



Analysis of Multiple Sclerosis as a Mendelian disease

Draft: October 26, 2006
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Summary

Initial evidence that a disease is Mendelian often comes in the form of identifiable inheritance patterns; final proof is provided by the identification of a gene that segregates cleanly with the disease in affected families. In MS, none of the typical Mendelian pedigree patterns have been consistently found in studies of multiplex families, and no one gene has emerged as deterministic in any of the candidate gene studies or genome screens conducted to date. While it is possible that familial evidence collected to date has been inadequate and/or that gene studies have simply been unlucky in their choices of loci, it is more likely that MS is not an inherited single-gene disease like cystic fibrosis or Huntington disease. The possibility does exist that what we call MS is actually a group of diseases, one or more of which are Mendelian in nature, or that a *somatic* mutation to a single gene is sufficient to cause MS. However, another reasonable interpretation of the existing evidence is that MS is not monogenic, and requires the activity or presence of multiple genetic and/or environmental factors.

Hypothesis

MS is a Mendelian disease, caused by a single defective gene (either dominant or recessive). No other genetic or environmental factors need to be present in order for MS to develop in an affected person.

Experimental tests of the hypothesis

Clues as to whether a disease is caused by a single gene acting in isolation or by multiple genetic and/or environmental factors acting in combination can come from studies of the inheritance patterns exhibited in families with multiple affected individuals and from studies searching for candidate susceptibility genes. Both types of studies have been and continue to be performed in MS.

Familial inheritance pattern analysis:

Inherited Mendelian disorders tend to exhibit particular identifiable pedigree patterns. Comparison of the major Mendelian pedigree patterns¹ with the characteristics of MS shows that MS does not appear to fit neatly into any of the existing categories. (For more details on the MS familial characteristics listed in this chart, please see our documents, "Analysis of inherited genetic susceptibility factors as a possible cause of Multiple Sclerosis," "Analysis of genetic mutations or alleles on the X or Y chromosome

as a possible cause for Multiple Sclerosis,” and “Analysis of mitochondrial DNA mutations as a possible cause of Multiple Sclerosis.”)

Mendelian pedigree patterns	Characteristics	MS characteristics
Autosomal dominant	<ul style="list-style-type: none"> • Affected person usually has at least one affected parent • Child with one affected parent has a 50% chance of being affected 	<ul style="list-style-type: none"> • Most cases of MS are sporadic (no other family members are affected) • Risk to first-degree relatives of people with MS (parents, children, siblings) is around 5% or less
Autosomal recessive	<ul style="list-style-type: none"> • After the birth of an affected child, each subsequent child has a 25% chance of being affected 	<ul style="list-style-type: none"> • Risk to first-degree relatives of people with MS is around 5% or less
X-linked dominant	<ul style="list-style-type: none"> • Children of affected females have a 50% risk of being affected • All daughters of affected males are affected 	<ul style="list-style-type: none"> • Risk to first-degree relatives of people with MS is on the order of 5% or less • Daughters of affected males are not necessarily affected
X-linked recessive	<ul style="list-style-type: none"> • Affects mainly males 	<ul style="list-style-type: none"> • Affects more females than males (in a ratio of approximately 2:1)
Y-linked	<ul style="list-style-type: none"> • Affects only males 	<ul style="list-style-type: none"> • Affects females as well as males
Mitochondrial	<ul style="list-style-type: none"> • Transmitted by mothers only 	<ul style="list-style-type: none"> • Father-child affected pairs do exist (and fathers may be more likely to transmit MS than mothers²)

In addition, the lack of complete concordance in monozygotic twins (reported to be 25-30%) provides further evidence that MS is not caused by an inherited Mendelian defect.

Results from genetic studies: Additional evidence arguing against the involvement of an inherited Mendelian genetic defect is provided by studies searching for the locations of MS susceptibility genes. For example, 55 full and partial genome screens and follow-up studies have been conducted to date for MS. (See the file *phase2-genetic-studies.xls* for details of each of these studies.) In these screens, a few hundred or even a few thousand markers are examined, usually distributed across all chromosomes except for Y. These studies have typically produced a number of loci that are of interest, but tend not to single out one locus as exerting a particularly strong effect. Furthermore, although the HLA region is the locus most often identified in these screens, even it does not

emerge as having a predominant effect when analyzing the results of these studies collectively. As one meta-analysis of three screens (American, British and Canadian) concludes, the lack of evidence definitively linking any single genomic region with MS could mean that MS involves multiple genes of modest effect acting together, or that there are genes of large effect causing MS only in certain families that cannot be detected in a genetically heterogeneous sample³.

