Summer 2026, Volume 11, Issue 42 (24- 43) DOI: 10.22034/ppmj.2026.743583

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Genetic Profiles That Increase Susceptibility to Multiple Sclerosis after Epstein–Barr Virus Infection: Focus on HLA, EBV-Specific Immune Response, and Polygenic Immune Risk

Kiana Ali-akbar-pourhemmati [1,*]

[1]**Department of Biological Sciences, Faculty of Biology, East Tehran Branch, Islamic Azad University, Tehran, Iran.**

ARTICLE INFO

Paper Type: Review Article

Submitted: 2026-05-15
Accepted: 2025-08-18

Keywords:
Epstein–Barr virus
Multiple sclerosis
HLA-DRB1*15:01
EBNA1
Genetic susceptibility

Corresponding author:
Kiana Ali akbar pourhemmati
Email: kianapourhemati41@gmail.com.

ABSTRACT

The Epstein–Barr virus (EBV) is recognized as the primary infectious agent linked to multiple sclerosis (MS), although the presence of EBV infection alone does not suffice to explain the progression of the illness, given that most patients infected with EBV do not manifest MS. This review examines host genetic profiles that may increase MS susceptibility among EBV-exposed individuals, with emphasis on HLA-mediated antigen presentation, EBV-specific immune responses, and non-HLA immune pathways. The strongest genetic risk signal is HLA-DRB115:01, often within the HLA-DR15 haplotype, which may promote presentation of EBV-derived antigens such as EBNA1 and facilitate CD4+ T-cell activation, molecular mimicry, and CNS-directed autoimmunity. In contrast, HLA-A02:01 appears protective, potentially through more effective CD8+ T-cell-mediated control of EBV-infected B cells; therefore, absence of HLA-A02:01 may represent an important risk-modifying feature. Emerging evidence also implicates HLA-E01:01, particularly in individuals with a history of infectious mononucleosis, suggesting a role for altered NK-cell and CD8+ T-cell regulation in EBV-associated MS risk. Beyond HLA, non-HLA loci such as CD86, CD40, IL2RA, and IL7R may amplify EBV-driven immune activation by modulating antigen-presenting cell function, B/T-cell costimulation, cytokine signaling, and immune tolerance. High anti-EBNA1 antibody titers, especially in HLA-DRB115:01-positive individuals, may serve as an immunological marker of dysregulated host–EBV interaction. Overall, the most plausible high-risk profile combines EBV positivity, infectious mononucleosis or elevated anti-EBNA1 responses, HLA-DRB115:01 positivity, absence of HLA-A02:01, possible HLA-E01:01 carriage, and increased non-HLA immune risk burden. These profiles remain research-based risk-enrichment models rather than clinical prediction tools. Longitudinal investigations focusing on functional genomics, single-cell methodologies, HLA peptidomics, and EBV vaccination are required to understand the reasons behind the selective development of MS in certain EBV-infected individuals and to shape preventive strategies.

How to Cite this Article:
K. Ali AKbari Pourhemmati, "Genetic Profiles That Increase Susceptibility to Multiple Sclerosis after Epstein–Barr Virus Infection: Focus on HLA, EBV-Specific Immune Response, and Polygenic Immune Risk" Personalized & Precision Medicine Journal, Vol. 11, no. 42, pp. 24- 43.

INTRODUCTION

Multiple sclerosis (MS) is a persistent immune-mediated disorder that results in demyelination within the central nervous system (CNS), marked

Authors retain the copyright and full publishing rights.
Published by AmitisGen TECH Dev Group. This article is an open access article licensed under the Creative Commons Attribution 4.0 International (CC BY 4.0)

by inflammatory lesions, neuroaxonal damage, and progressive neurological impairment (1). While the specific etiology is not fully elucidated, MS is generally seen as a complex ailment stemming from the convergence of genetic vulnerability, environmental influences, and immunological irregularities (2). Among environmental influences, the Epstein Barr virus (EBV) has surfaced as the most reliably linked infectious agent in the etiology of multiple sclerosis. EBV is a widespread gamma-herpesvirus that induces lifelong latency in memory B cells, forming a scientifically credible connection between viral persistence, B-cell dysfunction, and central nervous system autoimmunity (3, 4).

The association between EBV and MS has been strengthened substantially by longitudinal epidemiological evidence. In a substantial group of over 10 million young adults within the U.S. military, seroconversion for EBV occurred prior to the onset of MS, with the likelihood of developing MS escalating nearly 32 times following EBV infection, while infections from other viruses did not exhibit a similar correlation (3). This finding shifted the EBV–MS relationship from a long-standing epidemiological observation toward a more causal framework. However, EBV infection alone cannot explain MS occurrence, because more than 90% of adults worldwide are EBV-seropositive, whereas only a small minority develops MS (5). This discrepancy suggests that host factors, particularly genetic susceptibility, determine whether EBV infection remains clinically silent or contributes to autoimmune demyelination (6).

Genetic susceptibility to MS is strongly shaped by the major histocompatibility complex (MHC), especially the human leukocyte antigen (HLA) region (7). The most robust genetic risk factor identified to date is the HLA-DRB115:01 allele, commonly part of the HLA-DR15 haplotype (8). In contrast, HLA-A02:01 has been repeatedly associated with protection against MS (9). These HLA associations are biologically relevant in the context of EBV because HLA molecules determine the repertoire of viral and self-peptides presented to T cells. Therefore, specific HLA profiles may influence the quality, magnitude, and specificity of EBV-directed immune responses, potentially promoting molecular mimicry, bystander activation, or survival of autoreactive lymphocytes (10).

Recent mechanistic studies have begun to connect EBV infection directly with MS-associated HLA risk. CD4+ T cells restricted by HLA-DRB115:01 have been shown to recognize EBV-derived antigens, supporting the concept that HLA-DR15 may shape pathogenic anti-EBV immunity in genetically susceptible individuals (11). In addition, experimental and immunopeptidomic work suggests that EBV infection may alter antigen presentation in a way that interacts with HLA-DR15 and promotes MS-relevant immune responses. These data provide a mechanistic bridge between two of the strongest MS risk factors: EBV infection and HLA-DRB115:01 carriage (10).

Beyond classical HLA-DRB115:01 risk, emerging evidence indicates that additional HLA and non-HLA variants may modify EBV-associated MS susceptibility. A recent population-based study reported that carriers of HLA-E01:01 with a history of infectious mononucleosis (IM), a clinical manifestation of primary EBV infection, had an increased risk of MS independently of other MS-associated HLA alleles. This finding suggests that genetic variation affecting non-classical antigen presentation and antiviral immune control may help explain why symptomatic EBV infection confers higher MS risk in some individuals (12). Similarly, studies in pediatric-onset MS have implicated interactions between childhood EBV seropositivity, HLA-DRB1*15, and variants in genes involved in antigen-presenting cell function, including CD86 (13).

The overarching genetic framework of MS is polygenic. Extensive genome-wide association studies have discovered over 200 non-MHC susceptibility variations, a significant number of which are associated with immunological pathways related to T cells, B cells, monocytes, microglia, cytokine signaling, and antigen presentation. These variants do not appear to be EBV-specific. Still, they may create an immune background that amplifies EBV-driven inflammation, impairs viral control, or lowers the threshold for loss of self-tolerance. Thus, EBV-associated MS risk is likely not determined by a single allele, but by a composite genetic profile involving classical HLA risk alleles, protective HLA variants, EBV-specific immune response genes, and a broader polygenic autoimmune burden (11, 14, 15).

Despite rapid progress, the genetic determinants that distinguish EBV-infected individuals who develop MS from those who remain healthy remain incompletely defined. Understanding these determinants is clinically important because it may enable risk stratification after EBV infection, clarify mechanisms of virus-triggered CNS autoimmunity, and inform preventive strategies such as EBV vaccination, antiviral approaches, or early immune monitoring in genetically susceptible populations. This review aims to summarize current evidence on genetic profiles that increase the risk of MS among EBV-infected individuals, with emphasis on HLA-DRB115:01, absence of protective HLA-A02:01, EBV-specific humoral and cellular immunity, emerging HLA-E associations, non-HLA immune loci, and polygenic risk models.

EBV as a prerequisite or major trigger for MS

Overview: EBV as the leading infectious candidate in MS

EBV has emerged as the most significant infectious

agent associated with the development of MS (16). EBV is a widespread human gamma-herpesvirus that infects over 90% of people globally and maintains lifelong latency, mostly among memory B cells (17). This unique biology provides a plausible framework for its involvement in MS, a disease in which B cells, antigen presentation, ectopic lymphoid inflammation, and antibody-mediated immune responses have central pathogenic roles (18). Nonetheless, the widespread occurrence of EBV infection among the general population and the relatively low rate of MS suggest that EBV is probably not enough by itself. EBV is increasingly seen as an essential precursor or significant catalyst that operates with host genetic predisposition and several environmental risk factors (19).

Prospective epidemiological evidence linking EBV to MS

The most persuasive epidemiological data comes from extensive prospective studies indicating that EBV infection occurs before the start of MS (20). In a significant longitudinal investigation including over 10 million young individuals in the U.S. military, the occurrence of EBV seroconversion was associated with a notable rise in the risk of multiple sclerosis. Among individuals who later developed MS, nearly all were EBV-seropositive before disease onset, and the risk of MS increased approximately 32-fold after EBV infection. Importantly, this association was not observed with other common viruses, including cytomegalovirus, supporting a relatively specific link between EBV and MS rather than a nonspecific consequence of viral exposure or immune activation. The serum neurofilament light chain, an indicator of neuroaxonal damage, rose only after EBV seroconversion, hence reinforcing the chronological order in which EBV infection occurs prior to observable CNS harm (3).

EBV seronegativity and the timing of MS risk

Earlier prospective serological studies also support the concept that EBV infection is strongly associated with future MS risk. Individuals who remain EBV-seronegative appear to have an extremely low risk of developing MS, whereas risk rises after EBV seroconversion. In addition, elevated antibody responses to EBV nuclear antigen 1, particularly anti-EBNA1 IgG, have repeatedly been associated with increased MS risk years before clinical onset. EBNA1 is expressed during EBV latency, and heightened anti-EBNA1 responses may reflect altered host control of latent infection, enhanced EBV-specific immune activation, or a propensity toward cross-reactive immune responses (2, 4). These observations suggest that not only EBV infection itself, but also the quality and magnitude of the host immune response to EBV, may be relevant to MS susceptibility. (20-22).

IM as a clinical marker of high-risk EBV infection

IM, the symptomatic manifestation of primary EBV infection, further strengthens the EBV–MS association. A history of IM has consistently been associated with increased MS risk, suggesting that the intensity, timing, or immunological context of primary EBV infection may influence later autoimmune susceptibility (23).

Delayed primary EBV infection during adolescence or early adulthood often produces stronger systemic immune activation than asymptomatic childhood infection. This may help explain why IM is a particularly relevant clinical marker in MS risk studies. From the perspective of this review, IM is especially important because it provides a bridge between EBV exposure and host genetic susceptibility. Genetic variation may influence whether primary EBV infection is efficiently controlled, remains clinically silent, or develops into a symptomatic and immunologically intense infection that increases the likelihood of later autoimmune events (24, 25).

