Genetic Heterogeneity of Dominant Optic Atrophy, Kjer Type

Identification of a Second Locus on Chromosome 18q12.2-12.3

John B. Kerrison, MD; Veronique J. Arnould, MD; Juliana M. Ferraz Sallum, MD; M. Reza Vagefi, BA; M. Michael Barmada, PhD; Yingying Li, MD; Danping Zhu, MD; Irene H. Maumenee, MD

Objective: To evaluate a family with autosomal dominant optic atrophy, which has been previously linked to the Kidd blood group.

Design: Clinical evaluation with the assessment of visual acuity, color vision, and optic nerve appearance to determine affection status. Linkage analysis using polymorphic DNA markers.

Results: Visual acuities ranged from 20/20 to 6/200. Although linkage was excluded for chromosome 3q28-29, markers from chromosome 18 in the vicinity of the Kidd locus were linked to the disorder (D18S34 [maximal lod score (lodmax) of 5.38 at recombination fraction (θ) of 0.14], D18S548 [lod max = 7.26, θ = 0.09], D18S861 [lodmax = 5.32, θ = 0.07], and D18S479 [lodmax = 3.28, θ = 0.12]). Multipoint linkage analysis demonstrated lod scores of greater than 3 in an approximately 3-centimorgan region flanked by D18S34 and D18S479, using 98% penetrance and a phenocopy rate of 1/50.

Conclusions: Dominant optic atrophy is genetically heterogeneous, with loci assigned to chromosomes 3q28-29 and 18q12.2-12.3. Dominant optic atrophy linked to 18q shows intrafamilial variation similar to that previously reported in families linked to 3q, with visual acuities ranging from normal to legal blindness. The overall distribution of visual acuities appears more favorable with the 18q phenotype. Both phenotypes appear to have a similar rate of visual decline.

PATIENTS AND METHODS

The clinical features of this family have been reported previously by Elliott et al (family III). Eighty-six members underwent clinical evaluation for the present study to determine their disease status. The clinical evaluation included best-corrected visual acuity, an assessment of color vision with Ishihara plates, and ophthalmoscopic evaluation following dilation, with attention to the optic nerve. Some patients had undergone further testing, including visual fields and fundus photography. Patients with optic nerve pallor were classified as affected in the absence of other explanatory ocular disease.

Specimens of blood were drawn from 71 family members, and informed consent was obtained in accordance with a Johns Hopkins University institutional review board–approved protocol.

Leukocyte DNA was extracted and genotyped with polymerase chain reaction–based microsatellite markers as previously described. Chromosome-specific markers in the regions of interest were obtained from the manufacturer (MapPairs; Research Genetics, Inc, Huntsville, Ala). Two-point linkage analysis was performed using the MLINK and ILINK programs (version 5.1) of the FASTLINK package,23–25 assuming an autosomal dominant model with a gene frequency of 0.0001, no sex difference in recombination rates, a penetrance of 98%, equal allelic frequencies, and phenocopy rates of 0 and 1/50. Multipoint analysis was performed using the VITESSE algorithm.26 Table 1 and Table 2 show marker intervals for 3q and chromosome 18 that were obtained from the location database summary map at http://cedar.genetics.soton.ac.uk (accessed April 1998).29

Snellen lines.21 The scattergram of age vs visual acuity indicates that older persons had worse visual acuities. Longitudinal data are not presented. When the visual acuities from affected persons of this family are compared with those of affected persons from another family we have studied and those of affected persons from 26 previously reported pedigrees, all of whose disorder is linked to band 3q28-29,11,14,16 it appears that the overall visual acuities of this family are better than was available in the past. The family was genotyped with markers from chromosome 3q28-29, the OPA1 locus, followed by markers from chromosome 18, the location of the gene for the Kidd blood group antigen. This study confirms that dominant optic atrophy is genetically heterogeneous.

