

## Genomics and Multiple Sclerosis

The recent breakthroughs in genomics have contributed greatly to the advancement of multiple sclerosis treatments. With more information about genetics available than ever before, scientists and doctors have been able to isolate SNPs and other DNA discrepancies that can predict the risk of developing the condition, as well as influence its severity. MS is particularly challenging to treat, as it occurs in multiple forms and has symptoms similar to those of many other conditions. GWAS and other discovery methods have led to critical insights and launched research for MS therapies that will be more preventative and restorative than previously maintenance-oriented treatments.

### *What is Multiple Sclerosis?*

“Multiple sclerosis (MS) is a chronic neuro-inflammatory autoimmune disease believed to arise from complex interactions of both environmental and genetic factors.”  
(<http://www.ncbi.nlm.nih.gov/pubmed/20450971>)

Multiple sclerosis is characterized by a number of symptoms, though since the signs are not related strictly to MS it is often not the initial diagnosis. No one test stands alone as a reliable indicator of the condition, and multiple symptoms need to show over an extended period of time for any confident conclusion. Brain tumors, genetic disorders, and other irregularities with the central nervous system can also lead to the exhibition of MS-like symptoms. (<http://www.nationalmssociety.org/about-multiple-sclerosis/do-i-have-ms/index.aspx>)

As an autoimmune condition, MS occurs when the body attacks its own central nervous system. The ensuing demyelination can cause tingling, numbness, paralysis, and an entire array of issues that differ in severity. The disorder is characterized by its unpredictability, as its occurrence, chance of relapse, and complications are irregular and do not show uniformity between patients. However, enough similarities have been researched that different forms of the disease have been chronicled.

There are four different “courses” of the disease that can be recognizable to physicians as it progresses. The most common, relapsing-remitting, is experienced by 85% of those diagnosed and is characterized by exacerbations followed by inactivity, which worsen over time. A secondary-progressive course used to occur in half of those with an initial diagnosis of relapsing-remitting, showing steady degeneration without remission. Since better drugs and treatment options have become available, less patients have displayed this course, though a great amount of uncertainty surrounds this specific phenomenon. (<http://www.ncbi.nlm.nih.gov/pubmed/16545751>) Current, groundbreaking studies are working to better understand this relationship and provide future solutions. Approximately ten percent of patients display primary-progressive MS, in which from the start the disease is consistent in its attacks and does not show remission. MS’s rarest form, progressive-relapsing, is shown in five percent of patients. This form also leads to steady decline, with more severe attacks marking periods of “relapse.” (<http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/index.aspx>)

Multiple sclerosis is defined by its variability. While it is difficult to predict even after diagnosis, it is even more uncertain what precisely triggers the condition.

*The Complexity of Multiple Sclerosis*

“There is no single gene that causes the autoimmune condition multiple sclerosis (MS). Dozens of genetic variations act in concert with environmental factors to cause the debilitating neurological disease.” (<http://www.nature.com/news/genome-study-highlights-risk-factor-for-multiple-sclerosis-1.10967>)

Most people with multiple sclerosis start to display symptoms between the ages of fifteen and fifty, a remarkably wide and variable range. Women are more likely to be affected than men, especially in the case of relapsing-remitting MS. Caucasians and people of European descent are most likely to be afflicted, and there is a correlation between distance from the equator and the disease. Family history, vitamin D deficiency, and smoking have been linked to MS. (<http://www.mymsaa.org/about-ms/overview/>) Learning more about the genetic basis of the disease has led to more effective treatment options, though environmental factors hold great influence over its occurrence and course as well.

It is by no means conclusive how much heritability or genetics influences MS, only that a relationship between the two determines an individual’s case. “Estimates of the heritability of multiple sclerosis differ over a wide range; even estimates from well-conducted studies vary from 24-86%”. (<https://www.23andme.com/health/Multiple-Sclerosis/>) It is known that heritability is a factor, and that a family history does increase chances of an MS diagnosis. However, with such variability it can be impossible to predict how much of a risk the relationship holds. Additionally, the noted environmental factors, vitamin D deficiency and smoking, are attributed to many other conditions and do not link to every case of multiple sclerosis. At this point, the discovery of pertinent SNPs and new ways to prevent the onset of MS will be most effective in improving the

outlook of the disease. A better understanding of the genetics-environment relationship should follow as more in-depth genomic research is performed.

