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IgG heavy chain allotypes (Gm) in autoimmune diseases

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SUMMARY

Serum samples from 100 patients with myasthenia gravis, 322 with Graves' disease, 113 with Hashimoto's disease, 132 with systemic lupus erythematosus (SLE), 192 with insulin-dependent juvenile diabetes mellitus, 83 with Behçet's syndrome, 73 with psoriasis vulgaris, 258 with leprosy, 112 with Duchenne progressive muscular dystrophy and 343 non-related normal controls were studied for Gm allotypes. The incidence of Gm phenotypes with Gm(2) was significantly increased in patients with myasthenia gravis, Graves' disease, Hashimoto's disease, and high in SLE patients. The $Gm^{1,2,21}$ haplotype was increased in patients with myasthenia gravis ($\chi^2=34{\cdot}08$, corrected $P<0{\cdot}001$), Hashimoto's disease ($\chi^2=12{\cdot}39$, corrected $P<0{\cdot}05$), Graves' disease ($\chi^2=8{\cdot}65$, corrected $P<0{\cdot}05$), and SLE ($\chi^2=6{\cdot}41$, $0{\cdot}1>$corrected $P>0{\cdot}05$). The total chi-square for the four different Gm haplotypes was significantly increased in patients with myasthenia gravis ($\chi^2=44{\cdot}46$, corrected $P<0{\cdot}001$), SLE ($\chi^2=20{\cdot}70$, corrected $P<0{\cdot}005$), Hashimoto's disease ($\chi^2=17{\cdot}03$, corrected $P<0{\cdot}025$), and Graves' disease ($\chi^2=11{\cdot}87$, corrected $P<0{\cdot}025$). Our data suggest the presence of Gm-associated pathogenic polygenes in certain autoimmune disorders.

INTRODUCTION

Among specific immune response (Ir) genes, two main groups have been distinguished in humans and experimental animals; they are the genes linked to the major histocompatibility complex (MHC), and those that are linked to the genes which control immunoglobulin (Ig) allotypic determinants of the heavy (H) chain linkage group (McDevitt & Benaceraff, 1969; Shreffler & Davis, 1975; Blomberg, Geckler & Weigert, 1972; Wells, Fudenberg & Mackay, 1971; Pandy *et al.*, 1979). Furthermore, it has been demonstrated that genes controlling the idiotypes of specific antibodies are linked to the IgG H-chain gene complex (Lieberman *et al.*, 1976; Pisetski, Piodran & Sachs, 1978). The association between certain HLA antigens and several diseases suggests the existence of pathogenic polygenes in linkage-disequilibrium with the MHC complex (Svejgaard *et*

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al., 1975). While only limited evidence is available regarding the association between Gm allotypes of the IgG H-chains and the immune response to certain antigens in humans (Pandy *et al.*, 1979), a search for a relationship between autoimmune diseases and genetic markers of Ig structural genes might be rewarding. Therefore, we studied the relationship between autoimmune disorders and Gm allotypes to examine the possible association between pathogenic factors and the Gm loci.

PATIENTS AND METHODS

Serum samples from 100 patients with myasthenia gravis, 322 with Graves' disease, 133 with Hashimoto's disease, 132 with SLE, 83 with Behçet's syndrome, 73 with psoriasis vulgaris, 192 with insulin-dependent juvenile diabetes mellitus (JOD), 258 with leprosy, 112 with Duchenne progressive muscular dystrophy (PMD) and 343 non-related normal blood donors were examined for Gm allotypes. The diagnosis of the diseases was based on the clinical findings, including history, physical examination and laboratory results. The definite cases were selected for Gm-typing. Gm-typing of the sera was as described previously (Matsumoto, Takatsuki & Matsunaga, 1968; Nakao *et al.*, 1980) using a haemagglutination inhibition test on microflocculation slides. The Gm reagents used, and the factors determined in this study are listed in Table 1. The nine phenotypes observed in the Japanese population may be grouped into four haplotypes, i.e. $Gm^{1,21}$, $Gm^{1,2,21}$, $Gm^{1,13,15,16}$ and $Gm^{1,3,5,13}$.

The frequencies of these four haplotypes in the present series were calculated as described previously (Kurczynski & Steinberg, 1967). The statistical significance of the difference in the frequencies between normal controls and patient group was calculated by the chi-square tests. Haplotype frequencies, agreement of the data with the expected Hardy–Weinberg distributions and total chi-square values were calculated using computer programs. The P values are corrected for the number of variables tested ($n=9$ for Gm phenotypes, $n=4$ for Gm haplotypes).

