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New Serum Group, Gm(p)

Abstract. *The agglutination that occurs when rheumatoid arthritis serum Pond is added to erythrocytes sensitized with anti-D serum Moore is inhibited in the presence of some normal serums. The inhibitor, tentatively named Gm(p), is associated only with 7S gamma globulins and is apparently different from other previously defined serum groups. It is much more common in Caucasians than in Negroes, and probably is determined by a simple dominant gene.*

The first hereditary human γ-globulin group, Gm(a), was described by Grubb (*1*) in 1956. This description was soon followed by a number of papers describing other serum groups (*2*). A number of codominant alleles at two genetically independent loci determine two series of hereditary human γ-globulin factors: the Gm system, which includes Gm(a), Gm(b), Gm(x), Gm(c), and Gm(r), all associated only with the 7*S* γ-globulins; and the Inv system, which includes Inv(a) and Inv (b), associated with the macroglobulins and γ_{1A} globulins as well.

The frequencies of the various Gm and Inv phenotypes differ considerably in different ethnic groups (*3, 4*). The population that we studied was comprised of about 40 percent Negroes and 60 percent Caucasians.

The anti-Rh serum from one individual, Moore, whose gamma globulins were grouped as Gm(a−b+x−) was used to sensitize group O D+C+E−c− erythrocytes. The Moore serum was diluted 1 : 5 in saline, and for each milliter of this dilution, 0.02 ml of packed erythrocytes were added. Sensitization was carried out at 37°C for 1 hour. The cells were then washed three times with cold saline. Two rheumatoid arthritis serums, Baxter and Pond, agglutinated the cells sensitized with Moore serum. This agglutination was inhibited by certain normal serums. The serum inhibitor has been named, tentatively, Gm(p).

Most of our studies of Gm(p) were conducted with the Pond serum, which has a titer of 1 : 1024 against erythrocytes sensitized with anti-Rh serum Moore. The titration shows a pronounced prozone.

The Pond serum, which was also Gm(a−b+x−), reacted with most of the cells sensitized with the anti-Rh serums that were used for detecting Gm agglutination. This serum was subsequently shown to have anti-Gm(a) activity in addition to anti-Gm(p). Since the donor of the anti-Rh antibody (Moore) is Gm(a−), the Gm(a) factor is not involved in inhibition of the Gm(p) system. Although the Moore serum is Gm(a−b+x−), it was not suitable for Gm(b) typing with the anti-Gm(b) reagents that we have available.

Because of its prominent prozone, the differentiation between inhibitor, Gm(p+), and non-inhibitor, Gm(p−), was determined by titrations of the agglutinator Pond at 1 : 20 to 1 : 320 in serial double dilutions. The normal sera were diluted 1 : 10 and added in equal volume to the titrated agglutinator. Titration of normal sera 1 : 2 to 1 : 32, with addition of agglutinator Pond diluted 1 : 50 in equal volume, was also used. However, because of the prozone, sharper definition was obtained by titration of the agglutinator rather than the normal sera. All tests were performed on microflocculation test slides at room temperature, with a 0.3-percent suspension of sensitized cells as described by Steinberg (*4*).

Table 1. Typing reagents used for the serum groups.

Factor	Anti-D serum	Agglutinator
Gm(a)	Bea	Deas
Gm(a)	Bea	Lipscomb
Gm(a)	Ji	Lipscomb
Gm(a)	Bks	Chapman
Gm(b)	2269	Bomb
Gm(x)	Brand	Baxter
Gm(x)	Brand	Patterson
Gm(c)	Warren	Edwards
Gm(c)	Warren	Carp
Inv(a)	Lemire	Virmontois

We tested 485 serums obtained from individuals who applied for employment at the Medical College of Virginia, from donors to the Medical College blood bank, and from parents included in the family studies described herein. Included in this number were 60 serums used as controls in our laboratory, which were typed for some of the other serum groups by use of the reagents indicated in Table 1.

The results of typing each of these 60 control normal serums for Gm(p) and five other serum groups are shown in Table 2. Chi square values were calculated in "two by two tables" to test whether Gm(p) was contingent upon Gm(x), Gm(c), or Inv(a). These values (0.67, 1.19, and 0.03, respectively, all associated with probabilities greater than 0.25) showed no dependence. The exact probability of Gm(p) and Gm(a) contingency was found to be 0.042. This rather low probability is the result of the almost total absence of the Gm(a−) type among Negroes, and probably does not indicate any relationship between Gm(p) and Gm(a). The Gm(b) types were too infrequent in our samples to permit a statistical test of Gm(p) and Gm(b) contingency.

Table 3 shows the distribution of

Table 2. Serum types of 60 normal controls.

Number of		Serum groups					
Caucasians	Negroes	Gm(a)	Gm(b)	Gm(x)	Gm(c)	Inv(a)	Gm(p)
0	1	+	+	+	+	+	−
1	1	+	+	+	−	+	−
1	1	+	+	+	−	−	+
1	3	+	+	+	−	−	−
0	2	+	+	−	+	+	−
1	7	+	+	−	−	+	+
3	7	+	+	−	−	−	+
0	11	+	+	−	−	−	−
0	6	+	+	−	−	+	−
0	5	+	+	−	+	−	−
0	3	+	+	−	+	−	+
1	0	+	−	+	−	−	+
0	1	+	−	−	−	−	−
1	0	−	+	−	−	+	+
2	1	−	+	−	−	−	+

Table 3. Frequency of Gm (p+) serum among 485 normal individuals.