EBV latency in B cells and MS-relevant immune dysregulation

Several biological mechanisms may explain how EBV contributes to MS. First, EBV establishes latency in B cells, a cell population now recognized as central to MS immunopathology. B cells may function as antigen-presenting cells, generate pro-inflammatory cytokines, experience clonal proliferation, and facilitate T-cell activation. The therapeutic effectiveness of B-cell-depleting treatments in MS reinforces the significance of B-cell biology in disease processes (19, 26).

EBV-infected B cells may therefore contribute to MS by promoting abnormal antigen presentation, sustaining autoreactive lymphocyte populations, or creating a chronic reservoir of immune activation. Because EBV persists within the memory B-cell compartment, it has the potential to influence immune function over long periods, consistent with the long interval that can occur between primary EBV infection and clinical MS onset. This persistent viral latency may be particularly relevant in individuals whose genetic background favors inefficient EBV immune control or exaggerated EBV-directed immune responses (26, 27).

EBNA1-specific immunity and molecular mimicry

A second major mechanism by which EBV may promote MS is molecular mimicry between viral and CNS antigens. EBNA1 has received particular attention because it is expressed during EBV latency and because elevated anti-EBNA1 immune responses have been associated with increased MS risk before disease onset (19, 28).

A key mechanistic study showed that clonally

expanded B cells in MS can recognize both EBV EBNA1 and the CNS protein glial cell adhesion molecule, GlialCAM. The study provided evidence that anti-EBNA1 immune responses can cross-react with GlialCAM, and that EBNA1 immunization worsened disease in an experimental model (28). These findings offer a direct mechanistic link between EBV-specific immunity and CNS-directed autoimmunity. Nevertheless, molecular mimicry is unlikely to explain all EBV-associated MS cases. It is more likely one component of a broader pathogenic framework involving B-cell dysregulation, antigen presentation, chronic immune activation, and genetically determined loss of immune tolerance.

Interaction between EBV and host genetic background

A third and particularly relevant mechanism for this review is the interaction between EBV and the host genetic background. This is especially important for HLA alleles, which determine how viral and self-peptides are presented to T cells. The strong association between HLA-DRB1*15:01 and MS suggests that certain individuals may present EBV-derived peptides in a way that promotes autoreactive CD4+ T-cell responses or facilitates cross-reactivity with CNS antigens (10). Conversely, protective alleles such as HLA-A*02:01 may support more effective antiviral immune surveillance or reduce the presentation of pathogenic peptide repertoires (9).

Thus, EBV may act as a trigger whose pathological consequences depend strongly on genetically determined antigen presentation. This concept helps explain why EBV infection is common, while MS is rare. In most EBV-infected individuals, antiviral immunity resolves primary infection and maintains long-term viral control without CNS autoimmunity (29). In genetically susceptible individuals, however, EBV-directed immune responses may be shaped in a way that promotes persistent B-cell activation, autoreactive T-cell responses, or antibody cross-reactivity with CNS antigens (29, 30).

Figure 1 summarizes this model, showing how EBV infection may initiate MS-relevant immune pathways, while host genetic susceptibility determines whether these responses remain controlled or progress toward CNS autoimmunity.

HLA class II genetic susceptibility

*HLA-DRB1*15:01 as the major genetic risk factor for MS*

The most robust and consistently observed genetic risk factor in MS is found in the MHC class II region, namely the HLA-DRB1*15:01 allele, often inherited as part of the HLA-DR15 haplotype. This allele has reliably been identified as the primary genetic risk

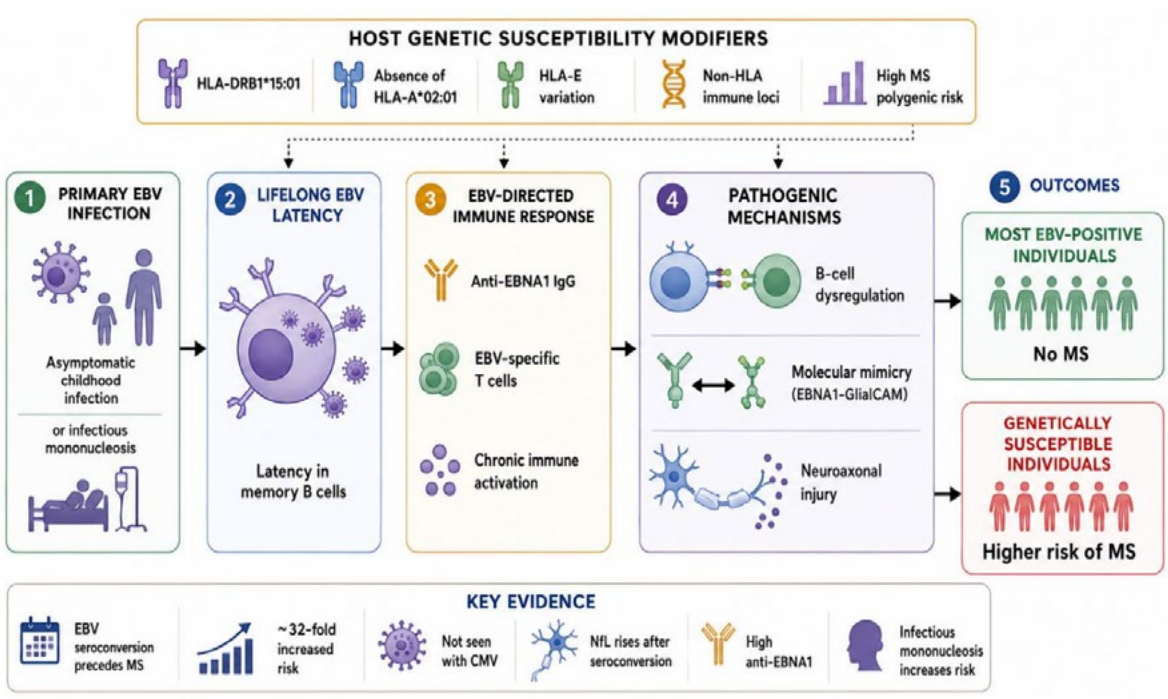


Fig 1. The conceptual framework of EBV as a nearly essential but inadequate catalyst for MS. EBV infection occurs before the development of MS and induces lifelong latency in memory B cells. In people with genetic predispositions, immune responses aimed against EBV may lead to B-cell dysregulation, irregularities in antigen presentation, molecular mimicry between EBNA1 and CNS antigens like GlialCAM, and persistent immunological activation. Given that EBV infection is prevalent and MS is seldom, genetic predisposition in the host is necessary to explain why only a fraction of those infected with EBV progress to MS.

determinant for MS in several groups, particularly among those of European descent. Its pivotal function in MS vulnerability underscores the significance of CD4+ T-cell-mediated immunity and antigen presentation in the development of the illness (31, 32).

The relevance of HLA-DRB115:01 becomes particularly important in the context of EBV, because HLA class II molecules determine which extracellular, endosomal, or B-cell-derived antigens are presented to CD4+ T cells (33). Since EBV establishes lifelong latency in B cells, and B cells are professional antigen-presenting cells, the combination of EBV persistence and HLA-DRB115:01-mediated antigen presentation provides a plausible biological bridge between the strongest environmental and genetic risk factors for MS. Recent reviews and mechanistic studies increasingly support the view that HLA-DR15 may shape EBV-specific CD4+ T-cell immunity in a way that contributes to MS-relevant immune dysregulation (34).

HLA-DR15 and antigen presentation of EBV-derived peptides

The HLA-DR15 haplotype comprises HLA-DRB1*15:01 and associated class II molecules that are involved in the presentation of peptide antigens to CD4+ T lymphocytes. In the context of EBV infection, this is especially significant since EBV-infected B cells are capable of processing and presenting viral antigens via MHC class II pathways. If these peptides produced from EBV are displayed in an immunologically favorable environment, they might facilitate the proliferation of EBV-specific CD4+ T cells, sustained immune activation, or cross-reactive reactions targeting CNS antigens (10, 35).

A recent study directly linked HLA-DRB115:01 to EBV-specific CD4+ T-cell recognition. Drosu and colleagues showed that CD4+ T cells restricted by **HLA-DRB115:01** can recognize EBV glycoprotein-derived antigens capable of intracellular antigen presentation (10). This finding is important because it provides a mechanistic connection between HLA-DRB1*15:01 and EBV-directed adaptive immunity, suggesting that the MS-associated HLA class II background can shape the repertoire of EBV-specific CD4+ T-cell responses (10).

This mechanism may be particularly relevant in EBV-infected B cells. Unlike many acute viral infections, EBV persists in the memory B-cell compartment, allowing repeated or chronic opportunities for viral antigen presentation (36). In individuals carrying HLA-DRB1*15:01, EBV-infected B cells may therefore act not only as viral reservoirs but also as antigen-presenting cells capable of sustaining CD4+ T-cell activation. This provides a biologically plausible route through which EBV latency, B-cell biology, and HLA class II genetic risk converge in MS (35).

EBNA1 as a key antigenic link between EBV and CNS autoimmunity

EBV nuclear antigen 1, or EBNA1, has become one of the most important EBV antigens in MS research. EBNA1 is expressed during latent EBV infection and is required for maintenance of the viral episome in infected cells. Elevated immune responses against EBNA1, especially anti-EBNA1 IgG, have repeatedly been associated with increased MS risk before disease onset. This makes EBNA1 not only a marker of EBV-directed immune activity but also a potential mechanistic contributor to disease development (37, 38).

In the context of HLA class II susceptibility, EBNA1 is important for two reasons. First, EBNA1-derived peptides may be presented to CD4+ T cells by MS-associated HLA class II molecules, including HLA-DRB115:01. Second, certain EBNA1 epitopes may share structural or sequence similarity with CNS antigens, creating the possibility of molecular mimicry. Therefore, an individual with HLA-DRB115:01 who mounts a strong EBNA1-directed immune response may have a higher probability of developing cross-reactive immune responses relevant to CNS autoimmunity (39).

This concept is supported by studies showing that anti-EBNA1 antibody titers and HLA-DR15 are both associated with MS risk. De Jager and colleagues reported that anti-EBNA1 antibody titers were associated with MS risk independently of the DR15 allele, suggesting that EBV-directed humoral immunity and HLA-DRB1*15:01 represent partially independent but potentially convergent risk dimensions (40).

Molecular mimicry involving EBNA1 and CNS antigens

A prominent mechanistic rationale for EBV-related MS is molecular mimicry, when immune responses aimed at EBV antigens inadvertently target structurally similar CNS proteins. The most often examined instance pertains to EBNA1 and GlialCAM, a central nervous system protein produced by glial cells. Lanz and associates revealed that clonally proliferated B lymphocytes from multiple sclerosis patients could attach to both EBV EBNA1 and GlialCAM, indicating a strong molecular resemblance between a dormant EBV antigen and a central nervous system target (28).

This finding is highly relevant to HLA-DRB115:01-mediated susceptibility. HLA-DRB115:01 may facilitate the activation or maintenance of CD4+ T-cell responses that support B-cell maturation, antibody production, and epitope spreading after EBV infection. In this model, EBNA1-specific immune responses may begin as antiviral responses but later extend toward CNS antigens such as GlialCAM. Recent evidence also suggests that antibody responses against EBNA1

and CNS-mimic antigens, including GlialCAM, may be elevated in individuals with MS carrying HLA-DRB1*15:01, supporting an additive interaction between genetic risk and EBV-related autoimmunity (41).

