Genetic Characteristics of Families of XO and XXY Patients, Including Evidence of Source of X Chromosomes in 7 Aneuploid Patients

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The development of techniques for the quantitative analysis of the parental source of the X chromosomes in series of patients with XO and XXY karyotypes (Fraser, 1963) created a need for a particular type of family data to test the theoretical framework against observable data. Patients with the syndromes of Turner and Klinefelter are not easy to identify and study in appreciable numbers in any locality outside the great metropolitan centres. This is due to the relative rarity of Turner's syndrome and the even greater rarity of karyotypically confirmed diagnoses of both these syndromes. Studies of the parents and sibs of such patients are difficult because some patients are in institutions, many are adults, and their close relatives may be dispersed or deceased. Thus the material presented in this report is not large but may be useful if pooled with similar data from other areas.

Reviews dealing with the area of genetic interest of this study and summarizing the earlier reports have been those of Lindsten (1963), McKusick (1964), Miller (1964), and Hambert (1966).

Patients and Methods

The patients were all of Caucasian origin, unrelated, and came from the usual variety of ethnic and national groups representative of the population of South Western Ontario. 40% of XO patients and 60% of XXY patients had homes in cities with populations of over 100,000, while only about 10% in each group came from a completely rural environment. The patients' ages at the time of study varied greatly; the means and standard deviations in years for the XO Turner's and XXY Klinefelter's series were 13.8 ± 9.5 and 25.0 ± 16.5 , respectively.

The nature of Klinefelter's syndrome particularly and the methods of screening for sex chromosome aneuploidy employed in this study result in a proportionally large number of patients who are mentally retarded.

The primary source of patients in the XXY series and to a lesser extent in the XO series was a sex chromatin survey of the Ontario Hospital School, Orillia, conducted by Professor Murray L. Barr and colleagues in 1958-9, augmented by sex chromatin surveys of the later admissions to this school, to the Ontario Hospital School at Cedar Springs, and to the Children's Psychiatric Research Institute in London, Ontario. To this basic group were added patients seen by private physicians and referred for the purposes of this study.

The series of families without sex chromosome aneuploidy used in the comparison of size and sex ratio of sibships were selected in the following manner. Each XO and XXY patient was matched by age and sex (female for XO, male for XXY) with a patient whose family history had been assembled in the same routine manner but who did not have any known chromosomal anomaly. These latter patients were referred for genetic investigation or counselling and included a variety of non-chromosomal genetic problems. In a number of instances it was not possible to match these patient pairs within a one-year age spread. In these cases a 'control' was chosen who was not necessarily the patient in the non-chromosomal group but might be a sib or parent.

Ascertainment of the patient was followed by documentary confirmation of the medical diagnosis and sex chromatin and chromosome findings. Arrangements were then made to interview the patient (or parents if the patient was a child or mentally retarded) and to carry out the various tests on the patient and his relatives and collect the necessary data for this study. This involved a detailed family history, buccal smears, blood samples for blood typing, colour vision testing (with the American Optical H.R.R. Pseudisochromatic Plates), and recording of dermatoglyphs for all available patients, parents, and sibs. Data will be presented from all these tests with the exception of the dermatoglyphs which will be reported separately (Uchida and Soltan, 1968). A more detailed analysis of the dermatoglyphs of these XXY patients is under investigation (C. J. Cushman, 1967, personal communication) and will be reported subsequently.

Chromosome studies of the patients were performed mainly by Dr. D. H. Carr and Dr. F. R. Sergovich.

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Preparations were obtained from cultured leucocytes according to a modification of the technique of Moorhead *et al.* (1960). Final cytological preparations were made using the method outlined by Carr and Walker (1961), and a minimum of 30 cells was examined. Karyotypes were constructed from photographs of five metaphase plates. All patients with Turner's syndrome had a leucocyte chromosome count of 45, the karyotype was consistent with an XO sex chromosome complement, and the buccal smear was negative for sex chromatin. All patients with Klinefelter's syndrome had a leucocyte chromosome count of 47, the karyotype was consistent with an XXY sex complement, and the buccal smear was positive for sex chromatin.

