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Polymorphisms and multiple sclerosis in Orkney

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SUMMARY Study of the blood group, isoenzyme, and serum protein systems representing polymorphic variants at 23 loci, in a population of 53 multiple sclerosis patients in Orkney, their relatives, and a control series, showed that patients were neither more homozygous nor more inbred than controls. Any possible association of the disorder with the ABO and rhesus blood groups was not directly causal, but was related to the families of the patients rather than to the patients themselves.

In an endeavour to assess the importance of the genetic component in the aetiology of multiple sclerosis (MS) in the Orkney Islands, which there has its highest reported prevalence, the genetic structure of the population was considered, and by direct methods the coefficients of inbreeding and of kinship in a series of patients and controls were calculated (Roberts *et al.*, 1979). At the same time, to provide an independent appraisal of the role of consanguinity and so to confirm or otherwise the results of the direct analysis, an attempt was made to examine inbreeding indirectly from the study of blood groups and other polymorphic variants.

There was a second object of the study. Recent discussion of associations of MS with the histocompatibility antigens (Arnason *et al.*, 1972; Bertrams *et al.*, 1972; Naito *et al.*, 1972; Compston *et al.*, 1976; Whitaker *et al.*, 1976; Opelz *et al.*, 1977; Poskanzer *et al.*, 1980) has reopened the question of whether patients possess a gene or genes rendering them genetically susceptible to the disease, and whether they represent a subsection of the population that is genetically identifiable. The association of the disease with blood groups has remained controversial throughout the 14 years since it was first suggested (McAlpine *et al.*, 1965) but from recent studies it seems that MS patients may be characterised by a slightly higher frequency of blood groups O and Rhesus ccddee. The Orkney population is of obvious relevance to this discussion in the light of its geographical situation at the extremes of the European gradients in frequency of these blood groups, and of its high prevalence of MS. The opportunity was therefore taken to examine in Orkney the suggestion from cross-sectional studies that there may be blood group associations with MS, and also to inquire whether these occur within families, for no family study of this kind has yet been made.

Material and methods

All patients with MS alive on 1 December 1974 in the Orkney Islands were identified, and two more in whom the diagnosis was confirmed in 1976. This gave a total of 53 patients, 45 of whom were diagnosed as probable cases and eight as possible cases, according to established international criteria. For each patient, except three who were not born in Orkney, an unrelated contiguous control was selected who was born in the same parish in the same year, and had lived in the same area for the first 15 years of life. At the same time a discontiguous control was selected who was of the same age and sex and who was born in an Orcadian parish not contiguous with the birthplace of the patient. All patients, contiguous controls, and, wherever possible, their close relatives, were examined; they included all available adult first-degree relatives, spouses, and any second-degree relatives who were present at the domiciliary visit, all of whom were unaffected. No relatives were included for the discontiguous controls.

A blood specimen was obtained from each patient, from all except four pairs of controls, and from 321 family members (including 134 first-degree relatives of patients and 115 first-degree relatives of contiguous controls). Comparisons can therefore be

made between the 53 patients, 48 contiguous controls, 48 discontiguous controls, all the other unaffected (321) subjects, the 134 first-degree relatives of patients, and the 115 first-degree relatives of contiguous controls. The blood specimens were tested by standard serological procedures with the following antisera:

Anti-A, A_1, B, A+B, C, c, D, E, e, M, N, S, s, K, k, P, Jk^a, Jk^b, Fy^a, Fy^b, Lu^a, Lu^b, and Le^a.

