0031-3998/85/1908-0846$02.00/0
PEDIATRIC RESEARCH

Vol. 19, No. 8, 1985
Printed in U.S.A.

Relation of Age, Race, and Allotype to Immunoglobulin Subclass Concentrations

PENELOPE G. SHACKELFORD, DAN M. GRANOFF, MOON H. NAHM, MITCHELL G. SCOTT, BRIAN SUAREZ, JANARDAN P. PANDEY, AND SUSAN J. NELSON

Departments of Pediatrics [P.G.S., D.M.G., S.J.N.], Pathology [M.H.N., M.G.S.], and Psychiatry [B.S.], Washington University School of Medicine; Division of Infectious Diseases, St. Louis Children's Hospital, St. Louis, Missouri 63178 and Department of Basic & Clinical Immunology and Microbiology [J.P.P.], Medical University of South Carolina, Charleston, South Carolina

ABSTRACT. Concentrations of IgG_1, IgG_2, and total IgG were measured by a solid phase radioimmunoassay in sera from 36 healthy adults and 114 healthy children. As expected, IgG_2 and total IgG had a positive correlation with age in children. In addition to age, several other factors were associated with significant differences in serum subclass concentrations. Female children had higher concentrations of IgG_1 than males, and black subjects had significantly higher concentrations of IgG_1, IgG_2, and total IgG than whites. Although Km(1) and Gm(23) immunoglobulin allotypes had no relation to subclass concentrations when tested as single factors, the Km(1) allotype interacted significantly with race so that Km(1)-positive black children had higher IgG_2 concentrations than other subjects. Our findings may explain, in part, recent observations of an association of the Km(1) allotype with altered immune responses of blacks to certain vaccines containing bacterial polysaccharides. In addition, our data indicate the need to control factors such as sex, race, and allotype in studies of subclass concentrations or immune responses. (*Pediatr Res* 19: 846–849, 1985)

Abbreviations

ANOVA, analysis of variance
ANCOVA, analysis of covariance
Hib, *Haemophilus influenzae* type b

Human IgG immunoglobulins have been divided antigenically into four subclasses, IgG_1, IgG_2, IgG_3, and IgG_4 (1–3). Of these, IgG_1 and IgG_2 comprise the major portion of total IgG, 60 and 30%, respectively. Although the biological importance of the four IgG subclasses is unknown, studies of myeloma proteins have revealed that these subclasses differ in their relative abilities to fix complement, to cross the placenta, and to bind to macrophages (4–6). In addition, antibodies to certain types of antigens, such as polysaccharides, are found to be relatively restricted to particular subclasses, *i.e.* IgG_2 in humans (7, 8) and IgG_3 in mice (9, 10). Finally, striking differences in the ontogeny of subclasses have been reported, with IgG_2 and IgG_4 maturing much later than IgG_1 and IgG_3 in normal children (11–13).

Received October 12, 1984; accepted March 27, 1985.
Address reprint requests to Penelope G. Shackelford, Department of Pediatrics, Washington University School of Medicine, Box 14871, St. Louis, MO 63178.
Supported by Public Health Service Grants R01-AI 19350, R01-AI 17962, AI 18727, AI 19676, MH 31302 and MH 14677 from the National Institutes of Health and by RR-36 from the General Clinical Research Center Branch.

It is known that antipolysaccharide antibodies play an important role in protective immunity against polysaccharide encapsulated bacterial pathogens (14–16). Recent studies indicate that genetic factors, particularly genes associated with certain Gm and/or Km immunoglobulin allotypes, may be associated with altered responsiveness to vaccines containing bacterial polysaccharides (17–19). In addition, black children lacking the Km(1) allotype have an increased relative risk of developing meningitis caused by Hib (17). Since human antipolysaccharide antibodies have been reported to be relatively restricted to the IgG_2 subclass, it was of interest to determine if factors which appear to influence the production of antipolysaccharide antibodies, *i.e.* race and immunoglobulin allotype, might do so by virtue of their relation to the maturation and distribution of IgG subclasses in serum.

In this study, we first established normal age-group values for serum concentrations of IgG, IgG_1, and IgG_2 in our laboratory. We then examined the effects of sex, race, and Km(1) and Gm(23) allotypes on these immunoglobulin concentrations in a group of children ages 7 to 38 months and in adults. We found that black subjects, particularly those with certain immunoglobulin allotypes, had higher serum concentrations of IgG, IgG_1, and IgG_2.