TABLE I
SIBSHIP SIZE, STILLBIRTHS, AND SPONTANEOUS
ABORTIONS AND SEX RATIOS IN FAMILIES OF
XO AND XXY PATIENTS

	XO Patients	Female Patients Without Known Chromo- somal Abnor- mality	XXY Patients	Male Patients Without Known Chromo- somal Abnor- mality
<i>Patient's Sibship Size</i>				
Mothers over 40 years at time of study	4.1 ± 0.6	4.7 ± 1.0	5.4 ± 0.7	4.8 ± 0.4
All sibships	3.6 ± 0.5	4.3 ± 0.5	5.2 ± 0.6	4.8 ± 0.3
<i>Minimum rate of stillbirths and spontaneous abortions expressed as percentage of all foetuses known to have been conceived</i>	9.5%	13.7%	6.0%	9.7%
<i>Sex Ratio</i>				
Patient's sibs	0.60	0.54	0.50	0.51
Mother's sibs	0.58	0.53	0.49	0.50
Father's sibs	0.48	0.49	0.52	0.57

Results and Discussion

Sibship Size, Sex Ratio, and Incidence of Twins. Thirteen mothers of XO patients and 29 mothers of XXY patients were older than 40 years at the time of study. If the assumption is made that reproduction in these families had been completed the patient's mean sibship size is 4.1 and 5.4, respectively (Table I). It cannot be determined from these data whether or not the mothers of XXY patients were more fertile than the mothers of XO patients, though the data suggest such a trend.

Table I also shows that the pregnancy wastage rate in XO families, expressed as a percentage of foetuses conceived and known to end in spontaneous abortions or stillbirth, was 9.5%. The comparable value for XXY families was 6.0%. Both these values are minimum values as should be expected from anamnestic data. One might specu-

late that the low value for the mothers of XXY patients may possibly have some significance when viewed in the context of the apparently high fertility of mothers of XXY patients. Lindsten (1963) observed an average number of abortions and/or stillbirths for the mothers of patients with Turner's syndrome.

A deficiency of females among the sibs of XO patients has been reported (Lindsten, 1963). When XO patients were pooled with patients with a presumptive X isochromosome a significant deficiency in the number of female sibs was found ($0.02 < p < 0.05$). In the present series sex ratios were computed for the patient's sibships and the sibship of each parent. The results are presented in Table I. The greatest (though non-significant) deficiency of female sibs was found in the sibship of the XO patient (sex ratio: 0.60).

In Lindsten's analysis of the families of XO patients a twin incidence of 1.8% was observed which was not significantly different from that in the Swedish population. When XO and X isochromosome patients were pooled the twin incidence was significantly higher than in the general Swedish population. Distribution of twin pairs by sex was not different from that which was expected (Lindsten, 1963). Miller (1964), in summarizing the reports on sex chromosome anomalies and twinning, maintained that evidence of an association between twinning and chromosome anomalies was still inconclusive, in spite of numerous reports. However, Nance and Uchida (1964) found seven pairs of twins in 34 sibships where XO Turner's syndrome occurred. They showed that this represented a five- to tenfold increase over the normal frequency of twin births and the frequency in sibships of patients with Down's syndrome. The increment probably consisted of monozygotic twins. All 7 pairs of twins were like-sexed; 4 were monozygotic, 2 were dizygotic, and 1 could not be tested. Nielsen (1966) reviewed the twin literature in Klinefelter's syndrome sibships and presented six new pairs of twins in 18 Klinefelter's syndrome sibships. This represents a twin frequency of 5.9% as compared to a frequency of 1.6% in Danish controls. In the present series of families not one of the 21 XO patients was a twin though one patient had identical twin sisters. Of 37 XXY patients, 3 were twins and a fourth patient had twin sibs.

In 1950, the mean year of birth of the XO patients, 1 in 85 confinements resulted in a multiple birth in Canada. Thus, if 1.18% is an acceptable approximation for the frequency of a twin birth in the general population, 1.26% observed in the sibship of the XO patient is not significant. However,

the frequency of twins among the fathers of XO patients and in their sibships does seem to be high (Table II). In 1939, the mean year of birth for the XXY patients, 1 in every 86 confinements resulted in a multiple birth. Thus, if 1.16% is an acceptable approximation for the frequency of a twin birth in the general population, the rate of 8.8% observed in the XXY patients is of a quite different order of magnitude.

