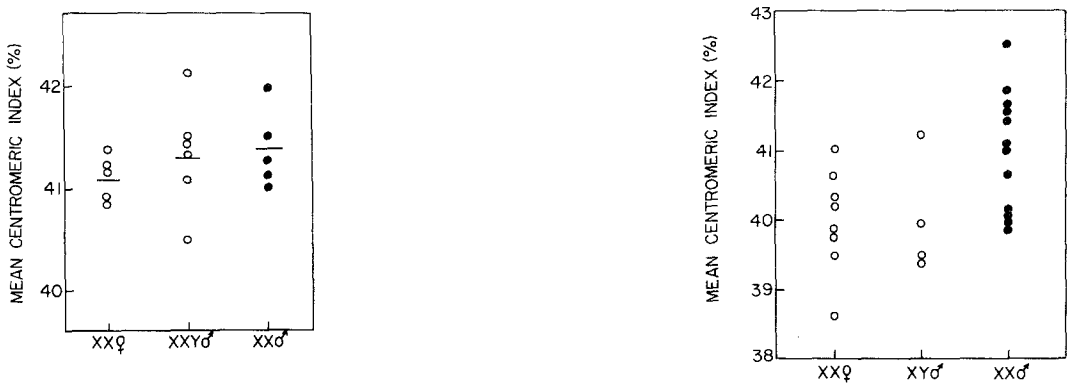

Fig. 4. Mean centromeric indexes of X chromosomes from normal XX females, normal XY males, XXY males and XX males. The diagram on the left depicts the results of de la Chapelle et al. (1979) in which the mean centromeric indexes of XX males (●) did not differ from those of XX females or XXY males (○). The diagram on the right depicts the results of Evans et al. (1979) in which the mean centromeric indexes for 7 of the XX males (●) were greater than those of XX females and XY males (○). Adapted from original papers

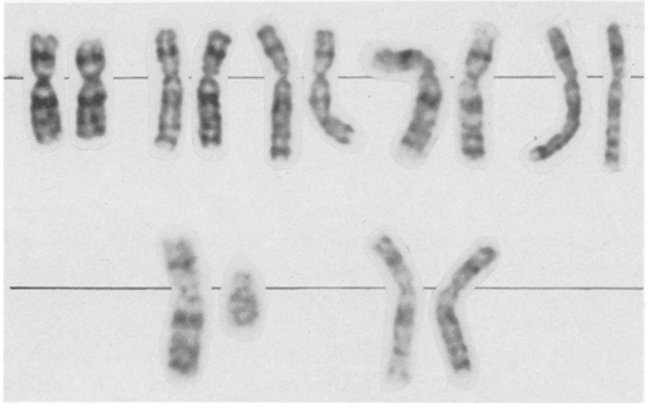

Fig. 5. *Upper line,* both X chromosomes from 5 different cells of an XX male (GTG-banding). The cells were chosen so as to depict mid-metaphase chromosome condensation *(left)* through early metaphase and prometaphase *(right).* Note variable appearance of several regions, including the distal part of the short arm, but absence of any consistent change in length or banding. *Lower line,* XY and XX sex chromosomes from the father and mother of the proband

The tentative conclusion from these studies is that in some instances one of the X chromosomes has undergone a morphologic alteration. But this does not apply to all, and probably not even to most, XX males, and it can only occasionally be corroborated by a measurable increase (or decrease) in short arm length (Fig. 5). The mechanisms underlying the presumptive morphologic abnormality are unknown.

Y Chromosome, Y Chromatin

The evidence of mosaicism in XX males is related either to the finding of occasional mitoses with a Y chromosome (e.g. 47,XXY or 46,XY) or interphase cells with Y chromatin. Furthermore, unidentified marker chromosomes are sometimes seen.

Mitoses with a Y Chromosome. In an earlier review (de la Chapelle 1972) two true hermaphrodites and 4 males with predominantly 46,XX were discussed. In those patients evidence had been presented of the existence of extremely infrequent or circumscribed cell lines with a Y chromosome.

