Studies on Hereditary Gamma Globulin Factors: Evidence that Gm (b) in Whites and Negroes is not the Same and that Gm-like is Determined by an Allele at the Gm Locus

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TWO GENETICALLY INDEPENDENT loci determine, through a number of codominant alleles, a series of gamma globulin factors detected by an agglutination-inhibition test. The Gm locus has been shown to determine factors Gm (a), Gm (b), Gm (x), Gm (r), a "silent factor" which does not react with any known reagent [see Steinberg, 1962, for review], and perhaps Gm (d) [Thomas and Kampf, 1961] and Gm (e) [Ropartz, Rivat and Rousseau, 1962]. The Inv locus determines factors Inv (a), Inv (b), a "silent" factor (Steinberg, 1962) and Inv (1) [Ropartz, personal communication]. Another gamma globulin factor, Gm-like, has, with one exception (Steinberg, Stauffer, and Dunsford, in preparation), been found in Negroes only.

Because the γ-globulin factors in serum from Negroes of unmixed ancestry tested with the standard reagents have all been Gm (a+ b+ x—) [the reagents for detecting Gm (r) and Gm (d) are not available, hence data for these factors and the newly found Gm (e) were not collected] it was not possible to determine the genetic relation of Gm-like to the Gm locus. Attempts to find segregation at the Gm locus and for Gm-like in American Negro families have thus far been unsuccessful.

Ropartz and his colleagues (Ropartz, Rousseau, Rivat, and Lenoir, 1961) using the factor Inv (a) demonstrated that Gm-like is independent of the Inv locus and we have confirmed their findings using the Inv (b) factor (Steinberg, Wilson, and Lanset, 1962).

We have recently found a system which appears to distinguish between the Gm (b) factor of whites and Negroes. This paper is a report of the data establishing the nature of the reactions with this system and of its use to ascertain the locus which determines Gm-like.

MATERIALS AND METHODS

The γ-globulin factors were detected by methods which we have described elsewhere (Steinberg, 1962) except that some of the tests were run in tubes as described by Linnet-Jepsen, Galatius-Jensen and Hauge (1958). The reagents used are shown in table 1.

The new agglutinator was discovered in May 1962, in the serum drawn in 1959 from

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a four year old Negro boy in the course of determining the γ-globulin factors in his serum and in the serum of members of his family. The data were to be used for a linkage study with the sickle locus (these data will be reported elsewhere). It was found that the boy's serum agglutinated cells coated with incomplete anti-D Roehm which we use to detect Inv (a). Small samples of blood were drawn on May 8, June 7, and July 26, 1962. These samples were used to characterize the system, Davis/Roehm, and for family tests.

The system, Davis/Roehm, works best when used as follows: One volume of group O, R^1R^1 washed, packed red blood cells is incubated with two volumes of anti-D Roehm plus five volumes of saline at 37° C. for two hours. The cells are washed and made into a 1.5 per cent suspension in saline.

The serum to be tested is diluted 1/16. The Davis serum is diluted 1/4. One drop of each is placed in a 10 x 75 mm. test tube and incubated for 15 minutes at room temperature, then one drop of the above cell suspension is added. Incubation is continued at room temperature for another 90 minutes. The tubes are spun at 1,000 G for one minute. The tests are read immediately after spinning, in the usual manner.

RESULTS

Tests of sera from white donors: Samples of serum from 99 white donors previously tested for the γ-globulin factors were tested with the Davis/Roehm system. The tests agreed with previous typings for the Gm (b) factor: 66 were Gm (b+) and 33 Gm (b—) on both series of tests.

Tests of sera from Negro donors: Serum from 291 unrelated Negroes whose γ-globulin types were known were tested with the Davis/Roehm system. The results of these tests are shown in table 2. For simplicity of presentation Gm-like (+) is recorded as c.

TABLE 1. REAGENTS USED FOR γ-GLOBULIN TYPING

System	Agglutinator		Anti-D		Dilution of Test Serum
Gm (a)	Wils	1/8	Kim	1/10	1/8, 1/16
Gm (b)	Bomb	1/64	Ivan	1/10	1/8, 1/16
Gm (x)	Taylor	1/32	Ham	1/10	1/16, 1/32
Gm (like)	Carp	1/32	Warren	1/5	1/16, 1/32
Inv(a)	Math	1/8	Roehm	1/5	1/16, 1/32
[1]Inv(b)	Lucas	1/8	Ham	1/5	1/16, 1/32

[1]This is a tube test.

