The X-linked Blood Group System Xg

Tests on British, Northern American, and Northern European Unrelated People and Families

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The red cell antigen Xg^a is an X-linked dominant character. The results of tests on unrelated white people and families made in this Unit up to September 1963 were reported in a previous paper (Gavin, Tippet, Sanger, and Race, 1964): the present paper brings the total account up to July 14, 1965.

The counts are confined to tests on people of northern European extraction. In the last report we assumed that these people were homogeneous in respect of the distribution of the Xg groups and we made no distinctions according to the sources of the samples. In preparing the present report we thought it worth while, since the numbers were now fairly large, to divide the samples according to their sources of origin—Britain, northern America, and the northern mainland of Europe. (Excluded from all the tables in this paper are other people we have tested: Sardinians, Greeks, Israelis, American Negroes, Chinese etc.; they have been dealt with in other publications.)

Unrelated People

In Table I are shown the results of testing 3418 unrelated white people subdivided according to the countries in which the samples were taken.

Source of the Samples. The supply of anti-Xg^a does not yet allow samples to be tested simply to establish the frequencies in different countries. The samples in Table I were tested for one of four reasons.

(i). Some were from members of laboratory staffs, or certain special donors, tested in the hope that their blood might set a net in which other examples of anti-Xg^a might be caught.

(ii). Some were from unrelated members of

normal families which were tested to consolidate the evidence for the way of inheritance of the Xg groups.

(iii). Many were from unrelated members of families tested in attempts to measure linkage between the Xg locus and the loci for many X-linked conditions (about half of the 60 or so listed by McKusick, 1962).

(iv). Some were from parents of families in which a child had an abnormality of number or of form of the X chromosome. The justification for including these parents is defended below.

The Counts. The proportion of Xg(a+) and Xg(a-) amongst the total males and females at the 3418 level is almost exactly the same as it was at the 2000 level of the previous report (Gavin *et al.*, 1964), but we are now doubtful about the propriety of pooling all the results.

In Table I it can be seen that the frequencies for England and Scotland are very like those for U.S.A. and Canada, and that the frequencies for the Scandinavian countries are very like those for the rest of the mainland of Northern Europe.

The figures for the three main divisions are summed at the foot of Table I. There may be logical objections to this manner of pooling, but the absolute numbers given in the table will allow other divisions to be made. The absolute numbers of males and females, Xg(a+) and Xg(a-), in the three main divisions are compared in Table II where it is seen that, while the British and North American distributions do not differ from each other, both differ significantly, and surprisingly, from that of the mainland of Northern Europe.

Of the 3418 samples from unrelated people recorded in Table I, 716 were from the parents of families which included a child with an abnormality of form or number of the X chromosomes: these

TABLE I
THE Xg GROUPS OF 3418 UNRELATED WHITE PEOPLE

Samples Posted From	Males					Females				Gene Frequency		χ^2_1 (see text)	
	Total	Xg(a+)	Xg(a-)	Proportion Xg (a-)	Total	Xg(a+)	Xg(a-)	Proportion Xg (a-)	Xga	Xg	Males	Females	
England	1947	953	625	328	0.344	994	895	99	0.100	0.670	0.330	0.88	0.90
Scotland	135	60	42	18	0.300	75	72	3	0.040				
U.S.A.	632	385	256	129	0.325	247	219	28	0.113	0.664	0.336	0.00	0.00
Canada	38	15	12	3		23	22	1					
Finland	76	33	19	14		43	31	12		0.592	0.408	0.13	0.01
Sweden	155	74	45	29	0.392	81	75	6	0.074				
Denmark	115	56	32	24	0.429	59	46	13	0.220				
Norway	15	15	7	8		0	0	0					
France	115	67	34	33	0.493	48	42	6	0.125	0.618	0.382	0.92	0.97
Holland	54	31	18	13		23	19	4					
N. Italy	23	11	7	4		12	10	2					
Switzerland	31	14	8	6		17	13	4					
N. Spain	33	14	8	6		19	19	0					
Poland	35	16	13	3		19	19	0					
Germany	14	7	5	2		7	6	1					
Total	3418	1751	1131	620	0.354	1667	1488	179	0.107	0.659	0.341	1.33	1.21
Britain	2082	1013	667	346	0.342	1069	967	102	0.095	0.675	0.325	1.27	1.26
N. America	670	400	268	132	0.330	270	241	29	0.107	0.671	0.329	0.00	0.00
N. Europe, mainland	666	338	196	142	0.420	328	280	48	0.146	0.600	0.400	0.57	0.46

children were mostly sufferers from the syndromes of Turner or of Klinefelter. We did not see why there should be any disturbance of the Xg groups in the parents to exclude them from the unrelated count, but, just in case, they were extracted and compared with the remaining unrelated people: the counts are given in Table III where the χ^2 tests give no hint of any disproportion of Xg distribution. The 716 parents were therefore left in Table I.