METHODS

Subjects. Normal subjects included 41 healthy adults and 114 healthy children, 7 months through 16 yr of age. These subjects were participants in various vaccine studies, or were recruited sequentially from among children presenting to a pediatric office for routine preventive care. Subjects in vaccine studies were included based on availability of sera and race (to include equal numbers of blacks and whites). In order to increase the sample size of sera from subjects with allotypes present in low numbers in the above sample [*e.g.* Km(1) positive whites and Km(1) negative blacks], we also included 10 serum samples that had previously been typed for Gm(23) and Km(1). After obtaining informed consent, serum was collected by venipuncture and stored at −20° C.

Laboratory methods. Serum IgG_1 and IgG_2 subclass concentrations were measured by a solid phase radioimunoassay (20) employing subclass specific reagents. In brief, a monoclonal antihuman IgG_1 reagent was prepared by immunization of a BALB/C mouse with "Cal," an IgG_1 myeloma protein (20). An antihuman IgG_2 reagent was prepared by immunization of a monkey (*Macaca fasicularis*) with two IgG_2 myeloma proteins, "Ziem" (IgG_2k) and "Gar" ($IgG_2\lambda$) (20). The animal was primed with Fc fragments and boosted with intact protein. Serum was rendered IgG_2 specific by extensive absorption and affinity pu-

rification using IgG_1 and IgG_2 conjugated sepharose 4B (Pharmacia, Piscataway, NJ) columns, respectively. Polyvinyl 96-well microtiter plates (Dynatech, Alexandria, VA) were coated with subclass-specific antisera in phosphate-buffered saline. After coating with antiserum, plates were washed with 0.05% Tween 20 in normal saline and uncoated sites were blocked with 1% bovine serum albumin. Serum and myeloma standards were added to the plates and serial 4-fold dilutions were performed in the plate. A proband myeloma, radiolabeled with ^{125}I by the chloramine T method (21), was added to each well. The plates were incubated overnight at room temperature, washed, and individual wells were counted. The concentration of IgG_1 or IgG_2 was calculated by comparison with the myeloma standard.

The specificity of the IgG_1 and IgG_2 assays was confirmed using a panel of 39 purified human myeloma proteins (20). The World Health Organization reference serum 67/97 (IgG content 7700 μg/ml) was included in each assay as an internal control. The mean ± SD value (μg/ml) determined for IgG, IgG_1 and IgG_2 in this reference serum, using our assays, compared well to those previously published (22) (in parentheses): IgG 8050 ± 332 (9000), IgG_1 6113 ± 1273 (5100), and IgG_2 2390 ± 285 (2500). The sensitivity of each assay was equal to the amount of standard protein which resulted in 50% inhibition of maximum binding. For IgG_1 this ranged from 50–129 ng/ml and for IgG_2 from 70–200 ng/ml.

Determination of the Gm(23) and Km(1) allotypes was performed on coded serum samples, using a hemagglutination inhibition assay with reagents described previously (23, 24). Sufficient sera for analysis was available from 36 adults and 64 children less than 38 months of age.

The concentration of total IgG in serum was measured by radial immunodiffusion using the kinetic (Fahey) method and commercial kits (ICL Scientific, Fountain Valley, CA).

Statistical analysis. Statistical analysis was performed using SPSS programs (25) on a Harris 500 computer. Correlation analysis was used to assess the association between age and immunoglobulin concentration. ANOVA was used to test for differences in immunoglobulin concentrations among all subjects when grouped by age and among adults grouped by sex, race, or allotype. To allow for multiple comparisons, the Scheffé procedure was used to compare the age group means. For children, ANCOVA was used to remove the effect of age when testing for mean differences based on sex, race, or allotype.

Normal values for immunoglobulin concentrations for the various age groups are expressed as geometic means. The normal range for each age group was determined by taking the antilog of mean logarithm (± 2 SD of the logarithms).