TABLE 2. RESULTS OF TESTS OF SERUM FROM 291 UNRELATED NEGROES (105 FROM A NON-RANDOM PANEL AND 186 RANDOM SAMPLES) WITH AGGLUTINATOR DAVIS AND ANTI-D ROEHM. NUMBERS IN PARENTHESES ARE DATA FROM THE RANDOM SAMPLE

Gm Phenotypes	Total	Davis/Roehm	
		+	—
(1) Gm [a+ b+ x− (c*+ or −)]	256(172)	55(35)†	201(137)‡
(2) Gm [a+ b+ x+ c−]	9(6)	3(2)	6(4)
(3) Gm [a− b+ x− c−]	8(4)	8(4)	0(0)
(4) Gm [a+ b+ x+ c+]	4(0)	0(0)	4(0)
(5) Gm [a+ b− x− c−]	11(3)	0(0)	11(3)
(6) Gm [a+ b− x+ c−]	3(1)	0(0)	3(1)
Totals	291(186)	66(41)	225(145)

*c = Gm-like

†8 of these 35 were Gm-like (+).

‡46 of these 137 were Gm-like (+) and 6 for various reasons were not classified for Gm-like.

None of the 14 samples which were Gm (b—) were Davis/Roehm (+). Similarly none of the four Gm (a+ b+ x+ c+) samples were Davis/Roehm (+). Each of the other groups showed (+) and (—) reactions with the Davis/Roehm system. Since we had established that this system tested for Gm (b) in whites we assumed, as a working hypothesis, that this system failed to detect the Gm (b) factor determined by the Gm^{ab} allele in Negroes (Steinberg, Stauffer and Boyer, 1960). The positive reactions among the samples from Negroes were assumed to be due to the Gm^{b} allele derived from white ancestors. Population and family data may be used to test this hypothesis.

Steinberg *et al.* (1960) showed that Negroes of unmixed ancestry have a Gm^{ab} allele and that the Gm^{b} allele derived from white ancestry occurs in the American Negro with a frequency (q) of .160 ± .020. Hence, $[1 - (.84)^2] \pm 2p\sigma_p = 29.4 \pm 3.4$ per cent of a random sample of sera from American Negroes should be Davis/Roehm (+). From the data in parenthesis in table 2 it will be seen that 41/186 or 22.0 ± 3.0 per cent were positive. The difference is not significant ($D/\sigma_D = 1.6$, $P = .11$).

Family studies: The sera from 47 American Negro families with 174 children were typed for Gm (a), Gm (b), Gm (x), Gm-like and for their reaction with the Davis/Roehm system. The data are presented in table 3. Davis/Roehm (+) is recorded as D in the table.

All of the 70 offspring from matings in which neither parent was D (matings 1-4) were Davis/Roehm (—). This is what would be expected if D were determined by a dominant gene. If we ignore Gm-like for the present, the genotypes of the parents in matings 1-3 may be assumed to be Gm^{ab}/Gm^{ab} and those for the parents in mating (4) Gm^{ab}/Gm^{a} X Gm^{a}/Gm^{a} since Gm (a+ b—) offspring appeared in each of the two matings of this type.

Consider now, matings 5-12 in which only one parent is D. We will dis-

TABLE 3. RESULTS OF TESTING SERA FROM 47 FAMILIES WITH 174 CHILDREN FOR GM (A), GM (B), GM (X), GM-LIKE AND FOR REACTIONS WITH THE DAVIS/ROEHM SYSTEM. ONLY POSITIVE REACTIONS ARE LISTED (GM-LIKE (+) IS RECORDED AS C AND DAVIS/ROEHM (+) AS D.)

