



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.

Received for publication July 6, 2006; accepted for publication October 31, 2006.

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., *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 "multiple sclerosis" for papers published between 1993 and 2004. The search was limited to human genetic studies written in the English language. We identified 96 papers that appeared to be relevant and critically evaluated them for inclusion or exclusion. Papers were included in this review if the investigators presented 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.

The studies we found exhibited extensive heterogeneity in terms of subject recruitment, clinical characteristics of cases, and choice of controls. Twenty-four papers were excluded from this review, for numerous reasons: Subjects were selected on the basis of genotype (3–6), frequencies of alleles were not included (7–11), investigators assessed an *HLA* allele that was not part of the haplotype under study (12–18), only microsatellite markers were used (16, 19), or other reasons (20–26).

Web tables 1 and 2 (posted on the *Journal's* website (<http://aje.oxfordjournals.org/>)) list the papers included in this review that used a case-control study design ($n = 60$), while Web table 3 lists the family-based studies ($n = 22$). In 10 articles,

researchers reported results from both a case-control design and a family-based design; those studies are included in both tables. Web tables 1 and 3 provide information on study characteristics such as geographic location, ethnic group studied, number of study participants, selection criteria, and laboratory methods used, if available. Web table 2 presents *HLA* allele frequency data from the case-control studies.

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 overrepresentation 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 opticospinal 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

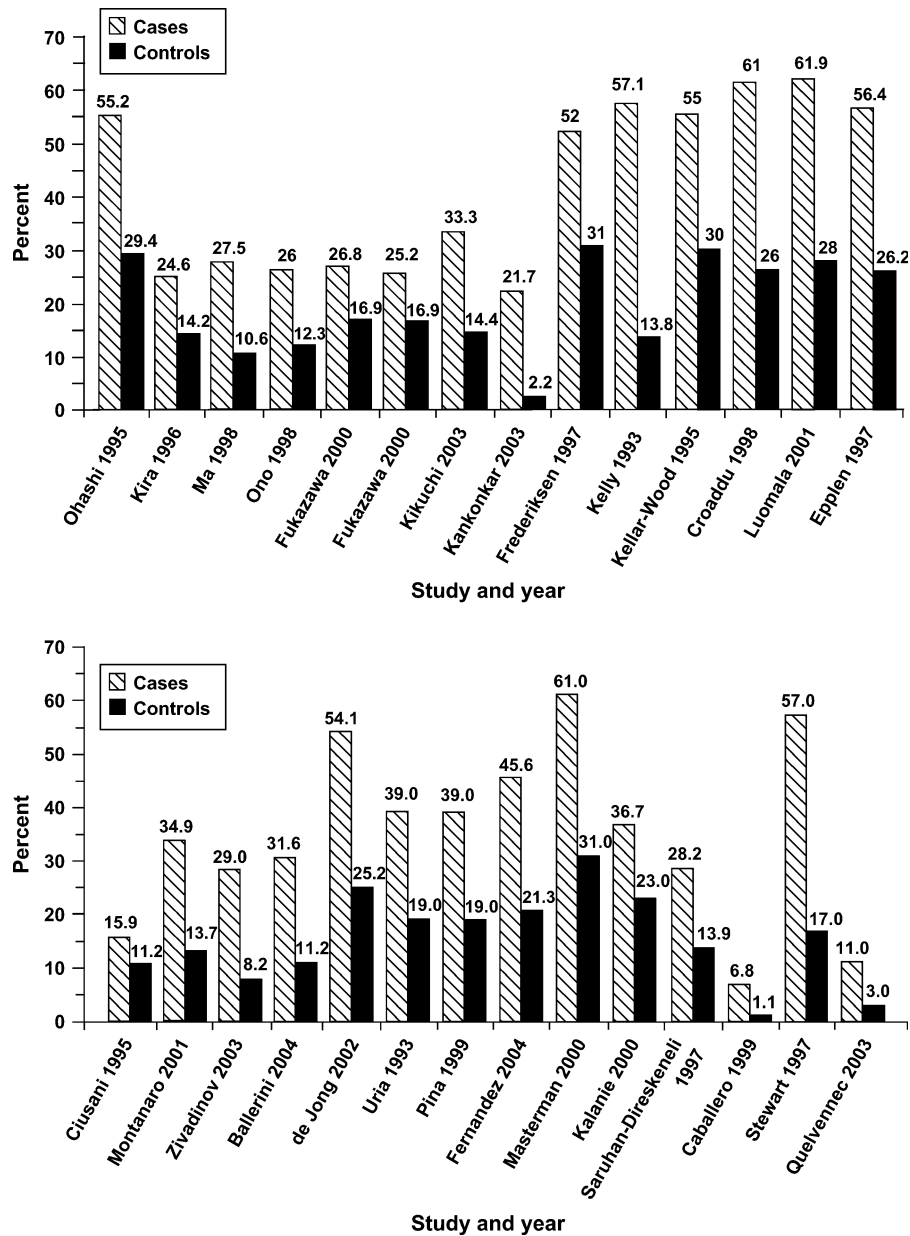


FIGURE 1. Frequency of the human leukocyte antigen *DRB1*1501* allele in English-language case-control studies of multiple sclerosis, 1993–2004.

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).

