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Epidemiology

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Introduction

The etiology of multiple sclerosis (MS) is complex and not fully understood, but there have been various environmental and genetic factors associated with increased MS risk.[1] The prevailing thought is that MS is an autoimmune disorder whereby either viral or environmental agents, or both, trigger a T cell–mediated inflammatory attack, causing demyelination in the central nervous system (CNS). This is thought to result from a complex interplay between genes and the environment. The environmental factors most thought to be involved are vitamin D and Epstein-Barr virus (EBV). Obesity, particularly when present early in life, appears to play a role. Cigarette smoking also has been linked.[1] The aim of this chapter is to discuss genetic and environmental risk factors, both infectious and noninfectious, that are associated with MS development.

Demographics

MS is the most common cause of nontraumatic disability in young adults.[1,2] **The exact etiology remains unknown, but it is thought to be associated with genetic factors and environmental exposures with environmental factors playing a role in altering gene expression.**[3] Genes are needed for the development of MS, but the environment plays a predominant role in determining risk. These factors must act at an early age.

The National MS Society Prevalence Initiative, using administrative databases from a variety of sources including Medicare, Medicaid, Veterans Health Administration, and private insurers, estimated nearly 1.1 million people are living with MS in the United States.[4] This is over twice the number reported since the late 1970s. Estimates of prevalence are important for public health initiatives regarding possible preventive strategies and cost to society, among others.

Lifetime risk for MS has a female predominance with an approximately three times greater risk in women than in men, and incidence of MS is approximately 1 in 200 for women.

The peak time for diagnosis is between 20 and 40 years of age. MS is less frequently diagnosed in childhood, and diagnosis tends to decline after 50 years of age.[66] It can begin within the first or second year of life and can also be diagnosed beyond the age of 70 years.[5] Symptoms of the disease may often be present for years before a diagnosis is made. Critical exposure seems to occur before the age of 15 years, according to migration studies. The advent of magnetic resonance imaging (MRI) and improved diagnostic criteria throughout the years has led to earlier diagnosis of the disease.

Individuals of higher socioeconomic background have a greater risk than those of lower socioeconomic background. MS is more common in Caucasian population, whereas less frequent in African American and Asian populations. Studies have shown African American men to have an approximately 40% lower risk than white men.[6] However, MS tends to have a more severe course in African Americans. It is rare in Inuits.

Life expectancy of patients with MS has increased in the recent years, and this can be one explanation for the increase in the prevalence seen.[7] Increased awareness and diagnosis of the disease and improved access to neurologists can also increase incidence. One of the difficulties with ascertaining prevalence and incidence has been the problems encountered in consistency in the methodologies and quality of epidemiological studies which have been done.

A retrospective analysis done in the United States looking at commercially insured patient claims from 2008 to 2012 showed a prevalence of about 150 per 100,000 individuals. Females were three times more likely to have MS than males, and peak prevalence occurred at ages 45 to 49 years. Prevalence was relatively consistent during this time span.[8] Population-based administrative data from British Columbia during the years 1991 to 2008 showed an increase in prevalence by 4.7% per year on average. This could be explained by increased peak prevalence of MS, longer survival rates for MS, and greater life expectancy of women compared with men.[9] Recent data published from a prospective epidemiological Danish study looking at incidence of MS between 1950 to 1959 and 2000 to 2009 revealed an increased incidence of MS over a 60-year period, particularly

