THE LUTHERAN-SECRETOR LINKAGE IN MAN: SUPPORT FOR MOHR'S FINDINGS

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THE first autosomal linkage to be recognised in Man was that between the Lutheran genes and genes responsible for the Lewis phenotype of red cells (Mohr, 1951*a*, 1951*b*, 1954, 1956). Owing presumably to the rarity of informative matings no confirmation of the linkage has appeared from other laboratories. When we last analysed our own family data for linkage (Race and Sanger, 1954) we had practically nothing to contribute to the Lutheran-Lewis comparison, but since that time two very informative families have been encountered. Our collected results now bring strong support for the linkage which, in the light of our present understanding of the Lewis phenotypes, now appears to be between the Lutheran and secretor genes—a possibility that had been appreciated by Mohr.

1. GENES

(i) *The Lutheran genes*

Nothing complicated is yet known about the Lutheran genes: Lu^a in single dose or in double dose causes the presence on the red cells of the antigen Lu^a. The antigen Lu^b, and therefore the gene Lu^b, was shown to have a positive existence when, in 1956, Cutbush and Chanarin discovered the antibody anti-Lu^b.

(ii) *The secretor genes*

The presence or absence of water-soluble ABH substance in the saliva still appears relatively straightforward. The secretor genes, *Se se*, so modify the action of the *ABO* genes that when the genotype is *se se* practically no ABH substance is to be found in the saliva, whereas large quantities of the appropriate substances are present when the genotype is *Se Se* or *Se se*. (The antigen H is not understood; it is certainly not the product of the gene *O*, but its presence or absence in the saliva of people of group O serves to classify them as secretors or non-secretors.) The words secretor and non-secretor refer to the presence or absence of the ABH substances alone; they should not be used for the presence or absence of other substances—such as Le^a which has a quite different genetic background.

(iii) *The Lewis genes*

The inheritance of the Lewis antigens is, on the other hand, most complex. Our present views are based mainly on the work of Grubb (1948, 1950, 1951), Ceppellini (1955*a*, 1955*b*), Ceppellini and Siniscalco (1955), Sneath and Sneath (1955), and Mäkelä and Mäkelä (1956).

The antigen Le^a is thought to be primarily an antigen of the body fluids, notably of the saliva, which only secondarily becomes hitched onto the red cells (Grubb, 1950 ; Ceppellini, 1955*a*, 1955*b* ; Sneath and Sneath, 1955). The gene which produces the antigen has been called *L* ; it is dominant in its effect and is not linked to the secretor or *ABO* genes (Ceppellini, 1955*a* ; Ceppellini and Siniscalco, 1955).

TABLE 1

Scheme of the Lewis system and secretion of ABH

(Slightly modified, from Grubb, 1951 and Ceppellini, 1955)

Genotypes	Phenotypes		
	Saliva		Red cells
	ABH	Le^a	
Se Se LL *Se Se Ll* *Se se LL* *Se se Ll*	+	+	Le(a−b+)
se se LL *se se Ll*	−	+	Le(a+b−)
Se Se ll *Se se ll*	+	−	Le(a−b−)
se se ll	−	−	Le(a−b−)

The Lewis phenotype of the red cells is thought to be the result of interaction between the *Ll* genes and the secretor genes as shown in table 1. It seems that there is a limited amount of substrate that can be made into water-soluble ABH substance or Le^a substance. The demands of the *A*, *B* and *O* and secretor genes are satisfied first and, consequently, in secretors but little substrate is left for the *L* gene to mould into Le^a substance : some Le^a substance does reach the saliva but not enough reaches the plasma to hook onto the red cells and make them give the Le(a+) reaction. When the *ABO* and secretor genes require none of this substrate (that is in non-secretors) all of it is available for moulding into Le^a substance by the gene *L* ; then the saliva is saturated with Le^a substance and enough reaches the plasma to hook onto the red cells and make them give the Le(a+) reaction.

There does not seem to be an *Le*^{b} gene, and the red cell antigen Le^b appears to be a product of the interaction of the *ABO* genes, the secretor gene *Se* and the gene *L*. A further complication is that the reactions of anti-Le^b sera are influenced by the ABO group of the red cells : using most anti-Le^b sera too many A_1 and A_1B red cells are classified as Le(b—).

Nevertheless, as a result of the interaction of the Lewis and secretor genes the red cell phenotype Le(a+) behaves like a recessive character for it reflects the presence of two *se* genes and the following relations hold :

Le(a+b—) red cells belong to non-secretors,
Le(a—b+) red cells belong to secretors,
Le(a—b—) red cells usually, but not always, belong to secretors.