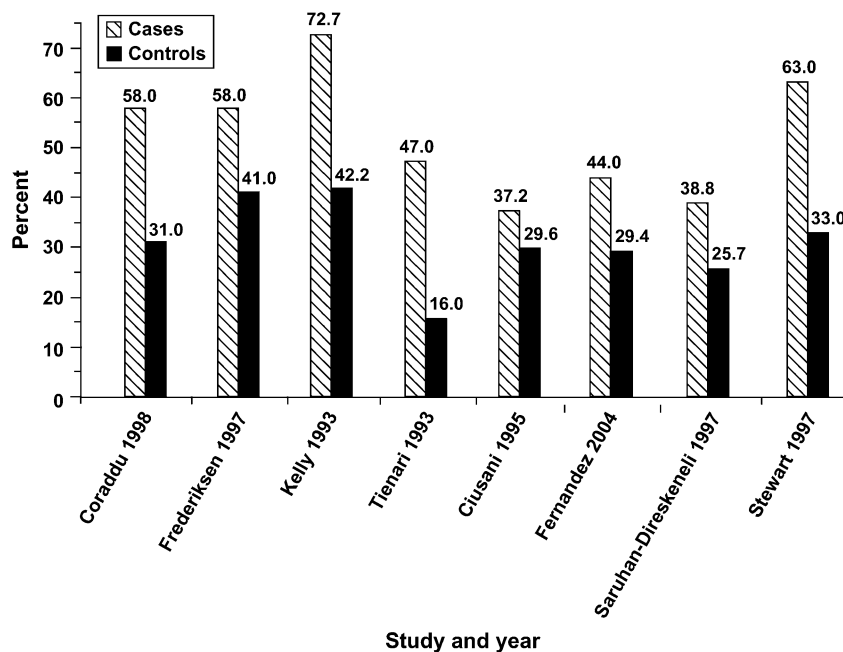


FIGURE 2. Frequency of the human leukocyte antigen *DQA1*0102* allele in English-language case-control studies of multiple sclerosis, 1993–2004.

*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 ($p = 0.014$; relative risk = 2.62) (77) and Turks ($p = 0.005$; 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

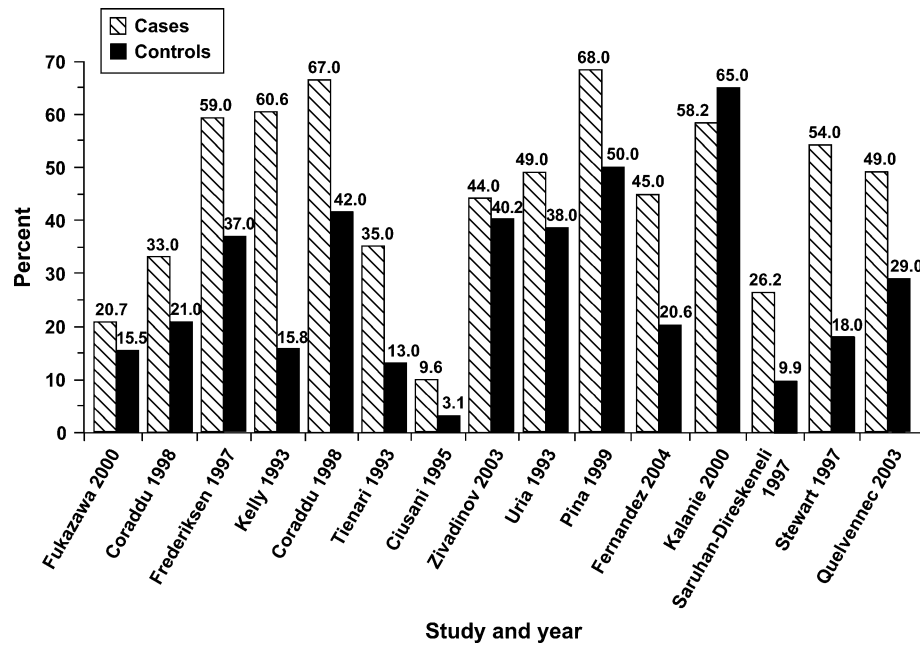


FIGURE 3. Frequency of the human leukocyte antigen *DQB1*0602* allele in English-language case-control studies of multiple sclerosis, 1993–2004.

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 lymphotropic 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).

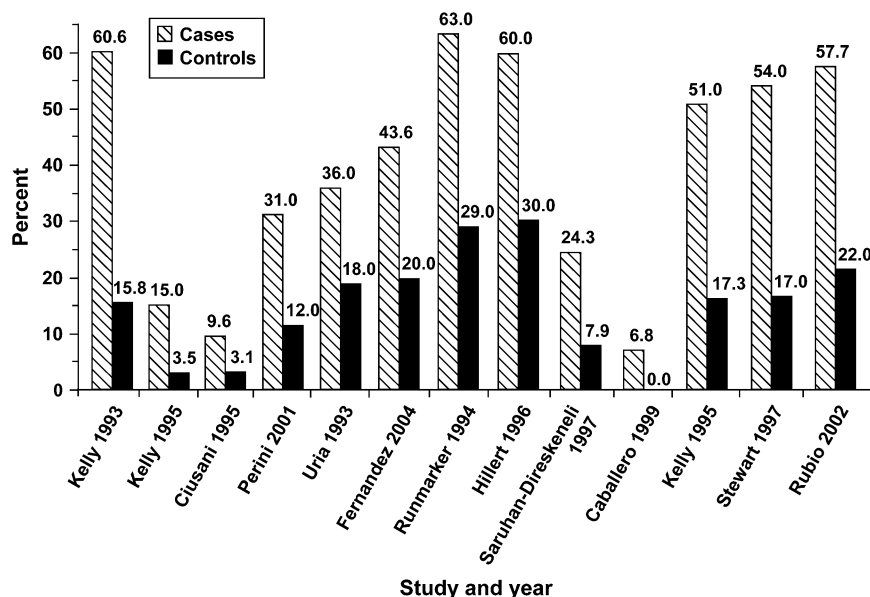


FIGURE 4. Frequency of the human leukocyte antigen (*HLA*) *DR15* haplotype (*HLA-DRB1*1501-DQA1*0102-DQB1*0602*) in English-language case-control studies of multiple sclerosis, 1993–2004.