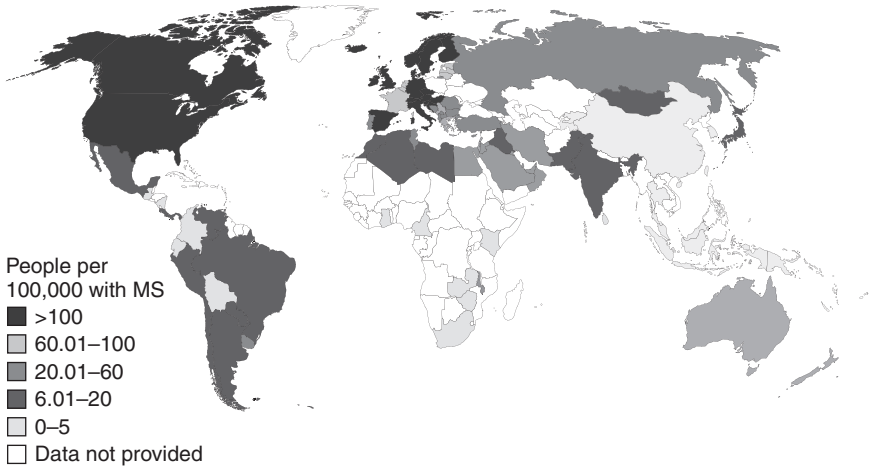

Figure 1.1. Worldwide prevalence of multiple sclerosis (MS) in 2013. Reprinted with permission from Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*. 2014;83(11):1022-1024. doi:10.1212/WNL.0000000000000768. See eBook for color figure.

in women and older age-groups, ages 50 to 64 years. The study analyzed 19,536 cases of MS with onset between 1950 and 2009 that were recorded in the Danish registry. Prevalence of risk factors, smoking and obesity, increased during this time period in Denmark, but in females, hormonal factors seem to have played an even more important role. Increased incidence in females seemed to parallel age at first pregnancy and had a link to fewer pregnancies. For older patients, improved MRI diagnostic ability to distinguish between smaller vascular lesions and MS lesions could also contribute to the increased incidence seen.[10,11] Prevalence of MS in Norway has increased 10-fold over the past 50 years, and female-to-male sex ratio has increased. Changes in lifestyle and improved health services and life expectancy with MS could be contributing factors.[10]

Where in the World Does MS Typically Occur?

MS is most common in the northern parts of North America and Europe (Figure 1.1).[12] Prevalence in these areas is between 0.1% and 0.2% of the population. Incidence is approximately 5 to 6 per 100,000 yearly.[13] Incidence being the risk of contracting the disease, and prevalence the proportion of cases in the population at any one time.

Geographic distribution appears to inversely parallel that of regional ultraviolet radiation with low incidence in subtropical and tropical regions and higher incidence with increasing latitudes both north and south of the equator,[3] with higher incidence in the northern parts of

North America and Europe, where the prevalence is between 0.1% and 0.2% of the population, and the incidence is about 5 to 6 per 100,000 population per year.[14] Because of this observation, it has been proposed that exposure to sunlight and higher vitamin D levels may have a protective effect.[69]

MS is rare in Asia, where the demyelinating disorder more commonly seen is neuromyelitis optica.

Migration effects: MS risk appears to decrease when people migrate from an area of higher incidence to that of lower incidence, particularly before the age of 15 years. When individuals move before their teenage years from an area of high MS prevalence to an area of low MS prevalence, their MS risk becomes similar to the region in which they moved. Children of immigrants from lower MS-prevalent regions born in a higher MS-prevalent region have a risk similar to those in the country of birth. Opposite migration does not appear to increase risk.[3,6]

Environmental Factors (Noninfectious)

Genetic factors are needed for MS to develop, but environmental factors play an important role in determining MS risk, particularly at an early stage in life.

Latitude

In temperate climate regions, MS incidence and prevalence increase with latitude.[6] Latitude appears to be the strongest risk factor for MS. In the northern hemisphere, MS prevalence tends to follow a north-south gradient and in the Southern hemisphere, a south-north gradient. However, this gradient appears to be decreasing. Over the last few decades, relative risk of MS was 2.02 comparing residence in northern US states to southern states for Vietnam veterans.[6]

For earlier born World War II veterans, the risk was 2.64. Recent studies have shown that the prevalence of MS in formerly considered low-risk areas such as South America and regions closer to the equator is increasing.[6] MS prevalence decreases with increasing light exposure.

