



The Basic Facts

Genetics

“What makes people susceptible to multiple sclerosis?” Most scientists and physicians who have studied this question are convinced that heredity—the genes we inherit from our ancestors—is one factor.

In 1992, the Society began a major targeted research initiative to search for the genes that make people susceptible to developing MS. Understanding how genes contribute to determining who gets MS should provide major clues to the cause, and may point to ways of preventing and treating it. Advances in the field of molecular genetics offer hope that we will be able to answer the question someday.

Two types of evidence support the connection between genes and susceptibility to MS:

- The first comes from population studies. People from different ethnic groups have different tendencies to develop MS. It is most common among people of Northern European ancestry, although African Americans and Hispanics develop MS as well. Other ethnic groups—Inuits, African blacks, and Southeast Asians—are much less likely to have MS.
- The second type of evidence comes from studies of families in which MS occurs more frequently than chance would dictate. The average person in the United States has about one chance in 750 of developing MS. But relatives of people with MS, such as children, siblings or nonidentical twins, have a higher chance—ranging from one in 100 to one in 40. The identical twin of someone with MS, who shares all the same genes, has a one in four chance of developing the disease.

These facts tell us that genes are important for determining who may get MS, but they are **not** the whole story: the identical twin of a person with MS would always get MS if genes were the only factor involved.

In addition to genes, other factors—perhaps exposure to germs or viruses—play a part in causing MS. That is why scientists say that MS is not directly inherited. Genetic factors determine who is susceptible to the unknown outside trigger.



**National
Multiple Sclerosis
Society**

GENES ARE THE RECIPES OF LIFE

Genes are the units of heredity discovered by Gregor Mendel more than a century ago. They contain the recipes, or instructions, for making the proteins of which all living things, from bacteria to humans, are built and which all organisms use to carry out their functions.

Since the 1970s, scientists have been developing a set of tools—the methods of molecular genetics—that can isolate and determine the chemical structure of genes.

Genes are pieces of the famous long molecule known as DNA (deoxyribonucleic acid). Genes are located along the chromosomes in the nuclei, the control centers of cells. The information carried in genes is a code. It is the sequence of chemical units—called bases—strung together in that section of DNA. The information written on this page is also a code made up of the sequence of individual letters. Like the bases in genes, each letter carries little information in itself, but strung together in the specific sequences, the letters make up words, sentences, and entire books.

The genetic “alphabet” has only 4 “letters” or bases, arranged in a sequence in each gene. The sequence of bases in a gene tells a cell how to assemble a specific protein.

Most of the trillions of cells in a person’s body have 2 complete sets of genes—one inherited from the mother and one from the

father. Each set, numbering approximately 25,000 genes, contains all the instructions needed to build all human proteins. The complete set is known as the human genome.

More recent discoveries have revealed that the structure of the human genome is even more complicated than previously thought. There is surprising variability from person to person in the number of copies of some of our genes contained on single DNA strands. Other changes outside of the region of the DNA responsible for specifying a protein can influence how, and in which cells, the DNA segment is turned on and off to make a protein. We are only beginning to appreciate the extent to which these additional changes in the architecture of our DNA influence our risk for disease. Genetic maps being developed by researchers reveal an intricacy—and a beauty—that would have been unimaginable to earlier generations of scientists.

ERRORS CAN CAUSE DISEASES

In order for genes to be inherited, or passed from one generation to another, they must be copied from the parents’ genes. The structure of DNA molecules helps insure that accurate copies are made. The cells that do the copying have “proofreading” mechanisms which correct most copying errors. Like human proofreaders, however, these cellular devices sometimes make

mistakes. Because the genome is copied many times for each generation, there are many slightly different versions of all the human genes.

Much of this variation is harmless and, indeed, is partly what gives each of us our unique characteristics.

No two people have exactly the same sequence of DNA bases in their genes. We now know that even identical twins have some differences in the fine structure of their DNA. Differences in the DNA sequence are so unique to an individual that DNA analysis can be used for identification. Sometimes, however, a difference in a single gene can be responsible for a disease that is inherited.

In the 1980s, scientists began to apply the tools of molecular genetics to human diseases. This work led to understanding of some diseases, most of them rare, caused by defects in a single gene—such as Duchenne muscular dystrophy and cystic fibrosis. News stories appear frequently about other advances in knowledge of human genes and diseases.

NORMAL VARIATIONS IN DNA CAUSE MOST COMMON DISEASES

The situation for MS is more complicated because no single gene is responsible for the disease. Scientists believe that most people become susceptible to developing MS

only if an unlucky combination of many genes is inherited. It is also likely that the cause of MS may be more genetic in some individuals, and less genetic in others. Until a few years ago, the problem of identifying MS genes seemed hopelessly difficult. Today, advances in molecular genetics, the identification of families in which several members have multiple sclerosis, and the collection of DNA from many thousands of people with MS worldwide, have changed the outlook, and research is now moving at breakneck speed to uncover MS susceptibility genes.

The research teams have the challenging task of finding an unknown number of genes that confer susceptibility to MS. This requires searching the 3.2 billion DNA bases that form the code of the 25,000 genes, and also the intervening DNA that influences how the genes function. To do this, scientists probe the DNA of white blood cells searching for identifiable patterns or markers in the DNA code inherited in common by the individuals with the disease but absent in healthy relatives and in matched control populations.

There are approximately 10 million different variations in single base pairs of DNA (called single nucleotide polymorphisms or SNPs) that are “common” in humans—that is, present in 5% or more of individuals. Thus, the search for the culprit changes leading to MS is a large task indeed.

Furthermore, because each variation is likely to confer only a very small risk for MS, large numbers of people with MS and controls need to be studied in order to be sure that the difference is valid and not due to a random statistical error.