Mating	No. of Families	No. of Offspring	Phenotypes of Offspring							
			ab	abc	abD	abcD	bD	a	ax	abxD
(1) ab X ab	3	18	18							
(2) ab X abc	5	31	14	17						
(3) abc X abc	4	13	7	6						
(4) ab X a	2	8	2					6		
(5) ab X abD	10	25	12		13					
(6) ax X abD	1	2			1					1
(7) ab X bD	1	6	1		5					
(8) a X abD	1	1			1					
(9) abx X abD	1	9	2		3				4	
(10) ab X abcD	6	27		17	10					
(11) abc X abD	4	10	3	5		2				
(12) abc X abcD	2	4		2	1	1				
(13) bD X abD	3	11			7		4			
(14) abD X abD	2	6			5		1			
(15) abD X abxD	1	2					2			
(16) abcD X abD	1	1			1					
Totals	47	174	59	47	47	3	7	6	4	1

cuss these matings in turn except for mating 7 which will be discussed with mating 13 after all the other matings have been reviewed. As before we will ignore Gm-like. In all of these matings (except 7) the phenotype of the Davis/Roehm (+) parent is abD. On the basis of our hypothesis the genotype of each of these parents is either Gm^{ab}/Gm^{b} or Gm^{a}/Gm^{b}. In either case the parents is heterozygous for the Gm^{b} allele (i. e., for D). Hence the ratio of D to non-D among the offspring should be 1:1. The ratio of D: non-D among the 78 offspring from these matings was 33: 45, which is not significantly different from 39: 39 ($\chi^2_{(1)} = 1.85$, P>.10).

Consider now, matings 14-16 in which both parents have the D factor. We will again ignore Gm-like (c in the table). In each of these matings the parents' phenotypes are abD or abxD, their genotypes are, according to our hypothesis, Gm^{ab}/Gm^{b} or Gm^{a}/Gm^{b} for the former, and Gm^{ax}/Gm^{b} for the latter. In any case both parents are heterozygous for Gm^{b} and therefore for for D. We would expect 1/4 of the nine offspring from these families to be non-D, but all nine were D. The probability of all nine offspring being D with p = .75 is approximately .075, hence the failure to observe non-D offspring is not significant ($\chi^2_{(1)}$ corrected for continuity = 1.81; P>.10; this is a two-tailed distribution).

If we combine the data from the two types of matings and compare the totals with the combined expected we have: observed 42: 45, expected 45.75: 41.25 of D vs. non-D. The differences are not significant ($\chi^2_{(1)} = 0.648$, .5>P>.3).

In the remaining two families (7 and 13) one parent is phenotypically bD. According to our hypothesis the corresponding genotype is Gm^{b}/Gm^{b}. Since the parent is homozygous for the Gm^{b} allele all the offspring from these matings should be D, but one child in mating 7 is non-D. In this mating the Gm^{b}/Gm^{b} parent was the father, hence the possibility exists that the non-D child is extra-marital, however, no exclusion was found on the basis of the ABO, MNS, Rh, Fy, K, P, Jk and Js blood types, and the Hp and Tf serum factors.

Sera from West African Negroes: Samples from 28 Yoruba and 27 Fulani were tested with the Davis/Roehm system. Data on their Gm types have been published (Steinberg, Stauffer, Blumberg, and Fudenberg, 1961).

According to our hypothesis all these samples should be negative for the Davis/Roehm system. Fifty-four of the 55 samples were negative. One serum from a Yoruba was positive with the Davis/Roehm system each of the three times it was tested. The Gm type of this sample was Gm (a+ b+ x—), Gm-like (+), in accordance with the usual pattern of the African Negro. If the donor was of unmixed ancestry, and he most probably was so, this is a distinct exception to our hypothesis and indicates that occasionally a variant of the Gm^{ab} allele which produces a Gm (b) factor positive to the Davis/Roehm system may occur.

Sera from Chinese: Chinese have the alleles Gm^{a}, Gm^{ab} and Gm^{ax} (Steinberg, Lai, Vos, Singh, and Lim, 1961), hence it seemed of interest to determine the reaction of the Gm (b) factor in Chinese with the Davis/Roehm system. Forty-seven samples collected by Dr. David Y.-Y. Hsia in Formosa

were tested with the results shown in table 4. All Gm (b+) samples were positive with the Davis/Roehm system and all Gm (b—) samples were negative with the Davis/Roehm system. Evidently the Gm (b) factor produced by the Gm^{ab} allele in Chinese is similar to that produced by the Gm^{b} allele in whites rather than to that produced by the Gm^{ab} allele in Negroes.