Month and Place of Birth

Studies from Canada, Australia, and northern Europe[1,6,15] showed latitude-related increased risks for spring births that may reflect lower maternal vitamin D levels in winter pregnancies. During winter months at latitudes >42°N, most ultraviolet B (UVB) radiation is absorbed by the atmosphere with little production of vitamin D in the skin.

High-Salt Diets

Diet has been discussed as a potential risk factor for MS in developed countries. With increased adoption of the western diet and use of more processed food, salt intake has increased, and this can play a role in MS pathogenesis.[16] Salt intake has been shown to participate in modulating the differentiation of human and mouse Th17 cells. Mice fed a high-sodium diet had more aggressive courses of experimental autoimmune encephalomyelitis associated with increased IL-17. Increased sodium intake can boost the induction of IL-17–producing CD4+ helper T cells, which have been shown to be involved in MS pathogenesis. High-salt diets also affect the renin-angiotensin aldosterone system, which potentially can modulate immune responses.

Sodium intake has been associated with increased disease activity in MS.[17] Farez and colleagues found a positive correlation between exacerbation rates and sodium intake.[17] Increased radiological disease activity was also noted.

Diet and Gut Microbiome

Specific gut bacteria seem to be more common in MS patients than in controls, and pro-inflammatory responses in human blood mononuclear cells could be produced by these bacteria and trigger experimental allergic encephalomyelitis, an animal model of MS.[18] Bacteria in the gut have been suggested to interact with myelin antigens to trigger autoimmune responses.[19,20]

The cause-and-effect relationship between dysfunctional gut bacteria and MS is still uncertain. In a case-control study in Canada, authors reported increased risk of MS in persons whose diet was higher in animal fats and lower risk in persons with diet consisting of more vegetables and higher dietary fiber. Eating a high-fiber diet helps to promote microbial diversity particularly species within the firmicutes and bacteroidetes phyla.[18] Low dietary polyunsaturated fatty acids may also be another modifiable risk factor for MS.[21]

Vitamin D

Vitamin D levels can play a role in decreasing MS risk. Exposure to sunlight and greater vitamin D absorption in latitudes closer to the equator may help explain the relatively low prevalence of MS in these areas. The incidence of MS diagnosis appears to be the lowest near the equator and increases with increasing latitude. Migration studies have shown that moving from areas of higher to lower incidence appears to decrease future risk of developing MS, with the change in MS risk being most significant when migration occurs

in childhood and early adolescence. These areas of low MS prevalence are noted to be areas with higher sunlight exposure, sunlight being the principal inducer of Vitamin D synthesis. Vitamin D has been shown to have immunomodulatory effects, mediating a shift to a more anti-inflammatory immune response by increasing Th2 and regulatory T cell functionality. In its hormonal form, it has been shown to prevent experimental autoimmune encephalomyelitis, an animal model of MS.[22]

Low vitamin D levels in early life in individuals who bear HLA-DRB1*15, a genetic variant associated with increased MS risk, could allow autoreactive T cells to escape deletion by the thymus.[23] This has prompted the question of whether exposure to sunlight and higher vitamin D levels earlier in life confer a protective effect for MS. A study done by Munger supported this view, showing a strong protective effect of 25-hydroxy vitamin D levels of 100 nmol/L or higher before the age of 20 years.[24] Patients with MS studied prospectively had significantly lower levels of vitamin D during adolescence before disease onset.[24] A cross-sectional study by Laursen suggested that shorter amount of sun exposure during adolescence as well as higher body mass index (BMI) at the age of 20 years were associated with an earlier age of onset of MS.[25] Increased time spent in the sun during childhood has also been shown to be associated with decreased risk of MS.[25] Exposure to sunlight is the major source of vitamin D for many people. Sunscreen use has increased, so there is less UVB absorption. In addition, people with MS are likely to spend more time indoors because of heat sensitivity, as heat can often exacerbate symptoms. UVB radiation converts cutaneous 7 dehydrocholesterol to previtamin D3, which isomerizes to vitamin D3. Vitamin D3 hydroxylizes first to 25 hydroxyvitamin D3 (25(OH)D3) and then to 1,25, dihydroxyvitamin D3, which is the biologically active hormone. At higher latitudes, >42°N, very little vitamin D is absorbed by the skin because most UVB is absorbed by the atmosphere, especially in the winter months.[26] One recent study examining Finnish women of reproductive age showed that women who had deficient levels of vitamin D (i.e., <30 nmol/L) had a 43% higher risk of MS compared with women who had adequate levels of vitamin D (i.e., >50 nmol/L).[27]

