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Heritability Estimates and Genetic and Environmental Correlations for the Human Immunoglobulins G, M, and A

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Concentrations of the serum immunoglobulins (Ig) G, M, and A have long been recognized to vary from person to person. Sex of the individual was found to be a major source of variation for IgM, in that young females had higher IgM levels than young males [1, 2]. For IgA, age of the individual was shown to be a major cause of variation since the concentration increased steadily from childhood to old age [2]. Although twin studies have suggested that genetic factors contribute to the variation in immunoglobulin concentrations [3–5], to our knowledge no heritability estimates based on family data have previously been reported. Consequently, family studies were conducted among the black and white populations of Virginia to determine the contribution of quantitative genetic factors to the variation in immunoglobulin concentrations. Heritability estimates measuring the relative contribution of genetic factors to the total phenotypic variation are presented in this report. Also presented are the genetic and environmental correlations which provide measures of the relative contribution of genetic and environmental factors to the phenotypic correlation among the three immunoglobulins.

SUBJECTS AND METHODS

Families for this study were ascertained through the Medical College of Virginia Hospital records by selecting mothers who were there for delivery during the years 1961–1963 and who at that time were married, had at least three living children, and lived in the city of Richmond or surrounding counties. All of their children who were 5 years of age and older at the time of sample collection in 1970 and 1971 were included in the study. The serum samples were stored frozen at −50°C until tested. A total of 444 individuals belonging to 64 families comprised the present study; approximately half the families were black and half white. All families with illegitimacy as determined from blood group antigens were excluded from the study. For three families, the father was not available for testing; one had died and two could not be reached for sample collection. The average size was five children per family. The age of the children ranged from 5 to 25 years.

A socioeconomic scale based on housing and living conditions but not income was

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applied to the families. The scale ranged from a score of 1 for the lowest to 4 for the most desirable living conditions.

Serum immunoglobulins were quantitated by the radial immunodiffusion technique as previously described [6], using specially prepared standardized antibody agar plates from Melpar (Springfield, Virginia) produced from the same antiserum lots. The IgG plates contained three times the usual commercial amount of anti-IgG, which permitted the use of undiluted serum and an incubation time of 48 hr (similar to the time for the IgM and IgA plates), instead of the 16–18 hr incubation time for the usual commercial IgG plates. For each well, 8μliter of undiluted serum was used, and testing was carried out under highly standardized conditions. Immunoglobulin concentrations, presented in International Units (IU), were based on the World Health Organization reference standards. Five different serum samples from each of six individuals were obtained at equal intervals over 1 year. Each sample was tested four times. An analysis-of-variance test revealed high reproducibility of results and no marked change in immunoglobulin concentrations over the duration of 1 year. One boy, aged 10, was excluded from correlation and regression analyses involving IgA because he completely lacked this immunoglobulin in his serum.

Information on each individual such as registration number, sex, race, age, socioeconomic score, blood and saliva groups, family number, birth order, and IgG, IgM, and IgA measurements was coded onto punch cards. Appropriate FORTRAN programs were developed and the data analyzed by electronic computer.

Estimates of heritability (H) were computed from the linear regressions of offspring on parent ($b \times 2 = H$), from the linear regressions of offspring on midparent ($b = H$), and from the sib-sib (full sibs only) correlations ($r \times 2 = H$).

The genetic correlations r_G, which provide a measure for the contribution of genetic factors to the correlation between two traits, were computed according to Falconer [7]:

$$r_G = \frac{\mathrm{cov}_{XY}}{\sqrt{\mathrm{cov}_{XX}\mathrm{cov}_{YY}}},$$

where cov_{XY} is the "cross-covariance" of, for example, IgG in children and IgA in parents, and vice versa. The cov_{XX} and cov_{YY} represent the offspring-parent covariances of each immunoglobulin class separately. Two genetic correlations were obtained between each of two immunoglobulin classes, such as IgG in children and IgA in parents, and IgA in children and IgG in parents. The arithmetic mean of the two genetic correlations was used because it is less biased by sampling error than the geometric mean [8]. The standard error of the estimate was determined according to Falconer [7].