Similar findings have continued to be reported. In an otherwise XX male patient, for instance, Malka et al. (1975) found mitoses with 47,XXY, 1 in 35 in lymphocytes and 1 in 8 in bone marrow cells. Likewise, among 550 mitoses obtained from a testis culture Kaiser et al. (1977) saw "one well-isolated metaphase with 47 chromosomes, whose 5th G-chromosome appeared quite similar to a Y chromosome," and considered the existence of a Y chromosome probable. Finally, Dosik et al. (1976) saw "an apparent Y chromosome" in one out of 201 lymphocyte mitoses. However, in none of these observations was the Y chromosome identified by its quinacrine fluorescence. Under such circumstances the identification of an extra small acrocentric chromosome as a Y can hardly be conclusive, even in cases where the unbanded chromosome clearly resembles a Y (Dosik et al. 1976). It is highly desirable that investigators studying numerous cells from XX males with a view to finding occasional Y chromosomes should use such methodology that QFQ-staining can be performed if necessary (Rubio et al. 1974). In at least two instances fluorescent evidence supporting extremely low-grade mosaicism (1 in 49 and 1 in 500 metaphases, respectively) has been found (Iinuma et al. 1975; Miró et al. 1978). A most remarkable case reported by Rios et al. (1975) does not lend itself to firm conclusions.

Y-Chromatin in Interphase Nuclei. The finding by Palutke et al. (1973) of numerous cells with a fluorescent spot in Sertoli cells from an XX male (who also had one cell with 47,XXY out of 100 lymphocyte mitoses—but without QFQ staining) sparked renewed interest in the question of possible low-grade or locally circumscribed mosaicism in XX males. Similar findings in testicular cells were reported by Iinuma et al. (1975) and Pawlowitzki et al. (1978) and in oral mucosa cells by Miró et al. (1978).

The key question concerns the origin of such interphase fluorescence. It is well known that after quinacrine staining of interphase nuclei brightly fluorescent spots represent not only the Y chromosome(s) but also brightly fluoresent material normally seen in several autosomes (3, 4, 13–15, 21, 22) in certain individuals (Caspersson et al. 1970). The more numerous such autosomal fluorescent spots, and the larger they are in any individual, the greater is the probability that his interphase nuclei will contain one or more fluorescent spots resembling typical Y-chromatin (cf. Rehder et al. 1975). Moreover, from a study of testicular cells from XX, XXY and XY males, de la

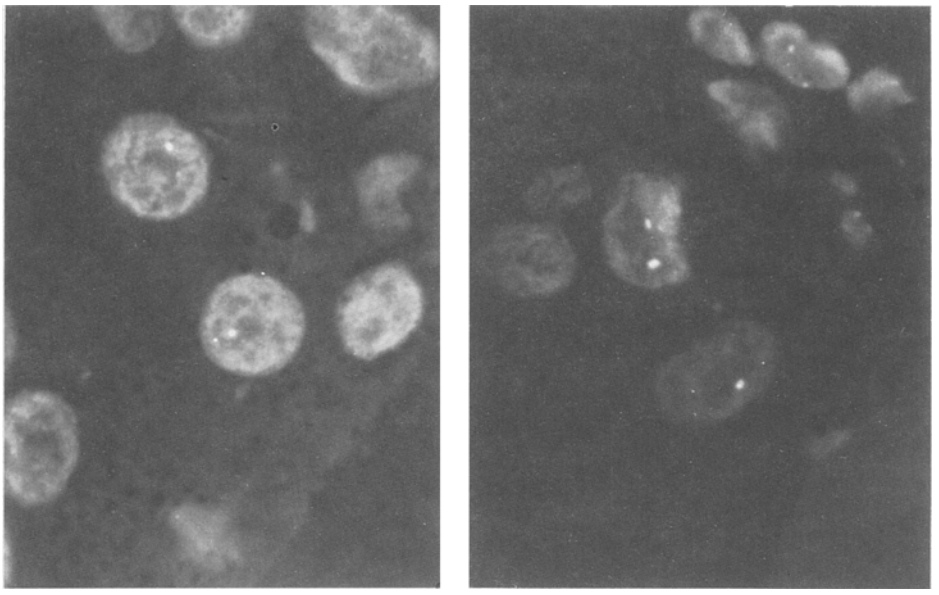

Fig. 6. Quinacrine fluorescence of testicular sections from an XX male *(left)* and an XXY male *(right)*. Sertoli cell nuclei of the XX male mostly contain one, and of the XXY male two, fluorescent spots. Only the larger spots seen in cells from the XXY individual are interpreted as Y-chromatin, while smaller spots (in both patients) probably emanate from brightly fluorescent autosomal regions

Chapelle et al. (1977) concluded that the interphase fluorescence pattern caused by quinacrine is expressed more strongly in Sertoli cells than in others (Fig. 6). Certain thyroid and brain cells may be similar in this respect (Sellyei et al. 1975), but the reason for this phenomenon is not yet understood. The conclusion drawn by de la Chapelle et al. (1977) was that the QFQ-fluorescent chromatin seen in the Sertoli cells of three XX males did not emanate from the Y.

