Analysis of phenotypic characteristics of Multiple Sclerosis that may indicate genetic causes of the disease

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Summary

Certain classes of genetic variants involved in human disease can manifest themselves strongly as characteristic phenotypes. These phenotypic features, when observed in a disease, provide valuable evidence to scientists working to determine its cause(s). Because the development of multiple sclerosis (MS) is thought to be at least partly determined by genetic factors, it is reasonable to analyze the MS phenotype for characteristics that either implicate or exclude particular classes of genetic causes.

None of the phenotypic features of MS as currently understood strongly indicate a particular type of genetic cause. However, some features suggest genetic factors to investigate; for instance, the involvement of the central nervous system and immune system suggests investigating genes known to function in these systems. Other features, such as age of onset, appear to exclude a few genetic causes, such as severe congenital defects. Further understanding and definition of MS phenotypic features may lead to additional productive areas of genetic research for this disease.

Hypothesis

Susceptibility to MS is influenced by genetic factors that translate into characteristic phenotypic features.

Experimental tests of the hypothesis

Despite our incomplete understanding of how genetic causes translate into the phenotypic features of a disease, a few correlations between genotype and phenotype have been documented for certain classes of genes or variants. Phenotypic characteristics of diseases that may reflect their underlying genetic causes include:

- Physiological effects: Mutations in genes known to function in a particular organ or system may lead to disease in that organ/system. However, because proteins are often involved in multiple organs and pathways, identifying the genes that influence a disease based on the affected systems is not always clear cut.
- Age of onset: Certain classes of genetic defects are associated with specific ages of onset; for instance, severe enzymatic deficiencies often manifest themselves in infancy.
- Progression: The progression pattern observed in a disease is occasionally influenced by the type of genetic defect involved. Progression is often a factor of

the affected pathway or tissue; it may also be influenced by the presence of environmental factors.

- Gender bias: Mutations to X- or Y-linked genes can produce diseases that affect men and women differently or in unequal proportions; hormonal effects can also create a gender bias.
- Variability in expression among individuals: Person-to-person variations in the phenotype of a genetic disease can be caused by a number of factors, such as allelic heterogeneity.

Each of these characteristics is reviewed below for its implications concerning the genetic causes of MS.

Physiological organs or systems involved: Predicting the gene(s) responsible for a genetic disease based on the organs or systems involved is not a straightforward task. The functions or effects of many proteins are not yet known. In addition, because proteins often operate in multiple cells, organs, and pathways, genetic mutations or variants affecting a protein could have a variety of effects. Nevertheless, when deciding which genes to investigate in a disease, it is reasonable to give higher priority to genes known or thought to play a major role in affected areas. The two main systems involved in MS are the central nervous system (CNS), which is the primary site of damage, and the immune system, components of which are present in lesions and which is regulated differently in people with MS compared with healthy controls. Most of the MS candidate gene studies performed to date have focused on genes that appear to be involved in the CNS or immune system.

Immune system genes: Several genes involved in the immune system have been investigated in MS. The most frequently examined of these has been the MHC (major histocompatibility complex) region (also known as the human leukocyte antigen or HLA region), with over 190 studies performed to date. (For an example of these studies, see Haines, et al. (1998)[1] and Harbo, et al. (2006)[2], and for a more comprehensive list of MS genetic studies, see the file *phase2-genetic-studies.xls* available on the Accelerated Cure Project website.) The MHC region has produced the strongest evidence of association with MS of any locus so far, although associations are not always consistent across studies, and sometimes differ across populations. Other immune system genes investigated for involvement in MS include genes encoding T cell receptors, immunoglobulin chains, and pro- and anti-inflammatory cytokines and receptors (e.g., Reboul, et al. (2000)[3]). Table 1 lists those immune system genes that have been investigated in at least three separate MS studies (many others have been studied only once or twice), and the overall results of these studies. It should be noted that problems affecting many of the candidate gene studies performed to date in MS (such as the use of sample groups too small to detect modest genetic effects, or the use of markers at unknown genetic distances from the gene) make their results difficult to interpret. Therefore, with the exception of the HLA region, none of the genes studied so far in MS can yet be either definitively included or excluded as susceptibility factors.