The environmental correlations r_E were computed as follows:

$$r_E = \frac{r_P - \sqrt{H_X H_Y} r_G}{\sqrt{1 - H_X}\sqrt{1 - H_Y}},$$

where r_P represents the phenotypic correlation, H the heritability, and r_G the genetic correlation for the two immunoglobulins in question.

RESULTS

The frequency distributions for the immunoglobulin levels are shown in figure 1. The distributions for IgM show some bimodality resulting from a sex effect. However, all six distributions approach normality with little indication of skewness; the data are therefore well suited for analyses with an assumption of normal

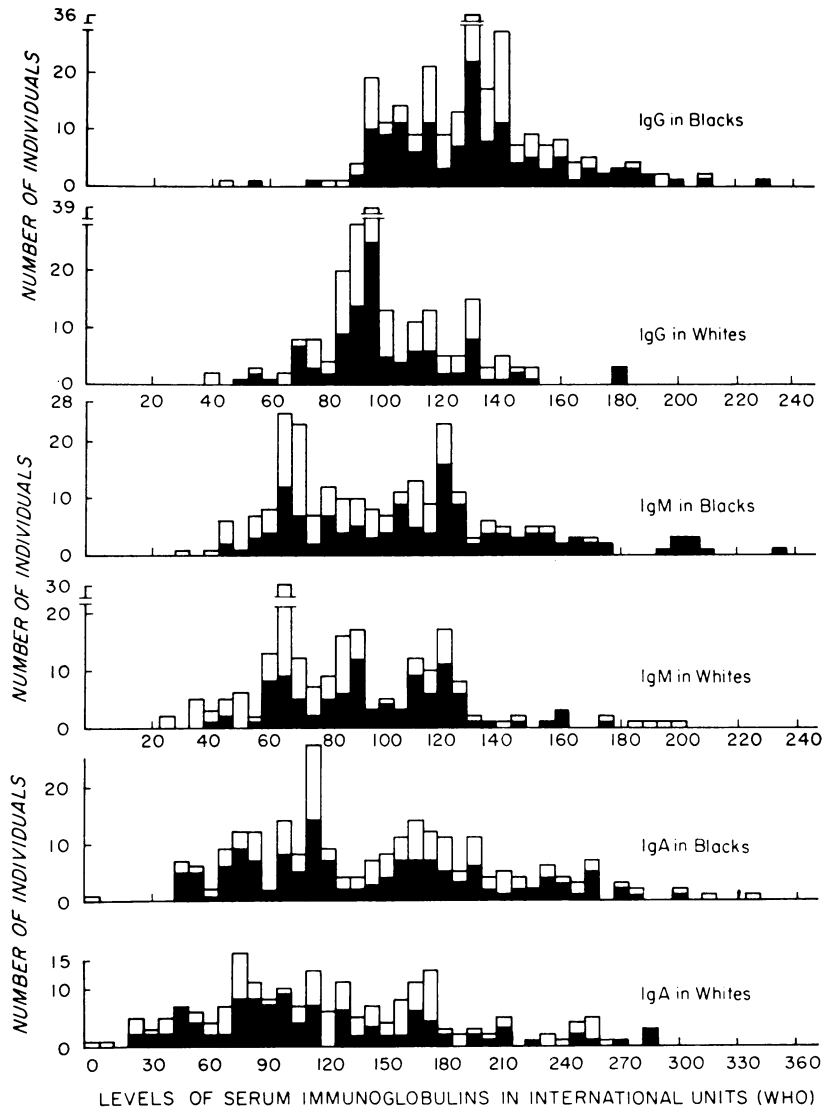

FIG. 1.—Frequency distribution of serum immunoglobulin levels in blacks and whites. Shaded area = females, unshaded = males.

distribution for each variable. An obviously higher IgG level in blacks than whites is clearly apparent.

