Blood Group Interaction and the World Distribution of the ABO Gene p^2 and the Rh Gene *r* (cde)

R. L. KIRK

Department of Zoology, University of Western Australia, Nedlands, Western Australia

THERE HAS BEEN for many years speculation about the role of natural selection in maintaining the frequencies of blood group genes in human populations. Before the discovery of the rhesus blood group system most workers believed that the blood group genes were selectively neutral. In consequence the striking differences which were demonstrated between populations in various parts of the world with respect to the ABO blood group frequencies were considered to be due to the operation of random genetic drift, or to the multiple origins of modern man. The change in attitude to this problem during the last two decades has been summarized by Mourant (1959). Clear-cut evidence for the operation of selection within a blood group system was presented by the demonstration of the role of the Rh blood groups in causing hemolytic disease of the newborn. Early attempts to explain the existing frequency of Rh negative persons in various populations in the face of loss of Rh genes resulting from the birth of heterozygous children to Rh negative mothers dismissed the possibility of adequate replacement by mutation (Fisher *et al.*, 1944). It has been suggested that existing frequencies in European populations are the result of hybridization between stocks of high and low frequency of the gene *r* (*cde*), and that the present frequency of *r* is changing under selective pressure (Haldane, 1942: Wiener, 1942). Alternatively, Glass (1950) has presented evidence that at least in persons of European stock where the average family size is small, mothers of children with hemolytic disease compensate by having larger families than mothers not so affected. On theoretical grounds, however, Li (1951) concludes that a compensatory mechanism of this type could not lead to a state of balanced polymorphism.

The renewed interest in selective mechanisms in the Rh blood group system has led to a re-examination of the problem of the ABO blood groups. Careful clinical studies have revealed that incompatibility within the ABO blood group system can result also in hemolytic disease of the newborn (Mollison, 1956; Zuelzer and Kaplan, 1954a; Hsia and Gellis, 1954). The disease is less frequent in European populations than hemolytic disease of the newborn due to Rh incompatibility (Levine *et al.*, 1956) and moreover the prognosis in the majority of cases is not so severe as for the comparable rhesus-induced condition. On the other hand several studies have shown that at least some chronic infertility or repeated abortion is associated with ABO blood group incompatibility or dis-

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turbances in the secretion of ABH substances (Levine, 1943; Matsunaga, 1959; McNeil *et al.*, 1957; Behrman *et al.*, 1960; Wren and Vos, 1961).

Finally, Brues (1954) has pointed out that although there is considerable variation in the ABO gene frequencies in different populations in the world, they occupy a portion only of the theoretically possible range for such frequencies. She argues that this restriction is due to the operation of selective pressures and she has constructed a mathematical model to give selection coefficients which could explain the present world distribution of the ABO blood groups. Livingstone (1960) also has computed the fitness of various ABO phenotypes necessary to account for the observed gene frequencies of the A and B genes in West African populations. He obtained values of the same order of magnitude as those calculated by Brues to account for the world distribution.

The work referred to above has been concerned with selection in the ABO and Rh blood group systems, each considered in isolation from the other. It has become clear in recent years however that the ABO and Rh blood group systems interact. Parents who are incompatibly mated for the ABO blood groups are less likely to have children with severe Rh hemolytic disease of the newborn if they are also incompatible for the Rh blood groups, (See Levine, 1958 for a review of the earlier literature). In consequence, therefore, alteration of gene frequencies in the Rh blood group system must lead inevitably to an alteration in gene frequencies in the ABO blood group system. Cohen and Glass (1959) have drawn attention to the implications of this interaction, and have produced a schematic model to illustrate the magnitude of the effects which might be expected in a European population.

The present communication is an examination of a further aspect of the consequences of such an interaction.

A search of the world literature has been undertaken to discover populations which have been adequately tested for both the A_1A_2BO and Rh blood group systems. The information has been collected where possible from the original papers or from the two surveys of Mourant (1954) and Mourant *et al.*, (1958). Since ABO blood group frequencies can show marked fluctuations in relatively short geographic distances (e.g. Mourant, 1950) only surveys which included tests for both the A_1A_2BO and Rh systems have been included. In the case of the former system samples have been retained where χ^2 for goodness of fit does not exceed 6. In the latter system only surveys in which tests with at least anti-C, anti-D and anti-E were carried out have been included. The frequency of r (*cde*) in such populations is likely therefore to be estimated with accuracy.