However, molecular mimicry should not be viewed as the only mechanism linking EBV and HLA-DRB1*15:01 to MS. It is more likely that molecular mimicry operates together with other processes, including B-cell dysregulation, altered antigen presentation, chronic EBV-specific T-cell stimulation, impaired viral control, and bystander inflammatory activation. This broader interpretation is important because MS is heterogeneous, and different patients may develop the disease through partially overlapping but non-identical EBV-related pathways (42).

EBV-induced immunopeptidome changes in the HLA-DR15 context

Recent mechanistic studies have broadened the understanding of EBV–HLA interaction beyond mere peptide imitation. Wang and associates indicated that EBV infection has the capacity to alter both the transcriptome and immunopeptidome of B cells affected by the MS-related HLA-DR15 haplotype. Their research indicates that EBV infection might modify the array of peptides shown by HLA-DR15 molecules, including both viral and self-originated antigens (35).

This is significantly vital for comprehending genetic predisposition in persons positive for EBV. If EBV infection alters antigen processing and presentation in HLA-DR15-positive B cells, then HLA-DRB1*15:01 could not just present specific EBV peptides; it might establish a more extensive antigen-presentation milieu that promotes the activation of autoreactive CD4+ T cells. This concept offers a more cohesive elucidation of how EBV infection and the inheritance of HLA-DR15 may collaboratively enhance immunological processes linked with MS (36, 43).

In practical terms, this means that the risk profile is unlikely to be explained by EBV seropositivity alone. Rather, MS risk may be enriched in individuals in whom EBV infection occurs within an HLA class II background that promotes persistent or pathogenic antigen presentation (44). This provides a direct rationale for considering EBV-positive / HLA-DRB1*15:01-positive individuals as a biologically meaningful high-risk subgroup.

*HLA-DRB1*15:01 as a possible co-receptor for EBV entry*

Another proposed mechanism linking HLA-DRB115:01 to EBV involves viral entry into B cells. A study reported that HLA-DRB115:01 may act as a co-receptor for EBV infection in a B-cell line, suggesting a direct molecular connection between the major MS genetic risk allele and EBV biology (45).

Although this finding requires further validation across primary human cells and diverse populations, it is conceptually important. If HLA-DRB115:01 facilitates EBV infection or alters the efficiency of viral entry, it could contribute to a higher burden of EBV-infected B cells or a qualitatively different pattern of EBV persistence. This would add another layer to the EBV–HLA interaction: HLA-DRB115:01 may influence not only antigen presentation after infection, but potentially the biology of EBV infection itself (46).

Integrative model: HLA-DR15 as a genetic amplifier of EBV-associated MS risk

Taken together, current evidence supports a model in which HLA-DRB1*15:01/HLA-DR15 acts as a genetic amplifier of EBV-associated MS risk. In this model, EBV provides the environmental trigger and persistent viral reservoir, whereas HLA-DRB1*15:01 shapes the antigenic and cellular immune context in which EBV is recognized. This may occur through several overlapping mechanisms: enhanced presentation of EBV-derived peptides, activation of EBV-specific CD4+ T cells, support of EBNA1-directed humoral immunity, facilitation of molecular mimicry with CNS antigens, and EBV-induced remodeling of the HLA-DR15 immunopeptidome. This framework helps explain why EBV infection alone is not sufficient to cause MS. Most EBV-infected individuals maintain lifelong viral latency without developing CNS autoimmunity. In contrast, individuals carrying HLA-DRB115:01 may be more likely to generate persistent, dysregulated, or cross-reactive EBV-directed immune responses. Therefore, the **EBV-positive / HLA-DRB115:01-positive** profile represents one of the most biologically plausible and best-supported genetic risk profiles for MS development.

This HLA class II–centered mechanism is illustrated in Figure 2, which summarizes how HLA-DRB1*15:01 may shape EBV antigen presentation and promote downstream EBNA1-directed immunity and CNS cross-reactivity.

While HLA-DRB115:01 represents the dominant HLA class II risk allele for MS, disease susceptibility is further modified by other HLA variants, including protective class I alleles such as HLA-A02:01.

HLA class I protection and risk modification

HLA class I alleles as modifiers of MS susceptibility

While the most significant genetic correlation in MS is found in the HLA class II area, namely HLA-DRB1*15:01, HLA class I alleles also play a role in vulnerability to the disease. HLA-A*02:01 is often identified as a protective allele. This protective connection has been reported across numerous independent investigations and does not seem to be

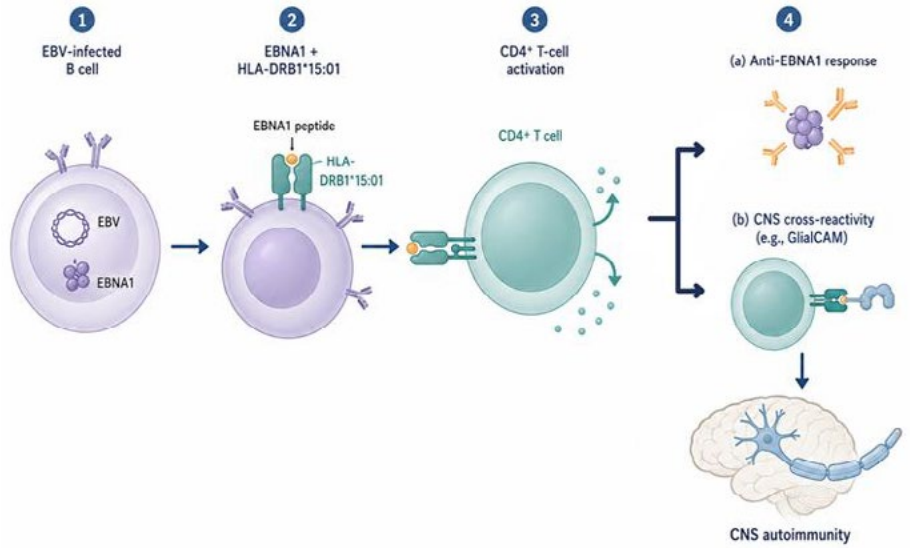


Fig 2. HLA-DRB1*15:01-mediated presentation of EBV antigens and CNS cross-reactivity. EBV-infected B cells may present EBNA1-derived peptides through HLA-DRB1*15:01, leading to activation of EBV-specific CD4+ T cells. In genetically susceptible individuals, this response may support anti-EBNA1 immunity and cross-reactive recognition of CNS antigens such as GlialCAM, thereby contributing to CNS autoimmunity and increased MS risk.

purely due to linkage disequilibrium with class II alleles, indicating that HLA-A*02:01 may have an independent immunological impact on MS risk (7, 47).

*HLA-A*02:01 as a protective allele in MS*

The protective effect of HLA-A02:01 has been confirmed in population-based and genetic association studies. Bergamaschi and colleagues reported a strong protective effect of **HLA-A02**, independent of HLA-DRB1*15 and other HLA-DRB1 alleles, supporting the idea that class I-mediated immune mechanisms modify MS susceptibility independently of classical class II risk (47). Similarly, Link and colleagues emphasized the importance of both HLA class I and class II effects in MS and confirmed the protective contribution of HLA-A*02 in Scandinavian cohorts (48). These findings indicate that MS risk is shaped not only by alleles that enhance susceptibility, but also by alleles that may actively reduce disease risk.

Biological rationale: CD8+ T-cell surveillance and EBV control

The biological relevance of HLA-A02:01 in EBV-associated MS risk is plausible because HLA class I molecules present intracellular peptides to CD8+ cytotoxic T cells, which are central to antiviral immune surveillance. Since EBV establishes latent infection in B cells, effective CD8+ T-cell recognition of EBV-derived peptides may be important for controlling the burden and activity of EBV-infected B cells. In this context, HLA-A02:01 may protect against MS by supporting efficient antiviral immune control, thereby reducing persistent EBV-driven B-cell activation and downstream autoimmune risk (49, 50).

*HLA-A*02:01 and EBV viral load in MS*

Evidence directly linking HLA-A02 to EBV control has been reported in MS cohorts. Agostini and colleagues found that MS patients expressing **HLA-A02** had significantly lower EBV viral load compared with HLA-A02-negative patients. This observation suggests that HLA-A02 may contribute to more effective immune control of EBV-infected cells, providing a mechanistic explanation for its protective association in MS (50). Although viral load is only one measure of EBV immune control, these data support a model in which HLA-A*02:01 reduces MS risk by limiting EBV persistence, reactivation, or antigenic stimulation.

*Absence of HLA-A*02:01 as part of a high-risk genetic profile*

The absence of HLA-A*02:01 can therefore be considered a risk-modifying feature rather than a primary risk allele. In individuals who already carry strong susceptibility factors such as HLA-DRB1*15:01, lack of HLA-A02:01 may remove a protective layer of antiviral immune surveillance. This produces a biologically plausible high-risk configuration: **HLA-DRB115:01-positive / HLA-A*02:01-negative**. In such individuals, HLA class II-mediated presentation may favor CD4+ T-cell activation against EBV or self-antigens, while the absence of protective class I-mediated CD8+ control may allow more persistent EBV-related immune stimulation (7, 48, 50).

*HLA-A*02:01, EBV-specific CD8+ T cells, and immune phenotype*

Recent studies further support the concept that MS-associated and MS-protective HLA class I alleles may

shape EBV-specific CD8+ T-cell responses differently. Work comparing EBV epitope-specific CD8+ T-cell responses in the context of HLA-A2 and higher-risk HLA class I backgrounds suggests that HLA-A2-restricted responses may recognize a broader or more effective EBV epitope repertoire, whereas some MS-associated class I contexts may be linked to more restricted or dysfunctional EBV-specific CD8+ T-cell responses (51). Although these data are still emerging, they are highly relevant to the present review because they connect HLA class I genetics, EBV immune surveillance, and MS risk modification.

HLA class I protection in the broader genetic–environmental model

The protective role of HLA-A02:01 should be interpreted within a broader gene–environment framework. Environmental factors such as EBV infection, smoking, vitamin D deficiency, and adolescent obesity may interact with HLA-mediated immune pathways to influence MS risk. For example, prior work has suggested that smoking-related MS risk may be more pronounced in individuals lacking protective **HLA-A02:01** or carrying HLA-DRB1*15:01, indicating that HLA class I protection may modify susceptibility across multiple environmental contexts, not only EBV infection (52). This reinforces the concept that absence of HLA-A*02:01 is best viewed as a risk amplifier within a multilayered susceptibility profile.

Integrative interpretation

Taken together, current evidence supports the view that HLA-A*02:01 is an important protective HLA class I allele in MS, likely acting through mechanisms related to CD8+ T-cell-mediated immune surveillance and control of EBV-infected B cells. Conversely, absence of HLA-A02:01 may increase vulnerability to EBV-associated immune dysregulation, particularly when combined with **HLA-DRB115:01**, high anti-EBNA1 responses, or other immune risk variants. Therefore, the EBV-positive / HLA-DRB115:01-positive / HLA-A02:01-negative profile represents a biologically coherent and clinically relevant high-risk configuration for MS susceptibility (7, 50, 51).

