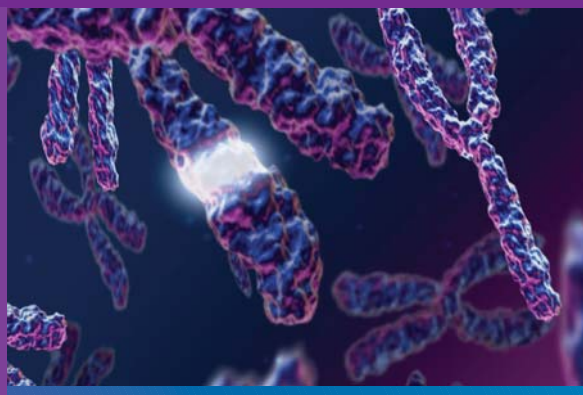
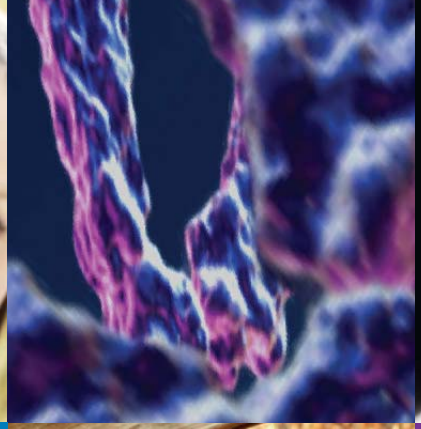
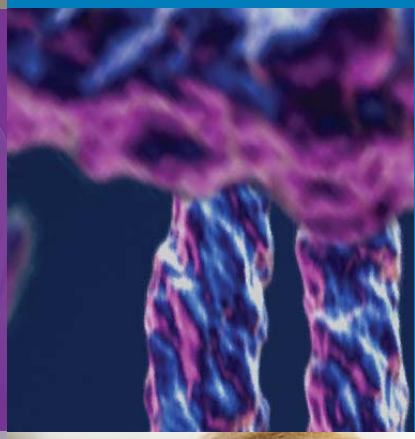
genetics in multiple sclerosis

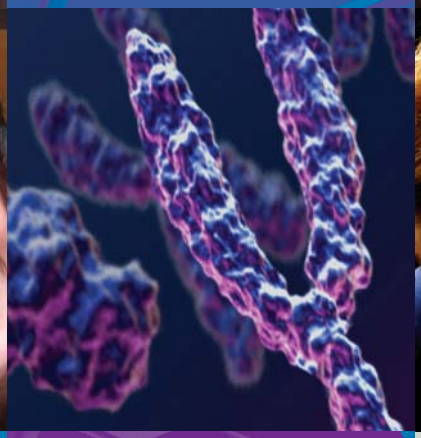
a guide for nurses





genetics in multiple sclerosis
a guide for nurses

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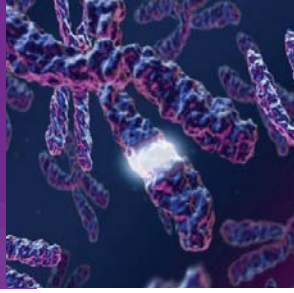

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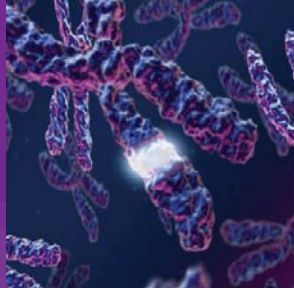
Foreword



Nurses who care for people with multiple sclerosis (MS) are in a position to educate and counsel patients on a variety of issues, including known genetic factors related to the disease. In order to identify educational needs for MS nurses, a survey was conducted to assess nurses' familiarity with the role of genetics in MS. The sampled population included registered nurses, advanced practice nurses, and licensed practical nurses who worked in MS nursing for 1–35 years. Respondents worked in a variety of settings, including MS centers and private practice, and treated between 30–5000 patients annually.

Results of the survey showed that the vast majority of nurses (71%) counseled patients about genetic factors in MS (ie, susceptibility, family history, and pregnancy); however, when queried regarding their level of knowledge regarding genetics in MS, respondents indicated that there was a need for additional education in this area. Specifically, respondents identified the following topics as being important for inclusion in an educational monograph for MS nurses:

- Basic principles of human genetics
- Principles of immunogenetics in MS
- Summaries of studies related to genetics in MS
- Strategies for genetic counseling in MS

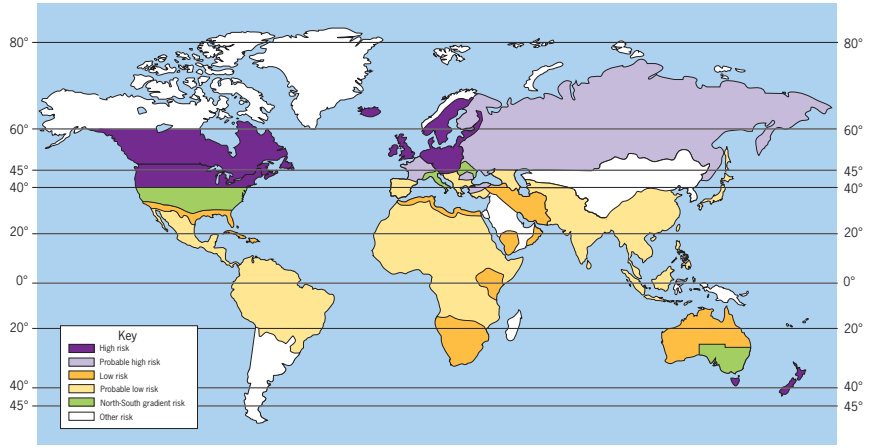
Based in part on the results of the survey, this monograph is designed as an educational resource for nurses seeking a greater understanding of this complex disease. The content includes the basic principles of human genetics, an immunology primer, a brief overview of MS, and a discussion of genetics in MS. It also includes 2 case studies that illustrate the nurse's role when counseling patients about familial tendencies and the risk of MS. The objective of this monograph is to further enhance MS nurses' understanding of genetic principles and the role of genetics in MS.