Consequently when no saliva has been available we can confidently assume that all people whose red cells give the reaction Le(a+) are non-secretors and that those whose red cells give the reaction Le(a—b+) are secretors. We would usually be right in assuming that the 6 per cent. or so of white people whose red cells give the reaction Le(a—b—) are secretors.

2. LINKAGE DATA

Table 2 contains all the families of two or more children whose red cells we have tested with ant-Lu^a and anti-Le^a and in which a parent is Lu(a+). When samples of saliva were available they have been classified as secretor or non-secretor ; most of them have been further tested for Le^a substance.

In the analysis the *u* statistics of Fisher (1935) have been used as elaborated by Finney (1940). Only " certain " families have been scored and they have been treated as Finney's Mating Types 13 and 14 (in his table 1). Finney's symbols have been translated thus : W = Lu(a+) and w = Lu(a—) ; T = secretor, Le^a present in saliva (L), or Le(a—) phenotype of red cells, t = non-secretor, Le^a absent from saliva (ll), or Le(a+) phenotype of red cells, according to the characters being analysed. In one comparison, that between secretor and L, Mating Type 15 has been used.

The results of the various comparisons are given in table 3. The last column but one shows the significance of the results : Finney states that if $\Sigma(\lambda)$ exceeds $2{\cdot}33\sqrt{\Sigma(\kappa)}$ linkage is established at the 1 in 100 level of probability. Linkage having been established, the last column shows the estimate of the recombination fraction which, again according to Finney, is $\frac{1}{2}\left[1-\sqrt{\frac{\Sigma(\lambda)}{\Sigma(\kappa)}}\right]$.

In table 4 the latest results of Mohr (1954, 1956) and of Ceppellini and Siniscalco (1955) are added to our own.

TABLE 2—*The families*

No.	Father	Mother	Children						
			1	2	3	4	5	6	7
1	Lu(a−) non-sec. Le(a+b−) L A_1	Lu(a+) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L A_1	Lu(a−) sec. Le(a−b+) L A_1	Lu(a−) sec. Le(a−b+) L O	Lu(a+) non-sec. Le(a+b−) L O	Lu(a−) sec. Le(a−b+) L A_1	Lu(a−) sec. Le(a−b+) L O	Lu(a+) sec. Le(a−b+) L A_1
2	Lu(a−b+) non-sec. Le(a+b−) L O	Lu(a+) sec. Le(a−b+) L O	Lu(a+b+) non-sec. Le(a+b−) L O	Lu(a+b+) non-sec. Le(a+b−) L O	Lu(a+b+) non-sec. Le(a+b−) L O	Lu(a−b+) sec. Le(a−b+) L O	Lu(a+b+) non-sec. Le(a+b−) L O		
3	Lu(a+) sec. Le(a−b−) ll O	Lu(a−) non-sec. Le(a+b−) L A_1	Lu(a+) Le(a−b+) O	Lu(a−) non-sec. Le(a+b−) L O	Lu(a−) sec. Le(a−b+) L O				
4	Lu(a+) Le(a−b+) O	Lu(a−) Le(a+b−) A_1	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a+b−) O					
5	Lu(a+) Le(a−b+) O	Lu(a−) Le(a+b−) A_1	Lu(a−) Le(a+b−) O	Lu(a−) Le(a+b−) A_1	Lu(a−) Le(a+b−) A_1	identical twins			
6	Lu(a−) non-sec. Le(a+b−) L B	Lu(a+) sec. Le(a−b+) L A_1	Lu(a+) sec. Le(a−) L A_1B	Lu(a−) sec. Le(a−) L A_1B	Lu(a+) sec. Le(a−b+) L O				
7	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a−b+) O	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a+b−) O					
8	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a+b−) A_1	Lu(a−) Le(a−b+) A_1					
9	Lu(a−) Le(a−) O	Lu(a+)* Le(a−) O	Lu(a+) Le(a+) O	Lu(a+) Le(a−) O					
10	Lu(a+) Le(a−) A_2B	Lu(a−) Le(a−) A_1	Lu(a−) Le(a−) A_1B	Lu(a+) Le(a+) B					
11	Lu(a−) sec. Le(a−) A_1	Lu(a+) sec. Le(a−) A_1	Lu(a−) sec. Le(a−) A_1	Lu(a+) non-sec. Le(a+) A_1	Lu(a+) Le(a−) A_1	Lu(a+) sec. Le(a−) A_1			
12	Lu(a−) Le(a−) A_1	Lu(a+) Le(a−) B	Lu(a+) Le(a−) A_1B	Lu(a−) Le(a+) A_1	Lu(a+) Le(a−) A_1B				
13	Lu(a+) sec. Le(a−b+) L A_1	Lu(a−) sec. Le(a−b+) L A_2	Lu(a−) sec. Le(a−b+) L A_2	Lu(a+) sec. Le(a−b+) L A_1	Lu(a−) non-sec. Le(a−b−) ll A_2	Lu(a−) sec. Le(a−b+) L A_1	Lu(a+) sec. Le(a−b−) ll A_2	Lu(a−) sec. Le(a−b+) L A_1	
14	Lu(a+) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L O	Lu(a+) sec. Le(a−b+) L O					
15	Lu(a−) sec. Le(a−b+) L O	Lu(a+) sec. Le(a−b+) L B	Lu(a−) sec. Le(a−b+) L B	Lu(a−) sec. Le(a−b+) L B					
16	Lu(a−) Le(a−b+) B	Lu(a+) Le(a−b+) B	Lu(a−) Le(a−b+) B	Lu(a+) Le(a−b+) O					
17	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a−b+) A_1					
18	Lu(a−) Le(a−b+) O	Lu(a+) Le(a−b+) A_1	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a−b+) O					
19	Lu(a−) sec. Le(a−b+) L A_1	Lu(a+) sec. Le(a−b+) L O	Lu(a+) Le(a−b−) O	Lu(a−) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b−) ll A_1				
20	Lu(a−) sec. Le(a−b+) L O	Lu(a+) sec. Le(a−b+) L A_1	Lu(a−) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L A_1	Lu(a+) sec. Le(a−b+) L O	Lu(a+) Le(a−b+) O			