In addition to traditional HLA-A and HLA-DR alleles, recent findings indicate that non-classical HLA molecules, especially HLA-E, might also alter the risk of EBV-related MS by affecting NK-cell and CD8+ T-cell reactions to EBV-infected B cells.

HLA-E and EBV immune control

HLA-E as an emerging modifier of EBV-associated MS risk

Beyond classical HLA class I and II molecules, recent evidence suggests that the non-classical HLA class I molecule HLA-E may modify the association between EBV infection and MS. HLA-E has a specialized immunological role because it interacts with receptors expressed on natural killer (NK) cells and CD8+ T cells, particularly the inhibitory receptor NKG2A/CD94, thereby influencing antiviral immune surveillance and immune regulation. This is relevant to EBV-associated MS because EBV persists in B cells, and effective long-term control of EBV-infected cells depends not only on conventional HLA-restricted T-cell responses but also on NK-cell and CD8+ T-cell mechanisms (30, 49).

HLA-E allelic variation and infectious mononucleosis

The potential relevance of HLA-E to MS emerged from studies showing that HLA-E allelic variation can influence the clinical outcome of primary EBV infection. IM, the symptomatic manifestation of primary EBV infection, is associated with strong immune activation and has consistently been linked to increased MS risk (12). A mechanistic study by Vietzen and colleagues showed that HLA-E-restricted immune responses are important for the control of EBV-associated diseases, including IM. The findings indicated that the prominently expressed HLA-E*01:03/01:03 genotype conferred protection against IM, in part by stimulating EBV BZLF1-specific HLA-E-restricted CD8+ T-cell responses that may restrict viral spread (30).

*HLA-E*01:01, infectious mononucleosis, and MS susceptibility*

A 2025 population cohort study directly connected HLA-E variation with MS susceptibility in the context of IM. Nova and colleagues reported that carriers of HLA-E*01:01 who had been diagnosed with infectious mononucleosis were at considerably increased risk of MS, independent of other MS-associated HLA alleles. Importantly, the association between HLA-E01:01 and MS was observed primarily among individuals with a history of IM, suggesting a gene–environment interaction rather than a general HLA-E effect on MS susceptibility (12). This finding positions HLA-E01:01 as an emerging EBV-context-dependent risk modifier.

Dose-dependent risk and independence from classical HLA effects

The reported HLA-E01:01–IM interaction appears to show a dose-dependent pattern. In summaries of the 2025 cohort study, MS risk among individuals with a history of IM was higher in heterozygous HLA-E01:01 carriers and even higher in HLA-E01:01 homozygotes, compared with individuals carrying two HLA-E01:03 alleles (12, 53). The study also reported that this effect persisted after accounting for other MS-related HLA variants, including HLA-DRB1*15:01 and HLA-A*02:01 (12). This is important because it

suggests that HLA-E may add a distinct layer of risk beyond the classical HLA class II risk and class I protection framework.

Possible mechanism: weaker EBV immune control

The most plausible interpretation is that HLA-E*01:01 could be related to less efficient immune control of EBV, particularly during or after symptomatic primary infection. In contrast, HLA-E01:03 has been associated with stronger HLA-E-restricted CD8+ T-cell responses against EBV antigens, including BZLF1, and reduced susceptibility to IM (30). If HLA-E01:01 supports weaker NK-cell or CD8+ T-cell-mediated control of EBV-infected B cells, this could result in greater viral persistence, more intense immune activation, or prolonged antigenic stimulation after IM. These processes could plausibly increase the likelihood of EBV-driven B-cell dysregulation and CNS-directed autoimmunity in genetically susceptible individuals (12, 30).

NK-cell and CD8+ T-cell pathways in EBV-associated autoimmunity

HLA-E is particularly interesting because it links EBV biology to both innate-like and adaptive antiviral pathways. HLA-E-presented peptides can regulate NK-cell activity through inhibitory NKG2A/CD94 signaling, while HLA-E-restricted CD8+ T cells can directly recognize EBV-derived peptides and contribute to viral control. In EBV infection, this balance may determine whether infected B cells are efficiently contained or whether viral persistence promotes chronic immune stimulation. Since MS involves both B-cell dysregulation and CD8+ T-cell accumulation in CNS lesions, HLA-E-mediated antiviral control provides a biologically plausible bridge between symptomatic EBV infection and later CNS autoimmunity (30, 54).

Interpretation within the EBV–genetics model of MS

Within the broader model of EBV-associated MS, HLA-E should be viewed as an emerging risk modifier, not yet as established as HLA-DRB1*15:01 or HLA-A*02:01. The current evidence suggests that HLA-E01:01 may increase MS risk specifically in individuals who experienced infectious mononucleosis, possibly by weakening EBV immune control or altering NK/CD8+ T-cell regulation. Therefore, a clinically meaningful high-risk configuration may include **EBV-associated IM + HLA-E01:01**, especially when combined with HLA-DRB1*15:01, absence of HLA-A*02:01, high anti-EBNA1 responses, or elevated MS polygenic risk. However, replication in additional ancestries and functional studies using primary human immune cells are needed before HLA-E typing can be incorporated into formal MS risk prediction (12, 53).

Table 1 summarizes HLA-mediated profiles that may modify MS risk among EBV-exposed individuals.

EBV-specific humoral immunity and host genetics

EBV antibody profiles as markers of MS-relevant immune response

EBV-specific antibody responses provide an important link between viral exposure and host immune susceptibility in MS. Because EBV seropositivity is highly prevalent in adults, simple EBV positivity has limited value for risk stratification. In contrast, quantitative and antigen-specific antibody patterns, particularly elevated antibodies against EBNA1, appear more informative. High anti-EBNA1 IgG titers have repeatedly been associated with increased MS risk years before clinical onset, suggesting that MS susceptibility is related not only to EBV infection itself, but also to an exaggerated or dysregulated immune response to latent EBV antigens (40, 55).

EBNA1 is especially relevant because it is expressed during EBV latency and is required for maintenance of the viral episome in infected B cells. Persistently elevated anti-EBNA1 IgG may reflect chronic antigenic stimulation, impaired control of EBV-infected B cells, or a tendency toward cross-reactive immune responses (56). This is consistent with mechanistic studies showing that EBNA1-directed antibodies can cross-react with CNS-associated antigens such as GlialCAM, providing a potential bridge between EBV-specific humoral immunity and CNS autoimmunity (28, 41).

Antibodies against EBV viral capsid antigen (anti-VCA IgG) are useful markers of prior EBV infection and are commonly used to define EBV serostatus in epidemiological studies. However, because anti-VCA IgG is widespread among EBV-exposed individuals, it appears less specific than anti-EBNA1 for MS risk prediction. Therefore, anti-VCA is best interpreted as a marker of EBV exposure history, whereas anti-EBNA1 may better reflect MS-relevant immune dysregulation related to latent EBV infection (21, 56).

Anti-EBNA1 titers, HLA-DRB1*15:01, and MS risk

The correlation between anti-EBNA1 reactions and MS is especially significant when considering host genetics. HLA-DRB1*15:01, the most significant genetic risk allele for multiple sclerosis, may affect CD4+ T-cell reactions to peptides produced from EBV and assist in T-cell support for EBNA1-specific B cells (57). De Jager and colleagues found that anti-EBNA1 antibody levels correlated with the incidence of multiple sclerosis, irrespective of HLA-DRB1*15:01, suggesting that EBV-targeted humoral immunity and HLA class II genetic predisposition are separate but intersecting factors in MS vulnerability (40).

The combination of HLA-DRB1*15:01 carriage and high anti-EBNA1 IgG titers may therefore

Table 1. HLA class I and class II profiles modifying EBV-associated MS risk.

HLA profile	Direction of effect on MS risk	EBV-related implication	Proposed mechanism	Strength of evidence
HLA-DRB1*15:01 positive / HLA-DR15 positive	Increased risk	May enhance pathogenic EBV antigen presentation	Presentation of EBV-derived peptides, including EBNA1-related antigens, to CD4+ T cells; possible promotion of EBV-specific and cross-reactive CNS-directed immune responses	Strong
HLA-A*02:01 positive	Protective	May improve antiviral immune surveillance	More effective CD8+ T-cell-mediated control of EBV-infected B cells; lower EBV viral load reported in HLA-A*02-positive MS patients	Strong to moderate
HLA-A*02:01 negative	Risk-modifying; loss of protection	May reduce protective EBV immune control	Absence of a protective class I pathway may permit greater EBV persistence or chronic EBV-driven immune stimulation	Moderate
HLA-DRB115:01 positive / HLA-A02:01 negative	Higher-risk combined profile	Combines class II risk with loss of class I protection	Potentially enhanced CD4+ T-cell activation against EBV/self-antigens together with reduced CD8+ antiviral control	Strong biological plausibility; moderate direct EBV-specific evidence
HLA-E*01:01 carrier + infectious mononucleosis history	Increased risk	May identify individuals with weaker EBV control after symptomatic primary infection	Altered HLA-E-mediated NK-cell and CD8+ T-cell regulation; possible reduced control of EBV-infected B cells after IM	Emerging 2025 cohort evidence
HLA-E*01:03/01:03	Potentially protective against IM; possible indirect MS relevance	May support stronger control of primary EBV infection	Induction of EBV BZLF1-specific HLA-E-restricted CD8+ T-cell responses that limit viral dissemination	Moderate for EBV/IM; indirect for MS
HLA-DRB115:01 positive + HLA-A02:01 negative + HLA-E*01:01 carrier + IM history	Proposed high-risk EBV-associated profile	Integrates EBV exposure, symptomatic infection, class II risk, loss of class I protection, and non-classical HLA risk	Persistent EBV antigenic stimulation, altered B-cell antigen presentation, weaker antiviral control, and increased likelihood of CNS cross-reactivity	Conceptual; requires validation

define a biologically meaningful high-risk profile among EBV-infected individuals. In this model, HLA-DRB1*15:01 may promote presentation of EBV-derived peptides to CD4+ T cells, while persistent anti-EBNA1 responses may amplify B-cell activation, antibody production, and potential CNS cross-reactivity. Although the statistical interaction varies across cohorts, the biological rationale for considering this combined profile is strong (58).

Recent studies have also suggested that anti-EBNA1 responses may be refined beyond total IgG titers. Antibodies directed against specific EBNA1 regions, including autoreactivity-associated domains, may better capture MS-relevant humoral responses than total anti-EBNA1 levels alone. This supports a shift from simple EBV serostatus toward more detailed EBV antibody profiling combined with HLA genotype (41, 59).

Integrative interpretation

Overall, EBV-specific humoral immunity represents a measurable interface between EBV exposure and genetically shaped immune risk. High anti-EBNA1 IgG, particularly in HLA-DRB1*15:01-positive individuals, is one of the most consistent EBV-related immune profiles associated with MS susceptibility. Anti-VCA IgG remains useful for documenting EBV exposure, but it is less specific for MS risk than anti-EBNA1. Thus, the profile EBV-seropositive / high anti-EBNA1 IgG / HLA-DRB1*15:01-positive, especially when combined with absence of protective HLA-A*02:01 or history of infectious mononucleosis, represents a plausible high-risk immunogenetic pattern (40, 58).

