The X-linked Blood Group System Xg

Tests on Unrelated People and Families of Northern European Ancestry

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The X-linked blood group system Xg was recognized in November 1961 (Mann *et al*, 1962). An account up to 14 July 1965 of its incidence and inheritance in people of northern European extraction tested in the Unit was published in this Journal by Noades *et al* (1966). This present paper brings our account up to 23 December 1969.

The red cell samples came from four main sources: (1) members of laboratory staffs and volunteer donors tested to set a net in which other examples of anti-Xg^a might be caught; (2) normal families; (3) very many families with X-linked dimorphisms tested for X-mapping purposes; (4) the parents of children with an abnormality of number or of form of the X chromosome (which parents have a normal distribution of the Xg groups).

Unrelated People

The results of testing 6784 unrelated people are in Table I. The gene frequencies for the total are Xg^a 0.659 and Xg 0.341, by chance exactly the same as they were at the 3418 level (Noades *et al* 1966).

The gene frequencies were calculated by the formula devised by Haldane (1963) for the purpose: frequency of gene Xg =

$$\frac{[4(2f+m)(b+2d)+a^2]^{1/2}-a}{2(2f+m)}$$

frequency of gene Xg^a = 1 - frequency of Xg where the letters represent the absolute numbers observed in the following categories:

	Xg(a +)	Xg(a -)	Total
Males	a	b	m
Females	c	d	f

The gene frequencies thus calculated from the male and female absolute numbers can be recombined to give the expected genotype and pheno-

type frequencies. For example, the expected frequencies for the total people of northern European extraction are:

Males	Females	
Xg ^a 0.659	Xg ^a Xg ^a 0.434	} 0.884
Xg 0.341	Xg ^a Xg 0.450	
	XgXg 0.116	

Such calculated genotype frequencies can be re-applied to the people from whom they were derived to see whether the observed male and female distributions of the Xg phenotypes are mutually concordant. The results of these tests are expressed in terms of χ^2 (for one degree of freedom) in the last two columns of Table I. There is serious disharmony in only one set of people: the disturbance in the Finns is highly significant. Here, we guess we are entangled in some complication of ascertainment resulting from the collecting, for other purposes, of certain samples from small Finnish isolates, which no doubt contain much hidden consanguinity.

The figures for the 4 main divisions are summed at the bottom of Table I and are compared each to each in Table II. An excess of Xg(a-) females in the Scandinavian sample, mainly contributed by the Danes, is certainly significant, but of what we cannot say. It could perhaps reflect a real difference in gene frequency in these people, for the excess of the allele Xg in females is exactly matched in the Scandinavian males.

Besides progressive publications from this Unit, summed in the present paper, substantial series of tests on unrelated people of northern European origin have been reported: 588 Canadians (Chown, Lewis, and Kaita, 1964), 1382 American whites (Dewey and Mann, 1967), and 558 Swiss (Metaxas and Metaxas-Bühler, 1970). All the frequencies are in good agreement.