TABLE 2—*continued*

No.	Father	Mother	Children						
			1	2	3	4	5	6	7
21	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a−b+) A_2B	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a−b+) B	Lu(a−) Le(a−b+) A_1B				
22	Lu(a+) Le(a−) O	Lu(a−) Le(a−) O	Lu(a−) Le(a−) O	Lu(a+) Le(a−) O					
23	Lu(a−) Le(a−) O	Lu(a+) Le(a−) A_1	Lu(a−) Le(a−) A_1	Lu(a−) Le(a−) A_1					
24	Lu(a−) Le(a−) A_1	Lu(a+) Le(a−) O	Lu(a+) Le(a−) A_2	Lu(a+) Le(a−) A_2					
25	Lu(a−) sec. Le(a−b+) L B	Lu(a+) sec. Le(a−b+) L O	Lu(a+) Le(a−b+) O	Lu(a+) sec. Le(a−b+) L B					
26	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−b+) A_1	Lu(a−) Le(a−b+) O	Lu(a+) Le(a−b+) A_1					
27	Lu(a+) Le(a−b+) B	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−b+) O	Lu(a+) sec. Le(a−b+) L B					
28	Lu(a+b+) Le(a−b−) O	Lu(a+b+) Le(a−b+) O	Lu(a+b+) Le(a−b+) O	Lu(a+) O	Lu(a+b+) Le(a−b+) O	Lu(a+b−) Le(a−b+) O			
29	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−) A_1	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−b+) O					
30	Lu(a−) Le(a−b+) B	Lu(a+) Le(a+b−) O	Lu(a+) Le(a−b+) B	Lu(a+) Le(a+b−) B					
31	Lu(a−) Le(a−b+) B	Lu(a+) Le(a+b−) B	Lu(a+) Le(a+b−) B	Lu(a+) Le(a+b−) B					
32	Lu(a−) Le(a−b+) A_1	Lu(a+) Le(a+b−) O	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−b+) O					
33	Lu(a−) Le(a−b−) O	Lu(a+) Le(a+b−) O	Lu(a+) Le(a−b+) O	Lu(a+) Le(a−b+) O					
34	Lu(a−) Le(a−) A_1	Lu(a+) Le(a+) A_2	Lu(a−) Le(a+) A_1	Lu(a+) Le(a+) A_1	Lu(a+) Le(a−) A_2	Lu(a+) Le(a−) O	Lu(a−) Le(a−) A_2	Lu(a−) Le(a−) O	dissimilar quadruplets
35	Lu(a−) Le(a−) A_1	Lu(a+) Le(a+b−) O	Lu(a+) Le(a−) O	Lu(a−) Le(a−) O					
36	Lu(a+) Le(a+) B	Lu(a−) Le(a−) A_1	Lu(a+) Le(a−) O	Lu(a−) Le(a−) B	Lu(a−) Le(a−) B	Lu(a+) sec. Le(a−) L A_1B			
37	Lu(a−) Le(a+b−) O		Lu(a+) Le(a−b−) O	Lu(a−) Le(a−b+) A_1	dissimilar twins				
38	Lu(a−) sec. Le(a−b−) ll O		Lu(a+) Le(a−b+) O	Lu(a−) sec. Le(a−b+) L A_2					
39	Lu(a+) A_1	Lu(a+) Le(a−b+) AB	Lu(a−) Le(a+b−) AB	Lu(a+) Le(a−b+) A_1B	Lu(a+) Le(a−b+) B				
40	sec. L	Lu(a+) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L O	Lu(a−) sec. Le(a−b+) L O					

Some of the unscored families could be scored but the results would be negligible. Some of the families (*e.g.* 31-36) are probably unscorable but we thought it better to include them.