Red cell isoenzymes were identified by horizontal starch gel electrophoresis, using gels of 9% BDH hydrolised starch. Adenylate kinase was examined by the method of Fildes and Harris (1966), acid phosphatase by the discontinuous buffer system of Hopkinson *et al.* (1963), glucose-6-phosphate dehydrogenase by the method of Fildes and Parr (1963). and phosphoglucomutase by using double the molar concentration of all ingredients of the buffer given by Spencer *et al.* (1964) at pH 7·4. Adenosine deaminase was typed by the method of Spencer *et al.* (1968). For 6-phosphogluconate dehydrogenase, lactate dehydrogenase, and malate dehydrogenase, a phosphate buffer pH 7·1 was used, the lower half of the gel slice stained using the reaction mixture of Fildes and Parr (1963) and the upper half stained for LDH and MDH as indicated by Kirk *et al.* (1969). Haptoglobin and transferrin were typed using the discontinuous buffer system of Poulik and Smithies (1957) at 450 volts for three to four hours in a cold room at 4°C and staining with benzidine to visualise the phenotypes. Altogether, nine blood group systems (12 loci) and 10 isoenzyme and serum protein systems (11 loci) were examined.

Gene frequencies were calculated on the assumption of Hardy Weinberg equilibrium. Comparison of phenotype frequencies in patients and the several control series was carried out by χ^2, or where necessary by exact probabilities. The intrafamilial analysis was carried out by the method of Clarke *et al.* (1956) in which each blood group occurring in each affected individual is compared against his own sibs. For each family which is segregating for the blood group in question the chance is assessed of the propositus being of that blood group. In the simple case of an affected member of a sibship of four persons, two of whom are group O and two group A, the chance of the patient being group O is 50%, and this (the expected) is scored as 0·5. If in fact the propositus is of group O, the observed score is 1, whereas if he is of group A, the observed score is 0. For each sibship, therefore, there is recorded an observed and an expected score which can be totalled for all the families being studied. By this method also a variance can be assigned to the expectation, against which the difference between the observed and expected can be compared and its significance tested.

The presence and extent of inbreeding may be examined by comparison of the observed and expected phenotype frequencies in each system, either codominant or partially codominant, where heterozygotes are distinguishable. The F coefficient is estimated by $F = 1 - (H/2pq)$ where H is the observed proportion of heterozygotes, and p and q are the respective gene frequencies. If the population is inbred, this value will be positive.

Results

In Table 1 are set out the phenotypes observed in the MS patients, compared with the numbers observed in the contiguous controls, the discontiguous controls, the two sets of first-degree relatives, and the total unaffected. On inspection of the data, there is only one barely significant difference between the affecteds and the unaffecteds, in the Lutheran system where the affecteds appear to have an excess of the Lu^a gene. There is a suggestion that patients of blood group O may be slightly in excess by comparison with the discontiguous controls and the large unaffected sample (49% compared with 30% and 41%); they share this elevation, however, with the contiguous controls (52%). In the rhesus system the phenotype ccddee occurs in 15% of affected, 8·7% of discontiguous controls, and 9·7% of other unaffecteds, again suggesting a slight elevation in the patients, and again this is shared with the contiguous controls (13%). It appears that the apparent differences may be due to local variation in ABO and rhesus frequencies within the Orkney Islands. The tendencies, however, are in the same direction as in the earlier suggestions of association.

The intrafamilial analysis shows no significant association in any system. For both group O and ccddee the observed number of affected is very close to that expected were the association with the disease random within sibships.

The number of loci at which each patient was heterozygous was counted, and similarly the number at which he was homozygous. The mean number of loci at which the patients were heterozygous was 4·72 by comparison with that in contiguous controls (4·02), discontiguous controls (4·24), and all unaffected (4·25). The mean number of loci at which homozygosity was established in the patients was 14·11, in contiguous controls 14·44, in discontiguous controls 14·26, and in unaffecteds 14·25. It appears that patients have no excess of homozygosity, and hence that they are unlikely to be more inbred than the controls.

The gene frequencies are set out in Table 2, and from these the expected phenotype frequencies in