The mean immunoglobulin levels according to race and sex are presented in table 1. Mean IgG concentrations are the same in males and females of the same race but are 29% higher in blacks than in whites; this difference is highly significant ($P < .001$). The IgM and IgA levels are significantly higher in blacks than whites when individuals of the same sex are compared, but the race

TABLE 1

SERUM IMMUNOGLOBULIN LEVELS ACCORDING TO RACE AND SEX

RACE AND SEX	NO. INDIVIDUALS	IMMUNOGLOBULINS (IU)		
		IgG	IgM	IgA
Black males	106	129.5 ± 2.45	84.9 ± 2.65	150.0 ± 3.68
Black females	136	129.9 ± 2.65	112.1 ± 3.73	139.8 ± 5.76
White males	97	100.8 ± 2.25	76.0 ± 2.99	129.4 ± 6.42
White females	105	100.5 ± 2.35	98.8 ± 3.21	117.0 ± 6.07

NOTE.—IU = International Units, based on the World Health Organization reference standards.

effect is not so striking as for IgG. There is a marked effect of sex on IgM level in that the means are almost one-third higher in females than in males. The IgA means are slightly, but not significantly, higher in males than in females.

The socioeconomic scale gave a mean of 3.1 points for whites and 1.8 points for blacks, indicating a markedly higher socioeconomic level for whites. The correlation coefficients between socioeconomic scale and immunoglobulin concentrations for blacks and whites, respectively, were: IgG, —0.05 and —0.10; IgM, —0.04 and —0.01; IgA, 0.06 and —0.08. Although five of the six coefficients are negative, none is significantly different from zero ($P > .05$). Therefore, socioeconomic scale was not further considered in the analyses.

The correlation coefficients between immunoglobulin levels and age for blacks and whites, respectively, were: IgG, 0.22 and 0.06; IgM, 0.11 and 0.14; IgA, 0.51 and 0.42. Because the correlations for IgA were significantly different from zero ($P < .001$), IgA levels were corrected for age of the individual in all subsequent analyses by adjusting to the mean age of the group. The changes with age of the individual were previously determined in another sample of individuals ranging in age from 10 to 95 years [2].

Regression and correlation coefficients among relatives were first computed by considering sex of the individual (e.g., son-father, daughter-mother, son-mother, daughter-father, brother-brother, sister-sister, and brother-sister). These detailed comparisons did not reveal any meaningful trends with the exception of an apparent effect of the X chromosome on IgM, a finding previously reported elsewhere [1]. For estimating heritability, the data were therefore pooled within each race into the following classes of comparisons: offspring-parent, offspring-midparent, and sib-sib. The results are shown in table 2.

All regression and correlation coefficients were positive and significantly different from zero ($P < .001$) with the exception of the correlation coefficients between parents, which, in general, were little different from zero ($P > .05$). Positive correlations between parents might result from environmental contributions common to spouses. The estimates of H, based on the regression coefficients of offspring on parent, agree well with those obtained from the regression of

TABLE 2

HERITABILITY ESTIMATES (H) BASED ON SIB-SIB CORRELATION COEFFICIENTS AND OFFSPRING-PARENT AND OFFSPRING-MIDPARENT REGRESSION COEFFICIENTS

COMPARISON	BLACKS			WHITES			RACES COMBINED		
	No. Pairs	Regression or Correlation Coefficients	H	No. Pairs	Regression or Correlation Coefficients	H	No. Pairs	Regression or Correlation Coefficients	H
IgG:									
Offspring-parent	352	0.18	0.36 ± 0.074	264	0.28	0.56 ± 0.118	616	0.22	0.44 ± 0.060
Offspring-midparent	172	0.35	0.35 ± 0.075	130	0.45	0.45 ± 0.110	302	0.39	0.39 ± 0.045
Sib-sib	501	0.30	0.60 ± 0.082	227	0.34	0.68 ± 0.118	728	0.32	0.64 ± 0.066
Father-mother	29	0.02	...	32	0.20	...	61	0.11	...
IgM:									
Offspring-parent	352	0.18	0.36 ± 0.084	264	0.24	0.48 ± 0.106	616	0.20	0.40 ± 0.064
Offspring-midparent	172	0.28	0.28 ± 0.083	130	0.48	0.48 ± 0.105	302	0.37	0.37 ± 0.062
Sib-sib	501	0.24	0.48 ± 0.084	227	0.28	0.56 ± 0.122	728	0.26	0.52 ± 0.075
Father-mother	29	0.15	...	32	0.03	...	61	0.09	...
IgA:									
Offspring-parent	350	0.15	0.30 ± 0.066	264	0.35	0.70 ± 0.090	614	0.24	0.48 ± 0.054
Offspring-midparent	171	0.26	0.26 ± 0.066	130	0.62	0.62 ± 0.085	301	0.42	0.42 ± 0.050
Sib-sib	495	0.25	0.50 ± 0.084	227	0.30	0.60 ± 0.122	722	0.26	0.52 ± 0.075
Father-mother	29	−0.01	...	32	0.12	...	61	0.06	...

offspring on midparent, except that the latter estimates are, in general, slightly lower. However, the estimates of H based on sib-sib correlations are generally higher than those based on offspring-parent comparisons, and were significantly higher for IgG and IgA in blacks.