Table 1. *IgG_1, IgG_2, and IgG concentrations in sera from 114 normal children and 41 healthy adults*

Age (mo)	*n*	Geometric mean (μg/ml) IgG_1	IgG_2	IgG
7–12	7	3655 (1541–8666)†	767* (260–2265)	6206* (2805–13,703)
13–18	19	5992 (2126–16,889)	891* (368–2155)	8232* (3808–17,795)
19–24	16	7058 (3416–14,585)	1020* (323–3226)	9524 (5383–16,850)
25–30	11	5924 (4144–8468)	1390 (703–2746)	9900 (5302–15,431
31–36	12	4914 (1435–16,819)	1187* (656–2150)	9143 (4439–18,832)
37–60	11	5806 (3833–8796)	1344 (444–4071)	8215 (4025–16,765)
61–84	10	5129 (2587–10,195)	1601 (510–5027)	10,245 (5120–20,497)
85–108	7	6601 (3242–13,440)	1363 (443–4191)	11,327 (6461–19,856)
109–156	9	5853 (3337–10,266)	1646 (466–5806)	10,271 (6789–15,538)
157–203	12	7695 (3270–18,105)	2024 (745–5498)	11,652 (6155–22,059)
Adults	41	6561 (3552–12,067)	2551 (878–7398)	12,410 (6616–23,281)

* Indicates a value for the age group which is significantly different by the Scheffe' procedure ($p \leq 0.05$) from the corresponding adult values.

† The normal bounds in parentheses were determined by taking the antilog of (mean logarithm ± 2 SD of the logarithms).

Table 2. *Immunoglobulin concentrations in normal subjects: relation to sex*

	n	Mean Ig concentrations (μg/ml) IgG_1	IgG_2	IgG
Children				
Male	25	5338*	1127	8445
Female	39	7044*	1140	8835
Adults				
Male	18	7437	3025	12,364
Female	18	6512	2865	13,520

* $p = 0.02$ by 1-way ANCOVA with age as a covariate.

RESULTS

The geometric mean IgG_1, IgG_2, and IgG concentrations in groups of normal subjects of various ages are shown in Table 1. As previously reported (11, 12), serum concentrations of IgG_1 increase rapidly during the 1st yr of life. Even in the youngest age group in this study (7–12 months) the concentrations were not significantly lower than those of adults.

The maturation of serum IgG_2 concentration differed considerably from that of IgG_1. In children 7–12 months of age, the mean concentration of IgG_2 was 30% of the adult value and rose to only 47% of the adult value by 31–36 months of age. Another measure of the prominent age-effect on IgG_2 was the positive correlation with age in children less than 38 months of age ($r = 0.46$, $p < 0.001$); in contrast, the correlation ($r = 0.07$) between age and IgG_1 was not significantly different from zero. Total serum IgG correlated with age in children less than 38 months of age ($r = 0.37$, $p = 0.002$).

The effects of sex, race, and the Gm(23) and Km(1) immunoglobulin allotypes on serum IgG_1, IgG_2, and IgG concentrations were tested. Data were analyzed separately for children and for adults. Children 7–38 months of age were chosen because of the significant linear correlation between age and both IgG and IgG_2 serum concentrations in these subjects. This correlation permitted the use of ANCOVA to test for the effects of sex, race, or immunoglobulin allotype on immunoglobulin concentrations in young children while controlling for age.

Female children were found to have significantly higher ($p = 0.02$) serum concentrations of IgG_1 than males (Table 2). In adults, there were no significant differences in the serum concentrations of IgG_1, IgG_2, or total IgG between males and females.

We used 2-way ANOVA and ANCOVA to test for both main and interactive effects of race and immunoglobulin allotypes on serum concentrations of IgG_1, IgG_2, and IgG. As summarized in Table 3, 2-way analysis of the relation of immunoglobulins to Km(1) and race showed no significant differences in IgG_1 concentrations between subjects of different races although there was a trend for IgG_1 to be higher in blacks than in whites (for adults, $p = 0.07$, and for children, $p = 0.09$). IgG_2 concentrations were significantly higher in black adults than in white adults ($p = 0.02$). However, in children, this difference was apparent only in subjects with the Km(1) allotype ($p = 0.02$, by ANCOVA

Table 3. *Immunoglobulin concentrations in normal subjects: relation to race and Km(1) immunoglobulin allotype*

		Mean Ig concentrations (μg/ml)		
	n	IgG_1	IgG_2	IgG
Children				
$Km(1)^-$				
White	27	5832	1066	7806
Black	12	6473	904	9334
$Km(1)^+$				
White	8	6407	1003	7691
Black	17	7163	1470	10,082
Probabilities (2-way ANCOVA)				
Main		NS*	NS	0.02 (race)
Interaction		NS	0.02	NS
Adults				
$Km(1)^-$				
White	16	6111	2113	11,591
Black	7	7858	3450	13,337
$Km(1)^+$				
White	3	6530	2278	10,823
Black	10	8005	4043	15,017
Probabilities (2-way ANOVA)				
Main		NS	0.02 (race)	NS
Interaction		NS	NS	NS

* No significant difference.