Table 1 *Phenotypes observed*

System	*Affected*	(%)	*Contiguous controls*	(%)	*Discontiguous controls*	(%)	*Not affected, excluding contiguous controls and discontiguous controls*	(%)	*First-degree relatives of propositi*	(%)	*First-degree relatives of contiguous controls*	(%)
ABO												
O	26	49·1	24	52·2	14	30·4	132	41·1	66	47·8	38	33·0
A_1	16	30·2	12	26·1	15	32·6	74	23·1	30	21·7	31	27·0
A_2	2	3·8	3	6·5	7	15·2	29	9·0	9	6·5	11	9·6
B	7	13·2	5	10·9	7	15·2	60	18·7	23	16·7	25	21·7
A_1B	1	1·9	2	4·4	2	4·4	22	6·9	9	6·5	8	7·0
A_2B	1	1·9			1	2·2	4	1·2	1	0·7	2	1·7
	53		46		46		321		138		115	
Rhesus												
CcDEE					1	2·2						
ccDEE	2	3·8	1	2·2	1	2·2	7	2·2	2	1·5	5	2·6
CCDEe							1	0·3			1	0·9
CcDEe	12	22·6	9	19·6	7	15·2	53	16·5	25	18·1	17	14·8
ccDEe	4	7·6	7	15·2	5	10·9	34	10·6	10	7·3	11	9·6
ccddEe					1	2·2	1	0·3			1	0·9
CCDee	10	18·9	10	21·7	12	26·1	64	19·9	31	22·5	20	17·4
CcDee	17	32·1	12	26·1	15	32·6	125	38·9	52	37·7	49	42·6
Ccddee							2	0·6				
ccDee			1	2·2			3	1·0	1	0·7	2	1·7
ccddee	8	15·1	6	13·0	4	8·7	31	9·7	17	12·3	9	7·8
	53		46		46		321		138		115	
MNS												
MMSS	2	3·8	3	6·5	2	4·4	17	5·3	10	7·3	4	3·5
MMSs	9	17·0	5	10·9	7	15·2	50	15·6	23	16·7	17	14·8
MMss	3	5·7	6	13·0	6	13·0	30	9·3	15	10·9	10	8·7
MNSS	2	3·8	2	4·4	1	2·2	5	0·6	2	1·5	2	1·7
MNSs	14	26·4	9	19·6	10	21·7	66	20·6	26	18·8	25	21·7
MNss	15	28·3	15	32·6	14	30·4	82	25·5	33	23·9	27	23·5
NNSS							3	0·9	1	0·7	1	0·9
NNSs							7	2·2	2	1·5	3	2·6
NNss	8	15·1	6	13·0	6	13·0	61	19·0	26	18·8	26	22·6
	53		46		46		321		138		115	
Fy												
a+b+	24	45·3	14	31·8	17	37·0	139	43·6	57	41·3	47	41·6
a+b−	11	20·8	13	29·5	12	26·1	77	24·1	36	26·1	27	23·9
a−b+	18	34·0	17	38·6	17	37·0	103	32·3	45	32·6	39	34·5
	53		44		46		319		138		113	
Jk												
a+b+	24	45·3	21	47·7	16	35·6	142	45·0	50	36·8	54	47·8
a+b−	11	20·7	12	27·3	15	33·3	82	26·0	44	32·4	25	22·1
a−b+	18	34·0	11	25·0	14	31·1	92	29·0	41	30·2	34	30·1
	53		44		45		316		136		113	
Lu												
a+b+	8	15·1	2	4·5	3	6·7	19	6·0	13	9·6	4	3·5
a−b+	45	84·9	42	95·5	42	93·3	297	93·7	122	89·7	109	96·5
a+b−									1	0·7		
	53		44		45		316		136		113	
P												
P+	41	77·4	41	89·1	34	73·9	265	82·6	114	82·6	90	78·3
P−	12	22·6	5	10·9	12	26·1	56	17·4	24	17·4	25	21·7
	53		46		46		321		128		115	
Kell												
KK							1	0·3	1	1·0		
Kk	5	9·4	1	2·2	2	4·4	24	7·5	13	9·4	8	7·0
kk	48	90·6	45	97·8	44	95·7	296	92·2	124	89·9	107	93·0
	53		46		46		321		138		115	
Lewis												
Le+	6	17·1	6	23·1	2	25·0	18	10·5	4	5·2	7	11·9
Le−	29	82·9	20	76·9	6	75·0	153	89·5	73	94·8	52	88·1
	35		26		8		171		77		59	