Gene Frequencies. The gene frequencies given in Table I were calculated by the formula of Haldane (1963).

$$\text{frequency of gene } Xg = \frac{[4(2f + m)(b + 2d) + a^2]^{\frac{1}{2}} - a}{2(2f + m)}$$

TABLE II

COMPARISON OF INCIDENCE OF Xg GROUPS OF SAMPLES FROM 3418 UNRELATED PEOPLE SENT FROM BRITAIN, NORTH AMERICA, AND FROM MAINLAND OF NORTHERN EUROPE

	Total Tested	Males			Females		
		Xg(a+)	Xg(a-)	χ^2_1	Xg(a+)	Xg(a-)	χ^2_1
Britain	2,082	667	346		967	102	
N. America	670	268	132		241	29	
				0.41			0.35
Britain	2,082	667	346		967	102	
Mainland							
N. Europe	666	196	142		280	48	
				6.78			6.79
N. America	670	268	132		241	29	
Mainland							
N. Europe	666	196	142		280	48	
				6.37			2.00

TABLE III

3418 UNRELATED PEOPLE OF TABLE I DIVIDED INTO 716 WHO ARE PARENTS OF PATIENTS WITH ABNORMALITIES OF X CHROMOSOME (A.X) AND THOSE WHO ARE NOT

Country		Males			Females		
		Xg(a+)	Xg(a-)	χ^2_1	Xg(a+)	Xg(a-)	χ^2_1
Britain and N. America	Parents of A.X	124	70		209	28	
	The rest	811	408		999	103	
Mainland of N. Europe				0.51			1.35
	Parents of A.X	79	57		129	20	
	The rest	117	85		151	28	
				0.00			0.32

frequency of gene $Xg^a = 1 - \text{frequency of } Xg$, 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 recomputed to give the expected genotype and phenotype frequencies. For example, the expected frequencies for Britain are:

Males		Females		
Xg^a	0.675	$Xg^a Xg^a$	0.455	} 0.894
Xg	0.325	$Xg^a Xg$	0.439	
		$Xg Xg$	0.106	

Those for North America are:

Males		Females		
Xg^a	0.671	$Xg^a Xg^a$	0.450	} 0.892
Xg	0.329	$Xg^a Xg$	0.442	
		$Xg Xg$	0.108	

And those for the mainland of Northern Europe are:

Males		Females		
Xg^a	0.600	$Xg^a Xg^a$	0.360	} 0.840
Xg	0.400	$Xg^a Xg$	0.480	
		$Xg Xg$	0.160	

These calculated genotype frequencies can be reapplied 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 1 degree of freedom) in the last two columns of Table I, where it can be seen that there is no evidence of disharmony at any level.

Families

From the frequencies above may be calculated the expected frequencies of the four mating types in the population being dealt with, and also the expected incidence of the Xg groups in their offspring. Table IV gives the formulae for families in which both parents have been tested, and Table V those for families in which only one parent has been tested. These formulae have been applied, in Tables VI to XI, to the analysis of the various categories of families. Though the parents of children with abnormalities of the X chromosomes were included in the 'unrelated' counts of Table I, such families are excluded from Tables VI to XI. The family list, like the 'unrelated' list, was made up to July 14, 1965.

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 (Tables IX and X): 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 has been entered in the tables.

