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The Xg Blood Groups and Sex-Chromosome Aneuploidy [and Discussion]

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The Xg blood groups and sex-chromosome aneuploidy

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Both the distribution and the inheritance of an X-linked character may give information about sex chromosome abnormalities. Colour blindness was used for this purpose by Polani, Lessof & Bishop as long ago as 1956, but the X-linked blood group system, Xg, recognized in 1961, is much more informative simply because of its more convenient gene frequencies.

There are two groups in the system, Xg(a+) and Xg(a−), depending on whether red cells have the antigen Xg^a or not. The antigen is a dominant character and is possessed by about 66 % of European males and by about 88 % of European females.

The following tables and figures illustrate the sort of information that Xg can give about aneuploidy.

There are two main groups of females with Turner's syndrome, those due to the presence of only one X and those due to the presence of one normal X plus a second but defective X. As a defective X is always inactivated both classes are alike in having only one functional X, and this is reflected in the Xg distribution (table 1) which does not differ significantly from that of males.

Table 1. The Xg blood groups of 430 females with only one sound X and with Turner's syndrome as a consequence

		deviation from normal	
	Xg(a+)	males	females
430 Turner's	69 %	← $P = 1$	← $P = 1$ in
normal males	66 %	← in 6	many
normal females	88 %		← millions

This table records the results of tests in the M.R.C. Blood Group Unit up to the end of March 1969. Included are the results up to the end of April 1968 given by Race & Sanger (1969) where can be found many references to publications concerning parts of the collection. The data of this table and of table 2 should not be pooled with those of earlier publications.

The Xg groups of the parents can often give information about the site of the accident which has caused the aneuploidy. For example, the single X of the Turner girl in figure 1 is her father's X, for she cannot have inherited her Xg(a+) from her mother who is Xg(a−). Families of this sort provided the first convincing proof that the single X of a Turner can be paternal in origin, previously it had been thought that the missing X was always the father's fault. Here the accident may have happened at either the first or the second meiotic division of oogenesis, or less likely, at an early division of the zygote.

Various karyotypes may be the cause of Klinefelter's syndrome but XXY is the commonest. Superficially, one might expect XXY males with two X chromosomes to have the female distribution of the Xg groups but they do not: table 2 shows that the difference is significant, with a probability of 1 in 77. This is because when the mother contributes two X chromosomes they

will occasionally be identical copies, in terms of the *Xg* locus, of one of her X chromosomes, and XXY Klinefelter's with such a background will show the male distribution of Xg, and this pushes the total a little from the female in the direction of the male distribution. This relatively slight divergence from the female distribution would, without any evidence from families, have been enough to show that XXY karyotypes must be heterogeneous in origin, that is to say, they can be caused by different accidents. Incidentally, the very highly significant departure of XXY Klinefelter's from the normal male Xg distribution shows that postzygotic mitotic errors play little or no part as a cause of XXY.

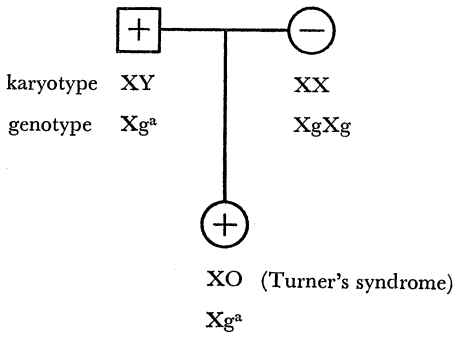

FIGURE 1. The single X of an XO girl with Turner's syndrome can be paternal in origin. In this and later figures + and − signs inside the male squares and female circles represent the Xg phenotypes, Xg(a+) and Xg(a−).