Parental Age. Parental age in the sex chromosome aneuploids has received much attention. No evidence of a maternal age effect in Turner's syndrome has been found (Lenz, 1959; Boyer, Ferguson-Smith, and Grumbach, 1961; Penrose, 1961; Nance and Uchida, 1964). Ferguson-Smith *et al.* (1964) found a maternal age effect in XXY Klinefelter's syndrome. In 45 families the mean maternal age was 32.5 years, which represents a significant increase over the mean maternal age for the general population. Mean paternal age was 33.8 years which was not significantly increased. These authors suggested that a maternal age effect is operative in the production of X^mX^mY patients but not in X^mX^pY patients. This age effect is smaller than that in Down's syndrome, because the contribution of X^mX^pY patients is greater in Klinefelter's syndrome than the contribution of Down's syndrome patients who are due to paternal non-disjunction. Similarly, the mean maternal age of a sample of XO patients is not different from that in the general population, because most XO patients are X^mO where there is no maternal age effect. Race's (1965) findings tend to substantiate this hypothesis, since all 8 mothers of X^mX^mY patients (determined by Xg studies) fit into an 'older mother' (over 28.7 years) category, whereas where 'younger mothers' were involved there were 4 X^mX^mY to 4 X^mX^pY patients. Hambert (1966) found mean maternal and paternal ages of 33.4 and 37.0 years in samples of 72 and 66 patients, respectively. Both these values are significantly higher than in the general Swedish population and both samples have a significantly wider age range distribution than in the general population. Although Nielsen (1966) could not demonstrate a maternal age effect in 18 Danish Klinefelter's patients, a bimodal distribution was apparent in his series of patients.

Data on mean parental ages in the series of XO and XXY patients studied are presented in Table III. Maternal age in the XO Turner's patients is not significantly different from that in the general population. Paternal ages of the 4 XO patients who were shown to lack the paternal sex chromosome were 25, 31, 36, and 47 years (mean: 34.7

TABLE II
TWINNING IN FAMILIES OF XO AND XXY PATIENTS

	Total Pregnancies	No. Twin Pregnancies	Twin Frequency (Observed)
<i>XO Families</i>			
Twinning among:			
Patients	21	0	0
Sibships of patients	79	1	1.26
Mothers	21	0	0
Sibships of mothers	113	0	0
Fathers	19	2	10.5
Sibships of fathers	96	5	5.2
Sibships of patients, mothers, and fathers	288	6	2.08
<i>XXY Families</i>			
Twinning among:			
Patients	34	3	8.8
Sibships of patients	200	4	2.0
Mothers	30	1	3.34
Sibships of mothers	153	4	2.88
Fathers	31	0	0
Sibships of fathers	168	1	0.595
Sibships of patients, mothers, and fathers	521	9	1.72

years). This study confirms that the maternal age of XXY patients tends to be slightly but significantly higher than that in the general population. The mean maternal age in the present series of 35 XXY patients was 31.1 years, which is significantly higher than the mean maternal age in the Ontario population for the most comparable year (1939). There is also a bimodality of the maternal age distribution (as illustrated in Fig. 1), thus providing some evidence for the contention of Ferguson-Smith *et al.* (1964) for the existence of an age-independent group of XXY patients (largely X^mX^pY) and a maternal age-dependent group (largely X^mX^mY). This latter group is now known to form the majority of XXY patients (Race, 1965). Yet the maternal ages of the 3 XXY patients who

TABLE III
MEAN PARENTAL AGES (IN YEARS) AT BIRTH OF XO AND XXY PATIENTS

	XO Patients			XXY Patients		
	Number	Mean Age	Standard Error	Number	Mean Age	Standard Error
Maternal	21	29.0	1.4	35	31.1	1.1
Paternal	20	34.4	1.4	34	35.0	1.5
Control Population*			Year	Maternal	Paternal	
Province of Ontario, Canada, (population in 1967 about 7 million)			1950 1939	27.2 27.5	Not available 31.9	

* The maternal age means are based on live births to all mothers, but the paternal age means are based on live births to women married to the father. Appropriate adjustments have been made in the XO and XXY series.