Overview of Multiple Sclerosis

Epidemiology and Etiology

MS is an autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, and axonal degeneration. In the United States, it is estimated that 400,000 adults have MS.[1] MS is most commonly diagnosed in patients who are 20–50 years of age and is 2–3 times more prevalent in women than men. MS also has been diagnosed in children, mostly age 10–17. It is estimated that 10,000 children in the United States have MS. The disease occurs with greater frequency in higher latitudes (above 40º) (Figure 1) and is more common in Caucasians than other ethnic groups.[1] However, MS in children is seen mostly in minority groups such as African Americans Latino, Asian, and Middle Eastern populations.[2] Genetic studies in adults and children can provide a better understanding of the triggers of MS.

Figure 1. World distribution of multiple sclerosis

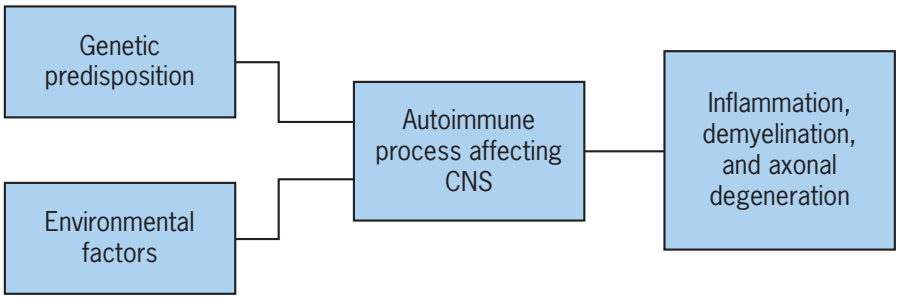


Adapted from: McAlpine D, Lumadan CE, Acheson ED. *Multiple Sclerosis: A Reappraisal*. London: Livingstone Ltd.; 1967.

The etiology of MS is unclear but is believed to be multifactorial, involving environmental and genetic factors. Through mechanisms that remain unknown, these factors interact to induce an autoimmune response directed at the CNS (Figure 2).

The pathologic process underlying the development of MS begins when $CD4^+$ T cells with receptors for CNS components are activated in the periphery. Activated T cells then cross the blood-brain barrier (BBB) with the help of intercellular adhesion molecules and

Figure 2. The multifactorial nature of multiple sclerosis



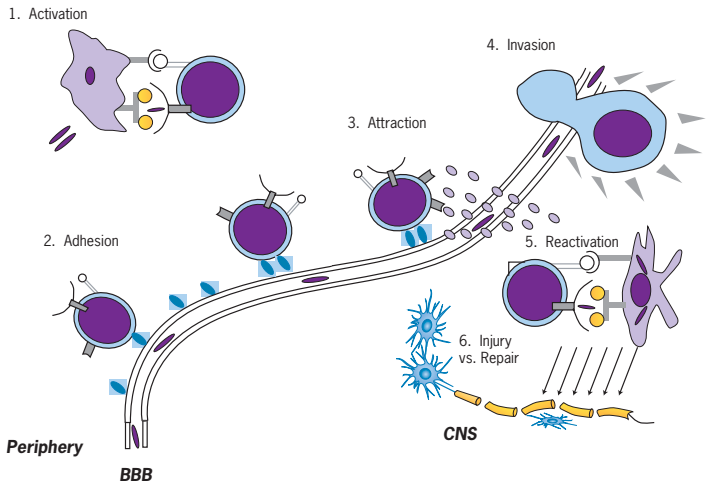
become reactivated when encountering CNS antigens (Figure 3). The activated $CD4^+$ T cells, B cells, macrophages, and $CD8^+$ T cells interact to produce an inflammatory response and subsequent myelin damage through a number of mechanisms, including the B-cell– mediated antibody/complement pathway (eg, antibodies to myelin basic protein), macrophage-induced oxidative damage, and TNF-α secretion. These cells interact to produce an inflammatory response directed at components of the CNS. This inflammation causes myelin damage and axonal degeneration.

Much research has been devoted to identifying individual factors that increase susceptibility to MS. Genetic factors are discussed in subsequent sections of this monograph. Environmental factors that contribute to the development of MS are believed to be

Figure 3. Schematic of entry of activated T cells into the CNS

Immune cells activated in the periphery (step 1) upregulate surface molecules that enable them to adhere more efficiently (step 2) to the endothelial cells of the blood-brain barrier and respond to local chemokine gradients (step 3). Active secretion of matrix proteases (step 4) facilitates immune-cell invasion into the CNS, where they may become reactivated (step 5) and have an impact on the biology of CNS elements (step 6).

Adapted from: Bar-Or A, Oliveira EM, Anderson DE, et al. *J Neuroimmunol.* 1999;100:252-259.



infectious agents, most likely a virus; however, no active or latent virus has been demonstrated in cultures of the cerebral spinal fluid (CSF) of patients with MS, and a variety of potential viral and bacterial targets have been studied without conclusive evidence that any one is the causative agent.[3]

Key Points

- MS is an autoimmune disease that is more common in women
- Genetic and environmental factors play a role in the development of MS

What environmental factors may increase my risk for MS?

Multiple studies have explored the relationship between different viruses and MS, such as human herpes virus 6, HTLV-1, Epstein-Barr virus, measles, rabies, and others
Bacterial agent—Chlamydia pneumonia—no confirmation
MS is an autoimmune disease, and as such, patients with MS may have antibodies to different organisms
Theories posit that MS has an infectious or virus-triggered immunopathology in genetically susceptible individuals
Based on migration studies, environmental factors affect MS risk independent of the effect of genes
No clear association between any viruses and triggering the disease
It is known that viruses may trigger exacerbation but not the disease itself
Upper respiratory infections preceded relapse in 27% of patients
Hormonal factors
Cigarette smoking—The risk of MS was higher among smokers than among never-smokers in both men and women
Vitamin D deficiency—Women who took supplemental vitamin D had a 40% lower risk of MS than women who did not use vitamin D supplements
Residence—Living in an area with a high prevalence of MS is a risk to develop MS

(Ebers et al, 1994[4]; Marie, 2004[5]; Miller et al, 2003[6]; Munger et al, 2004[7]; Sadovnick et al, 2005[8]; Riise et al, 2003[9])

Can I avoid getting MS by moving to an area with a lower risk?