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 (≤ 18.4 percent vs. 28.8–41.2 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*, *DQA1*, 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 theo-

retically 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. Quelvenec 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. Quelvenec 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

Drs. Dhelia Williamson and Allison Ashley-Koch were supported by a grant from the Agency for Toxic Substances and Disease Registry.

Conflict of interest: none declared.

REFERENCES

- Dorman JS, Bunker CH. *HLA-DQ* locus of the human leucocyte antigen complex and type 1 diabetes mellitus: a HuGE review. *Epidemiol Rev* 2000;22:218–27.
- Kalanie H, Kamgooyan M, Sadeghian H, et al. Histocompatibility antigen (HLA) associations with multiple sclerosis in Iran. *Mult Scler* 2000;6:317–19.
- Fogdell A, Hillert J, Sachs C, et al. The multiple sclerosis- and narcolepsy-associated HLA class II haplotype includes the *DRB5*0101* allele. *Tissue Antigens* 1995;46:333–6.
- Bennetts BH, Teutsch SM, Buhler MM, et al. *HLA-DMB* gene and *HLA-DRA* promoter region polymorphisms in Australian multiple sclerosis patients. *Hum Immunol* 1999;60:886–93.
- Dekker JW, Easteal S, Jakobsen IB, et al. *HLA-DPB1* alleles correlate with risk for multiple sclerosis in Caucasoid and Cantonese patients lacking the high-risk *DQB1*0602* allele. *Tissue Antigens* 1993;41:31–6.
- Spurkland A, Celius EG, Knutsen I, et al. The *HLA-DQ*(α *I*0102*, β *I*0602*) heterodimer may confer susceptibility to multiple sclerosis in the absence of the *HLA-DR*(α *I*01*, β *I*1501*) heterodimer. *Tissue Antigens* 1997;50:15–22.
- Oturai A, Larsen F, Ryder LP, et al. Linkage and association analysis of susceptibility regions on chromosomes 5 and 6 in 106 Scandinavian sibling pair families with multiple sclerosis. *Ann Neurol* 1999;46:612–16.
- Haegert DG, Swift FV, Benedikz J. Evidence for a complex role of HLA class II genotypes in susceptibility to multiple sclerosis in Iceland. *Neurology* 1996;46:1107–11.
- Ristori G, Carcassi C, Lai S, et al. *HLA-DM* polymorphisms do not associate with multiple sclerosis: an association study with analysis of myelin basic protein T cell specificity. *J Neuroimmunol* 1997;77:181–4.
- Weinshenker BG, Santrach P, Bissonet AS, et al. Major histocompatibility complex class II alleles and the course and outcome of MS: a population-based study. *Neurology* 1998;51:742–7.
- Modin H, Olsson W, Hillert J, et al. Modes of action of *HLA-DR* susceptibility specificities in multiple sclerosis. *Am J Hum Genet* 2004;74:1321–2.
- Bitti PP, Murgia BS, Ticca A, et al. Association between the ancestral haplotype *HLA A30B18DR3* and multiple sclerosis in central Sardinia. *Genet Epidemiol* 2001;20:271–83.
- Hillert J, Olerup O. Multiple sclerosis is associated with genes within or close to the *HLA-DR-DQ* subregion on a normal *DR15,DQ6,Dw2* haplotype. *Neurology* 1993;43:163–8.
- Ito H, Yamasaki K, Kawano Y, et al. *HLA-DP*-associated susceptibility to the optico-spinal form of multiple sclerosis in the Japanese. *Tissue Antigens* 1998;52:179–82.
- Marrosu MG, Murru MR, Costa G, et al. Multiple sclerosis in Sardinia is associated and in linkage disequilibrium with *HLA-DR3* and *-DR4* alleles. *Am J Hum Genet* 1997;61:454–7.
- Palacio LG, Rivera D, Builes JJ, et al. Multiple sclerosis in the tropics: genetic association to STR's loci spanning the *HLA* and *TNF*. *Mult Scler* 2002;8:249–55.
- Yamasaki K, Horiuchi I, Minohara M, et al. *HLA-DPB1*0501*-associated opticonspinal multiple sclerosis: clinical, neuroimaging and immunogenetic studies. *Brain* 1999;122:1689–96.
- Marrosu MG, Fadda E, Mancosu C, et al. The contribution of HLA to multiple sclerosis susceptibility in Sardinian affected sibling pairs. *Ann Neurol* 2000;47:411–12.
- Boon M, Nolte IM, Bruinenberg M, et al. Mapping of a susceptibility gene for multiple sclerosis to the 51 kb interval between G511525 and D6S1666 using a new method of haplotype sharing analysis. *Neurogenetics* 2001;3:221–30.
- Teutsch SM, Bennetts BH, Buhler MM, et al. The *DRB1* Val86/Val86 genotype associates with multiple sclerosis in Australian patients. *Hum Immunol* 1999;60:715–22.
- Hauser SL, Oksenberg JR, Lincoln R, et al. Interaction between *HLA-DR2* and abnormal brain MRI in optic neuritis and early MS. Optic Neuritis Study Group. *Neurology* 2000;54:1859–61.
- Rasmussen HB, Kelly MA, Clausen J. Additive effect of the *HLA-DR15* haplotype on susceptibility to multiple sclerosis. *Mult Scler* 2001;7:91–3.
- Hensiek AE, Sawcer SJ, Feakes R, et al. *HLA-DR 15* is associated with female sex and younger age at diagnosis in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002;72:184–7.
- Oh HH, Kwon SH, Kim CW, et al. Molecular analysis of HLA class II-associated susceptibility to neuroinflammatory diseases in Korean children. *J Korean Med Sci* 2004;19:426–30.
- de la Concha EG, Arroyo R, Crusius JB, et al. Combined effect of *HLA-DRB1*1501* and interleukin-1 receptor antagonist gene allele 2 in susceptibility to relapsing/remitting multiple sclerosis. *J Neuroimmunol* 1997;80:172–8.
- Marrosu MG, Murru MR, Costa G, et al. *DRB1-DQA1-DQB1* loci and multiple sclerosis predisposition in the Sardinian population. *Hum Mol Genet* 1998;7:1235–7.
- Allcock RJ, de la Concha EG, Fernandez-Arquero M, et al. Susceptibility to multiple sclerosis mediated by *HLA-DRB1* is influenced by a second gene telomeric of the *TNF* cluster. *Hum Immunol* 1999;60:1266–73.
- Allen M, Sandberg-Wollheim M, Sjogren K, et al. Association of susceptibility to multiple sclerosis in Sweden with HLA class II *DRB1* and *DQB1* alleles. *Hum Immunol* 1994;39:41–8.

