The genetics of multiple sclerosis

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1. Introduction

The role of genetic factors in multiple sclerosis (MS) has been a subject of controversy since 1896 when Eichhorst labeled MS as an ‘inherited, transmissible disease’ whereas Gowers [1] stated that the familial incidence of MS was ‘quite exceptional’. Curtius [2] published what is possibly the first report on the familial incidence of MS. It was only in 1972 that the first objective evidence for the role of genetic factors in the etiology of MS was published by Jersild et al. [3] who reported an association between the disease and certain alleles of the human leukocyte antigen (HLA).

At present, it is accepted that both genetic and non-genetic (environmental) factors are important in the etiology of MS. The following statements are compatible with the results of genetic epidemiological and molecular genetic studies to date:

A) MS results from an interaction of genetic (hereditary) and non-genetic (environmental) factors,
B) the familial aggregation of MS (i.e. the excess of MS found in biological relatives of persons with MS) is due to the genetic material these relatives have in common (i.e. identical by descent or IBD) with the individual having MS,
C) MS appears to be oligogenic (more than one gene involved),
D) HLA does not appear to be a ‘deterministic’ gene for MS,
E) genetic susceptibility factors may overlap, at least to some extent, among the general population of individuals with what is now called MS.

2. Genetic epidemiological studies

In conducting genetic studies, important first steps are to determine whether the observed rate of a disorder among family members is indeed different from the expected rates for the appropriate general populations and, secondly, to ensure that reportedly affected family members do indeed have the disease being studied as the ‘best estimate’ diagnosis. Although family members had long reported what appeared to be an increased rate of MS, there had been no systematic, population-based study to determine whether in fact this was true until the mid-1980s. Given the variable age of onset for MS [4], it was obvious that age-adjusted family risks were needed to be compared with the lifetime prevalence for comparable general populations. It was also imperative to determine as accurately as possible whether the ‘best estimate’ diagnosis for reportedly affected family members was MS. The first such study [5] clearly showed that the age-adjusted familial risks for MS were significantly greater than the lifetime prevalence for the general population (see Table 1). For example, as shown in Table 1, the risk to a relative of a person with MS increases as the degree of relationship (amount of genetic sharing) increases. A first-degree relative such as a sib or child has an overall lifetime risk to develop MS of 3–5% (or 15–25 × the risk for the background population) whereas a monozygotic co-twin of a person with MS has a risk of 38% (or 190 × the background rate). Subsequent familial risk studies such as those from the United Kingdom [6] and Belgium [7] have found similar results.

Using the classical genetic epidemiological approach, studies on specific family relationships, in particular population-based twin studies [8,9] which compared MS concordance rates among monozygotic twins (who share 100% of their genetic material) and dizygotic twins (who share 50% of their genetic material), further supported a role for genetic factors in the etiology of MS. However,
as the monozygotic concordant twin rate did not approach 100%, it became clear that non-genetic (environmental) factors were also important. Whether these non-genetic factors were familial or more ubiquitous, population based ones was unresolved by the early 1990s.

Once it is objectively shown that a disease occurs more often among family members compared with the general population, the next step is to determine the relative roles of nature (genetics) and nurture (especially a common family environment). In psychiatric genetics, such studies have often focussed on monozygotic twins raised apart. It is not feasible, because of sample size, to conduct such studies in MS. Therefore, other family relationships had to be identified which could provide information to tease out the relative roles of genes and environment. Much of the preliminary work in this area for MS has been (and is still being) done through the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) which involves all the Canadian MS clinics [10] and includes data on over 20,000 MS patients and their relatives (for methodological details, see Sadovnick et al.[11]).

A study of MS patients who were adopted and of adopted/adoptive parents, sibs and children of MS patients indicated that the excess of MS among relatives is dependent upon the sharing of genetic material [12], rather than a shared family environment. However, anyone who follows the MS literature is aware that it has often been characterized by lack of replication and consensus. Therefore, the CCPGSMS was designed to allow replicative studies in different samples. With respect to the results of the ‘adoption’ study, a replication study was done on a second sample [13] consisting of full sibs (who share 50% of their genetic material with the MS patient) and half-sibs (who share 25% of their genetic material with the MS patient) of MS patients attending Canadian clinics. The half-sib design compares favorably to adoption and twin studies as a means of detecting a genetic (single-locus or multifactorial) component to familial aggregation. Results of the half-sib study confirmed the findings of the adoption study, i.e. that the familial aggregation of MS appears to be due to the genetic sharing rather than common family environment (see Table 1).

In summary, genetic epidemiological studies have shown that while MS in general results from the interaction of genetic and non-genetic factors, the excess of MS in biological relatives results from the sharing of genetic material (see Table 1). Factors such as age of MS onset in affected family members and whether one parent has MS can also influence the risk among sibs [14]. This information is relevant to genetic counseling for MS [15] as well as molecular genetic studies.

### Table 1
Comparison of age-adjusted lifetime risks by relationship to the person with MS-data for a Northern European population living in a temperate climate

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age-adjusted lifetime risk (%)</th>
<th>Relative risk compared with general population</th>
<th>% Gene sharing (i.e. genes identical by descent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>3–5</td>
<td>15–25</td>
<td>50</td>
</tr>
<tr>
<td>Dizygotic twin</td>
<td>3–5</td>
<td>15–25</td>
<td>50</td>
</tr>
<tr>
<td>Monozygotic twin</td>
<td>38</td>
<td>190</td>
<td>100</td>
</tr>
<tr>
<td>‘Adopted’ first-degree relative</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Half-sib</td>
<td>1.3</td>
<td>6.5</td>
<td>25</td>
</tr>
<tr>
<td>Offspring of conjugal MS</td>
<td>29.5</td>
<td>147.5</td>
<td>50*</td>
</tr>
</tbody>
</table>

* The child shares 50% of the genetic material with the affected mother and 50% of the genetic material with the affected father (table adapted from [15]).