The risk of MS is lessened by migrating from a high MS prevalence area to a low prevalence area, if migrating before the age of 15 years

Age at migration was an important risk factor for developing MS

Migration studies of European Jewish people and Sephardic Jewish people (Jewish people that immigrated from Africa or Asia) show a decreased risk for MS in both groups if migrating prior to age 15, which implies that an environmental factor plays a role

Jewish people that migrated to Israel as children had a lower risk of developing MS

Jewish people born in Israel of immigrants from Europe and America have MS at rates comparable to those of their parents, which implies that a genetic factor plays a role

Israeli-born children of Sephardic Jewish parents have a higher rate of MS than their parents, which implies that an environmental factor plays a role

The MS risk increased in Vietnamese people migrating to France

Children born in the United Kingdom to parents who immigrated from the West Indies had a prevalence of MS similar to that of native Londoners

Immigrants from the United Kingdom to South Africa before age 15 had lower risk for MS; if immigrating later in life, they maintain the higher risk of their origin place (Europe)

Studies showed that people adopt the low risk or high risk rates of the areas to which they migrate

In the United States, migrating from a high-risk to a low-risk area of MS, the risk of MS was lower in those who migrated at early ages

Risk reduction was also seen in children >15 years of age, but it was less than the risk reduction in those <15 years of age

An Australian study did not find an association between age at migration and risk of MS

Risk of MS relates to both genetic and environmental factors

(Alter et al, 1996[10]; Ebers et al, 1994[4]; Kurtzke et al, 1970[11]; Marie, 2004[5]; Miller et al, 2003[6])

Can people of color get MS?

MS has been rare among African, Asian, and West Indians who immigrated to the United Kingdom but has a higher prevalence in their children

MS is rare among black Africans

The rate of MS among African Americans is half that of white Americans

A recent study showed that African Americans had a relative risk of 0.64 for developing MS compared to Caucasian Americans

According to the New York State Multiple Sclerosis Consortium, 329 of 5602 registrants (6%) were African American. African Americans had younger onset of disease and greater disability with disease duration. Types of MS were the same for African Americans and non–African Americans

Africans and African Caribbean people have increased prevalence of neuromyelitis optica (Devic's disease)

MS is not seen in American Indians

MS is almost never seen in a few groups: Eskimos, Hungarian gypsies

Groups of people that have a low prevalence of MS even though they live in high-prevalence areas include Hungarian gypsies, Amerindians, Saudis, Hispanics, American blacks, and Asians

Japanese and Chinese people have very low prevalence of MS regardless of where they live

Japanese and other Asians have a low risk of MS after immigrating to the United States

Other studies show that the rate of MS among Japanese Americans is higher than among Japanese people who remain in their native country

Japanese people commonly have optical-spinal form of disease (Devic's disease)

(Cree et al, 2004[12]; Ebers et al, 1994[4]; Miller et al, 2003[6]; Weinstock-Guttman et al, 2003[13])

Does gender play a role in disease course?

Men tend to have a worse course of disease than women
Men have a worse prognosis
Men tend to have more severe clinical outcomes
Men are affected by progressive subtype
Men have a tendency to have a progressive disease from the onset
Men have a mean age of onset 1–2 years later than women
Genes linked to MS may differ between men and women
The frequency of HLA DR2 is significantly higher in females than in males
Women have smaller white-matter volumes than men
Women have larger gray-matter volumes than men
The male brain does not age as well as the female brain
Men have greater increases in white-matter content than women while aging
Men have greater losses of gray-matter volume than women while aging

(Coyle, 2005[14]; Ebers et al, 1994[4]; Hawker et al, 2004[15]; Reipert, 2004[16]; Rooney et al, 2003[17]; Van Lambalgan et al, 1986[18]; Weinshenker et al, 1989[19])

Basic Principles of Human Genetics

Introduction and Terminology

Genetics is the study of heredity, including the structure and function of genes and how they are passed from generation to generation. A gene is the basic unit of heredity; genes are composed of deoxyribonucleic acid (DNA), which provides the blueprint for the synthesis of the structural and functional proteins necessary to maintain life. Ribonucleic acid (RNA) serves as the template for translation of genes into proteins. Genes are contained within the nucleus of cells in structures known as chromosomes (Figures 4 and 5). Each chromosome contains thousands of genes. The genes carry the instructions for making all the thousands of proteins that are found in a cell. The proteins in a cell determine what that cell will look like and what jobs that cell will do. The genes also determine how the many different cells of a body will be arranged. In these ways, DNA controls how many fingers you have, where your legs are placed on your body, and the color of your eyes. DNA makes us look like our parents.

DNA is organized into stretches of genes—stretches where proteins attach to coil the DNA into chromosomes, stretches that "turn a gene on" and "turn a gene off." When a gene is turned on (expressed), the DNA contained in the gene is decoded and used to link amino acids in a long chain, which folds up to form a protein. The action of these proteins leads to the development of biochemical, physiological, and morphological characteristics that are known as phenotypes. Phenotypes reflect the genetic composition

Figure 4. Inside a human cell

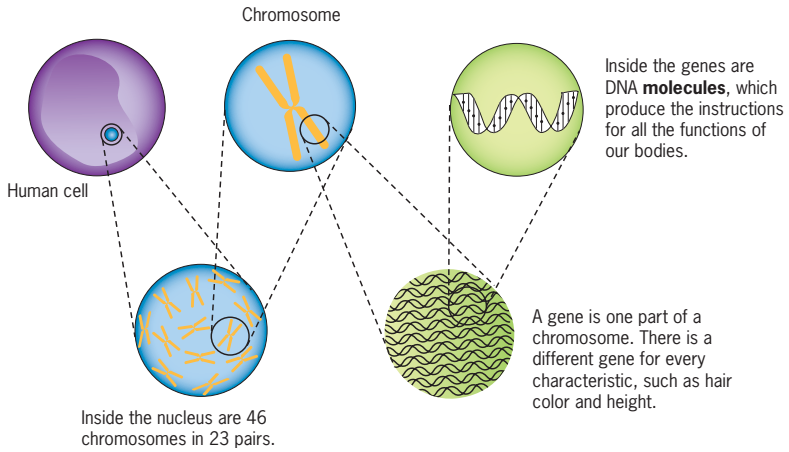


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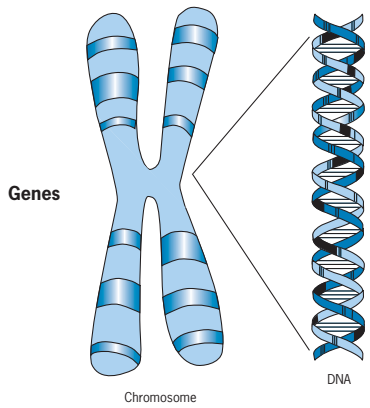
Figure 5. Schematic of a chromosome showing the location of 2 genes, which are composed of DNA



