The Basics of Genetics in Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system. The etiology of multiple sclerosis is unknown. MS is seen as an interplay of genetic susceptibility, environmental exposure, and dysregulation of the immune system. MS is probably triggered by an environmental factor in persons who are genetically susceptible. The roles of genes and environment are not fully understood in MS. Familial tendency in MS plays a major role in the understanding of genetics and environmental factors in MS (Ebers et al., 1995; Sadovnick et al., 1996).

The Basics of Genetics

Genes are the units of heredity. Genes are pieces of a long spiral molecule known as deoxyribonucleic acid (DNA). Each gene occupies a specific site called a locus on a chromosome and each chromosome carries many genes. In humans, it is estimated that 30,000-40,000 genes are carried on different chromosomes. The complete set of genes is known as the human genome. Many genes have more than two alleles. Alleles represent different forms of a gene (Cummings, 2003; Gelehrter, Collins, & Ginsburg, 1998).

In humans, a cluster of genes on chromosome 6, known as the major histocompatibility complex (MHC), produces human lymphocyte antigens (HLA genes). For example, successful organ transplants and skin grafts depend on matches between the histocompatibility antigens of the donor and recipient. HLAs are proteins found on the surface of white blood cells that play a role in the immune response. The HLA complex consists of several gene clusters. One group called class I, consists of HLA-A, HLA-B, and HLA-C. Adjacent to this is a cluster called class II, which consists of HLA-DR, HLA-DQ, and HLA-DP. Each of us carries two copies of chromosome 6, therefore, we each have two HLA haplotypes (Gelehrter, Collins, & Ginsburg 1998). Furthermore, because so many alleles combinations are possible, it is rare that any two individuals have a perfect HLA match. The exception is identical twins, who have identical HLA haplotypes, and siblings, who have a 25% chance of being matched.

The unique sequences of HLA alleles determine the ability of the immune system to respond to an antigen. The HLA system determines whether antigens belong to self or non-self. Therefore, a dysfunction in the HLA system can lead to an autoimmune disease. Researchers have discovered a relationship between certain HLA alleles and specific autoimmune diseases, such as, MS. These diseases probably result from a combination of HLA and non-HLA effects with environmental activation, i.e., infection (Edlin, 1990).

Differences in the DNA sequence are unique and copied through generations. Sometimes a difference in a single gene can lead to a disease that is inherited. MS is a disease that probably is triggered by multiple genes, and not by a single gene.

The Role of Genetics in MS

Genetic factors can affect an individual's immune system and its response to foreign antigens. Genes determine the variety of MHC molecules that individuals carry on their cells. Genes also influence the array of T cell receptors present on T cells. Some MHC genes are associated with autoimmune diseases, such as MS. However, genes are not the only factors involved determining a person's susceptibility to an autoimmune disease. For example, some individuals who carry disease-associated MHC molecules on their cells will not develop an autoimmune disease (Haines et al., 1996; DeJager & Hafler, 2004). New findings show that variants of the interferon gamma gene located on chromosome 12 might be related to susceptibility to MS (Kantarci et al., 2005). These variants present differently in males and females, and it might be related to the high prevalence of multiple sclerosis in women (Kantarci et al., 2005). Therefore, probably multiple different genes are related to MS susceptibility. In 1996, researchers reported that 20 locations in the genome may contribute to MS susceptibility (National MS Society, 2002). In summary, scientists believe that a person is susceptible to developing MS only if a specific combination of genes is inherited.

Epidemiological findings support a polygenic hereditary predisposition to MS. Human leukocyte antigen (HLA) DR2 carriership is associated with an increased risk for MS. HLA-DR2 is one of the definite genetic associations for MS. Sixty percent (60%) of MS patients in Northern Europe are DRB1 1501 (DR2 haplotype) positive compared with 30% in healthy individuals. Therefore, HLA-DR2 is associated with a cluster of alleles, which have a two-fold increased risk for developing MS. The risk by this haplotype is small, and it is neither necessary nor sufficient for development of MS (DeJong et al., 2002). There is a blood test that detects presence or absence of HLA-DR2. But because the data is not compelling, this test is not routinely recommended in clinical practice.