Average diet and supplement intake in the United States is <400 IU/d. Studies done in vitamin D–deficient mice treated with vitamin D supplements have shown induction of regulatory T cells. Reduction in risk for developing MS with 25(OH)D levels > 100 nmol/L was stronger before the age of 20 years than at age 20 years or older.

Vitamin D supplementation and increase in blood levels are also beneficial in patients who already have the disease. Serum levels tend to increase by 0.8 to 1 nmol/L for every 1 μg ingested. In a study done by Munger et al examining vitamin D levels and MS risk, among whites, there was a 41% decrease in MS risk for every 50 nmol/L increase in 25 hydroxyvitamin D.[28]

Stress and Trauma

Regarding physical trauma and its association with development of MS, studies have not shown evidence to support a relationship between MS and trauma. The relationship between MS and psychologic or emotional stress, however, is possible.[1] An MRI prospective study done by Mohr et al. looked at life stress and new brain lesion formation. It reported that new MRI lesions increased after a lag of 8 weeks following increase in stress such as family or job conflict or changes in routine but not after major stressful events and that the MRI changes were not associated with clinical changes.[29]

Cigarette Smoking

There have been several prospective epidemiological studies linking smoking with increased risk of MS. Compared with nonsmokers, smokers had 40% to 80% increased risk of MS.[30] A British study using information obtained from The General Practice Database assessed the association between cigarette smoking and progression of MS. This was done using a nested case-control study design, and it was found that the risk of developing secondary progressive MS was over three times higher in smokers than in nonsmokers who had relapsing onset of disease. A Swedish study by Hedstrom et al. investigating the interaction between smoking and HLA genotype showed that smokers carrying HLA-DRB1*15 and lacking HLA-A*02 had a 13-fold increased risk compared with nonsmokers without those genetic factors.[31] Risk of MS with positive HLA genotypes was strongly influenced by smoking status. For those who have the disease, smoking has also been associated with increased risk of progression from relapsing to secondary progressive MS.[30] The mechanism may involve the components of cigarette smoke and lung irritation. Secondhand cigarette smoke exposure has also been observed to increase MS risk. This lung irritation causes increased pro-inflammatory cell activation in the lung.[31] CNS autoreactive aggressive T cells in the lungs can potentially be activated by smoking and then enter the CNS and induce autoimmune responses in genetically susceptible individuals. Earlier age of smoking can increase the risk of more severe MS.[32] Oral tobacco use has not been associated with increased risk of MS. Cigarette smoking can also increase the risk of other autoimmune diseases and respiratory infections. Animal models have suggested that cigarette smoke exposure affected innate and adaptive immunity, natural killer cells and B and T lymphocytes. Free radical nitric oxide may also play a role. Nitric oxide has been shown to block axonal conduction and cause axonal degeneration. Cigarette smoke contains nitric oxide. Smoking increases plasma levels of nitric oxide and may increase nitric oxide levels in the CNS that can contribute to axonal

degeneration and progressive disease.[30,32] Oligodendroglia, as compared with astrocytes and microglia, are more vulnerable to the harmful effects of nitric oxide.