However, elevated EBV antibody titers should not be interpreted as diagnostic markers of MS. Many individuals with high anti-EBNA1 titers never

develop MS, indicating that humoral EBV responses act as risk markers within a broader framework that includes HLA background, non-HLA immune loci, environmental exposures, and possibly early biomarkers of neuroaxonal injury. In this context, EBV antibody profiling is best viewed as a readout of host virus interaction rather than a stand-alone predictor of disease (59).

Non-HLA loci and antigen-presenting cell pathways

Non-HLA genetic architecture of MS and immune-cell pathways

Although HLA alleles account for the strongest genetic effects in MS, the broader genetic architecture of the disease is highly polygenic. The large 2019 International MS Genetics Consortium study analyzed 47,429 MS cases and 68,374 controls and identified 200 autosomal non-MHC susceptibility variants, in addition to MHC and chromosome X signals. Many of these non-HLA variants map to immune-cell pathways involving peripheral immune cells and microglia, supporting the concept that MS susceptibility is shaped by multiple genes involved in immune activation, antigen presentation, cytokine signaling, and lymphocyte regulation (14, 60, 61).

This non-HLA genetic background is particularly relevant to EBV-associated MS because EBV persists in B cells, which can function as antigen-presenting cells. EBV-infected B cells may present viral or self-antigens, supply costimulatory signals to T cells, and sustain chronic immune activation. Therefore, genetic variants affecting B-cell activation, antigen-presenting cell function, and B/T-cell costimulation may influence whether EBV infection remains controlled or contributes to autoreactive immune responses (14).

CD86 and B/T-cell costimulation in EBV-associated MS risk

Among non-HLA loci, CD86 is especially relevant because it encodes a costimulatory molecule expressed on antigen-presenting cells, including B cells and dendritic cells. CD86 interacts with CD28 and CTLA-4 on T cells, thereby influencing T-cell activation, tolerance, and immune regulation (62). In the setting of EBV infection, altered CD86-mediated costimulation could amplify T-cell responses to EBV-infected B cells and promote a more persistent or dysregulated adaptive immune response (14).

A notably significant article for this analysis is the 2024 publication about gene-environment interactions in pediatric-onset MS. Ziaei and associates presented findings indicating an interaction between childhood EBV infection and both HLA-DRB1*15 and the GG genotype of the CD86 risk variation rs2255214. The researchers determined that these results underscore a significant function of antigen-presenting cells in the likelihood of pediatric-onset MS linked with EBV. This positions CD86 as one of the most evident non-HLA instances presently documented that connects EBV exposure, APC biology, and vulnerability to MS (63).

CD40 and EBV-driven B-cell activation

CD40 is another biologically relevant non-HLA locus because it plays a central role in T-cell-dependent B-cell activation, germinal center responses, immunoglobulin class switching, and antigen presentation (64). In MS, B cells are not only antibody-producing cells but also antigen-presenting cells capable of shaping T-cell responses. Because EBV establishes latency in B cells, CD40-mediated signaling may influence the survival, activation, and antigen-presenting function of EBV-infected B cells (4).

EBV biology further strengthens the relevance of CD40-related pathways. EBV latent membrane protein 1, or LMP1, can mimic aspects of CD40 signaling and promote B-cell activation, survival, and upregulation of antigen-presentation machinery. Recent EBV–MS reviews note that EBV LMP1 expression can enhance expression of MHC class I, MHC class II, and costimulatory molecules, thereby enhancing antigen presentation by infected B cells (65). This provides a plausible mechanism through which host variants affecting CD40 or related B-cell activation pathways could modify EBV-driven immune responses in MS (19).

IL2RA and IL7R: cytokine receptor loci shaping T-cell regulation

Non-HLA MS risk loci also include cytokine receptor genes such as IL2RA and IL7R, which influence T-cell activation, survival, and immune tolerance. IL2RA encodes the alpha chain of the IL-2 receptor and is important for regulatory T-cell biology, while IL7R encodes the IL-7 receptor alpha chain and contributes to T-cell development and homeostasis. Variants in these genes may alter the balance between effector and regulatory immune responses, potentially lowering the threshold for autoreactive T-cell activation after EBV-driven antigen presentation (66).

The connection between IL2RA/IL7R and EBV-associated MS is likely indirect rather than EBV-specific. Unlike CD86, where a direct EBV interaction has been reported in pediatric-onset MS, IL2RA and IL7R are better understood as part of a broader immune susceptibility background. These variants may not determine EBV infection itself, but they may influence how the immune system responds to persistent antigenic stimulation, including stimulation derived from EBV-infected B cells (14).

Integrative interpretation

Taken together, non-HLA loci appear to modify EBV-associated MS risk by shaping the immune context in which EBV is controlled. CD86 provides the most direct current example of a non-HLA gene–EBV interaction, particularly in pediatric-onset MS, where the CD86 rs2255214 GG genotype interacted with childhood EBV infection. CD40, IL2RA, and IL7R are also biologically relevant because they regulate B-cell activation, T-cell costimulation, and cytokine-dependent immune homeostasis, although their EBV-specific effects are less directly established (63).

Thus, the non-HLA contribution to EBV-associated MS should be interpreted as a polygenic immune-amplification background. In genetically susceptible individuals, EBV-infected B cells may provide antigenic stimulation, while variants in APC and costimulatory pathways may enhance B/T-cell interactions, sustain chronic immune activation, and increase the probability of autoreactive responses. This model complements the HLA-centered framework by showing that antigen presentation is not determined only by peptide-binding HLA alleles, but also by the broader genetic regulation of APC function and lymphocyte activation (63).

Figure 3 illustrates how non-HLA loci involved in antigen-presenting cell pathways, including CD86, CD40, IL2RA, and IL7R, may modify immune responses to EBV and influence MS susceptibility.

Polygenic risk score and EBV-positive risk stratification

Polygenic risk score (PRS) and shared genetic architecture of EBV activity and MS

Recent large-scale genetic research has begun to illuminate how polygenic risk influences both EBV activity and MS susceptibility. A new study developed PRSs for EBV DNA positivity using genome-wide association data from over 600,000 individuals and applied these scores to large population cohorts, including the UK Biobank. Individuals in the top decile of the EBV DNA PRS showed a significantly higher prevalence of MS compared with those in the bottom decile, and most of this association was attributable to variants within the MHC region. These findings suggest that genetic variants that influence EBV activity also contribute to MS risk, supporting the concept of a shared genetic architecture between EBV persistence and MS susceptibility (67).

This work provides some of the strongest evidence to date that polygenic risk related to EBV biology can stratify individuals by MS risk, particularly when MHC (including classical HLA risk and protective alleles) is included. It supports the idea that PRS can capture genetic variation influencing EBV–host interactions and highlights the potential utility of PRS in research settings to identify subgroups at elevated EBV–MS risk (67).

Integration of PRS, HLA, and EBV serology in risk models

While the EBV DNA PRS mentioned above is based on EBV activity rather than solely on traditional MS GWAS, it aligns with the broader observation that MHC variation drives much of the overlap between EBV-related genetic signals and MS genetic susceptibility. In the UK Biobank analysis, PRS constructed from variants inside the HLA region showed a stronger association with MS risk than PRSs based on non-MHC variants, suggesting that HLA-mediated effects are especially critical for stratified genetic risk in EBV-positive individuals (67).

Several earlier epidemiological studies have also explored the combination of HLA genotypes and EBV serology for MS risk discrimination. For example,

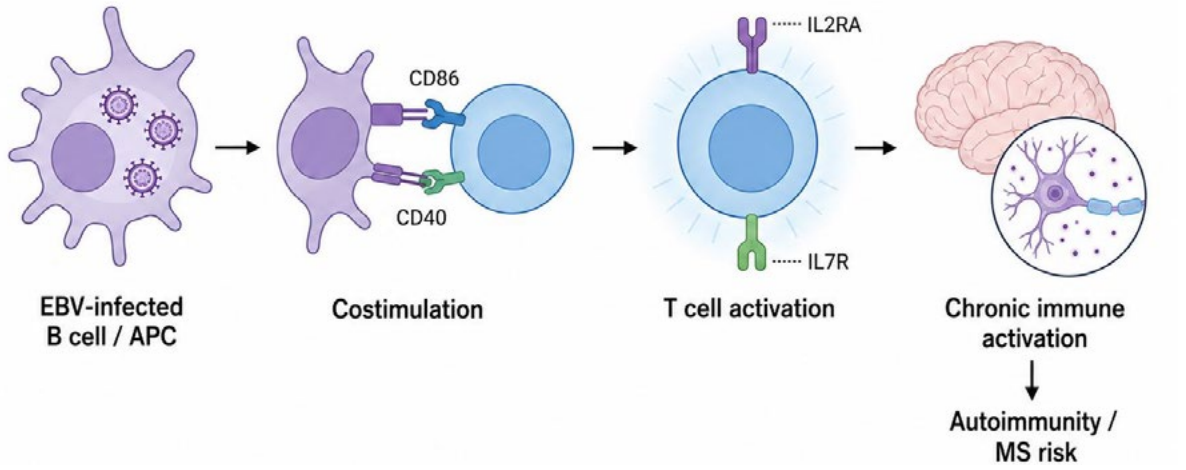


Fig 3. Non-HLA loci shaping EBV-driven immune activation in MS. EBV-infected B cells act as antigen-presenting cells. Genetic variants in CD86 and CD40 modulate B/T-cell costimulation, while IL2RA and IL7R influence T-cell survival and regulatory pathways. Together, these non-HLA variants create a polygenic background that can amplify EBV-associated immune responses and increase the risk of autoreactive CNS-directed immunity.

case control analyses indicated that higher levels of anti-EBV antibodies together with risk HLA-DR alleles discriminate MS cases from controls more effectively than either measure alone, which implies that host genetics and EBV immune markers can be jointly informative (68). Such studies provide conceptual support for multivariate risk models that incorporate HLA, anti-EBV serology, and broader genetic risk scores.

Limitations and current research status

Despite these promising research findings, the use of PRS combined with HLA and EBV serology for individual MS risk prediction remains largely experimental. Several key limitations still constrain clinical application: PRS models depend heavily on population ancestry and large reference datasets; the effect sizes of many non-HLA variants are modest; and EBV infection is nearly universal, reducing the specificity of simple seroprevalence for risk prediction. Therefore, integrated risk stratification using PRS + HLA + EBV serology is currently a research tool that may enrich study cohorts or elucidate biological mechanisms, but it is not yet ready for routine clinical use (67).

Future studies with larger and more diverse cohorts, refined EBV-related genetic scores, and longitudinal validation will be needed to determine if this combined approach can achieve sufficient predictive accuracy for clinical risk stratification. Researchers are also exploring whether additional biomarkers, such as EBV DNA load or multiplex antibody signatures, can further improve integrated risk models.

Proposed high-risk genetic profiles

This review supports a model in which EBV infection acts as a major upstream trigger for MS, but disease risk becomes substantially enriched only in individuals with a permissive immunogenetic background. Because EBV infection is highly prevalent in the general population, EBV seropositivity alone has limited predictive value. A more informative approach is to define risk-enrichment profiles that integrate EBV exposure, HLA risk and protective alleles, EBV-specific immune responses, and selected non-HLA immune loci. These profiles should not be interpreted as diagnostic categories, but as biologically plausible frameworks for stratifying EBV-positive individuals in research settings (34).