3. Molecular genetic studies: candidate genes

Once genetic factors have been identified to have a role in the etiology of a disease, the search begins in earnest for any candidate gene(s). The only consistently positive finding in this search has been for the major histocompatibility complex (MHC) located on chromosome 6p21. Allelic association of MS to the HLA class II haplotype Dw2 was first reported by Jersild [3,16] and has been reported in many ethnically distinct populations such as Northern Europeans, Ashkenazi Jews and African-Americans. Recent data suggest that the association of MS with HLA-DRB1*15 may in fact be due to linkage disequilibrium with a nearby locus and/or the presence of disease-influencing allele(s) in DRB1*15-negative haplotypes [17]. For more details on candidate genes suspected to have a role in the etiology of MS, see [18–21].
4. Molecular genetic studies: MS genome screens

Results of three genome screens [22–24] were reported in the same 1996 issue of *Nature Genetics*. Each of these screens typed a set of microsatellite markers covering the genome with an average separation of 10–15 cm. Data were collected for affected and unaffected informative individuals from families with affected sibling pairs and/or other relatives with MS. There were, however, differences among the screens in analytical methodology and the format in which results were presented for publication. In genome screens, results are dependent upon the specific genetic markers used. Selection of markers often varies among research teams. Only 43 markers were common to all three screens and each research group used a large number of study-specific markers. Results of a meta-analysis [25] are shown in Table 2. A second-stage genome screen of the Canadian families has recently been completed [26]. Markers at 5p14 and 17q22 were analysed in 333 sibling pairs. The resultant LOD scores were 2.27 and 1.14, respectively. Significance (P = 0.0015) was found in D17S789 at 17q22.

The results from this second stage analysis highlight the problems of searching for genes believed to have only mild-to-moderate effects on disease susceptibility (as suspected in many common, complex diseases including MS), although large effects of specific loci may be seen in individual families [26].

5. Relevance of genetic studies to the treatment and management of MS

While much remains to be resolved about the genetics of MS, it is unlikely that a single gene with a major effect will be identified. Genetic/etiologic heterogeneity has not been ruled out. There are, however, practical applications of the current results from ongoing genetic studies. Persons with MS are increasingly asking about risks for other family members (e.g. children, sibs) to develop the disease. In addition, asymptomatic relatives of persons with MS are also concerned about their own risk to develop the disease in the future. It is now clear that genetic counseling information should be based on individual family structure, i.e. taking into account family-specific factors such as age of MS onset for affected relatives, twin status and whether one or even both parent has MS. A practical guide for genetic counseling for neurologists who are asked about familial risks for MS has been published [15].

It is possible to identify certain groups of asymptomatic relatives of MS patients who are at a higher risk to develop MS. Given the anticipated complexity associated with the genetics of MS as well as problems in the interpretation of laboratory results such as MRI in the clinically asymptomatic individual, it is unlikely that predictive testing will be an option for MS in the very near future. However, it is possible that as MS therapies improve and become more innocuous, asymptomatic individuals with a relatively high risk of developing clinical disease may be given the option of prophylactic treatment. At present, genetic epidemiological studies have identified high risk groups to include monozygotic co-twins of MS patients [8,9], offspring of conjugal MS matings (i.e. when both parents have MS) [27,28] and sisters of MS patients who have an early onset of the disease and who also have one parent affected with MS [14].

A final reminder about the practical applications of the results from genetic studies is that genetic counseling [15] must often address the effect of possible teratogenic agents on a developing fetus. The majority of MS patients have the disease onset during their reproductive years and women develop the disease about twice as often as men. The practicing neurologist must weigh the pros and cons of current therapies against potential teratogenic effects on developing fetuses when young women with MS are contemplating pregnancies. Information about effect of MS on reproduction and of reproduction on MS, has been sporadic and often contradictory. A recent critical literature review pertaining to MS and reproduction has allowed for the development of a comprehensive, up-to-date reproductive counseling guide for individuals with MS who are planning a pregnancy or are already pregnant [29,30]. Pregnancy is not contraindicated for individuals with MS.

Table 2
Peaks with NPL scores of more than 2.0 [25]

<table>
<thead>
<tr>
<th>Region</th>
<th>NPL (all)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>17q11</td>
<td>2.58</td>
<td>0.005</td>
</tr>
<tr>
<td>6p21</td>
<td>2.47</td>
<td>0.007</td>
</tr>
<tr>
<td>5q11</td>
<td>2.37</td>
<td>0.009</td>
</tr>
<tr>
<td>17q22</td>
<td>2.30</td>
<td>0.011</td>
</tr>
<tr>
<td>16p13</td>
<td>2.26</td>
<td>0.012</td>
</tr>
<tr>
<td>3p21</td>
<td>2.14</td>
<td>0.016</td>
</tr>
<tr>
<td>12p13</td>
<td>2.10</td>
<td>0.018</td>
</tr>
<tr>
<td>6qtel</td>
<td>2.01</td>
<td>0.020</td>
</tr>
</tbody>
</table>

* The values quoted are the exact nominal P values calculated by Genehunter [25].

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References

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