29. Ballerini C, Guerini FR, Rombola G, et al. HLA-multiple sclerosis association in continental Italy and correlation with disease prevalence in Europe. *J Neuroimmunol* 2004;150:178–85.
30. Boiko AN, Guseva ME, Guseva MR, et al. Clinico-immunogenetic characteristics of multiple sclerosis with optic neuritis in children. *J Neurovirol* 2000;6(suppl 2):S152–5.
31. Boiko AN, Gusev EI, Sudomoina MA, et al. Association and linkage of juvenile MS with *HLA-DR2(15)* in Russians. *Neurology* 2002;58:658–60.
32. Ciusani E, Allen M, Sandberg-Wollheim M, et al. Analysis of HLA-class II *DQA1*, *DQB1*, *DRB1* and *DPB1* in Italian multiple sclerosis patients. *Eur J Immunogenet* 1995;22:171–8.
33. Corradu F, Sawcer S, Feakes R, et al. HLA typing in the United Kingdom multiple sclerosis genome screen. *Neurogenetics* 1998;2:24–33.
34. Corradu F, Reyes-Yanez MP, Parra A, et al. HLA associations with multiple sclerosis in the Canary Islands. *J Neuroimmunol* 1998;87:130–5.
35. de Jong BA, Huizinga TW, Zanelli E, et al. Evidence for additional genetic risk indicators of relapse-onset MS within the *HLA* region. *Neurology* 2002;59:549–55.
36. Epplen C, Jackel S, Santos EJ, et al. Genetic predisposition to multiple sclerosis as revealed by immunoprinting. *Ann Neurol* 1997;41:341–52.
37. Fernandez O, Fernandez V, Alonso A, et al. *DQB1*0602* allele shows a strong association with multiple sclerosis in patients in Malaga, Spain. *J Neurol* 2004;251:440–4.
38. Fogdell-Hahn A, Ligera A, Gronning M, et al. Multiple sclerosis: a modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. *Tissue Antigens* 2000;55:140–8.
39. Frederiksen JL, Madsen HO, Ryder LP, et al. HLA typing in acute optic neuritis. Relation to multiple sclerosis and magnetic resonance imaging findings. *Arch Neurol* 1997;54:76–80.
40. Fukazawa T, Kikuchi S, Sasaki H, et al. Genomic HLA profiles of MS in Hokkaido, Japan: important role of *DPB1*0501* allele. *J Neurol* 2000;247:175–8.
41. Fukazawa T, Yamasaki K, Ito H, et al. Both the *HLA-CPBI* and *-DRB1* alleles correlate with risk for multiple sclerosis in Japanese: clinical phenotypes and gender as important factors. *Tissue Antigens* 2000;55:199–205.
42. Ghabanbasani MZ, Gu XX, Spaepen M, et al. Importance of *HLA-DRB1* and *DQA1* genes and of the amino acid polymorphisms in the functional domain of *DR* beta 1 chain in multiple sclerosis. *J Neuroimmunol* 1995;59:77–82.
43. Harbo HF, Lie BA, Sawcer S, et al. Genes in the HLA class I region may contribute to the HLA class II-associated genetic susceptibility to multiple sclerosis. *Tissue Antigens* 2004;63:237–47.
44. Hillert J, Kall T, Olerup O, et al. Distribution of *HLA-Dw2* in optic neuritis and multiple sclerosis indicates heterogeneity. *Acta Neurol Scand* 1996;94:161–6.
45. Jersild C, Kurtzke JF, Riisom K, et al. Multiple sclerosis in the Faroe Islands. VI. Studies of HLA markers. *Tissue Antigens* 1993;42:105–10.
46. Kankonkar S, Jeyanti G, Singhal BS, et al. Evidence for novel *DRB1*15* allele association among clinically definite multiple sclerosis patients from Mumbai, India. *Hum Immunol* 2003;64:478–82.
47. Kellar-Wood HF, Wood NW, Holmans P, et al. Multiple sclerosis and the *HLA-D* region: linkage and association studies. *J Neuroimmunol* 1995;58:183–90.