System	*Affected*	(%)	*Contiguous controls*	(%)	*Discontiguous controls*	(%)	*Not affected, excluding contiguous controls and discontiguous controls*	(%)	*First-degree relatives of propositi*	(%)	*First-degree relatives of contiguous controls*	(%)
ADA												
1–1	48	90·6	41	91·1	41	91·1	277	87·9	121	90·3	103	89·6
1–2	5	9·4	4	8·9	4	8·9	38	12·1	13	9·7	12	10·4
	53		45		45		314		134		115	
6PGD												
AA	53	100	44	97·8	44	97·8	308	98·1	133	99·3	109	95·6
CA			1	2·2	1	2·2	6	7·9	1	0·7	5	4·4
	53		45		45		314		134		114	
LDH												
N	53	100	45	100·0	45	100·0	314	100·0	134	100·0	114	100·0
MDH												
N	53	100·0	45	100·0	45	100·0	314	100·0	134	100·0	114	100·0
AK												
1	46	86·8	41	91·1	38	84·4	284	90·5	117	87·3	103	90·4
1–2	7	13·2	4	8·9	7	15·6	29	9·2	17	12·7	11	9·6
2	0		0		0		1	0·3				
	53		45		45		314		134		114	
AP												
AA	7	13·2	6	13·3	5	11·1	41	13·1	17	12·7	16	14·0
BA	23	43·4	22	48·9	22	48·9	133	42·4	47	35·1	52	45·6
BB	15	28·3	13	28·9	13	28·9	114	36·3	58	47·0	39	37·9
CB	6	11·3	3	6·7	3	6·7	15	4·8	5	3·7	3	2·6
CA	2	3·8	1	2·2	2	4·4	11	3·5	7	5·2	4	3·5
	53		45		45		314		134		114	
PGM_1												
1–1	29	54·7	27	61·4	30	68·2	178	57·2	79	59·9	61	54·0
1–2	17	32·1	14	31·8	9	20·4	105	34·1	46	34·9	36	31·9
2–2	7	13·2	3	6·8	5	11·4	28	8·7	7	5·3	16	14·2
	53		44		44		311		132		113	
PGM_3												
1–1	53	100·0	45	100·0	45	100·0	314	100·0	134	100·0	114	100·0
Hp												
1–1	5	9·8	12	26·1	6	13·3	60	19·0	22	16·4	24	21·1
1–2	28	54·9	19	41·3	27	57·8	139	45·3	57	42·5	56	49·0
2–2	18	35·3	14	30·4	13	28·9	113	35·8	54	40·3	33	29·8
Neg.	0		1	2·2			4	1·3	1	0·7	1	0·1
	51		46		46		316		134		114	
Tf												
CC	53	100·0	46	100·0	45	97·8	311	98·4	134	100·0	111	96·5
CB	0		0		1	2·2	5	1·6	0		4	3·5
	53		46		46		316		134		115	

each system were calculated. Comparisons of the proportion of heterozygotes observed with that expected gave the F coefficients as estimated from each system, as set out in Table 3. For the 15 estimates in the patients only four are positive, and none are significant. In the contiguous controls six are positive, and two are significant (Duffy and ABO groups). In the discontiguous controls again six are positive and two are significant (Kidd and PGM), while in the three groups combined four are positive and three are significant (MN, Duffy, and PGM). This distribution is reflected in the mean F (Table 3), which is negative in both the affected (−0·0291) and the contiguous controls (−0·0053) by comparison with the positive value in the discontiguous controls (+0·0352) and overall (+0·0013). Again it appears from this indirect analysis that the patients are not more inbred than the controls.

