International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

Check for updates

Review of Causes and Treatments in Multiple Sclerosis

Shreya Ramasubramanian Iyer *

Independent researcher.

International Journal of Biological and Pharmaceutical Sciences Archive, 2025, 10(02), 001-005

Publication history: Received on 02 September 2025; revised on 08 October 2025; accepted on 10 October 2025

Article DOI: https://doi.org/10.53771/ijbpsa.2025.10.2.0073

Abstract

Multiple sclerosis (MS) is a complicated neurological disease in which the central nervous system gradually deteriorates. The body's immune system wrongly targets the protective myelin coating around nerves, treating it as a threat and damaging it. Due to the loss of the myelin sheath, signals cannot be transmitted anymore. While its exact causes remain unknown, previous research suggests that it has genetic and environmental causes.

This paper examines the causes and existing treatment options, with a particular focus on the Human Leukocyte Antigen (HLA) system, specifically the HLA-DRB1 gene. As is well known, the HLA-DRB1 gene is one of the candidates for the control of immune system function and has been strongly and constantly associated with the risk of developing multiple sclerosis. This paper shows how HLA-DRB1 variations influence the susceptibility to MS, and what consequences this could have for further research and treatment approaches. It also includes the environmental causes of the disease, along with an overview of the existing treatments for the same. While no experiment was done to observe the effects, through different sources, research has been done to understand the relationship between the HLA gene, the environment, and the increased risk of MS.

Keywords: Human Leukocyte Antigen; Multiple Sclerosis; HLA-DRB1; Myelin

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disorder in which the immune system mistakenly attacks the nerves, leading to disability. It mistakes the myelin sheath covering the nerves as an invader and eats it up. Due to the loss of the myelin sheath, signals cannot be transmitted anymore. This leads to communication issues between the body and the brain. The symptoms of MS can differ widely among individuals, and in severe cases, some patients may lose the ability to walk without assistance. Depending on the type of MS, some individuals can experience extended periods of remission without developing new symptoms. While environmental factors can be numerous, including smoking, age, certain infections (such as the Epstein-Barr virus), and family history, the genetic cause primarily focuses on the Human Leukocyte Antigen (HLA) complex. Evidence has linked variations in the HLA-DRB1 gene to a higher incidence of multiple sclerosis. Multiple sclerosis symptoms may arise from autoimmune reactions and inflammation caused by changes in the HLA-DRB1 gene, which harm nerves and their protective myelin sheath. This is because the HLA-DRB1 gene is implicated in the immune system. The precise contribution of HLA-DRB1 gene variations to the onset of multiple sclerosis is still unknown.

1.1. Genetic Architecture of MS

Multiple Sclerosis is acknowledged as a partially heritable autoimmune inflammatory disease, where genetic factors significantly influence an individual's susceptibility (Ward & Goldman, 2022). People with a family history of MS are at a higher risk of developing the disease. Data shows that identical twins (monozygotic) have a higher chance of developing MS, as they have concordance rates of 25-30% as compared to non-identical twins (3-7%). Moreover,

* Corresponding author: Shreya Ramasubramanian Iyer

patients with MS (15-20%) have reported that they have a family history of the disease, which is much higher than the prevalence in the general population. The risk of developing MS increases substantially, rising from approximately 1 in 1,000 in the general population to about 1 in 4 for identical twins when one twin is affected, highlighting the strong genetic component (Parnell & Booth, 2017).

Moreover, a study by Jovanovic et al. (2024) focused on cases of familial multiple sclerosis (FMS) in Belgrade. They found that FMS cases accounted for 6.4% of the population's total MS cases and also observed that in such cases, the younger generations developed symptoms earlier than the older ones (even after adjustment, accounting for difference in length of follow-up, the age-at-onset disparity persisted, though reduced (30.0 vs. 36.4 years; $p = 0.040$).

Starting in the 1970s, research demonstrated a strong link between various HLA class II factors and MS susceptibility, with some of the earliest findings noting a higher incidence of specific HLA types in MS patients (Naito et al., 1972; Svejgaard, 2008). Subsequent linkage and association studies further solidified this connection, particularly highlighting the strong association with HLA-DR15 (formerly known as DR2 or Dw2) (Haile et al., 1980; Hillert, 2006). This early work established the HLA system, especially the HLA-DRB1 gene, as a major and enduring contributor to MS risk, laying the groundwork for understanding the immunogenetic basis of the disease (Hollenbach & Oksenberg, 2015; Martinł, 1997; Svejgaard, 2008). It was not only increased gene expression alone that was not enough to explain MS risk; only when this higher expression was combined with certain structural features unique to the DRB1*1501 allele did risk increase, suggesting that both gene expression levels and allele structure must act together to affect susceptibility.