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TABLE I

Xg GROUPS OF 6784 PEOPLE OF NORTHERN EUROPEAN EXTRACTION NOT KNOWN TO BE RELATED

Samples Posted From	Males				Females				Gene Frequency		χ^2 (see text)	
	Total	Xg(a+)	Xg(a-)	Proportion Xg(a-)	Total	Xg(a+)	Xg(a-)	Proportion Xg(a-)	Xg ^a	Xg	Males	Females
England 3408	1665	1090	575	0.345	1743	1569	174	0.100	0.669	0.331	1.66	1.61
Scotland 353	160	115	45	0.281	193	179	14	0.073	0.725	0.275	0.03	0.03
USA 941	627	414	213	0.340	314	276	38	0.121	0.658	0.342	0.02	0.04
Canada 72	34	24	10	0.294	38	33	5	0.132	0.669	0.331	0.14	0.19
Finland 357	188	132	56	0.298	169	130	39	0.231	0.605	0.395	7.36	7.25
Sweden 279	137	84	53	0.387	142	125	17	0.120	0.634	0.366	0.27	0.24
Denmark 286	137	85	52	0.380	149	120	29	0.195	0.585	0.415	0.69	0.54
Norway 31	21	13	8		10	10	0					
Iceland 3	1	1	0		2	2	0					
France 264	140	79	61	0.436	124	110	14	0.113	0.612	0.388	1.35	1.37
Netherlands 188	116	86	30	0.259	72	63	9	0.125	0.705	0.295	0.74	1.31
N. Italy 61	29	15	14	0.483	32	30	2	0.063	0.633	0.367	1.69	1.42
Switzerland 51	23	15	8		28	22	6					
N. Spain 64	27	18	9	0.333	37	33	4	0.108	0.669	0.331	0.08	0.04
Poland 173	87	56	31	0.356	86	78	8	0.093	0.669	0.331	0.24	0.25
Germany 164	81	53	28	0.346	83	75	8	0.096	0.672	0.328	0.11	0.11
Belgium 89	40	24	16	0.400	49	45	4	0.082	0.661	0.339	0.66	0.54
Total 6784	3513	2304	1209	0.344	3271	2900	371	0.133	0.659	0.341	0.20	0.21
Britain 3761	1825	1205	620	0.340	1936	1748	188	0.097	0.674	0.326	1.68	1.58
N. America 1013	661	438	223	0.337	352	309	43	0.122	0.658	0.342	0.05	0.10
Scandinavia (excluding Finland) 559	296	183	113	0.382	303	257	46	0.152	0.614	0.386	0.02	0.02
Mainland of Europe 1054	543	346	197	0.363	511	456	55	0.108	0.654	0.346	0.69	0.70

TABLE II

COMPARISONS BY χ^2 (FOR 1 df) OF Xg GROUPS OF SAMPLES FROM FOUR MAIN AREAS

(The observed numbers on which the calculations are based are given in the last 4 rows of Table I)

	Males			Females		
	Mainland of N. Europe	Scandinavia (excluding Finland)	N. America	Mainland of N. Europe	Scandinavia (excluding Finland)	N. America
Britain	0.99	1.99	0.70	0.50	8.38	2.06
N. America	0.85	1.77		0.44	1.22	
Scandinavia (excluding Finland)	0.30			4.32		

Families

From the gene and phenotype frequencies may be calculated the expected frequencies of the 4 mating types in the population being dealt with, and also the expected incidence of the Xg groups in their offspring. Table III gives the formulae for families in which both parents have been tested, and also those for families in which only one parent has been tested. These formulae have been applied, in Tables IV and V, to the analysis of the various categories of families.

Analysis, row by row, using the local frequencies did not expose any tendencies not shown by applying the grand total frequencies which, for simplicity,

alone are used in Tables IV and V. On the whole, the fit between the observed and expected distribution of mating types and offspring therefrom is good. The only significant departure is that too high a proportion of sons of the Xg(a+) mothers of Table V are Xg(a-), χ^2 for 1 df being 6.3. This excess was carried over from the 1966 account (Noades *et al.*), where a probable reason was given; however, as the families tested since 1966 do not show the disturbance it need not be discussed again.

An excess of sons over daughters is often notable: this is due to selection of families with sons for the X-linkage work. On the other hand, there was sometimes selection for daughters in families in which only the father had been grouped (Table V):

TABLE III
EXPECTED DISTRIBUTION OF Xg GROUPS IN PARENTS AND OFFSPRING (From Noades *et al*, 1966)

Mating			Proportion of Xg Groups:						
Total	Type		Frequency	In Sons			In Daughters		
	Father	Mother		Obs. Total	Xg(a +)	Xg(a -)	Obs. Total	Xg(a +)	Xg(a -)
P _n	Xg(a +)	Xg(a +)	p _n × Xg ^a × ♀Xg(a +)	s ₁	s ₁ × (a)	s ₁ × (b)	d ₁	All	None
	Xg(a +)	Xg(a -)	p _n × Xg ^a × ♀Xg(a -)	s ₂	None	All	d ₂	All	None
	Xg(a -)	Xg(a +)	p _n × Xg × ♀Xg(a +)	s ₃	s ₃ × (a)	s ₃ × (b)	d ₃	d ₃ × (a)	d ₃ × (b)
	Xg(a -)	Xg(a -)	p _n × Xg × ♀Xg(a -)	s ₄	None	All	d ₄	None	All
P ₁	Xg(a +)	?	p ₁ × Xg ^a	s ₅	s ₅ × Xg ^a	s ₅ × Xg	d ₅	All	None
P ₂	Xg(a -)	?	p ₁ × Xg	s ₆	s ₆ × Xg ^a	s ₆ × Xg	d ₆	d ₆ × Xg ^a	d ₆ × Xg
	?	Xg(a +)	p ₂ × ♀Xg(a +)	s ₇	s ₇ × (a)	s ₇ × (b)	d ₇	d ₇ × (c)	d ₇ × (d)
	?	Xg(a -)	p ₂ × ♀Xg(a -)	s ₈	None	All	d ₈	d ₈ × Xg ^a	d ₈ × Xg