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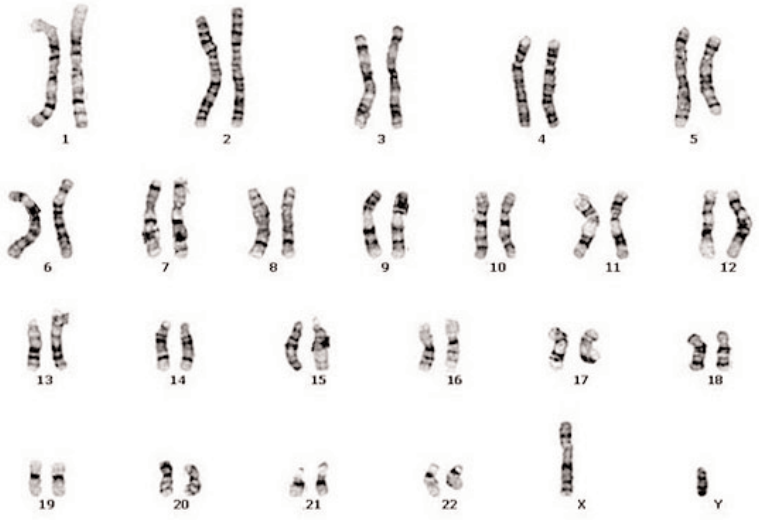
of an individual, which is referred to as the genotype. These phenotypes represent the characteristics of humans. Examples of phenotypes are eye color and hair color.

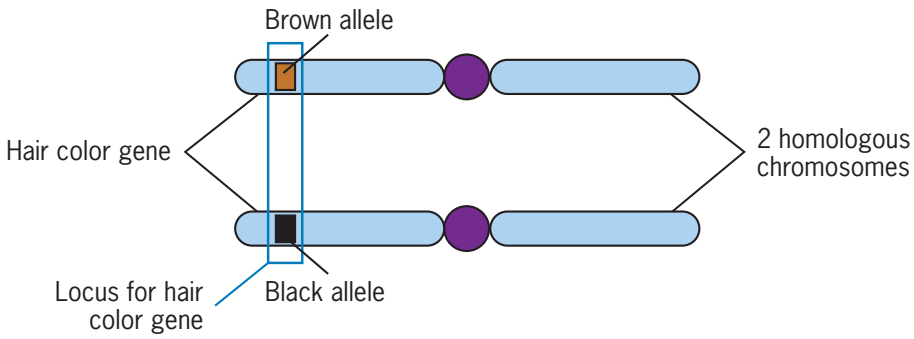
Humans have 46 chromosomes: 22 pairs of autosomes (each member of the pair carries the same arrangement of genes; they are known as homologous chromosomes) and 2 sex chromosomes (XX in females, XY in males) (Figure 6). Therefore there are 23 pairs of chromosomes in a human cell. One of each pair is inherited from the mother and the other from the father.

Figure 6. Human male karyotype showing 22 pairs of homologous chromosomes and 2 sex chromosomes (karyotype = chromosomal characteristics of an individual cell)



Children inherit 1 set of chromosomes (23) from each parent, resulting in every person having 2 copies (alleles) of each autosomal gene. These alleles may be slightly different from each other, allowing for expression of different traits. Genes that have several alleles are said to be polymorphic. An example of a polymorphic gene with different alleles is shown in the schematic below (Figure 7). In this figure, each homologous chromosome carries a different allele of the hair color gene.

Figure 7. Schematic representation of a chromosome pair containing a gene with different alleles



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Key Points

- Genes, the basic unit of heredity, are composed of DNA and grouped together on structures called chromosomes
- A gene may have several different versions, known as alleles, that can result in the expression of different phenotypic traits
- Genes control what cells look like and what they do
- Genes control how babies develop and how we reproduce
- Understanding how genes work is essential to our understanding of life

Patterns of Inheritance

Genetics, specifically the inheritance of abnormal alleles, play an important role in the development of many diseases. Diseases whose major effects are due to abnormalities in a single gene are inherited through classical or Mendelian patterns, which are summarized in the box below. Mendelian patterns are named after the scientist Gregor Mendel, whose observations regarding the inheritance of certain traits in pea plants provided the foundation for modern genetic science.

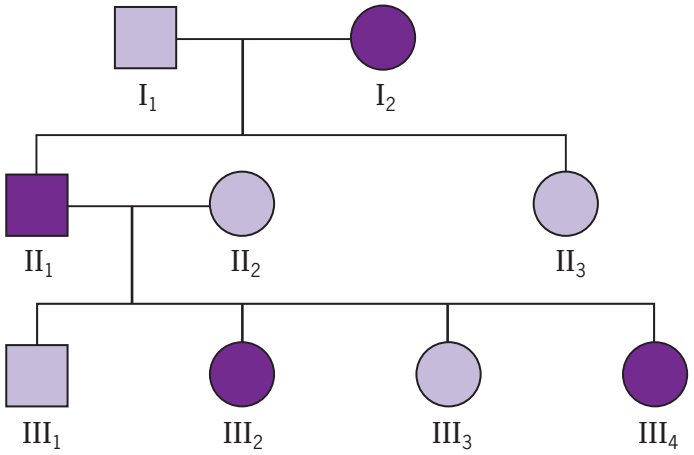
Mendelian Patterns of Inheritance

- Autosomal recessive: the gene is on an autosomal chromosome, and both alleles must be abnormal to express the disease phenotype (eg, cystic fibrosis, sickle cell anemia, phenylketonuria)
- Autosomal dominant: the gene is on an autosomal chromosome, and only 1 abnormal allele is required for expression of the disease phenotype (eg, Huntington's disease, Marfan syndrome)
- X-linked recessive: the gene is on the X chromosome, and both alleles must be abnormal alleles to express the disease phenotype in females (eg, Duchenne muscular dystrophy, hemophilia)
- X-linked dominant: the gene is on the X chromosome, and only 1 abnormal allele is required for expression of the disease phenotype in females (eg, hereditary nephritis, Coffin-Lowry syndrome)

Note: All X-linked disorders are dominant in males because they have only 1 X chromosome.