48. Kelly MA, Cavan DA, Penny MA, et al. The influence of *HLA-DR* and *-DQ* alleles on progression to multiple sclerosis following a clinically isolated syndrome. *Hum Immunol* 1993;37:185–91.
49. Kelly MA, Jacobs KH, Penny MA, et al. An investigation of HLA-encoded genetic susceptibility to multiple sclerosis in subjects of Asian Indian and Afro-Caribbean ethnic origin. *Tissue Antigens* 1995;45:197–202.
50. Kikuchi S, Fukazawa T, Niino M, et al. HLA-related subpopulations of MS in Japanese with and without oligoclonal IgG bands. *Neurology* 2003;60:647–51.
51. Kira J, Kanai T, Nishimura Y, et al. Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. *Ann Neurol* 1996;40:569–74.
52. Luomala M, Elovaara I, Ukkonen M, et al. The combination of *HLA-DR1* and *HLA-DR53* protects against MS. *Neurology* 2001;56:383–5.
53. Ma JJ, Nishimura M, Mine H, et al. *HLA-DRB1* and tumor necrosis factor gene polymorphisms in Japanese patients with multiple sclerosis. *J Neuroimmunol* 1998;92:109–12.
54. Marrosu MG, Muntoni F, Murru MR, et al. Role of predisposing and protective *HLA-DQA* and *HLA-DQB* alleles in Sardinian multiple sclerosis. *Arch Neurol* 1993;50:256–60.
55. Marrosu MG, Murru R, Murru MR, et al. Dissection of the HLA association with multiple sclerosis in the founder isolated population of Sardinia. *Hum Mol Genet* 2001;10:2907–16.
56. Masterman T, Ligera A, Olsson T, et al. *HLA-DR15* is associated with lower age at onset in multiple sclerosis. *Ann Neurol* 2000;48:211–19.
57. McDonnell GV, Mawhinney H, Graham CA, et al. A study of the *HLA-DR* region in clinical subgroups of multiple sclerosis and its influence on prognosis. *J Neurol Sci* 1999;165:77–83.
58. Montanaro D, Sanna V, Matarese G, et al. The fine specificity of human T cell lines towards myelin basic protein peptides in southern Italian multiple sclerosis patients. *Clin Exp Immunol* 2001;123:288–93.
59. Ohashi T, Yamamura T, Inobe J, et al. Analysis of proteolipid protein (PLP)-specific T cells in multiple sclerosis: identification of PLP 95-116 as an *HLA-DR2,w15*-associated determinant. *Int Immunol* 1995;7:1771–8.
60. Ono T, Zambenedetti MR, Yamasaki K, et al. Molecular analysis of HLA class I (*HLA-A* and *-B*) and HLA class II (*HLA-DRB1*) genes in Japanese patients with multiple sclerosis (Western type and Asian type). *Tissue Antigens* 1998;52:539–42.
61. Perini P, Tagliaferri C, Belloni M, et al. The *HLA-DR13* haplotype is associated with “benign” multiple sclerosis in northeast Italy. *Neurology* 2001;57:158–9.
62. Pina MA, Ara JR, Lasierra P, et al. Study of HLA as a predisposing factor and its possible influence on the outcome of multiple sclerosis in the sanitary district of Calatayud, northern Spain. *Neuroepidemiology* 1999;18:203–9.
63. Runmarker B, Martinsson T, Wahlstrom J, et al. HLA and prognosis in multiple sclerosis. *J Neurol* 1994;241:385–90.
64. Tienari PJ, Wikstrom J, Koskimies S, et al. Reappraisal of HLA in multiple sclerosis: close linkage in multiplex families. *Eur J Hum Genet* 1993;1:257–68.
65. Uria DF, Gutierrez V, Menes BB, et al. HLA class II susceptibility and resistance genes in patients with multiple sclerosis from northern Spain, by DNA-RFLP genotyping. *J Neurol Neurosurg Psychiatry* 1993;56:722–3.
66. Weatherby SJ, Thomson W, Pepper L, et al. *HLA-DRB1* and disease outcome in multiple sclerosis. *J Neurol* 2001;248:304–10.

