Discussion

The possibility that NF-I is linked to markers on chromosome 4q appears to have been excluded by the data in Table 2, a conclusion consistent with the findings of other investigators. In addition, the genes for TGFA, EGF, GRL, and EGFR, which may be considered 'candidate genes' for NF-I, show no evidence of close linkage. Eleven other loci selected on the basis of convenience also show no evidence of linkage.

References


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Linkage analysis of British and Indian families with Von Recklinghausen neurofibromatosis

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SUMMARY Linkage analysis has been undertaken in two British and three South African Indian families with Von Recklinghausen neurofibromatosis. Eleven polymorphic DNA probes were studied, including both random DNA sequences and candidate oncogenes. Although no evidence for linkage of these probes to the disease was detected, substantial exclusion regions were established on six of the chromosomes studied.

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Von Recklinghausen neurofibromatosis (VRNF) is a relatively common autosomal dominant disorder characterised by café au lait spots, cutaneous neurofibromas, and an increased risk of central nervous system tumours. The pathogenesis of the disorder is unknown and no laboratory diagnostic test is available. Several genetic linkage studies have been undertaken in order to map the locus of the VRNF gene, but none of these has detected a significant linkage between a marker and the disorder. We have therefore tested a further 11 polymorphic DNA markers as part of the international effort to locate the affected gene.

Materials and methods

Families were ascertained through the British Neurofibromatosis Patients' Association, LINK, and the records of the Department of Human Genetics, University of Cape Town Medical School. The criteria for the diagnosis of VRNF were as follows. (1) In adults, six or more café au lait spots >1.5 cm in diameter and multiple cutaneous neurofibromas. (2) In children, an affected parent and six or more café au lait spots >1.5 cm in diameter.

All subjects included in the linkage analysis were more than five years old. Blood specimens were obtained from two British families and three South African families of Indian descent. A total of 73 subjects was sampled, which included 37 affected subjects and 62 potentially informative meioses. DNA isolation, blotting, and hybridisation were performed as described previously. The probes used were as follows: seven locus specific minisatellite sequences (unpublished data), the hypervariable region 3' to the α globin genes, the erb A2 and sis oncogenes, and 22cl-18, which is a random sequence on chromosome 22.

Likelihood computations were carried out using a modification of the LINKAGE programme. The VRNF gene was assumed to have a population frequency of $2 \times 10^{-4}$ and a penetrance of 100%. Rapid computation of lod scores for the minisatellite sequences, which have multiple alleles, was facilitated by recoding the genotypes of some subjects so that at most four alleles were used.

Results and discussion

The lod scores at recombination fractions from 0 to 4 are shown in the table. No evidence for linkage of any of the probes tested to the VRNF gene was obtained. However, use of the highly polymorphic minisatellite probes has established large regions of exclusion on chromosomes 1, 5, 6, 7, 11, and 12. Assuming that the exclusions do not overlap and that none of the probes is located near the end of a chromosome, a total of 236 cM (approximately 8% of the human genome) has been excluded for VRNF at a lod score of -2 or less. The data also appear to exclude the sis and erb A2 oncogenes as candidate genes for VRNF. Future work will concentrate on the use of probes with high frequency restriction fragment length polymorphisms from regions of the genome where large exclusions for the VRNF gene have not been reported. The exclusion map published in this issue will facilitate the search.

We would like to thank Margaret Ponder for assistance in obtaining the family material, D Higgs for the hybridisations with the α globin gene HVR probe, and M Ormerod for advice on a linkage computer programme. We also thank P Middleton, A Hall, and C Buys for the erb A2, sis, and 22cl-18 probes. This work was supported by grants from the Cancer Research Campaign, the Medical Research Council, and ‘LINK’, the neurofibromatosis associa-

<table>
<thead>
<tr>
<th>Gene</th>
<th>Probe</th>
<th>Chrom</th>
<th>Z at recombination fraction</th>
<th>Z max</th>
<th>Exclusion θ at Z = -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1S7</td>
<td>λMS1</td>
<td>1p</td>
<td>-x</td>
<td>-20.38</td>
<td>0.05</td>
</tr>
<tr>
<td>D1S8</td>
<td>λMS2</td>
<td>1q</td>
<td>-x</td>
<td>-13.79</td>
<td>0.00</td>
</tr>
<tr>
<td>D5S43</td>
<td>λMS8</td>
<td>5</td>
<td>-x</td>
<td>-32.19</td>
<td>0.00</td>
</tr>
<tr>
<td>D6*</td>
<td>λMS9</td>
<td>6</td>
<td>-x</td>
<td>-26.78</td>
<td>0.00</td>
</tr>
<tr>
<td>D7S21</td>
<td>λMS11</td>
<td>7pter-q22</td>
<td>-x</td>
<td>-26.18</td>
<td>0.00</td>
</tr>
<tr>
<td>D11*</td>
<td>pMS51</td>
<td>11p14-qter</td>
<td>-x</td>
<td>-14.09</td>
<td>0.00</td>
</tr>
<tr>
<td>D12S11</td>
<td>λMS42</td>
<td>12</td>
<td>-x</td>
<td>-26.18</td>
<td>0.00</td>
</tr>
<tr>
<td>HRA</td>
<td>pChTIVR.64</td>
<td>16p13</td>
<td>-x</td>
<td>-4.20</td>
<td>0.00</td>
</tr>
<tr>
<td>ERB A2</td>
<td>pHEA2</td>
<td>17q11</td>
<td>-x</td>
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<td>0.00</td>
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<tr>
<td>SIS</td>
<td>V-SIS</td>
<td>22q12→13</td>
<td>-x</td>
<td>-2.40</td>
<td>0.00</td>
</tr>
<tr>
<td>D22S10</td>
<td>22cl-18</td>
<td>22</td>
<td>-x</td>
<td>-2.10</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*These minisatellite probes have not yet been assigned HGM symbols. The regional assignments of λMS1 and λMS2 are provisional.

Chrom=chromosomal localisation.

TABLE Lod scores for linkage between VRNF and 11 polymorphic DNA probes.
Linkage analysis of neurofibromatosis

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Summary Linkage analysis of neurofibromatosis was performed using genes on chromosomes 1, 8, 11, and 12. No linkage was found between NF and C-myc, AT 3, IGF-1, PTH, and gamma globin genes. Evidence for linkage was found between C-ets 1, on the long arm of chromosome 11 and NF in two families with a lod score of 1.88 at θ=0. More families are being studied to confirm this linkage.

Neurofibromatosis (NF) is one of the common autosomal dominant neurological disorders with a frequency of approximately 1 in 3000. The disease is mainly characterised by café au lait spots and neurofibromas. These patients have an unusually high frequency of malignancy compared to the normal population. The intriguing question is, what gene do they carry that predisposes them to malignancy? In order to localise the gene for NF, linkage analysis using DNA markers was performed.

Three multi-generation families shown in table 1 were used.

Oncogene C-myc, insulin like growth factor-1, antithrombin-3, parathyroid hormone, and gamma globin genes were not linked to neurofibromatosis in our families. The lod scores are shown in table 2.

We found a positive lod score of 1.88 with oncogene C-ets 1 in two informative families (no recombinants observed in six informative meioses). These data provide suggestive evidence that the NF

References


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