Pedigrees are often used to track disease inheritance through multiple generations and are particularly useful in predicting which family members will be affected by a disease caused by a single gene. An example of a pedigree for an autosomal dominant disease, in which any individual receiving the abnormal allele has the disease, is shown in Figure 8.

Figure 8. Pedigree for autosomal dominant disease. Affected individuals are represented by dark shading. (A pedigree is a representation of the inheritance of a trait through several generations of a family.)



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Mendelian patterns are not the only pattern of disease inheritance; in fact, relatively few disorders are caused by abnormalities in a single gene. Rather, the majority of genetic diseases are due to abnormalities in several genes. These diseases are known as polygenic diseases. MS is a polygenic disease; other polygenic diseases include diabetes, cancer, spina bifida, pyloric stenosis, cleft lip, and cleft palate. The transmission of polygenic diseases between generations is described by a pattern known as multifactorial inheritance. Multifactorial inheritance refers to a phenotypic effect, which results from a combination of abnormalities in several genes and interactions with environmental factors. The basic principles behind the multifactorial pattern of inheritance as they apply to polygenic diseases are summarized in the box below.[20]

Principles of Multifactorial Inheritance for Polygenic Diseases

- Several, but not an unlimited number of, genes involved in the expression of the disease
- No gene is dominant or recessive relative to the others
- The genes act together in a cumulative fashion, each adding or detracting a small amount to the disease characteristics

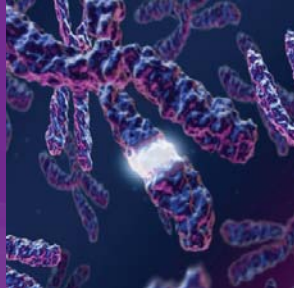
No single gene is completely responsible for polygenic diseases; the pattern of inheritance is far more difficult to predict than that for Mendelian diseases such as hemophilia. Polygenic diseases are often said to "run in families," with each relative's risk of developing the disease roughly proportional to the number of abnormal alleles they have in common with the affected individual (ie, how closely they are related). While pedigrees can be used to depict the occurrence of disease through several generations, their usefulness in predicting risk to future generations is limited, given the number of interactions required for disease development.

Separating the genetic factors from environmental factors in polygenic diseases is often difficult. "Twin studies" provide the best source for separating genetic contributions to the disease being studied from environmental influences. To do this, researchers compare the occurrence of disease in pairs of monozygotic twins (identical twins who have the same genome) with the occurrence of disease in dizygotic (fraternal) twins, who have different genomes. The concordance rate (percent of the time that both twins are affected) in monozygotic twins can be compared to the concordance rate in dizygotic twins to estimate the genetic component of the trait. Differences in concordance rates between the two groups help to determine the extent of involvement of genetic and environmental factors. For example, if the trait is 100% genetic, monozygotic twins will be 100% concordant, while dizygotic twins, having approximately half their genes in common, will have a lower concordance rate. If the trait is 100% environmental, monozygotic and dizygotic twins will have the same concordance rate.

$$\frac{\text{Number of pairs with both twins affected}}{\text{Number of pairs with both twins affected + Number of pairs with one twin affected}} \times 100 = \text{Concordance rate}$$

Key Points

- Genes contain the DNA blueprint for an organism
- Disorders caused by abnormalities in several genes are known as polygenic diseases
- Polygenic diseases are passed from generation to generation in a pattern known as multifactorial inheritance
- Concordance rates can be used to estimate the influence of the genetic component of polygenic diseases



History of Genetics in MS

As discussed in the previous section, the etiology of MS is unknown but is believed to occur in genetically susceptible individuals following exposure to environmental risk factors, the nature of which remains undefined. Evidence that genetic factors play a role in the development of MS began accumulating in the 1890s, when the familial aggregation of MS was noted.[21] Other observations, including differences in disease occurrence according to gender and ethnicity, provided further evidence of genetic involvement.[22,23]

History of Genetics in MS

1890s – Genetic factors such as familial aggregation may have a role in MS

1920s – Differences in geographic and ethnic distribution of disease noted

1950s – Multiple genes believed to contribute to MS susceptibility[24]

1970s – Descriptions of associations with HLA alleles

1990s – Beginning of genome screening for MS susceptibility genes

2005 – First whole genomic scan identifies 80 potential MS susceptibility genes

The first descriptions of associations between genes and MS came in the 1970s, when reports of associations with certain HLA alleles were published.[25-28] Extensive research has since confirmed the association of carriership of the DR2 allele[29-31] with the development of MS, but no other definitive associations have been made. Given recent advances in molecular genetics and sequencing of the human genome, as well as enhanced understanding of MS pathology, researchers are continually identifying and evaluating candidate genes for possible associations with MS.

Key Points

- Genetic factors have long been suspected to contribute to MS
- Different people have different forms of MS, implying genetic factors
- Family members with MS can present with different forms of MS, implying environmental factors
- People with MS or family members with MS may respond differently to the available treatments for MS
- A combination of genetic and environmental factors increase the susceptibility of MS
- Additional work is necessary to identify specific genes with a role in the development in MS

Genetic Influence on the Immune Response: The Human Leukocyte Antigen System

The genes that code for human major histocompatibility complex (MHC) molecules are part of the Human Leukocyte Antigen (HLA) cluster, which is located on the short arm of chromosome 6. The HLA-A, HLA-B, and HLA-C genes code for MHC class I molecules, and the HLA-DR, HLA-DQ, and HLA-DP genes code for class II molecules. A large number of alleles have been identified for many HLA genes, and 2 alleles are expressed in each individual (1 from each copy of chromosome 6, a pattern of expression known as co-dominance), making millions of allele combinations possible. The multitude of potential allele combinations results in the production of a large variety of MHC molecules, allowing antigen-presenting cells (APCs) to present a broad range of antigens to T cells.

In this manner, HLA genes affect the kinds of antigens presented to T cells, thus determining the ability of the immune system to respond to an antigen. While this is generally a positive response, allowing the body to respond to foreign pathogens, certain HLA alleles are associated with a greater likelihood of inducing an immune response to self-antigens, a process known as autoimmunity. Selected HLA alleles that have been associated with autoimmune diseases are shown in the table below.

