Multiple sclerosis, vitamin D, and *HLA-DRB1*15*

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ABSTRACT

Background: Multiple sclerosis (MS) has a remarkable geographic distribution inversely paralleling that of regional ultraviolet radiation, supporting the hypothesis that vitamin D plays a central role in the disease etiology. The major histocompatibility complex exerts the largest genetic contribution to MS susceptibility, but much risk remains unexplained and direct gene-environment interaction is a strong candidate for this additional risk. Such interactions may hold the key for disease prevention.

Recent developments: Several recent studies strengthen the candidacy of vitamin D as a key player in the causal cascade to MS. This includes a newly identified gene-environment interaction between vitamin D and the main MS-linked HLA-DRB1*1501 allele and evidence showing that vitamin D levels are significantly lower in patients with MS as compared to controls. Also, a recent study in twins with MS supports the notion that vitamin D levels are under regulation by genetic variation in the 1α-hydroxylase and vitamin D receptor genes, perhaps pointing to their importance in the disease pathogenesis.

Conclusions: These findings have important practical implications for studies of disease mechanisms and prevention. Missing genetic risk may partly be explained by gene-environment interactions. More practically important is that these observations highlight a pressing need to determine if vitamin D supplementation can reduce the risk of multiple sclerosis (MS). However, the timing of action and the tissues in which this interaction takes place are not clear and future studies in prospective cohorts and animal models will be essential for deciphering the role of vitamin D in MS. ***Neurology*® 2010;74:1905–1910**

GLOSSARY

MHC = major histocompatibility complex; **MS** = multiple sclerosis; **VDR** = vitamin D receptor; **VDRE** = vitamin D response element.

In 1902, Sir Archibald Garrod[1] noted that "the influences of diet can mask some inborn errors of metabolism," giving birth to the concept of gene-environment interactions in human disease. The impact of background genes in the phenotype have finally been given more play[2] but now, over a century later, gene-environment interactions are being hailed as the future of public health. Their potential in disease prevention strategies seems vast.

A unifying theme emerging from recent work is that gene-environment interactions are likely to underpin many complex neurologic traits. Such interactions can be observed at statistical and biological levels. An example of statistical interaction is seen between smoking and the *CFH* gene. Both the presence of the *CFH* Y402H risk variant and a history of smoking synergistically confer an increased risk to age-related macular degeneration, as compared with either factor alone.[3] Although the mechanism behind the interaction is not fully understood, this has led to lifestyle recommendations that may prevent age-related macular degeneration in high-risk individuals.

A biological interaction is defined as the observation of a direct physical or chemical reaction and coparticipation between environmental and genetic factors in the causal mechanism of disease development. Examples of fully understood interactions are rare. Here we consider a

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recent study that puts the theory of biological gene-environment interactions into practice by demonstrating direct links between a leading candidate environmental factor, vitamin D, and the main susceptibility region which contains the *HLA-DRB1* locus. Accordingly, we review the existing evidence for a possible role of vitamin D in MS and discuss the relevance of recent findings.

MS: GENES AND ENVIRONMENT Epidemiologic studies in MS provide overwhelming evidence that both genes and environment are important in the etiology of the disease. If genetic factors are held constant, the environment and stochastic events presumably set the disease threshold. Although the effect of the environment in MS is not necessarily mediated by a single factor, latitude demonstrates the strongest association.[4] In the Northern hemisphere, MS prevalence shows a north-south gradient, mirrored by a south-north gradient in the Southern hemisphere. In accordance with the disease geography, sunlight, specifically through its role in generating active vitamin D, has been implicated as a key environmental factor in MS.[5]

Recent support for this theory comes from the finding that patients with MS studied prospectively had significantly low levels of circulating vitamin D [25(OH)D] during their adolescence prior to disease onset compared to age-, sex-, and ethnicity-matched controls.[6] In the Caucasian population, there was a 41% decrease in MS risk for every 50 nmol/L increase in 25(OH)D. Other key observations that had lent credence to this hypothesis include age-dependent low risk of MS in UK migrants to sunny South Africa,[7] differential twin concordance rates by latitude of birthplace,[8] and month of birth effects highlighting a risk factor that varies seasonally in MS.[9] A detailed list of reports supporting this concept is summarized in table 1 and expanded in table e-1 on the *Neurology*® Web site at www.neurology.org.

