# Evidence for genetic basis of multiple sclerosis

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## Summary

**Background** Increased familial risks in multiple sclerosis (MS) range from 300-fold for monozygotic twins to 20–40-fold for biological first-degree relatives, suggesting a genetic influence. Yet if one identical twin has MS the other usually will not. One way of sorting out the contributions of genes and environment is to study half-sibs.

**Methods** In a Canadian population-based sample of 16 000 MS cases seen at 14 regional MS clinics one half-sib (or more) was reported by 939 index cases. By interview we elicited information on family structure and an illness in half-sibs and any full brothers or sisters.

**Findings** The age-adjusted MS rate in the 1839 half-sibs of these index cases was 1·32% compared with 3·46% for the 1395 full sibs of the same cases ($p<0·001$; likelihood ratio test). There were no significant differences in risk for maternal versus paternal half-sibs (1·42% *vs* 1·19%) or for those raised together versus those raised apart from the index case (1·17% *vs* 1·47%).

**Interpretation** Besides demonstrating the power and the feasiblity of using half-sib studies to throw light on the aetiology of complex disorders, our findings show that a shared environment does not account for familial risk in MS and that maternal effects (such as intrauterine and perinatal factors, breastfeeding, and genomic imprinting) have no demonstrable effect on familial risk. Halving the number of potentially contributory genes (by comparing full-sib and half-sib rates) lowers the risk of MS by a factor of 2·62, an observation consistent with a polygenic hypothesis.


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## Introduction

Multiple sclerosis (MS) is thought to be a complex disease resulting from an autoimmune reaction against central-nervous-system antigens.[1,2] Although familial aggregation of MS is well recognised, the degree to which this results from genetic or from environmental (non-genetic) factors remains uncertain.[3] The risk for monozygotic twins is at least 300 times greater than that for the general population.[4–6] Although this increased risk is consistent with genetic risk factors, a role for environmental sharing cannot be readily dismissed—indeed, concordance for MS in monozygotic twin pairs is unusual.

The rarity of conjugal MS suggests that any environmental factors that result in familial aggregation are operative during childhood, and migration studies also suggest this.[7,8] A study of identical twins separated early in life would help differentiate the role of genes and environment but such twins are too rare for this approach to be feasible in MS (or any other autoimmune disease).

Half-sibs (one biological parent in common) represent a special and largely unexplored group of individuals in which the recurrence risk of disease might shed light on genetic and environmental factors. Half-sibs often have a different familial environment; the proportion of half-sibs raised together is roughly equal to the proportion raised apart; and those raised together will usually share a family environment up to age 15, by which time MS susceptibility is thought to be determined.[1,2]

Half-sib studies require large population and patient pools and ascertainment that is free of bias. They have been used with success in studying the heritability of common behavioural disorders,[9,10] congenital malformations,[11] and normal variation (eg, stature[12]) but not so far for an autoimmune disorder such as MS. Because autoimmune diseases are less common than, say, behaviour disorders, affected individuals with half-sibs are infrequent and pairs of affected half-sibs are unusual. Nevertheless, the half-sib design does compare favourably with adoption and twin studies as a means of detecting a genetic (single-locus or multifactorial) component to familial aggregation.[13] We have applied this method to MS.

## Patients, families, and methods

16 000 consecutive, well-characterised patients with clinically definite MS[14] were surveyed. These were identified from the registered active caseloads of the fourteen regional Canadian MS clinics. Because these clinics are population-based, ascertainment of more than one family member through the clinic system was considered independent ascertainment. Across centres, family history data were systematically collected by direct personal interviews and by standardised telephone interviews from informed family members, including the index case. The data were verified according to a standard protocol.[15,16]

Each index case was asked if he or she had any maternal and/or paternal half-sib(s); those who had were asked about any

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| Relation to index case | No | No with MS | Crude risk % | Age-adjusted risk % (SE) |
|---|---|---|---|---|
| **Full sibs** | | | | |
| Brother | 697 | 12 | 1·72 | 2·23 (0·64) |
| Sister | 698 | 27 | 3·87 | 4·69 (0·88) |
| **Total** | 1395 | 39 | 2·80 | 3·46 (0·55) |
| **Maternal sibs** | | | | |
| Half-brother | 526 | 3 | 0·57 | 0·82 (0·47) |
| Half-sister | 507 | 8 | 1·58 | 2·02 (0·71) |
| **Paternal sibs** | | | | |
| Half-brother | 410 | 2 | 0·49 | 0·71 (0·50) |
| Half-sister | 396 | 5 | 1·26 | 1·67 (0·74) |
| **Total** | 1839 | 18 | 0·98 | 1·32 (0·31) |

Table 1: **MS risks of full and half-sibs of MS index cases**

full sibs. This study thus included full sibs (same mother and father), maternal half-sibs (same mother, different father), and paternal half-sibs (same father, different mother). Family informants were systematically asked about the length of time half-sibs shared a "common environment"—ie, had lived together as a family unit. Half-sibs were readily separable into two groups: (I) those who lived together for at least a year before age 15; (IIa) half-sibs who visited occasionally (less than once a year on average) or (IIb) half-sibs who only knew of each other but had never met before age 15.

Data for control diseases in full sibs and half-sibs of MS index cases (not shown) demonstrated similar rates, indicating that there was not a general lack of awareness of medical disorders affecting these relatives.

All risk analyses were based on modifications of the maximum likelihood approach.[17] Distributions were compared by likelihood ratio test. Risk estimates are given with SEs.