None of the previously quoted studies in which interphase chromatin in Sertoli cells was thought to represent a Y has been followed up by unequivocal demonstration of a Y chromosome in mitotic testicular cells. Without such evidence there can be no justification for the claim that a Y chromosome occurs in Sertoli cells of otherwise XX males.

Unidentified Marker Chromosomes

An extra small chromosome whose provenience could not be determined with certainty has been noted in a few XX males (e.g. Kasdan et al. 1973; Bartsch-Sandhoff et al. 1974; Bartsch-Sandhoff 1974). The suggestion by Bartsch-Sandhoff that the marker chromosome represents part of the missing Y cannot, in the absence of positive means of identification, be proved or disproved.

Parental Age

In an earlier study the mean parental age at birth of an XX male was 27.8 ± 0.97 years for 35 mothers and 30.8 ± 1.19 years for 29 fathers, these values being remarkably similar to the mean ages at any birth in comparable population groups (de la Chapelle 1972). The addition of data from a further 22 mothers (Pietriga 1977) did not appreciably change the mean maternal age (28 years). Hence it may be concluded that there is no difference in parental age at the birth of an XX male relative to all births. This contrasts with the finding of a higher maternal age (32.6 ± 0.65 years) at the birth of an XXY son (de la Chapelle 1972).

Familial Cases

In the majority of cases described, sibs and other close relatives of XX males are reported as unaffected, and consanguinity of parents, as absent. In the other reports, family data are not mentioned. A few notable exceptions are on record. These are summarized in Fig. 7.

In the case of Kasdan et al. (1973), two brothers were XX males. They had a normal XX sister and a normal XY brother. Their parents were non-consanguineous and had normal sex chromosomes, but one of the father's 4 brothers was an XX male. The father's other 3 brothers and only sister had children. A very small marker chromosome segregated in the family but appeared not to have any effect on sex determination (Fig. 7A). It frequently associated with acrocentric chromosomes.

The likely interpretation of the findings in this family is, as suggested by the authors, that two separate male-determining loci segregated in the family: the Y chromosome and an autosomal locus.

In the sibship described by Nicolis et al. (1972), a pair of identical twins were XX males (Fig. 7B). While this finding does not suggest any etiologic mechanism it may be noteworthy that the XX male twins had had 2 deformed brothers, both of whom had died during the first year of life. A sister was normal and had children. The parents were not known to have been consanguineous.

The family reported by Minowada et al. (1979) consisted of non-consanguineous parents with normal karyotypes and two 46,XX sons (Fig. 7C).

Finally, there is a pedigree in which three XX males were independently ascertained (de la Chapelle et al. 1977, 1978). The normal XY fathers of two XX males were found to be paternal first cousins (Fig. 7D). Hence, since a genetic mechanism is likely to be involved, it could not have been inherited with the X chromosome, thus effectively ruling out an inherited X-Y interchange or other structural abnormality of the X. In addition, pedigree analysis showed that these two XX males were distantly related to another XX male, the first ever described (de la Chapelle et al. 1964). Inheritance by all three probands of a

causative factor from one common ancestor (born in 1664) is possible, but somewhat far-fetched. Since the third proband was related to the first two through several females in earlier generations, dominant inheritance and Y-to-autosome translocation are theoretically excluded. Further circumstantial evidence in favor of a recessive mechanism comes from the fact that not only the fathers of the three probands, but also the mothers of two of them were mutually related (de la Chapelle et al. 1978).

As a further test of the hypothesis that a gene mutation is responsible for the XX male condition I have conducted a search for further XX males in the pedigrees of four of the Finnish XX males. Through parish records, all living males who were second cousins ore more closely related to the probands were identified. Amongst these, there were 88 childless males over the age of 25 years, who were all approached and asked to contribute a blood sample for karyotyping. As can be seen from Table 4 a karyotype was obtained from 73 of these (83%). No XX male was found. It needs to be stated, of course, that many of these childless males were normal young men who had not yet married. Yet these data are interpreted as evidence against a dominant gene or a heritable translocation being a common cause of XX males. Further, these findings, together with the observation that consanguinity of the parents of XX males is apparently rare, argue against a recessive gene being a common cause.