Table 4. *Immunoglobulin concentrations in normal subjects: relation to race and Gm(23) allotype*

		Mean Ig concentrations (μg/ml)		
	n	IgG_1	IgG_2	IgG
Children				
$Gm(23)^-$				
White	15	5337	1013	6769
Black	23	6571	1314	9318
$Gm(23)^+$				
White	20	6434	1081	8538
Black	6	8055	937	9891
Probabilities (2-way ANCOVA)				
Main		NS	NS	0.006 (race)
Interaction		NS	NS	NS
Adults				
$Gm(23)^-$				
White	5	5693	1775	10,314
Black	13	7568	4325	15,043
$Gm(23)^+$				
White	14	6350	2269	11,883
Black	4	9167	2088	11,993
Probabilities (2-way ANOVA)				
Main		0.02 (race)	0.04 (race)	NS
Interaction		NS	0.03	NS

with age as the covariate). Black children had significantly higher concentrations of total IgG (mean 9973 μg/ml) than white children (7780 μg/ml) ($p = 0.02$). Although IgG concentrations also tended to be higher in black adults, this difference was not statistically significant ($p = 0.07$).

The effects of race and Gm(23) allotype on immunoglobulin concentrations are shown in Table 4. In this analysis, with Gm(23) as the second factor in the 2-way ANOVA, the higher mean concentration of IgG_1 in black adults was statistically significant ($p = 0.02$). IgG_1 concentrations also tended to be higher in black children than in white children ($p = 0.09$). IgG_2 concentrations were again found to be significantly higher in black adults ($p = 0.04$). In addition, a significant interaction effect between race and Gm(23) allotype was found in black adults but not black children. Black adults who lacked the Gm(23) allotype had very high serum concentrations of IgG_2 (mean = 4325 μg/ml), approximately twice the mean concentrations of IgG_2 in the other three adult groups. Finally, as in the 2-way analysis with Km(1), serum concentrations of IgG were significantly higher in black children than in white children ($p = 0.006$) and tended to be higher in black adults than in white adults ($p = 0.07$).

DISCUSSION

Employing solid phase inhibition assays, we obtained values for IgG_1 and IgG_2 which are similar to those previously reported (11–13). We developed these assays in order to test large numbers of samples, including some at low concentrations of IgG subclasses using small quantities of antisera (20). Our data confirm earlier observations of age-related changes in immunoglobulin concentrations, and indicate further that IgG_1 and IgG_2 concentrations are influenced by sex and race of the subject, and by the presence or absence of the Km(1) and Gm(23) allotypes.

Specifically, IgG_2 concentrations were lower in children up to 108 months (9 yr) of age than in adults. On the other hand, IgG_1 concentrations of only the youngest children (7–12 months) were less than those of normal adults, and in older children concentrations of IgG_1 were higher than in adults. Higher concentrations of IgG_1 in older children have been noted in previous studies (13) and may reflect response to hyperimmunization resulting from routine childhood immunization and frequent infections.

Although normal age group values for IgG, IgA, and IgM have been established separately for males and females, only one previous study of IgG subclass concentrations in children has addressed the possible influence of gender. Van Der Giessen *et al.* (13) found no significant differences in subclass concentrations between boys and girls more than 48 months of age. In our analysis of the values in children 7–38 months of age, we found significantly greater concentrations of IgG_1 in females than in males. This difference was not noted in adults.

In 1968, Buckley *et al.* (26) reported significantly higher concentrations of IgG in black subjects 6 through 14 yr of age compared to those in whites of comparable age. No significant differences in IgG concentrations were found in black and white children less than 6 yr of age; however, no correction was made for age so the effect of race on IgG in this group of children may have been masked by inclusion of a greater proportion of blacks who were very young (<9 months). Using ANCOVA to correct for age, we found that black children between 7 and 38 months of age had significantly higher serum concentrations of IgG than white children (Table 3). In addition, black adults had higher IgG_1 and IgG_2 concentrations than white adults. Although IgG_1 tended to be higher in black children, serum IgG_1 and IgG_2 concentrations did not differ significantly in black and white children when only the single effect of race was tested.

