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Further Observations on Kell Blood Groups in Families Ascertained via a Mongol Propositus

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Genes located on the unpaired portion of the human X chromosome can readily be recognized, but as far as the autosomes are concerned it is not known upon which autosome any human gene is located.

The common variety of mongolism is characterized by 21-trisomy, and offers a possible approach to the localization of human autosomal genes. The model on which this approach is based was first formulated by Bateman (1960) and later developed by Shaw and Gershowitz (1962), Penrose (1963), Kaplan *et al.* (1964), and Goodman (1965). The essential experimental finding would be a reduced incidence of a recessive phenotype or homozygous genotype in the 21 trisomics as compared with non-trisomics, which would indicate that the genes controlling the polymorphism involved were located on chromosome 21. Results testing the ABO blood group system were published by Shaw and Gershowitz (1962, 1963), Chown and Lewis (1963), Kaplan *et al.* (1964), and Goodman and Thomas (1966). From these results it seems very unlikely that the ABO locus is on autosome 21.

Evans *et al.* (1966) analysed data collected in Liverpool, in Buffalo, New York, U.S.A., and from a London series in the paper of Lang-Brown, Lawler, and Penrose (1952/53). Data on nine blood group systems and salivary ABH secretion were analysed. The only significant association between blood group phenotype and mongolism was found in the case of Kell where a significant excess of Kell-positive mongols was found. This finding raised the possibility that the Kell locus might be on chromosome 21.

Objections to concluding that the human Kell locus was on chromosome 21 were discussed. Among others it was pointed out that since a number of polymorphisms had been investigated the statistical significance level of a result on a single system would have to be weighted appropriately, and that the ideal confirmatory procedure would be to analyse statistically only the Kell blood grouping results from an entirely new population of mongols and their sibs.

The present paper presents the results of such a confirmatory procedure.

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Materials and Methods

The studies were carried out independently in Liverpool and Winnipeg. Where the methods were different this is stated.

Subjects. Mongol propositi were located in the following ways:

(i) In England from the general practice list of one of us (P.J.J.W.) and his partners at Chorley; from investigations at Lisieux Hall Mental Institution, Whittle-le-Woods, near Chorley, Lancashire, and from lists supplied by the Medical Officers of Health of Chorley, Birkenhead, and S.W. Lancashire, all of whom have responsibilities for providing educational facilities for mentally backward children.

(ii) In Manitoba from investigations at the Manitoba School for Retardates; or through a list supplied by the school; or through reference by private physicians or the Public Health Service. An attempt was made to see, examine, and test every mongol in Manitoba (population 1,000,000).

Diagnosis of Mongolism. All Manitoba mongols were seen by one of us (I.U.) as part of her study of mongolism. The diagnosis was made on clinical grounds and was confirmed by dermatoglyphs and by karyotypes. Only trisomics and their relatives, and only families in which at least the mongol and both parents had been blood grouped, have been analysed in this paper.

The diagnosis of the British mongols was a purely clinical one. Mongol propositi were not accepted unless they had typical physiognomic features. Karyotyping facilities were not available in Liverpool for the large number of subjects involved.

TABLE I

MANITOBA FAMILIES ASCERTAINED VIA A TRISOMIC PROPOSITUS

Kell Typing	All Members of Families K−k+ Kp(a−b+)	Families which have members not K−k+ Kp(a−b+)				Total	% Kell Positive	
		k^bk^b	k^ak^b	Kk^b	KK			
Male mongols	112	10	1	8	Nil	131	6·87	6·82
Female mongols	110	14	2	7	Nil	133	6·77	
Fathers of mongols	215	16	2	24	Nil	257	10·12	8·37
Mothers of mongols	215	25	5	12	Nil	257	6·61	
Brothers of mongols	289	22	6	30	Nil	347	10·37	8·80
Sisters of mongols	258	32	1	20	1	312	7·05	

Note: For the purpose of this analysis k^a is taken as equivalent to K. There were three sets of monozygous female mongols; they were each counted as one. There were also two non-mongol sibs whose sex was not recorded; they have been omitted.

Relatives of Mongol Propositi. All available sibs and the parents were ascertained for the Manitoba mongols.

In the British mongols a non-mongol sib was ascertained along with each mongol propositus. Mongols without an available non-mongol sib were not investigated. Wherever possible the non-mongol sib nearest in age to the mongol propositus and the parents of the propositi were examined.

