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**Commentary****Maternal effect in multiple sclerosis**

The genetics of complex diseases is a fascinating but complicated issue. Often, many genes might be involved in a single disorder, each exerting a small effect. To fully understand the pathogenic mechanisms, a comprehensive knowledge of the effect of the individual genes is needed. However, before that, one should try to ascertain how important genes are compared with environmental factors. Such an assessment can be made by examining the rate of concordance in identical versus dizygotic twins or the extent of clustering in families.

We know that multiple sclerosis has a genetic component, since one gene--*HLA-DRB1*1501*--has been identified that confers an increased risk of the disease. About 60% of patients with multiple sclerosis in northern Europe are *DRB1*1501*-positive compared with 30% of healthy individuals.¹ However, although many genome-linkage and association studies^{2,3} have been done, no other gene has yet been unequivocally associated with the disease. Therefore, a reassessment of the importance of genetic factors in multiple sclerosis is welcome.

Results of several studies,⁴⁻⁶ assessing clustering of multiple sclerosis in families, indicate a greater risk for the disease in first-degree relatives of patients than among the general population. The design of these studies, however does not allow the investigation to conclude whether this difference in risk is the result of shared genetic factors or shared intrafamilial environmental factors--such as food or infection. More convincing evidence for the part played by genetic factors was provided by two pieces of work done by the Canadian Collaborative Study Group, in adopted children⁷ and in half-siblings.⁸ In both instances, a link with the children's biological parents, independent of the environment in which the children were raised, was clear. It is noteworthy, however, that although these trials provided a strong case for genetic factors, the data are also compatible with an influence of prenatal or perinatal environmental factors on disease susceptibility.

The study in today's *Lancet* by [George Ebers and colleagues](#) is an extension of the study done with half-siblings in 1996⁸ and brings us one step closer to the factors involved in disease pathogenesis. In the original trial, 939 individuals with multiple sclerosis were identified from a panel of 16 000 patients. These index cases had a total of 1839 half-siblings and 1395 full-siblings. The risk for multiple sclerosis was not significantly different in half-siblings raised together and those raised apart from the index case. Additionally, there was a slightly higher risk of disease in half-siblings who shared a mother than in those who shared a father. This finding was not significant. However, in the latest study by Ebers and colleagues, which involves double the number of half-siblings, the results are significant (2.35% for shared mother and 1.31% for shared father), indicating a maternal effect. Furthermore, risk for multiple sclerosis in siblings who share only a mother compared with risk in full siblings--ie, those who share a mother and a father--did not differ significantly (2.35% vs 3.11%, $p=0.1$). This finding indicates that maternal effects might even be the major component of family aggregation.

Parent-of-origin effects have been described for various diseases, including multiple sclerosis, on the basis of an excess of mother-to-child or father-to-child

combinations in affected parent-child pairs.^{9,10} This approach is biased in multiple sclerosis, which has a female-to-male ratio of about two-to-one. The half-sibling approach avoids such bias, since it does not depend on the parents being affected.

The origin of the possible maternal effect in multiple sclerosis is unknown, but could be genetic (eg, mitochondrial genes), epigenetic (eg, imprinted genes), or environmental (intrauterine or perinatal). That there is a maternal effect at all is relevant to future directions of genetic studies of multiple sclerosis. Mitochondrial genes are by no means unlikely candidates; a phenotype similar to multiple sclerosis has, for example, been noted in individuals with mitochondrial DNA mutations associated with Leber's hereditary optic neuropathy.¹¹ However, so far, mitochondrial mutations have not been linked with a genetically determined susceptibility in multiple sclerosis.^{12,13} Imprinted genes are a well defined class of genes, and several specific genomic regions that contain them have been identified.¹⁴ As such, they could be the preferential target of future linkage and association studies. However, the third possibility, environmental factors, whether intrauterine or perinatal, cannot be discounted. Despite the new data, the nature-nurture dilemma remains. The findings of Ebers and colleagues do, however, give us some clues about directions for future research.

We have no conflict of interest to declare.

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1 Thorsby E. HLA associated diseases. *Hum Immunol* 1997; **53**: 1-11. [[PubMed](#)]

2 Giordano M, D'Alfonso S, Momigliano-Richiardi P. Genetics of multiple sclerosis: linkage and association studies. *Am J Pharmacogenomics* 2002; **2**: 37-58. [[PubMed](#)]

3 Herrera BM, Ebers GC. Progress in deciphering the genetics of multiple sclerosis. *Curr Opin Neurol* 2003; **16**: 253-58. [[PubMed](#)]

4 Robertson NP, Fraser M, Deans J, Clayton D, Walker N, Compston DA. Age-adjusted recurrence risks for relatives of patients with multiple sclerosis. *Brain* 1996; **119**: 449-55. [[PubMed](#)]

5 Sadovnick AD, Dircks A, Ebers GC. Genetic counselling in multiple sclerosis: risks to sibs and children of affected individuals. *Clin Genet* 1999; **56**: 118-22. [[PubMed](#)]

6 Carton H, Vlietinck R, Debruyne J, et al. Risks of multiple sclerosis in relatives of patients in Flanders. *Belgium J Neurol Neurosurg Psychiatry* 1997; **62**: 329-33. [[PubMed](#)]

7 Ebers GC, Sadovnick AD, Risch NJ, and the Canadian Collaborative study Group. A genetic basis for familial aggregation in multiple sclerosis. *Nature* 1995; **377**: 150-51. [[PubMed](#)]

8 Sadovnick AD, Ebers GC, Dyment DA, Risch NJ, for the Canadian Collaborative Study Group. Evidence for genetic basis of multiple sclerosis. *Lancet* 1996; **347**: 1728-30. [[Text](#)]

9 Sadovnick AD, Bulman D, Ebers GC. Parent-child concordance in multiple sclerosis. *Ann Neurol* 1991; **29**: 252-55. [[PubMed](#)]

10 Moffatt MF, Cookson WO. The genetics of asthma: maternal effects in atopic disease. *Clin Exp Allergy* 1998; **28**: (suppl 1) 56-61. [[PubMed](#)]

11 Harding AE, Riordan-Eva P, Govan GG. Mitochondrial DNA diseases: genotype and phenotype in Leber's hereditary optic neuropathy. *Muscle Nerve* 1995; **3**: S82-84. [[PubMed](#)]

12 Chalmers RM, Robertson N, Compston DA, Harding AE. Sequence of mitochondrial DNA in patients with multiple sclerosis. *Ann Neurol* 1996; **40**: 239-43. [[PubMed](#)]

13 Kalman B, Alder H. Is the mitochondrial DNA involved in determining susceptibility to multiple sclerosis? *Acta Neurol Scand* 1998; **98**: 232-37. [[PubMed](#)]

14 Morison IM, Paton CJ, Cleverley SD. The imprinted gene and parent-of-origin effect database. *Nucleic Acids Res* 2001; **29**: 275-76. [[PubMed](#)]

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