All estimates of H are slightly higher for whites than for blacks; the reason for this difference is not known. The estimates of H for "races combined" represent the weighted mean of the two races. For IgA and IgM, the weighted means were similar to those obtained by computing H from the data of both races combined. For IgG, however, the estimates of H based on both races (black and white families analyzed together) were 0.76, 0.57, and 0.94 for offspring-parent, offspring-midparent, and sib-sib, respectively. These unusually high estimates result in part from the marked difference in mean IgG concentrations in the two races as shown in table 1.

The phenotypic correlation coefficients among immunoglobulin concentrations are presented in table 3. For both blacks and whites, the correlation coefficients

TABLE 3

PHENOTYPIC CORRELATIONS BETWEEN IMMUNOGLOBULIN CONCENTRATIONS IN BLACKS AND WHITES

	BLACKS		WHITES	
	No. Individuals	Correlation Coefficient (r)	No. Individuals	Correlation Coefficient (r)
IgG/IgA	241	0.28***	202	0.33***
IgG/IgM	242	0.17**	202	0.20**
IgM/IgA	241	0.11	202	0.12

** $P < .01$ for difference from zero.
*** $P < .001$ for difference from zero.

are largest between IgG and IgA, intermediate between IgG and IgM, and lowest between IgM and IgA. The genetic correlations (table 4) are much higher between

TABLE 4

GENETIC AND ENVIRONMENTAL CORRELATIONS AMONG IMMUNOGLOBULINS IN BLACKS AND WHITES BASED ON OFFSPRING-MIDPARENT COMPARISONS

	IgG	IgM	IgA
Blacks:			
IgG	...	0.15 ± 0.16	0.43 ± 0.11
IgM	**0.18**	...	0.13 ± 0.12
IgA	**0.22**	**0.10**	...
Whites:			
IgG	...	0.07 ± 0.17	0.35 ± 0.16
IgM	**0.31**	...	0.03 ± 0.19
IgA	**0.32**	**0.22**	...

NOTE.—Genetic correlations in regular type, environmental correlations in boldface type.

IgG and IgA than for the other combinations. Only the coefficients between offspring and midparent are presented because those between offspring and parent were of similar magnitude. The genetic correlations between IgG and IgA are significantly different from zero both in blacks and whites ($P < .01$, $P < .05$, respectively), while the others are not ($P > .05$). It may be concluded that only the association between IgG and IgA concentrations is markedly controlled by related genetic factors.

In blacks, the environmental correlation is higher between IgG and IgA than between IgM and IgG or IgM and IgA. In whites, all environmental correlations are of similar magnitude, indicating that environmental factors may simultaneously influence all three classes of immunoglobulins.

DISCUSSION

The present results disclose wide variation in the concentration of serum immunoglobulin concentrations and reveal that part of this variation is under genetic control. Blacks and whites gave almost identical results with respect to the effect of sex on IgM and age on IgA. These results suggest that essentially the same biologic mechanisms are at work in blacks and whites, although the mean concentrations of all three immunoglobulins were higher in blacks than whites. Higher immunoglobulin levels in blacks have previously been reported [9–11].

The differences in mean immunoglobulin concentrations between blacks and whites presumably resulted mainly from genetic differences, although a possible effect of socioeconomic factors is not entirely excluded. The question of the effect of genetic and environmental factors on immunoglobulin levels in the two races has previously been raised. Goldstein et al. [10] favored the importance of genetic factors because their healthy black and white controls were selected from the same socioeconomic and occupational groups; however, no information is provided on possible differences in housing conditions. The degree of admixture by Caucasian genes in the blacks of the present study has not been determined as yet. Reed [12] lists about 10% admixture for blacks in Evans and Bullock Counties of Georgia and 20% or higher for blacks in Washington and Baltimore. Virginia is located between these two areas and a degree of admixture between 10% and 20% may be assumed for the blacks of the present study.