HLA Alleles Associated With Autoimmune Diseases

Disease	HLA allele	Frequency in affected individuals
Ankylosing spondylitis	B27	>90%
Rheumatoid arthritis	DR4	70%
Multiple sclerosis	DR2	59%
Pernicious anemia	DR5	25%
Psoriasis	B17	38%
Systemic lupus erythematosus	DR3	50%

The HLA system is of interest to those investigating the genetic basis of MS, as an association of HLA-DR2 with MS has been established.[31]

Key Points

- Genes that code for MHC molecules are part of the HLA cluster on chromosome 6
- HLA genes help T cells to distinguish self from non-self
- Variations in several HLA genes are seen in autoimmune diseases, when the body mounts an immune response against its own tissues

Genetic Influence on Immune Function in MS

No single gene is responsible for causing MS; however, it is believed that variations in several genes can increase an individual's susceptibility to developing the disease. To date, the most widely known allele associated with MS is the HLA DR2 allele.[31] HLA DR2 is part of the MHC on chromosome 6 and is one of the loci that codes for the production of MHC class II molecules. Although the precise role of this gene in the pathogenesis of MS is unclear, approximately 60% of patients with MS have this allele, compared with 30% of the healthy population.[31] In addition to HLA DR2, there is evidence that other genes within the HLA complex have an effect on disease susceptibility, but the precise identity of these genes and their role in MS susceptibility remains to be determined.[31]

The fact that MS is an autoimmune disease has resulted in many studies examining other genes responsible for immune function. Many studies have identified specific areas on chromosomes thought to contain genes affecting MS susceptibility, but additional research using modern analytic and molecular genetic techniques is needed to precisely locate the genes and the role they play in MS pathogenesis. Some of the types of genes under investigation are listed below.

Genes Under Investigation for Roles in MS[32,33]

- T-cell receptor genes
- Immunoglobulin genes
- Myelin protein genes
- Cytokine genes
- Interferon-gamma genes
- Oligodendrocyte growth factor genes
- Co-stimulatory molecule genes
- Intracellular adhesion molecule genes

Further research into these genes may help to develop novel therapeutic advances for the treatment of MS and also allow for the development of genetic screening tests that may be useful in determining susceptibility to the disease, particularly in relatives of affected patients.

Key Points

- HLA DR2 is an allele associated with an increased risk of MS
- Additional genes involved in the immune response are under investigation for possible involvement in MS

MS in Families

Twin and Adoption Studies: Evidence for a Genetic Component of MS

Twin studies are useful to estimate the degree of genetic involvement in polygenic diseases. A number of twin studies have been conducted in patients with MS, and the results are summarized in the table below. As would be expected in a disease that has a genetic component, monozygotic twins were more often concordant for MS than dizygotic twins (26.7% vs 3.5%). However, concordance rates decrease with increasing age, suggesting that environmental factors also play a substantial role in disease development of MS.[34,35]

Summary of Concordance Studies in MS[4]

Reference	Monozygotic concordance rate	Dizygotic concordance rate
Heltberg et al, 1982	4/19 (21.05%)	1/28 (3.57%)
Bobowick et al, 1978	2/5 (40%)	0/4 (0%)
Kinnunen et al, 1988	2/7 (28.57%)	0/6 (0%)
Sadovnick et al, 1993	8/26 (30.8%)	2/43 (4.7%)
Mumford et al, 1994	11/44 (25%)	2/61 (3.3%)
Total	**27/101 (26.7%)**	**5/142 (3.5%)**

Adapted from: Ebers GC, Sadovnick DA. The role of genetic factors in multiple sclerosis susceptibility. *J Neuroimmunol.* 1994;54:1-17.

Adopted relatives, although raised from infancy with the MS patient, have the same susceptibility to MS as the general population.[36] This finding indicates that the familial risk of MS is related to genetic sharing rather than to a shared environment.

Key Points

- Twin studies provide evidence that MS has a genetic component
- Studies in adopted relatives indicate that familial risk of MS is related to common genetic makeup rather than a shared environment

Other Relatives: Risk of MS

Although 80% of people who develop MS have no relatives with the disease, 20% of MS patients have at least 1 relative with MS. It is therefore necessary for nurses who care for patients with MS to understand the potential risks for their family members. The risks of developing MS for various relatives of an affected person are presented in the table below. The difference in risk between males and females reflects the predominance of MS in females. For purposes of comparison, note that the risk of MS for a person in the general population who has no relatives with MS is 1 in 750.[1]

Risk of MS in Relatives of an Affected Individual[37]

Family Group	Risk Recurrence Rate
Parents	3%
Sons	1%
Daughters	5%
Siblings	4%
Aunts/uncles	2%
Nieces/nephews	2%
First cousins	1%

There is also evidence that there is a maternal effect in transmission of MS, as studies of half-siblings and full siblings demonstrated a 2.35% risk for MS in siblings with a shared mother affected by MS and 1.31% with a shared father affected by MS.[36,38]

Overall, 4% of first-degree relatives (parents, children, siblings) of MS patients develop MS. The risk decreases as family members are increasingly removed from the affected individual (ie, cousins, aunts, uncles) but still remains higher than that in the general population.

Key Points

- Twin studies provide evidence that MS has a genetic component more than an environmental component
- Female twins have a higher chance of transmitting MS to their twins than male twins[39,40]
- Adopted relatives indicate that familial risk of MS is related to common genetic makeup, rather than a shared environment
- Risk of MS is highest for first-degree relatives of an affected individual
- Children of affected mothers are more likely to develop MS than children of affected fathers
- Family, twin, and sibling studies show that genetic and environmental factors trigger MS

How can genetic factors cause my MS if no one in my family has or had MS?

Multiple genes are involved in the susceptibility to MS
Both genetic and environmental factors play a role in developing MS
Environmental factors affect MS risk, independent of the effect of genes
Family members with MS can present with different forms of MS, implying environmental factors play a role
People with MS or family members with MS may respond differently to the available treatments for MS
80% of people who develop MS have no relatives with the disease; 20% of MS patients have at least 1 relative with MS
The risk of MS for a person in the general population who has no relatives with MS is 1 in 750

(National Multiple Sclerosis Society, 2005[1]; Willer et al, 2005[41])

My mother has MS and I have MS; will I be like her?