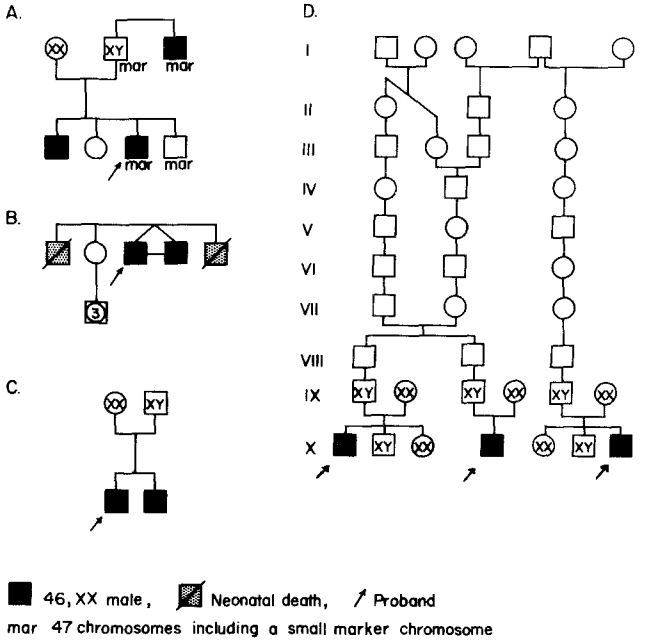

Fig. 7. Pedigrees showing familial occurrence of XX males. **A**, from Kasdan et al. (1973); **B**, from Nicolis et al. (1972); **C**, from Minowada et al. (1979); **D**, from de la Chapelle et al. (1977, 1978). Adapted from original papers

Marker Studies; Inactivation of X

The Blood Group Xg

The blood group Xg is a useful X-chromosomal marker because its dominant mode of inheritance is remarkably regular (for a full review of the subject, see Race and Sanger 1975). When the first family with an XX male tested for Xg gave the result shown in Fig. 8, it was concluded that both X chromosomes of the proband must be maternal in origin. Results of parental tests performed by Drs. Sanger and Race and their staff are summarized in Table 5. In 38 families the distribution was not informative with respect to the source of the Xg blood group. In 9 families the inheritance pattern was incompatible with the paternal Xg allele having passed on to the XX male son; and similar cases have been documented elsewhere. One further family was informative: here the XX male son must have the father's allele, since the mother is negative. An identical pattern has been reported in at least three further families studied elsewhere (Mori et al. 1969; Yunis et al. 1975; Roe and Alfi 1977).

With 9 of the informative families indicating the absence of the father's Xg allele in the XX male son, two fundamentally different interpretations are possible. Firstly, both X chromo-

Table 4. Chromosome investigations of childless male relatives of four XX males. Designation of probands according to de la Chapelle et al. (1977)

Proband	No. of childless male relatives		Normal karyotype
	Identified	Karyotyped	
E and F	24	19	19
D	11	7	6[a]
C	53	47	46[b]
Total	88	73	71

[a] A paternal cousin of the proband's father was 47,XY,+mar
[b] A cousin of the proband was 47,XXY

Table 5. Parental data on the blood group Xg for 48 males with the karyotype 46,XX. Adapted from Race and Sanger (1975) and containing updated results of the Medical Research Council Blood Group Unit; R. Sanger, personal communication (1980)

Xg phenotype of			No. of families		Interpretation
Father	Mother	XX son			
+	+	+	21	38	Not informative
−	+	+	9		
n.t.	+	+	7		
n.t.	+	−	1		
+	+	−	4	9	No paternal contribution
+	−	−	4		
n.t.[a]	−	−	1		
+	−	+	1[b]		Paternal contribution established[b]

[a] This father must have been +, for 3 sisters of the proband were +. n.t., not tested
[b] Three further families of this type are known (cf. text)

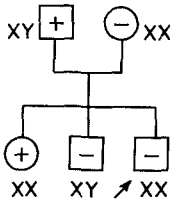

Fig. 8. Xg phenotypes in the family of the first XX male described (de la Chapelle et al. 1964)

somes could be of maternal origin. Secondly, the father might have contributed an X chromosome without the Xg locus or with a functionally altered Xg locus. But the pattern shown in 4 families, *viz.* evidence of paternal contribution to the Xg phenotype of the XX son indicates that the paternal X may also be passed on with an unaltered Xg locus.