FIG. 1. Ages of the mothers (in years) at birth of patients. (A) 21 XO patients. (B) 35 XXY patients.

were shown to have two maternally derived X chromosomes were 26, 31, and 35 years (mean: 30.7 years).

Familial Occurrence and Sex Chromatin Studies. Many reports exemplify the presence of two chromosome anomalies in the same family, one of these being a sex chromosome anomaly. The earlier reports have been reviewed by McKusick (1964) and Miller (1964). These associations may be in twins, in sibs, and in other relatives and also in the same individual but very rarely in parent and child. Lindsten (1963) was unable to find any relatives with chromosomal abnormalities in the families of his 57 XO patients.

Reports of two or more sex chromosome abnormalities in the same family are infrequent. Josso *et al.* (1963) reviewed 14 reports of familial Turner's syndrome. Both patients were sex chromatin negative in only two of these families (two sisters and one aunt-niece combination). Only one of two brothers with Klinefelter's syndrome in a family showing familial 'spinal cerebellar degeneration' was sex chromatin positive (Indemimi and Ammann, 1961). But Rosenkranz found an XO Turner's patient who had an XXY Klinefelter's brother and two other mothers of XXY patients who were XXX; one of these was a mosaic of the XX/XXX type. Therefore secondary non-disjunction was invoked as the cause of each patient's XXY karyotype (Rosenkranz *et al.*, 1964; Rosenkranz, 1960).

In the present series of over 50 families of XO and XXY patients there was no known case of Down's syndrome in the patient's or either parent's sibship. Buccal smears were obtained from all available parents and sibs in these families, and in each smear examined the sex chromatin finding was in accordance with the individual's phenotypic sex (Table IV).

Blood Typing. Although typing with anti-Xg^a was the main aim of the blood group studies, all available patients, parents, and sibs were tested

TABLE IV
SEX CHROMATIN EXAMINATION IN
FAMILIES OF XO AND XXY PATIENTS

	Total No. of Living Relatives	Sex Chromatin Examined (%)
XO Families (21)		
Fathers	21	71
Mothers	21	76
Brothers	32	56
Sisters	19	100
Totals	93	73
XXY Families (36)		
Fathers	30	73
Mothers	26	73
Brothers	58	34
Sisters	69	38
Totals	183	48

for ABO, MNS, P, Rh, Kell, Lutheran, Duffy, Kidd, and Lewis. Non-paternity or non-maternity was not proved in any of these families, except in the case of one XXY patient whose 'daughter' was excluded by means of several blood types.

Studies Employing X Chromosome Marker Genes for Red-green Colour-blindness and Xg. Identifying the alleles at certain X-linked loci in patient and parents has determined the parental source of the X chromosome or chromosomes in some sex chromosome aneuploids. Certain XO patients may be assigned X^mO or X^pO , and certain XXY patients may be assigned X^mX^mY or X^mX^pY . This technique has raised the question of the frequency of non-disjunction of the sex chromosomes during oogenesis and spermatogenesis and the frequency of paternal as opposed to maternal sex chromosome loss during abnormal mitoses in the early cleavage divisions in Turner's syndrome.

A number of X-linked loci have been used in these studies, but it is obvious that the most useful will be those where at least two alleles occur with appreciable frequencies in the population under study. The locus for red-green colour-blindness was the first to be used for this purpose (Nowakowski, Lenz, and Parada, 1959; Stern, 1959). More recently, the loci for glucose-6-phosphate dehydrogenase and the Xg blood group system have been used. Reviews of the earlier findings with X-linked marker genes can be found in McKusick (1964) and Miller (1964).