67. Zipp F, Windemuth C, Pankow H, et al. Multiple sclerosis associated amino acids of polymorphic regions relevant for the HLA antigen binding are confined to *HLA-DR2*. *Hum Immunol* 2000;61:1021–30.
68. Zivadinov R, Uxa L, Zacchi T, et al. HLA genotypes and disease severity assessed by magnetic resonance imaging findings in patients with multiple sclerosis. *J Neurol* 2003; 250:1099–106.
69. Alvarado-de la Barrera C, Zuniga-Ramos J, Ruiz-Morales JA, et al. HLA class II genotypes in Mexican Mestizos with familial and nonfamilial multiple sclerosis. *Neurology* 2000; 55:1897–900.
70. Amirzargar A, Mytilineos J, Yousefipour A, et al. HLA class II (*DRB1*, *DQA1* and *DQB1*) associated genetic susceptibility in Iranian multiple sclerosis (MS) patients. *Eur J Immunogenet* 1998;25:297–301.
71. Arcos-Burgos M, Palacio G, Sanchez JL, et al. Multiple sclerosis: association to *HLA DQ α* in a tropical population. *Exp Clin Immunogenet* 1999;16:131–8.
72. Barcellos LF, Thomson G, Carrington M, et al. Chromosome 19 single-locus and multilocus haplotype associations with multiple sclerosis. Evidence of a new susceptibility locus in Caucasian and Chinese patients. *JAMA* 1997;278:1256–61.
73. Caballero A, Alves-Leon S, Papais-Alvarenga R, et al. *DQB1*0602* confers genetic susceptibility to multiple sclerosis in Afro-Brazilians. *Tissue Antigens* 1999;54:524–6.
74. Haegert DG, Francis GS. *HLA-DQ* polymorphisms do not explain HLA class II associations with multiple sclerosis in two Canadian patient groups. *Neurology* 1993;43:1207–10.
75. Haegert DG, Muntoni F, Murru MR, et al. *HLA-DQA1* and *-DQB1* associations with multiple sclerosis in Sardinia and French Canada: evidence for immunogenetically distinct patient groups. *Neurology* 1993;43:548–52.
76. Karni A, Kohn Y, Safirman C, et al. Evidence for the genetic role of human leukocyte antigens in low frequency *DRB1*1501* multiple sclerosis patients in Israel. *Mult Scler* 1999;5:410–15.
77. Kwon OJ, Karni A, Israel S, et al. HLA class II susceptibility to multiple sclerosis among Ashkenazi and non-Ashkenazi Jews. *Arch Neurol* 1999;56:555–60.
78. al Din AS, El Khateeb M, Kurdi A, et al. Multiple sclerosis in Arabs in Jordan. *J Neurol Sci* 1995;131:144–9.
79. Najim Al-Din AS, Kurdi A, Mubaidin A, et al. Epidemiology of multiple sclerosis in Arabs in Jordan: a comparative study between Jordanians and Palestinians. *J Neurol Sci* 1996;135: 162–7.
80. Oksenberg JR, Barcellos LF, Cree BA, et al. Mapping multiple sclerosis susceptibility to the *HLA-DR* locus in African Americans. *Am J Hum Genet* 2004;74:160–7.
81. Quelvennec E, Bera O, Cabre P, et al. Genetic and functional studies in multiple sclerosis patients from Martinique attest for a specific and direct role of the *HLA-DR* locus in the syndrome. *Tissue Antigens* 2003;61:166–71.
82. Rubio JP, Bahlo M, Butzkueven H, et al. Genetic dissection of the human leukocyte antigen region by use of haplotypes of Tasmanians with multiple sclerosis. *Am J Hum Genet* 2002; 70:1125–37.
83. Saruhan-Direskeneli G, Esin S, Baykan-Kurt B, et al. *HLA-DR* and *-DQ* associations with multiple sclerosis in Turkey. *Hum Immunol* 1997;55:59–65.
84. Stewart GJ, Teutsch SM, Castle M, et al. *HLA-DR*, *-DQA1* and *-DQB1* associations in Australian multiple sclerosis patients. *Eur J Immunogenet* 1997;24:81–92.
85. Kelly MA, Zhang Y, Penny MA, et al. Genetic susceptibility to multiple sclerosis in a Shanghai Chinese population. The role of the HLA class II genes. *Hum Immunol* 1995;42: 203–8.
86. Lampis R, Morelli L, Congia M, et al. The inter-regional distribution of HLA class II haplotypes indicates the suitability of the Sardinian population for case-control association studies in complex diseases. *Hum Mol Genet* 2000;9: 2959–65.
87. Barcellos LF, Oksenberg JR, Green AJ, et al. Genetic basis for clinical expression in multiple sclerosis. *Brain* 2002;125: 150–8.
88. Barcellos LF, Oksenberg JR, Begovich AB, et al. *HLA-DR2* dose effect on susceptibility to multiple sclerosis and influence on disease course. *Am J Hum Genet* 2003;72:710–16.
89. D'Alfonso S, Nistico L, Zavattari P, et al. Linkage analysis of multiple sclerosis with candidate region markers in Sardinian and Continental Italian families. *Eur J Hum Genet* 1999;7: 377–85.
90. Eoli M, Pandolfo M, Amoroso A, et al. Evidence of linkage between susceptibility to multiple sclerosis and HLA-class II loci in Italian multiplex families. *Eur J Hum Genet* 1995;3: 303–11.
91. Fogdell A, Olerup O, Fredrikson S, et al. Linkage analysis of HLA class II genes in Swedish multiplex families with multiple sclerosis. *Neurology* 1997;48:758–62.
92. Haines JL, Terwedow HA, Burgess K, et al. Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. The Multiple Sclerosis Genetics Group. *Hum Mol Genet* 1998;7:1229–34.
93. Hillert J, Kall T, Vrethem M, et al. The *HLA-Dw2* haplotype segregates closely with multiple sclerosis in multiplex families. *J Neuroimmunol* 1994;50:95–100.
94. Laaksonen M, Pastinen T, Sjoroos M, et al. HLA class II associated risk and protection against multiple sclerosis—a Finnish family study. *J Neuroimmunol* 2002;122:140–5.
95. Ligers A, Dyment DA, Willer CJ, et al. Evidence of linkage with *HLA-DR* in *DRB1*15*-negative families with multiple sclerosis. *Am J Hum Genet* 2001;69:900–3.
96. Villoslada P, Barcellos LF, Rio J, et al. The *HLA* locus and multiple sclerosis in Spain. Role in disease susceptibility, clinical course and response to interferon-beta. *J Neuroimmunol* 2002;130:194–201.
97. Voskuhl RR, Goldstein AM, Simonis T, et al. *DR2/DQw1* inheritance and haplotype sharing in affected siblings from multiple sclerosis families. *Ann Neurol* 1996;39:804–7.
98. Yaouanq J, Semana G, Eichenbaum S, et al. Evidence for linkage disequilibrium between *HLA-DRB1* gene and multiple sclerosis. The French Research Group on Genetic Susceptibility to MS. *Science* 1997;276:664–5.
99. Minden SL, Marder WD, Harrold LN, et al. Multiple sclerosis: a statistical portrait. A compendium of data on demographics, disability, and health services utilization in the United States. Cambridge, MA: Abt Associates, Inc, 1993.
100. Baum HM, Rothschild BB. The incidence and prevalence of reported multiple sclerosis. *Ann Neurol* 1981;10:420–8.
101. Sadovnick AD, Dyment D, Ebers GC. Genetic epidemiology of multiple sclerosis. *Epidemiol Rev* 1997;19:99–106.
102. Haines JL, Ter Minassian M, Bazyk A, et al. A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. The Multiple Sclerosis Genetics Group. *Nat Genet* 1996;13:469–71.
103. Willer CJ, Ebers GC. Susceptibility to multiple sclerosis: interplay between genes and environment. *Curr Opin Neurol* 2000;13:241–7.
104. Ascherio A, Munch M. Epstein-Barr virus and multiple sclerosis. *Epidemiology* 2000;11:220–4.