The imposition of these restrictions leaves some 67 populations which satisfy all the necessary criteria and the data for which are available to the author. These populations are listed in Table 1, together with the gene frequencies for p^2 and r, respective symbols for the genes controlling the A_2 antigen and the rh phenotype.

The two sets of gene frequencies are plotted in Fig. 1. With two notable exceptions, the Swedish Lapps (Allison *et al.*, 1956) and the Norwegian Lapps (Allison *et al.*, 1952) there is a correlation between the overall world frequencies

TABLE 1. VALUES OF p^2 AND r FOR VARIOUS POPULATIONS

Population	Locality	Frequency of Gene p^2	Frequency of Gene r(cde)	Reference
Pagan tribes	Jos plateau	0.019	0.243	11
Nigerians	S.E. Highlands	0.043	0.238	11
Nigerians	S.W. Nigeria	0.035	0.184	11
Bahutu	Central Africa	0.050	0.194	24
Batutsi	Central Africa	0.061	0.217	24
Luo	Kenya	0.036	0.042	3
Kikuya	Kenya	0.066	0.129	3
Amba Pygmoids	Uganda	0.037	0.133	25
Iraqw	Tanganyika	0.035	0.209	4
Hima	Uganda	0.041	0.278	4
Nilotes	Sudan	0.028	0.197	43
Touaregs	Air	0.024	0.158	37
Bantu	Sth. Africa	0.081	0.154	37 and 39
Bushmen	Kalahari Desert	0.049	0	56
Zabidi Arabs	Aden	0.055	0.199	37
Yemenite Arabs	Yemen	0.062	0.130	37
Parsees	Karachi	0.040	0.270	35
Muslims	"	0.049	0.250	35
Sikhs	Nth. India	0.044	0.299	8
Pakistanis	Nth. West Pakistan	0.030	0.244	37 and 39
Kapol Vania	Bombay	0.007	0.292	55
Bhangi Harijans	"	0.038	0.100	55
Cutchi Lohana	"	0.014	0.200	55
Audichya Brahmans	"	0.043	0.308	55
Leva Patidars	"	0.025	0.292	55
Talavia Dubla	"	0.017	0.137	55
Chenchu	Sth. India	0.006	0.072	47
Basques	Biarritz	0.064	0.493	22
"	Mostly Spain	0.041	0.532	10
"	San Sebastian	0.047	0.481	10
Greeks	Greece	0.067	0.274	16
"	Petromagouca	0.073	0.185	37 and 39
Turks	Mersin	0.081	0.308	1
Dutch	Netherlands	0.085	0.390	21
"	Bunshouten & Spakenburg	0.104	0.501	22
Austrians	Vienna	0.056	0.365	37 and 39
Danes	Copenhagen	0.076	0.388	"
English	London	0.056	0.397	"
Italians	Milan	0.034	0.253	"
"	Ferrara	0.048	0.290	"
"	Sardinia	0.091	0.224	"
Latvians	Latvia	0.025	0.366	41
Lapps	Norway	0.356	0.188	2
"	Sweden	0.323	0.201	5
Walsers	Vals	0.023	0.312	26
"	Safien, Tenna & Versam	0	0.515	26
Ainu	Hokkaido	0	0	48
Chinese	N.Y. City	0	0	54
Chinese	Malaya	0	0	44
Thais	Bangkok	0	0	50

TABLE 1—*Continued*

Population	Locality	Frequency of Gene p^2	Frequency of Gene r(cde)	Reference
Melanesians	New Hebrides	0	0	51
Micronesians	Gilbert Is.	0	0	19
Maoris	New Zealand	0	0	45
Polynesians	Cook Is.	0	0	52
Micronesians	Marshall Is.	0	0	46
Papuans	Schouten Is.	0	0	40
Aborigines	Sth. Australia	0	0	49
Eskimos	Hudson Bay	0.010	0	37
Eskimos	Ungava district	0	0	13
Cree Indians	James Bay	0.007	0.082	13
Sarcee Indians	Alberta	0	0	12
Stoney Indians	"	0	0.097	12
Totonacans	Mexico	0	0	6
Tarascans	Mexico	0	0	6
Huastecans	Mexico	0	0	6
Otomis	Mexico	0	0	6
Chamulas	Mexico	0	0	6