On the whole, the agreement between the observed and the expected incidence of mating types and proportion of $Xg(a+)$ and $Xg(a-)$ amongst the offspring is good. However, summations from Tables VI, VII, IX, and X (dealing with Britain and North America) show that there was a very significant excess of $Xg(a-)$ sons of $Xg(a+)$ mothers ($\chi^2 = 14.9$). This tendency we noted in the previous report (Gavin *et al.*, 1964), and for it we offered the following explanation: 'the excess of $Xg(a-)$ sons of $Xg(a+)$ mothers could perhaps

TABLE IV
EXPECTED DISTRIBUTION OF Xg GROUPS IN PARENTS AND OFFSPRING IN FAMILIES IN WHICH BOTH PARENTS HAVE BEEN TESTED

Mating			Proportion of Xg Groups					
Type		Frequency	In Sons			In Daughters		
Father	Mother		Obs. Total	$Xg(a+)$	$Xg(a-)$	Obs. Total	$Xg(a+)$	$Xg(a-)$
$Xg(a+)$	$Xg(a+)$	$p_n \times Xg^a \times \varphi Xg(a+)$	s_1	$s_1 \times (a)$	$s_1 \times (b)$	d_1	All	None
$Xg(a+)$	$Xg(a-)$	$p_n \times Xg^a \times \varphi Xg(a-)$	s_2	None	All	d_2	All	None
$Xg(a-)$	$Xg(a+)$	$p_n \times Xg \times \varphi Xg(a+)$	s_3	$s_3 \times (a)$	$s_3 \times (b)$	d_3	$d_3 \times (a)$	$d_3 \times (b)$
$Xg(a-)$	$Xg(a-)$	$p_n \times Xg \times \varphi Xg(a-)$	s_4	None	All	d_4	None	All

Xg^a and Xg = the gene frequencies in the appropriate population. $\varphi Xg(a+)$ and $\varphi Xg(a-)$ = the calculated frequency of the two phenotypes in the females of the appropriate population. p_n = the total number of families in the sample.

$$(a) = \frac{Xg^a}{\varphi Xg(a+)}$$

$$(b) = 1 - (a)$$

TABLE V

EXPECTED DISTRIBUTION OF Xg GROUPS IN FAMILIES IN WHICH ONLY ONE PARENT HAS BEEN TESTED

Mating				Offspring					
Total	Type		Expected Incidence	Sons			Daughters		
	Father	Mother		Total	Xg(a+)	Xg(a-)	Total	Xg(a+)	Xg(a-)
P ₁	{ Xg(a+) Xg(a-)	?	p ₁ × Xg ^a p ₁ × Xg	s ₁ s ₂	s ₁ × Xg ^a s ₂ × Xg ^a	s ₁ × Xg s ₂ × Xg	d ₁ d ₂	all d ₂ × Xg ^a	none d ₁ × Xg
P ₂	{ ? ?	Xg(a+) Xg(a-)	p ₂ × ? Xg(a+) p ₂ × ? Xg(a-)	s ₃ s ₄	s ₃ × (a) none	s ₃ × (b) all	d ₃ d ₄	d ₃ × (c) d ₄ × Xg ^a	d ₃ × (d) d ₄ × 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.

$$(a) = \frac{Xg^a}{?Xg(a+)}$$

$$(b) = 1 - (a)$$

$$(c) = Xg^a + (b)$$

$$(d) = 1 - (c)$$

TABLE VI

Xg GROUPS OF 441 BRITISH FAMILIES WITH 968 CHILDREN

Mating					Offspring					
Type		Number		Total	Sons		Total	Daughters		Total Offspring
Father	Mother	Observed	Expected		Xg(a +)	Xg(a -)		Xg(a +)	Xg(a -)	
Xg(a +)	Xg(a +)	267	266.1	311	228	83	278	277	1*	589
Xg(a +)	Xg(a -)	32	31.6	38	234.8 5*	76.2 33	31	278.0 30	1*	69
Xg(a -)	Xg(a +)	130	128.1	150	104	38.0 46	137	31.0 101	36	287
Xg(a -)	Xg(a -)	12	15.2	10	113.2 0	36.8 10	13	103.4 0	33.6 13	23
Total		441	441.0	509		10.0	459			968

* See text.

have arisen in this way—families with Xg(a+) mothers and Xg(a-) sons are scorable for linkage and in such families a son, unco-operative or inaccessible at the first visit, might subsequently be pursued more enthusiastically than he would have been were he not known to have an Xg(a-) brother'. We now suggest that a more powerful

reason may be that when a mother proved herself to be heterozygous for Xg, and therefore informative from the linkage point of view, her sisters and their families were energetically pursued. In other words, there has been selection for heterozygotes amongst Xg(a+) mothers. Had we included in the family lists only the family of the propositus in a kindred