Later in the study all available non-mongol sibs were ascertained in families where one or other of the parents of British mongols had been shown to possess the Kell antigen.

Control Families. In England a control non-mongol matched propositus was selected from the general practice list at Chorley already indicated. Each mongol propositus in the Chorley series was matched by a control non-mongol propositus of the same sex, age, socio-economic status, location of domicile, and cultural background. A non-mongol sib, and wherever possible, the parents of the control non-mongol matched propositus were also investigated in the same manner as for mongol propositi.

Blood Samples. The Manitoba samples were collected from 1962 to November 1967. All were venous samples. They were collected in mental institutions, in hospitals, in the genetics laboratory, and in the homes of propositi or their relatives, and were delivered as soon as convenient to the Rh Laboratory. All were typed for the ABO, MNSs, Rh, P, Kell, Lutheran, Lewis, Duffy, Kidd, and Xg systems, many for the Bu^a—Sm system, and for a variety of high and low frequency antigens. The facts so obtained were used to check paternity, but only the Kell data were statistically analysed in the present study.

The British blood samples were taken by venepuncture from almost all subjects. Blood from a few uncooperative mongol subjects was obtained by ear-prick. The blood samples taken at Chorley were sent by overnight letter post to the blood grouping laboratory in Liverpool and the samples taken in Birkenhead and South West Lancashire were taken there immediately. All British blood samples were typed for their Kell blood group with anti-K antiserum within 36 hours of collection. Typing with anti-k antiserum was not regularly performed.

Antisera. The sera of the Kell system used in the Manitoba study and the methods by which they were used were the same as described by Chown *et al.* (1963), save that latterly the anti-Kp^b has been used by the indirect Coombs technique. All samples were tested with anti-K, -k, -Kp^a, and -Kp^b.

The British blood samples were tested with orthoimmune specific anti-Kell (anti-K) active by indirect Coombs test only. No other blood group systems were tested.

Method of C. A. B. Smith for Evaluating Associations within Families. This method utilizes segregating sibships, and is fully explained in the paper of Clarke *et al.* (1956) where it was first used to test the association between blood group O and duodenal ulcer within sibships.

Results

Manitoba families are analysed in Table I, and it will be seen that the frequency of the Kell antigen is not higher in the trisomics than in their parents or sibs.

Data on British families of phenotypically characteristic mongols and on families of controls are presented in Tables II and III, respectively.

Table IV shows data from Chorley families. The frequency of Kell-positive is not higher in the mongols than in their parents or sibs. The frequency of Kell-positive is not higher in mongols than in control non-mongol matched propositi. It is also clear than the matings which give rise to mongols do not have a different incidence of Kell-positive from those which have produced control non-mongol propositi.

The frequency of Kell positive in the parents of Manitoba trisomics and in the parents of the British phenotypically characteristic mongols is seen to be similar in Table V.

TABLE II

KELL TYPING INFORMATION ON BRITISH FAMILIES ASCERTAINED BY MEANS OF PHENOTYPICALLY CHARACTERISTIC MONGOL PROPOSITUS

Area from Which Family Derived	Family Member	Sex	No. Tested	Kell Positive	Kell Negative
Chorley	Mongol	M	42	2	40
	,,	F	28	1	27
	Sib	M	33	0	33
	,,	F	37	6	31
	Father	M	67	6	61
	Mother	F	71	6	65
Birkenhead	Mongol	M	6	1	5
	,,	F	11	1	10
	Sib	M	10	0	10
	,,	F	7	0	7
	Father	M	17	1	16
	Mother	F	17	3	14
SW Lancs.	Mongol	M	15	0	15
	,,	F	18	2	16
	Sib	M	19	1	18
	,,	F	13	2	11
	Father	M	27	3	24
	Mother	F	31	2	29

TABLE III

KELL TYPING INFORMATION ON CONTROL FAMILIES DERIVED FROM CHORLEY

Family Member	Sex	No. Tested	Kell Positive	Kell Negative
Control non-mongol matched propositus	M	43	1	42
Sib ,, ,, ,,	F	28	3	25
,,	M	30	5	25
Father	F	40	2	38
Mother	M	67	3	64
	F	70	7	63

An analysis of the sibships segregating for the presence of the Kell antigen is shown in Table VI. There is no significant difference between the observed number of Kell positive mongols and the number expected by chance. (Appendices giving the results in full are available on application to one of us (D.A.P.E.)).

