

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, including the Society’s targeted initiative, 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 typically a disease that affects people of Northern European heritage. Other ethnic groups—Inuits, African blacks, and Southeast Asians—are 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 non-identical 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 three 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.

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 deoxyribonucleic acid or DNA. 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. Information on this page is also a code made up of the sequence of individual letters. 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 30,000 to 40,000 genes, contains all the instructions needed to build all human proteins. The complete set is known as the human genome.

ERRORS CAN CAUSE DISEASES

In order for genes to be passed from one generation to another, or inherited, 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 “proof-reading” 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. Except for identical twins, no two people have exactly the same sequence of DNA bases in their genes. 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 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.

NEEDLES IN THE HAYSTACK

The situation for MS is more complicated because no single gene is responsible for the disease. Scientists believe that a person is susceptible to developing MS only if an unlucky combination of several genes is inherited. Until a few years ago, the problem of identifying those genes seemed hopelessly difficult. Today, both advances in molecular genetics and the identification of families in which several members have multiple sclerosis—called “multiplex” MS families—changed the outlook, and research to uncover MS susceptibility genes is now going forward. Many

multiplex families throughout the world have agreed to participate.

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 30,000 to 40,000 genes. To do this, scientists probe the DNA of white blood cells from multiplex families searching for identifiable patterns or markers in the DNA code inherited in common by the individuals with the disease but absent in their healthy relatives.



There are hundreds of these marker areas throughout the human genome. When one of them 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 gene. Eventually the absolute location of a gene can be identified. This process of moving closer to a gene until it is identified has to be repeated for each of the marker regions found in the DNA from multiplex MS families.

In the early 1990s, three large “whole genome” screens focusing on the MS markers were performed in the United States, the United Kingdom, and Canada. The studies were completed

and published in 1996. The investigators reported that as many as 20 locations in the genome may contain genes that contribute to MS susceptibility. Moreover, no single gene was shown to be the major influence on MS susceptibility. The genes themselves appear normal. Susceptibility is probably related to the combinations.

Each of these studies pursued different sets of markers and used somewhat different criteria for people included in the study. Some of these studies may have underestimated the “heterogeneity” of MS, that is, the variety of symptoms and, perhaps, the variety of genes involved in different people with MS. Many other regions in the genome have also been identified as potentially being involved in MS.

THE SEARCH TODAY

The Society is currently targeting research on the genetic aspects of MS, with a multi-year multimillion-dollar commitment.

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. The needles may

still be very small, but this strategy may reduce the size of the haystack.

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, click on “Researchers Need You” and select “Tissue and Gene Banks”.

AFTER THE GENES ARE LOCATED

When susceptibility genes are, at last, identified, the role those genes play in the immunological and neurological aspects of MS will have to be determined.

Because the immune system is involved in producing the damage in multiple sclerosis, many scientists think that at least some of the susceptibility genes will be related to the immune system. Indeed, there have already been reports linking immune system genes including those for the immunoglobulins and for the major histocompatibility complex (or MHC), and to MS. Results reported to date have confirmed that the MHC region holds one or more genes that seem likely to be related to MS susceptibility.

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 the genes themselves. Research suggests there will be too many of them.

The knowledge will 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. 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*
- ❖ *Putting the Brakes on MS*

Ask your chapter for copies of these brochures.

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