No evidence for the involvement of interleukin 2 or the immunoglobulin heavy chain gene cluster in determining genetic susceptibility to multiple sclerosis

Author
Feakes, R, Sawcer, S, Smillie, B, Chataway, J, Broadley, Simon, Compston, D Alastair S

Published
2000

Journal Title
Journal of Neurology, Neurosurgery and Psychiatry

DOI
https://doi.org/10.1136/jnnp.68.5.679

Copyright Statement
Copyright remains with the author[s] 2000. The attached file is reproduced here in accordance with the copyright policy of the publisher. For information about this journal please refer to the journal’s website or contact the author[s]

Downloaded from
http://hdl.handle.net/10072/55066
The chromosome 14 markers are listed in map order. Each microsatellite was amplified by PCR from genomic DNA with fluorescent labelling of the forward meet the Poser criteria, 95% having clinically definite, category A or B, disease.

In the case of the immunoglobulin heavy chain gene cluster, we investigated its role as a susceptibility gene. The immunoglobulin heavy chain gene cluster is another highly promising candidate. Here we report the investigation of two clusters encoded towards the telomere of chromosome 14q26. To investigate its role as a susceptibility candidate, we typed a microsatellite marker in 502 families.

The results suggest that neither of the tested candidates has any major effect in determining genetic susceptibility to multiple sclerosis. However, in considering these data it is important to remember that the negative results could represent a type II error as, even with the large numbers of simplex families used, the power of this type of candidate gene study is limited when the effects attributable to the susceptibility genes are modest. A further possibility is that the available evidence for linkage disequilibrium is observed only in regions where there is no significant linkage disequilibrium observed in regions where the negative results are genuine but unexplained by the available data suggesting that alternative candidates from these regions are responsible for the observed linkage disequilibrium.

We thank J Deans and M Fraser for help with the collection of samples and the members of the Association of British Neurologists for notifying families. Financial support was provided by the Wellcome Trust.

We favour this explanation with the available data suggesting that alternative candidates from these regions are responsible for the observed linkage disequilibrium.

**Table 1 Transmission disequilibrium testing results**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Het</th>
<th>χ²</th>
<th>df</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2</td>
<td>0.89</td>
<td>7.31</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>TCF7</td>
<td>0.73</td>
<td>0.08</td>
<td>2</td>
<td>0.96</td>
</tr>
<tr>
<td>D14S1419</td>
<td>0.56</td>
<td>2.31</td>
<td>3</td>
<td>0.51</td>
</tr>
<tr>
<td>D14S1420</td>
<td>0.67</td>
<td>0.74</td>
<td>2</td>
<td>0.69</td>
</tr>
<tr>
<td>D14S826</td>
<td>0.74</td>
<td>1.74</td>
<td>4</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Each microsatellite was amplified by PCR from genomic DNA with fluorescent labelling of the forward primer and genotyped using the Applied Biosystems GENESCAN-GENTYPER system (primers as shown in table). TDT was performed using the TRANSMIT program version 1.1, considering both the single allele and with a frequency of greater than 10% (corresponding to the number of degrees of freedom (df) in the table). The chromosome 14 markers are listed in map order.

The families were recruited from throughout the United Kingdom. All are white and the affected offspring meet the Poser criteria, 95% having clinically definite, category A or B, disease.

No evidence for the involvement of interleukin 2 or the immunoglobulin heavy chain gene cluster in determining genetic susceptibility to multiple sclerosis

Here we report the investigation of two promising candidate multiple sclerosis susceptibility genes. Each is biologically plausible, having a function suggesting possible involvement in the pathogenesis of the disease and positional, having existing linkage evidence supporting its candidacy. The two differ, however, in the origin of the supporting linkage evidence. This comes mainly from the analysis of animal models in the case of interleukin 2 (IL-2) and from human studies in the case of the immunoglobulin heavy chain gene cluster.

Interleukin 2 is a cytokine intimately involved with both the function and regulation of the immune system. It has both proinflammatory and anti-inflammatory actions, promoting T cell proliferation during cell mediated immune response and, conversely, being crucial both for the development and maintenance of self tolerance. Genetic analysis of experimental autoimmune encephalomyelitis (EAE) provides strong evidence supporting the candidacy of IL-2 as a susceptibility gene.

The immunoglobulin heavy chain gene cluster is another highly promising candidate. Plasma cells and B lymphocytes are readily detected in areas of acute demyelination and the occurrence of oligoclonal immunoglobulin bands in the cerebrospinal fluid of affected individuals is a distinctive feature of the disease. Moreover, the cluster is encoded towards the telomere of chromosome 14q where linkage evidence from the United Kingdom sibling pair families is at its strongest (lod score 3.0).

The gene for IL-2 is encoded on chromosome 4q26. To investigate its role as a susceptibility factor in multiple sclerosis, we typed a closely encoded microsatellite marker in 502 trio families (both parents and a single affected offspring). Transmission disequilibrium testing (TDT) of these data disclosed no significant evidence for linkage disequilibrium (table). The expression of IL-2 is under the control of transcription factor 8 (TCF8), the gene for which is encoded on chromosome 10p11. Because variation in IL-2 expression could contribute to susceptibility of multiple sclerosis, we also typed a microsatellite encoded close to the TCF8 gene in the same 502 families. Again, the TDT results (table) were negative.

We typed three microsatellite markers encoded within the immunoglobulin heavy chain gene cluster in 460 simplex families. Once again TDT failed to show evidence for linkage disequilibrium (table) at any of these markers. As the markers are encoded within a 200 kb region, we also subjected them to multipoint TDT analysis but no haplotypes showing significant transmission distortion were found.

These results suggest that neither of the tested candidates has any major effect in determining genetic susceptibility to multiple sclerosis. However, in considering these data it is important to remember that the negative results could represent a type II error as, even with the large numbers of simplex families used, the power of this type of candidate gene study is limited when the effects attributable to the susceptibility genes are modest. A further possibility is that the available evidence for linkage disequilibrium is observed only in regions where there is no significant linkage disequilibrium observed in these regions. The lod scores observed in the immunoglobulin heavy chain gene cluster region is significantly short of the 5% genomewide significance threshold suggested by Lander and Kruglyak (lod score=4.0). A third possibility is that the linkages are genuine but unrelated to the candidates we have tested. We favour this explanation with the available data suggesting that alternative candidates from these regions are responsible for the observed linkage disequilibrium.

We thank J Deans and M Fraser for help with the collection of samples and the members of the Association of British Neurologists for notifying families. Financial support was provided by the Multiple Sclerosis Society of Great Britain and Northern Ireland, the Medical Research Council, and the Wellcome Trust.