The Xg locus has yielded the greatest amount of information. The genetic uses of X-linked marker genes in this type of investigation were greatly advanced by the rapid exploitation of the Xg blood group system. Using Xg as the marker gene, patients who were X^mO , X^pO , X^mX^mY , and X^mX^pY were identified rapidly (Lindsten *et al.*, 1963; Frøland *et al.*, 1963). An unbiased observation of the proportions of X^mO to X^pO individuals with Turner's syndrome will come only from families where the father is Xg(a+) and the mother Xg(a-). This mating occurs with a frequency of only 8% in Caucasian populations.

A generalized theoretical solution to the problem of the frequency of maternally and paternally derived X chromosomes in XO and XXY patients, using maximum likelihood methods, was proposed by Fraser (1963). Data of the necessary type have been collected from many parts of the world. By September 1966 some 130 families with an XO patient and 50 families with an XXY patient had been typed with anti-Xg^a and analysed by Fraser's method. The analysis showed that some 75% of

Turner's patients with an XO karyotype were X^mO , and 65% of Klinefelter's patients with an XXY karyotype were X^mX^mY (Edwards *et al.*, 1966). A comparable analysis of 22 North American families with XO Turner's syndrome demonstrated that 20% of the patients were X^mO and therefore 80% must be X^pO (Nance and Uchida, 1964).

TABLE V
RESULTS OF TESTING FOR RED-
GREEN COLOUR-BLINDNESS IN
FAMILIES OF XO AND XXY
PATIENTS

	No. Tested	Red-green Colour-blind
<i>XO Families</i>		
Patients	13	0
Brothers	18	1
Sisters	18	0
Mothers	16	0
Fathers	16	1*
<i>XXY Families</i>		
Patients	31	1†
Brothers	22	1
Sisters	28	0
Mothers	23	0
Fathers	19	0

Informative Pedigrees:

* Father colour-blind, mother and patient normal. Therefore patient (T_4) is X^mO .

† Father and mother normal, patient and maternal grandfather colour-blind. Therefore patient (K_3) is X^mX^mY .

In the present study colour-blindness and Xg were used. The colour-vision data are presented in Table V. Of the 13 XO patients who could be tested for colour vision, none was colour-blind. One of 18 brothers and one of 16 fathers were colour-blind. This finding is in accordance with the expected frequency of 5-9% red-green colour-blindness in Caucasian males. In the family where the father was colour-blind (mild red-green defect of unclassifiable type according to the H.R.R. terminology) and the XO daughter normal, it is concluded that the single X of the patient is of maternal origin (Family T_4 in Fig. 2). One of 31 XXY patients who could be tested was colour-blind (medium to strong protan). This finding suggests a colour-blindness frequency of approximately 3% in XXY patients. A brother of another patient was colour-blind (Table V). In the former family (K_3 in Fig. 2) both father and mother had normal colour vision, but the maternal grandfather was reported to be colour-blind by his daughter who gave numerous examples of his inability to distinguish red and green. Thus the patient is most likely X^mX^mY , having received his two X chromosomes in one of the following ways: by non-dis-

TABLE VI
RESULTS OF TESTING XO AND
XXY PATIENTS AND THEIR
IMMEDIATE RELATIVES WITH
ANTI-Xg^a

	No. Tested	% Xg(a-)
XO Families		
Patients	17	35
Fathers	16	19
Mothers	16	6
Brothers	21	38
Sisters	18	0
XXY Families		
Patients	24	33
Fathers	19	32
Mothers	20	5
Brothers	21	43
Sisters	28	21

junction at meiosis II of oogenesis; by crossing-over followed by non-disjunction at meiosis I as suggested by Stern (1959) and illustrated in Polani (1961); or by mitotic non-disjunction (at an early cleavage division) of a maternally derived X chromosome bearing the 'recessive' allele for protan colour-blindness.

The results of testing XO and XXY patients and their immediate relatives with anti-Xg^a are presented in Table VI. The frequency of Xg(a-) XO patients is 35%. This is identical to the normal Xg(a-) frequency in males (Chown, Lewis, and Kaita, 1964) and confirms the observations that XO patients have male phenotypic frequencies for X-linked traits, as predicted by theory (Edwards *et al.*, 1966). The frequency of XXY patients who are Xg(a-) has been reported as midway between the normal male and female Xg(a-) frequency. This finding indicates the genetic contribution of both X^mX^mY and X^mX^pY karyotypes to the pool of XXY patients. Eight out of 24 XXY patients were Xg(a-) in this study; this represented 33%. This figure is close to the expected normal male frequency

FIG. 2. X-linked marker gene studies I. Evidence for maternal origin of the X chromosome(s) of one XO and one XXY patient (dotted symbols), using red-green colour-blindness.

and far removed from the expected female frequency of 12% (Chown *et al.*, 1964).