105. Casetta I, Granieri E. Clinical infections and multiple sclerosis: contribution from analytical epidemiology. *J Neurovirol* 2000;6(suppl 2):S147–51.
106. Haahr S, Munch M. The association between multiple sclerosis and infection with Epstein-Barr virus and retrovirus. *J Neurovirol* 2000;6(suppl 2):S76–9.
107. Freedman DM, Dosemeci M, Alavanja MC. Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates. *Occup Environ Med* 2000;57:418–21.
108. Hayes CE, Cantorna MT, DeLuca HF. Vitamin D and multiple sclerosis. *Proc Soc Exp Biol Med* 1997;216:21–7.
109. McMichael AJ, Hall AJ. Does immunosuppressive ultraviolet radiation explain the latitude gradient for multiple sclerosis? *Epidemiology* 1997;8:642–5.
110. van der Mei I, Ponsonby AL, Blizzard L, et al. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* 2001;20:168–74.
111. Casetta I, Granieri E, Malagu S, et al. Environmental risk factors and multiple sclerosis: a community-based, case-control study in the province of Ferrara, Italy. *Neuroepidemiology* 1994;13:120–8.
112. Flodin U, Soderfeldt B, Noorlind-Brage H, et al. Multiple sclerosis, solvents, and pets. A case-referent study. *Arch Neurol* 1988;45:620–3.
113. Gronning M, Albrektsen G, Kvale G, et al. Organic solvents and multiple sclerosis: a case-control study. *Acta Neurol Scand* 1993;88:247–50.
114. Landtblom AM, Flodin U, Karlsson M, et al. Multiple sclerosis and exposure to solvents, ionizing radiation and animals. *Scand J Work Environ Health* 1993;19:399–404.
115. Nelson NA, Robins TG, White RF, et al. A case-control study of chronic neuropsychiatric disease and organic solvent exposure in automobile assembly plant workers. *Occup Environ Med* 1994;51:302–7.
116. Naito S, Namerow N, Mickey MR, et al. Multiple sclerosis: association with *HLA-A3*. *Tissue Antigens* 1972;2:1–4.
117. Bertrams J, Kuwert E. *HLA-A* antigen frequencies in multiple sclerosis. Significant increase of *HLA-A3*, *HLA-A10* and *W5*, and decrease of *HLA-A12*. *Eur Neurol* 1972;7:74–8.
118. Alizadeh M, Babron MC, Birebent B, et al. Genetic interaction of *CTLA-4* with *HLA-DR15* in multiple sclerosis patients. *Ann Neurol* 2003;54:119–22.
119. Dymont DA, Steckley JL, Willer CJ, et al. No evidence to support *CTLA-4* as a susceptibility gene in MS families: The Canadian Collaborative Study. *J Neuroimmunol* 2002;123:193–8.
120. Harbo HF, Celius EG, Vartdal F, et al. *CTLA4* promoter and exon 1 dimorphisms in multiple sclerosis. *Tissue Antigens* 1999;53:106–10.
121. Rasmussen HB, Kelly MA, Francis DA, et al. *CTLA4* in multiple sclerosis. Lack of genetic association in a European Caucasian population but evidence of interaction with *HLA-DR2* among Shanghai Chinese. *J Neurol Sci* 2001;184:143–7.
122. Beall SS, Biddison WE, McFarlin DE, et al. Susceptibility for multiple sclerosis is determined, in part, by inheritance of a 175-kb region of the *TcR V* beta chain locus and HLA class II genes. *J Neuroimmunol* 1993;45:53–60.
123. Buhler MM, Bennetts BH, Heard RN, et al. T cell receptor beta chain genotyping in Australian relapsing-remitting multiple sclerosis patients. *Mult Scler* 2000;6:140–7.
124. Hillert J, Leng C, Olerup O. No association with germline T cell receptor beta-chain gene alleles or haplotypes in Swedish patients with multiple sclerosis. *J Neuroimmunol* 1991;32:141–7.
125. Hockertz MK, Paty DW, Beall SS. Susceptibility to relapsing-progressive multiple sclerosis is associated with inheritance of genes linked to the variable region of the *TcR* beta locus: use of affected family-based controls. *Am J Hum Genet* 1998;62:373–85.
126. Vandevyver C, Buyse I, Philippaerts L, et al. HLA and T-cell receptor polymorphisms in Belgian multiple sclerosis patients: no evidence for disease association with the T-cell receptor. *J Neuroimmunol* 1994;52:25–32.
127. Wood NW, Sawcer SJ, Kellar-Wood HF, et al. The T-cell receptor beta locus and susceptibility to multiple sclerosis. *Neurology* 1995;45:1859–63.
128. Cournu-Rebeix I, Genin E, Lesca G, et al. Intercellular adhesion molecule-1: a protective haplotype against multiple sclerosis. *Genes Immun* 2003;4:518–23.
129. Mycko MP, Kwinkowski M, Tronczynska E, et al. Multiple sclerosis: the increased frequency of the *ICAM-1* exon 6 gene point mutation genetic type *K469*. *Ann Neurol* 1998;44:70–5.
130. Nejentsev S, Laaksonen M, Tienari PJ, et al. Intercellular adhesion molecule-1 *K469E* polymorphism: study of association with multiple sclerosis. *Hum Immunol* 2003;64:345–9.
131. Cocco E, Mancosu C, Fadda E, et al. Lack of evidence for a role of the myelin basic protein gene in multiple sclerosis susceptibility in Sardinian patients. *J Neurol* 2002;249:1552–5.
132. Guerini FR, Ferrante P, Losciale L, et al. Myelin basic protein gene is associated with MS in *DR4-* and *DR5-positive* Italians and Russians. *Neurology* 2003;61:520–6.
133. von Herrath MG. Obstacles to identifying viruses that cause autoimmune disease. *J Neuroimmunol* 2000;107:154–60.
134. Lang HL, Jacobsen H, Ikemizu S, et al. A functional and structural basis for *TCR* cross-reactivity in multiple sclerosis. *Nat Immunol* 2002;3:940–3.
135. Alperovitch A, Berr C, Cambon-Thomsen A, et al. Viral antibody titers, immunogenetic markers, and their interrelations in multiple sclerosis patients and controls. *Hum Immunol* 1991;31:94–9.
136. Shao W, Tang J, Dorak MT, et al. Molecular typing of human leukocyte antigen and related polymorphisms following whole genome amplification. *Tissue Antigens* 2004;64:286–92.
137. Zhou L, Vandersteen J, Wang L, et al. High-resolution DNA melting curve analysis to establish HLA genotypic identity. *Tissue Antigens* 2004;64:156–64.
138. Kenealy SJ, Pericak-Vance MA, Haines JL. The genetic epidemiology of multiple sclerosis. *J Neuroimmunol* 2003;143:7–12.