The intricacy of MS is reflected in its genetic makeup. A variety of genes are significantly related to the occurrence and expression of the disease; in researching these genetic factors, MS and other neurodegenerative disease can be better understood.

### *GWAS and Multiple Sclerosis*

“The successful accomplishment of genome-wide association studies (GWAS), analyzing >100,000 single nucleotide polymorphism markers simultaneously based on chip technology, has recently brought interesting new insights into the genetic background of this complex disease.” (<http://www.ncbi.nlm.nih.gov/pubmed/20450971>)

Genome-wide association studies (GWAS) have been used to isolate genes, loci, and SNPs for a great number of diseases and abnormalities. Through this mechanism, specific sequences have been linked to multiple sclerosis. While more than one hundred sequences made it to the second-stage analysis in this study of over three hundred thousand SNPs from nine hundred and thirty-one families, only two genes and one locus were isolated as significant. “Alleles of *IL2RA* and *IL7RA* and those in the HLA locus are identified as heritable risk factors for multiple sclerosis.”

(<http://www.nejm.org/doi/full/10.1056/NEJMoa073493>) Another study looking at the polymorphisms in *IL2*, *IL2RA* and *IL2RB* focused specifically on their MS-related risk factors and found them and the HLA locus to be significantly associated with the occurrence of multiple sclerosis. (<http://www.ncbi.nlm.nih.gov/pubmed/22516854>)

MS is an autoimmune condition, and the functions of these relevant genes show that. The HLA region is made up of many genes related to multiple histocompatibility complex, a significant piece of the human immune system. The other *IL2RA* and *IL7RA*

genes, as well as their variants, play a significant role in the development and activation of lymphocytes. All of these discoveries are significant in decoding multiple sclerosis and the immune system's specific role in the progression of the disease. Identifying the precise genetic material that contributes to risk of MS can be used both to examine heredity and to target those sequences in the future.

Recent research has led to breakthroughs and insights. "2012 witnessed important developments for multiple sclerosis, including successful phase III trials of novel oral therapeutics and identification of the potassium channel KIR4.1 as an autoimmune target. Additionally, the lung was highlighted as an important site for immune-cell programming, and the relevance of a TNF receptor variant was clarified."

(<http://www.ncbi.nlm.nih.gov/pubmed/23338282>) Identifying significant regions and receptors inspires continuing trials and treatments for MS patients. TNF (tumor necrosis factor) is a large family of genes that influence a variety of conditions.

(<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=334>)

Blocking the TNF receptor was helpful in treating other neurological conditions, but exacerbated MS. The differences between diseases are often very revealing and can help to redesign old therapies to create innovative alternatives. Better understanding of the immune system especially is helpful in treating all autoimmune and other conditions.

More progress can be made, as MS and other neurological disorders are studied side by side. "Clinical practice can be informed by comparing GWAS across common autoimmune diseases and by investigating the functional consequences of the disease-associated genetic variation." (<http://www.ncbi.nlm.nih.gov/pubmed/22801493>) The subtleties in allele variation and significant loci between diseases offers an incredible

amount of insight to which genes affect neurological and immune function, and specifically how. Finding a treatment or discovering something about another condition can also enlighten researchers about MS. “A considerable overlap of susceptibility genes among multiple autoimmune diseases is becoming evident and integration of these genetic variants with our current knowledge of affected biological pathways will greatly improve our understanding of mechanisms of general autoimmunity and of tissue specificity.” (<http://www.ncbi.nlm.nih.gov/pubmed/21247752>)

Though GWAS offers an incredible amount of new insight and even more information to the pool of knowledge, it is not holistic. MS is influenced by highly variable environmental factors in addition to genomic abnormalities, meaning a comprehensive understanding of the disorder cannot be found solely in SNPs. Researchers and experts must take into account other genetic factors, including epigenetics, to decipher the condition. “It is likely that a major fraction of genetic MS risk that cannot be explained by GWAS, sometimes termed the ‘dark matter’ of GWAS, is caused by other factors, such as structural variations of the genome, rare sequence variants, or inherited epigenetic modifications.” (<http://www.ncbi.nlm.nih.gov/m/pubmed/22430841/>) However, though GWAS cannot offer complete understanding, it has definitely led to advances and innovative new treatment studies for people suffering from MS.

