Human Genome Epidemiology (HuGE) Review

HLA-DR15 Haplotype and Multiple Sclerosis: A HuGE Review

Hollie Schmidt1, Dhelia Williamson2, and Allison Ashley-Koch3

1 Accelerated Cure Project for Multiple Sclerosis, Waltham, MA.
2 Division of Health Studies, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.
3 Center for Human Genetics, Duke University Medical Center, Durham, NC.

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An association between multiple sclerosis (MS) and the human leukocyte antigen (HLA) complex, a dense cluster of genes on the short arm of chromosome 6, was first noted over 30 years ago. In Caucasian populations of Northern European descent, the DR15 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) has been hypothesized to be the primary HLA genetic susceptibility factor for MS. However, studies of other populations have produced varying results. Thus, the authors reviewed the literature for articles on the association between the DR15 haplotype and MS. They identified 72 papers meeting the inclusion criteria: human genetic studies written in English that were published between 1993 and 2004 and that reported allele frequencies for HLA-DRB1*1501, HLA-DQA1*0102, or HLA-DQB1*0602 or the frequency of the DRB1*1501-DQA1*0102-DQB1*0602 haplotype. Most of the studies identified used a case-control design (n = 60), while the remainder used a family-based design (n = 22). In most of these papers, investigators reported a higher frequency of the DR15 haplotype and/or its component alleles among MS cases than among controls. However, the authors’ confidence in these results is tempered by factors related to study design that may have biased the outcomes.

epidemiology; genetics; HLA antigens; HLA-DR15; multiple sclerosis

Abbreviations: HLA, human leukocyte antigen; MS, multiple sclerosis; PCR, polymerase chain reaction.

Editor's note: This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm).

GENE

The human leukocyte antigen (HLA) complex is a dense cluster of genes located on the short arm of chromosome 6 at p21.3. It encompasses approximately 3,500 kilobases of DNA and contains at least 150 genes (1), most of which encode proteins that function in the immune system. Located within the HLA complex, in a section called the class II subregion, are the genes for the classical HLA class II molecules. These molecules participate in the recognition and presentation of antigens to T cells and are primarily expressed by antigen-presenting cells such as macrophages, B cells, and dendritic cells. Class II molecules have been associated with susceptibility to several autoimmune or immune-mediated disorders, including multiple sclerosis (MS) (2). It has been speculated that this association stems from the ability of class II molecules to bind and present certain self-peptides.

There are three HLA class II molecules: DP, DQ, and DR. Each is a combination of two proteins, an alpha chain and a beta chain, which associate inside the cell, bind to a peptide, and travel to the cell surface for presentation of the
peptide to T cells. Each alpha or beta chain is encoded by a separate gene and, with the exception of the DR alpha chain, there are multiple genes and/or pseudogenes for each class II chain.

**GENE VARIANTS**

The *HLA* region is characterized by considerable genetic diversity. For some of the genes in this region, hundreds of alleles have been described. In the *HLA* class II subregion, scientists to date have identified 30 *DQA1* alleles, 60 *DQB1* alleles, and 388 *DRB1* alleles (European Bioinformatics Institute IMGT/HLA Database (http://www.ebi.ac.uk/imgt/hla/)). This degree of polymorphism is thought to contribute to a robust immune capability at the population level, by equipping populations with the ability to respond to a broad variety of pathogenic antigens. Because of extensive linkage disequilibrium in the *HLA* region, these alleles are not randomly distributed among individuals in a population; instead, gene variants tend to be associated with other variants in a set of common haplotypes. Nomenclature for *HLA* class II variants typically consists of the gene locus (e.g., *DRB1*), followed by an asterisk and four digits (e.g., *DRB1*1501). The first two digits correspond to the gene’s serologic type, and the last two digits specify a unique allele within that serologic group.

The *DR15* haplotype (*DRB1*1501-*DQA1*0102-*DQB1*0602) and its individual alleles have been linked with a number of diseases and conditions, such as narcolepsy, systemic lupus erythematosus, and, most prominently, MS. *DR15* has been investigated as a genetic risk factor for MS in case-control and family-based studies from countries around the world. On occasion, other *HLA* alleles and haplotypes have also produced evidence of association with MS in certain populations; however, none have yet been examined to the same extent as has *DR15*.