However, the environment cannot explain why African American, Asian, and North American Aboriginal individuals are inherently more resistant to MS compared to white individuals, despite residing in temperate regions with high disease prevalence.[10] This emphasizes the important role of genetics. The largest MS genetic association in Northern Europeans is with the extended major histocompatibility complex (MHC) haplotype *HLA-DQB1*0602-DQA1*0102-DRB1*1501-DRB5*0101(DR2)*.[11] Other haplotypes in this region also demonstrate epistatic interactions to modify risk, highlighting the MHC as the key susceptibility locus in MS.

Several investigators have suggested that the frequency of MS tracks the distribution of northern European genes,[12-14] and that susceptibility genes show much of the same geographical patterns as the distribution of MS.[15] For example, increased prevalence of MS in Scotland compared to England has been credited to the higher frequency of the *DR2* haplotype in the general Scottish population.[16] This is especially true in the Orkneys, where the frequency of *DR2* and the disease incidence are both the highest recorded in the world.[17]

However, the geography of the disease cannot be solely linked to genetic clines, as individuals from the same ethnic derivation can also have very different risks for MS in areas separated by latitude.[18] US data reveal a north-south as well as an east-west gradient attributed to the latitude differences and the pattern of Scandinavian immigration.[19] Collectively, these observations point to the conclusion that the distribution of MS cannot be explained by any single known environmental or genetic factor in isolation. A heterogeneous distribution of genes, environmental factors, and particularly their interplay appears to be required.

INTERACTION BETWEEN VITAMIN D AND *HLA-DRB1* Ultraviolet radiation–dependent metabolism provides the major source of vitamin D in humans but at high latitudes solar radiation is too low to produce adequate levels of vitamin D, particularly in the winter and adjacent months.[20] Biological effects of the active form of vitamin D (1,25-dihydroxyvitamin D3) are mediated by the vitamin D receptor (VDR). This receptor is a member of the steroid receptor superfamily and influences the rate of transcription of vitamin D–responsive genes by binding to vitamin D response elements (VDREs) in the genome. The effects of vitamin D on MHC class II gene expression have long been appreciated and early studies demonstrate that vitamin D can alter HLA-DR antigen expression and presentation.[21]

In an attempt to couple genetics with the environment, Ramagopalan et al.[22] recently searched known MS susceptibility loci for VDREs, to determine if they could be regulated by vitamin D. A single VDRE in the *HLA-DRB1* promoter region was identified. Strikingly, this VDRE showed haplotype-specific differences, being highly conserved (no mutations on over 600 chromosomes) in the major MS-associated *DR2* haplotype bearing the *HLA-DRB1*15* allele but not conserved generally among non–MS-associated haplotypes. Functional assays were then used to demonstrate that this VDRE influenced gene expression, thereby conferring 1,25-dihydroxyvitamin D3 sensitivity to *HLA-DRB1*15*.

Table 1 Circumstantial evidence for a role of vitamin D in multiple sclerosis

References	Findings
Geography and migration	
18, 19, 37, 38	Global distribution of MS increases with distance north or south of the equator and correlates with latitude.
7, 39	MS prevalence in UK migrants to different regions in Australia and correlates with latitude and to sunny South Africa results in age-dependent low risk of MS.
8	Twin concordance rates for MS vary with latitude of birthplace.
Sunlight exposure	
5, 40, 41	Average annual hours of sunshine, ambient UV radiation, and December daily solar radiation at place of birth are inversely associated with MS.
42, 43	Outdoor work and residence in a high sunlight area and occupational exposure to UV light are associated with lower MS risk and mortality rates.
44–46	Increased amounts time spent in the sun during childhood are associated with lower rates of MS.
Vitamin D intake and circulating 25(OH)D levels	
47	Intake of vitamin D from supplements is inversely associated with risk of MS.
6	High circulating levels of vitamin D are associated with a lower risk of MS prior to disease onset.
24, 27, 48, 49	Lower levels of 25(OH)D are associated with higher MS risk, relapse rate, and disability.
Genetics	
34	Genetic variants in the vitamin D receptor gene are associated with MS.
33	Rare vitamin D–dependent rickets type I caused by a mutation in the 1α-hydroxylase gene coassociates with MS.
50	Vitamin D binding protein which transports 25(OH)D is downregulated in CSF samples of patients with MS compared to controls.
22	The main MS-associated HLA-DRB1*1501 allele is regulated by vitamin D.
32	Genome-wide association study identifies MS risk variants proximal to the 1α-hydroxylase gene.
Season, pregnancy, and other	
51	Clinical remission of MS is observed during pregnancy coincident with known increase in 1,25(OH)(2)D levels.
9, 52	Increased risk of MS among people born in May (or end of winter months) compared to November.
53	Maternal diabetes and obesity during pregnancy (contribute to vitamin D deficiency) are associated with higher risk of MS.

