Parent-of-origin effect in multiple sclerosis: observations in half-siblings

G C Ebers, A D Sadovnick, D A Dyment, J M L Yee, C J Willer, Neil Risch

Multiple sclerosis is a complex trait in which occurrence rates in offspring are 20–50-fold greater than in the general population. Parent-of-origin effects have been difficult to screen for, since most cases are sporadic. We have compared recurrence risks in half-siblings with respect to their parent in common. Of the 1567 index cases with half-siblings in multiple sclerosis clinics across Canada, we recorded 3436 half-siblings and 2706 full-siblings. Age-adjusted full-sibling risk was 3.11%. By contrast, half-sibling risk in the same families was significantly lower at 1.89% (χ² test, p=0.006), but higher than expected if familial risk was simply polygenic. For maternal half-siblings, the risk was 2.35% (34 affected siblings of 1577), and 3.13% for paternal half-siblings (15 of 1577), (p=0.048). The difference in risk suggests a maternal parent-of-origin effect in multiple sclerosis susceptibility.

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Multiple sclerosis has characteristics of a complex trait. Susceptibility genes are implicated by an increased risk in monozygotic twins (20–30%) compared with dizygotic twins (3–5%). A moderate excess of haplotype sharing in affected relative pairs has accompanied multiple sclerosis associations with major histocompatibility antigens on a population level. Other genetic and environmental factors implicated by genetic epidemiology have remained elusive. With rising divorce rates, study of recurrence risks in half-siblings is a powerful method to test for parent-specific effects. We have reported that in half-siblings of patients with multiple sclerosis, (1) no increased risk of the disease attributable to shared versus unshared familial environment was detectable, and (2) full-sibling occurrence risks exceeded those for half-siblings raised together. We have investigated recurrence risk within a family by looking at half-siblings and full-siblings of patients with multiple sclerosis.

Index cases (n=20 653) meeting criteria for clinically definite or probable multiple sclerosis and attending population-based regional multiple sclerosis clinics across Canada were resurveyed. Relatives who were affected with multiple sclerosis, (1) no increased risk of the disease attributable to shared versus unshared familial environment was detectable, and (2) full-sibling occurrence risks exceeded those for half-siblings raised together. We have investigated recurrence risk within a family by looking at half-siblings and full-siblings of patients with multiple sclerosis.

Table 1:

<table>
<thead>
<tr>
<th>Number of siblings (with MS)</th>
<th>Crude risk (Davie’s SE)</th>
<th>Age-adjusted recurrence risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-siblings</td>
<td>2706 (71)</td>
<td>2.62% (0.34)</td>
<td>3.11%</td>
</tr>
<tr>
<td>Half-siblings</td>
<td>3436 (49)</td>
<td>1.43% (0.23)</td>
<td>1.89%</td>
</tr>
</tbody>
</table>

MS=multiple sclerosis.

Table 1: Age-adjusted risks for full-siblings and half-siblings of 1567 index cases
halving of the genes in common. However, our risk comparison does not conform to this expectation: the half-sibling rate was more than half the full-sibling rate. The non-significant excess of maternal half-sibling risk identified in our original study suggested that parentally transmitted risk could be asymmetrical.

With the addition of new half-sibling families and the added follow-up of those surveyed in our original study, we show evidence for a significant maternal effect in multiple sclerosis occurrence, for which there are many potential explanations. Environmental factors might have a role in such an effect, and parental imprinting remains a possible candidate.

Our results entail important implications for the understanding of multiple sclerosis inheritance patterns and susceptibility. More generally applicable is the demonstration of the practicability, feasibility, and power of half-sibling data, which can answer basic questions about environmental sharing, pattern of inheritance, and the effect of parent of origin.

Contributors
G C Ebers and A Sadovnick were the principal investigators of the Canadian Collaborative Study. D Dyment, C Willer, and I Yee contributed to the analyses and manuscript preparation. N Risch provided discussion and statistical supervision.

Conflict of interest statement
None declared.

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