Relation of Gm-like to the Gm locus: In table 3 Gm-like is represented by the letter c and positive reactions with the Davis/Roehm system are represented by D. In matings 10, 11, 12, and 16 one or both parents have factors c and D and offer possibilities for studying segregation between the alleles determining Gm-like and Gm (b) (i. e., Gm^{b}). The data for these matings are presented again with additional information in table 5. Most information is provided by mating 10 (ab X abcD). With c and D present in one parent and absent in the other, none of the 27 offspring showed both factors or neither factor. This would be expected if Gm-like were due to an allele at the Gm locus, or to a closely linked gene, with the cD parent in repulsion in all six matings of this type. Since Gm-like appears not to occur in the absence of Gm (b) (Steinberg, 1962) and since earlier evidence suggested a relation between Gm-like and Gm (b) (Steinberg, Stauffer, Blumberg and Fudenberg, 1961), we will assume that Gm-like is produced by an allele at the Gm locus and call the factor Gm (c). We have already indicated our belief that in whites D is produced by the Gm^{b} allele. The genotypes of the parents in mating 10 are therefore Gm^{ab}/Gm^{ab} or Gm^{ab}/Gm^{a} for phenotype ab and Gm^{abc}/Gm^{b} for phenotype abcD (table 5). Hence the offspring would inherit Gm^{abc} or Gm^{b} from the latter parent and none should have neither or both of factors c and D. Furthermore, the two types of offspring should occur with equal frequency. The ratio of 17: 10 does not differ significantly from 13.5: 13.5 ($\chi^2_{(1)} = 1.81$, $P>.1$). The genotypes of the parents of mating 10, already referred to, and of matings 11, 12, and 16 and the frequencies of the phenotypes among their offspring expected as a consequence of this hypothesis are presented in table 5. The hypothesis appears to be consistent with the data.

If Gm-like is caused by an allele at the Gm locus, the four phenotypic classes, c+ D+, c+ D—, c— D+, c— D—, in the random population sample in table 2 should occur in accordance with the Hardy-Weinberg distribution.

The frequency of the Gm^{b} allele, hereafter referred to as D, may be estimated by direct count. It is equal to

$$p = \frac{abcD + abD + abxD + 2bD}{2T}, \text{ (Where abcD, etc.,}$$

TABLE 4. TESTS WITH THE DAVIS/ROEHM SYSTEM OF SERUM FROM 47 MAINLAND CHINESE LIVING IN FORMOSA

Gm phenotype	No.	Reaction with Davis/Roehm +	Reaction with Davis/Roehm —
ab	31	31	0
abx	8	8	0
ax	2	0	2
a	6	0	6
Totals	47	39	8

TABLE 5. GENOTYPES OF MATINGS 10, 11, 12 AND 16 OF TABLE 3, AND OBSERVED AND EXPECTED NUMBERS OF PHENOTYPES AMONG THEIR OFFSPRING ON THE ASSUMPTIONS THAT Gm-LIKE IS PRODUCED BY AN ALLELE Gm^{abc} AND THAT Gm^{b} PRODUCES THE FACTOR WHICH IS POSITIVE WITH THE DAVIS/ROEHM SYSTEM

Mating	Phenotype	Most likely genotypes	Phenotypes of Offspring for c and D							
			c		D		cD		neither	
			Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
10	ab X abcD	Gm^{ab}/Gm^{ab} X Gm^{abc}/Gm^{b}	17	13.5	10	13.5				
11	abc X abD	Gm^{abc}/Gm^{ab} X Gm^{ab}/Gm^{b}	5	2.5	0	2.5	2	2.5	3	2.5
12	abc X abcD	Gm^{abc}/Gm^{ab} X Gm^{abc}/Gm^{b}	2	2.0	1	1.0	1	1.0		
16	abcD X abD	Gm^{abc}/Gm^{b} X Gm^{ab} Gm^{b}	0	0.25	1	0.5	0	0.25		
			24	18.25	12	17.5	3	3.75	3	2.5

$\chi^2_3 = 3.786, \quad .3>P>.2$

are the phenotypes and T equals the total sample.).