Xg^a and Xg = the gene frequencies in the appropriate population. ♀Xg(a +) and ♀Xg(a -) = the calculated frequency of the two phenotypes in the females of the appropriate population.

$$(a) = \frac{Xg^a}{\varphi Xg(a+)} \quad (b) = 1 - (a) \quad (c) = Xg^a + (b) \quad (d) = 1 - (c)$$

P_n = total number of families with both parents grouped; p₁ = mother not grouped; p₂ = father not grouped.

TABLE IV
Xg GROUPS OF 1348 FAMILIES OF NORTHERN EUROPEAN EXTRACTION WITH 3272 CHILDREN
(The expectations are based on the gene frequencies Xg^a = 0.659 and Xg = 0.341)

Matings	No.	Offspring					
		Sons			Daughters		
		Total	Xg(a +)	Xg(a -)	Total	Xg(a +)	Xg(a -)
<i>Xg(a +) father × Xg(a +) mother</i>							
England and Scotland	456	500	372	128	462	459	3*
North America	96	169	124	45	122	122	0
Scandinavia (excluding Finland)	31	43	27	16	33	33	0
Finland	88	156	135	21	105	105	0
Netherlands	63	119	93	26	107	107	0
Rest of N. Europe	57	81	61	20	54	54	0
Total Expected	791 785.3	1068	812 795.7	256 272.3	883	880 883.0	3
<i>Xg(a +) father × Xg(a -) mother</i>							
England and Scotland	46	51	7*	44	40	39	1*
North America	10	16	0	16	8	8	0
Scandinavia (excluding Finland)	10	16	0	16	12	12	0
Finland	16	23	0	23	19	19	0
Netherlands	15	24	0	24	19	19	0
Rest of N. Europe	10	12	0	12	13	13	0
Total Expected	107 103.1	142	7	135 142.0	111	110 111.0	1
<i>Xg(a -) father × Xg(a +) mother</i>							
England and Scotland	235	260	186	74	228	168	60
North America	46	78	50	28	55	37	18
Scandinavia (excluding Finland)	14	13	11	2	9	7	2
Finland	39	56	43	13	46	37	9
Netherlands	28	50	44	6	52	42	10
Rest of N. Europe	30	34	19	15	41	24	17
Total Expected	392 406.3	491	353 365.8	138 125.2	431	315 321.1	116 109.9
<i>Xg(a -) father × Xg(a -) mother</i>							
England and Scotland	24	23	0	23	22	0	22
North America	9	12	0	12	13	0	13
Scandinavia (excluding Finland)	6	9	0	9	11	0	11
Finland	9	16	0	16	8	0	8
Netherlands	5	9	0	9	4	0	4
Rest of N. Europe	5	8	0	8	11	0	11
Total Expected	58 53.3	77	0	77 77.0	69	0	69 69.0
Grand total	1348	1778			1494		3272

* Exceptional children, see text.

TABLE V

X_g GROUPS OF 1192 PARENTS AND 2552 CHILDREN OF NORTHERN EUROPEAN EXTRACTION
(ONE PARENT NOT TESTED)

(The expectations are based on the gene frequencies $X_g^a = 0.659$ and $X_g = 0.341$)

