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Who Did It?: A Review on the Possible Causes of Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is an incurable autoimmune disorder that attacks the myelin sheath surrounding nerve cells. Steady demyelination of these cells over time results in painful inflammation and reduced mobility. Genetic abnormalities could be responsible for the onset of this disease. Chromosomal mutations found in MS patients as well as environmental factors influencing the expression of certain genes will be analyzed in this review. Moreover, treatments regulating gene expression in MS patients will be discussed. Further genetic research would not only provide scientists and medical professionals with a deeper understanding of MS and other autoimmune disorders, but also lead to the development of more effective treatments. Recent findings have enabled scientists to identify genes in MS patients that are absent in healthy patients, but researchers struggle to find a common thread tying these genes together. This is just one of the many reasons why MS is still considered an idiopathic disease.

KEYWORDS: multiple sclerosis (MS), demyelination, gene expression, gene regulation, treatment

INTRODUCTION

Multiple sclerosis is a neurological autoimmune disorder that degrades an individual's quality of life. The body's immune cells attack each neuron's myelin sheath, causing chronic inflammation and degradation of myelin tissue.¹ Electrical signals sent from the brain cannot travel at high enough speeds without this myelin coating.¹ These unfavorable immune responses are a result of malfunctioning immune cells. Killer T-cells and B-cells misidentify the body's own tissues as foreign, provoking an unnecessary response.² Over time, this nerve damage can be so intense it could cause other unrelated health issues to develop.²

Due to the depth and complexity of the immune system, there is no known cause or cure for multiple sclerosis. MS can present in a variety of ways, making it difficult to diagnose. Common symptoms include limb weakness, vision impairment, and depression; however, patients have identified ailments like urinary tract infections and trouble swallowing as symptoms as well.³ Another prevalent symptom is Lhermitte's sign, which causes intense pain in the spinal column.⁴ Though frequently seen in MS diagnoses, this symptom can also appear in individuals that suffered spinal cord trauma or have depleted vitamin B12 levels.⁴ Furthermore, uncommon symptoms do not indicate a better prognosis for the afflicted.⁵ Incidences of relapse between individuals presenting either common or uncommon symptoms are almost identical.⁵ A viable way to make sense out of these symptoms is through genetic research. Tying these symptoms to chromosomal loci can make MS easier to identify and treat. Evidence now suggests that a combination of genetics and the environment influences the onset of the disease. This allows researchers to narrow their scope and assess how geographical, cultural, or socioeconomic surroundings could influence gene expression in MS patients. Though recent evidence is promising, this research framework still possesses several limitations, including the ability to directly link these genetic abnormalities to one another. This review will focus on gene interaction and expression, as well as environmental factors that influence their expression. Moreover, drug therapies affecting gene regulation will also be explored.

GENETIC FINDINGS

Mutations

Mutations in certain genes are not only common to MS patients, but also result in abnormal T-cell production. For example, mutations in the *FoxP3* gene lead to the production of malformed regulatory T-cells, causing immune responses to go unmonitored.⁶ Consequently, the body cannot stop attacks on its own tissues.⁶ Moreover, with the sequencing of the human genome, scientists have identified NR1H3 as a problem in MS patients, especially in those with a family history of the disease.⁷ NR1H3 codes for receptors that regulate fatty acid formation and function as well as inflammatory response.⁸ A mutation in this gene creates pathogenic variants that inhibit production of the receptor in highly metabolic tissues, including ones in the brain.⁷ Deregulation of these receptors can cause inflammatory episodes like the ones seen in multiple sclerosis patients.

Gene Expression

Patients that develop multiple sclerosis exhibit a vast range of symptoms, but current research data cannot unanimously determine just one genetic abnormality that triggers MS. However, recent developments support a hypothesis that alternative gene expression could play a role in onset of the disease. Comparison of blood assays between healthy and afflicted individuals showed 99 alternatively spliced RNA sequences, with 19 of them bearing statistical significance.⁹ Most of the pathologically spliced genes were responsible for inflammatory and developmental disorders, especially in skeletal and muscular tissues.⁹ These instances of alternative gene expression would drive inflammation in the myelin tissue of multiple sclerosis patients.

To make matters even more complicated, gene expression patterns are inconsistent and can vary based on the tissue. A recent study showed that based on the type of MS diagnosis and its duration in the patient, tissues in the brain can be at different stages of myelination.¹⁰ The same study also observed expression patterns of twelve genes seen in brain lesions caused by demyelination disorders.¹⁰ Among the four tissue types tested from patients at different stages of MS diagnosis, only half of the observed genes (NKX2-2, SOX10, SEMA3B, CXCL12, STAT6, MOG) showed an increase or decrease in expression rate, while the other half (IGF1, IGF2, IL4, IL4R, MAL, PLP1) showed no trend in expression rate.¹⁰ The irregularity in expression rate across these tissue types makes it near impossible to determine which genes have the greatest effect at varying stages of MS. Even in the genes that do exhibit a trend, it is still unclear how these genes are regulated and how they might affect one another.

ENVIRONMENTAL INFLUENCES

Twin studies are one of the most reliable ways to test genetics against environment. Research suggests that external influences, especially during embryonic and childhood development, has a greater influence on the expression of MS than the genetics themselves. According to a meta-analysis conducted on multiple twin studies, the shared environment and similar upbringing experienced by twins (either monozygotic or dizygotic) causes MS to manifest similarly in both individuals 10% to 30% of the time.¹¹ This correlation establishes a link between quality and type of living and MS diagnosis.