Candidate gene studies have likewise failed to reveal any one gene as having a Mendelian relationship with MS. (See the file *phase2-genetic-studies.xls* for details.) Most genes that have been evaluated for an association with MS have provided at best inconsistent results. Even the HLA-DR2 haplotype, which has demonstrated the most consistent association with MS to date, was estimated by one study to explain at most 62% of the genetic basis for MS in one group of multiplex families⁴.

Conclusions

The inability to find inheritance patterns in MS that are typical of a Mendelian disease and the failure of multiple studies to find a single causal, deterministic MS gene together provide strong evidence that MS is not a disease that results solely from the inheritance of a single defective gene. While it is theoretically possible that the work to date has not given a completely accurate picture of the genetic basis of MS, and that at some point in the future a Mendelian MS gene will emerge, at this time the evidence indicates that MS requires multiple causal factors (genetic and/or environmental).

However, two scenarios do still exist whereby a single gene could be sufficient to cause MS:

- There could be multiple etiological routes to MS, one or more of which involve relatively rare inherited Mendelian mutations affecting a subset of MS families. This appears to be the case in other diseases such as Parkinson's disease, in which highly penetrant single gene mutations sufficient to cause the disease have been identified in a subset of families⁵. Large multigenerational pedigrees, while rare, may similarly lead to the identification of completely penetrant genes in MS. (One recently published paper describes such a pedigree⁶.)
- MS, or one form of MS, could be caused by a chance somatic mutation to a particular gene in a particular type of cell (e.g., the TCR receptor gene in a T cell or immunoglobulin gene in a B cell) that then becomes capable of triggering MS. T and B cells have been implicated in the pathogenesis of MS, but whether a single cell and its successors could be sufficient to cause MS is unknown.

References

- 1 T. Strachan and A. P. Read, *Human Molecular Genetics, 2nd edition*.
- 2 O. Kantarci, L. Barcellos, E. Atkinson, P. Ramsay, R. Lincoln, S. Achenbach, M. D. Andrade, S. Hauser and B. Weinshenker, *Men transmit MS more often to their children vs women: the Carter effect*. *Neurology*, 2006. **67**(2): p. 305-10. PubMed ID: 16864824.

A study of affected parent-child pairs selected from MS registries in the UK and Ireland revealed that affected fathers were more likely to transmit MS to their children than affected mothers. Greater genetic loading in men may underlie these findings.

- 3 *A meta-analysis of genomic screens in multiple sclerosis. The Transatlantic Multiple Sclerosis Genetics Cooperative.* Mult Scler, 2001. 7(1): p. 3-11. PubMed ID: 11321191.

Meta-analysis of American, British, and Canadian genome-wide screens found eight regions with an NPL score greater than 2.0. The highest score belonged to region 17q11 (NPL score 2.58), although this result did not reach genome-wide significance. The results suggest that MS is likely to have multiple genetic risk factors.

- 4 J. L. Haines, H. A. Terwedow, K. Burgess, M. A. Pericak-Vance, J. B. Rimmner, E. R. Martin, J. R. Oksenberg, R. Lincoln, D. Y. Zhang, D. R. Banatao, N. Gatto, D. E. Goodkin and S. L. Hauser, *Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity.* The Multiple Sclerosis Genetics Group. Hum Mol Genet, 1998. 7(8): p. 1229-34. PubMed ID: 9668163.

Linkage to HLA-DR2 was confirmed in a dataset of 98 families, although stratification of the results by DR2 showed that linkage was limited to those families segregating HLA-DR2 alleles. Preliminary calculations based on this dataset indicate that the MHC explains between 17 and 62% of the genetic basis of MS.

- 5 M. H. Polymeropoulos, J. J. Higgins, L. I. Golbe, W. G. Johnson, S. E. Ide, G. Di Iorio, G. Sanges, E. S. Stenroos, L. T. Pho, A. A. Schaffer, A. M. Lazzarini, R. L. Nussbaum and R. C. Duvoisin, *Mapping of a gene for Parkinson's disease to chromosome 4q21-q23.* Science, 1996. 274(5290): p. 1197-9. PubMed ID: 8895469.

Markers on chromosome 4q21-q23 were found to be linked to Parkinson's disease (Z_{\max} for marker D2S2380 = 6.00) in a large kindred demonstrating autosomal dominant inheritance.

- 6 D. A. Dymant, M. Z. Cader, C. J. Willer, N. Risch, A. D. Sadovnick and G. C. Ebers, *A multigenerational family with multiple sclerosis.* Brain, 2002. 125(Pt 7): p. 1474-82. PubMed ID: 12076998.

A family was described with 15 affected individuals in three and possibly four generations. The segregation within the pedigree was consistent with an autosomal dominant mode of inheritance with reduced penetrance. 11 out of 14 cases were positive for HLA DRB1*15 allele, and TDT analysis for this allele was significant ($p = 0.0054$). The inheritance pattern suggests a single major locus responsible for MS susceptibility with DRB1 acting as a modifier.