Matings	No.	Offspring						Total Children
		Sons			Daughters			
		Total	Xg(a +)	Xg(a -)	Total	Xg(a +)	Xg(a -)	
<i>Xg(a +) father, mother not tested</i>								
England and Scotland	80	42	27	15	102	102	0	144
North America	16	5	4	1	18	18	0	23
Scandinavia (excluding Finland)	7	5	4	1	7	7	0	12
Finland	24	31	26	5	29	29	0	60
Netherlands	13	28	24	4	25	25	0	53
Rest of N. Europe	8	8	5	3	7	7	0	15
Total Expected	148 147.0	119	90 78.4	29 40.6	188	188 188.0	0	307
<i>Xg(a -) father, mother not tested</i>								
England and Scotland	33	16	11	5	37	20	17	53
North America	21	18	7	11	30	24	6	48
Scandinavia (excluding Finland)	2	0	0	0	3	3	0	3
Finland	6	2	1	1	5	4	1	7
Netherlands	8	6	6	0	16	7	9	22
Rest of N. Europe	5	7	4	3	7	4	3	14
Total Expected	75 76.0	49	29 32.3	20 16.7	98	62 64.6	36 33.4	147
<i>Father not tested, Xg(a +) mother</i>								
England and Scotland	398	509	377	132	293	273	20	802
North America	204	359	242	117	142	130	12	501
Scandinavia (excluding Finland)	27	18	10	8	22	19	3	40
Finland	88	130	98	32	77	68	9	207
Netherlands	72	106	80	26	65	58	7	171
Rest of N. Europe	65	93	60	33	59	46	13	152
Total Expected	854 856.6	1215	867 905.2	348 309.8	658	594 601.4	64 56.6	1873
<i>Father not tested, Xg(a -) mother</i>								
England and Scotland	44	46	0	46	31	20	11	77
North America	36	41	0	41	29	15	14	70
Scandinavia (excluding Finland)	6	5	0	5	2	1	1	7
Finland	14	20	0	20	16	9	7	36
Netherlands	5	5	0	5	8	7	1	13
Rest of N. Europe	10	12	0	12	10	9	1	22
Total Expected	115 112.4	129	0 129.0		96	61 63.3	35 32.7	225
Grand total	1192	1512			1040			2552

this was because maternal grandfathers were specially sought, in the hope of getting three-generation linkage information. When kindreds were tested, each separate family unit within the kindred was entered in the tables.

Exceptional Children. In Table IV there are 11 children who appear to break the rules of X-linked inheritance, all 11 are in the England plus Scotland division. No exceptions are disclosed in Table V. Exceptions could be explained by illegitimacy, but all the families in Tables IV and V were tested for a variety of other groups besides X_g and any members shown to be illegitimate by these other groups were omitted from the counts. Of course, 45,X daughters of $X_g(a+)$ fathers are often

$X_g(a-)$ and 47,XXY sons of $X_g(a-)$ mothers are sometimes $X_g(a+)$, but families with such X chromosome abnormalities (Sanger, Tippett, and Gavin, 1971) are excluded from these tables.

$X_g(a-)$ Daughters of $X_g(a+)$ Fathers. One $X_g(a-)$ daughter (Mary Ro. PRU 1492/4036) from the mating $X_g(a+) \times X_g(a+)$ was a patient of Professor Polani. She was trisomic for one of the D group chromosomes and died at birth. The sample of blood was 1 week old before the X_g tests were done, but it looked in good condition and the other blood group reactions appeared to be normal. Her parents were tested some time later, so the baby was not recognized as exceptional in her X_g group until it was too late to confirm the $X_g(a-)$ re-

action by absorption tests. The other blood groups afforded no reason to doubt the paternity of the baby.

A second Xg(a-) girl (K.M.) from the mating Xg(a+) × Xg(a+) was the 7-year-old sister of a patient of Dr J. D. Allan. Her autosomal groups were compatible with those of her parents but a slightly unusual genotypic interpretation had to be invoked.

A third Xg(a-) girl (B.W.) from the mating Xg(a+) × Xg(a+) was a patient of Professor J. H. Edwards. She was aged nearly 3. The sample of blood was rather small so only a limited number of autosomal groups could be done, but as far as they went they were compatible with those of her parents.

The Xg(a-) girl (Carol Ow. PRU 1428/3806) from the mating Xg(a+) × Xg(a-) was a patient of Professor Polani: she was trisomic for one of the E group of chromosomes and died at the age of 4 weeks. An elder sister is Xg(a+) and a brother is Xg(a-). The Xg(a-) reaction of the baby was confirmed by absorption tests and the reactions of the parents were confirmed on second samples of their blood. Paternity in this family could be established, for both the father and the baby were found by Professor H. Lehmann to have a peculiar type of haemoglobin.