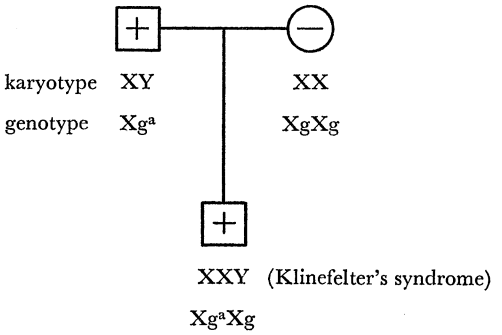

FIGURE 2. Klinefelter's syndrome caused by non-disjunction at the first meiotic division of spermatogenesis.

In Klinefelter's syndrome the Xg groups of the family can sometimes pin down more precisely the site of the accident than they can in Turner's syndrome. The extra X of the XXY son in figure 2 has come from his father as shown by his Xg^a antigen which he could not have had from his mother because she lacks it. The son's Y must have come from his father too, so the

TABLE 2. THE Xg GROUPS OF 329 XXY MALES WITH KLINEFELTER'S SYNDROME

		deviation from normal	
	Xg(a+)	females	males
329 XXY males	84%	← $P = 1$ in 77	← $P = 1$ in many millions
normal XX females	88%		
normal XY males	66%		

See footnote to table 1

father's sperm must have carried an X and a Y. If an X and a Y are to get into one sperm they must take the false step at the first meiotic division. If the accident were delayed to the second meiotic division sperm with two X chromosomes or sperm with two Y chromosomes could result but not a sperm with an X *and* a Y. Families with this Xg arrangement gave the first proof in man that XXY karyotypes could arise from an accident at spermatogenesis. In other families the Xg groups can show that both X chromosomes are of maternal origin, but cannot show whether the accident happened at the first or the second meiotic division.

When both parents of an XXY man can be tested the Xg groups will straightforwardly show whether his extra X is of paternal or maternal origin in one case in nine. But more subtle analysis of the Xg family results by the method devised by Dr George Fraser allows the estimate

in table 3 to be made: in 40 % of patients the extra X is paternal and in the rest both X chromosomes are maternal—different maternal X chromosomes in 50 %, different in terms of the *Xg* locus; and duplicates of one maternal X in 10 %. It is this 10 % that pushes the Xg distribution of XXY Klinefelter's a little away from the female.

TABLE 3. ESTIMATED SOURCE OF THE TWO X CHROMOSOMES IN XXY KLINEFELTER'S

		distribution of Xg
X^MX^PY	40 %	female
$X^{M1}X^{M2}Y$	50 %	female
$X^{M1}X^{M1}Y$ / $X^{M2}X^{M2}Y$	10 %	male

TABLE 4. THE CAUSES OF THE TWO COMMONEST FORMS OF SEX-CHROMOSOME ANEUPLOIDY

	accident to sex chromosome of	
	father	mother
XXY Klinefelter's	X^MX^PY 40 %	X^MX^MY 60 %
XO Turner's	X^MO 75 %	X^PO 25 %

Figure 3 illustrates Klinefelter's syndrome caused by a rarer karyotype. The Xg groups show that the father has given an X to his son, for the son is Xg(a+) and the mother Xg(a−). The father has also given two Y chromosomes to his son. Here non-disjunction has happened at both meiotic divisions in the formation of the sperm that produced the Klinefelter. At the first meiotic division the X and the Y instead of parting and going into two cells have stayed together and gone both into one cell. At the second meiotic division the two X chromatids have parted correctly but this time the two Y chromatids have stayed together, the final result being a sperm with one X and two Y chromosomes. This sperm has fertilized a normal ovum to produce the XXYY son. Some years ago this family provided the first evidence that non-disjunction can happen at both meiotic divisions consecutively. We have tested another identical family since.

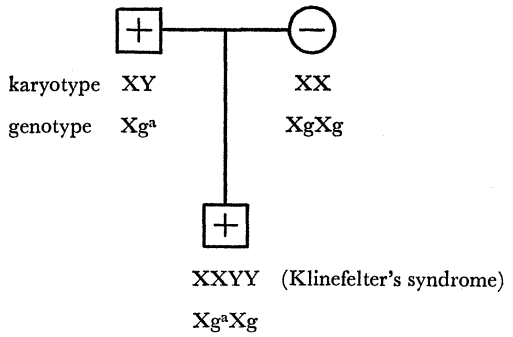

FIGURE 3. Klinefelter's syndrome caused by non-disjunction at first and second meiotic divisions of spermatogenesis.