Discussion

The indirect method of estimating inbreeding levels from relevant polymorphic systems is crude and, particularly when sample sizes are small, it is liable to

Table 2 *Gene frequencies*

System		*Affected*	*Contiguous controls*	*Discontiguous controls*	*Not affected, excluding contiguous controls and discontiguous controls*
ABO	p_1	0·184	0·156	0·207	0·149
	p_2	0·026	0·044	0·123	0·068
	q	0·089	0·072	0·123	0·134
	r	0·701	0·728	0·547	0·649
Rhesus	C	0·462	0·446	0·511	0·483
	c	0·538	0·554	0·458	0·517
	D	0·612	0·639	0·670	0·675
	d	0·388	0·361	0·330	0·325
	E	0·189	0·196	0·185	0·160
	e	0·811	0·804	0·815	0·840
MNS	m	0·557	0·587	0·598	0·541
	n	0·443	0·413	0·402	0·459
	S	0·292	0·261	0·250	0·269
	s	0·708	0·739	0·750	0·731
Fy	a	0·434	0·455	0·446	0·459
	b	0·566	0·546	0·554	0·541
Jk	a	0·434	0·511	0·511	0·485
	b	0·566	0·489	0·489	0·515
Lu	a	0·075	0·023	0·033	0·033
	b	0·925	0·977	0·967	0·967
P	P_1	0·524	0·670	0·489	0·582
	p	0·476	0·330	0·511	0·418
Kell	K	0·047	0·011	0·022	0·041
	k	0·953	0·989	0·978	0·960
ADA	ADA^1	0·953	0·956	0·956	0·940
	ADA^2	0·047	0·044	0·044	0·060
6PGD	PGD^A	1·0	0·989	0·989	0·990
	PGD^C		0·011	0·011	0·010
LDH	N	1·0	1·0	1·0	1·0
MDH	N	1·0	1·0	1·0	1·0
AK	AK^1	0·934	0·956	0·922	0·951
	AK^2	0·066	0·044	0·078	0·049
AP	p^a	0·368	0·389	0·378	0·360
	p^b	0·557	0·567	0·567	0·599
	p^c	0·075	0·044	0·056	0·041
PGM_1	PGM_1^1	0·708	0·773	0·784	0·743
	PGM_1^2	0·292	0·227	0·216	0·257
PGM_2	PGM_2^1	1·0	1·0	1·0	1·0
Hp	Hp^1	0·373	0·478	0·422	0·416
	Hp^2	0·627	0·522	0·578	0·584
Tf	Tf^C	1·0	1·0	0·989	0·992
	Tf^D	—	—	0·011	0·008
Gene combinations					
Rhesus					
CDe		0·462	0·446	0·478	0·468
cDE		0·189	0·196	0·239	0·136
cde		0·349	0·332	0·283	0·344
cDe		—	0·027	—	0·016
Cde					0·011
CDE					0·004
cdE					0·021
MNS					
MS		0·226	0·207	0·206	0·230
NS		0·070	0·067	0·046	0·040
Ms		0·300	0·351	0·374	0·311
Ns		0·404	0·375	0·374	0·420

give estimates grossly at variance with true population levels. For that reason little can be extracted from the results other than the overall impressions given here, that there is no evidence that the patients in Orkney are more inbred than the controls. This interpretation is supported by the straight counts of loci at which each subsample is homozygous or heterozygous. These findings support

Table 3 *Inbreeding estimates*

	Affected		*Contiguous controls*		*Discontiguous controls*		*Combined*	
	F	χ^a	*F*	χ^a	*F*	χ^a	*F*	χ^a
AB	−0·009	0·01	−0·506	11·79	+0·196	1·77	−0·080	0·93
MN	−0·185	1·82	−0·166	1·27	−0·130	0·78	−0·160	3·73
Ss	−0·049	0·13	+0·211	2·04	+0·015	0·01	+0·053	0·40
Cc	−0·101	0·54	+0·076	0·27	−0·001	0	−0·010	0·01
Ee	+0·014	0·01	−0·106	0·51	+0·062	0·18	−0·010	0·01
Fy^{a+b+}	+0·078	0·32	+0·358	5·91	+0·252	2·92	+0·221	7·08
Jk^{a+b+}	+0·078	0·32	+0·045	0·09	+0·288	3·84	+0·140	2·83
Lu^{a+b+}	−0·083	0·36	−0·025	0·03	−0·036	0·06	−0·049	0·34
Kk	−0·050	0·13	−0·078	0·01	−0·025	0·03	−0·028	0·11
ADA 2–1	−0·051	0·14	−0·048	0·10	−0·048	0·10	−0·048	0·33
6PGD(CA)	0	—	−0·012	0·01	−0·012	0·01	−0·006	0·01
AK 2–1	−0·071	0·26	−0·048	0·10	−0·084	0·33	−0·067	0·65
AP(BA)	−0·060	0·19	−0·109	0·55	−0·142	0·93	−0·102	1·51
PGM 2–1	+0·225	2·68	+0·094	0·41	+0·396	7·20	+0·240	8·35
Hp 2–1	−0·175	1·62	+0·172	1·37	−0·203	1·90	−0·074	0·80
Mean F	−0·029		−0·005		+0·035		+0·001	