2. Environmental Factors

Multiple Sclerosis cannot be explained only through genetic factors. While the HLADRB-1 alleles have a clear role, researchers have also noticed that not everyone who carries a high-risk allele develops the disease, and identical twins, who share the same genetic background, are often discordant for MS. This has led to the exploration of environmental factors that may interact with the genetic susceptibility of the disease and influence the onset and progression. Several key factors emerged, including vitamin D levels, viral infections such as Epstein–Barr virus, smoking, and geographic location, all of which appear to modulate immune activity in ways that may trigger MS in genetically predisposed individuals. Moreover, research on migration suggests that the age at which one migrates influences the likelihood of developing multiple sclerosis, and there is a variation based on geographical latitude (Simpson et al. 2011). For individuals who move from a low-risk to a high-risk country before puberty, their risk of MS aligns more closely with that of the high-risk nation (Gale and Martyn 1995; Ahlgren et al. 2010, 2012; Berg-Hansen et al. 2015).

3. Epstein-Barr Virus (EBV)

It is a common viral infection that spreads through bodily fluids and saliva. Most EBV infections don't cause any symptoms. However, it can occasionally lead to infectious mononucleosis (IM), especially in adolescents and young adults. Data show that people who have had noticeable infectious mononucleosis (IM) face more than double the risk of developing multiple sclerosis (MS), according to a recent meta-analysis (Handel et al. 2010). Those with MS show much higher levels of antibodies against EBNA1 and a specific fragment (amino acids 385–420) (Sundstrom et al. 2009; Sundqvist et al. 2012). It was also found by Levin et al. that all those who initially tested negative for the ENBA-1 tested positive after developing MS. This suggests a close association between acquiring EBV (specifically a primary infection marked by EBNA1 antibodies) and the onset of MS. The HLA gene and the IM interact together to increase the risk of MS (Sundqvist et al. 2012). The risk of developing MS is also dependent on a specific time frame of EBV. For example, it was noted that infection throughout childhood does not indicate an increased risk of developing multiple sclerosis, but infection during adolescence or later does (Ascherio and Munger 2015).

4. Smoking and Tobacco Usage

Free radicals are abundant in tobacco. According to reports, oxidative stress brought on by free radicals mutates genetic material and contributes to several neurological diseases, including MS and Parkinson's disease. Smoking lowers blood levels of serum immunoglobulins, lowers the generation of cytokines by antigen-presenting cells, and lowers the numbers of peripheral B lymphocytes and natural killer cells. Cigarette smoke contains nitric oxide (NO) and carbon monoxide (CO), which boost the inflammatory response and weaken various immune systems, making a person more vulnerable to infections and autoimmune diseases. Additionally, Cigarette smoke may irritate the lungs and trigger the production of autoaggressive T cells, which can then trigger a CNS-directed autoaggressive response that results in multiple sclerosis. Tobacco contains a polyphenol-rich glycoprotein that stimulates B cell differentiation and T cell proliferation, creating a proinflammatory environment. Proinflammatory cells, such as G-protein-coupled receptor 15

(GPR15) T cells, which are associated with multiple sclerosis, are more prevalent in smokers. Furthermore, Acrolein and hydrogen cyanide, which are found in cigarette smoke, can suppress the immune system and lead to neurodegeneration.

5. Vitamin D deficiency

Animal research has revealed that mice with sufficient vitamin D levels are immune to experimental autoimmune encephalomyelitis (EAE), according to a Cleaveland Clinic report. Vitamin D in hormone form may act as a selective immune regulator and delay the onset of illness. It is thought that the amount of sunshine exposure affects how much vitamin D is produced. Despite the lack of data, some research indicates that MS patients who took more oral vitamin D supplements experienced fewer recurrences. Multiple studies have demonstrated a link between vitamin D levels and the count or volume of T2 lesions visible on magnetic resonance imaging (MRI). For example, Bäcker-Koduah et al. found that patients with higher serum 25(OH)D concentrations had significantly fewer T2 lesions (25 lesions) compared to those with lower 25(OH)D levels (60 lesions). Additionally, Cree et al. identified a short-term correlation between reduced serum vitamin D levels and increased risk of localized MRI disease activity, including greater T2 lesion volume. However, some studies have found no apparent correlation between lack of Vitamin D and the onset of MS; hence, it is still being debated whether it is a significant risk factor or not.