TABLE IV

INCIDENCE OF KELL POSITIVE IN CHORLEY FAMILIES

Family Member	Families Ascertained by Means of Phenotypically Characteristic Mongol Propositus		Families Ascertained by Means of Control Non-mongol Matched Propositus	
	No. Tested	% Kell Positive	No. Tested	% Kell Positive
Propositus	70	4·29	71	5·63
Sib	70	8·57	70	10·00
Parents	138	8·69	137	7·30

Conclusion

The data contained in the present report lend no support to the tentative suggestion made earlier by Evans *et al.* (1966) that the Kell locus may be on chromosome 21.

Summary

A previously reported examination of multiple blood group systems in mongol propositi and a control non-mongol sib of each propositus yielded *prima facie* evidence that genes controlling the Kell blood group might be located on autosome 21. This suggestion has now been re-examined by the investigation of two entirely new populations of mongol propositi and their relatives. Statistical analyses of these results are presented and give no support to the original suggestion.

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TABLE V

COMPARISON OF KELL POSITIVE AND KELL NEGATIVE IN PARENTS OF TRISOMIC MANITOBA MONGOLS WITH SAME REACTIONS IN PARENTS OF BRITISH PHENOTYPICALLY CHARACTERISTIC MONGOLS

	Kell Positive	Kell Negative	Total
Manitoba parents	43	471	514
British parents	21	209	230
Total	64	680	744

Note: For purpose of this analysis k^a is taken as equivalent to K.

$\chi^2 = 0{\cdot}12$; $p > 0{\cdot}50$.

TABLE VI

ALL FAMILIES ASCERTAINED BY MEANS OF MONGOL PROPOSITUS AND SEGREGATING FOR PRESENCE OF KELL ANTIGEN
[K here includes the antigen K and the antigen k[a]]

Family No.		x No. of Mongols with Kell Antigen in Family	N_K No. of Offspring with Kell Antigen in Family	N Total No. of Offspring in Family	N_L No. of Offspring without Kell Antigen in Family	$\frac{N_K}{N}$ Expected No. of Mongols with Kell Antigen in Family	$\frac{N_K N_L}{N^2}$ Variance
Manitoba	209	0	2	7	5	0·2857	0·2041
	161	0	3	5	2	0·6000	0·2400
	93	1	4	6	2	0·6667	0·2222
	227	1	2	3	1	0·6667	0·2222
	174	1	2	4	2	0·5000	0·2500
	2	1	2	3	1	0·6667	0·2222
	256	1	4	5	1	0·8000	0·1600
	187	0	3	5	2	0·6000	0·2400
	207	1	3	5	2	0·6000	0·2400
	240	0	1	3	2	0·3333	0·2222
	206	0	1	2	1	0·5000	0·2500
	92	1	6	9	3	0·6667	0·2222
	117	1	1	4	3	0·2500	0·1875
	180	0	1	3	2	0·3333	0·2222
	203	0	2	3	1	0·6667	0·2222
	72	1	2	3	1	0·6667	0·2222
	13	0	2	4	2	0·5000	0·2500
	193	0	3	7	4	0·4286	0·2449
	94	0	1	3	2	0·3333	0·2222
	122	0	1	5	4	0·2000	0·1600
	262	0	3	6	3	0·5000	0·2500
	195	1	7	8	1	0·8750	0·1094
	21	0	1	6	5	0·1667	0·1389
	49	1	3	7	4	0·4286	0·2449
	127	1	2	4	2	0·5000	0·2500
Chorley	24	0	1	3	2	0·3333	0·2222
	25	0	2	3	1	0·6667	0·2222
	36	0	1	2	1	0·5000	0·2500
	37	1	1	2	1	0·5000	0·2500
	48	0	1	2	1	0·5000	0·2500
	61	0	1	2	1	0·5000	0·2500
Birkenhead	8	1	1	2	1	0·5000	0·2500
	12	1	4	6	2	0·6667	0·2222
	13	0	1	4	3	0·2500	0·1875
SW Lancs.	33	0	1	2	1	0·5000	0·2500
Totals		15				17·6514	7·7736

$$\frac{S\left(\frac{N_K}{N}\right) - S(x)}{\sqrt{\text{Variance}}} = \frac{2{\cdot}6514}{2{\cdot}7882} = 0{\cdot}9509$$

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