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Multiple sclerosis: Genetic factors, risk and prevalence

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Abstract
Multiple sclerosis (MS) is a neurodegenerative disabling disease of the central nervous system commonly affecting young adults. MS is characterized mostly with autoimmune response. MS is more often transmitted to the next generation by mothers than fathers suggesting an epigenetic influence. Many gene expression studies have been undertaken to look at the specific patterns of gene transcript levels in MS. One of the possible reasons of this parent-of origin effect might be the human leukocyte antigen (HLA). Major environmental risk factors for MS, vitamin D deficiency, smoking and Ebstein–Barr virus are all known to exert epigenetic changes. Further research is needed to establish mechanisms of early diagnosis, treatment and prevention in humans and to explore preventative strategies. This review highlight, the genetic factors, challenges, risks, and ways of prevention for better understanding of MS disease.

Keywords: HLA, gene transcript, Ebstein Barr virus

1. Introduction
Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. The CNS consists of the brain and spinal cord. This disorder damages the protective layer "myelin" surrounding the nerves "axons" and nerves within the CNS. As a result, messages from the brain and spinal cord may short circuit, causing reduced body function. Many studies over the last two to three decades have indicated that MS is a T cell-mediated autoimmune disease [1]. MS is genetically complex and there may be no single genes of major attributable risk. Instead, MS may result from the contribution of several genes exhibiting low or moderate effect [2]. The most dangerous complication is usually infection, which may occur when patient is suffering from MS for a long time and is not as strong as an normal individual. Infection may often be successfully treated if recognized early. The effects and symptoms of MS vary within each individual. Some people experience symptoms for a short period of time and afterward may remain symptom-free for years, while others may experience a more steady progression of the disease.

Major Causes for MS
Studies have shown variety of possible causes for MS. The most popular theory involves a commonly known slow acting virus such as measles, herpes, human T-cell lymphoma, and Epstein-Barr. After being exposed to one of these viruses, some researchers explained that MS may develop in genetically susceptible people. Some scientists are also looking for a connection between MS and nutritional factors, including deficiencies in vitamin D and fish oil.

Role of Immune system
Immune mechanisms are believed to play an important role in the disease process. Focal demyelinated plaques are infiltrated by heterogeneous populations of immune cells and soluble immune mediators, including T cells, B cells, macrophages and microglia, as well as cytokines, chemokines, complement and other toxic agents. Demyelinated axons are exposed to the inflammatory mediators leading to axonal damage and neuronal loss in the pathoanatomical substrate of irreversible functional impairment and disability [3, 4]. Normal appearing white and gray matter are also different in MS compared with healthy controls.

Genetics of MS
Various studies about genetics of MS suggested the involvement of multiple genes located on human leukocyte antigen. One of the first major susceptibility gene which is located in the short arm of chromosome 6. HLA locus contains many genes that have pivotal functions in the immune system. Although there are some changes depending on the genetic background, association studies indicate an HLA class II haplotype (DRB1*15:01– DQA1*01:02–DQB1*06:02) susceptibility to MS [5]. The disease progression of MS is highly variable and is likely to depend on complex heritable genetic and environmental factors [6, 8]. According to recent studies, Ms is believed to result from the interaction of allelic variants of several yet unknown genes. Incomplete penetrance, epigenetic changes and many environmental factors determine the susceptibility of the disease. Epidemiological studies indicate that 1.9–4.7 % of MS patients have another MS patient in their families. The risk of MS is 30 times higher in first-degree relatives. The most convincing evidence comes from twin studies [5]. Multiplex families seem to possess the same susceptibility genes as sporadic cases of MS, albeit in greater number [6, 7]. It has been estimated that there are potentially 350 candidate susceptibility genes outside the MHC [8]. The most recent association studies find there are now over 50 genetic loci having confirmed association, with many other candidate loci identified at lower probabilities awaiting confirmation with larger scale studies [9, 11], including

genes involved in vitamin D metabolism [12, 13]. However, the identified associations explain only a small fraction of the familial aggregation of MS [14, 15].