Abbreviations: MS = multiple sclerosis; UV = ultraviolet.

The variant VDRE present on other, non–MS-associated *HLA-DRB1* haplotypes was not responsive to 1,25-dihydroxyvitamin D3. It should be noted that several MS and autoimmune disease–associated haplotypes not addressed in this study could perhaps harbor conserved VDREs and call for a more detailed examination of this region, but the non–MS-associated *HLA-DRB1*04*, *07*, and *09* haplotypes contain polymorphisms, resulting in a nonfunctional VDRE.

These experiments provide evidence for a direct biological interaction between *HLA-DRB1*, the main MS susceptibility locus, and vitamin D, a key candidate for mediating the environmental effect. The role of this interaction in disease etiology remains to be discovered but it is plausible that a lack of vitamin D in early childhood can affect the expression of *HLA-DRB1* in the thymus. It can be speculated that a general reduction in the expression of disease-associated class II alleles including *HLA-DRB1*15* in the thymus during early life might result in loss of central tolerance, perhaps increasing the risk of autoimmunity in later life.

PUTTING THE INTERACTION IN CONTEXT Understanding this HLA–vitamin D interaction will undoubtedly be critical for dissecting disease mechanisms and future prevention strategies. The frequency of the MS-associated *HLA-DRB1*1501* allele varies substantially between ethnic backgrounds, being high in Caucasian individuals and low in African and Asian individuals. Therefore, this finding partially illuminates the geographical distribution of MS and offers some explanation as to why low prevalence of MS is observed in races with dark skins living in temperate clines regardless of heightened vitamin D deficiency due to the high ultraviolet-filtering capability of cutaneous melanin. Moreover, given that the frequency of *HLA-DRB1*15* is significantly higher in female patients with MS as compared to male patients with MS,[23] this interaction, at least in part, may explain why higher levels of vitamin D are associated with a lower incidence of MS, specifically in women.[24]

In addition, a recent report on multigenerational MS pedigrees provides evidence for an increased penetrance of *HLA-DRB1*15* over time in a female-specific manner, paralleling the increasing risk of MS in females.[25] The intriguing possibility that decreasing levels of vitamin D in the general population[26] due to changes in lifestyle (lack of outdoor activities, increased use of sun protection, and high obesity levels) have amplified the frequency of *HLA-DRB1*15* in MS over time warrants further consideration. Female bias may arise from gender differences in lifestyle choices and vitamin D metabolism. Indeed, lower vitamin D intakes and circulating concentrations of 25(OH)D have been observed in females compared to males and estrogen has been shown to control vitamin D3–mediated resistance to experimental autoimmune encephalomyelitis.

The timing of action and tissues in which this interaction might occur can only be speculated upon. It is tempting to hypothesize that the increased risk of MS among people born in May reflects maternal end-of-winter deficiencies in vitamin D. The recent observation that the month of birth effect is medi-

ated by patients with MS bearing the *HLA-DRB1*1501* allele as compared to those with non-*HLA-DRB1*1501* alleles supports this notion. Epigenetics may underpin gene-environment interactions and the resulting expression changes due to fetal reprogramming could later predispose adult disease. Such an argument can be further extrapolated to include the grandmaternal environment as she houses cells of 3 generations during her pregnancy.

However, the role of vitamin D in MS may extend beyond its interaction with HLA-*DRB1*15* and many MS relevant loci may be regulated by vitamin D. For example, active vitamin D has been shown to upregulate the biological activity of indoleamine 2,3-dioxygenase, resulting in a significant increase in the number of CD4+ CD25+ T-regulatory cells.[27] Accordingly, a recent study shows that serum levels of 25(OH)D correlate with the ability of T-regulatory cells to suppress T-cell proliferation in patients with MS.[28] This observation perhaps accounts for the potential beneficial effects of vitamin D via a peripheral mechanism in adulthood and following disease onset.

VITAMIN D LEVELS AND SUPPLEMENTATION

Can vitamin D supplementation reduce the risk of MS? To answer this question, let us consider a classic example of gene-environment interaction. Tryon's[29] artificial selection experiment produced a remarkable difference in maze-running ability in 2 selected lines of rats after 7 generations of selecting the "best" and "worst" maze-running rats and breeding within their respective categories. Amazingly, the difference in ability disappeared in a single generation, if those rats were raised in an enriched environment with more objects to explore. This elegantly demonstrates that a genetic effect is only seen under some environmental conditions. Similarly, it is reasonable to hypothesize that the effect of *HLA-DRB1*15* is only significant in the absence of sufficient vitamin D levels.