When one suspicious area, or marker, is identified as being consistently inherited by people with MS, the scientists focus on that area, seeking additional markers that may be closer to the actual genetic change that is responsible. Eventually the causative MS variant can be identified, and its function determined.

State of the art technology now permits the automated screening of 1 million SNP variants from thousands of different individuals in just several weeks time! The major limitations to identifying the genetic changes that cause MS have now become the problems of 1) how to collect DNA from very large numbers of people with well-characterized MS, and 2) how to analyze the unprecedented amounts of data that result. These experiments also require that experts from different disciplines be brought together—not only MS scientists and geneticists, but also engineers, statistical experts, and even project managers, to solve this problem in a coordinated fashion.

MS GENETICS: A NEW ERA OF SOPHISTICATION

The first major accomplishment occurred in July 2007 with two publications—in the *New England Journal of Medicine* and *Nature Genetics*—of the first studies of MS genetics using these novel tools. In the first paper, DNA was examined from more than 4,000 people with MS and 8,000 controls. In addition to a region on chromosome 6 containing the “master switch”—or HLA—genes controlling the immune response and previously known to be involved in MS, two other critical genes in the immune pathway, the interleukin-7 (IL-7) and interleukin-2 (IL-2) receptors, were found. Other suspected genetic changes were also reported in this study that have been subsequently confirmed (see below). The second paper reported a detailed study of the IL-7 receptor, revealing that the MS change altered in a fundamental way the function of this protein. This opens up an entirely new avenue in the understanding of what leads to MS, and perhaps also how to prevent, and more effectively treat, MS.

THE STATE OF MS GENETICS: 2009

Additional work, building on the success of the National MS Society-supported landmark study of 2007, has now identified approximately a dozen genes that increase the risk of MS. The genes identified to date all appear to function primarily within

the immune system; some make proteins that interact with each other, raising the possibility that a specific pathway of related genetic changes could lead to MS. These results confirm what has long been suspected—that MS is primarily a disease of the immune system. Very recent tantalizing data suggest that some other MS genes may work by affecting the health of nerve cells. These results are potentially important because if correct, they may provide a molecular clue to how nerve cells deteriorate in progressive forms of MS.

Studies of large populations of African-American and Asian subjects with MS are also underway, with highly promising results that are likely to add to our understanding of the genetic cause of MS. A gene within the HLA region, called DRB5, appears to make MS less severe. This gene is absent from the DNA of many individuals of African heritage, which may explain in part why MS is more severe in some African-Americans. Other genetic studies are beginning to show that some people with MS inherit genes that predispose them not only to MS, but also to some other autoimmune diseases such as immune thyroid disease, among others.

It's important to note that none of the genes identified to date are strong enough predictors of MS to be useful in a practical sense for genetic counseling. It is now clear that there will probably be at least 50–100 different genetic changes involved in

determining who is at risk for MS, and how MS behaves once it begins. Most or all of the genes are yet to be found, and because they haven't yet appeared in the studies performed to date it is highly likely that these will also have small effects on risk.

An extraordinarily ambitious study is now underway at the Sanger Center in the United Kingdom, utilizing DNA from 10,000 MS patients collected worldwide through the International MS Genetics Consortium initially established through funding by the National MS Society. Once the markers that are related to MS are identified (expected in summer or fall of 2009), confirmation will be performed with 10,000 additional MS samples, currently being collected with Society funding. It is possible that all of the common DNA changes leading to MS will be identified within two years.

These results will all be placed in the public domain for the benefit of researchers worldwide, permitting rapid translation into practical discoveries for the benefit of people with MS.

THE FUTURE IS NOW

More has been learned about MS genetics in the past 24 months than in the prior 100 years! Because of its tremendous potential, the Society is committed to continue funding research on the genetic aspects of MS.

Some research groups are now concentrating on the biology of MS, hoping to identify one or more proteins that are basic to the MS process. They hope to chase down the genes known to be involved in building that protein or proteins. This is possible today, thanks to exciting advances in protein chemistry and should complement genome screening.

Other strategies, funded by the Society and its partners, include:

- A DNA bank, to store samples from individuals with MS for use by investigators worldwide.
- Developing finer DNA probes for locating the genes of interest more closely.
- Additional DNA studies of families in which MS is unusually common.
- DNA studies in geographically isolated populations, such as Tasmania and Finland; and studies among ethnic and racial groups where MS is extremely common or extremely rare.

Individuals in families with many blood relatives who have MS can help these studies. Please go to “Research” on our web site (nationalmssociety.org); click on “Researchers Need You” and select “Participate in Genetic Studies.”

HOPE FOR BETTER TREATMENTS

The most important reason for finding the susceptibility genes is the hope of developing more effective treatments. But new treatments are not likely to involve trying to change individual genes themselves. Understanding the molecular pathways involved in MS risk should lead to therapies that target these specific pathways. The knowledge will also provide other benefits. It might become possible to predict the course of MS, making it easier for doctors to tailor therapies and for individuals and their families to make sensible plans for the future. 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. An early, definitive test for diagnosis might become possible; many physicians believe that the sooner MS is treated, the better the long-term outcome. And, finally, knowledge of the function of all the genes involved in MS will reveal the basic cause of the disease—an unthinkable possibility only a few years ago.

SUPPORTING LITERATURE FROM THE SOCIETY

- Research Directions in Multiple Sclerosis
- Just the Facts

- What is Multiple Sclerosis
- The Disease-Modifying Drugs

Ask your chapter for copies of these brochures.

The National Multiple Sclerosis Society is proud to be a source of information about multiple sclerosis. Our comments are based on professional advice, published experience and expert opinion, but do not represent individual therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.

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