Organic Solvents

Organic solvent exposure and nonspecific lung irritation have also been studied to show increased risk of MS in individuals who carry the HLA-DRB1*15 susceptibility gene, and particularly if someone also smokes, the risk is increased by 30-fold.[33,34]

Obesity

Increased rates of obesity in industrialized countries over the last 50 years have also played a role in increased incidence of MS.[35,36]

There does seem to be an association between higher BMI at the age of 20 years and lower age at the onset of MS. Observational studies have shown that obesity in early life can increase the risk of developing MS twofold. One US prospective study showed women with BMI >30 kg/m^2 at age 18 years had over twofold risk of developing MS than leaner women, and a Danish study showed that individuals with a childhood BMI >95th percentile were 70% more likely to develop MS than those with a childhood BMI <85th percentile.[37,38] Richards and colleagues used Mendelian randomization approach to evaluate causality between obesity and MS risk and suggested that early life obesity does seem to be causally related to MS risk.[39] This raises important public health signals for continued strategies to decrease childhood obesity. Vitamin D is stored in fat, so people who are obese have lower serum vitamin D levels than thin people.

Sex Hormones

Estrogens in high levels seem to shift immune response from pro-inflammatory type 1 to noninflammatory type 2. There is decreased risk of relapses during pregnancy when levels are high and increased risk postpartum.

Vaccinations

A nested case-control analysis in two large cohorts of nurses in the United States, in the Nurses' Health Study 1 and Nurses' Health Study II using vaccination records did not reveal any association between hepatitis B vaccination and the development of MS.[40]

Environmental Factors (Infectious)

Hygiene Hypothesis

Hygiene hypothesis proposes that early life infections downregulate allergic and autoimmune disorders and lower incidence of early life infections increases incidence of allergic and autoimmune diseases. Later age of infection in genetically susceptible individuals could increase risk.[3] Higher sibling exposure early in life in Caucasians also is associated with decreased MS risk.[41]

HHV-6

Human herpes virus (HHV) variant A is more commonly reported in MS patients. Interaction of HHV-6 variant A has been postulated to play a role in infecting EBV-positive B cell lines and activating the latent EBV genome.[42]

Parasitic Infections

According to the hygiene hypothesis, in developed countries where there is decreased incidence of early childhood infections, the immune system may not develop normally and can turn on itself. Parasitic worms may play a beneficial role. Several studies in animal and human models have demonstrated the ability of helminths to alter immune responses. Correale and Farez showed evidence of parasitic infection leading to increased production of regulatory cells that inhibit T cell proliferation, suppress interferon gamma production, and produce IL-10 and TGF-B that can lead to decreased inflammatory activity in MS.[43]

EBV

EBV is a double-stranded DNA virus of the herpes family, which is responsible for the highly immunogenic infection of B lymphocytes. Infants are susceptible to the virus as maternal protection subsides. It is a common early life infection, especially in developing countries, often seropositive in children by the age of 3 years, usually transmitted by saliva.[3,42] Once infection occurs, antigen-specific cytotoxic T cells expand in response and persist at high levels. If some of the cells carrying T cell receptors recognize self peptides, autoimmunity could result.[42] The virus remains latent with intermittent reactivation. If exposure, as is often the case in developed countries, is delayed into adolescence or adulthood, infectious mononucleosis can occur in 35% to 50% of cases. There is a low risk of

MS in EBV antibody–negative individuals, but in EBV antibody–positive individuals, particularly if they have had infectious mononucleosis, there is an increased risk. This risk has been noted across racial groups and ethnicities, in whites, blacks, and Hispanics.[44] As so many individuals are infected with EBV and do not develop MS, cofactors such as age at time of infection, genetic susceptibility, or infection with other microbes along with EBV may be required.

CMV

Cytomegalovirus (CMV) is also a common early life infection in low-/middle-income countries. Early infection is often asymptomatic; however, if delayed into adulthood, particularly in females, can result in birth defects from congenital CMV. A large population-based multiethnic study of incident MS cases conducted by Langer-Gould noted CMV serum positivity at an early age showed inconsistent association between CMV seropositivity in whites and later development of MS; however, it did support the hygiene hypothesis. Higher CMV virus exposure was noted in the Hispanic population studied. Previous studies have shown inverse association between CMV seropositivity and MS.[44]

Breastfeeding

Whether breastfeeding is a modifiable risk factor for MS remains unclear. It can result in vertical transmission of virus such as HIV (human immunodeficiency virus) and CMV, but can also protect against common early childhood infections. Several studies in Europeans and Mexicans has found that breastfeeding, especially for greater than 4 months of age, was associated with lower risk of MS.[45,46]