TABLE VII

Xg GROUPS OF 128 NORTH AMERICAN FAMILIES WITH 380 CHILDREN

Mating				Offspring							
Type		Number		Sons			Daughters			Total Offspring	
Father	Mother	Observed	Expected	Total	Xg(a +)	Xg(a -)	Total	Xg(a +)	Xg(a -)		
Xg(a +)	Xg(a +)	77	76.6	143	105 107.5	38 35.5	92	92 92.0	0	235	
Xg(a +)	Xg(a -)	8	9.3	12	0	12 12.0	6	6 6.0	0	18	
Xg(a -)	Xg(a +)	38	37.6	68	42 51.1	26 16.9	47	29 35.3	18 11.7	115	
Xg(a -)	Xg(a -)	5	4.5	6	0	6 6.0	6	0 6.0	6 6.0	12	
		128	128.0	229				151			380

TABLE VIII

Xg GROUPS OF 111 FAMILIES WITH 317 CHILDREN FROM MAINLAND OF NORTHERN EUROPE

Mating				Offspring						
Type		Number		Sons			Daughters			Total Offspring
Father	Mother	Observed	Expected	Total	Xg(a +)	Xg(a -)	Total	Xg(a +)	Xg(a -)	
Xg(a +)	Xg(a +)	62	55.9	105	81 75.0	24 30.0	81	81 81.0	0	186
Xg(a +)	Xg(a -)	15	10.7	20	0	20 20.0	11	11 11.0	0	31
Xg(a -)	Xg(a +)	27	37.3	48	41 34.3	7 13.7	34	26 24.3	8 9.7	82
Xg(a -)	Xg(a -)	7	7.1	13	0	13 13.0	5	0	5 5.0	18
Total		111	111.0	186			131			317

TABLE IX

Xg GROUPS OF 326 BRITISH FAMILIES IN WHICH ONLY ONE PARENT WAS TESTED

Mating				Offspring						
Type		Number		Sons			Daughters			Total Offspring
Father	Mother	Observed	Expected	Total	Xg(a +)	Xg(a -)	Total	Xg(a +)	Xg(a -)	
Xg(a +)	?	37	38.5	27	17	10	47	47	0	74
Xg(a -)	?	20	18.5	11	8	3	24	14	10	35
?	Xg(a +)	245	240.5	319	228	91	186	169	17	505
?	Xg(a -)	24	28.5	22	0	22	26	17	9	48
		326	326.0	379			283			662

we should not have been troubled by this bias, but our main concern is to report as many family units as possible so that the rare and important exceptions to the rules of X-linked inheritance may be put in their proper perspective.

The North European families (Tables VIII and XI), on the other hand, do not show the excess of Xg(a-) sons of Xg(a+) mothers. This is probably because nearly all these families belonged either to four large kindreds in Holland, or were Finnish or Danish families with rare X-linked eye conditions. All available members of these families were tested, according to a prearranged plan.

Exceptional Children. Seven children who appear to break the rules of X-linked inheritance are to be seen in Table VI, but none in Tables VII to XI.

Two families account for five of the seven exceptions, and these have been recorded elsewhere (Sanger, Race, Tippet, Gavin, Hardisty, and Dubowitz, 1964): in Table VI two of the Xg(a+) sons from the mating Xg(a+) × Xg(a-) belong

to the Je. family and three to the Bu. family. Possible causes of this apparent breaking of the rules of X-linked inheritance were discussed by Sanger *et al.* (1964). A similar family is to be seen in the series of Chown, Lewis, and Kaita (1964).

This leaves two exceptional children to be accounted for in Table VI. The Xg(a-) daughter (Mary Ro.) from the mating Xg(a+) × Xg(a+) was studied by Professor Polani. She was trisomic for one of the D group of chromosomes and died at birth. The sample of blood was 1 week old before the Xg 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 its Xg group until it was too late to confirm the Xg(a-) reaction by absorption tests. The other blood groups afforded no reason to doubt the paternity of the baby.