The heritability (H) values were significantly different from zero for all three immunoglobulins, revealing that quantitative genetic factors contribute importantly to the variation in immunoglobulins. The H values varied somewhat but were generally lower in blacks than in whites (average values 0.30 and 0.45, respectively). Thus, of the total variation in immunoglobulin levels, roughly 30% in blacks and 45% in whites is accounted for by genetic variation. It should be pointed out that the individuals studied were relatively young and that the contribution of genetic factors might be lower in elderly individuals than in young individuals.

The sib-sib comparisons generally gave higher heritability estimates than the offspring-parent and offspring-midparent comparisons. This can be explained by the fact that the sib-sib correlations contain a component of environmental

variance shared by full sibs plus one-quarter of the dominance variance and one-half of the additive genetic variance [7]. For IgG, for example, the H value based on sibs is 0.64 while that based on offspring-parent comparisons is 0.44 (table 2). Thus, variation resulting from a common environment of sibs and/or dominance variation accounts for about 20% of the phenotypic variation among the offspring. Offspring-parent and offspring-midparent comparisons furnish more meaningful estimates of heritability.

The present H values are much lower than those from twins, where they ranged from 0.71 to 0.83 [4]. The present results have revealed that environmental variance common to sibs and possible dominance variance may inflate the estimate of H, a source of bias expected to be even more prevalent in twin than in familial data.

As in other studies [2, 13], the concentration of IgA was found to increase markedly with the age of the individual. This increase with age contributed markedly to the total variation of IgA in the population under study. The correlation coefficients between IgA concentration and age were 0.51 and 0.46 for blacks and whites, respectively. The r^2 values provide a measure for the contribution of age to the total variation in IgA; thus 26% and 21% of the total variation in blacks and whites, respectively, resulted from variation in age, while the estimated contributions of quantitative genetic factors were 28% and 48% (table 2: offspring-midparent). Therefore, in the present data genetic factors contributed a larger fraction to the total variation in IgA than age of the individual. In a previous sample which included elderly individuals, 35% of the total variation in IgA was found to result from variation in age of the individual [2]; that is, age contributed a relatively larger fraction to the total variation than in the present study comprised of younger individuals.

The major causes of variation other than quantitative genetic factors are thus different for the three immunoglobulins: for IgG it is the difference between blacks and whites reflecting perhaps both genetic and environmental factors; for IgM it is sex effect; and for IgA it is an age effect.

Genetic and environmental correlations have been widely used in animal improvement programs when establishing efficiency of selection for more than one trait [7]. In the present study, they were employed to evaluate the cause of interrelation among the three immunoglobulins, particularly whether predominantly genetic or environmental causes of variation are responsible for the phenotypic correlations. The relatively high and positive genetic correlations between IgA and IgG provide evidence that regulation of the concentration of these immunoglobulins is interrelated. Their production may in part be controlled by the same or by interrelated control mechanisms. These conclusions are further supported by a previous report on individuals with selective IgA deficiency which indicated that IgG but not IgM compensated for the deficiency in IgA [14]. The finding of close linkage between the structural loci for the heavy chains of IgG and IgA in the mouse [15] and man [16, 17], suggesting that one class of immunoglobulins has evolved from the other, may provide an explanation for the interrelation in control mecha-

nisms for IgG and IgA. However, the data also reveal that this interrelation is not complete: (1) the genetic and phenotypic correlations are smaller than expected with complete interdependence; (2) the increase with age of the individual is more striking for IgA than for IgG; and (3) sex exerted some effect on IgA but not on IgG concentrations.

Low genetic correlations were found between IgM and the other immunoglobulins; the phenotypic correlation coefficients between IgM and IgA were also very low. In early life, IgM is produced first, a phenomenon which has also been observed in the immunoglobulin classes of antibodies produced in many infections. The very low genetic correlations of IgM with IgG and IgA indicate that concentrations of the immunoglobulin produced first does not control the concentration of the other two. The fact that the X chromosome carries quantitative genes for IgM but not for IgG and IgA [1] also indicates that regulation of IgM concentrations differs from that for IgG and IgA.