RESULTS

In all subjects, phenotypic frequencies expected on the basis of the Hardy–Weinberg equilibrium coincide with observed frequencies. In the 343 normal sera, the frequency of the nine Gm phenotypes was as follows (Table 2): Gm(1,21,13,15,16)—23·9%; Gm(1,21)—21·0%; Gm(1,2,21)—15·7%; Gm(1,21,3,5,13)—10·8%; Gm(1,2,21,13,15,16)—9·9%; Gm(1,3,5,13,15,16)—7·3%; Gm(1,2,21,3,

Table 1. Anti-Rho and anti-Gm sera used in Gm-typing

Gm			
Original	WHO*	Anti-Rho antibodies	Anti-Gm
a	1	2866	2618
x	2	2089	2984
f	3	Kover-Root, H0568	2871
b^1	5	2684	2490, 5875
b^3	13	2684	2933, 981
s	15	3068	2624
t	16	3068	2639, R-36
g	21	Eggen	R-1642, R-29

* The nomenclature is that proposed by the World Health Organization (WHO) meeting on human immunoglobulin allotypic markers (WHO, 1976).

Table 2. Gm phenotypes in patients with autoimmune and allied disorders*

Subjects	Number tested	1,21 a,g	1,21,13,15,16 a,g,b3,s,t	1,2,21 a,x,g	1,21,3,5,13 a,g,f,b1,b3	1,2,21,13,15,16 a,x,g,b3,s,t	1,3,5,13,15,16 a,f,b1,b3,s,t	1,13,15,16 a,b3,s,t	1,2,21,3,5,13 a,x,g,f,b1,b3	1,3,5,13 a,f,b1,b3
Normal controls	343	72 (21·0)	82 (23·9)	54 (15·7)	37 (10·8)	34 (9·9)	25 (7·3)	19 (5·5)	13 (3·8)	7 (2·0)
Myasthenia gravis	100	12 (12·0)	19 (19·0)	36 (36·0)	7 (7·0)	15 (15·0)	3 (3·0)	0 (0)	7 (7·0)	1 (1·0)
SLE	132	21 (15·9)	33 (25·0)	29 (21·9)	7 (5·3)	22 (16·6)	2 (1·5)	13 (9·8)	3 (2·2)	2 (1·5)
Graves' disease	322	64 (19·9)	60 (18·6)	74 (23·0)	31 (9·6)	39 (12·1)	15 (4·6)	21 (6·5)	15 (4·6)	3 (0·9)
Hashimoto's disease	133	23 (17·3)	22 (16·5)	30 (22·5)	10 (7·5)	25 (18·8)	11 (8·3)	4 (3·0)	6 (4·5)	2 (1·5)
JOD	192	42 (21·9)	44 (22·9)	37 (19·3)	21 (10·9)	11 (5·7)	10 (5·2)	20 (10·4)	5 (2·6)	2 (1·0)
Behçet's syndrome	83	15 (18·1)	20 (24·1)	19 (22·9)	8 (9·6)	6 (7·2)	4 (4·8)	7 (8·4)	2 (2·4)	2 (2·4)
Psoriasis vulgaris	73	17 (23·3)	15 (20·5)	16 (21·9)	5 (6·8)	8 (10·9)	4 (5·5)	5 (6·8)	1 (1·4)	2 (2·7)
Leprosy	258	56 (21·7)	54 (20·9)	54 (20·9)	27 (10·5)	19 (7·4)	16 (6·2)	20 (7·8)	6 (2·3)	6 (2·3)
Duchenne PMD	112	30 (26·8)	25 (22·3)	9 (8·0)	15 (13·4)	11 (9·8)	9 (8·0)	5 (4·5)	7 (6·2)	1 (0·9)

* Gm alleles are indicated by both the WHO (numerical) and the original (alphabetical) system. Figures in parentheses express results as a percentage.
JOD = insulin-dependent juvenile-onset diabetes mellitus, PMD = progressive muscular dystrophy.
Statistical analysis of Gm phenotypes is presented in Table 3.

Table 3. Comparison of frequencies in Gm phenotypes with or without Gm(2) allele.