From the Xg groups it can be calculated that the accident which results in XXY Klinefelter's happens more commonly at oogenesis and that which causes XO Turners more commonly at spermatogenesis (table 4).

There are several other ways in which Xg can give information, but time is short and perhaps enough has been said to give some general impression of how X-linked characters, such as the Xg blood groups, can give a little insight into the origin of abnormalities of number of the sex chromosomes.

The Xg tests on all these people were done by colleagues in the M.R.C. Blood Group Unit. It is not possible to acknowledge all the physicians or cytogeneticists, in many countries, who

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sent the samples; the majority came from the following: Dr K. Boczkowski, Dr A. de la Chapelle, the late Professor W. M. Court Brown, Dr Gudrun Dahl, Professor J. H. Edwards, Dr M. A. Ferguson-Smith, Dr A. Frøland, Dr J. de Grouchy, Dr J. Insley, Professor M. Lamy, Professor J. Lejeune, Dr J. Lindsten, Dr V. A. McKusick, Dr Margareta Mikkelsen, Dr J. Philip, Professor P. E. Polani, Dr W. H. Price, Dr C. Salmon, Professor R. Turpin, Dr H. van den Berghe and Dr J. J. van Went.

References (Race)

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Discussion on papers by K. Fredga, p. 15 and R. R. Race, p. 37

C. D. Darlington, F.R.S. (*Botany School, Oxford*): Has Race considered the position of the Xg gene in relation to the differential and pairing segments? If the separation of the differential segments of the X is equational at the first division, then non-disjunction at the second division will produce the results he attributes to the first (Darlington 1965, *Cytology*, London: Churchill). This could affect the interpretation of some of his results.

R. R. Race (*Lister Institute, London*): We do not know where Xg is located. It has alternately proved to be on the long arm and on the short arm!

R. G. Edwards: In *Microtus oregonii* non-disjunction occurs in the male and female germ lines. When does this non-disjunction occur; is it early in the germ cell line or during meiosis?

K. Fredga: According to Ohno it is early, perhaps in the primordial germ cells in both sexes.

C. E. Ford (*M.R.C. Radiobiological Research Unit, Harwell*): A recent paper by Castro-Sierra & Wolf (1968, *Cytogenetics* **7**, 291–298) on male *Elobius* reaches the conclusion that an X_1X_2Y system probably operates in males, i.e. a mechanism similar to that in mongoose. There is very little evidence about oocyte meiosis. The female could be $X_1X_1X_2X_2$ as a zygote, followed by non-disjunction to give a $X_1OX_2X_2$ soma but retaining $X_1X_1X_2X_2$ oocytes. The gametes would then all be of one kind, i.e. X_1X_2 in females, but X_1X_2 and Y in males.

K. Fredga: In the mongoose association occurred between the X and an autosomal bivalent in diplotene and diakinesis. Wolf *et al.* could find no such association at these stages, although at pachytene an association was found between the sex vesicle and an autosomal bivalent in approximately 25 % of cells. But several chromosomes can be associated with the sex vesicle at this stage in other species having a normal sex chromosome mechanism and even though Wolf's explanation is attractive it was not convincingly supported by evidence.

A. G. Searle (*M.R.C. Radiobiological Research Unit, Harwell*): I have one comment on the question of whether Xg^a is on the pairing or differential segments. Partial sex linkage would be expected if it was located on a pairing segment. I do not think any human sex-linked gene has so far exhibited this phenomenon.

R. R. Race: The data did not indicate partial sex linkage. An interchange between the X and Y chromosomes might have occurred in only three families out of some thousands, and although partial sex linkage was one possible explanation, there were others.

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