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Recommended Citation

Pandey, Janardan P.; Goust, Jean-Michel; Salier, Jean-Philippe; and Fudenberg, H. Hugh, "Immunoglobulin G Heavy Chain (Gm) Allotypes in Multiple Sclerosis" (1981). *MUSC Faculty Journal Articles*. 74. <https://medica-musc.researchcommons.org/facarticles/74>

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Immunoglobulin G Heavy Chain (Gm) Allotypes in Multiple Sclerosis

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ABSTRACT Serum samples from 70 Caucasian patients with multiple sclerosis were typed for nine Gm markers. Significant association was found with the Gm 1,17;21 phenotype, and the relative risk for individuals with this phenotype was calculated at 3.6. The data indicate that Caucasians positive for Gm 1,17;21 are almost four times more likely to develop multiple sclerosis than those without this phenotype.

INTRODUCTION

Several observations have indicated that genetic factors play an important role in predisposition to multiple sclerosis (MS).¹ Concordance is higher in monozygotic than in dizygotic twins, and the disease is ~20 times more frequent among relatives of probands than in the general population (1). Several studies have shown that human leukocyte antigens (HLA) A3, B7, Dw2, and DRw2 are present significantly more often in MS patients than in normal individuals (2). The most consistent finding in MS patients, along with demyelination, is intrathecal (3) and systemic (4) production of immunoglobulin (Ig) G of restricted heterogeneity. In the cerebrospinal fluid the IgG producing an oligoclonal pattern is predominantly of IgG1 subclass (5, 6), although IgG2 has also been detected (7). It has been suggested that this abnormality may be caused by a basic disorder of immunoglobulin-producing cells (8, 9), such as defective immunoregulation and/or overrepresentation of some B cell clones. Because of the observed anomalies in IgG production, it seemed of interest to ascertain whether the frequencies of certain Gm phenotypes (genetic markers of IgG) in these patients differ from those in the normal population. A significant association was found between the Gm 1,17;21 phenotype and MS.

Received for publication 27 February 1981 and in revised form 23 March 1981.

¹ *Abbreviation used in this paper:* MS, multiple sclerosis.

METHODS

Patients. Serum samples from 50 MS patients and 50 patients with other neurological diseases, coded at random, were shipped from the Human Neurospecimens Bank (Dr. W. W. Tourtelotte, Wadsworth Veterans Administration Hospital, Los Angeles, Calif.); the code was held by Dr. W. Reynolds (National Multiple Sclerosis Society, New York), and the diagnoses remained unknown to the investigators until the end of the study. Serum samples from 20 additional patients living in the area of Charleston, S. C., were also studied. The diagnosis of MS was established according to widely accepted criteria (10).

Immunoglobulin allotyping and statistical analyses. Our standard hemagglutination inhibition technique (11) was used to detect Gm antigens 1,2,3,17;5,6,13,14, and 21. Statistical significance of the results was determined by use of a 2×2 contingency chi-square, and the strength of association (12) was measured by relative risk (x) using Woolf's formula: $x = \frac{pd(1 - pc)}{(1 - pd)pc}$, where pd and pc are the frequencies of the phenotype in patients and control individuals, respectively. The relative risk indicates how many times more frequent the disease is in individuals carrying the haplotype than in those lacking it. P values were corrected for the number of comparisons made.

RESULTS

Fifteen patients were excluded from statistical analysis. Eight of these had nonspecific anti-IgG antibodies, and after absorption of the antibody the remaining serum was insufficient to type for all the markers. Two patients were excluded because they were Black, three because of mixed ancestry, and two because they had a very unusual Gm phenotype, Gm 2,3;5,13,14. The genetic transmission of the haplotype(s) responsible for the latter phenotype is being studied in family members of these two patients. (Different races have a distinct array of Gm haplotypes, and therefore it is imperative to match patients and controls for ethnicity.) The Gm phenotypes of the remaining 55 patients were compared with those of 906 control individuals.

Five Gm phenotypes, commonly present in Caucasians, were found in the MS patients (Table I).

TABLE I
Distribution of Gm Phenotypes in Multiple Sclerosis Patients
(n = 55) and Normal Controls (n = 906)

Gm phenotype	MS patients	Normal controls
	Percent incidence	
1,17;21	11*	3
1,2,17;21	4	4
3;5,13,14	44	47
1,3,17;5,13,14,21	29	31
1,2,3,17;5,13,14,21	13	14

* Chi-square = 8.30; $P = 0.004$; relative risk = 3.6.

The frequency of Gm 1,17;21 was significantly increased in the patient group as compared with normal individuals. The frequencies of various phenotypes in our control population were similar to those reported by other investigators for populations of several thousand individuals (13).

The chi-square for Gm 1,17;21 was significant at the 0.004 level, but since five comparisons were made (of which only this one was significant), the chi-square should be considered as significant at the $5 \times 0.004 = 0.02$ level. This overall significance level, sometimes called the "experimentwise error rate," is very conservative; Hartley (14) has recommended 0.1 or higher levels for rejection points.