Moreover, geographic location can trigger MS in those with a family history of the disease.¹² This phenomenon could have to do with the way circadian rhythm genes are expressed in individuals who live in these extreme northern or southern regions of the Earth. Two genotypic variants on both ARNTL and CLOCK, which regulate circadian rhythm, display a statistically significant correlation with MS diagnosis.¹² Another experiment hypothesized that ZMIZ1, a gene poorly expressed in MS patients, was influenced by vitamin D levels, which are affected by accessibility to sunlight.¹³ In this study, blood samples of MS patients and healthy controls were collected separately in the summer and winter months to see how ZMIZ1 expression was affected by the time of year.¹³ ZMIZ1 expression was the same in MS patients for both the summer and winter months, but expression increased in the winter for the healthy controls.¹³ Therefore, the results of this study concluded that while ZMIZ1 expression is an issue in MS patients, vitamin D and sunlight availability are not factors influencing the expression of that gene.

The genes discussed here are not directly related and do not have the same effects on the body, indicating the need for more investigation into the theory of geography and sunlight. Other factors, such as diet, exercise, and lifestyle could also be altering gene expression, but there is currently not enough research to support any one of these factors.

TREATMENTS

Although scientists have yet to find a cure for multiple sclerosis, a number of drug therapies are being explored to regulate gene expression in MS patients. Most of these experimental drugs are administered to mice with an induced form of MS known as experimental autoimmune encephalomyelitis (EAE).^{6, 14} Atorvastatin is one of these drugs, which involves the *FoxP3* and STAT6 genes discussed in a previous section.¹⁵ In mice with low STAT6 expression, a 1 mg/kg dose of atorvastatin prevented EAE from maturing and reversed inflammatory damage in mice with more advanced stages of EAE.¹⁵ Conversely, a 10 mg/kg dose of atorvastatin did not increase presence of regulatory T-cells created by *FoxP3*, suggesting that gene expression was not enhanced by this drug.¹⁵ Further genetic research might lead to the development of a drug that increases *FoxP3* expression and the production of healthy T-cells.

Additionally, these treatment studies have allowed scientists to focus on specific proteins, such as the myelin binding protein (MBP). Pathogenic conformations of this protein trigger immune responses, while the appropriate conformations shut these responses down. Evidence suggests that when administered, MBP₈₇₋₉₉ turns off production of MBP₇₂₋₈₅, the harmful protein that can cause an inflammatory episode (Table 1).¹⁴ Furthermore, researchers have adopted genetic engineering techniques to help fix MBP expression levels. XBD173 is an artificial protein ligand developed to treat experimental autoimmune encephalomyelitis by targeting MBP.¹⁶ Three separate groups were administered XBD173 in doses of either 10 mg/kg, 20 mg/kg, or 30 mg/kg.¹⁶ Although scientists anticipated the highest dose to have the greatest impact, the results concluded that the lowest dose was the most effective at lessening symptom intensity and restoring MBP expression levels.¹⁶ Smaller doses of the ligand taken over an extended period of time presented less side effects and had a more therapeutic outcome than larger doses (Table 1).¹⁶ There are a variety of ways to approach MS treatment with genetics, and studies like this show a promising future for development of treatments influencing genetic makeup.

Table 1. Comparison of Treatment Methods Involving Myelin Basic Protein (MBP) in Mice with Experimental Autoimmune Encephalomyelitis (EAE).

Treatment	Type of Substance	# Subjects Tested	Age of Subjects	Frequency of Dosage	Success Rate (%)	Side Effects	References
MBP ₈₇₋₉₉	protein sequence	54	12 weeks	2 days before EAE inoculation	66.6%	none	14
XBD173 (10 mg/kg)	protein ligand	26	9-11 weeks	every 2 days after EAE inoculation from day 4 to day 30	77%	weight loss	16
XBD173 (20 mg/kg)	protein ligand	26	9-11 weeks	every 2 days after EAE inoculation from day 4 to day 30	58%	weight loss	16
XBD173 (30 mg/kg)	protein ligand	8	9-11 weeks	every 2 days after EAE inoculation from day 4 to day 30	55%	weight loss	16

CONCLUSION

The research conducted on multiple sclerosis impacts studies on all autoimmune diseases, especially when it comes to their genetic components. Being able to isolate loci on chromosomes allows us to identify new biomarkers that code for pathogenic characteristics. While there is no known cause or cure for multiple sclerosis, genetic research has allowed scientists to narrow their focus to target individual genes, proteins, and metabolic pathways. In many cases, genetics alone aren't to blame, as certain environmental stressors increase the odds of the disease being expressed. Although there are still significant gaps in MS research, new drug therapies are constantly being

developed to help patients cope with debilitating symptoms. Continued research in the field of genetics would improve accuracy of diagnosis, explain why MS can present in so many ways, and lead to the development of drugs that could regulate expression of specific genes. If all gene loci associated with multiple sclerosis are identified, genetic screening could be used to determine pre-disposition to the disease and assess risk factors. This has the potential to improve prognosis and give diseased individuals the opportunity to lead a normal life.

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