Table 1 Immune system genes investigated as susceptibility factors for MS.

Gene	# of studies	Summary of results
CC chemokine ligand 3	4	Mixed results
CCL11	3	Mixed results
CCR5, CCR2B	15	Mostly negative

CD24	3	Mixed results
CD28	3	Mixed results
Complement factor 3	4	Mixed results
Complement factor 4	4	Mostly negative
CTLA-4	25	Mixed results
Immunoglobulin G heavy chain	19	Mixed results
Interferon alpha/beta	3	Mixed results
Interferon alpha/beta receptor 1	3	Mixed results
Interferon alpha/beta receptor 2	3	Mixed results
Interferon gamma	12	Mostly negative
Interferon gamma receptor 1	3	All negative
Interleukin 1 alpha	4	All negative
Interleukin 1 beta	10	All negative
Interleukin 1 receptor antagonist	14	Mostly negative
Interleukin 10	12	Mostly negative
Interleukin 12 p40	5	Mostly negative
Interleukin 2	8	Mostly negative
Interleukin 4	8	Mostly negative
Interleukin 4 receptor	7	Mixed results
Interleukin 6	7	All negative
Interleukin 7 receptor	3	All positive
Interleukin 9	3	All negative
Intracellular adhesion molecule 1	8	Mostly negative
MHC class I and II	192	Results dependent on alleles/haplotypes examined
Monocyte chemotactic protein 1	3	Mixed results
Monocyte chemotactic protein 3	3	Mixed results
Myeloperoxidase	6	Mixed results
Nitric oxide synthase 1	3	All negative
Nitric oxide synthase 2A	5	Mixed results
Osteopontin	5	Mixed results
Platelet endothelial cell adhesion molecule-1	4	All negative
Properdin factor B	8	Mostly negative
PTPN22	5	All negative
PTPRC	11	Mostly negative
RANTES	3	Mixed results
T cell receptor alpha chain	9	Mostly negative
T cell receptor beta chain	21	Mixed results
TAP	8	Mostly negative
TGF beta 1	9	Mostly negative
TGF beta 2	3	Mostly negative
TNF receptor 1	4	All negative
TNF receptor 2	4	Mixed results
Tumor necrosis factor	36	Mixed results
Vitamin D receptor	7	Mixed results

Central nervous system genes: The possibility that defects in myelination, remyelination, or other nervous system functions increase susceptibility to MS has motivated several candidate gene studies. Genes investigated include those that encode myelin components; factors that regulate the proliferation, migration, and maturation of oligodendrocytes; proteins that play a role in cell survival and regeneration;

and proteins implicated in other neurodegenerative diseases. (See Seboun, et al. (1999)[4] and Mertens, et al. (1998)[5] for examples of these studies.) So far none of these genes has been shown to have a strong influence on MS. Most have only been studied once or twice, and those that have received more attention have not demonstrated consistent associations with the disease.

Table 2 Myelin component genes studied as MS risk factors

Gene	# of studies	Summary of results (if 3 or more studies)
CNPase	3	All negative
Myelin basic protein	20	Mostly negative
Myelin oligodendrocyte glycoprotein	7	Mostly negative
Myelin-associated glycoprotein	4	All negative
Oligodendrocyte transcription factor 1	1	--
Oligodendrocyte myelin glycoprotein	4	All negative
Proteolipid protein	3	All negative

Table 3 Neural growth, development and survival factor genes investigated in MS

Gene	# of studies	Summary of results (if 3 or more studies)
Brain-derived neurotrophic factor	1	--
CCT5	1	--
Ciliary neurotrophic factor	2	--
Epidermal growth factor receptor	1	--
Erb-B2	1	--
Erb-B3	1	--
Erb-B4	1	--
Fibroblast growth factor 1	1	--
Fibroblast growth factor 2	1	--
Fibroblast growth factor receptor 1	1	--
Fibroblast growth factor receptor 2	1	--
Fibroblast growth factor receptor 3	1	--
Insulin-like growth factor 1	1	--
Insulin-like growth factor 1 receptor	1	--
Leukemia inhibitory factor	1	--
Microtubule-associated protein 1B	1	--
Neuregulin 1	2	--
Neurotrophic tyrosine kinase, receptor, type 3	1	--
Neurotrophin 3	1	--
Platelet-derived growth factor A	1	--
Platelet-derived growth factor B	1	--
Platelet-derived growth factor receptor	1	--

alpha		
Synapsin III	2	--
TGF beta 1	9	Mostly negative
TGF beta 2	3	Mostly negative
TGF beta 3	1	--
TGF beta receptor 1	1	--
TGF beta receptor 2	1	--
TGF beta receptor 3	1	--