for the genes controlling blood group A_2 and the Rh negative group rh (cde/cde). The distribution of the values of p^2 and r is distorted by the large number of populations in which the value of both p^2 and r is zero. Eighteen such populations have been listed in the present compilation. If these are excluded from the computation, together with the two Lapp samples which lie so far removed from the distribution of all other populations in the world as to merit special consideration, the remaining 47 populations give a correlation coefficient between p^2 and r of $+0.30$ ($0.05 > P > 0.01$). If the distribution of these 47 populations is considered together with the 18 for which p^2 and r are both zero, the relationship between these two gene frequencies would appear to be of much greater significance.

If the world populations are divided into continental groups the correlation between the genes p^2 and r within each continental area with the exception of those areas where both values are zero, is greatly reduced. This may be due in part to sampling errors which become relatively more important when the overall range of values of p^2 and r is restricted, or to the small number of samples available at present for one particular area. In addition one might expect differences in populations subject to various disturbing influences such as a) extreme isolation over long periods of time with consequent inbreeding and genetic drift, b) migration from one part of a continent to another, or c) changes in average size of family which will result in differential change in the selection coefficients for the genes p^2 and r.

The highly aberrant values of the two Lapp samples may be the result of genetic drift in these reproductively isolated populations, or alternatively a selective factor of unique characteristics has resulted in the abnormal increase of the frequency of p^2. Livingstone (1960) has suggested some possible mechanisms for gross disturbance in ABO frequencies.

If it is accepted that for the world population there is a biologically meaningful relationship between the frequencies of p^2 and r it becomes necessary to pos-

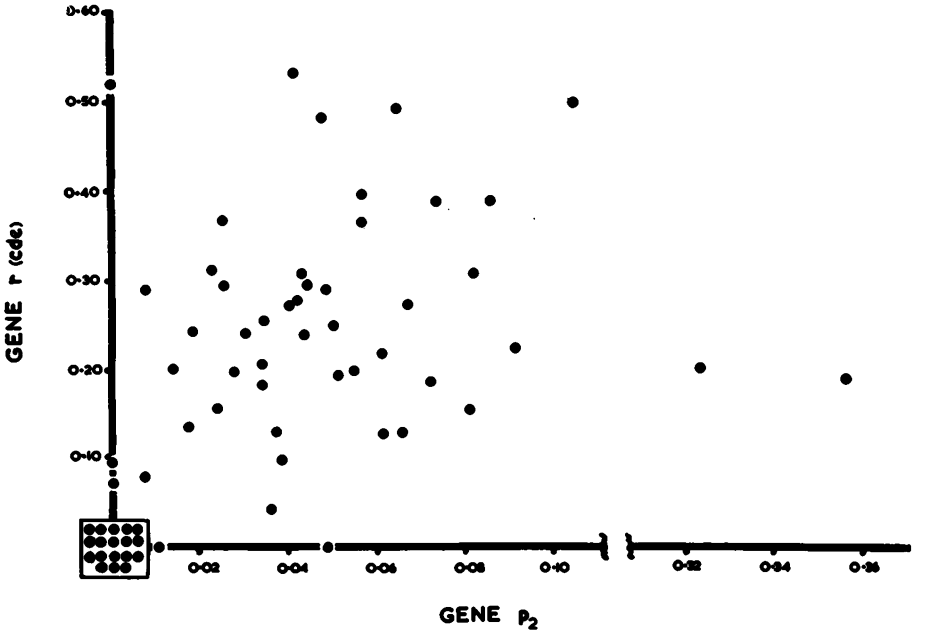

FIG. 1. The distribution of frequencies for the genes p^2 and r in 67 populations.

tulate the nature of the mechanism which controls this relationship. The following scheme suggests tentatively the way in which selection in both the A_1A_2BO and Rh blood group systems could result in the observed correlation.

1. Hemolytic disease of the newborn due to Rh incompatibility negatively selects heterozygous infants to homozygous Rh negative mothers.