We reviewed the literature for an association between the *DRB1*1501-*DQA1*0102-*DQB1*0602 haplotype and MS. We searched MEDLINE using the keywords “HLA” and an asterisk as such in the tables and excluded from the figures. Discrepancies that could not be resolved were indicated as such in the tables and excluded from the figures.

**Case-control studies**

Of the 60 case-control studies that met our criteria (2, 27–85), 48 examined the association between *DRB1*1501 and MS, 21 studied *DQA1*0102, 29 studied *DQB1*0602, and 24 analyzed the *DRB1*1501-*DQA1*0102-*DQB1*0602 haplotype (Web table 2). The majority of studies (57 percent; *n* = 34) were conducted in Europe, although populations in Asia, South America, North America, and Australia were also evaluated. In the papers that specified subject selection, cases were generally selected from hospitals or neurology clinics, while controls were often convenience samples (i.e., blood donors, hospital staff, or other groups that may not have truly reflected the population at risk). The majority of these studies utilized polymerase chain reaction (PCR) for genotyping.

Figures 1–4 present the frequencies of positivity for the risk allele or haplotype (i.e., persons possessed either one copy or two copies of the allele or haplotype under study) evaluated in these case-control studies, for each of the individual alleles and the *DR15* haplotype. The results are also presented in tabular form in Web table 2. Genotype frequencies (i.e., the prevalence of the allele or haplotype when each genotype from each subject is counted individually) were reported in some articles and are flagged accordingly in the tables but are not included in the figures. Some of the studies contained discrepancies that complicated the task of identifying allele or haplotype frequencies. When discrepancies were found, we contacted the paper’s authors to ask for a resolution, and in most cases they were able to provide one. Discrepancies that could not be resolved were indicated as such in the tables and excluded from the figures.

**DRB1*1501**. In nearly all of the studies that analyzed the *DRB1*1501 allele, researchers found the frequency of this allele to be considerably higher in cases than in controls (Web table 2; figure 1). For example, Masterman et al. (56) evaluated this allele in a Swedish population and reported a frequency of 61 percent in MS cases as compared with 31 percent in controls (*p* < 0.0001; odds ratio = 3.5). This over-representation of *DRB1*1501 in MS cases was seen not only in studies of primarily Caucasian populations but also in studies of other ethnic groups such as Japanese and Middle Eastern populations. In the Japanese studies, significantly higher frequencies of this allele were typically found only among patients with “conventional” MS (see the discussion of optoclinical MS versus conventional MS in the “Associations” section below).

In a few studies, investigators reported slightly lower prevalence of *DRB1*1501 in MS cases than in controls (70, 85) and/or low frequencies of this allele (<10 percent) in both cases and controls (70, 73, 76, 80). These studies were all performed in non-European populations—Chinese, Iranians, African Americans, and Afro-Brazilians—reflecting
genetic heterogeneity across populations at this locus. However, low prevalence of \( DRB1^*1501 \) did not necessarily indicate lack of association; Oksenberg et al. (80) reported a significant association of \( DRB1^*1501 \) in African Americans with MS (\( p = 0.03; \) odds ratio = 1.7).