6. Treatment for MS

Even though there is no cure for MS, there are some treatment options that can help control the disease progression. Disease-modifying therapies (DMT) do not cure the disease but slow down its progression and reduce long-term disability. They can be of different types, such as self-injection, oral, or infusion therapies (Robertson and Moreo, 2016) with different mechanisms of action. Some notable examples include Dimethyl Fumarate, Teriflunomide, and Fingolimod, which work by altering the behavior of immune cells or activating protective pathways, offering the convenience of pill-based treatment. Flingolimod acts by trapping certain immune cells in lymph nodes, preventing them from entering the brain and spinal cord. Teriflunomide slows the production of immune cells by interfering with the building blocks of DNA and reduces autoimmune attacks on myelin, thereby lowering relapse rates. Dimethyl Fumarate activates antioxidant pathways, which protect nerve cells from damage by immune cells. Other types, such as interferon-beta and glatiramer acetate, modulate immune system molecules to reduce inflammation and mimic parts of myelin to produce a positive anti-inflammatory response. Apart from these, infusion therapies use monoclonal antibodies, which are specifically designed to target specific immune cells. For example, natalizumab blocks certain immune cells from crossing into the brain and spinal cord, preventing them from attacking myelin. Ocrelizumab and alemtuzumab work by depleting particular immune cells, such as B cells or broader lymphocyte populations, which are responsible for the autoimmune response (Hauser & Cree, 2020).

Another type of treatment for MS relapses includes the use of corticosteroids such as Methylprednisolone. Short-term, high-dose methylprednisolone, administered orally or intravenously over 3–5 days, can accelerate recovery from relapses. However, this therapy does not affect the likelihood of future relapses or long-term disability. Some studies also suggest that pulsed methylprednisolone treatment may provide long-term benefits for individuals with multiple sclerosis.

7. Conclusion

In conclusion, Multiple sclerosis is a complex disease of the nervous system influenced by both genetic factors, such as the HLA-DRB1 gene, and environmental factors like vitamin D deficiency, smoking, and lifestyle choices. These elements work together to cause immune system dysfunction, which weakens the myelin sheath surrounding nerve fibers. Disease-modifying therapies were developed to reduce relapses, slow the progression of the disease, and provide a better quality of life. These include oral pills, self-injections, immunosuppressants, etc. Understanding MS as the result of genetic susceptibility, environmental influences, and immune dysregulation is crucial for developing more effective, personalized treatments. It is anticipated that further research on genetic factors and treatment options will lead to a better quality of life for MS patients.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares that they have no conflicts of interest in the subject matter or materials discussed in this manuscript.

References

[1] Robertson, D., & Moreo, N. (2016). Disease-Modifying Therapies in Multiple Sclerosis: Overview and Treatment Considerations. *Federal Practitioner*, *33*(6), 28. https://pmc.ncbi.nlm.nih.gov/articles/PMC6366576/

[2] Williams A, Eldridge R, McFarland H, Houff S, Krebs H, McFarlin D. Multiple sclerosis in twins. Neurology. 1980 Nov;30(11):1139-47. doi: 10.1212/wnl.30.11.1139. PMID: 7191511.

[3] Hauser, S. L., & Cree, B. A. (2020). Treatment of Multiple Sclerosis: A Review. The American Journal of Medicine, 133(12), 1380. https://doi.org/10.1016/j.amjmed.2020.05.049

[4] Finkelsztejn, A. (2014). Multiple Sclerosis: Overview of Disease-Modifying Agents. Perspectives in Medicinal Chemistry, 6, 65. https://doi.org/10.4137/PMC.S13213

[5] Hajeer, S., Nasr, F., Nabha, S., Saab, M., Harati, H., Desoutter, A., Al Ahmar, E., & Estephan, E. (2023). Association between vitamin D deficiency and multiple sclerosis- MRI significance: A scoping review. Heliyon, 9(5), e15754. https://doi.org/10.1016/j.heliyon.2023.e15754

[6] Sintzel, M. B., Rametta, M., & Reder, A. T. (2017). Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurology and Therapy, 7(1), 59. https://doi.org/10.1007/s40120-017-0086-4

[7] Nishanth, K., Tariq, E., Nzvere, F. P., Miqdad, M., & Cancarevic, I. (2020). Role of Smoking in the Pathogenesis of Multiple Sclerosis: A Review Article. Cureus, 12(8), e9564. https://doi.org/10.7759/cureus.9564

[8] Cleveland Clinic. (2022, July 13). Epstein-Barr virus (EBV) - Symptoms, causes & treatment. https://my.clevelandclinic.org/health/diseases/23469-epstein-barr-virus