Subjects	Number	Gm phenotype frequency	
		Gm phenotypes with Gm(2)	Gm phenotypes without Gm(2)
Normal controls	343	101 (29·4)	242 (70·5)
Myasthenia gravis	100	58 (58·0)*	42 (42·0)
SLE	132	54 (40·9)†	78 (59·1)
Graves' disease	322	128 (39·8)	194 (60·2)
Hashimoto's disease	133	61 (45·8)§	72 (54·2)
Insulin-dependent JOD	192	53 (27·6)	139 (72·4)
Behçet's syndrome	83	27 (32·5)	56 (67·5)
Psoriasis vulgaris	73	25 (34·2)	48 (65·7)
Leprosy	258	79 (30·6)	179 (69·3)
Duchenne PMD	112	27 (24·1)	85 (75·9)

Figures in parentheses express results as a percentage.
JOD = juvenile-onset diabetes mellitus, PMD = progressive muscular dystrophy.
* $\chi^2 = 26{\cdot}75$, corrected $P < 0{\cdot}005$.
† $\chi^2 = 5{\cdot}55$, corrected $P < 0{\cdot}1$.
‡ $\chi^2 = 7{\cdot}81$, corrected $P < 0{\cdot}05$.
§ $\chi^2 = 11{\cdot}50$, corrected $P < 0{\cdot}01$.

5,13)—3·8%; and Gm(1,3,5,13)—2·0%. The sera from myasthenia gravis patients, on the other hand, exhibited a Gm phenotype distribution different from that of the normal controls (Table 2) and Gm phenotypes with Gm(2) were significantly increased in these patients (Table 3). Furthermore, the frequency of Gm haplotypes in normals and patients showed these differences even more strikingly (Table 4). The Gm haplotype $Gm^{1,2,21}$ was significantly increased ($\chi^2 = 34{\cdot}08$, corrected $P < 0{\cdot}001$) in myasthenia gravis patients and the total chi-square for four different haplotypes was also significantly increased ($\chi^2 = 44{\cdot}46$, corrected $P < 0{\cdot}001$).

Increased frequencies of Gm phenotypes with Gm(2) were also demonstrated in the sera from patients with Graves' disease ($\chi^2 = 7{\cdot}81$, corrected $P < 0{\cdot}05$), Hashimoto's disease ($\chi^2 = 11{\cdot}50$, corrected $P < 0{\cdot}01$) and SLE ($\chi^2 = 5{\cdot}55$, corrected $P < 0{\cdot}1$) (Table 3) and the haplotype $Gm^{1,2,21}$ was significantly increased in Graves' disease ($\chi^2 = 8{\cdot}65$, corrected $P < 0{\cdot}05$) and Hashimoto's disease ($\chi^2 = 12{\cdot}39$, corrected $P < 0{\cdot}05$), and showed an increased frequency in SLE ($\chi^2 = 6{\cdot}41$, corrected $P > 0{\cdot}05$) (Table 4). The total chi-square for the four different Gm haplotypes in each disease was significantly increased in SLE (total $\chi^2 = 20{\cdot}70$, corrected $P < 0{\cdot}005$), Graves' disease (total $\chi^2 = 11{\cdot}87$, corrected $P < 0{\cdot}025$) and Hashimoto's disease (total $\chi^2 = 17{\cdot}03$, corrected $P < 0{\cdot}025$).

DISCUSSION

It is suggested that the development of an autoimmune disease requires an appropriate genetic background, and polygenes have been proposed to be related to disease susceptibility (Svejgaard *et al.*, 1975; Daussett & Svejgaard, 1977; Vladitiu & Rose, 1974; Farid *et al.*, 1979). Specific HLA antigens are found with increased frequency in organ-specific autoimmune diseases such as Graves' disease, Hashimoto's disease, insulin-dependent JOD, Addison's disease and myasthenia gravis (Svejgaard *et al.*, 1975; Vladitiu & Rose, 1974; Dawkins, 1978; Nakao *et al.*, 1978; Nerup *et al.*, 1977). In these disorders, the frequencies of the antigens HLA-B8 and DRw3 are increased in Caucasians. It is clear, however, that despite the observed associations between HLA antigens and autoimmune diseases, the relationships are not direct.