\( DQA1^*0102 \). In most of the studies that evaluated the \( DQA1^*0102 \) allele, investigators reported a higher prevalence in MS cases than in controls (Web table 2; figure 2). However, not all of these increased frequencies achieved statistical significance (32, 83). In addition, as with the \( DRB1^*1501 \) allele, there were exceptions to the pattern of increased prevalence in MS cases. In two studies performed on the Mediterranean island of Sardinia, researchers reported lower frequencies of \( DQA1^*0102 \) in MS cases than in controls (54, 75); this may be due to the greater influence of other \( HLA \) alleles in determining MS risk in Sardinians. The Sardinian population has historically been well isolated from other European populations, and as a result this group possesses a genetic structure that differs at many loci, including the \( HLA \) region, from that of other Caucasian groups (86). A slightly lower prevalence of \( DQA1^*0102 \) was also detected in Chinese cases versus controls (85).
**DQB1*0602.** As with the two other alleles, **DQB1*0602** was consistently found to be more prevalent in cases than in controls in European and Caucasian populations, although some studies failed to detect a significant association, particularly those conducted in Southern European regions such as Sardinia (54, 75) and northeastern Italy (68) (Web table 2; figure 3). **DQB1*0602** was found to be significantly associated with MS in certain non-Caucasian populations, including African Americans (80) and Martinicans (81). None of the Asian or Middle Eastern populations studied had a significantly greater frequency of the **DQB1*0602** allele in cases than in controls, with the exception of Ashkenazi Jews \( (p = 0.014; \text{relative risk} = 2.62) \) (77) and Turks \( (p = 0.005; \text{odds ratio} = 3.2) \) (83).

**DR15 haplotype.** Consistent with the results for its component alleles, the **DR15** haplotype was found to be more prevalent in cases than in controls in studies of European Caucasian populations, with the exception of the Sardinian study (75) (Web table 2; figure 4). The **DR15** haplotype was also found to be significantly associated with MS in Asian Indians residing in England (49), in Ashkenazi and non-Ashkenazi Jews living in Israel (77), in African Americans (80), and in Turks (83). Higher MS prevalence estimates were also identified in Chinese (72), Iranian (70), and Israeli (76) populations, but these differences did not reach statistical significance.

**Family-based studies**

We also examined 22 family-based studies that met our search criteria (Web table 3) (29–31, 34, 47, 54, 55, 64, 76, 80, 87–98). In general, results of the family-based studies were consistent with those of the case-control studies. In data sets composed of families of Caucasian descent, there is considerable evidence for a role of the **DR15** haplotype. In some studies, there is evidence for both linkage and association (34, 90, 92), while in others there is only evidence for association (47). Also consistent with the case-control studies, it appears that in Sardinians, other **HLA** alleles may have a greater influence than the **DR15** haplotype and alleles in determining MS risk (54, 55). Several groups of investigators who examined both case-control and family-based data sets (29, 47, 54) concluded that the association with **HLA** class II was present in sporadic MS cases as well as in familial MS cases. This suggests that a common genetic etiology is involved in both forms of MS. Furthermore, many researchers observed evidence for genetic heterogeneity in the family-based samples (34, 90, 92), which is consistent with the hypothesis that MS has a complex genetic etiology involving multiple genes.

**DISEASE**

MS is the most common demyelinating disorder of the brain and spinal cord. The etiology of the disease is unknown, although MS is often suggested to involve a T-lymphocyte-mediated autoimmune attack on the myelin sheaths of the central nervous system. The disease progression is variable, and the clinical course ranges from relatively benign to aggressive with rapid progression in disability from onset. There are three main types of MS: relapsing-remitting, primary progressive, and secondary progressive. Symptoms of
MS include difficulty with walking, abnormal sensations such as numbness, pain and loss of vision due to optic neuritis, tremor, incoordination, slurred speech, sudden onset of paralysis similarly to stroke, and a decline in cognitive function. MS is usually not fatal, but severe disability and decreased quality of life are common.

Age, gender, race/ethnicity, and geography

MS preferentially affects women, young adults, and Caucasians (99). Approximately twice as many women are affected by MS as men (100). MS can be diagnosed at any age, but the age of disease onset typically ranges from 10 years to 59 years, with incidence rising steadily from the teens to age 35 years and declining gradually thereafter (99). Men usually have a slightly later age of onset than women. Caucasians of Northern and Central European ancestry are at highest risk of developing MS, although people of all races and ethnicities may be affected (99). In general, the prevalence of MS varies with latitude, with disease estimates increasing with increasing latitude.