It should be noted, when considering the two exceptional baby girls who were trisomic, that the antigen Xg^a is not always developed fully before birth (Toivanen and Hirvonen, 1969) and that we have evidence that the Xg^a antigen of babies with the trisomies of Down, Edwards, and Patau tends to be weaker than that of normal babies.

It seems to us that, for one reason or another, the 4 exceptions above do not carry the weight of those about to be described.

Xg(a+) Sons of Xg(a-) Mothers. The 7 such sons in Table IV belong to 3 families, Je., Bu., and Wa., which have been recorded elsewhere (Sanger *et al*, 1964 and 1968):

Je. family: father Xg(a+), mother Xg(a-), both of two sons Xg(a+).

Bu. family: father Xg(a+), mother Xg(a-), all three sons Xg(a+).

Wa. family: father Xg(a+), mother Xg(a-), both of two sons Xg(a+).

A possible explanation which we had come to favour was that in the ancestry of the fathers of the Xg(a+) boys a small portion of an X, involving the Xg locus (occupied by the allele Xg^a), had become translocated on to a Y, or even on to an autosome. However, when family Wa. was tested the groups

of three generations excluded, in their case at any rate, a translocation on to a Y.

A further family (Buckton *et al*, 1971), not included in this series of families because it was tested after 23 December 1969 (and which would not have qualified anyhow because it involved a sex chromosome abnormality), perfectly explains itself and offers a possible solution to the earlier families. The peripheral blood of a mother was found at the MRC Clinical and Population Cytogenetics Unit to be mosaic 45,X/46,XX, the two cell lines being in the approximate proportion of 1 to 2. The mother and her husband were phenotypically Xg(a-) but one son and one daughter were Xg(a+). It was assumed, because of her fertility, that her gonads were, at least in part, 46,XX, and, because of the exceptional Xg inheritance that her genotype must be Xg^aXg but that her red cells were derived from a predominantly 45,X line; the latter presumption was supported when the karyotype of her marrow showed about 90% of the cells to be 45,X.

Trying to put these Xg(a+) sons of Xg(a-) mothers into their proper perspective Sanger *et al* (1964) asked the following questions:

(1) How uncommon is it for Xg(a+) sons to have Xg(a-) mothers? The answer, brought up to 23 December 1969, is that in all the families we have tested—British, North American, northern European, Sardinian, Israeli, Negro, Chinese, etc—3231 Xg(a+) sons have sprung from 1897 mothers, 1894 of whom are Xg(a+) and 3 (Mrs Je., Mrs Bu., and Mrs Wa.) are Xg(a-).

(2) How uncommon is it for Xg(a-) mothers to have Xg(a+) sons? The December 1969 count shows that 303 Xg(a-) mothers of sons have been tested: 300 of them have 523 Xg(a-) sons and 3 (Mrs Je., Mrs Bu., and Mrs Wa.) have 7 Xg(a+) sons.

It should be added that Chown *et al* (1964) in a series of 294 white families, mainly Canadian, also found one in which an Xg(a-) mother had an Xg(a+) son.

Xg and Lyonization. The existence of these Xg(a+) sons of Xg(a-) mothers could be attributed to Lyonization, provided the Xg locus when carried on a structurally normal X is subject to inactivation, and provided that inactivation happens at such an early stage of embryonic life that there are very few ancestral cells of the erythroid series.

Our present opinion is that Xg locus of a structurally normal X is not involved in inactivation (Gorman *et al*, 1963; Fialkow, 1970; Fialkow *et al*, 1970; Lawler and Sanger, 1970). The only

evidence in favour of its inactivation (Lee *et al.*, 1968) could not be confirmed (Weatherall *et al.*, 1970).

Gandini and his collaborators (1968) from a study of women heterozygous at the locus for glucose-6-phosphate dehydrogenase estimated that at the time of inactivation the primordial cells destined to form the erythroid series number 8 or less.