Hence,

$$p = \frac{8 + 27 + 2 + 8}{360} = .1250.$$

The frequency of the Gm^{abc} allele, referred to as c, may be estimated as follows:

$$q = 1 - \frac{\sqrt{ab + abD + abx + abxD + bD + a + ax}}{T}$$

$$= 1 - \frac{\sqrt{85 + 27 + 4 + 2 + 4 + 3 + 1}}{180}$$

$$= 1 - \sqrt{.700} = .1633.$$

Finally, the combined frequency of the alleles which do not lead to either c or $D = \mu = 1 - p - q = .7117$. The phenotypes may be represented as c+ D+, c+ D—, c— D+, and c— D— by ignoring the factors a, b, and x. When this is done the observed and expected frequencies (the latter computed on the Hardy-Weinberg equilibrium) of the four classes are as shown in the first and second rows of table 6. The agreement between the observed and the expected frequencies is satisfactory.

Ropartz *et al.* (1962) used the factor Gm (e), which is determined by an allele at the Gm locus and which segregates in Negroes, to test whether Gm-like is determined by an allele at the Gm locus or by one at a separate locus. As is well known, this test consists of determining whether the four phenotypes (in this case c+ e+, c+ e—, c— e+, and c— e—) resulting from the two factors may be assumed to be due to random distribution of the factors. If the answer is yes, the assumption is that two loci are involved. Ropartz's analysis showed that c (Gm-like) and e were randomly distributed with respect to each other and he concluded, therefore, that Gm-like is due to an allele at a different locus from the Gm locus. Our data, analysed in the same manner (table 6, rows one and three), also may be assumed to show independent assortment of c and D, *i. e.*, to show that c is due to an allele at a locus other than the Gm locus.The point is simply that the population sample is not sufficiently large to distinguish between the alternative hypotheses.

Unfortunately, it is customary for investigators to apply only one of the

TABLE 6. COMPARISON OF OBSERVED AND EXPECTED FREQUENCIES OF c+ D+, c+ D—, c— D+, AND c— D— PHENOTYPES (SEE TEXT)

	c+D+	c+D-	c-D+	c-D-·	Total
Observed	8	46	33	93	180
Expected[a]	7.3	46.7	34.8	91.2	180.0
Expected[b]	12.3	41.7	28.7	97.3	180.0
	(a) $\chi^2_{(1)}$	= 0.21		.7>P>.5	
	(b) $\chi^2_{(1)}$	= 2.79		.10>P>.05	

[a]Computed on the basis of the Hardy-Weinberg equilibrium.

[b]Computed on the assumption of random distribution of alleles at two loci.

above tests to their data if the analysis shows a satisfactory fit. The analyses of our data show that it would be wise to test population data by both methods before drawing conclusions.

For the reasons stated earlier, we consider Gm-like to be due to an allele at the Gm locus. Ideally, we would test a larger population sample to exclude independent distribution of the c and 'D' factors. Since the donor is a child it it difficult to obtain sufficient reagents to do this in a reasonable period of time; accordingly we have decided to present the data as they are.

DISCUSSION

The donor of the agglutinating serum is a healthy Negro boy whose serum is negative for rheumatoid factor activity as measured by the latex test (Singer, Altmann, Goldenberg, and Plotz, 1960) and by the modified Waaler-Rose test (Podliachouk, Eyquem, and Jacqueline, 1958). The agglutinating activity was first identified in a sample drawn when the child was only four years old. It was still present in samples drawn three years later. None of the other members of his family has serum which agglutinates red blood cells coated with the anti-D sera which we use routinely in our laboratory. It will be of interest to study the serum and the clinical status of this boy during the course of the next several years.

The Gm and Inv types, as determined by our usual reagents (table 1), of the donor and the members of his family and the reactions of their sera with the Davis/Roehm system are shown in table 7. It is of interest that the donor's genotype is probably Gm^{ab}/Gm^{ab}. This supports our contention that the Gm (b) produced by the Gm^{ab} allele is different from the Gm (b) produced by the Gm^{b} allele. Healthy donors of agglutinating sera have invariably been negative for the factor which their sera detect.