The fact that all environmental correlations were positive indicates that environmental factors may exert similar effects on the concentration of all three classes of immunoglobulins. The relatively high environmental correlation between IgG and IgA in whites suggests that these two immunoglobulins, particularly, are influenced in the same directions by environmental factors. Nutrition, infections, and sanitary conditions are factors which might influence immunoglobulin concentrations. Since the data were corrected for age of the individual, age is not expected to have influenced either the genetic or the environmental correlations.

Much information on the structure and biological properties of immunoglobulins and antibodies has been summarized in recent reviews [18–20]. The human fetus may synthesize IgM and less frequently IgA, but IgG is probably not synthesized prenatally [19]. After birth, IgM synthesis increases rapidly and IgM reaches adult levels at 1–2 years of age [9]. The IgG levels increase rapidly in early childhood [9] and very slowly thereafter, but IgA levels increase markedly throughout life [2, 12]. Repeated sample collections from the same persons over a short period, 1 year in the present study and 6 months in a study by Allansmith et al. [21], have shown that the IgG, IgM, and IgA levels remain relatively constant in healthy adults. Since the levels are maintained by synthesis and catabolism [22], consistency in these three immunoglobulins over 1 year indicates that rates of synthesis and catabolism are tightly controlled in a healthy person, although levels differ between individuals. Specific antibodies produced in response to an antigenic stimulation show more fluctuation in titer than the levels of the various classes of immunoglobulins [22].

The Gm and Inv markers of immunoglobulins have widely been applied in population studies because they were found to provide powerful tools to detect similarities and differences between populations [23]. The Gm antigens, the markers of the constant regions of the heavy chains of IgG, were also found to be associated with the relative quantities of the various subtypes of IgG [24]. However, total levels of IgG were not influenced by the Gm types [6, 24], nor did the Gm types have any effect on serum IgM, IgA, and isoantibody levels [6].

Also, the Inv markers situated on the constant regions of the light chains did not influence the concentrations of serum IgG, IgM, or IgA [6].

Individuals with immunoglobulin deficiencies frequently encounter problems with infections [25]. It is not known to what extent variation in immunoglobulins within normal ranges is associated with efficiency in combating infections. As was pointed out elsewhere [1], the higher IgM levels in girls may provide an explanation for the observation that girls are more resistant to certain types of infections than are boys. However, the steady increase of IgA with age does not indicate an association between IgA levels and immunological efficiency because elderly individuals encounter more difficulties in combating new infections than younger adults [26]. The level of hemolytic isoantibodies, which show a marked decline after childhood [27], may provide a more meaningful tool for estimating the immunological potential than the immunoglobulin levels.

SUMMARY

The contribution of quantitative genetic factors to the variation in concentration of serum immunoglobulins G, M, and A was determined among families of the black and white populations of Richmond, Virginia. Heritability (H) estimates were computed from offspring-parent, offspring-midparent, and sib-sib comparisons. The H values were highly significant for all three classes of immunoglobulins, averaging 0.30 in blacks and 0.45 in whites. Thus, in the population under study from 30% to 45% of the total variation in immunoglobulin levels was accounted for by quantitative genetic variation. The H values based on offspring-parent and offspring-midparent were generally lower than those based on sib-sib comparisons, suggesting that H values based on sibs were inflated by environmental and/or dominance variation common to full sibs.

Genetic correlations between IgG and IgA were relatively high, suggesting that regulation of concentration of these immunoglobulins is interrelated. However, IgM showed low genetic correlations with IgG and IgA indicating that regulation of concentration of IgM is independent of the other two classes of immunoglobulins. All environmental correlations were positive suggesting that environmental causes of variation may simultaneously influence the concentration of all three classes of immunoglobulins.

In addition to the quantitative genetic variation, race displayed a marked effect in that immunoglobulin levels were higher in blacks than whites. The difference between races was most strikingly expressed for IgG. Both in blacks and whites the IgM concentrations were significantly higher in females than in males, and the IgA concentrations showed a marked increase with the age of the individual.

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