The existence of HLA-B8-, DRw3-negative patients with organ-specific autoimmune diseases

Table 4. Gm haplotypes in patients with autoimmune and allied disorders

Subjects	Number	Gm haplotype frequency				Total χ^{2}* (corrected P value)
		1,21 (a,g)	1,2,21 (a,x,g)	1,13,15,16 (a,b^3,s,t)	1,3,5,13 (a,f,b^1,b^3)	
Normal control	343	0·4503 ± 0·019† (154·4)‡	0·159 ± 0·014 (54·5)	0·2609 ± 0·1297 (89·5)	0·1297 ± 0·123 (42·2)	
Myasthenia gravis	100	0·3728 ± 0·0342 (37·3)	0·3472 ± 0·0337§ (34·7)	0·185 ± 0·0275 (18·5)	0·095 ± 0·0207 (9·5)	44·46 (<0·001)
SLE	132	0·3958 ± 0·0301 (52·2)	0·2292 ± 0·0259¶ (30·2)	0·3144 ± 0·0286 (41·5)	0·0606 ± 0·0147 (8·0)	20·70 (<0·005)
Graves' disease	322	0·4314 ± 0·0195 (138·9)	0·2223 ± 0·0164** (71·6)	0·2422 ± 0·0169 (77·9)	0·104 ± 0·012 (33·5)	11·87 (<0·025)
Hashimoto's disease	133	0·3773 ± 0·0297 (50·2)	0·2581 ± 0·0268†† (34·3)	0·2481 ± 0·0265 (33·0)	0·1165 ± 0·0197 (15·5)	17·03 (<0·025)
Insulin-dependent JOD	192	0·471 ± 0·0255 (90·4)	0·1514 ± 0·0183 (29·1)	0·2734 ± 0·0227 (52·5)	0·1042 ± 0·0156 (20·0)	2·24 (n.s.)
Behçet's syndrome	83	0·4444 ± 0·0386 (36·9)	0·1821 ± 0·03 (15·1)	0·2651 ± υ·0343 (22·0)	0·1084 ± 0·0241 (9·0)	1·10 (n.s.)
Leprosy	258	0·4625 ± 0·0219 (119·3)	0·1693 ± 0·0165 (43·7)	0·250 ± 0·0191 (64·5)	0·1182 ± 0·0142 (30·5)	0·94 (n.s.)
Psoriasis vulgaris	73	0·4607 ± 0·0417 (33·6)	0·190 ± 0·0325 (13·9)	0·2534 ± 0·036 (18·5)	0·0959 ± 0·0244 (7·0)	2·19 (n.s.)
Duchenne PMD	112	0·482 ± 0·0334 (54·0)	0·1252 ± 0·0221 (14·0)	0·2455 ± 0·0288 (27·5)	0·1473 ± 0·0237 (16·5)	2·85 (n.s.)

* Total chi-square is calculated for the four different haplotypes in each disease. Statistical significance is shown as corrected P value. n.s. = Not significant.

† Mean frequency ± s.e.

‡ The estimated number of Gm haplotypes is calculated by multiplying the total number of tested sera with the frequency of the Gm haplotype (× 100).

JOD = juvenile-onset diabetes mellitus; PMD = progressive muscular dystrophy.

Statistical significance between the Gm haplotype of normal controls and that of patients is calculated by the chi-square test: § $\chi^2 = 34{\cdot}08$, corrected $P < 0{\cdot}001$; ¶ $\chi^2 = 6{\cdot}41$, corrected $P > 0{\cdot}05$; ** $\chi^2 = 8{\cdot}65$, corrected $P < 0{\cdot}05$; †† $\chi^2 = 12{\cdot}39$, corrected $P < 0{\cdot}05$.

and the lack of any association with HLA-B8, DRw3 in Japanese patients (Nakao *et al.*, 1978; Dawkins, 1978; Wakisaka *et al.*, 1976) support this view. Therefore, the existence of a polygenic background in autoimmune diseases represents a reasonable hypothesis in explaining disease susceptibility. Previously, there has been only limited evidence to suggest an association between Gm allotypes and disease susceptibility (Yount *et al.*, 1970; Morell *et al.*, 1977; Farid *et al.*, 1977). Whereas the 6th (Smith & Hirshhorn, 1978) or 14th (Croce *et al.*, 1979) chromosome have been proposed as the locus of genes for human IgG H-chain, the linkage of HLA and Gm loci has been excluded (Weitkamp, May & Johnston, 1975). Although the Gm genes may be in the 6th chromosome, they cannot be very close to the HLA region (Bender *et al.*, 1979; Lamm *et al.*, 1975). Our data, therefore, suggest the existence of disease-susceptible genes linked to Gm genes and different from the HLA-linked susceptibility genes. Our hypothesis is supported by our study of myasthenia gravis (Nakao *et al.*, 1980), in which the haplotype $Gm^{1,2,21}$ was found to be associated more significantly with Japanese myasthenics with *thymoma*, whereas HLA-DRw4 is increased in myasthenic patients with *hyperplasia* (Wakisaka, Aizawa & Itakura, 1979). Furthermore, there were no associations between Gm haplotypes and Behçet's syndrome (associated with HLA-B5) or insulin-dependent JOD (associated with HLA-Bw54, DRw4) (Ohno *et al.*, 1978; Okimoto *et al.*, 1978; Wakisaka *et al.*, 1976).