2. Sensitization to the Rh antigen is less likely to occur when parents are incompatibly mated for the ABO blood group antigens. Indeed in obligatory incompatible matings, for instance O mothers married to AB husbands or homozygous A or B husbands, Rh sensitization will occur very infrequently unless stimulated by incompatible blood transfusion or extra marital pregnancy.

3. The phenotype A_2 is just as effective as A_1 in reducing the risk of sensitization to Rh antigens.

4. Through the operation of protection against negative selection in the Rh groups, the genes p^1, p^2 and q (p^1 and q being symbols for the A_1 and B antigens respectively) will tend to increase in frequency. This will lead to increased selection due to incompatibility within the ABO blood group system.

5. Within the ABO system A_1 is selected against more severely than A_2.

6. Where Rh incompatibility is tending to select positively for p genes and within the ABO system p^1 is being negatively selected, p^2 will increase proportionately to p^1.

This scheme makes a number of assumptions, not all of which have been validated fully by investigations carried out so far. The following comments seem appropriate however at this stage.

Assumptions numbers 1 and 2 are backed by considerable evidence and need not be discussed further. Assumption number 3 is more difficult to prove since few of the family studies reported in connection with ABO-Rh antagonism have given the sub-types of A. But there seems to be good indirect evidence in its favour. For instance, there is at present no well-authenticated case of a group O Rh-negative mother married to a group AB father becoming sensitized to Rh antigens except where a previous marriage has resulted in compatible children or sensitization has been caused by incompatible blood transfusion (Levine, 1958). Approximately 20 per cent of AB persons should be A_2B. If A_2 does not confer the same protection as A_1 with respect to Rh immunization we should expect to find this proportion of matings of A_2B Rh-positive fathers with group O Rh-negative mothers. Sufficient data has been accumulated in the studies summarized by Levine to make the absence of this particular combination highly significant.

Assumption number 4 raises problems of the magnitude of the effects due to selection in ABO incompatible matings. The papers cited in the earlier part of the present study are relevant to this discussion. It is not even clear whether negative selection operates more severely against A or B before conception (Behrman *et al.*, 1960 and *cf.* Cohen and Glass, 1956) or during pregnancy (Levine 1943, and others) or in the post-natal period due to hemolytic disease of the newborn or other post-natal disorders (*cf.* Struthers, 1951). It is possible that negative selection may be operating in the ABO blood group system at all these stages.

Evidence for assumption number 5 rests solely on the demonstration that A infants suffering from ABO hemolytic disease of the newborn are almost invariably group A_1. Even though they may be typed as A_2 at birth, later retesting shows them to be A_1 (Zuelzer and Kaplan, 1954b).

The deduction in number 6 is consequential on the preceding five assumptions.

It is particularly striking that in those populations in the world, chiefly mongoloid, oceanic and Australian aboriginal, where the frequency of the Rh negative gene r is extremely low or zero the p^2 frequency is also low or zero. At the other extreme, among European populations where the incidence of hemolytic disease of the newborn due to Rh incompatibility is approximately 0.66 per cent of all births the gene p^2 reaches its highest frequency. At this level of Rh incompatibility the effect of ABO-Rh interaction is highly significant. Reepmaker (1955), has calculated on the basis of studies on European populations that there would be an increase of 23 per cent in the incidence of Rh hemolytic disease if the effects of ABO-Rh antagonsism were removed.

Thus it seems clear that in the case of the ABO and Rh blood groups there exists a dynamic equilibrium between the negative selection of two genetically distinct systems and the positive selection resulting from mutual interaction which reflects itself on a world scale in the correlated distribution of the genes p^2 and r. Further detailed analysis of the kind initiated by Cohen and Glass (1959) should lead to a clearer understanding of the role of the p^2 gene in populations where selection against the gene r is still in progress.

SUMMARY

A statistical study of 67 populations in the world for which reliable information on the distribution of the ABO and Rh blood groups is available reveals a significant relationship between the genes controlling the A_2 antigen (p^2) and the Rh negative phenotype (r).

It is suggested that this relationship is a result of the interaction between the ABO and Rh blood group systems which results in positive selection of the gene p^2 in situations where there is negative selection against the Rh gene r.

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