Further information on the mechanism leading to XX males can be obtained simply by studying the Xg groups of as many probands as possible and comparing the distribution of phenotypes with that of other groups of individuals. Table 6 lists the present counts for 76 European XX males.

The χ^2 values indicate that the Xg distribution is far more likely to be male than female, and more likely to be male than XXY. It might be noted that, as growing numbers of XX males have been tested over the years, this distribution has changed. When the number of XX males tested was only 45 the distribution was more like that of XXY than of XY males.

The chromosomal location of the gene coding for Xg has recently been determined. It has been known for some time that *Xg* is linked to the locus for the X-chromosomal form of ichthyosis, their distance being approximately 11 cM (Race and Sanger 1975). Ichthyosis is believed to be caused by deficiency of a microsomal enzyme, steroid sulfatase (STS) (EC 3.1.6.2), the gene for which has been localized to the distal half (p22→pter) of the X chromosome by somatic cell hybridization (Mohandas et al. 1979). Hence Xg, too, must be in the distal part of Xp.

It now becomes of considerable interest to determine the inheritance of other X-linked genes in the pedigrees of XX males.

Table 6. Xg groups of XX males. (Medical Research Council, Blood Group Unit; R. Sanger, personal communication 1980)

Total tested	Xg(a+)		χ^2 comparison with		
	No.	Proportion	XY males	XX females	XXY
76	53	0.697	0.49	25.91	13.22
Expected, normal XY males		0.659			
Expected, normal XX females		0.884			
Observed in 395 individuals with XXY		0.848			

Table 7. Xg and Xm phenotypes in two families (adapted from de la Chapelle 1972)

		Xg	Xm
Family 1	Father	+	+
	Mother	–	–
	Sister	+	+
	Brother	–	–
	XX male proband	–	–
Family 2	Father	+	–
	Mother	–	+
	XX male proband	–	–

Results for two markers, the serum group Xm and color blindness, are so far available.

The Serum Group Xm

This marker was extensively studied in the 1960's (Berg and Bearn 1966); the antiserum characterizing it is no longer available. The gene is located some 10 cM from the linkage group containing the loci for color-blindness, hemophilia and glucose-6-phosphate dehydrogenase. These loci are all in the distal part of Xq (de la Chapelle and Miller 1979). Hence Xg and Xm are far apart, as was established by linkage analysis (Berg and Bearn 1968).

Two XX male pedigrees were studied for both Xg and Xm. The results are shown in Table 7. In family 1 the data show identical inheritance of Xg and Xm, the interpretation being that the father had contributed neither his Xg nor his Xm to the XX son. In family 2, the XX son did not manifest his father's Xg allele, but Xm was uninformative.

Since Xg and Xm are located near each end of the chromosome, it would seem to follow that in family 1 the father's X was not transmitted to the XX son. Alternative explanations related to inactivation are discussed below.

Color-Blindness

Data assembled for a previous review (de la Chapelle 1972) indicated that 20 males with XX had been tested for color vision, and in all of them it was normal. A further 20 patients have now been tested (Powers et al. 1970; Lubetzki et al. 1972; Sutherland et al. 1972; Fromantin et al. 1973; Kasdan et al. 1973; Takayasu et al. 1973; Cullen et al. 1976; Pawlowitzki et al. 1978; Giammarini et al. 1980; J. Lindsten, personal communication 1980; personal observations 1980) with the same result. In fact no color-blind XX male has yet been described. Hence the distribution of color vision (40 normal verus none color-blind) is closer to that of females than that of males ($P < 0.05$) indicating a 95% probability of a female rather than a male distribution.

There is thus a discrepancy between the distribution of Xg and of color vision. One likely interpretation is that the long arm, or at least the gene for color vision, is normally inherited and functions as in normal females, whereas the gene for Xg and possibly other genes linked to it on the short arm are either not normally inherited or do not function normally (cf. discussion on inactivation).

Inactivation

It has long been known that Xg is not inactivated when on a structurally normal X (Race and Sanger 1975), but probably inactivated when on a structurally abnormal X (Polani et al. 1970; Bernstein et al. 1978). Results obtained by somatic cell hybridization show that the STS locus, too, escapes inactivation (Mohandas et al. 1979). On the other hand, inactivation of the genes for G6PD, HPRT, PGK and several diseases does occur (Race and Sanger 1975). It would seem therefore, that the only two loci that are currently known not to be inactivated are linked and located close to each other on the short arm, while those that are inactivated are located in different parts of the long arm.