[9] Zhou, Y., Zhu, G., Charlesworth, J. C., Simpson, S., Jr, Rubicz, R., Göring, H. H., Patsopoulos, N. A., Laverty, C., Wu, F., Henders, A., Ellis, J. J., van der Mei, I., Montgomery, G. W., Blangero, J., Curran, J. E., Johnson, M. P., Martin, N. G., Nyholt, D. R., Taylor, B. V., & ANZgene consortium (2016). Genetic loci for Epstein-Barr virus nuclear antigen-1 are associated with risk of multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England), 22(13), 1655–1664. https://doi.org/10.1177/1352458515626598

[10] Ascherio, A., Munger, K. L., White, R., Köchert, K., Simon, K. C., Polman, C. H., Freedman, M. S., Hartung, H. P., Miller, D. H., Montalbán, X., Edan, G., Barkhof, F., Pleimes, D., Radü, E. W., Sandbrink, R., Kappos, L., & Pohl, C. (2014). Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA neurology, 71(3), 306–314. https://doi.org/10.1001/jamaneurol.2013.5993

[11] Alfredsson, L., & Olsson, T. (2019). Lifestyle and Environmental Factors in Multiple Sclerosis. Cold Spring Harbor Perspectives in Medicine, 9(4), a028944. https://doi.org/10.1101/cshperspect.a028944

[12] Smith, K. J., Pyrdol, J., Gauthier, L., Wiley, D. C., & Wucherpfennig, K. W. (1998). Crystal structure of HLA-DR2 (DRA*0101, DRB1*1501) complexed with a peptide from human myelin basic protein. The Journal of experimental medicine, 188(8), 1511–1520. https://doi.org/10.1084/jem.188.8.1511

[13] Patsopoulos, N. A. (2018). Genetics of Multiple Sclerosis: An Overview and New Directions. Cold Spring Harbor Perspectives in Medicine, 8(7), a028951. https://doi.org/10.1101/cshperspect.a028951

[14] Heywood, A. L. (2025, March 3). Is multiple sclerosis hereditary? Healthline. https://www.healthline.com/health/multiple-sclerosis/is-multiple-sclerosis-hereditary

[15] National Library of Medicine. (2025, September 5). HLA-DRB1 gene. MedlinePlus Genetics. https://medlineplus.gov/genetics/gene/hla-drb1/

[16] Kular, L., Liu, Y., Ruhrmann, S., Zheleznyakova, G., Marabita, F., Gomez-Cabrero, D., James, T., Ewing, E., Lindén, M., Górnikiewicz, B., Aeinehband, S., Stridh, P., Link, J., Andlauer, T. F. M., Gasperi, C., Wiendl, H., Zipp, F., Gold, R., Tackenberg, B., Weber, F., Hemmer, B., Strauch, K., Heilmann-Heimbach, S., Rawal, R., Schminke, U., Schmidt, C. O., Kacprowski, T., Franke, A., Laudes, M., Dilthey, A. T., Celius, E. G., Søndergaard, H. B., Tegnér, J., Harbo, H. F., Olafsson, S., Eggertsson, H. P., Halldorsson, B. V., Hjaltason, H., Olafsson, E., Jonsdottir, I., Stefánsson, K., Olsson, T., Piehl, F., Ekström, T. J., Kockum, I., Feinberg, A. P., & Jagodic, M. (2018). DNA methylation as a mediator of HLA-DRB1*15:01 and a protective variant in multiple sclerosis. Nature Communications, 9, 2397. https://doi.org/10.1038/s41467-018-04732-5

[17] Balnyte, R., Rastenyte, D., Vaitkus, A., Mickeviciene, D., Skrodeniene, E., & Uloziene, I. (2013). The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania. BMC Neurology, 13, 77. https://doi.org/10.1186/1471-2377-13-77

[18] National Library of Medicine. (2025, September 5). HLA-DRB1 gene [PDF]. MedlinePlus Genetics. https://medlineplus.gov/download/genetics/gene/hla-drb1.pdf

[19] Mayo Clinic. (2024, November 1). Multiple sclerosis – Symptoms and causes. https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269

[20] National Institute of Neurological Disorders and Stroke. (2025, January 31). Multiple sclerosis. https://www.ninds.nih.gov/health-information/disorders/multiple-sclerosis

[21] Cleveland Clinic. (2023, February 1). Multiple sclerosis. https://my.clevelandclinic.org/health/diseases/17248-multiple-sclerosis

[22] Myhr, K. M., & Mellgren, S. I. (2009). Corticosteroids in the treatment of multiple sclerosis. Acta neurologica Scandinavica. Supplementum, (189), 73–80. https://doi.org/10.1111/j.1600-0404.2009.01213.x

[23] Multiple Sclerosis Trust. (2022, March 1). Steroids (methylprednisolone). https://mstrust.org.uk/a-z/steroids-methylprednisolone.