* The mother in family 9 is heterozygous Lu^aLu^b because her mother is Lu^bLu^b

L = Le^a substance present in the saliva : ll = Le^a substance absent.

For more subtle analysis of the families shown in table 2 the following Caucasian gene frequencies will be needed :

Lu^a	0·0390	*Se* 0·5077	*L* 0·6870
Lu^b	0·9610	*se* 0·4923	*l* 0·3130

The Lu^a and Lu^b frequencies are taken from Race and Sanger (1958) ;

TABLE 3

Linkage analysis of the " certain " families of table 2

Comparisons	Families scored	$\Sigma(\lambda)$	$\Sigma(\kappa)$	$2{\cdot}33\sqrt{\Sigma(\kappa)}$	$\frac{1}{2}\left[1-\sqrt{\frac{\Sigma(\lambda)}{\Sigma(\kappa)}}\right]$
Lutheran : secretor .	1, 2, 3, 11, 13	+17·172	34·660	13·7	0·15
Lutheran : *Ll* . .	13 and 19	−1·387	2·232	3·5	...
Secretor : *Ll* . .	13	+0·057	1·059	2·4	...
Lutheran : Le^a phenotype of red cells	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12	+19·792	38·667	14·5	0·14

TABLE 4

The linkage results of Mohr and of Ceppellini and Siniscalco added to our own

Comparison	Source	$\Sigma(\lambda)$	$\Sigma(\kappa)$	$2{\cdot}33\sqrt{\Sigma(\kappa)}$	$\frac{1}{2}\left[1-\sqrt{\frac{\Sigma(\lambda)}{\Sigma(\kappa)}}\right]$
Lutheran : secretor .	Present paper . .	+17·172	34·660	13·7	0·15
Lutheran : *Ll* . .	Ceppellini and Siniscalco	−0·556	4·333		
	Present paper . .	−1·387	2·232		
	Total . .	−1·943	6·565	6·0	
Secretor : *Ll* . .	Ceppellini and Siniscalco	−3·556	41·358		
	Present paper . .	+0·057	1·059		
	Total . .	−3·499	42·417	15·2	
Lutheran : Le^a phenotype of red cells .	Mohr	+48·965	62·556		
	Present paper . .	+19·792	38·667		
	Total . .	+68·757	101·223	23·4	0·09

the *Se* and *se* frequencies are taken from Clarke *et al.* (1956) ; the *L* and *l* frequencies are taken from Grubb (1951). The following approximate red cell phenotype frequencies may also be of use : Le(a+b−) 22 per cent., Le(a−b+) 72 per cent., Le(a−b−) 6 per cent.

3. DISCUSSION

Table 4 shows that the Lutheran and secretor genes are linked : it also shows that the Lutheran genes are linked to genes responsible for the Lewis phenotypes of the red cells. According to the present view the Lewis phenotypes of the red cells are controlled by the *Ll* genes and the secretor genes. The evidence against linkage between the *Ll* genes and the secretor genes is weighty. Therefore the linkage between the Lutheran genes and the Lewis phenotype of the red cells can most economically be explained by the Lutheran-secretor linkage : there is no need to postulate linkage between the Lutheran genes and the *Ll* genes and, indeed, the direct evidence against such linkage is slowly being collected. The collection is bound to be slow for the only really informative type of mating, Lu^aLu^b, $Ll \times Lu^bLu^b$, *ll* has a frequency in England of three in a thousand, and, to contribute usefully the mating would have to have produced, at the very least, four children.

At present then it seems certain that the Lutheran genes are linked to the secretor genes and most unlikely that they are linked to the Lewis genes as we now understand them.

4. SUMMARY

The first autosomal linkage to be recognised in Man was that discovered by Mohr between the Lutheran genes and genes responsible for the Le(a+) and Le(a−) reactions of red cells. The linkage gains support from our results which, when combined with those of Mohr, suggest a recombination fraction of 0·09.

It is now becoming clear that the linkage is in fact between the Lutheran genes and the secretor genes and not between the Lutheran and Lewis (*Ll*) genes. The appearance of linkage with the Lewis genes is due to their phenotypic expression on red cells being controlled by the secretor genes.

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