Stargardt’s disease is not allelic to the genes for neuronal ceroid lipofuscinoses

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Abstract
Stargardt’s disease is an autosomal recessive condition characterised by a rapid and bilateral loss of central vision at around 7 to 12 years, with typical changes in the macular and perimacular region. It is one of the most frequent causes of macular degeneration in childhood and accounts for 7% of all retinal dystrophies. Considering that inclusions of lipofuscin-like substances are observed in retinal pigmentary cells of patients with Stargardt’s disease on one hand, and that the early symptoms of neuronal ceroid lipofuscinosis (CLN3) are suggestive of Stargardt’s disease on the other hand (age of loss of visual acuity, appearance of the fundus), we decided to test allelism of Stargardt’s disease with the infantile (CLN1) and juvenile forms of neuronal ceroid lipofuscinosis (CLN3), which map to chromosomes 1p32 and 16p12-p11 respectively. Using highly informative microsatellite DNA markers in eight multiplex families, we were able to exclude Stargardt’s disease from the vicinity of the CLN1 and CLN3 loci. These results strongly reject the hypothesis of allelism of Stargardt’s disease with the neuronal forms of ceroid lipofuscinosis.

Results and discussion
Hypervariable microsatellites linked to the CLN1 and CLN3 gene loci on chromosomes

Figure 1 Families with Stargardt’s disease.
**Pairwise lod scores between Stargardt’s disease gene and markers on chromosomes 1p32 and 16p12–16cen**

<table>
<thead>
<tr>
<th>Probe</th>
<th>Locus</th>
<th>0</th>
<th>0.01</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>Zmax</th>
<th>θmax</th>
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</thead>
<tbody>
<tr>
<td>AFM260zg5</td>
<td>D1S255</td>
<td>-x</td>
<td>-10.79</td>
<td>-5.35</td>
<td>-3.20</td>
<td>-1.29</td>
<td>-0.47</td>
<td>-0.11</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>AFM199ye9</td>
<td>D1S232</td>
<td>-x</td>
<td>-7.90</td>
<td>-3.35</td>
<td>-1.68</td>
<td>-0.49</td>
<td>-0.13</td>
<td>-0.04</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>AFM120xd4</td>
<td>D1S209</td>
<td>-x</td>
<td>-4.58</td>
<td>-1.97</td>
<td>-1.00</td>
<td>-0.27</td>
<td>-0.05</td>
<td>-0.01</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>AFM165yb6</td>
<td>D16S410</td>
<td>-x</td>
<td>-14.68</td>
<td>-7.70</td>
<td>-4.21</td>
<td>-0.60</td>
<td>-0.13</td>
<td>0</td>
<td>0.50</td>
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<tr>
<td>AFM049xd2</td>
<td>D16S403</td>
<td>-x</td>
<td>-4.54</td>
<td>-1.41</td>
<td>-0.37</td>
<td>0.21</td>
<td>0.21</td>
<td>0.07</td>
<td>0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>AFM025yg9</td>
<td>D16S403</td>
<td>-x</td>
<td>-12.24</td>
<td>-7.50</td>
<td>-3.03</td>
<td>-0.32</td>
<td>-0.07</td>
<td>0</td>
<td>0.50</td>
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</tr>
<tr>
<td>AFM161xa1</td>
<td>D16S409</td>
<td>-x</td>
<td>-12.19</td>
<td>-5.63</td>
<td>-3.15</td>
<td>-1.16</td>
<td>-0.40</td>
<td>-0.09</td>
<td>0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

1p32 and 16p12 respectively were chosen from the Genethon linkage map on the basis of their informativeness, at an average genetic distance of $\theta = 0.1$ (table). The orders:

1. D1S255
2. AFM260zg5
3. AFM199ye9
4. AFM120xd4
5. AFM165yb6
6. AFM049xd2
7. AFM025yg9
8. AFM161xa1

Recombination fraction $\theta$

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![Figure 2](http://jmg.bmj.com/)  
*Figure 2. Multipoint analysis. (A) Exclusion of the Stargardt’s disease gene from a 64 cM region of chromosome 1p32. Distances between markers were fixed according to the Genethon Data Base. (B) Exclusion of the Stargardt’s disease gene from a 54 cM region of chromosome 16p12–p11. Distances between markers were fixed according to the Genethon Data Base.*

These were previously established by analysis of CEPH reference families (J Weissenbach, personal communication). Genotyping was carried out as previously described and linkage analysis was performed using the MLINK and LINKMAP options of the 5.1 version of the LINKAGE program. Negative lod score values with probes AFM260zg5, AFM199ye9, and AFM120xd4 at loci D1S255, D1S232, and D1S209 were obtained for each family and the combined families, excluding the Stargardt gene from close proximity to the CLN1 gene on chromosome 1p32 (table). Multipoint analysis excluded the Stargardt gene from a large area (64 cM) including the CLN1 locus on the short arm of chromosome 1p (fig 2A). Similarly, negative lod score values were obtained with probes AFM155yb6, AFM049xd2, AFM025yg9, and AFM161xa1 at loci D16S410, D16S403, D16S401, and D16S409 respectively, excluding the disease gene from the vicinity of the CLN3 gene (table, fig 2B).

The present study excludes the Stargardt gene from close proximity to the CLN1 and CLN3 genes in eight informative families and strongly rejects the hypothesis of allelism of Stargardt’s disease with the neuronal forms of ceroid lipofuscinoses.

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