Potential risk factors

Genetic susceptibility. In the past two decades, MS genetic research has focused on the apparent immune mechanism of the disease and the involvement of the HLA region, the immunoglobulin heavy chain, T-cell receptor, tumor necrosis factor, and myelin basic protein loci (101, 102). Genetic association and linkage analysis methods have been used to examine the role of these genes in the risk of MS, with conflicting results. Aside from the HLA genes, there have been no consistently replicated associations with any candidate genes (103). In addition, nearly 50 genome-wide screens have been conducted in which multiple markers located across the genome are evaluated in MS families or in MS patients and controls. Results from these studies have failed to converge on a single locus or even a consistent set of loci. These findings suggest that a single-locus model for MS is unlikely and that MS may actually be a collection of diseases with different genetic etiologies.

Viruses. Several viruses have been investigated for an association with MS susceptibility, including canine distemper, measles, herpes, rubella (German measles), human T-cell lymphotrophic virus I, and Epstein-Barr (104–106). However, none of these viruses has been conclusively associated with MS etiology. Because the relapsing-remitting phase of MS in many ways is analogous to the recurrence of herpesvirus infections, a herpesvirus is an attractive etiologic candidate. Furthermore, the timing of viral infections may prove important in MS risk; it has been postulated that infection early in life may protect against MS, and, conversely, that later infection in a mature immune system may increase risk.

Ultraviolet light. The distribution of MS prevalence by latitude has led to speculation that climate factors could be associated with disease risk. In particular, ultraviolet radiation, which is strongly associated with latitude, has been suggested to be a protective factor because of its immunosuppressive properties, possibly mediated by the effect of sunlight on melatonin or vitamin D synthesis (107–110).

Other environmental factors. A number of other environmental exposures have been investigated as possible etiologic factors for MS, including metals, solvents, and diet. However, findings have been inconsistent (111–115).

ASSOCIATIONS

An association between MS and HLA was first noted over 30 years ago (116, 117). Since then, many candidate gene studies have further explored this association. The DR15 haplotype has been the primary HLA MS genetic susceptibility factor in Caucasian populations of Northern European descent (87). However, studies of other populations have produced varying results. Associations between this haplotype and the clinical subtypes of MS have also been investigated.

In addition to addressing whether the DR15 haplotype and its alleles are overrepresented in MS cases compared with controls, some of the studies identified in our search also explored the question of whether these variants are associated with particular clinical characteristics of MS or whether they varied by gender, disease severity, or age of onset.

Clinical course

Several studies examined whether particular alleles or the DR15 haplotype influence the initial clinical course of disease (23, 31, 57, 77). In Ireland, both the phenotype and genotype DRB1 allele frequencies for persons with primary progressive MS or relapsing-remitting MS were twice those of controls (57). In the Ashkenazi population, DR15 allele frequencies were higher in the primary progressive MS group than in the relapsing-remitting MS group, while in the non-Ashkenazi population, allele frequencies were higher in the relapsing-remitting group than in the primary progressive group (77). However, in studies performed in the United Kingdom and the United States, no association between DR15 status and clinical course was found (10, 23). Overall, no clear association of these variants with clinical course could be identified.

Gender

Inconsistent results were also obtained when examining the association between gender and the DR15 haplotype. Three studies found no gender difference (29, 37, 44), while four found some degree of overrepresentation of the DR15 haplotype in females (23, 41, 52, 66) and one found a slightly higher prevalence in males (57).

Disease severity

Several studies (10, 23, 54, 57, 61) examined the genetic association with disease severity. Most found no statistically significant connection.

Age at onset

Although three studies (23, 56, 66) found DRB1*15 to be associated with a younger age at onset, several others (2, 29, 37) did not. Furthermore, in two studies that examined the frequency of the DRB1*1501 allele in Russian children and

adults with MS, Boiko et al. (30, 31) found little difference between the two groups.

Opticospinal MS versus conventional MS

Five studies analyzed the \( DRB1^*1501 \) allele in two MS clinical subgroups that have been described in Japanese subjects: opticospinal or “Asian-style” MS and conventional or “Western-style” MS (40, 41, 51, 53, 60). Patients with opticospinal MS had lesions restricted to the optic nerve and spinal cord, whereas patients with conventional MS were determined to have lesions in other regions of the central nervous system. In all studies, the frequency of \( DRB1^*1501 \) was lower in opticospinal MS patients than in patients with conventional MS (38.4 percent vs. 5.6 percent; data not shown). In the only study examining \( DQB1^*0602 \), Fukazawa et al. (40) also found a difference between these two subgroups (23.1 percent in conventional MS patients vs. 7.1 percent in opticospinal MS patients; data not shown).