the direct observations of consanguinity and inbreeding in the Orkney patients (Roberts *et al.*, 1979).

There are few other data in the literature on gene frequencies in Orkney, and such as they are, these relate only to the ABO blood group system. Allan and Lewis (1969) gave frequencies of the A gene, B gene, and O gene respectively of 21·1%, 9·6%, and 69·3%; Brown (1965) gave 22·9%, 11·3%, and 65·8%; and Boyce *et al.* (1973) gave 18·4%, 11·7%, and 70·0%. All show an elevation of the B gene frequency which distinguishes the Orcadians from the remainder of Britain. There is general agreement with these figures in the present series. Boyce also notes from unpublished data that there appear to be gene frequency differences between the different islands of Orkney, and this would partly explain the greater similarity of our patients to contiguous than to discontiguous controls.

The first suggestion that susceptibility to MS may be associated with the patient's blood group was made in 1965 by McAlpine *et al.*, who drew together data on ABO blood groups of 384 patients from various centres in Britain, and showed a frequency of blood group O among the MS patients 7·4% higher than among the controls. An earlier study by Alexander *et al.* (1950) showed a similar slight excess of group O of 4·9%. Simpson *et al.* (1965) in the north-east of England were unable to detect any significant difference, but again in their series there was a slight excess of blood group O amounting to 1·4% overall. In a subsequent study in the north-east of England, MacDonald *et al.* (1976) showed an excess of O that was significant compared with one normal series but not with another. Similarly, they showed a significant difference in the rhesus system, particularly striking in the excess of cde homozygotes.

In the light of these findings, the current results are of interest in that the suggestions are in the same direction although they do not reach significance. Here, however, sample size is critical, for from the nature of blood group data there would need to be very gross differences in gene frequencies for them to be detected in a small sample of 53 patients. However, the present study shows that it is not so much the features of the patients themselves that are responsible for the tendency. For when the first-degree relatives of propositi and the first-degree relatives of controls are selected from among the unaffected series (Table 1), it is obvious that the former share elevated frequencies of O and cde homozygous phenotypes by comparison with the first-degree relatives of controls. This suggests that it is the families themselves, rather than the patients, who are characterised by this excess. A similar finding comes from the intrafamilial analysis, which indicates that it is the sibships rather than the patients that are so characterised.

These results suggest that the association, if it exists, between MS and the ABO or rhesus alleles is not directly causal. Instead, the association appears to be familial, so that the population consists of a number of family groups where blood group O and a higher susceptibility to MS are associated together. This is compatible with a polygenic hypothesis of genetic involvement in MS in which the O gene or a cde combination are pleiotropic and their presence increases the liability to develop the disease, as well as exerting their own serological effect.

One possible interpretation of the previously suggested associations with O and rhesus ccddee blood groups, that it reflects homozygosity, is eliminated by the present material, for it appears that patients have no excess of homozygosity, and hence that they are unlikely to be more inbred than the

controls. This finding supports the direct observations of consanguinity and inbreeding in the Orkney patients (Roberts *et al.*, 1979).

Despite the comprehensive nature of the present study, the possibility of association of MS with the ABO and rhesus blood groups remains neither established nor disproved. The results suggest, however, that if it in fact occurs, then it is at the familial rather than the individual level, that a number of family groups within the population are particularly liable to develop the disorder, and this is compatible with a polygenic hypothesis of genetic involvement in multiple sclerosis.

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