Given that a high frequency of vitamin D insufficiency has been observed in the general population, a strong argument can and has been made for supplementation in the general population. We discuss critical time periods relevant to MS in table 2. There is an emerging consensus that public health recommendations for vitamin D intake (200 IU/day) fall below the level required for protection against MS and other vitamin D–related diseases (1,000–4,000 IU/day).[30] Tailoring vitamin D supplementation to genetic profile (i.e., selecting for the presence of *HLA-DRB1*15*) may be the most efficient method of identifying benefits.

Evidence also suggests that levels of active vitamin D are genetically regulated and are influenced by variation in the 1α-hydroxylase gene,[31] which controls the rate-limiting step in making vitamin D active. Therefore, it is not surprising to find that a recent large Australian study reports an association of polymorphisms proximal to the 1α-hydroxylase gene with MS,[32] although the causal variant remains to be fine mapped. Further support for a role of 1α-hydroxylase in MS comes from previous coassociation of rare vitamin D–dependent rickets type 1 (caused by a mutation in the 1α-hydroxylase gene) with MS.[33] Whether these mutations interact with the vitamin D–regulated *HLA-DRB1*15* allele needs to be tested.

Similarly, the vitamin D receptor gene has tentatively been disease-associated in some populations[34] but not replicated in others.[35] It is intriguing that studies reporting positive associations with both of these genes were performed in populations with relatively high exposure to vitamin D. Therefore, it can be hypothesized that such polymorphisms are perhaps more penetrant in MS cohorts from countries with sufficient exposure to vitamin D levels. Indeed, this has been shown to be true in type 1 diabetes, where ultraviolet radiation levels in the winter could inversely determine the association of vitamin D re-

Table 2 Possible time periods for a vitamin D effect

Time period	Circumstantial evidence
Gestational period	Higher disease risk in dizygotic twins vs full siblings and a maternal effect suggest intrauterine factors in MS.[53] Support for a role of vitamin D during gestation has come from a recent disease association of maternal diabetes and obesity, known to contribute to insufficient prenatal vitamin D levels.[9]
	Several studies show latitude-related increased risks for May births perhaps reflecting maternal end-of-winter deficiencies in vitamin D.[54]
	This time period coincides with rapid development of the nervous system. The observation that developmental vitamin D deficiency can alter the expression of genes encoding mitochondrial and synaptic proteins in the adult rat brain[7] may be potentially important in the MS etiology.
Early childhood and adolescence	Migration studies were instrumental in Acheson's original proposal for a role of vitamin D in the pathogenesis of MS. Northern European migrants to sunny South Africa have a low rate of MS. Migration before the age of 15 is necessary to alter risk.[46]
	Childhood avoidance of sun[6] and low 25(OH)D during adolescence[22] significantly increase the risk of MS.
	This time period coincides with thymic development. A general reduction in the expression of *HLA-DRB1*15* due to lack of vitamin D[39] in the thymus during early life can result in loss of central tolerance perhaps resulting in autoimmunity in later life.
Adulthood	Australian migration data suggest that risk can be altered up to adulthood.[42] Outdoor work and residence in a high sunlight area are associated with lower risk of MS.[55]
	After disease onset, vitamin D levels are lower in patients compared to controls.[56] Also, vitamin D levels are lower during relapses compared to remissions.
	It has been shown that the ability of T-regulatory cells to suppress T-cell proliferation in MS is dependent on vitamin D levels.[28] Collectively, this information suggests that vitamin D can play a role in adulthood and post diagnosis.

Abbreviation: MS = multiple sclerosis.

ceptor gene polymorphisms in several individual studies.[36]

CONCLUSION Several lines of evidence discussed in this review are circumstantial and each individual study is open to an alternative interpretation. However, there is no single alternative interpretation that could easily explain all lines of evidence supporting a role of vitamin D in MS pathogenesis. Recent findings substantially strengthen the case for a role of vitamin D in MS and implications are now too great for prevention to remain an unanswered question. The interaction between *HLA-DRB1*15* and vitamin D provides new insight into how vitamin D status may contribute to MS pathogenesis and pinpoints the MHC as the likely site of environment-gene interaction in this disease.

Future studies in prospective cohorts and animal models will be essential for understanding where and when vitamin D plays a role in MS. This will forge new avenues of research ultimately resulting in appropriate intervention strategies for high-risk individuals. As a result, vitamin D represents a key player that will be at the heart of future MS research and clinical practice.

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