IDENTIFICATION OF PRIMARY RISK ALLELE

In order to fully understand the contribution of the HLA gene region to the risk of developing MS, it will be necessary to determine the biologic effect of these variants on gene expression or protein structure. This task is complicated by the extensive linkage disequilibrium that exists in this gene region, which makes it difficult to distinguish the particular variant(s) that influence MS risk from those that are simply in linkage disequilibrium with those variants. Nevertheless, a variety of attempts have been made to determine which variants are the “true” MS risk alleles and the mechanism by which they affect MS risk.

One approach has been to investigate whether one of the HLA genes included in this haplotype (\( DRB1, \text{DQA1}, \text{or DQB1} \)) plays a more significant role in MS susceptibility than the others. Analyses conducted to ascribe a “primary” or “secondary” role to an allele typically include testing of each variant individually to see whether its association holds up in subjects negative for the overall haplotype (e.g., determining whether \( DRB1^*1501 \) is associated with MS in subjects negative for \( DQB1^*0602 \) and \( DQA1^*0102 \)). Results from these studies have not been consistent. Some studies found evidence supporting an independent role for \( DQB1^*0602 \) (6, 74), while others found that this allele’s contribution was secondary to that of \( DRB1^*1501 \) and \( DQA1^*0102 \) (39). Other investigators could find no evidence showing a dominant role for any of these alleles (26, 49). However, of these three alleles, \( DRB1^*1501 \) was more often reported to have an independent association with MS than the others (34, 42, 77, 80, 81).

Another approach has been to look for associations at the codon/amino-acid level (e.g., \( DQB1 \) Leu26) rather than at the allele level (e.g., \( DQB1^*0602 \)). This approach, in addition to fine-tuning the level of association, also has the potential benefit of resolving discrepancies between associations found in different ethnic populations. That is to say, an amino acid residue that affects MS risk may theoretically be present in two or more alleles or haplotypes that are each found to be associated with MS in different ethnic groups, which may explain the disparate results achieved in different studies. To date, a number of amino acid residues have been investigated for an association with MS, but these inquiries so far have produced limited or inconclusive results. Regarding \( DRB1 \), studies have reported an association for Val86 in Swedish (28) and Spanish Caucasian (25) populations, but other studies in Icelandic (8) and Israeli Jewish (77) groups have found no such association. Similar mixed results have been produced for Gln34 in \( DQA1 \) and Leu26 in \( DQB1 \). Other residues have shown evidence of possible association but only in a limited number of studies, such as Pro11, Arg13, and Ala71 in \( DRB1 \) (42, 67).

Finally, some investigators have attempted to elucidate differences or similarities in peptide presentation among HLA molecular variants to explain why some variants appear to predispose people to MS while others do not. Quelvennec et al. (81) identified a similarity between \( DRB1^*1501 \) and \( DRB1^*1503 \) (which is associated with MS in Martinicans) in terms of how they present the myelin basic protein 85–99 peptide to T cells. Quelvennec et al. noted that these two variants are identical in the regions that encode the P4 pocket, which is important in binding myelin basic protein 85–99. This genetic similarity may underlie the association that both variants have shown with MS.

INTERACTIONS

It is currently hypothesized that MS is a complex disease with a multifactorial etiology determined by both environmental factors and genetic susceptibility. Several studies have focused on exploring interactions between HLA genes and other genes and environmental risk factors such as viruses.