DISCUSSION

This investigation is the first report of an association between a Gm phenotype and MS. The frequency of the Gm 1,17;21 phenotype was significantly increased ($P = 0.02$) in patients with MS as compared with normal individuals. Gm 1 and 17 are located on the constant region of IgG1, whereas 21 is on the constant region of IgG3, but they are inherited together as a complex (haplotype) because of a strong linkage disequilibrium between alleles coding for these markers in Caucasians. The most probable genotype of the Gm 1,17;21 phenotype is Gm 1,17;21/Gm 1,17;21. The only other phenotype involving the Gm 1,17;21 haplotype is 1,3,17;5,13,14,21, for which the most probable genotype is Gm 1,17;21/Gm 3;5,13,14. Since this phenotype is not associated with MS, it follows that homozygosity of the Gm 1,17;21 haplotype is required for predisposition to MS. The relative risk of 3.6 indicates that Caucasians with this phenotype are about four times as likely to develop MS as those without it.

Both population and family studies suggest the involvement of HLA antigens in the etiology and pathogenesis of MS. However, different HLA genotypes have been found to be associated with MS

in different ethnic groups. For instance, increased frequencies of A3, B7, Dw2, and DRw2 in populations originating from Northern Europe (15), lower frequencies of A3 and B7 in Israeli patients than in controls (16), no increase in A3 and B7 in Japanese (17), and a slight increase in B7 in Black American (18) patients were reported. These ethnic differences in the association of HLA and MS indicate that the locus or loci responsible for the susceptibility to MS is not HLA per se but another locus whose alleles are in linkage disequilibrium with the HLA loci. A recent study (19) suggests that MS may result from an epistatic interaction between two MS susceptibility genes, only one of them located in or near the HLA complex. The data reported in the present investigation suggest that in addition to an HLA-linked gene, another gene whose alleles are in linkage disequilibrium with the Gm 1,17;21 complex may also be involved in the pathogenesis of MS, although a lod score analysis involving several MS families must be performed to determine the linkage relationship of the MS susceptibility gene with the Gm complex. Moreover, our data suggest that the putative Gm-linked MS susceptibility gene probably is recessive rather than dominant, because only the homozygous Gm 1,17;21 phenotype and not the heterozygous Gm 1,17;21/3;5,13,14 is associated with predisposition to the disease.

The HLA complex on chromosome 6 most likely includes immune response genes (20), which presumably would exert their influence through regulatory T lymphocytes as already shown in mice (21). The imbalance in T cell subsets reported in several studies (9, 22–25) of MS patients may be related to the predominance of certain HLA phenotypes. Another category of immune response genes linked to the structural loci coding for immunoglobulin allotypes (Gm), probably on chromosome 14 (26), may also be involved in the pathogenesis of MS, as suggested by this investigation, and may be associated with B cell hyperactivity as recently reported (9). It is noteworthy that two of the allotypes associated with a greater relative risk for MS, namely, Gm 1 and 17, are both found on IgG1, which is the predominant IgG subclass in cerebrospinal fluid from MS patients (5, 6). This particular haplotype has also been shown by three independent studies (27–29) to be associated with an augmented antibody response to *Salmonella adelaide*. Whether or not it may also be associated with the higher antiviral antibody responses documented in MS patients (30) deserves investigation.

Growing evidence indicates that the genes from the major histocompatibility complex and those coding for the constant region of immunoglobulin heavy chains somehow interact to produce an immune response. For instance, Whittingham et al. (29) have reported that the immune response to monomeric flagellin is dependent

upon the interaction between major histocompatibility complex- and Gm-linked genes. Similar cooperation may also occur in pathological conditions. Indeed, Berman and Patrick (31) have identified two loci in mice that determine susceptibility to experimental myasthenia gravis; i.e., highly susceptible strains have both the H-2^b and Ig-1^b phenotypes, coded within the major histocompatibility complex on chromosome 17 and within the structural gene for immunoglobulin heavy chains on chromosome 12, respectively. However, the influence of the H-2^b phenotype on disease susceptibility is greater than the influence of the Ig-1^b allotype. More recently, in humans, Whittingham et al. (32) have shown that in the presence of HLA-B8, genes linked to the Gm 1,2,17;21 complex are important contributory causes of autoimmune chronic active hepatitis. Compared with the low risk group (controls who were HLA-B8 negative and Gm 1,2,17;21 positive), the relative risk was 15 times greater in subjects with HLA-B8 but lacking Gm 1,2,17;21 and 39 times greater in subjects with both Gm 1,2,17;21 and HLA-B8. A similar situation may exist in MS, which has been reported (32) to be more severe in patients with both the A3-B7 phenotype and oligoclonal bands of IgG in their cerebrospinal fluid than in patients with only one of these markers. Studies aimed at evaluating the interactive effect of HLA and Gm loci in MS are currently in progress.

ACKNOWLEDGMENT

We thank Sharon Jackson for excellent technical assistance and Charles L. Smith for excellent editorial assistance.

Publication No. 423 from the Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina. Research supported in part by U. S. Public Health Service grants NS-16269, HD-09938, and CA-25746, and National Multiple Sclerosis Society grant RG-1167B2.

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