Core EBV–HLA risk profile

The most established high-risk profile is EBV-positive / HLA-DRB1*15:01-positive, especially when the individual also belongs to the broader HLA-DR15 haplotypic background. HLA-DRB115:01 is the strongest genetic risk allele for MS, and its relevance in EBV-associated MS is biologically coherent because it can shape CD4+ T-cell responses to EBV-derived antigens. In this model, EBV-infected B cells provide the antigenic source, while HLA-DRB115:01 determines how viral and potentially cross-reactive peptides are presented to CD4+ T cells (34).

This core profile becomes more compelling when combined with evidence of enhanced EBV-specific humoral immunity, particularly high anti-EBNA1 IgG titers. Anti-EBNA1 responses have been associated with MS risk, and EBNA1 is mechanistically relevant because EBNA1-directed immunity can cross-react with CNS-associated antigens. Therefore, the profile EBV-positive / HLA-DRB1*15:01-positive / high anti-EBNA1 IgG represents one of the most biologically supported EBV-associated MS risk configurations (69).

Loss of HLA class I protection

A second layer of risk involves the absence of protective HLA class I alleles, particularly HLA-A*02:01. In contrast to HLA-DRB115:01, which increases MS susceptibility, HLA-A02:01 has been repeatedly described as protective. In EBV-associated models, this protection may reflect more effective CD8+ T-cell-mediated immune surveillance of EBV-infected B cells. Therefore, the absence of HLA-A*02:01 may remove an important protective mechanism and contribute to a higher-risk state (43).

The combined profile HLA-DRB115:01-positive / HLA-A02:01-negative may therefore be more informative than either allele considered alone. In this configuration, class II-mediated presentation may favor EBV-specific or cross-reactive CD4+ T-cell activation, while reduced class I protection may allow less efficient control of EBV-infected B cells. This profile can be conceptualized as a combination of "increased pathogenic antigen presentation" and "loss of protective antiviral surveillance (43, 70)."

Infectious mononucleosis and HLA-E*01:01

A tertiary risk-enrichment profile includes infectious mononucleosis and HLA-E*01:01. Infectious mononucleosis serves as a clinical indicator of symptomatic primary EBV infection and has historically been linked to a heightened risk of multiple sclerosis. Recent population-centric research suggests that individuals with HLA-E*01:01 who have had infectious mononucleosis have a markedly elevated risk of MS, irrespective of other HLA alleles linked to MS. This indicates that HLA-E*01:01 could delineate a subpopulation where symptomatic EBV infection is followed by diminished or dysregulated immunological response to EBV (12).

This HLA-E profile is particularly important because it expands the EBV–MS model beyond classical HLA-DR and HLA-A alleles. HLA-E regulates NK-cell and

CD8+ T-cell responses, and the 2025 findings support the hypothesis that non-classical HLA variation may influence how efficiently EBV infection is controlled after infectious mononucleosis. Thus, IM history + HLA-E*01:01, especially when combined with HLA-DRB115:01 or absence of HLA-A02:01, represents an emerging high-risk configuration that deserves further replication and functional validation (12).

Non-HLA immune amplification profile

Beyond HLA, non-HLA immune loci may amplify EBV-associated immune activation. The clearest current example is CD86, a costimulatory molecule involved in antigen-presenting cell and T-cell interactions. In pediatric-onset MS, a study reported interactions between childhood EBV infection and both DRB1*15 and the GG genotype of the CD86 risk variant rs2255214, supporting a role for antigen-presenting cells in EBV-associated pediatric MS risk (63).

Other non-HLA loci, including CD40, IL2RA, and IL7R, may contribute less specifically by shaping B-cell activation, T-cell costimulation, cytokine signaling, and immune tolerance. These genes may not be EBV-specific risk factors, but they can create a polygenic immune environment in which EBV-infected B cells are more likely to drive persistent T-cell activation or autoreactive responses. Therefore, a broader risk profile may include high non-HLA immune genetic burden, particularly involving antigen-presenting cell and B/T-cell costimulatory pathways (43).

Proposed tiered model of EBV-associated MS risk

Based on the evidence reviewed above, EBV-positive individuals can be conceptually stratified into three research-oriented risk categories. A lower-risk EBV-positive profile would include EBV seropositivity without HLA-DRB115:01, presence of protective HLA-A02:01, no history of infectious mononucleosis, low or moderate anti-EBNA1 titers, and low polygenic immune risk. In these individuals, EBV latency may remain effectively controlled without progression toward CNS autoimmunity (43).

An intermediate-risk profile may include EBV seropositivity with either HLA-DRB115:01 positivity or absence of HLA-A02:01, together with elevated anti-EBNA1 IgG or a history of infectious mononucleosis. This category reflects partial enrichment of risk, where one or more immunogenetic features may increase EBV-driven immune activation but the full high-risk configuration is not present (12).

A high-risk EBV-associated MS profile can be proposed as: EBV-positive, especially with infectious mononucleosis history; HLA-DRB115:01/HLA-DR15 positive; HLA-A02:01 negative; high anti-EBNA1 IgG; HLA-E*01:01 carrier; and elevated non-HLA immune risk involving APC or costimulatory pathways such as CD86. This profile integrates the strongest established genetic risk factor, loss of a protective HLA class I allele, EBV-specific humoral dysregulation, emerging HLA-E evidence, and non-HLA immune amplification (12).

Interpretation and clinical caution

These proposed profiles should be interpreted as risk-enrichment models, not clinical prediction tools. At present, no combination of EBV serology and genetic markers can determine whether an individual EBV-positive person will develop MS. The profiles are most useful for organizing mechanistic evidence, designing prospective studies, enriching high-risk research cohorts, and developing future preventive strategies such as EBV vaccination trials or immune monitoring in genetically susceptible groups (53).

In summary, the most plausible high-risk configuration for EBV-associated MS is not defined by a single genetic variant, but by the convergence of HLA class II risk, loss of HLA class I protection, EBV-specific humoral activation, non-classical HLA-mediated antiviral control, and non-HLA immune costimulatory pathways. This integrated model helps explain why EBV infection is common, but MS is rare, and why only a genetically susceptible subset of EBV-infected individuals progresses toward CNS-directed autoimmunity (43).

Table 2 summarizes the proposed EBV-associated MS risk profiles, integrating EBV exposure, HLA class I and II alleles, EBV-specific humoral responses, and non-HLA immune loci into a tiered research-oriented framework.

Knowledge gaps and future directions

Despite major progress in defining the relationship between EBV, host genetics, and MS, several important knowledge gaps remain. First, most available evidence supports EBV as a major upstream trigger, but the precise sequence of immunological events between EBV infection and clinical MS onset is still incompletely understood. The interval between EBV seroconversion and MS diagnosis may span years, indicating that future studies need to focus on the preclinical phase of MS. Large longitudinal cohorts with repeated sampling before and after EBV infection are needed to track EBV serology, EBV DNA load, neurofilament light chain, HLA genotype, polygenic risk score, and immune-cell phenotypes over time. Such studies would clarify whether EBV-specific immune dysregulation precedes neuroaxonal injury, follows early CNS inflammation, or evolves in parallel with other risk factors (3).

A second major limitation is the lack of ethnic and ancestral diversity in many genetic studies of MS. Most HLA and polygenic risk findings have been

Table 2. Proposed EBV-associated MS risk profiles

Risk category	EBV-related features	HLA profile	Non-HLA / immune features	Interpretation
Lower-risk EBV-positive profile	EBV seropositive; no IM history; low/moderate anti-EBNA1	HLA-DRB115:01 negative; HLA-A02:01 positive	Low polygenic immune burden	EBV latency likely controlled; lower likelihood of CNS autoimmunity
Intermediate-risk profile	EBV seropositive; elevated anti-EBNA1 or IM history	HLA-DRB115:01 positive or HLA-A02:01 negative	Some immune risk variants	Partial enrichment of EBV-associated immune risk
High-risk EBV-associated MS profile	EBV positive; IM history; high anti-EBNA1 IgG	HLA-DRB115:01/HLA-DR15 positive; HLA-A02:01 negative; possible HLA-E*01:01	CD86 risk genotype or high non-HLA immune PRS	Strongest proposed risk-enrichment profile; research use only
Pediatric-onset enriched profile	Childhood EBV infection	HLA-DRB1*15 positive	CD86 rs2255214 GG genotype	Supports APC/costimulation involvement in EBV-associated pediatric MS
Emerging IM–HLA-E profile	Infectious mononucleosis history	HLA-E*01:01 carrier	Possible weaker NK/CD8 EBV control	Emerging profile requiring replication

Note: These profiles are proposed for mechanistic and research stratification. They should not be used as stand-alone clinical predictors of MS.

generated in European-ancestry populations, yet HLA allele frequencies, linkage disequilibrium patterns, EBV infection timing, infectious mononucleosis prevalence, and MS incidence vary across populations. This limits the generalizability of proposed profiles such as HLA-DRB115:01-positive / HLA-A02:01-negative / high anti-EBNA1. Future studies should include diverse ancestries and underrepresented populations to determine whether the same EBV–HLA interactions apply globally or whether population-specific HLA haplotypes and EBV immune-response patterns modify risk differently (71).

Functional genomics will be essential for moving beyond association toward mechanism. GWAS and PRS identify risk loci, but they do not explain how specific variants alter EBV control, B-cell activation, antigen presentation, or CNS-directed autoimmunity. Future research should integrate transcriptomics, epigenomics, chromatin accessibility, proteomics, and CRISPR-based perturbation studies in EBV-infected B cells, dendritic cells, CD4+ T cells, CD8+ T cells, and NK cells. This would help determine whether variants in CD86, CD40, IL2RA, IL7R, and other immune loci directly alter responses to EBV or instead act as broader autoimmune susceptibility modifiers (71).

Single-cell technologies represent another important direction. MS is immunologically heterogeneous, and bulk profiling may obscure rare but pathogenic EBV-reactive or autoreactive lymphocyte populations. Single-cell RNA sequencing, paired TCR/BCR sequencing, spatial transcriptomics, and single-cell epigenomics could identify EBV-specific B-cell and T-cell clones, define their activation states, and determine whether they are enriched in individuals carrying high-risk HLA profiles. These approaches could also clarify whether EBV-reactive immune cells migrate into the CNS, acquire tissue-resident phenotypes, or participate in intrathecal antibody production and meningeal inflammation (72).

HLA peptidomics is likely to become particularly important for this field. The central hypothesis of this review is that genetically determined antigen presentation shapes EBV-associated MS risk, but the exact viral and self-peptide repertoires presented by risk HLA molecules remain incompletely defined. Recent work showing that EBV infection can reprogram the transcriptome and immunopeptidome of HLA-DR15-positive B cells provides a strong rationale for larger studies using immunopeptidomics across different HLA backgrounds, EBV latency states, and immune-cell types. Such studies could identify the EBV-derived and CNS-derived peptides most relevant to molecular mimicry, epitope spreading, and autoreactive CD4+ T-cell activation (35).