Our data suggest that Gm genes *per se* are not always necessary for the development of the diseases, but rather that such genes, or polygenes, are in linkage-disequilibrium with Gm genes. Therefore, attention should be focused on the role of Gm-associated pathogenic polygenes which may be related to the genes that control idiotype regulation (Lieberman *et al.*, 1976; Pisetski *et al.*, 1978), Ir-genes (Wells *et al.*, 1971; Pandy *et al.*, 1979), or the genes governing B cell receptors and B cell alloantigens (Eardley *et al.*, 1979; Subbarao, Ahmed & Paul, 1979; Rubin, Hertel-Wulff & Kimura, 1979). Although further investigations are required, the present data suggest a definite polygenic background to certain autoimmune diseases.

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REFERENCES

BENDER, K., MÜLLER, C.R., SCHMIDT, A., STROHMAIER, U. & WIENKER, T.F. (1979) Linkage studies on the human Pi, Gm, GLO and HLA genes. *Hum. Genet.* **49,** 159.

BLOMBERG, B., GECKLER, W.R. & WEIGERT, M. (1972) Genetics of the antibody response to dextran in mice. *Science*, **177,** 178.

CROCE, C.M., SHANDER, M., MARTINIS, J., CICUREL, L., D'ANCONA, G.G., DOLBY, T.W. & KOPROWSKI, H. (1979) Chromosomal location of the genes for human immunoglobulin heavy chains. *Proc. Natl. Acad. Sci. USA*, **76,** 3416.

DAUSSETT, J. & SVEJGAARD, A. (1977) *HLA and Disease*. Munksgaard, Copenhagen.

DAWKINS, R.L. (1978) Myasthenia gravis. In *Histocompatibility Testing 1977* (ed. by W. F. Bodmer *et al.*), p. 224. Munksgaard, Copenhagen.

EARDLEY, D.D., SHEN, F.W., CANTOR, H. & GERSHON, R.K. (1979) Genetic control of immunoregulatory circuits. Genes linked to the Ig locus govern communication between regulatory T-cell sets. *J. exp. Med.* **150,** 44.

FARID, N.R., SAMPSON, L., NOEL, E.P., BARNARD, J.M., MANDEVILLE, R., LARSEN, B. & MARSHALL, W.H. (1979) A study of human leukocyte D locus related antigens in Graves' disease. *J. clin. Invest.* **63,** 108.

FARID, M.K., SAMPSON, L., NOEL, E.P. & MARSHALL, W.H. (1977) Gm phenotypes in autoimmune thyroid diseases. *J. Immunogenet.* **4,** 429.

KURCZYNSKI, T. & STEINBERG, A.G. (1967) A general program for maximum likelihood estimation of gene frequencies. *Am. J. Hum. Genet.***19,** 178.

LAMM, L.U., THORSEN, I.L., PETERSEN, G.B., JORGENSEN, J., HENNINSEN, K., BECH, B. & KISSMEYER-NIELSEN, F. (1975) Data on HL-A linkage group. *Ann. Hum. Genet.* **38,** 383.

LIEBERMAN, R., POTTER, M., HUMPHREY, W., JR & CHEN, C.C. (1976) Idiotypes of inulin-binding antibodies and myeloma proteins controlled by genes linked to the allotype locus of the mouse. *J. Immunol.* **117,** 2105.

MCDEVITT, H.O. & BENACERAFF, B. (1969) Genetic control of specific immune response. *Adv. Immunol.* **11,** 31.

MATSUMOTO, H., TAKATSUKI, K. & MATSUNAGA, E. (1968) Gm factors in Japan: populations and family history. *Jpn J. Hum. Genet.* **13,** 10.

MORELL, A., KASER, H., SCHERZ, R. & SKAVRIL, S. (1977) Evidence for an association between uncommon Gm phenotypes and neuroblastoma. *Lancet*, **i,** 23.