Genetics of Multiple Sclerosis

MS Risk in Families

It has long been noted that there is an important genetic component in the development of MS. Prior family studies have indicated that MS aggregates in families, with increased family risks ranging from ~300-fold for monozygotic twins[47,48] to 20-40-fold for first-degree relatives (dizygotic twins, nontwin siblings, and parent-offspring pairs)[49] compared with the general population. Prior twin studies have shown relatively higher concordance rates of MS in monozygotic twins (24%-30%) than dizygotic twins (3%-5%), and there was no significant difference in concordance rates between dizygotic twins and nontwin siblings.[48,50] Although shared environment may contribute to familial aggregation of MS, the significant excess risk for

monozygotic twins and similar concordance rates between dizygotic twins and nontwin siblings suggested that this aggregation is more likely to be genetically determined.[48] This was further supported by findings from a large population-based study, which showed that the frequency of MS among first-degree nonbiological relatives living with the MS index cases was significantly lower than that among biological relatives and very similar to that of the general population.[51]

As the prevalence of MS is higher in women, it was hypothesized that affected males, compared with affected females, had a stronger genetic predisposition, and thus their offspring would have a higher risk for MS, a phenomenon known as the Carter effect.[52] A previous study of 441 children (45 with definite MS) of an affected father or mother (197 families of interest) from 3598 individuals suggested that fathers with MS are 2.2-fold more likely to transmit MS to their children than mothers with MS.[52] However, another study with a relatively larger sample size, including a total of 8401 offspring (798 had MS) from 3088 nuclear families with one affected parent, indicated that there was equal transmission of MS from affected fathers versus affected mothers (9.41% vs. 9.76%).[12] In addition, the sex ratio among affected offspring was the same between affected fathers and affected mothers.[12] Thus, while whether men or women transmit MS more often to their children needs further investigation, there is a great interest in another parent-of-origin effect imparted by the unaffected mothers of MS patients. The first line of evidence was from a study including 1567 index MS cases with half-siblings which reported that the MS risk was significantly higher for maternal half-siblings (2.35%) than that for paternal half-siblings (1.31%).[53] This maternal parent-of-origin effect in MS was further supported by observations from avuncular pairs that the number of avuncular pairs with MS connected through an unaffected mother was significantly higher compared with those connected through an unaffected father.[54] Although the mechanisms remain unclear, the observed maternal effect in MS might be due to the maternal uterine environment and/or potential gene-environment interactions rather than maternal genetic predisposition.

MS Genetic Loci

Until very recently, MS susceptibility genes have been poorly understood. Many candidate-gene and family-based linkage studies (or genome-wide linkage studies) have demonstrated that the human leukocyte antigen (HLA) is the main genetic susceptibility locus associated with MS.[55] For example, the *HLA DRB1**1501 allele has been associated with a three to four times increased risk of MS.[56] Despite the success of identification of MS-associated *HLA* locus, candidate-gene and family-based linkage studies have failed to identify any other loci beyond the *HLA*.

With rapid improvements in high-throughput single nucleotide polymorphism (SNP) genotyping technology and the development of the HapMap project, the method for identifying susceptibility genes has changed dramatically. Genome-wide association study (GWAS) is currently the most commonly used approach for searching novel loci associated with MS. The largest GWAS for MS to date, conducted by the International Multiple Sclerosis Genetics Consortium (IMSGC), including a total of 80,094 individuals of European ancestry (14,498 MS cases and 24,091 controls in the discovery phase; 14,802 MS cases and 26,703 controls in the replication phase), identified 48 new genetic variants associated MS.[57] To date, more than 100 genetic loci beyond the HLA have been identified through GWAS.[58] The previously identified *HLA* loci have been confirmed by the GWAS and showed the largest genetic effect on MS (odds ratio [OR] = 3.10, $P < 1.0 \times 10^{-320}$), while other non-*HLA* genetic variants showed modest effect on MS (OR = 1.1-1.3). Many of these identified variants are in or near to genes which are involved in the immune system, particularly in T cell–mediated immune mechanisms.[57,58] Yet, the MS genetic loci identified so far only explain a small proportion (~27%) of MS heritability.[59] There are a number of theories unproven as yet which may explain the missing heritability, including rare variants with larger effects, common variants with smaller effects, structural variants, epigenetics, and pathway involvement, gene-gene interactions, and gene-environment interactions.[55,58]