Interactions between HLA-DR15 and other genes

Several investigators studying the role of non-HLA genes in MS have attempted to stratify results on the basis of \( DR15 \) status, to see whether results differ between \( DR15 \)-positive and -negative groups. Possible interactions with \( DR15 \) have been explored for a variety of genes, including those for cytotoxic T-lymphocyte antigen 4 (118–121), T-cell receptor beta chain (36, 122–127), intercellular adhesion molecule 1 (128–130), and myelin basic protein (72, 131, 132). To date, no variants of these genes have been consistently determined to interact with HLA in influencing risk of MS. This may mean that no such interactions exist for these genes or that factors such as genetic heterogeneity or study design characteristics have prevented their detection. Interactions between the \( DR15 \) haplotype and other non-\( DR15 \)-linked HLA alleles have also been explored. For example, Fogdell-Hahn et al. (38) found associations for \( HLA-A^*0301 \) (positive) and \( HLA-A^*0201 \) (negative) which were independent of the \( DR15 \) association but appeared to modulate MS risk in \( DR15 \)-positive subjects.
Interactions between HLA-DR15 and viruses

Susceptibility to infections and the characteristics of the immune response to an infection are influenced by a person’s genetic background. Because the HLA genes are involved in binding and presentation of antigens from pathogens, and since a number of pathogens have been postulated as triggers of MS, particularly viruses such as Epstein-Barr virus and human herpesvirus 6 (104, 106, 133), it is conceivable that interactions between particular viruses and HLA molecules can influence a person’s susceptibility to MS. A few initial attempts have been made to identify and explain possible connections between HLA variants, viruses, and MS risk. For example, Lang et al. (134) found that a T-cell receptor from one MS subject was capable of recognizing both a myelin basic protein peptide presented by DRB1*1501 and an Epstein-Barr virus peptide presented by DRB5*0101. Findings such as these support the hypothesis that “molecular mimicry,” or immunologic similarities between a viral peptide and a self-peptide, may trigger an autoimmune response and lead to the development of MS. However, no definitive case has yet been made for this etiologic pathway.

Further support for an interaction between HLA genes and specific pathogens in the development of MS would be provided by evidence showing a greater simultaneous presence of particular HLA variants and infectious disease markers (e.g., antibodies) in persons with MS than in controls. A few investigators have looked for such combinations; for example, Alperovitch et al. (135) analyzed interrelations between HLA variants, immunoglobulin Gm allotypes, and viral antibody titers in MS, and they found potential differences between cases and controls in terms of associations between DQw1 (DQB1*0602) status and measles titers. However, these associations have not been extensively explored, and no recent studies of this nature appear to have been published.

LABORATORY TESTS

The HLA region is among the most polymorphic in the human genome, which makes accurate typing a substantial hurdle. For reasons of ease and cost, typing often begins at low resolution in order to capture the presence of a particular allele or haplotype (such as the presence or absence of DR15), as opposed to an extensive high-resolution analysis of the region. HLA typing is performed either by genotyping techniques or serologic analysis.

Historically, serologic testing was the most common method for typing the HLA region. However, with the molecular advances afforded by PCR, serologic testing has quickly been replaced with genotyping methods. Several genotyping techniques have been developed for genomic DNA, which can be easily isolated from a variety of sources (lymphocytes, dried blood spots, buccal brushes, etc.). Current genotyping methods rely primarily on PCR-based techniques to first amplify the HLA region and then follow with hybridization of allele-specific probes. More recently, methods have emerged for applying whole genome amplification prior to the HLA-specific genotyping so that one may even utilize precious samples with very little DNA available (136). In addition to the allele-specific method of genotyping, sequencing and high-resolution melting curve analysis (137) may also be used post-PCR for detecting specific HLA alleles. Melting curve analysis, in particular, can be especially helpful for the higher-resolution typing (137).

POPULATION TESTING

Currently there is no cure for MS, nor is there a biomarker that is appropriate for early detection of the disease. Consequently, there has been no effort to establish population-wide testing for MS. The diagnosis is made on an individual basis by a qualified neurologist, after the patient has experienced symptoms of the disease. Several medications are available to ameliorate symptoms or decrease the progression of the disease, and clinical trials of these medications are a rich area of research.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

Association with the HLA region remains the most consistently replicated genetic finding in MS (138). With few exceptions, most of the studies we identified in our search showed higher prevalence of the DR15 haplotype and/or its alleles in MS cases than in controls. Despite this strong pattern, our confidence in the results was tempered by factors related to study design that may have biased the outcomes. For example, in many of these papers, the processes used to select cases were not specified, nor were the clinical criteria used for classifying subjects as having MS. In several studies, controls were convenience samples chosen from blood donors, organ donors, and/or hospital staff. In addition, we identified several situations where different studies were performed by the same authors in the same population but the authors failed to specify whether the same subjects were included in both studies or whether all subjects were unique. Although we omitted studies for which it was clear that participants’ data had already been reported in another study, it is possible that our compilation included cases that were analyzed in multiple studies.

