From the Serological Laboratory of the Office of the Chief Medical Examiner of New York City
and the Bay Ridge Hospital of Brooklyn, N. Y.

Observations on the rare genes r'^{w} and R^{z} of the Rh-Hr allelic series

by

Dr. A. S. Wiener, Dr. G. J. Brancato and *Eve B. Gordon*

The theory (1) that the Rh-Hr types are inherited by multiple allelic genes has been substantiated by statistical studies on the distribution (2) of the Rh-Hr types in the general population, and by studies on the hereditary transmission of the Rh-Hr types in families (3, 4). Since the publication of these original observations, the statistical investigations have been extended to numerous ethnic groups, and hundreds of thousands of Rh typings have been carried out, but not a single exception to the theory of multiple alleles has been encountered (5) Moreover, studies on families are being carried out continuously, because of the importance of the Rh-Hr types in the pathogenesis of erythroblastosis fetalis. By now thousands of families have been tested by Wiener and his collaborators (6) and similar large series of families have been examined by other investigators, especially by Race et al. (7) In all these investigations no contradiction to the theory of multiple alleles has been found, which could not be explained on the basis of illegitimacy. In fact, for many years the Rh-Hr tests have been part of the routine examination in medicolegal cases of disputed paparentage.

In the earliest investigations on the heredity of the Rh-Hr types, in which only the sera anti-Rh_o and anti-rh' were available, it was found necessary to postulate the existence of four allelic genes. Following the discovery (1, 2) of the rh'' antibody it was possible to increase the number of identifiable alleles to six, namely, r, r', r'', R^0, R^1 and R^2. To these, shortly afterwards, the two rarer alleles, r^y and R^z were added, increasing the number of allelic genes to eight (8) At about the same time, it was noticed that rare individuals had blood cells giving reactions of intermediate intensity with one or more of the Rh antisera (9) and family studies proved that these so-called intermediate Rh types were the result of corresponding genes in the Rh-Hr allelic series. In fact, studies on the racial distribution showed that certain of the variants, notably $\mathfrak{R}h_o$, were not infrequent among Negroids (10).

These observations have been extended by other investigators, notably Levine and his collaborators in America, and Race and Sanger and their collaborators in England. With the resulting discovery of the additional Rh-Hr antibodies, anti-rh^w, anti-hr', anti-hr'', anti-hr, and more recently anti-V, the number of identifiable Rh-Hr blood types has been markedly increased, so that at the present time more than

Ricevuto il 2. II. 1956

20 different genes are known to exist in the Rh-Hr allelic series (11). Thus, these recent studies, while extending the knowledge of the Rh-Hr types, and disclosing an ever increasing complexity, have, nevertheless, in no way created the need to modify the original principle that the types are inherited by multiple allelic genes. It may be mentioned in passing that the only other example of multiple allelism exceeding the human Rh-Hr types in complexity is also in the field of blood grouping, namely, the observations of Stormont (12) on cattle blood groups.

The various Rh-Hr alleles differ considerably in the frequency of their occurrence in the general population. While the number of observations involving the more common alleles is considerable, the number of families tested, in which the rare alleles occur, is necessarily more limited. There is ample direct evidence to substantiate the validity of the theory as it relates to the more common alleles, but there is less direct evidence for the rare alleles, so that the validity of the theory, as far as the rare genes are concerned, is largely based on analogy and inference. Therefore, particularly to strengthen the standing of the Rh-Hr blood tests as evidence in medicolegal cases, there is need for the publication of family studies illustrating the transmission of the rarer Rh-Hr types. The purpose of this paper is to describe two unusual families, which illustrate the transmission of the rare alleles r'^{w} and R^{z}.

Family 1. This family came to our attention when the mother, who was found to be Rh negative was referred for antenatal Rh antibody tests. In connection with these investigations we had the opportunity to type the blood of her husband and two children. For these studies the following antisera were used, anti-***Rh$_o$***, anti-***rh'***, anti-***rh''***, *anti-**rh^w*** and anti-***hr'***.

Table 1 - Family illustrating hereditary transmission of the rare agglutinogen rh'^{w}

Blood of	A-B-O Group	M-N Type	Kell Type	Rh-Hr Type	
				Phenotype	Genotype
Father	B	M	k	rh'^{w}rh	$r'^{w}r$
Mother	B	MN	k	rh	rr
1st	O	MN	k	rh'^{w}rh	$r'^{w}r$
2nd child	B	MN	k	rh'^{w}rh	$r'^{w}r$

The results of the Rh-Hr tests are shown in table 1, together with the A-B-O groups, the M-N types, and the Kell types. It will be seen that the father and both children belong to type rh'^{w}rh. Although the rare type rh'^{w} has previously been encountered by Race and Sanger (7), and another example has been found by one for us (13) in a pregnant woman who was sensitized to the ***Rh$_o$*** factor, the family described here appears to be unique, and to our knowledge is the first family which demonstrates directly the hereditary transmission of this rare blood type (13) This family supplies evidence supporting the inference that gene r'^{w} is subject to the same hereditary laws as the other more common alleles of the Rh-Hr series of allelic genes.