One way of explaining the apparent discrepancy between the distribution of Xg and color vision phenotypes in XX males is related to inactivation. The observed pattern might be produced if the loci for color-blindness and other genes on the long arm were inactivated randomly, and the Xg locus (and perhaps STS and some neighboring genes) inactivated non-randomly. If, for instance, the Xg locus (and the hypothetical gene exerting negative control of male determination; see later) were non-randomly inactivated by an unknown mechanism, then both the

apparent absence of a paternal Xg contribution, and the occurrence of male sex determination in occasional XX individuals could be explained. The same effect could be brought about by a chromosomal deletion of a part of Xp. On the other hand, an ordinary mutation causing abnormal function in the very gene involved in sex determination would not explain the Xg inheritance in many XX males unless the Xg locus itself were involved in sex determination, which appears unlikely.

Y-Specific DNA

At least two male-specific DNA fractions, 3.4 and 1.8 kb long respectively, can be released from whole-genome male DNA by restriction endonuclease *Hae* III. They hybridize with various portions of the Y chromosome, but occasionally also with autosomal regions, mostly in the acrocentric chromosomes (Steffensen and Gosden 1979). According to Evans et al. (1979), the 3.4 (or 3.5) kb fragment was found in one out of three XX males tested. Recent information from the Edinburgh group (A. Mitchell, personal communication 1980) indicates that of altogether four XX males now tested, three showed no evidence of the 3.4 kb fragment. In the fourth, who was originally reported as positive by Evans et al. (1979), the male-specific fragment seems to hybridize with a small extra marker chromosome also present in the patient's cells.

From these data I conclude that present evidence obtained with restriction endonuclease on DNA fragments does not allow of any conclusions regarding the presence of male-specific DNA in most XX males.

H-Y Antigen

Virtually all XX males tested have been positive for H-Y antigen (Wachtel et al. 1976; Noel and Tous 1978; de la Chapelle et al. 1978). The tests consist of absorption of H-Y antisera with cells from the subjects followed by determination of the ability of the sera to kill sperm or Raji cells in the presence of complement. Since these tests are described and commented on in detail in several of the papers in this issue they will not be dealt with here. It should be noted that quantitative assessment of H-Y antigen strength by the test methods is difficult and can at most be only suggestive. Nevertheless, H-Y antigen strength has been reported as intermediate between male and female control values (Wachtel et al. 1976; de la Chapelle et al. 1978). However, Noel and Tous (1978) report normal male levels. These and other findings have been interpreted as evidence that, on the one hand, H-Y antigen has a primary function in male sex determination (Wachtel et al. 1975; Wachtel 1979) and, on the other hand, that male-determining genes are present in XX males.

In the pedigree with three XX males (Fig. 7D) H-Y antigen was found in each of the three clinically normal mothers, and there was a suggestion that the fathers may have had an excess of H-Y antigen over control males (de la Chapelle et al. 1978). These data were thought to support the idea that the structural gene for H-Y antigen is repetitious or comprises a family of genes. The locus was believed to be in the Y chromosome under normal circumstances. Abnormalities of sex determination could arise as a consequence of translocation of different parts of this locus onto other chromosomes. Whether the mode of inheritance was dominant (Fraccaro et al. 1979) or recessive would depend on the particular portion or number of H-Y genes involved in the translocation. This hypothesis was supported by similar observations in intersex goats (Wachtel et al. 1978) and cocker spaniels (Selden et al. 1978).

It is now held by some that the H-Y structural gene is not located in the Y chromosome. An X-chromosomal locus exerting negative control of male determination (as opposed to the positive control locus in the Y) has been proposed (Wolf et al. 1980a and b; and see Bernstein et al. 1980). The existence of these loci and their nature is still a matter of controversy and speculation. Whatever the final assessment of the mechanism by which male sex determination is brought about, the present theories have to take account of the etiology of XX maleness. These questions will be briefly discussed below.

Theories About Etiology

Ideally, one should seek a hypothesis that covers all the available facts and provides an explanation of all XX males. However, this is not possible at present, and different mechanisms may well be responsible in different cases.