MS manifests differently in each individual and in different family members

The pattern of MS is not necessarily the same from generation to generation

Early treatment in MS and in clinically isolated syndromes minimize the progression of the disease

The available treatments for MS and the ongoing research trials promise better control of the disease

Will I catch MS from my partner?

Current evidence indicates that MS is not a transmissible disease

Conjugal MS occurs only by chance

(Sadovnick et al, 1999[42])

Can genetic testing predict if I or my children will get MS?

Currently there is no available genetic testing to predict risk of MS

HLA DR2 antigen is present in 60% of western whites

– This HLA is not an essential antigen for the development of MS

Multiple genes have been identified as potentially triggering the disease

Current family studies around the country focus on exploring gene markers in family members with MS

More than 90% of the human genome has been excluded for major gene linkages to MS

MS is a polygenic disease, implying that a few genes may trigger the disease

(Ebers et al, 1994[4]; Kenealy et al, 2003[43]; Miller et al, 2003[6]; Oksenberg et al, 2005[44]; Sadovnick et al, 1996[45])

Genetic Counseling

Genetic counseling is a process of communication that deals with the occurrence or risk of a genetic disorder in a family. This process is intended to help individuals and families affected by genetic disorders to understand the medical issues, inheritance risk, and options available in the context of family values, goals, and beliefs. For patients with MS, in addition to genetic counselors, sources of such information may include MS nurses/nurse practitioners and physicians.

Providing genetic counseling to patients with MS is somewhat challenging because screening tests identifying patients susceptible to MS are not yet available. Therefore, information on risk is based on family history, which can be used to create a family tree, as well as rates of disease occurrence in studies evaluating many families affected by MS.[42] In addition to providing an overview of the genetic components and risks of MS, nurses and counselors are pivotal in offering emotional support and reassurance to patients and their families. MS counseling and support should be aimed at promoting patient autonomy and decision making while maintaining confidentiality, particularly when sessions involve more than one participant. A basic outline of information that would be included in a genetic counseling session is presented below.

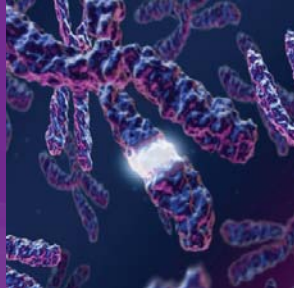
Topics of Discussion in an MS Genetic Counseling Session

- An overview about genetics in MS
- An overview of family history
- Information about the risk of developing MS in their family: Age-based and relative risk, gender effects, ethnicity effects

Key Points

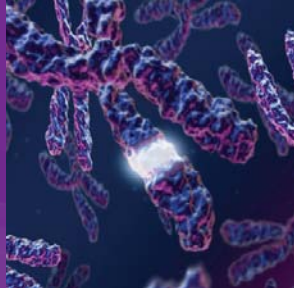
- Answer all your patients' questions
- Provide simple answers about genetics
- Do not provide patients with numbers or percentages related to risk of MS
  - You may say: Risk is higher in patients with a family history of MS than in the general population
  - It is not a reason for not having children; however, this is an individual decision
- Refer to other specialists as needed

Summary



MS is an autoimmune disease caused by a combination of genetic and environmental factors. Genes affecting the immune response, such as members of the HLA family, are under investigation for their potential role in increasing susceptibility to MS. Specific genes have yet to be implicated in the pathogenesis of MS; however, multiple studies of MS patients and their families have helped to narrow the focus of researchers on specific locations in the genome, provided evidence of the genetic component of MS, and provided insight into the familial risk of MS. Although genetic testing to determine susceptibility to MS is unavailable, genetic counseling can be of great value to patients with MS, answering questions they may have about implications of the disease for them and their families.

Case Studies



Case Study

A 27-year-old female with relapsing-remitting MS is considering having children and asks about genetic susceptibility of MS for her future children.

- How would you counsel her regarding the risk of MS for her future children?
  - Review with the patient that the risk of MS for her children is slightly higher than that of the general population, and the risk for a girl is higher than for a boy. Reassure the patient that the prevalence of MS remains low and that there is no reason not to have a child.
- What are the steps in discussing this sensitive topic?
  - Develop a relationship with the patient based on trust and mutual respect
  - Find a quiet place to talk
  - Discuss facts in a positive way so as not to frighten the patient
  - Involve her partner in the discussion when appropriate
  - Make a referral to an MS support group for ongoing peer support
- What information would you give the patient?
  - One approach might include sharing some general information about the disease, including the etiology and pathophysiology of MS, treatment options, and lifestyle interventions for good health. When counseling about family planning, specific recommendations about when to start disease-modifying agents should be made.

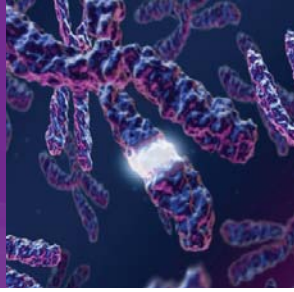
Case Study

A 25-year-old female consults with you because of her strong family history of MS. Her mother has MS, and she wants to talk to you about her risk for MS and what she should do.

- What is this patient's risk of developing MS?
  - The risk of developing MS is higher than that of the general population. However, in the scheme of things, the prevalence of MS remains low, so her risk is relatively low. It is also important to counsel the patient that MS is not a purely genetic disease and that MS specialists believe that an environmental trigger also plays a role in developing the disease.