The distinction between the Gm (b) factor of whites and Negroes was foreshadowed by Ropartz's observation (personal communication), confirmed by us, that sera from some Gm (b+) Negro donors were negative with SNagg Letendre which tests for Gm (b) in the serum of white donors. We have other agglutinators which also fail to detect the Gm (b) factor in the serum of some Gm (b+) Negroes but not in all. It is apparent that the Gm (b) factor in Negroes, at least, is very variable. This is similar to the variation in Negroes of the D factor of the Rh locus (Race and Sanger, 1962).

The observation that the Gm (b) factor produced by the Gm^{ab} allele in Chinese is similar to the Gm (b) factor in whites indicates that the distinctness

TABLE 7. GM AND INV TYPES OF THE DAVIS FAMILY AS DETERMINED BY STANDARD REAGENTS (TABLE 1) AND REACTIONS OF THEIR SERA TO DAVIS/ROEHM SYSTEM (ONLY POSITIVE REACTIONS ARE SHOWN)

	Gm	Inv	Davis/Roehm	Probable Gm Genotype
Fa	ab	b	–	Gm^{ab}/Gm^{ab}
Mo	ab	ab	+	Gm^{ab}/Gm^{b}
1*	ab	b	–	Gm^{ab}/Gm^{ab}
2	ab	ab	–	Gm^{ab}/Gm^{ab}
3	ab	b	+	Gm^{ab}/Gm^{b}

*Donor.

of Gm (b) in Negroes is not due to its production by an allele which also produces Gm (a).

The two exceptions to our hypothesis (a child who was negative to Davis/Roehm when he should have been positive, and an African Negro positive to Davis/Roehm when he should have been negative) are disturbing. The exceptional child could be due to extra-marital origin, but it seems unlikely that the African Negro donor had mixed ancestry. Although sera from several populations were sent from Dr. Blumberg's laboratory at the same time, it is unlikely that this serum was from a non-Negro donor because it is Gm (c+). It is possible that the reaction of this serum represents a mutation from the Gm^{ab} allele found in Negroes to the Gm^{ab} allele found in Chinese or, less likely, to the Gm^{b} allele found in whites. Clearly, further data are required.

We suggest that Gm (b) factors detected by the Davis/Roehm system be called Gm (bw) and that the alleles determining these factors be indicated as $Gm^{\underline{bw}}$, $Gm^{a\underline{bw}}$, etc.

The family data, although not as extensive as one would desire, indicate that Gm-like is due to an allele at the Gm locus. This conclusion is bolstered by the observation that Gm-like has been observed only when the factors Gm (a) and Gm (b) were also present. The failure of our relatively small population sample to exclude the hypothesis of two loci does not appear to be of great import. The fit to the Hardy-Weinberg distribution is also satisfactory and indeed somewhat better than that obtained from a comparison with a random distribution.

If our assumption that Gm-like is due to an allele at the Gm locus is correct, the Gm factor should be found if at all on the B fraction resulting from the digestion of gamma globulin with papain, and not in the A-C fraction (Franklin, Fudenberg, Meltzer, and Stanworth, 1962; Harboe, Osterland, and Kunkel, 1962). Furthermore, it should not be present in Bence-Jones proteins or in β_{2M} or β_{2A} globulins which do not appear to have a fraction corresponding to the B fraction.

SUMMARY

A serum from a four year old healthy Negro boy (Davis) was found to cause red blood cells coated with an incomplete anti-D serum (anti-D Roehm) to agglutinate. The serum had been tested three years after it was drawn. Further tests showed that this system (Davis/Roehm) detected the Gm (b) factor determined by the Gm^{b} allele in whites and the Gm^{ab} allele in Chinese but not by the Gm^{ab} allele in Negroes. The Davis/Roehm system has enabled us to demonstrate that Gm-like is determined by an allele at the Gm-locus or by a gene closely linked to this locus. On the basis of earlier studies we have concluded that the former is more likely. Accordingly, we have decided to refer to Gm-like as Gm (c). Negroes apear to have an allele Gm^{abc} which produces factors Gm (a), Gm (b), and Gm (c).

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