Family 2. Among the rarer Rh-Hr genes, the gene R^z is one of the more common, and many families have been described, which illustrate its hereditary transmission. Recently a family was encountered in which this gene occurred, which is unusual in the large number of children available for testing. The family was called to our attention, when the fifth child was born. This child exhibited severe manifestations of erythroblastosis fetalis at birth and was treated by exchange transfusion, with complete recovery. It was noticed that the mother was Rh negative, while the affected baby belonged to type Rh_1Rh_2. Therefore, the remaining members of the family were typed and the results are shown in table 2.

Table 2 - Family with 5 children illustrating the hereditary transmission of the agglutinogen Rh_z

Blood of	A-B-O Group	M-N Type	Rh-Hr Type	
			Phenotype	Genotype
Father	B	M	Rh_1Rh_2	R^zr
Mother	A_1	M	rh	*rr*
1st child ♂	A_1	M	rh	*rr*
2nd child ♀	A_1	M	rh	*rr*
3rd child ♀	A_1	M	Rh_1Rh_2	R^zr
4th child ♂	A_1B	M	rh	*rr*
5th child ♀	A_1	M	Rh_1Rh_2	R^zr

Since the mother belongs to type rh, and the affected baby to type Rh_1Rh_2, the genotype of the baby had to be R^zr according to the theory of multiple alleles. Accordingly, the father had to belong to one of those phenotypes, corresponding to which at least one of the possible genotypes involved the gene R^z. In fact, he did belong to type Rh_1Rh_2. When the other four children were typed, it was found that three were type rh, while one was type Rh_1Rh_2. The fact that there were children of type rh indicated, according to the genetic theory, that the father's genotype was R^zr. Accordingly, one would expect that among the children of this particular couple half would belong to type rh like the mother, and half to type Rh_1Rh_2 like the father. In fact, among the five children, two were type Rh_1Rh_2 and three were type rh. Thus, this family demonstrates again that the rare gene R^z is subject to the same genetic laws as the more common Rh-Hr genes.

Summary

The history of the development of knowledge of the Rh-Hr types is briefly reviewed, with special reference to the theory of multiple allelic genes. It is pointed out that this theory has been confirmed by numerous statistical studies of the Rh-Hr types in the population as well as extensive studies on families. In addition to corroborating the genetic theory, the newer studies have disclosed the great complexity of this blood group system, so that as many as 20 allelic genes have been identified up to the present time. In the case of the more common genes there is ample direct evidence to verify the genetic theory, but observations on the rarer blood types are necessarily limited, so that the validity of the genetic theory, as it pertains to the rarer Rh genes, is based mainly on analogy. In this paper, two unusual families are recorded, which illustrate the hereditary transmission of the rare agglutinogens rh'^{w} and Rh_z. These observations serve to justify the inference that the rarer Rh genes are subject to the same laws of heredity as the more common alleles of the Rh-Hr allelic series.

https://doi.org/10.1017/S1120962300019922 Published online by Cambridge University Press

References

1. Wiener, A. S., & Landsteiner, K.: 1943. Heredity of variants of the Rh type. Proc. Soc. Exp. Biol. and Med., *53*: 167-170.
2. Wiener, A. S.: 1943. Distribution and heredity of variants of the Rh type. Science, *98*: 182-184.
3. — 1943. Genetic theory of the Rh blood types. Proc. Soc. Exp. Biol. and Med., *54*:316-319.
4. — Sonn, E. B., and Belkin, and Belkin, R. B.: 1943. Heredity and distribution of the Rh blood types. Proc. Soc. Biol. and Med., *54*: 238-240.
5. Mourant, A. E.: 1954. The Distribution of Human Blood Groups. 438 pp., Blackwell Scientific Publications, Oxford.
6. Wiener, A. S.: 1954. Rh-Hr Blood Types. Applications in Clinical and Legal Medicine and Anthropologie 763 pp. Grune & Stratton, N. Y.
7. Race, R. R. & Sanger, R.: 1954. Blood Groups in Man. 2nd Edition. 400 pp. Blackwell Scientific Publications, Oxford.
8. Wiener, A. S.: 1948. Genetic transmission of two rare blood group genes. Nature, *2*: 735.
9. — 1944. The Rh series of allelic genes. Science, *100*; 595-597.
10. Wiener, A. S., Unger, L. J., & Sonn, E. B.: 1945. New data on the distribution of the Rh blood types Proc. Soc. Exp. Biol. and Med., *58*: 89-92.
11. — 1955. Rh-Hr Syllabus. 88 pp., Georg Thieme, Stuttgart.
12. Stormont, C., Owen, R. D., & Irwin, M.M. R.: 1951. The B and C systems of bovine blood groups. Genetics, *36*: 134-161.
13. Wiener, A. S.: 1953. Present status of the Rh-Hr blood types. Vox. Sang. *4*: 53-56.