Previous studies suggested an effect of immunoglobulin allotype on serum concentrations of IgG subclasses (13, 22, 27) but the results were conflicting. In one study, both IgG_2 and IgG_4 concentrations were higher in persons with the Gm(23) phenotype (22). In a subsequent study (27) IgG_4 but not IgG_2 concentrations were increased in subjects with Gm(23) compared with the corresponding values of subjects lacking Gm(23). In a third study (13), mean IgG_2 concentrations were higher in sera positive for Gm(23) than in sera lacking this allotype. In the present study, with one exception, there were no significant differences in subclass concentrations related to this allotype. The exception was higher IgG_2 concentrations in black adults lacking Gm(23) (Table 3). However, the Gm(23) allotype, frequent in whites, is rarely found in African blacks (28). Thus, we believe that the relation of serum IgG_2 concentrations with Gm(23) allotype in our North American blacks reflects the influence of racial admixture rather than an allotype effect, since black race itself was

associated with higher IgG_2 concentrations than white race, and Gm(23) was not associated with altered IgG_2 concentrations in whites. However, another posibility is that genes associated with the Gm(23) locus are interacting with other gene products present in blacks, but not whites, and affecting IgG_2 levels. For example, there are reports of interactive effects of allotype and major histocompatibility loci on immune responses (29–31), and in humans, the frequency of HLA specificities differs among races.

In this study, we found that black children who were Km(1) positive had significantly higher concentrations of IgG_2 than black children who lacked this allotype (Table 3). Antibody against the polysaccharide capsule of Hib is protective against invasive disease (14–16). Further, antibodies to many other polysaccharide antigens are reported to be relatively restricted to the IgG_2 subclass (7, 8). Recent studies suggest that genes associated with the Km(1) immunoglobulin allotype may influence the antibody response to vaccines containing bacterial polysaccharides (17–19). For example, black children with the Km(1)-positive allotype have increased antibody responses to Hib polysaccharide-pertussis vaccine compared with those of blacks who lack this allotype (17). More recently, blacks with Km(1) also were found to have higher antibody responses to the purified type b polysaccharide (32). In addition, Km(1)-positive black children had a lower relative risk of Haemophilus meningitis than blacks who lack this allotype (17). Thus, in blacks, high responsiveness to Hib vaccines and low susceptibility to Hib disease appear to be related to genes associated with the Km(1) locus. The present data suggest that these genes in turn may be associated with high concentrations of the IgG_2 immunoglobulin subclass.

In conclusion, IgG subclass concentrations in children are influenced by many factors, the most important of which is age. It appears that race and the Km(1) immunoglobulin allotype also may affect serum concentrations of the late maturing IgG_2 subclass. These data may explain, in part, recent observations of the asssociation of Km(1) immunoglobulin allotypes with different immune responses to vaccines containing polysaccharides. Our findings emphasize the need to control for factors such as race, sex, and immunoglobulin allotype in future studies assessing subclass concentrations and their possible influence on immunologic responses.

Acknowledgments. The authors thank Anthony Quinn, Jill Crouse, Audrey Wolf, and Kim Macke for excellent technical assistance.