The usefulness of Xg in identifying X^mO and X^mX^mY patients is illustrated in Table VII. Among the 12 XO families where both parents were Xg(a+), 2 patients were identified as X^mO (T₁ and T₂), and among the 12 XXY families where both parents were Xg(a+), 2 patients were identified as X^mX^mY (K₁ and K₂). Both patients from the informative but rare mating where the father is Xg(a+) and the mother is Xg(a-) were shown to possess only maternally derived X chromosomes, X^mO (T₃) and X^mX^mY (K₃).

The 7 informative families (one by means of

TABLE VII
Xg AND EVIDENCE FOR SOURCE OF X CHROMOSOME(S)
IN XO AND XXY PATIENTS

Mating Type: Father × Mother	Percentage Frequency in Canadian Population*	XO Families		XXY Families		Informative Families: (T ₁ , T ₂ , T ₃ , K ₁ , K ₂ , and K ₃)
		No. and % of Matings	No. of Xg(a-) Patients	No. and % of Matings	No. of Xg(a-) Patients	
Xg(a+) × Xg(a+)	57	12 (75%)	2	12 (63%)	2	T ₁ : X ^m O T ₂ : X ^m O K ₁ : X ^m X ^m Y K ₂ : X ^m X ^m Y T ₃ : X ^m O K ₃ : X ^m X ^m Y
Xg(a+) × Xg(a-)	8	1 (6%)	1	1 (5%)	1	—
Xg(a-) × Xg(a+)	31	3 (19%)	3	6 (32%)	2	—
Xg(a-) × Xg(a-)	4	0 (0%)	0	0 (0%)	0	—

* Chown *et al.* (1964).

FIG. 3. X-linked marker gene studies II. Evidence for maternal origin of the X chromosome(s) of 3 XO and 3 XXY patients (dotted symbols) using the Xg blood group system.

colour vision, 5 by means of Xg, and 1 by both marker genes) are depicted in Fig. 2 and 3. The value of studies involving several X-linked marker genes is illustrated by Family K₃. Xg studies demonstrated that the patient was X^mX^mY. Colour vision studies not only confirmed the X^mX^mY chromosome complement but also suggested two distinct mechanisms to account for the abnormality, if the abnormality occurred at oogenesis. Non-disjunction could have happened at the second

meiotic division or at the first meiotic division on the assumption of a preceding cross-over event.

Comment

The relatively few data on X-linked marker genes presented above have demonstrated the usefulness of such studies in sex chromosome aneuploids. Analysis of such data by the techniques developed by Fraser (1963) or Nance and Uchida (1964) and the comparison of the results derived from different

populations will not only enable us to establish accurately the frequency of maternal and paternal 'non-disjunction' and possible variations in this frequency, but also to study *the time and place* of the abnormal cell division. This finding should lead to more fruitful investigations of the causal factors.

Summary

The families of patients with Turner's syndrome and XO karyotype and Klinefelter's syndrome and XXY karyotype were studied from a number of different aspects.

Twinning tended to appear more frequently than expected among XXY patients but not among XO patients in this series. Parental age at birth of the patient was normal for XO patients, but maternal age in the XXY series of patients was slightly but significantly increased over the most comparable population mean. The majority of the parents and sibs of the patients were examined for sex chromatin and in no instance was there a discrepancy between the sex chromatin findings and the phenotypic sex.

Studies with the X-linked marker genes for red-green colour-blindness and Xg blood group system revealed 4 patients who could be assigned as X^mO and 3 patients who could be assigned as X^mX^mY . In one of the latter families both colour vision and Xg data provided evidence of the maternal origin of the patient's two X chromosomes. The several possibilities for the origin of the X chromosome aneuploidy in this patient are discussed.

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