Genetic linkage studies with neurofibromatosis: the question of heterogeneity


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DNA linkage analysis in Von Recklinghausen neurofibromatosis


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SUMMARY We have used DNA linkage analysis in 11 families with Von Recklinghausen neurofibromatosis (VRNF) in order to search for the chromosomal localisation of the defective gene causing this serious neurological disorder. Three groups of polymorphic DNA markers were used: (1) markers for chromosome 22, because of possible allelic genetic heterogeneity between VRNF and bilateral acoustic neurofibromatosis; (2) markers near the centromere of chromosome 4, since there was preliminary evidence for linkage between the VRNF gene and Gc; and (3) oncogenes and growth factors as possible candidate genes for VRNF. Our data exclude close linkage between any of these markers and the gene for VRNF.

DNA linkage analysis was performed in 11 families with Von Recklinghausen neurofibromatosis (VRNF) according to diagnostic criteria which are in agreement with those recently established by NIH.1 Seven of these families have been described previously,2 and the other four families are among those described by Upadhyaya et al in this issue. Blood samples from 161 subjects were collected, comprising 80 samples from affected persons and 79 potentially informative meioses.

Lymphocytes were isolated from these blood samples and transformed into permanent lymphoblastoid cell lines by Epstein-Barr virus.3 DNA was isolated and digested with appropriate restriction enzymes. The resulting DNA fragments were separated according to their molecular weights by gel electrophoresis, transferred to nylon membrane, and hybridised to radiolabelled DNA probes which were known to reveal restriction fragment length polymorphisms (RFLPs) in human genomic DNA.3 DNA linkage analysis was performed by use of the linkage programme LIPEX, assuming a penetrance of the defect of 95%.

As shown in the table, three groups of polymorphic DNA markers were used for linkage analysis. (1) Markers for chromosome 22, since acoustic neuromas and meningiomas from patients with bilateral acoustic neurofibromatosis show highly specific deletions on this autosome, suggesting that the gene causing bilateral acoustic neurofibromatosis is located on chromosome 22.4,5 Furthermore, Krone and Hogemann6 reported in a recent cytogenetic study that cultured peripheral neurofibromas from patients with VRNF were associated with various chromosomal aberrations, the most consistent of which was monosomy for chromosome 22. (2) Markers near the centromere of chromosome 4 (ALB, D4S1, and D4S35), since there was preliminary evidence for linkage between Gc on chromosome 4 and VRNF.2 (3) Oncogenes, growth factors, and their receptors as possible candidate genes for VRNF, a disease which is associated with tumour formation. However, the linkage data presented in the table exclude close linkage between any of these DNA markers and the gene for VRNF.

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TABLE

Lod scores for linkage between DNA loci and Von Recklinghausen neurofibromatosis.

<table>
<thead>
<tr>
<th>DNA marker</th>
<th>Chromosomal localisation</th>
<th>0 (recombination fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-00</td>
</tr>
<tr>
<td>NGFB</td>
<td>1p22-1</td>
<td>-∞</td>
</tr>
<tr>
<td>RAF2</td>
<td>4p16-r→p15</td>
<td>-∞</td>
</tr>
<tr>
<td>ALB</td>
<td>4q11-1→q13</td>
<td>-2-50</td>
</tr>
<tr>
<td>D4S1</td>
<td>4p15-1→q11</td>
<td>-3-70</td>
</tr>
<tr>
<td>D4S35</td>
<td>4p15-1→q12</td>
<td>-15-35</td>
</tr>
<tr>
<td>ABL</td>
<td>9p34</td>
<td>-∞</td>
</tr>
<tr>
<td>HRA51</td>
<td>11p15</td>
<td>-∞</td>
</tr>
<tr>
<td>KRAS2</td>
<td>12p12</td>
<td>-∞</td>
</tr>
<tr>
<td>IGF1</td>
<td>12q22-→q24-1</td>
<td>-∞</td>
</tr>
<tr>
<td>D2S59</td>
<td>22q11</td>
<td>-∞</td>
</tr>
<tr>
<td>D2S81</td>
<td>22q11-2→q13</td>
<td>-∞</td>
</tr>
<tr>
<td>SIS</td>
<td>22q12;3-4→q13-1</td>
<td>-∞</td>
</tr>
</tbody>
</table>

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(See Note added in proof on p 538.)

Linkage studies in peripheral neurofibromatosis

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SUMMARY Peripheral neurofibromatosis (NF) is one of the most common major genetic disorders in man. Its chromosomal location is unknown and questions regarding such factors as genetic heterogeneity remain unanswered. We have ascertained and sampled several large multi-generation families for linkage studies including one family of 66 subjects, 28 of whom were affected with NF. Recombinant DNA studies of several restriction fragment length
DNA linkage analysis in Von Recklinghausen neurofibromatosis.


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