REFERENCES

1. Dray S 1960 Three gammaglobulins in normal human serum revealed by monkey precipitins. Science 132:1313–1314
2. Terry WD, Fahey JL 1964 Heterogeneity of H chains of human 7S gammaglobulin. Fed Proc 23:454
3. Grey HM, Kunkel HG 1964 H chain subgroups of myeloma proteins and normal 7S gammaglobulin. J Exp Med 120:253–266
4. Natvig JB, Kunkel HG 1973 Human immunoglobulins: classes, subclasses, genetic variants, and idiotypes. Adv Immunol 16:1–59
5. Spiegelberg HL 1974 Biological activities of immunoglobulins of different classes and subclasses. Adv Immunol 19:259–294
6. Shakib F, Stanworth DR 1980 Human IgG subclasses in health and disease. Ric Clin Lab 10:463–479
7. Yount WJ, Dorner MM, Kunkel HG, Kabat EA 1968 Studies on human antibodies. VI. Selective variations in subgroup composition and genetic markers. J Exp Med 127:633–646
8. Riesen WF, Skvaril F, Braun DG 1976 Natural infection of man with group A streptococci. Scand J Immunol 5:383–390
9. Perlmutter R, Hansburg D, Briles D, Nicolotti R, Davie JM 1978 Subclass restriction of murine anticarbohydrate antibodies. J Immunol 121:566–572
10. Slack J, DerBalian G, Nahm M, Davie JM 1980 Subclass restriction of murine antibodies. II. The IgG plaque forming cell response to thymus independent type 1 and type 2 antigens in normal mice and mice expressing an x-linked immunodeficiency. J Exp Med 151:853–862
11. Morell A, Skvaril F, Hitzig WH, Barandum S 1972 IgG subclasses: Development of the serum concentrations in "normal" infants and children. J Pediatr 80:960–964
12. Schur PH, Rosen F, Norman ME 1979 Immunologic subclasses in normal children. Pediatr Res 13:181–183
13. Van Der Giessen M, Rossouw E, Algra-Van Veen T, Loghem E Van, Zegers BJM, Sander PC 1975 Quantification of IgG subclasses in sera of normal adults and healthy children between 4 and 12 years of age. Clin Exp Immunol 21:501–509
14. Anderson P, Johnston RB Jr, Smith DH 1972 Human serum activities against *Haemophilus influenzae* type b. J Clin Invest 51:31–44
15. Schneerson R, Rodrigues LP, Parke JC Jr, Robbins JB 1971 Immunity to disease caused by *Haemophilus influenzae* type b. II. Specificity and some biologic characteristics of "natural," infection-acquired, and immunization-induced antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Immunol 107:1081–1089
16. Peltola H, Koyhty H, Sironen A, Mäkelä PH 1977 *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: A double-blind field study of 100,000 vaccinees three months to five years of age in Finland. Pediatrics 60:730–737
17. Granoff DM, Pandey JP, Boies E, Squires J, Munson RS Jr, Suarez B 1984 Response to immunization with *Haemophilus influenzae* type b polysaccharide pertussis vaccine and risk of *Haemophilus* meningitis in children with the Km(1) immunoglobulin allotype. J Clin Invest 74:1708–1714
18. Pandey JP, Fundenberg HH, Virella G, Kyong CU, Loadholt CB, Galbraith RM, Gotschlich EC, Parke JC Jr 1979 Association between immunoglobulin allotypes and immune responses to *Haemophilus influenzae* and meningococcus polysaccharides. Lancet 1:190–192
19. Ambrosino DM, Siber GR, Loghe E van, Schiffman G 1981 Increased antibody response to immunization with *Haemophilus influenzae* type b and pneumococcal capsular polysaccharide vaccines in adults with G2M(n) allotype. Pediatr Res 16:234A(abstr)
20. Scott MG, Nahm MH 1984 Mitogen induced human IgG subclass expression. J Immunol 133:2454–2460, 1984.
21. Hunter WM, Greenwood FC 1962 Preparation of iodine-131 labeled human growth hormone of high specific gravity. Nature 194:495–496
22. Morrell A, Skvaril F, Steinberg AG, Loghem E van, Terry WD 1972 Correlations between the concentration of the four subclasses of IgG and Gm allotypes in normal human sera. J Immunol 108:195–206
23. Vyas GN, Fudenberg HH, Pretty HM, Gold ER 1968 A new rapid method for genetic typing of human imunoglobulins. J Immunol 100:274–279
24. Pandey JP, Shannon BT, Arala-Chaves MP, Fudenberg HH 1982 Gm and Km frequencies in a Portugese population. Hum Genet 61:154–156
25. Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH 1975 SPSS: Statistical Package for the Social Sciences. McGraw Hill, New York
26. Buckley RH, Dees SC, O'Fallon WM 1968 Serum immunoglobulins: I. Levels in normal children and in uncomplicated childhood allergy. Pediatrics 41:600–611
27. Steinberg AG, Morell A, Skvaril F, Loghem E van 1973 The effect of Gm(23) on the concentration of IgG_2 and IgG_4 in normal human serum. J Immunol 110:1642–1645
28. Grubb R 1970 The genetic markers of immunoglobulins. Molecular Biology Biochemistry and Biophysics, Vol 9. Springer-Verlag, New York
29. Granoff DM, Boies E, Squires J, Pandey JP, Suarez B, Oldfather J, Rodey GE 1984 Interactive effect of genes associated with immunoglobulin allotypes and HLA specificities on susceptibility to *Haemophilus influenzae* disease. J Immunogenet 11:181–188
30. Kagnoff MG 1982 Two genetic loci control the murine immune response to A-gliadin, a wheat protein that activates coeliac sprue. Nature 296:158–160
31. Whittingham S, Mathews JD, Schanfield MS, Matthews JV, Tait BD, Morris PJ, Mackay IR 1980 Interactive effect of Gm allotypes and HLA-B locus antigens on the human antibody response to a bacterial antigen. Clin Exp Immunol 40:8–15
32. Granoff DM, Boies EG, Pandey J 1985 Further studies of the responses to *Haemophilus influenzae* type b vaccine in relation to the Km(1) and Gm(23) allotypes. Pediatr Res 19:294A, 1985