NAKAO, Y., KISHIHARA, M., BABA, Y., KUMA, K., FUKUNISHI, T. & IMURA, H. (1978) HLA antigens in autoimmune thyroid disease. *Arch. Intern. Med.* **138,** 567.

NAKAO, Y., MATSUMOTO, H., MIYAZAKI, T., NISHITANI, H., OHTA, K., FUJITA, T. & TSUJI, K. (1980) Gm allotypes in patients with myasthenia gravis. *Lancet*, **i,** 677.

NERUP, J., CATHELINEAU, C., SEIGNALET, J. & THOMSEN, M. (1977) HLA and endocrine disease. In *HLA and Disease* (ed. by J. Daussett and A. Svejgaard), p. 149. Munksgaard, Copenhagen.

OHNO, S., ASANIMA, T., SUGIURA, S., WAKISAKA, A., AIZAWA, M. & ITAKURA, K. (1978) HLA Bw51 and Behçet's disease. *JAMA*, **240,** 529.

OKIMOTO, K., JUJI, T., ISHIBA, S., MARUYAMA, H., TOHYAMA, H. & KOSAKA, K. (1978) HLA Bw54 antigen in juvenile onset diabetes mellitus in Japan. *Tissue Antigens*, **11,** 418.

PANDY, J.P., FUDENBERG, H.H., VIRELLA, G., KYONG, C.U., LOADHOLT, C.B. & GALBRAITH, R.M. (1979) Association between immunoglobulin allotypes and immune response to *Haemophilus influenzae* and meningococcus polysaccharides. *Lancet*, **i,** 190.

PISETSKI, D.S., PIODRAN, S.E. & SACHS, D.H. (1978) Genetic control of the immune response to staphylococcal nuclease. *J. Immunol.* **122,** 842.

RUBIN, B., HERTEL-WULFF, B. & KIMURA, A. (1979) Alloantigen specific idiotype-bearing receptors on mouse T lymphocytes. I. Specificity characterization and genetic association with the heavy-chain IgG allotype. *J. exp. Med.* **150,** 307.

SHREFFLER, D.C. & DAVIS, D.S. (1975) The H-2 major histocompatibility complex and immune response region: genetic variations, function and organization. *Adv. Immunol.* **20,** 125.

SMITH, M. & HIRSHHORN, K. (1978) Location of the genes for human heavy chain immunoglobulin to chromosome 6. *Proc. Natl. Acad. Sci. USA*, **75,** 3367.

SUBBARAO, B., AHMED, A. & PAUL, W.E. (1979) Lyb-7, a new B cell alloantigen controlled by genes linked to the IgG locus. *J. Immunol.* **122,** 2279.

SVEJGAARD, A., PLATZ, P., RYDER, L.P., NIELSEN, L.S. & THOMSEN, M. (1975) HLA and disease association—a survey. *Transplant. Rev.* **22,** 3.

VLADITIU, A.O. & ROSE, N.R. (1974) HL-A antigens and susceptibility to disease. *Immunogenetics*, **1,** 305.

WAKISAKA, A., AIZAWA, M. & ITAKURA, K. (1979) HLA-DR antigens in patients with myasthenia gravis. *Jpn J. clin. Immunol.* **2,** 28.

WAKISAKA, A., AIZAWA, M., MATSUMURA, N., NAKAGAWA, E., ITAKURA, K., OKUNO, K. & WAGATSUMA, Y. (1976) HLA and juvenile onset diabetes mellitus in the Japanese. *Lancet*, **ii,** 970.

WEITKAMP, L.R., MAY, A.G. & JOHNSTON, E. (1975) The relationship of HL-A with other genetic marker systems. *Hum. Hered.* **49,** 159.

WELLS, J.V., FUDENBERG, H.H. & MACKAY, I.R. (1971) Relation of the human antibody response to flagellin to Gm genotypes. *J. Immunol.* **107,** 1505.

WHO (1976) Meeting on human immunoglobulin allotypic markers. Review of the notation for the allotypic and related markers of human immunoglobulins. *J. Immunol.* **117,** 1056.

YOUNT, W.J., HONG, R., SELIGMAN, M., GOOD, R.A. & KUNKEL, H.G. (1970) Imbalance of gammaglobulin subgroups and gene defects in patients with primary hypo-gammaglobulinemias. *J. clin. Invest.* **49,** 1957.