Mosaicism; Loss of Preexisting Y Chromosome

The evidence for the presence in a few patients of a small number of mitoses containing a Y chromosome was reviewed above and found to be weak. Likewise, the observation of brightly fluorescent spots in numerous Sertoli cells of males in whom other tissues are XX does not at present justify the interpretation that the spots represent Y chromosomes. Finally, the small size of the teeth of XX males indicates the unlikelihood that a Y chromosome was ever present.

Thus, evidence in support of mosaicism or early loss of a Y is lacking or inconclusive and at any rate very rare. As regards maternal meiotic non-disjunction the absence of any maternal age effect argues against such an explanation. A preexisting XXY karyotype with two identical maternal X chromosomes fits some of the Xg data, but a maternal age effect would be expected. I regard it as highly unlikely that this theory could explain any significant number of cases.

A Mendelian Gene Mutation

The familial cases reported are few, but sufficiently numerous to merit careful analysis.

An Autosomal Dominant Gene transmitted by the phenotypically normal father or arising in the gonads of either parent would explain the instances of affected sibs. But the conspicuous rarity of families with affected sibs argues against this hypothesis (1 in 4 should be affected). A further argument against this hypothesis is the demonstrated absence of affected relatives in the 4 large Finnish kindreds reported in this paper.

An Autosomal Recessive Gene. The families with two affected children born of normal parents are, of course, compatible with recessive inheritance. So is the observed geographical variation in the incidence. Again, however, the great scarcity of familial cases argues against this theory (even though only 1 in 8 should be affected) and consanguinity would perhaps be expected more often. The H-Y antigen findings and pedigree in the Finnish family with 3 affected individuals are compatible with a recessive mode of inheritance (of subcritical portions of the H-Y gene complex?), but conclusive evidence is still lacking.

An X-Chromosomal Gene. As it is difficult to distinguish between the effects of a mutation, a deletion, a translocation and an inter-

change, and even an abnormality of inactivation involving the X chromosome, these hypotheses are considered together below.

Conclusions. An autosomal gene mutation would account for a number of instances of XX males. These would be the equivalent of the well-known examples of presumptive autosomal mutations causing male differentiation in XX goats (Soller et al. 1969), mice (Cattanach et al. 1971), and other animals (de la Chapelle 1972). But the scarcity of familial human cases, and the virtual absence of consanguinity argue against this as a common mechanism. The paucity of affected siblings and relatives could be explained, if, under certain conditions, the presumptive gene mutation were associated with a lethal effect. But there is no evidence for this, and no indication of an increase in spontaneous abortions or of subfertility in the families of XX males. Finally, an autosomal gene mutation does not account for the abnormal inheritance of X-chromosomal markers summarized above.

Translocation; Interchange of Y-Chromosomal Gene

Translocation of the male-determining gene from the Y to an autosome would lead to a situation comparable to an autosomal dominant (or possibly recessive) mutation, which has already been dealt with.

In the paper by Evans et al. (1979) there is an exhaustive account of the various consequences of the putative X-Y translocation or interchange proposed by Ford (1961). Assuming a single locus for Xg on Xp (X^{xg}) and a single locus for male determination on Yp (Y^{ym}), let us consider three recombinations following X-Y interchange in paternal meiosis, the normal male condition being $X^{xg}Y$.

If the two loci were interchanged, $X^{ym}Y^{xg}$, a 46,X^{ym}X male without his father's Xg allele could be produced. This corresponds to the actual situation in the 9 families listed in Table 5.

As a counterpart there should be 46,XY^{xg} females without the male-determining gene, but with a paternal Xg contribution. H-Y antigen-negative XY females with pure gonadal dysgenesis (Wachtel et al. 1976; Ghosh et al. 1978; Wolf 1979) are compatible with this model, but evidence of a paternal Xg contribution is lacking (less than 10% of all matings would be informative).

If an unequal interchange had produced $X^{xgym}Y$, a 46,X^{xgym}X male with paternal Xg contribution could be produced. This corresponds to the actual situation in 4 families (Table 5). The counterpart, a 46,XY female without a paternal Xg allele, is compatible with XY pure gonadal dysgenesis (H-Y antigen negative).

If an unequal interchange had produced XY^{ymxg}, any resulting 46,XY^{ymxg} males would be normal and have the paternal Xg allele. In fact at least 3 families with an Xg(a+) son of an Xg(a−) mother would fit this model (Race and Sanger 1975, Table 98). The counterpart, a normal 46,XX female without any paternal Xg allele is compatible with the finding of four Xg(a−) daughters of Xg(a+) fathers, but other explanations appear more likely (Race and Sanger 1975, p. 581).