Table 4 MS candidate genes implicated in other neurological disorders

Gene	# of studies	Summary of results (if 3 or more studies)
ADCY2	1	--
Alpha-2-macroglobulin	1	--
Apolipoprotein E	24	Mostly negative
Arylsulfatase A	1	--
CYP2D6	2	--
Low-density lipoprotein receptor-related protein	1	--
MASS1	1	--
Notch3	1	--
SCA1	1	--
SCA2	3	Mixed results
SCA3	1	--
SCA6	1	--
SCA7	2	--

Age of onset: Certain classes of genetic defects manifest themselves at a specific age, although for most genetic diseases the factors that determine the age of onset are not well understood. MS is typically diagnosed in the third or fourth decade of life, which is an age range that does not correspond to any particular known class of genetic defect. However, it does rule out congenital defects such as severe enzyme deficiencies or major chromosomal abnormalities, which generally manifest themselves in infancy. Onset in early adulthood suggests the involvement of reproductive hormones (see "Gender-specific effects" below), although a small percentage of MS cases are diagnosed in children who have not yet reached adolescence.

Another phenomenon related to age of onset is anticipation, in which later generations in an affected family manifest the disease at younger ages than previous generations. This phenomenon, which can result from a triplet repeat expansion that lengthens with each generation, has not been widely documented in MS. One study did find an anticipation effect in a set of Italian multiplex families, but this finding was based on only nine parent-child pairs[6]. Another study on Sardinian families also found evidence of anticipation; however, the authors attributed it not to genetic factors but to widespread environmental changes[7].

Progression: The key MS progression patterns are primary progressive MS (PPMS), which progresses steadily from onset; relapsing-remitting MS (RRMS), characterized by periods of relapse followed by remission; and secondary progressive MS (SPMS), which becomes steadily progressive after an initial period of relapsing-remitting disease. At this time we know very little about what drives the progressive forms of MS and what initiates relapses in RRMS, but it is possible that genetic factors influence these events. Certain genetic factors have been found to shape progression in other diseases; these factors are analyzed below for the possibility of involvement in MS.

- Relapses/remissions: In some genetic diseases characterized by relapses, new clinical activity is caused by spontaneous mutations. For example, in xeroderma pigmentosum, a disease caused by defective DNA repair genes, relapses in the form of neoplasms or other symptoms are triggered by spontaneous damage to DNA, often caused by UV radiation. At present, there is no evidence that relapses in MS are caused by recurring mutations (e.g., spontaneous mutations taking place in central nervous system cells that eventually produce a lesion). In other genetic diseases, relapses and remissions are not a factor of somatic mutations but rather of dynamic physiological conditions that allow the genetic defect to repeatedly manifest itself. For instance, vaso-occlusive episodes in sickle cell anemia are thought to be triggered by the adherence of cells to vessel walls, which depends on local flow conditions and the presence of adhesion molecules on cell surfaces. Similarly, the relapsing/remitting nature of MS may be due to dynamic features of the physiological systems involved, such as transient openings in the blood-brain barrier that allow cellular infiltration. Alternatively, evidence suggests that while MS requires a particular genetic predisposition, it also requires an environmental trigger to initiate disease. An environmental factor that is only present or active periodically (such as reactivated viruses or intermittent environmental pollutants) might account for relapses and remissions. However, at this point too little is known about what these environmental factors might be to speculate on their influence on progression.
- Progression: Steady progression in genetic diseases may be caused or influenced by genetic changes over time (e.g., somatic increases in the length of repeat expansions during cell division) or by factors associated with accumulation of damage (such as oxidative damage to mitochondrial DNA). At this time there is not enough information available to determine whether or how genetic factors such as these are directly involved in the progression of disability in MS.