TABLE VI

DISTRIBUTION OF 1523 $X_g(a+)$ MOTHERS OF SONS ACCORDING TO NUMBER AND X_g GROUP OF THEIR SONS

(Extracted from the families of Tables IV and V)

Normal Families

535 Mothers with:

Sons Xg(a -)	Sons Xg(a +)								
	0	1	2	3	4	5	6	7	8
0		253 258.7	72 81.6	28 23.3	5 4.2	2		1	
1	94 88.3	45 33.6	4 8.0	2 1.0					
2	15 16.8	9 8.0	1 1.5						
3	1 2.7	0 1.0	1						
4	0 0.3	1					1		
5									

X-Linkage Families

988 Mothers with:

Sons Xg(a -)	Sons Xg(a +)								
	0	1	2	3	4	5	6	7	8
0		358 348.9	161 178.7	73 73.8	28 29.8	14 12.7	4	1	2
1	110 119.1	67 73.6	31 25.4	7 7.2	1 2.0	1		2	
2	61 36.8	21 25.4	12 10.9	7 4.0	1				
3	8 8.5	5 7.2	2 4.0	1					
4	5 1.8	0 2.0	1			1			1
5	1 0.4			1					

If, against the weight of other evidence, the X_g locus were subject to inactivation, and if the number of primordial erythroid cells were as few as 8, then there should be a slight excess of $X_g(a-)$ amongst the 3271 females of Table I when analysed by the gene frequencies given by the 3513 males of

that table. That there is a non-significant shortage of $X_g(a-)$ females (expected 386.0, observed 371) brings no support for the inactivation of X_g . If the number of primordial erythroid cells, at the time of inactivation, were as few as 4 the observed shortage of $X_g(a-)$ females would be highly significant evidence against X_g being involved.

Professor J. H. Edwards suggested we should make a count of $X_g(a+)$ mothers according to the number of their $X_g(a+)$ and $X_g(a-)$ sons, in the form shown in Table VI. If the X_g locus were subject to inactivation and if inactivation does happen at the very early stage '8 cells or less' of erythroid development then some discrepancies might emerge between the observed and expected contents of some of the boxes of such a table. A count was therefore made of sons of $X_g(a+)$ mothers in Tables IV and V of this paper and the fit between observed and expected was very close in all but two of the boxes. Clearly something was wrong with the two son families: much too often both sons were $X_g(a-)$ (observed 76, expected 53.6) and somewhat too seldom both were $X_g(a+)$ (observed 233, expected 260.3).

There were two classes of families in this first count: (1) 'normal' families involved in blood group problems unrelated to X_g and (2) families with X-linked conditions and X_g grouped for X-mapping purposes. When the two groups are separated, as in Table VI, the excess of mothers with $X_g(a-)$ sons in the two son families is seen to be confined to class (2). We presume this must reflect the energetic pursuit of relatives of mothers who had proved themselves heterozygous, $X_g^a X_g$, and therefore informative for X-linkage (Noades *et al.*, 1966). We do not know why this presumed selection appears to affect only the two-son families.

Apparent exceptions to the dominant X-linked inheritance of the antigen X_g^a , when not due to frank X-chromosome aneuploidy, are rare and their causes unresolved.

Summary

The accounts of the X_g blood groups of white people of northern European ancestry tested at the MRC Blood Group Unit are brought up to 23 December 1969. The samples were sent from Britain, North America, Scandinavia, and from the mainland of northern Europe.

From 6784 unrelated people the calculated gene frequencies are: X_g^a 0.659 and X_g 0.341 which, curiously and conveniently, are exactly those of the last report, in 1966, when only 3418 of these people had been tested.

The gene frequencies are used to analyse the

results of testing 2540 families of northern European ancestry with 5824 children, and the observed and calculated numbers fit well. Eleven of the children, belonging to 7 families, appear to break the rules of X-linked inheritance, and possible explanations are discussed.

We thank the very many physicians who sent samples from the families here recorded. Many of the families have been published in separate papers dealing with the search for linkage between Xg and other X-linked conditions.

Much involved in the Xg testing were past members of the Unit: Miss Jean Hamper, Miss Jean Noades, Mrs Ann Gooch, and Mrs Joan Whittaker.

Our thanks for magnificent gifts of anti-Xg^a and the rather special antiglobulin-serum it requires are expressed in another paper in this issue (p. 425).

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