The Xg(a-) girl (Carol Ow.) from the mating Xg(a+) × Xg(a-) was also studied by Professor Polani: she was trisomic for one of the E group of chromosomes and died at the age of 4 weeks. An

TABLE X

Xg GROUPS OF 241 NORTH AMERICAN FAMILIES IN WHICH ONLY ONE PARENT WAS TESTED

Mating				Offspring					
Type		Number		Sons			Daughters		
Father	Mother	Observed	Expected	Total	Xg(a+)	Xg(a-)	Total	Xg(a+)	Xg(a-)
Xg(a+)	?	15	22.8	4	3	1	17	17	0
					2.7	1.3		17.0	
Xg(a-)	?	19	11.2	13	6	7	25	20	5
					8.7	4.3		16.8	8.2
?	Xg(a+)	177	184.6	312	215	97	115	104	11
					234.6	77.4		105.7	9.3
?	Xg(a-)	30	22.4	34	0	34	24	12	12
						34.0		16.1	7.9
Total		241	241.0	363			181		
									544

TABLE XI

Xg GROUPS OF 92 FAMILIES FROM THE MAINLAND OF NORTHERN EUROPE IN WHICH ONLY ONE PARENT WAS TESTED

Mating				Offspring					
Type		Number		Sons			Daughters		
Father	Mother	Observed	Expected	Total	Xg(a+)	Xg(a-)	Total	Xg(a+)	Xg(a-)
Xg(a+)	?	14	10.8	22	18	4	24	24	0
					13.2	8.8		24.0	
Xg(a-)	?	4	7.2	7	7	0	5	3	2
					4.2	2.8		3.0	2.0
?	Xg(a+)	68	62.2	104	73	31	64	56	8
					74.3	29.7		56.7	7.3
?	Xg(a-)	6	11.8	10	0	10	6	5	1
						10.0		3.6	2.4
Total		92	92.0	143			99		
									242

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 Dr. Lehmann to have a peculiar type of haemoglobin.

The only exceptions to the normal manner of X-linked inheritance which will disclose themselves are Xg(a+) sons of Xg(a-) mothers and Xg(a-) daughters of Xg(a+) fathers.

Taking the first type of exception and trying to put the Je. and Bu. families 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 July 14, 1965, is that, in all the families we have tested, British, North American, Northern European, Sardinian, Israeli, Negro, Chinese, etc., 2044 Xg(a+) sons have sprung from 1148 mothers, 1146 of whom are Xg(a+) and 2 (Mrs. Je. and Mrs. Bu.) are Xg(a-).

(2) How uncommon is it for Xg(a-) mothers to have Xg(a+) sons? The present count shows that 163 Xg(a-) mothers of sons have been tested: 161 of them have 293 Xg(a-) sons and 2 (Mrs. Je. and Mrs. Bu.) have 5 Xg(a+) sons.

The second type of exception to the normal manner of X-linked inheritance that can be shown by the Xg groups, Xg(a-) daughters of Xg(a+) fathers, is illustrated by the two trisomic babies. The rarity of these two exceptions may be appreciated from the answers to the following two questions:

(1) How uncommon is it for Xg(a-) daughters to have Xg(a+) fathers? The present count of all the families we have tested shows that 177 Xg(a-) daughters had 132 fathers, 130 of whom are Xg(a-) and 2 (Mr. Ro. and Mr. Ow.) are Xg(a+).

(2) How uncommon is it for Xg(a+) fathers to have Xg(a-) daughters? The present count shows that 617 Xg(a+) fathers of daughters have been tested: 615 of them have 1019 Xg(a+) daughters, one of them (Mr. Ow.) had an Xg(a+) and an

Xg(a—) daughter, and another (Mr. Ro.) has only one daughter, who is Xg(a—).

The exceptions in the Ro. and Ow. families may possibly be due to serological difficulties, but those in the Je. and Bu. families are solidly established. Of the several explanations discussed by Sanger *et al.* (1964), we still prefer the idea that the Xg locus may be sited near the top of the short arm and that in the ancestry of Mr. Je. and of Mr. Bu. the Xg locus may have become translocated on to a Y, or perhaps on to an autosome.

The Xg^a antigen is inherited as an X-linked dominant character. Apparent exceptions to this manner of inheritance, which are not due to obvious abnormalities of the X chromosome, are rare and their causes remain a matter of conjecture.

Summary

The Xg groups are recorded of 3418 samples sent to the Blood Group Research Unit up to July 14, 1965, from unrelated white people in Britain, North America, and from the mainland of Northern Europe. The calculated gene frequencies are:

	Great Britain	N. America	N. Europe
Xg ^a	0.675	0.671	0.600
Xg	0.325	0.329	0.400

These frequencies are used to analyse the results of testing 1339 families with 3113 children: four families include apparent exceptions to the rules of X-linked inheritance.

We are greatly indebted to the many physicians who sent samples of blood from the families here recorded. Many of the families have been or will be published in separate papers dealing with the search for linkage between Xg and other X-linked conditions.

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