Conclusions. The Xg data fit the X-Y interchange hypothesis, and so does the female distribution of color-blindness (CB) in XX males, assuming that the exchange involves the Xg locus (on the short arm), but not the CB locus (on the long arm). However, the evidence on the Xm groups in family 1 (Table 7) is incompatible with this hypothesis, since the Xm locus is in the long arm and the proband does not possess the paternal Xm allele. The male-to-male transmission in the Finnish pedigree in which the two affected members are second cousins also excludes an X-Y interchange product having been inherited by the probands from their common paternal great-grandfather, and this mechanism would also preclude them from having sisters and paternal aunts, which they have.

The interchange hypothesis does not easily explain the lower-than-male levels of H-Y antigen found in XX males. If the X has acquired the H-Y gene from the Y, why is the H-Y antigen not fully expressed? If the active region on the X has been lost and if this region contains a locus exerting negative control on the H-Y gene (Wolf et al. 1980a), why is H-Y expression lower than normal in XX males? How can the interchange hypothesis explain the finding of H-Y antigen expression in 3 clinically normal mothers of XX males (de la Chapelle et al. 1978)?

Finally, the evidence regarding a morphological abnormality (Xp+) in the short arm of one of the X chromosomes in certain XX males is, of course, compatible with an interchange. I have indicated that such evidence is both inconclusive and controversial (Fig. 5). But if the interchange comprises roughly equal portions of each chromosome, the absence of any visible abnormality is still compatible with the hypothesis.

Deletion or Inactivation of X-Chromosomal Gene(s) Affecting Testis Determination

To resolve the problems of interpretation mentioned above, a simpler model to explain XX males is to assume either deletion or inactivation of the region on Xp which normally escapes inactivation. This region, as discussed above, comprises the Xg and STS loci, and possibly the hypothetical gene exerting negative control on testis determination and the expression of H-Y antigen (Wolf et al. 1980a and b). The theory further rests on the assumption that the structural gene for H-Y antigen (and testis determination) is autosomal. If either the paternal or the maternal X is preferentially affected (deleted or inactivated) in different cases, all abnormalities of inheritance of the Xg groups can be readily accounted for. Likewise, the lower than male expression of H-Y antigen can be explained by the absence of the Y chromosome.

On the other hand, it is not easy to visualize why 45,X individuals do not usually develop testes [but do very occasionally (LoCurto et al. 1974; Forabosco et al. 1977; personal observations 1980)] even though they are H-Y antigen-positive (Wolf et al. 1980b). The H-Y antigen expression in three mothers of XX males is likewise difficult to explain.

This model has the advantage that only one chromosomal breakage event (terminal deletion) or mutation (inactivation) need be postulated, whereas an interchange requires at least two events of breakage followed by reunion.

Regarding the cytogenetic appearance of the hypothetical inactivation or deletion, such evidence is totally lacking. Available evidence places the STS locus very close to the end of the short arm of the X (Mohandas et al. 1979; Müller et al. 1980b; Tiepolo et al. 1980). No visible alteration in length or banding would therefore necessarily be expected. It may be recalled in this context that measurements designed to test the possibility of measurable Xp− in five XX males did exclude such a phenomenon (de la Chapelle et al. 1979).

This hypothesis is compatible with the female distribution of color-blindness, but not with the inheritance of Xm in family 1 in Table 7. If the control of inactivation is governed by an

autosomal locus (dominant or recessive), all familial instances (Fig. 7), including the kindred with 3 affected males, could be accounted for. However, if the putative X-chromosomal deletion were heritable, it could not have been transmitted to the affected second cousins (Fig. 7D) and carriers could have no daughters.

The hypothesis that a deletion or inactivation of the pertinent region on the X chromosome could account for XX males is amenable to testing by gene dosage studies (Müller et al. 1980a) and by somatic cell hybridization. Such studies are in progress.

General Conclusion

As yet there is no unifying hypothesis that can explain all the facts known about XX males. While mosaicism appears very unlikely in most cases, Mendelian gene mutation, translocation, X-Y interchange, a minimal deletion, or preferential inactivation of an X chromosome remain possible. It may well be that the etiology of the XX male condition is heterogeneous.

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