Multiple sclerosis is more common in women than in men at a ratio of 2:1. A recent study showed that interferon gamma (γ) expression varies by gender. Interferon γ is associated with a worsening effect on MS. Genetic variants that affect expression of interferon gamma might influence the susceptibility to MS and the severity of the disease. In general, higher interferon γ expression leads to an increased Th-1 cell response that corresponds with higher susceptibility to MS. The interferon γ gene is located on chromosome 12. This study suggests that men have the gene variant that causes high levels of interferon gamma less often than women (Kantarci et al., 2005). In summary, polymorphism of interferon gamma gene may contribute to differences in susceptibility to MS.

Familial Risk of Multiple Sclerosis

The risk of developing MS in people who have no relatives with MS is about 1 in 1,000. Eighty percent (80%) of people who develop MS have no relatives with MS, and 20% have at least one affected relative with the disease. The risk of MS in the siblings of a person with MS is significantly higher. A measure of the size of the genetic component of disease susceptibility is the sibling risk, which is defined as the ratio of the disease risk in a sibling of an affected individual to the general population. The sibling risk for MS may range from 1 in 20 to 1 in 50. As one moves from siblings to first and third cousins, the risk decreases. However, the first, second, and third-degree relatives of people with MS are more likely to have the disease than the general population (Dyment, Ebers, & Sadovnick, 2004). Adoptive relatives, although raised from infancy with the MS patient, have the same susceptibility to MS as the general population. This evidence substantiates the fact that familial aggregation of MS is related to genetic sharing rather than to a shared environment (Ebers et al., 1995).

The half-sibling and full sibling studies showed a 2.35% for MS in siblings with a shared mother who had MS, and 1.31% for a shared father who had MS, indicating a maternal effect. The risk of transferring MS from mother to siblings was higher (Dyment, Ebers, & Sadovnick, 2004; Ebers, 1996).

Identical monozygotic twins are more often concordant for MS than dizygotic twins (26% versus 2.4%), which correlate with a genetic component. However, following monozygotic twins past age 50, and using clinical findings and MRI data, less than 50% were concordant, suggesting a role for environmental factors (Ebers et al., 1986; Hupperts et al., 2001).

High infant contact in the first six years of life was associated with a reduced risk of MS. High infant contact was also associated with a reduced risk of elevated Epstein Barr Virus antibodies or infectious mononucleosis among healthy controls. This emphasizes the fact that the association between infant contact and MS relates to early infection exposure and the immune response to infections. In addition, increasing numbers of younger siblings was strongly associated with a reduced risk of MS (Ponsonby et al., 2005). This study strengthens the belief that MS is mediated by self-reactive T cells that may be induced by viral or other environmental factors.

Nursing Implications

Genetic counseling is a process of communication that deals with the occurrence or risk of a genetic disorder in a family, such as multiple sclerosis. MS counselors, nurses, social workers, psychologists, and physicians may provide MS couples with information

about the risk of developing MS in their family. Tests assessing the risks to develop MS were identified, but they are not available yet for public use. Therefore, the information provided to patients with MS is based on the family history of each MS patient (i.e., pedigree chart) (Sadovnick, Dircks, & Ebers, 1999).

Nurses are able to provide patients and their families with a basic overview of the genetic component in MS. Nurses can provide emotional support, and reassurance to patients while providing information about the genetic susceptibility to MS in their families. A few families have MS in each of their generations. Richard Cohen, author of the book, *Blindsided,* is the third member of his family to be diagnosed with MS; his paternal grandmother, and his father both had MS. "It never occurred to me that I, too, would be in line for a neurological debacle." (Cohen, 2004). This said the risk of MS from parents to their children is still very low, at about 3-5%.