RIASSUNTO

Si passa brevemente in rassegna la storia dello sviluppo delle conoscenze scientifiche riguardanti i gruppi Rh- Hr, soffermandosi particolarmente sulla teoria dei geni allelomorfi. Si mette in evidenza che questa teoria è stata avvalorata da numerose inchieste statistiche sui vari tipi di Rh-Hr riscontrati tra la popolazione, come pure da seri studi relativi alle famiglie. Oltre a confermare la teoria genetica, i recenti studi hanno rivelato la complessità del sistema di classificazione dei gruppi sanguigni, sistema così vasto che fino ad oggi sono stati identificati ben 20 geni allelomorfi. Nel campo dei geni comuni si hanno ampie prove in appoggio alla teoria genetica; quanto ai gruppi sanguigni rari, i dati acquisiti sono necessariamente limitati, di modo che la validità della teoria genetica, in materia di geni Rh rari, si fonda in gran parte su fattori analogici. La presente comunicazione riguarda due casi-tipo di famiglie poco comuni e illustra la trasmissione ereditaria degli agglutinogeni $rh^{/w}$ ed Rh_z. Le osservazioni contribuiscono a corroborare il postulato secondo cui i geni Rh rari sarebbero regolati da quelle medesime leggi della eredità che governano i geni comuni della categoria allelomorfa Rh-Hr.

RÉSUMÉ

L'historique du développement des connaissances scientifiques concernant les groupes Rh-Hr est brièvement passé en revue, l'attention étant spécialement attirée sur la théorie des gènes multiples allélomorphes. On souligne que cette théorie a été corroborée par de nombreuses enquêtes statistiques sur les types Rh-Hr rencontrés parmi la population, ainsi que des études poussées relatives aux familles. En outre de confirmer la théorie génétique, les études récentes ont révélé la complexité du système de classification des groupes sanguins, si vaste que jusqu'à 20 gènes allélomorphes ont été identifiés à ce jour. Dans le domaine des gènes communs, il existe d'amples preuves à l'appui de la théorie génétique; touchant aux groupes sanguins rares, les données acquises sont nécessairement limitées, de sorte que la validité de la théorie génétique, en matière des gènes Rh rares, se fonde en grande mesure sur des facteurs d'analogie. La présente communication rapporte deux cas-types de familles peu communes, illustrant la transmission héréditaire des agglutinogènes rares $rh^{/w}$ et Rh_z. Ces observations contribuent à justifier le postulat selon lequel les gènes Rh rares seraient régis par les mêmes lois de l'hérédité qui gouvernent les gènes communs de la catégorie allélomorphe Rh-Hr.

ZUSAMMENFASSUNG

Ein kurzer Überblick wird geboten, wie sich die Kenntnis der Rh-Hr Blutgruppe entwickelt hat, wobei in Besonderen die Theorie der multiplen allelischen Erbfaktoren betont wird. Es wird darauf hingewiesen, dass die Richtigkeit dieser Theorie durch zahlereiche statistische Untersuchungen der Rh-Hr Blutgruppen in der Bevölkerung sowie durch ausgedehnte Untersuchungen von Familien bestätigt wurde. Abgesehen davon, dass die Richtigkeit der genetischen Theorie nachgewiesen wurde, haben die neuern Untersuchungen die grosse Vielfältigkeit des Blutgruppensystems aufgezeigt, insofern als dass etwa 20 allelische Genen bis zum jetzigen Zeitpunkt nachgewiesen werden konnten. Was die häufiger vorkommenden Erbfaktoren anbelangt, liegen genügend direkte für die genetische Theorie vor, jedoch sind Beobachtungen der weniger häufig vorkommenden Blutgruppen zwangsweise begrenzt, sodass die Gültigkeit der genetischen Theorie, was die seltener vorkommenden Rh Erbfaktoren anbelangt, in erster Linie auf einer Analogie beruht. Die vorliegende Arbeit beschäftigt sich mit den ungewöhnlichen Fällen zweier Familien, die erbliche Übertragung der selten auftretenden Agglutinogene $rh^{/w}$ und Rh_z aufzeigen. Die gemachten Beobachtungen rechtfertigen die Annahme, dass die selteneren Rh Genen den gleichen Vererbungsgesetzen unterliegen wie die häufiger auftretenden Genen der Rh-Hr allelischen Reihen.