Epigenetic Face of MS

Epigenetics represents all heritable or non-heritable changes that are not related to modified DNA sequences and lead to altered expression or translation of the genome. It operates using many mechanisms including DNA methylation, histone modifications and RNA interference. Epigenetic changes are specific to tissues and cannot be detected by association or linkage studies that are based on conventional DNA amplification methods. MS is twice as common in females than males. This obvious gender influence also underscores a possible epigenetic effect in MS since none of the predisposing genes are located in the X chromosome. Moreover, MS is more often transmitted to the next generation by mothers than by fathers [16]. This parent-of-origin effect might be mediated through the HLA-DRB1*15 allele, since mothers are more likely than fathers to transmit their HLA-DRB1*15 allele to their children [17].

Prevalence of MS

MS affects mainly young adults with predominance for females and prevalence in the USA and northern Europe of 100 per 100000 people [18]. From 250,000 to 350,000 patients in the U.S. have MS and 50% of patients will need help walking within 15 years after the onset of the disease [19]. Twice as many women are affected as men, and persons of Northern European descent appear to be at highest risk for MS [20]. The disease is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid (CSF). MS typically presents in adults 20 to 45 years of age; occasionally, it presents in childhood or late middle age. The cause is unknown, but it appears to involve a combination of genetic susceptibility and a non genetic trigger, such as a virus, metabolism, or environmental factors, that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS [21].

Discussion

Multiple sclerosis is a chronic inflammatory demyelinating disease of central nervous system white matter. A widely accepted view of the process of demyelination suggests that T cells, immunoglobulin and complement components have roles in pathogenesis. Adhesion molecules, cytokines, chemokines and HLA molecules are critical participants in the development of the inflammatory response in brain. MS diagnosis is based upon an individual's history of clinical symptoms and neurological examinations. A qualified physician often a neurologist must thoroughly review all symptoms experienced by an individual to suspect MS. Other conditions with similar symptoms often require various lab tests. Treatments have been available for MS since the late 1980s, based on immune suppression strategies. These treatments do not stop the inflammatory process within the CNS seen on magnetic resonance imaging (MRI) which has been used to assist in the diagnosis of MS for more than 20 years. The MRI consists of a computer, radiofrequency stimulator, and large electromagnet. An MRI picture looks like an x-ray, but a magnet and radio waves are used to produce a picture of the brain. For those with MS, the MRI is used to show the size and location of active lesions and plaques. Sometimes dye is given to the person with MS to better illuminate areas of inflammation. Disease modifying therapies may be more effective if started earlier in the course of the disease and the diagnostic criteria have been recently revised to recognize the importance of early treatment [22]. However due to the clinical complexity of the disease, the heterogeneity of the tissues used in expression studies, as well as the variable DNA chips used for the gene profiling, it is difficult to interpret the available information. A large number of aetiological factors have been identified to play a role in MS including genetic susceptibility, smoking [23], exposure to the Epstein-Barr virus (EBV) [24] and low exposure to sunlight which presumed to be mediated through vitamin D insufficiency [25, 26]. Although this information is essential for the understanding of the pathogenesis of MS, it is difficult to decipher and define the gene pathways involved in the disorder.

Conclusion

Understanding the clinical course and molecular pathways involved in MS are highly variable and should lead to therapies that target these specific pathways. This also depends on complex genetic and environmental factors. Emerging evidence has established a preliminary role for epigenetic mechanisms in MS. Despite advances in understanding the immunopathogenesis of MS and the availability of innovative therapeutic strategies, efficacious treatment of MS remains an unmet need. Characterization of epigenetic factors that can be used in prediction of treatment responsive and non-responsive MS patients will meet an important deficiency in this field. A number of different experiments for gene expression studies through microarrays revealed hundreds of significantly altered expressed genes. Some of these genes have been further investigated and have provided increased understanding of the complex pathological mechanisms involved in MS. Many more genes need further analysis and represent an interesting and exciting future in MS research. Novel approaches to repair of the damaged nervous system may also be suggested. It may even be possible to begin to understand how to interrupt MS before it begins.

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