## Results

We excluded 25 half-sibs because the parent not in common with the index case was of non-European ethnic background (none had MS) and 329 half-sibs because their age and/or health status was not available. The potential index cases excluded for those reasons numbered 354. That left 939 of the 16 000 MS patients of European ethnic background who replied that they had at least one half-sib. 475 index cases had at least one maternal half-sib; 353 had at least one paternal half-sib; 111 had at least one maternal half-sib and one paternal half-sib. These 939 MS patients had 1395 full sibs and 1839 half-sibs (1033 maternal, 806 paternal) for whom current age (or age at death) and health status were known (table 1).

39 of the 1395 full sibs and 18 of the 1839 half-sibs had MS (table 1). The age-adjusted risk for half-sibs (1·32% [SE 0·31]) was significantly lower than that for full sibs of these same MS index cases (3·46 [0·54%]; $p<0·001$). The age-adjusted risks for maternal (1·42 [0·42]%) and paternal (1·19 [0·45]%), were not significantly different (table 2).

| Half-sibs | No | No with MS | % MS risk | |
|---|---|---|---|---|
| | | | Crude | Age-adjusted (SE) |
| Maternal | 1033 | 11 | 1·06 | 1·42 (0·42) |
| Paternal | 806 | 7 | 0·89 | 1·19 (0·45) |

Table 2: **Age-adjusted MS risks for half-sibs, controlling for "maternal effect"**

| Half-sibs | No | No with MS | % MS risk | |
|---|---|---|---|---|
| | | | Crude | Age-adjusted (SE) |
| Who lived together | 897 | 6 | 0·67 | 1·17 (0·41) |
| Who never liver together | 942 | 10 | 1·06 | 1·47 (0·46) |

Table 3: **Age-adjusted MS risks for half-sibs, controlling for "shared environment"**

The usual female:male ratio in MS approaches 2:1[1,2] and this was demonstrable for both full sibs and half-sibs in our study. The age-adjusted risk for full sisters was 4·69 (0·88%) while for full brothers it was 2·23 (0·64)%; for half-sisters and half-brothers the rates were 1·87 (0·51)% and 0·77 (0·34)% respectively.

The age-adjusted risk for half-sibs who lived together was 1·17 (0·41)%, which was not significantly different from that for half-sibs who never lived together (1·47 [0·46]%) (table 3). To do this analysis, it was necessary to have accurate information on current age or age at death.

## Discussion

The familial risk of MS in biological relatives is substantial compared with the risk in the general population. For monozygotic twins, the risk is about 300 times that for the general population while the risk for first-degree relatives ranges from 20 to 40 times that for the general population. For siblings, longitudinal studies have demonstrated an age-adjusted recurrence risk of some 3·6%,[16] and this was confirmed in our study. The rate for half-sibs has not been previously estimated, but this group represents a useful approach to determine the relative importance of genetic and environmental factors. Furthermore, since this study included roughly equal numbers of maternal and paternal half-sibs, comparison of recurrence risks in these two groups could be used as a measure of any maternal environmental effect and also to address the question of maternal influences on heritability, including genomic imprinting and mitochondrial factors.

The age-adjusted risk for full sibs (3·46%) was significantly greater than that for half-sibs (1·32%). To control for familial environment, age-adjusted risks for full sibs (3·46%) and for those half-sibs raised together (1·17%) were compared, and the full sib risk was significantly higher ($p<0·005$), providing further evidence that it is the full sibs' increased genetic relatedness rather than the common familial environment that is the important factor in the familial aggregation of MS.

We found no evidence to support the notion that there are maternal factors influencing risks. There was no significant difference in MS risk between maternal and paternal half-sibs. The larger number of maternal than paternal half-sibs included in the analyses reflects a general tendency of index cases to know more about their maternal than their paternal half-sibs. Divorce, remarriage, and out-of-wedlock unions—the social circumstances that lead to half-sibs—tend to favour maternal derivation of information.

The similar risk in half-sibs raised together and those raised apart does not support the notion that there are specific environmental exposures common to childhood and adolescence that are critical to the familial aggregation of MS in Canada. Indeed, the risk was higher in those raised apart than in those raised together, a finding we attribute to chance. Our results support the interpretation that the difference between sibling and half-sib risk is entirely attributable to genes.

Our data are consistent with studies on birth order[18,19] and conjugal MS,[20–23] with the similar age of MS onset among affected sibs,[24] and with the existence within high-risk areas of ethnic groups such as the Inuit,[25] Japanese,[26]

and Lapps[27] who are relatively resistant to the disease. The results also confirm and extend data on non-biological (adopted, adopting) first-degree relatives of MS patients, who were found to be at no greater risk of MS than the general population.[16]

It is unlikely that an environment shared in childhood and adolescence plays a significant part in the familial aggregation of MS. Although non-heritable factors (eg, geographical latitude) do have a role in MS susceptibility, these factors may be more profitably sought by looking at whole populations rather than the microenvironment of families.

Together, results from this study and the concurrent one on non-biological first-degree relatives[16] strongly suggest that familial aggregation in MS is genetic but they shed little light on the complexity of inheritance of that susceptibility. The recurrence risk in offspring of conjugal pairs[28,29] should give a better indication of this complexity. Environmental (non-genetic) risk factors—which are clearly important since most monozygotic twins remain discordant[4-6] and because populations of similar genetic background in different geographical locations differ in MS risk[1,30]—do act at a population level. However, the similar MS rates for maternal and for paternal half-sibs show that factors such as the intrauterine and perinatal environment, breastfeeding, and genomic imprinting have no demonstrable effect on MS risk.

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