In some studies, choice of nomenclature complicated our efforts to assemble the study tables. Fortunately, nomenclature has become clearer in recent years, with most authors using genotype names for alleles rather than names based on serology. Variations in the presentation of results (e.g., genotype frequencies vs. phenotype frequencies) or in statistical methods used to assess the association (e.g., frequency, odds ratio, relative risk, or p value) also made it difficult to compile and compare data. Furthermore, in a surprisingly large number of studies we reviewed, we encountered typographic errors or miscalculations which made reporting of results difficult.

For future research exploring the association between HLA-DR15 and MS, we recommend the development of a standardized reporting format for genetic results. This format should include minimum required information, such as demographic data on the study population (age, gender, race/ethnicity), the process used to select study participants,
the criteria used for MS diagnosis, laboratory methods used, genotype name, and frequency. We also encourage population-based research that is designed to take into account the multifactorial basis of this disease, so that the environmental and genetic factors that cause MS and their interactions can be more fully understood. Collaboration among researchers with varied expertise in neurology, genetics, and epidemiology is essential to further explore the potential etiologies of this disease.

INTERNET SITES

Internet sites pertaining to the HLA locus and MS genetics are listed in the Appendix table.

ACKNOWLEDGMENTS

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Conflict of interest: none declared.

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APPENDIX TABLE 1. Internet sites pertaining to the relation between the human leukocyte antigen gene complex and multiple sclerosis

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<th>Genetics of MS*</th>
<th>OMIM* overview of genetic risk factors in MS</th>
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<td>Home page of the Multiple Sclerosis Genetics Group at the University of Cambridge</td>
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<td><a href="http://www.ucsf.edu/msdb/">http://www.ucsf.edu/msdb/</a></td>
<td>Discussion of MS as a genetic disease provided by the Multiple Sclerosis Genetics Group (a collaboration between the University of California, San Francisco, Duke University, and Vanderbilt University)</td>
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<td><a href="http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/">http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/</a></td>
<td>Description of the GAMES (Genetic Analysis of Multiple Sclerosis in Europeans) project for identifying risk factors for MS in European populations</td>
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<td><a href="http://www.nationalmssociety.org/Brochures-Genetics1.asp">http://www.nationalmssociety.org/Brochures-Genetics1.asp</a></td>
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<td><a href="http://www.anthonynolan.org.uk/HIG/">http://www.anthonynolan.org.uk/HIG/</a></td>
<td>Home page of the HLA Informatics Group, including sequence databases and nomenclature information (see next link)</td>
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<td><a href="http://www.anthonynolan.org.uk/HIG/lists/nomenc.html">http://www.anthonynolan.org.uk/HIG/lists/nomenc.html</a></td>
<td>Comprehensive lists of the official names for HLA class I and II genes and other genes in the HLA region</td>
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<td>Home page of the MHC* Haplotype Project, which is generating complete sequences for several common MHC haplotypes</td>
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<tr>
<td><a href="http://www.ashi-hla.org/">http://www.ashi-hla.org/</a></td>
<td>Home page of the American Society for Histocompatibility and Immunogenetics</td>
</tr>
<tr>
<td><a href="http://www.ebi.ac.uk/imgt/hla/">http://www.ebi.ac.uk/imgt/hla/</a></td>
<td>HLA sequence database maintained by the international ImMunoGeneTics (IMGT) project</td>
</tr>
</tbody>
</table>

* MS, multiple sclerosis; OMIM, Online Mendelian Inheritance in Man; HLA, human leukocyte antigen; MHC, major histocompatibility complex.