Gender-specific effects: The gender distribution in MS is approximately 2:1 female: male. Although defects in genes on the X or Y chromosomes can result in a bias in susceptibility between genders, the existence of females with MS and father-son affected pairs rule out a Mendelian susceptibility gene on either the X or Y chromosome. Genes on the X or Y chromosomes may still contribute in a polygenic manner to MS susceptibility; however, to date no locus on either chromosome has been conclusively associated with MS.

Variants in genes involved in sex hormone production may also produce gender-specific effects. The possibility that the MS gender bias may be due to hormonal differences

between males and females has led to a few studies of genes encoding sex hormones as candidate susceptibility factors for MS. However, these studies have been limited in number or inconclusive. For instance, of the four studies conducted on the estrogen receptor gene, two found an association with one allele, another found a conflicting association, and the fourth found no association with any of the alleles studied.

Variations in clinical characteristics: MS is characterized by significant interindividual variation in clinical characteristics such as age of onset, disease course, relapse rate, progression rate, symptoms experienced, response to treatment, and severity. Genetic features that have been found to contribute to heterogeneity in other diseases are analyzed below for their potential to play a role in MS.

- Allelic/genetic heterogeneity: It is quite possible that MS is not a single disease but rather a group of phenotypically similar diseases with different environmental triggers and susceptibility genes. If this is the case, then it may be that some of the clinical variation seen in MS is due to underlying differences in susceptibility genes. In addition, genetic variants that do not contribute to susceptibility to MS may still influence its phenotype. Support for the idea that genetic heterogeneity may result in phenotypic variation comes from investigations of the "Japanese-type" and "Western-type" clinical subtypes of MS in Japan. These studies have identified different potential genetic associations for these two subtypes which may help determine their differing phenotypes. There is also evidence that certain mitochondrial DNA (mtDNA) mutations are associated with increased occurrence of optic neuritis in MS (although conflicting results have also been published). (See the ACP documents "Analysis of Multiple Sclerosis as a disease triggered by incompletely penetrant genetic factors" and "Analysis of mitochondrial DNA mutations as a possible cause of Multiple Sclerosis" for more information.)
- Mitochondrial DNA heteroplasmy: In inherited diseases caused by mtDNA mutations, severity can be influenced by the ratio of mutated to normal mtDNA transmitted by a mother to an affected child. Therefore severity in these diseases can vary greatly, even among members of the same family. While severity in MS can also vary substantially, at this time there is no strong evidence suggesting that inherited defects in mtDNA increase susceptibility to or affect the severity of MS.
- Somatic mosaicism: In certain genetic diseases like McCune-Albright syndrome that are caused by post-embryonic somatic mutation, the number and nature of the systems involved can vary based on at what point in development the mutation occurs and which cell originates the mutation. There is no evidence that this type of phenomenon accounts for any of the heterogeneity observed in MS. Somatic mutations in the form of T cell receptor and immunoglobulin rearrangements may play a role in MS etiology, but it is unclear whether or how these would result in phenotypic variations among affected individuals.

Conclusions

Analysis of the MS phenotype does reveal some characteristics that could reflect specific underlying genetic causes. For instance, involvement of the central nervous system and immune system suggests the involvement of genes functioning in those

areas; progression patterns suggest factors such as cumulative DNA damage; the gender susceptibility bias suggests involvement of X- or Y-linked genes or sex hormone genes; and clinical variability suggests factors such as genetic heterogeneity or mtDNA heteroplasmy. However, for the most part investigations into the involvement of these types of factors have either excluded them as major susceptibility enhancers or have not yet produced sufficient evidence associating them with MS.

The fact that no strong genotype-phenotype relationships have been found in MS may reflect the involvement of genetic factors that have not yet been found to produce a distinctive phenotype. It is also consistent with the idea of MS as a multifactorial disease or set of etiologically heterogeneous diseases with no one dominant genetic cause. Perhaps further documentation of the MS phenotype, including investigations of intermediate phenotypes (e.g., blood biomarkers), will lead to better understanding of the disease and help identify its genetic causes.

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