Another key challenge is translating integrated risk models into clinically meaningful tools. Combining PRS + HLA genotype + EBV serology is conceptually attractive, but current models are not ready for individual-level prediction. EBV infection is too common, MS is relatively rare, and many high-risk genetic or serological markers have limited positive predictive value when used alone. Future work should test whether integrated models can reliably identify enriched-risk groups for research enrollment, longitudinal monitoring, or prevention trials. These models should include not only HLA-

DRB115:01, HLA-A02:01, HLA-E variation, and non-HLA immune loci, but also dynamic biomarkers such as anti-EBNA1 domain-specific antibodies, EBV DNA load, neurofilament light chain, and possibly single-cell immune signatures (73).

Finally, EBV vaccination and EBV-targeted prevention strategies represent one of the most important future directions. If EBV is a near-necessary upstream trigger for MS, preventing primary EBV infection or reducing symptomatic infectious mononucleosis could theoretically lower MS incidence. However, EBV vaccine-based MS prevention trials face major practical challenges, including the long delay between EBV infection and MS onset, the need for very large cohorts, and the difficulty of selecting appropriate endpoints. Recent discussions emphasize that such trials may require long-term follow-up and risk-enriched recruitment strategies, potentially using HLA genotype, EBV serology, and PRS to identify individuals most likely to benefit from monitoring or preventive intervention (73).

Overall, the field is moving from epidemiological association toward mechanistic and translational stratification. The next generation of studies should combine longitudinal sampling, diverse populations, functional genomics, single-cell immune profiling, HLA peptidomics, and EBV vaccine research. This integrated approach will be necessary to determine whether EBV-associated MS can be predicted, prevented, or intercepted before irreversible CNS injury occurs.

CONCLUSION

EBV is a major trigger for MS, but infection alone is not sufficient; host genetic background determines who progresses to CNS autoimmunity. HLA-DRB115:01 enhances presentation of EBV antigens and promotes autoreactive immune responses, while absence of HLA-A02:01 and carriage of HLA-E*01:01 may reduce antiviral control and further elevate risk. Non-HLA loci such as CD86, CD40, IL2RA, and IL7R can amplify EBV-driven immune activation, creating a permissive environment for autoimmunity. The highest-risk research profile combines EBV positivity, especially with infectious mononucleosis or high anti-EBNA1 titers, HLA-DRB115:01, absence of HLA-A02:01, possible HLA-E*01:01, and increased non-HLA immune burden. These profiles are currently useful for research and mechanistic studies rather than clinical prediction. Future longitudinal, functional, and single-cell studies, along with HLA peptidomics and EBV vaccine trials, will be critical to clarify why only a subset of EBV-infected individuals develop MS and to guide potential preventive strategies.

Acknowledgements
Not mentioned in the article.

Author Contributions
Not specified in the article. The authors' individual contributions need to be provided by the corresponding author.

Funding
No funding information is provided in the article.

Availability of Data and Materials
Not mentioned in the article. Since this is a review article, please confirm whether any new datasets were generated or analyzed.

Ethics Approval and Consent to Participate
Not mentioned in the article. As this is a review of previously published studies, this statement may be considered not applicable, subject to author confirmation.

Consent for Publication
Not mentioned in the article. Please confirm whether the manuscript contains any identifiable personal information or images.

Competing Interests
No competing interests statement is included in the article. Please confirm whether the authors have any competing interests

REFERENCES

1. Lassmann H. Multiple sclerosis pathology. Cold Spring Harb Perspect Med. 2018;8(3):a028936. https://doi.org/10.1101/cshperspect.a028936
2. Landry RL, Embers ME. The probable infectious origin of multiple sclerosis. NeuroSci. 2023;4(3):211–34. https://doi.org/10.3390/neurosci4030019
3. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296–301. https://doi.org/10.1126/science.abj8222
4. Guan Y, Jakimovski D, Ramanathan M, Weinstock-Guttman B, Zivadinov R. The role of Epstein-Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. Neural Regen Res. 2019;14(3):373–86. https://doi.org/10.4103/1673-5374.245462
5. Pakpoor J, Ramagopalan SV. Epstein-Barr virus is a necessary causative agent in the pathogenesis of multiple sclerosis: yes. Mult Scler. 2013;19(13):1690–1. https://doi.org/10.1177/1352458513506505
6. Huang J, Tengvall K, Lima IB, Hedström AK, Butt J, Brenner N, et al. Genetics of immune response to Epstein-Barr virus: prospects for multiple sclerosis pathogenesis. Brain. 2024;147(10):3573–82. https://doi.org/10.1093/brain/awae110
7. Hollenbach JA, Oksenberg JR. The immunoge-

netics of multiple sclerosis: a comprehensive review. J Autoimmun. 2015;64:13–25. https://doi.org/10.1016/j.jaut.2015.06.010
8. Mohme M, Hotz C, Stevanović S, Binder T, Lee JH, Okoniewski M, et al. HLA-DR15-derived self-peptides are involved in increased autologous T cell proliferation in multiple sclerosis. Brain. 2013;136(6):1783–98. https://doi.org/10.1093/brain/awt108
9. Silva A, Bettencourt A, Pereira C, Santos E, Carvalho C, Mendonça D, et al. Protective role of the HLA-A*02 allele in Portuguese patients with multiple sclerosis. Mult Scler. 2009;15(6):771–4. https://doi.org/10.1177/1352458509104588
10. Drosu N, Anderson M, Bilodeau PA, Nishiyama S, Mikami T, Bobrowski-Khoury N, et al. CD4 T cells restricted to DRB1*15:01 recognize two Epstein-Barr virus glycoproteins capable of intracellular antigen presentation. Proc Natl Acad Sci U S A. 2024;121(44):e2416097121. https://doi.org/10.1073/pnas.2416097121
11. Ricaurte-Fajardo A, Garcia Gonzalez K, Merino Campo S, Alvarado-De la Hoz C, Cardenas AF, Zarco L. Integrated determinants of multiple sclerosis susceptibility: Genetics, environment, infection and the microbiota. J Neurol Sci. 2026;484:125865. https://doi.org/10.1016/j.jns.2026.125865
12. Nova A, Gentilini D, Di Caprio G, Bourguiba-Hachemi S, Vince N, Gourraud PA, et al. Stratifying multiple sclerosis susceptibility risk: the role of HLA-E*01 and infectious mononucleosis in a population cohort. Eur J Neurol. 2025;32(4):e70131. https://doi.org/10.1111/ene.70131
13. Morandi E, Jagessar SA, 't Hart BA, Gran B. EBV infection empowers human B cells for autoimmunity: role of autophagy and relevance to multiple sclerosis. J Immunol. 2017;199(2):435–48. https://doi.org/10.4049/jimmunol.1700178
14. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science. 2019;365(6460):eaav7188. https://doi.org/10.1126/science.aav7188
15. Afrasiabi A, Parnell GP, Fewings N, Schibeci SD, Basuki MA, Chandramohan R, et al. Evidence from genome wide association studies implicates reduced control of Epstein-Barr virus infection in multiple sclerosis susceptibility. Genome Med. 2019;11(1):26. https://doi.org/10.1186/s13073-019-0640-z
16. Aloisi F, Cross AH. MINI-review of Epstein-Barr virus involvement in multiple sclerosis etiology and pathogenesis. J Neuroimmunol. 2022;371:577935. https://doi.org/10.1016/j.jneuroim.2022.577935
17. Soldan SS, Lieberman PM. Epstein-Barr virus infection in the development of neurological disorders. Drug Discov Today Dis Models. 2020;32:35–52. https://doi.org/10.1016/j.ddmod.2020.01.001
18. Wanleenuwat P, Iwanowski P. Role of B cells and antibodies in multiple sclerosis. Mult Scler Relat Disord. 2019;36:101416. https://doi.org/10.1016/j.msard.2019.101416
19. Wahbeh F, Sabatino JJ. Epstein-Barr virus in multiple sclerosis: Past, present, and future. Neurol Neuroimmunol Neuroinflamm. 2025;12(6):e200460. https://doi.org/10.1212/NXI.0000000000200460
20. Levin LI, Munger KL, O'Reilly EJ, Falk KI, Ascherio A. Primary infection with the Epstein-Barr virus and risk of multiple sclerosis. Ann Neurol. 2010;67(6):824–30. https://doi.org/10.1002/ana.21978
21. DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A. Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. Arch Neurol. 2006;63(6):839–44. https://doi.org/10.1001/archneur.63.6.noc50328
22. Sundstrom P, Juto P, Wadell G, Hallmans G, Svenningsson A, Nystrom L, et al. An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. Neurology. 2004;62(12):2277–82. https://doi.org/10.1212/01.WNL.0000130496.51156.D7
23. Goldacre R. Risk of multiple sclerosis in individuals with infectious mononucleosis: A national population-based cohort study using hospital records in England, 2003–2023. Mult Scler. 2024;30(4-5):489–95. https://doi.org/10.1177/13524585241237707
24. Ascherio A, Munger KL. Epstein-Barr virus infection and multiple sclerosis: A review. J Neuroimmune Pharmacol. 2010;5(3):271–7. https://doi.org/10.1007/s11481-010-9201-3
25. Lucas R, Hughes A, Lay MJ, Ponsonby A, Dwyer D, Taylor B, et al. Epstein-Barr virus and multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011;82(10):1142–8. https://doi.org/10.1136/jnnp-2011-300174
26. Pender MP, Burrows SR. Epstein-Barr virus and multiple sclerosis: potential opportunities for immunotherapy. Clin Transl Immunology. 2014;3(10):e27. https://doi.org/10.1038/cti.2014.25
27. Márquez AC, Horwitz MS. The role of latently infected B cells in CNS autoimmunity. Front Immunol. 2015;6:544. https://doi.org/10.3389/fimmu.2015.00544
28. Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, et al. Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. Nature. 2022;603(7900):321–7. https://doi.org/10.1038/s41586-022-04432-7
29. Tangye SG, Palendira U, Edwards ES. Human im-