	Total	No. +	% +
	Caucasians		
Males	49	45	91.8
Females	80	67	83.8
Total	129	112	86.8
	Negroes		
Males	167	62	37.1
Females	189	80	42.3
Total	356	142	39.9

Gm(p) serum groups in all of the 485 individuals tested. The inhibitor was much more common in Caucasians, of whom 86.8 percent were Gm(p+), than in Negroes, of whom 39.9 percent were Gm(p+) ($\chi^2 = 81.75$, $p <<< .0001$). Within each race, however, there appeared to be no relationship between sex and Gm(p) type (for Caucasians, $\chi^2 = 1.10$ $p > .25$; and for Negroes, $\chi^2 = 0.80$, $p > .35$).

Test of the protein fractions obtained from inhibitor and noninhibitor serums by starch block electrophoresis (*5*) and by DEAE-chromatography (diethylaminoethyl cellulose) (*6*) revealed that inhibitory activity was confined to the γ-globulin fraction of the serum proteins. Further chromatographic and sucrose density gradient separations (*7*) of the γ-globulin fractions obtained by starch block electrophoresis disclosed that the inhibitor was present in the 7*S* but absent in the 19*S* component of the γ-globulin.

Test of the 3.5*S* fragments "A-C" and "B" produced by papain digestion of isolated 7*S* normal and myeloma globulins (*8*) disclosed that Gm(p) activity was restricted to fragment B. These data exclude allelism of *Gm(p)* to the gene at the Inv locus since the Inv factors are restricted to fragment A-C in the 7*S* γ-globulins, both normal (*8*) and pathological (*9*). The restriction of Gm(p) activity to papain fragment B suggests (but does not prove) that *Gm(p)* is in close proximity to, or located within, the previously delineated Gm genetic region, since a third genetic region controlling elaboration of hereditary factors at the 7*S* γ-globulin (and to fragment B thereof) seems improbable in view of the current concepts of the relation of the hereditary γ-globulin factors to the structural subunits of human γ-globulin (*10*).

Table 4. Frequency of Gm(p) serum types among the children in 18 families.

Name of couple	Number of children*			
	Sons		Daughters	
	+	−	+	−
Type of marriage: Gm(p+) × Gm(p+)				
La	0	0	1	2
Le	1	0	2	0
Li	2	0	1	0
Wa	1	2	1	1
Type of marriage: Gm(p+) × Gm(p−)				
An	2	3	0	0
Bl	1	0	2	2
Ca	1	1	2	0
Cl	0	3	5	1
Di	0	3	0	0
Go	0	1	1	0
Me	0	1	0	3
Ne	1	1	0	2
Wl	4	0	0	0
Type of marriage: Gm(p−) × Gm(p−)				
Cu	0	1	0	2
Ho	0	0	0	2
Lp	0	1	0	3
Po	0	2	0	1
Wi	0	3	0	0

* Each set of monozygotic twins is recorded as one child.

Eighteen families, comprising 113 individuals, were studied for inheritance of the Gm(p) characteristic. Because of the higher incidence of non-inhibitor among Negroes, only Negro families were included. Several families were selected because of the presence of one or more sets of twins. Eight of these sets were monozygotic; within each of these sets, the twins were concordant for their Gm(p) serum type. Of the seven sets of dizygotic twins in the study, two sets showed discordance with respect to their Gm(p) serum types.

The family data are summarized in Table 4. The types of offspring produced by the three different kinds of marriages are consistent with the hypothesis that the presence of Gm(p) agglutination inhibitor is caused by a simple dominant gene. Thus, all of the fifteen children of Gm(p−) couples were Gm(p−); but the children of Gm(p+) and mixed couples included both Gm(p+) and Gm(p−) individuals, because some of the Gm(p+) parents were heterozygous.

Some statistical tests were made to determine whether the results of the family studies were consistent in yet other ways with the genetic hypothesis. Gene frequencies, where needed, were estimated from the data presented in Table 3. The allele frequency test described by Stern (*11*) was used to determine whether segregation of the progeny from Gm(p+) × Gm(p−) marriages was as expected. The results [17.47 Gm(p−) offspring expected, 21 observed; $\chi^2 = 1.27$, $p > .20$] indicated consistency. Similarly, the tests described by Smith (*12*) for segregation of presumed homozygous recessive individuals in families containing at least one such offspring and for the relative frequency of such families, were also consistent with the hypothesis when applied to the Gm(p+) × Gm(p−) families (in the former test $\chi^2 = 0.477$, $p > .45$; and in the latter, $\chi^2 = 0.539$, $p > .40$). Marriages of the type Gm(p+) × Gm(p+), and their progeny, were too few in our study to make at all reliable the application of these statistical tests to them. Nonetheless, the other data presented in this paper are sufficient to conclude that the hypothesis of Gm(p+) inheritance by means of a simple dominant gene is very probable (*13*).

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