Genetic research and GWAS have contributed significantly to the increasing knowledge of MS. Better understanding of the disease leads to more beneficial and effective treatments and inspires groundbreaking clinical trials, which are huge improvements upon previous therapies.

*The Evolution of Multiple Sclerosis Treatments*

“MS also serves as an example of a chronic relapsing inflammatory disease where disease modification is the goal of treatment.”

(<http://www.ncbi.nlm.nih.gov/pubmed/22796801>)

Treatment plans differ enormously between individuals. Strategies generally involve multiple drugs and therapies to combat each case of MS. Corticosteroids and plasmapheresis can be used to alleviate symptoms. Drugs such as beta interferons, Glatiramer acetate, Fingolimod, Natalizumab, Mitoxantrone, and Teriflunomide work, in different ways, to prevent further damage to the central nervous system. Physical therapy, Dalfampridine, and muscle relaxants can also be incorporated into plans to alleviate pain and boost patient mobility. This great variety of medications, which is only the shortened list, are not applicable to all cases. People exhibit different symptoms, which require diverse management. MS patients are prescribed medicine to treat neurological symptoms such as spasms and mobility issues, behavioral changes, pain, weakness, and many other markers of the disease. Many of these drugs can produce serious side effects, but patients would have extreme difficulty functioning without them.

(<http://www.mayoclinic.com/health/multiplesclerosis/DS00188/DSECTION=treatments-and-drugs>)

While these therapies do exist to treat MS, they work mostly to avert relapse or maintain myelin levels. None of them are totally effective in completely preventing further harm or, importantly, rebuilding damaged tissue. Recent breakthroughs in genetics have allowed researchers to create treatments that are theoretically less harmful for the patient and more effective in treating the disease. In the study “Evaluation of Autologous

Mesenchymal Stem Cell Transplantation (Effects and Side Effects) in Multiple Sclerosis,” adult marrow-derived stromal cells (MSCs) will be utilized. Use of these cells means that the patient can be the donor, eliminating rejection risk and improving chances of success. Preliminary research showed that “[MSCs] were shown to induce similar (to the neuronal stem cells) immunomodulatory and neuroregenerative effects and were shown in our laboratory to induce neuroprotection.” Therefore, no genetic therapy has to be engineered to modify the cells; they naturally perform the desired function. The study is set to look at the effects of stem cells through MRIs, brain atrophies, number of relapses, EDSS, and MSFC. In evaluating this progress, steps can be made to improving future trials and working toward a more effective treatment.

(<http://clinicaltrials.gov/show/NCT01377870>)

In another study that isn't estimated to be completed until September 2016, researchers are studying the effects of a drug, Siponimod, on secondary progressive MS. (<http://clinicaltrials.gov/show/NCT01665144>) Usually, in this course of the condition, patients display steady degeneration without remittance. Such cases have decreased in number as more effective drugs enter the market and become available to patients. These drugs, some currently still in trials like Siponimod, become more effective as research advances. As mentioned previously, the TNF receptor plays a role in cases of multiple sclerosis. When drugs that worked for other disorders by blocking TNF were tested to help MS patients, they actually caused symptoms to worsen. “It is unclear how TNF influences MS, but in patients with the gene variant, the TNF-blocking drugs could be providing a double-whammy by suppressing TNF signalling further.”

(<http://www.nature.com/news/genome-study-highlights-risk-factor-for-multiple-sclerosis->

[1.10967](#)) The relationship between genetic research and pharmaceutical development is crucial, and the interaction between the two leads to better therapies for patients. While MS is still an incurable condition, more managing treatments are available today. And, with the continuance of ingenious genetic research, a cure is closer than ever before.

In summary, multiple sclerosis is a multifaceted disease that progresses very diversely among patients. Historically, treatments have not seen incredible success. Identifying the gene sequences that affect the phenotype have offered insight and will inspire future research and hopefully effective therapies. One such therapy, currently in the clinical trial phase, uses stem cells and shows a lot of promise. Using a patient's own stem cells to improve neurological and physical function and even do some repair work has the potential to greatly improve the quality of life and prognosis of MS patients. Genetic research provides a lot of hope to people suffering from degenerative disease everywhere.

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