munity against EBV-lessons from the clinic. J Exp Med. 2017;214(2):269–83. https://doi.org/10.1084/jem.20161846
30.Vietzen H, Berger SM, Kühner LM, Furlano PL, Bsteh G, Berger T, et al. Ineffective control of Epstein-Barr-virus-induced autoimmunity increases the risk for multiple sclerosis. Cell. 2023;186(26):5705–18.e13. https://doi.org/10.1016/j.cell.2023.11.015
31.Thomas O, Olsson T. Mimicking the brain: epstein-Barr virus and foreign agents as drivers of neuroimmune attack in multiple sclerosis. Front Immunol. 2023;14:1304281. https://doi.org/10.3389/fimmu.2023.1304281
32.Patsopoulos NA, Barcellos LF, Hintzen RQ, Schaefer C, Van Duijn CM, Noble JA, et al. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. PLoS Genet. 2013;9(11):e1003926. https://doi.org/10.1371/journal.pgen.1003926
33.Pieters J. MHC class II restricted antigen presentation. Curr Opin Immunol. 1997;9(1):89–96. https://doi.org/10.1016/S0952-7915(97)80164-1
34.Lanz TV, Robinson WH. Connecting the dots: Presentation of EBV antigens on HLA class II risk alleles connects the two main risk factors of multiple sclerosis. Proc Natl Acad Sci U S A. 2024;121(49):e2420070121. https://doi.org/10.1073/pnas.2420070121
35.Wang J, Qiu Y, Marti Z, Li F, Wacker M, Oldrati P, et al. EBV infection and HLA-DR15 jointly drive multiple sclerosis by myelin peptide presentation. Cell. 2026;189(2):569–84.e14. https://doi.org/10.1016/j.cell.2025.12.046
36.Czechowski M, Sikora G, Woźniak M, Kutnik K, Koguc K, Kusibab K, et al. Molecular and immunological mechanisms linking EBV infection to multiple sclerosis: literature review. J Educ Health Sport. 2025;85:66520. https://doi.org/10.12775/JEHS.2025.85.66520
37.Mizzi K, Cauchi RJ. Epstein-Barr virus in multiple sclerosis pathogenesis: the path towards mechanistically faithful models. Mult Scler Relat Disord. 2026;107:106952. https://doi.org/10.1016/j.msard.2025.106952
38.Munger K, Levin L, O'Reilly E, Falk K, Ascherio A. Anti-Epstein-Barr virus antibodies as serological markers of multiple sclerosis: a prospective study among United States military personnel. Mult Scler. 2011;17(10):1185–93. https://doi.org/10.1177/1352458511408991
39.Tschochner M, Leary S, Cooper D, Strautins K, Chopra A, Clark H, et al. Identifying patient-specific Epstein-Barr nuclear antigen-1 genetic variation and potential autoreactive targets relevant to multiple sclerosis pathogenesis. PLoS One. 2016;11(2):e0147567. https://doi.org/10.1371/journal.pone.0147567
40.De Jager P, Simon K, Munger K, Rioux J, Hafler D, Ascherio A. Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis. Neurology. 2008;70(13 Pt 2):1113–8. https://doi.org/10.1212/01.wnl.0000294325.63006.f8
41.Sattarnezhad N, Kockum I, Thomas OG, Liu Y, Ho PP, Barrett AK, et al. Antibody reactivity against EBNA1 and GlialCAM differentiates multiple sclerosis patients from healthy controls. Proc Natl Acad Sci U S A. 2025;122(11):e2424986122. https://doi.org/10.1073/pnas.2424986122
42.Kakalacheva K, Comabella M. Epstein-Barr virus and multiple sclerosis: causation or association? Future Microbiol. 2010;5(11):1617–9. https://doi.org/10.2217/fmb.10.123
43.Olsson T. Epstein Barr virus infection and immune defense related to HLA-DR15: Consequences for multiple sclerosis. Eur J Immunol. 2021;51(1):56–9. https://doi.org/10.1002/eji.202049030
44.Läderach F, Münz C. Epstein Barr virus exploits genetic susceptibility to increase multiple sclerosis risk. Microorganisms. 2021;9(11):2191. https://doi.org/10.3390/microorganisms9112191
45.Menegatti J, Schub D, Schäfer M, Grässer FA, Ruprecht K. HLA-DRB1*15:01 is a co-receptor for Epstein-Barr virus, linking genetic and environmental risk factors for multiple sclerosis. Eur J Immunol. 2021;51:2348–50. https://doi.org/10.1002/eji.202149179
46.Li Q, Cohen JI. Epstein-Barr virus and the human leukocyte antigen complex. Curr Clin Microbiol Rep. 2019;6(3):175–81. https://doi.org/10.1007/s40588-019-00120-9
47.Bergamaschi L, Leone M, Fasano M, Guerini F, Ferrante D, Bolognesi E, et al. HLA-class I markers and multiple sclerosis susceptibility in the Italian population. Genes Immun. 2010;11(2):173–80. https://doi.org/10.1038/gene.2009.101
48.Link J, Kockum I, Lorentzen ÅR, Lie BA, Celius EG, Westerlind H, et al. Importance of human leukocyte antigen (HLA) class I and II alleles on the risk of multiple sclerosis. PLoS One. 2012;7(5):e36779. https://doi.org/10.1371/journal.pone.0036779
49.Veroni C, Aloisi F. The CD8 T cell-Epstein-Barr virus-B cell trialogue: a central issue in multiple sclerosis pathogenesis. Front Immunol. 2021;12:665718. https://doi.org/10.3389/fimmu.2021.665718
50.Agostini S, Mancuso R, Guerini FR, D'Alfonso S, Agliardi C, Hernis A, et al. HLA alleles modulate EBV viral load in multiple sclerosis. J Transl Med. 2018;16(1):80. https://doi.org/10.1186/s12967-018-1450-6

51.Reijm S, Marques AM, Rip J, Corsten CE, Wierenga-Wolf AF, de Wit H, et al. Multiple sclerosis-associated HLA demarcates EBV-specific CD8+ T cells with an exhausted and brain residency phenotype. iScience. 2026;29(5):115744. https://doi.org/10.1016/j.isci.2026.115744
52.James LM, Georgopoulos AP. Negative association between multiple sclerosis immunogenetic profile and in silico immunogenicities of 12 viruses. Sci Rep. 2023;13(1):18654. https://doi.org/10.1038/s41598-023-45931-5
53.Kiani L. Genetic susceptibility determines Epstein-Barr-virus-associated risk of multiple sclerosis. Nat Rev Neurol. 2025;21(6):293. https://doi.org/10.1038/s41582-025-01099-2
54.Van Langelaar J, Rijvers L, Smolders J, Van Luijn MM. B and T cells driving multiple sclerosis: identity, mechanisms and potential triggers. Front Immunol. 2020;11:760. https://doi.org/10.3389/fimmu.2020.00760
55.Lünemann JD, Tintoré M, Messmer B, Strowig T, Rovira A, Perkal H, et al. Elevated Epstein-Barr virus-encoded nuclear antigen-1 immune responses predict conversion to multiple sclerosis. Ann Neurol. 2010;67(2):159–69. https://doi.org/10.1002/ana.21886
56.Dreyfus DH, Farina A, Farina GA. Molecular mimicry, genetic homology, and gene sharing proteomic “molecular fingerprints” using an EBV (Epstein-Barr virus)-derived microarray as a potential diagnostic method in autoimmune disease. Immunol Res. 2018;66(6):686–95. https://doi.org/10.1007/s12026-018-9045-0
57.Sundström P, Nyström L, Jidell E, Hallmans G. EBNA-1 reactivity and HLA DRB1*1501 as statistically independent risk factors for multiple sclerosis: a case-control study. Mult Scler. 2008;14(8):1120–2. https://doi.org/10.1177/1352458508092353
58.Xiao D, Ye X, Zhang N, Ou M, Guo C, Zhang B, et al. A meta-analysis of interaction between Epstein-Barr virus and HLA-DRB1*1501 on risk of multiple sclerosis. Sci Rep. 2015;5(1):18083. https://doi.org/10.1038/srep18083
59.Vietzen H, Kühner LM, Berger SM, Ponleitner M, Graninger M, Pistorius C, et al. Early identification of individuals at risk for multiple sclerosis by quantification of EBNA-1381-452-specific antibody titers. Nat Commun. 2025;16(1):6416. https://doi.org/10.1038/s41467-025-61751-9
60.Bashinskaya V, Kulakova O, Boyko A, Favorov A, Favorova O. A review of genome-wide association studies for multiple sclerosis: classical and hypothesis-driven approaches. Hum Genet. 2015;134(11):1143–62. https://doi.org/10.1007/s00439-015-1601-2
61.Lundmark F, Duvefelt K, Iacobaeus E, Kockum I, Wallström E, Khademi M, et al. Variation in interleukin 7 receptor α chain (IL7R) influences risk of multiple sclerosis. Nat Genet. 2007;39(9):1108–13. https://doi.org/10.1038/ng2106
62.Mir MA, Agrewala JN. Influence of CD80 and CD86 co-stimulation in the modulation of the activation of antigen presenting cells. Curr Immunol Rev. 2007;3(3):160–9. https://doi.org/10.2174/157339507781483487
63.Ziaei A, Solomon O, Casper TC, Waltz M, Weinstock-Guttman B, Aaen G, et al. Gene-environment interactions: epstein-Barr virus infection and risk of pediatric-onset multiple sclerosis. Mult Scler. 2024;30(3):308–15. https://doi.org/10.1177/13524585231224685
64.Watanabe M, Fujihara C, Radtke AJ, Chiang YJ, Bhatia S, Germain RN, et al. Co-stimulatory function in primary germinal center responses: CD40 and B7 are required on distinct antigen-presenting cells. J Exp Med. 2017;214(9):2795–810. https://doi.org/10.1084/jem.20161955
65.Graham JP, Arcipowski KM, Bishop GA. Differential B-lymphocyte regulation by CD40 and its viral mimic, latent membrane protein 1. Immunol Rev. 2010;237(1):226–48. https://doi.org/10.1111/j.1600-065X.2010.00932.x
66.Traboulsee AL, Bernales CQ, Ross JP, Lee JD, Sadovnick AD, Vilariño-Güell C. Genetic variants in IL2RA and IL7R affect multiple sclerosis disease risk and progression. Neurogenetics. 2014;15(3):165–9. https://doi.org/10.1007/s10048-014-0403-3
67.Yasumizu Y, Kim N, Rivier CA, Moon J, Kojima S, Chen HL, et al. Host genetic architecture between Epstein-Barr virus activity and multiple sclerosis reveals shared pathways. medRxiv [Preprint]. 2025:2025.12.11.25342083. https://doi.org/10.64898/2025.12.11.25342083
68.Strautins K, Tschochner M, James I, Choo L, Dunn D, Pedrini M, et al. Combining HLA-DR risk alleles and anti-Epstein-Barr virus antibody profiles to stratify multiple sclerosis risk. Mult Scler. 2014;20(3):286–94. https://doi.org/10.1177/1352458513498829
69.Thomas OG, Bronge M, Tengvall K, Akpinar B, Nilsson OB, Holmgren E, et al. Cross-reactive EBNA1 immunity targets alpha-crystallin B and is associated with multiple sclerosis. Sci Adv. 2023;9(20):eadg3032. https://doi.org/10.1126/sciadv.adg3032
70.Sundqvist E, Sundström P, Lindén M, Hedström A, Aloisi F, Hillert J, et al. Epstein-Barr virus and multiple sclerosis: interaction with HLA. Genes Immun. 2012;13(1):14–20. https://doi.org/10.1038/gene.2011.42
71.Soldan SS, Lieberman PM. Epstein-Barr vi-

rus and multiple sclerosis. Nat Rev Microbiol. 2023;21(1):51–64. https://doi.org/10.1038/s41579-022-00770-5

72.Behrens M, Comabella M, Lünemann JD. EBV-specific T-cell immunity: relevance for multiple sclerosis. Front Immunol. 2024;15:1509927. https://doi.org/10.3389/fimmu.2024.1509927.

73.Zane GK, Sutton A, Brumwell A, Hossain MR, Hawes SE, Giovannoni G, et al. The path to prevention of multiple sclerosis: considerations for Epstein-Barr virus vaccine-based prevention studies. Mult Scler. 2025;31(8):905–15. https://doi.org/10.1177/13524585251340812.