No evidence of genetic heterogeneity in dominant optic atrophy

Dominique Bonneau, Eric Souied, Sylvie Gerber, Jean-Michel Rozet, Esther D’Haens, Hubert Journel, Ghislaine Plessis, Jean Weissenbach, Arnold Munnich, Josseline Kaplan

Abstract
Autosomal dominant optic atrophy (OPA, MIM 165500) is an eye disease causing a variable reduction of visual acuity with an insidious onset in the first six years of life. It is associated with a central scotoma and an acquired blue-yellow dyschromatopsia. A gene for dominant optic atrophy (OPA1) has recently been mapped to chromosome 3q in three large Danish pedigrees. Here, we confirm the mapping of OPA1 to chromosome 3q28-qter by showing close linkage of the disease locus to three recently reported microsatellite DNA markers in the interval defined by loci D3S1314 and D3S1265 in four French families (Zmax = 5.13 at θ = 0 for probe AFM 308yfl at locus D3S1601). Multipoint analysis supports the mapping of the disease gene to the genetic interval defined by loci D3S1314 and D3S1265. The present study provides three new markers closely linked to the disease gene for future genetic studies in OPA.

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Autosomal dominant optic atrophy (OPA, MIM 165500) and mitochondrialy inherited Leber’s hereditary optic neuropathy (LHON) represent the commonest forms of inherited, uncomplicated optic atrophy. Each disease has an incidence of 1/50 000.1 OPA was originally described by Kjer2 in Danish pedigrees and later by Smith,3 Kline and Glaser,4 Hoyt,5 and Elliott.6 The disease usually starts in the first six years of life with a progressive reduction of visual acuity. The visual prognosis is relatively good with stable or slowly progressive visual loss but impairment can vary considerably among affected relatives.6 An acquired blue-yellow dyschromatopsia with a central, paracentral, or centrocecal scotoma and an inversion of the peripheral field, more confined to blue than to red test objects, are present in most cases. Appearance of the optic nerve ranges from mild temporal pallor to complete atrophy.

Recently, a gene responsible for OPA has been mapped to the distal long arm of chromosome 3 (OPA1, 3q28-qter) by linkage analysis in three large Danish families.7 Here, we confirm the localisation of OPA1 to chromosome 3q in four unrelated French families and provide evidence for genetic homogeneity of this condition.

Materials and methods
Eighteen affected subjects and 14 healthy relatives belonging to four unrelated families of

Figure 1 Pedigrees of families with OPA.
Pairwise lod scores between OPA1 and five polymorphic DNA markers on chromosome 3q

<table>
<thead>
<tr>
<th>Locus</th>
<th>0</th>
<th>0-01</th>
<th>0-05</th>
<th>0-10</th>
<th>0-20</th>
<th>0-30</th>
<th>Zmax</th>
<th>lmax</th>
</tr>
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<tr>
<td>D3S1314</td>
<td>-0.82</td>
<td>1.52</td>
<td>1.96</td>
<td>1.91</td>
<td>1.50</td>
<td>0.94</td>
<td>1.98</td>
<td>0.06</td>
</tr>
<tr>
<td>D3S2747</td>
<td>4.54</td>
<td>4.45</td>
<td>4.07</td>
<td>3.60</td>
<td>2.60</td>
<td>1.58</td>
<td>4.54</td>
<td>0.00</td>
</tr>
<tr>
<td>D3S1601</td>
<td>5.13</td>
<td>5.03</td>
<td>4.60</td>
<td>4.07</td>
<td>2.99</td>
<td>1.94</td>
<td>5.13</td>
<td>0.00</td>
</tr>
<tr>
<td>D3S2748</td>
<td>2.22</td>
<td>2.19</td>
<td>2.03</td>
<td>1.81</td>
<td>1.29</td>
<td>0.72</td>
<td>2.22</td>
<td>0.00</td>
</tr>
<tr>
<td>D3S1265</td>
<td>-∞</td>
<td>-3.56</td>
<td>-1.40</td>
<td>-0.68</td>
<td>-0.14</td>
<td>0.00</td>
<td>0.02</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Results**

Linkage analyses using microsatellite DNA markers of chromosome 3 showed a maximum pairwise lod score for marker AFM308yf1 at the D3S1601 locus (Zmax = 5.13 at 0.00, table). The location score method was used to estimate the position of the OPA1 gene. In this procedure, the map of the marker loci is fixed and the position of the disease locus is varied throughout the map. The order 3pter-D3S1314-(0.02)-D3S2747-(0.03)-D3S1601-(0.02)-D3S2748-(0.06)-D3S1265-3qter (with recombination estimates in parentheses) has been established by analysis of Généthon markers in CEPH reference families. The maximum likelihood estimate of OPA1 was obtained in the interval defined by loci D3S1314 and D3S1265 (location score in log base 10 = 5.19, fig 2). A recombination event at locus D3S1265 was observed in one affected member of family 1 and at locus D3S1314 in two affected subjects in family 3 (data not shown). No linkage disequilibrium between OPA and one particular allele was observed with the markers tested.

**Discussion**

We report the mapping of a gene for dominant optic atrophy to the long arm of chromosome 3 in four pedigrees of French ancestry. This study gives support to the recent localisation of OPA1 to chromosome 3q28-qter in Danish families. Eiberg et al7 showed that a disease gene is located in the 10 cM genetic interval defined by loci D3S1314 and D3S1265. The present study gives support to the localisation of the disease gene in this interval and provides no evidence of genetic heterogeneity of OPA, as all families hitherto tested were consistent with linkage to chromosome 3q.

In the last few years, several protein coding
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genes have been mapped to 3q28-pter, including tracheobronchial mucin 4 (MUC4),12 melanoma associated antigen p97 (MIF2),13 and A2HS-glycoprotein (AHSG).14 None of them can be regarded as candidate genes for OPA1. Continuing studies will help to narrow the genetic interval encompassing the disease gene and hopefully to identify the disease causing gene.

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