Sex-specific genetic effects have been also analyzed in two GWAS[60,61]; however, only a few genetic loci showed suggestive sex differences in associations with MS. For example, in the IMSGC, SNP rs1800693 in *TNFRSF1A* was associated with MS at the genome-wide significance in women (OR = 1.16; $P = 8.9 \times 10^{-11}$) but not in men (OR = 1.05; $P = 0.14$), while SNP rs2293370 in *TIMMDC1* and SNP rs13333054 near *IRF8* were associated with MS at the genome-wide significance in men (OR = 1.26 and 1.24; $P = 1.4 \times 10^{-8}$ and 2.1×10^{-9}, respectively) but not in women (OR = 1.11 and 1.06; $P = 0.008$ and 0.04, respectively).[60] Given significant differences in prevalence and clinical phenotypes of MS between women and men, future GWAS with larger sample sizes are needed to identify sex-specific genetic loci which may help explain the sex differences in MS risk.

In addition, differences in MS risk have been observed across racial and ethnic groups, which might be, at least partially, due to genetic backgrounds. For example, the frequency of HLA-DRB1*1501 allele was high in Caucasian individuals and low in African and Asian individuals.[55] However, most existing GWAS of MS were largely conducted among individuals of European ancestry,[57] and race-/ethnicity-specific genetic effects for other MS genetic loci have not been well studied. Thus, GWAS in multiple racial and ethnic groups are warranted to identify more population-specific genetic loci which may help explain ethnic differences in MS risk.

Gene-Environment Interactions in MS

Besides genetic variants, gene-environment interactions may play an important role in the development of MS. Of note, several nongenetic risk factors for MS, such as smoking, EBV infection, and low vitamin D levels caused by insufficient sun exposure deficiency, have been reported to interact with MS genes, mostly HLA locus, in relation to MS risk in recent studies.[62] For example, a pooled analysis of 6 datasets suggested that smokers carrying HLA-DRB1*15 and lacking HLA-A*02 had an ~13-fold increased risk for MS (OR = 12.7, 95% CI 10.8-14.9) compared with never smokers without these genetic risk factors.[32] In a pattern of gene-environment interaction similar to that observed with smoking, infectious mononucleosis significantly accentuated the genetic effects of *HLA* on MS risk.[63,64]

There is a great interest in the role of vitamin D, vitamin D–associated genetic variants, and their interactions with MS genetic loci in the development of MS. Genetic variants in *CYP27B1*, a central vitamin D metabolism enzyme gene, have been identified to be associated with increased risk of MS through GWAS.[57] A more recent study using whole genome sequencing data identified a low-frequency coding variation in *CYP2R1*, which has large effects on lower vitamin D levels and increased MS risk.[65] Moreover, two Mendelian randomization analyses demonstrated the significant association between vitamin D–associated genetic variants and MS risk, suggesting a potential causal effect of vitamin D in MS.[66-68] Interestingly, in vitro experiments have provided evidence for a direct biological gene-environment interaction between vitamin D and *HLA-DRB1*,[26] the main MS susceptibility locus, although this interaction has not been well studied in human populations. It has been speculated that vitamin D deficiency in early childhood can reduce the expression of *HLA-DRB1* in the thymus, which might result in loss of central tolerance and then increase the risk of autoimmunity and MS in later life.[26] Thus, it is very important to clarify the role of the interaction between vitamin D and *HLA-DRB1* in the MS etiology, which will help provide new insights into the early prevention of MS.

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