- What would be the counseling steps?
  - Remember to say things in a positive way
  - Advise the patient to take care of herself and give her some self-care strategies
  - Encourage her to have frequent check-ups with her healthcare professional, and educate her on the early signs and symptoms of MS
  - Give the patient tips for living with uncertainty—for example, finding meaning in each day and living life to its fullest
  - Reassure her that with the available effective treatment options and ongoing research efforts, there is hope for the future of the patient with MS

Glossary



Adaptive response: immune response that requires prior exposure to antigen in order to occur; ie, the immune system "remembers" the antigen

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 its surface

Autoimmune disease: a condition in which the immune system mistakenly attacks the body's own organs and tissues

Autosome: a chromosome other than a sex chromosome

Chromosomes: structures in the nucleus that contain DNA which carry and transmit genetic information; each chromosome is comprised of thousands of genes

Concordance: probability that a certain trait will be expressed by both members of a twin pair

DNA: a helical molecule consisting of 2 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 disorder in a family

Heterozygous: having 2 different alleles of a gene

Homozygous: having 2 identical alleles of a gene

Homologous chromosomes: members of a chromosome pair that are identical in structure and contain the same genes

Human Leukocyte Antigen (HLA): designation for a cluster of genes contained on the short arm of chromosome 6 that code for MHC molecules

Innate response: first immune response to a foreign pathogen; does not require prior exposure (immune "memory") to occur

Karyotype: chromosomal characteristics of an individual cell

Major histocompatibility complex (MHC) molecules: located on the surface of antigen-presenting cells, these molecules contain processed antigens that are recognized by T cells

Phenotype: the physical manifestation of a genetic trait that results from a specific genotype and its interaction with the environment

Polygenic disease: disease caused by abnormalities in several genes

Polymorphic: term used to describe genes that have several different alleles

Sex chromosome: a chromosome that is responsible for differences between the two sexes; ie, the X and Y chromosomes in humans

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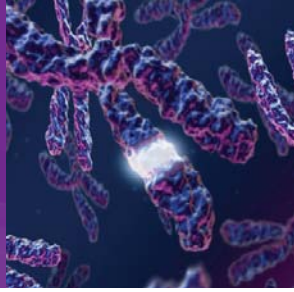

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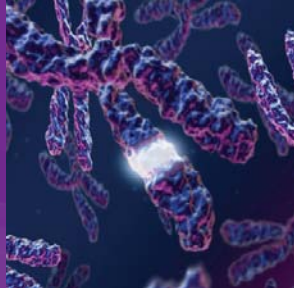
Author Biographies



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Aliza Ben-Zacharia is a board-certified nurse practitioner at The Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai Medical Center, New York, NY. She is an adult primary care nurse practitioner certified by the Academy of Nurse Practitioners and an acute nurse practitioner certified by the American Nurses Credentialing Center. Prior to her position at The Corinne Goldsmith Dickinson 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, she has been an educator and a clinical nurse specialist who has served on many internal and external committees. Ms. Ben-Zacharia is an active CEU reviewer in the Education Committee for the Association of Rehabilitation Nurses and a member of the Nursing Research Committee at Mount Sinai Hospital. Ms. Ben-Zacharia received a Recognition of Excellence Award in Rehabilitation Practice in 1994, and in 2002 she received a Recognition of Excellence Service Award by the Mount Sinai Medical Center for her outstanding work in neurology and in the MS Center. Ms. Ben-Zacharia has initiated a number of educational programs for patients and professionals in tackling ways to address the management and symptoms of MS. She performs specialized work focused on MS and rehabilitation and has published work on palliative care in MS, disease-modifying agents, and MS symptomatology. She was among the first group of nurses to be certified in MS nursing. Currently, Ms. Ben-Zacharia is completing a doctoral program at Case Western Reserve University. Her dissertation addresses an important issue in MS, screening for depression in patients with MS.

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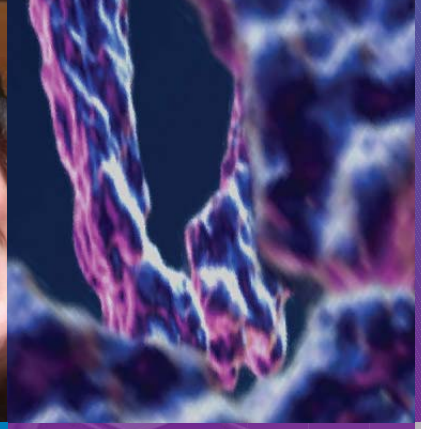
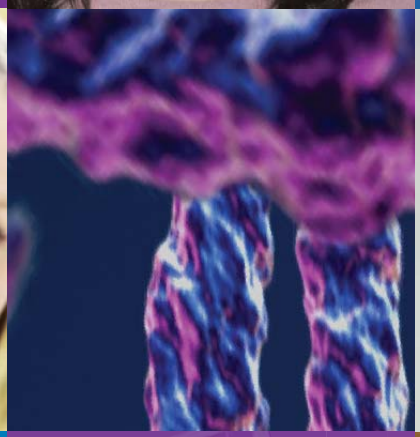
Linda Morgante is a clinical nurse specialist and has worked in the field of MS for the past 20 years. She is currently a full-time assistant professor of nursing at Saint Joseph's College, New York, NY. Prior to this faculty appointment, Ms. Morgante coordinated care for patients and families at The Corinne Goldsmith Dickinson Center for Multiple Sclerosis at the Mount Sinai School of Medicine and at the Maimonides MS Center in Brooklyn, NY. She was a clinical consultant for the National Multiple Sclerosis Society (NMSS) and served on its Clinical Care Committee for many years. She was also a member of the New York City chapter's Clinical Advisory Committee for 18 years. Ms. Morgante is a founding member of the International Organization of MS Nurses,

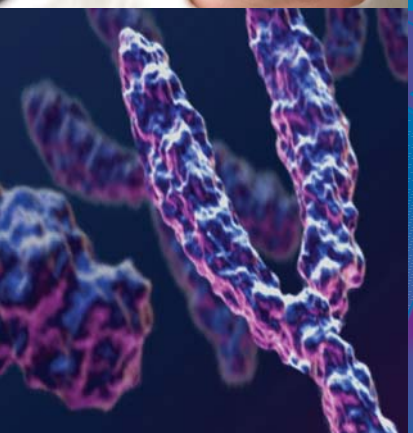
served as vice president of the charter board, and was elected secretary in 2004 (a 2-year term). Ms. Morgante is active in the Consortium of MS Centers, helping to establish and coordinate their educational Web site, and is a frequent presenter at the annual meeting. She has presented internationally on issues related to patient care, symptom management, current therapies and research, adherence issues, and most notably, hope, in MS. Ms. Morgante has also published numerous articles and book chapters. She acted as a co-investigator on a nursing research study entitled "A Prospective Study of Adherence to Glatiramer Acetate in Individuals with Multiple Sclerosis." The article related to that study was published in the *Journal of Neuroscience Nursing* in June 2004 and won the journal's Writing Excellence Award for that year. In 2005, Ms. Morgante was inducted into the NMSS Volunteer Hall of Fame for her contributions to education and research.





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