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

World Wide Web URL	Description of site
Genetics of MS*	
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=126200	OMIM* overview of genetic risk factors in MS
http://www.acceleratedcure.org	Home page of the Accelerated Cure Project for Multiple Sclerosis
http://wwwchg.duhs.duke.edu/diseases/ms.html	MS information from the Duke Center for Human Genetics
http://www-gene.cimr.cam.ac.uk/MSgenetics/welcome.shtml	Home page of the Multiple Sclerosis Genetics Group at the University of Cambridge
http://www.ucsf.edu/msdb/	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)
http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/	Description of the GAMES (Genetic Analysis of Multiple Sclerosis in Europeans) project for identifying risk factors for MS in European populations
http://www.nationalmssociety.org/Brochures-Genetics1.asp	National MS Society brochure on genetics in MS
HLA* complex	
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=142857	OMIM overview of <i>HLA-DRB1</i> , <i>-DQA1</i> , and <i>-DQB1</i> genes
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=146880	
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=604305	
http://www.anthonynolan.org.uk/HIG/nomen/dictionary/dictionary2004.html	HLA dictionary produced by the World Marrow Donor Association providing a translation between <i>HLA</i> allele names and their serologic equivalents
http://www.anthonynolan.org.uk/HIG/	Home page of the HLA Informatics Group, including sequence databases and nomenclature information (see next link)
http://www.anthonynolan.org.uk/HIG/lists/nomenc.html	Comprehensive lists of the official names for <i>HLA</i> class I and II genes and other genes in the <i>HLA</i> region
http://www.sanger.ac.uk/HGP/Chr6/MHC/	Home page of the MHC* Haplotype Project, which is generating complete sequences for several common MHC haplotypes
http://www.ashi-hla.org/	Home page of the American Society for Histocompatibility and Immunogenetics
http://www.ebi.ac.uk/imgt/hla/	<i>HLA</i> sequence database maintained by the international ImMunoGeneTics (IMGT) project

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