Summary

Genes are definitely involved in triggering MS, which makes some people more susceptible to the disease (Ebers & Sadovnick, 1994; Sadovnick et al., 1988). The goal is identifying the genes involved and their roles. By finding the genes that confer susceptibility to MS, we can better understand the cause for MS, and develop new preventative measures and effective therapeutic approaches.

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Biography

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Aliza Ben-Zacharia, ANP-BC, is the Nurse Practitioner board certified at The Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai Medical Center. Aliza is a certified adult primary care nurse practitioner by The Academy of Nurse Practitioners and certified as an acute nurse practitioner by ANCC. Prior to accepting her position at the Center, Ms. Ben-Zacharia worked as an Acute Nurse Practitioner in Rehabilitation Medicine, caring for inpatients with diverse acute medical problems, with an emphasis on rehabilitation. Throughout her career, Ms. Ben-Zacharia has been an excellent educator who serves on many internal and external committees, performs specialized work focused on MS and rehabilitation, and has published work on Palliative Care in MS, the disease modifying agents, and MS Symptomatology. She was among the first group of nurses to be certified in Multiple Sclerosis Nursing. Currently, Ms. Ben-Zacharia is enrolled in a doctoral program at CWRU, in the education track.

Linda Morgante, RN, MSN, CCRN, MSCN

Linda Morgante has been working as an MS nurse specialist since 1986. She joined the Multiple Sclerosis practice at Mount Sinai Medical Center in March 2004. Her role includes direct patient care, education, counseling, advocacy, and coordinating services for patients and families at Mount Sinai and at Maimonides MS Care Center in Brooklyn. Ms. Morgante was awarded the prestigious June Halper Award for Excellence in MS Nursing from the International Organization of MS Nurses (IOMSN). Ms. Morgante is the current Secretary of the International Organization of MS Nurses. She has lectured widely throughout the United States, Canada, and Europe on MS nursing.

Glossary

Allele – One of the possible alternative forms of a gene usually distinguished from other alleles by its phenotypic effects.

Antigen – A substance or molecule that is recognized by the immune system.

Antigen-presenting cell – A cell that displays an antigen with an MHC molecule on the cell surface.

Autoimmune disease – Condition in which the immune system mistakenly attacks the body's own organs and tissues.

Chromosomes – Structures in the nucleus that contain DNA, which carry and transmit genetic information; each chromosome is comprised of thousands of genes.

Concordance – Agreement between traits exhibited by both twins.

Dizygotic (DZ) twins – Twins derived from two separate and nearly simultaneous fertilizations, each involving one egg and one sperm. Such twins share, on average 50% of their genes.

DNA – A helical molecule consisting of two strands of nucleotides that is the primary carrier of genetic information.

Gene – The fundamental unit of heredity.

Genetic counseling – A process of communication that deals with the occurrence or risk of a genetic disease.

Genotype – The basic combination of genes of an organism

Haplotype – A cluster of closely linked genes that are inherited together. In the immune system, the HLA alleles on chromosome 6 are a haplotype.

Human Leukocyte Antigen (HLA) – HLA genes (MHC) encode integral membrane proteins essential in the presentation of antigen to immune cells, T-lymphocytes. Certain HLAs have been associated with certain diseases, usually autoimmune diseases.

Major Histocompatibility Complex (MHC) – The complex of human leukocyte antigen (HLA) genes on the short arm of chromosome 6. MHC molecules are found on cell surfaces and display antigen; the antigen-MHC molecules may then interact with a t-cell receptor. MHC is a cluster of highly polymorphic genes (HLA genes) important in the regulation of the immune response.

Multifactorial – Disease resulting from interaction of many factors
Pedigree chart – A schematic method for classifying genetic data

Phenotype – The expression of the gene or trait in an individual

Prevalence rate – Proportion of the population affected by a disease at a specific time

Recurrence risk – The ratio of the reappearance of a disease in a diseased population after a remission.

Relative risk – Ratio of the frequency of a disease in populations exposed and not exposed to a particular factor.

*** Note: Glossary definitions taken from the following resources:
Cummings, 2003; Gelehrter, Collins, & Ginsburg, 1998.