As observed in other families with dominant optic atrophy, visual acuity in this family varied from 20/20 and a phenocopy rate of 0, linkage was initially observed with marker D18S54 (lodmax = 5.38, θ = 0.14) located at band 18q12.2–21.1. The most closely linked markers were D18S548 (lodmax = 7.26, θ = 0.09) and D18S641 (lodmax = 5.32, θ = 0.07). Changing the phenocopy rate to 0.02 slightly changed the lodmax and optimal θ for each marker by 2-point analysis (Table 2).

Multipoint analysis was performed using 11 markers from chromosome 18—D18S77, D18S47, D18S456, D18S57, D18S468, D18S34, D18S458, D18S641, D18S479, and D18S64. Although penetrance was maintained at 98%, the phenocopy rate varied from 0 to 0.02 (Figure 3). Allowing for phenocopies substantially increased the lod scores between these markers. The lodmax by multipoint analysis peaked between markers D18S641 and D18S479 (lodmax = 6.53). This data set suggests that the gene is located within an approximately 3-centimorgan interval flanked by D18S34 and D18S479.

The increase in the lodmax using a phenocopy rate of 0.02 was due to 2 persons (IV:11 and V:4) who appear to be affected, yet have inherited the normal chromosome haplotype throughout the region (Figure 4). The person designated as IV:11 is a 31-year-old woman with a visual acuity of 20/40, dyschromatopsia, and mild disc pallor in each eye. One of her sons, V:4, was 8 years old and had a visual acuity of 20/60 OD and 20/70 OS and had dyschromatopsia as well as mild disc pallor in each eye.

COMMENT

In a previous study of this family using erythrocyte, serum, and urinary electrophoretic markers, linkage to the Kidd blood group antigen had been suggested. The lod score of 2.0, however, at a recombination fraction of 0.18, failed to reach the accepted threshold of 3.0 for establishing linkage. The development of polymorphic microsatellite markers has permitted the reexamination of this family using a better-defined array of genetic markers than was available in the past. The family was genotyped with markers from chromosome 3q28-29, the OPA1 locus, followed by markers from chromosome 18, the location of the gene for the Kidd blood group antigen. This study confirms that dominant optic atrophy is genetically heterogeneous.

As observed in other families with dominant optic atrophy, visual acuity in this family varied from 20/20

Table 1. Two-Point Linkage Analysis With Markers From the Distal End of 3q*

<table>
<thead>
<tr>
<th>Distance</th>
<th>Marker</th>
<th>Recombination Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>210.22</td>
<td>D3S1601</td>
<td>-21.08</td>
</tr>
<tr>
<td>210.32</td>
<td>D3S3669</td>
<td>-23.83</td>
</tr>
<tr>
<td>212.43</td>
<td>D3S642</td>
<td>-9.47</td>
</tr>
<tr>
<td>212.77</td>
<td>D3S1265</td>
<td>-29.42</td>
</tr>
<tr>
<td>213.12</td>
<td>D3S1272</td>
<td>-27.98</td>
</tr>
</tbody>
</table>

*Marker order and distances were obtained from the location database summary map of Collins et al.29

ARCH OPHTHALMOL/VOL 117, JUNE 1999

©1999 American Medical Association. All rights reserved.
Two persons (III:18 and IV:8) from this family had visual acuities of 20/20, consistent with previous observations\textsuperscript{4,7,11,16,21} that some affected persons may have dyschromatopsia and disc pallor with excellent visual acuity. Whereas the range of visual acuities appears similar, the overall distribution of visual acuities for this family appears to be more favorable in comparison with chromosome 3q28-29–linked families (Table 3).\textsuperscript{11,14,16,21}

Two longitudinal studies\textsuperscript{7,11} have shown slow, progressive vision loss for patients with dominant optic atrophy. In a study of 3 pedigrees linked to the distal end of 3q with a mean follow-up of 14 years, Kjer et al\textsuperscript{11} reported that vision loss progressed in 20 (67%) of 30 patients and tended to be slow, although a few persons had a rapid decline in visual acuity. In a previous study of this family with a mean follow-up of 18 years, Elliott et al\textsuperscript{7} reported that acuity declined in both eyes in 5 (45%) of 11 patients (family III). On reexamination for the present study, older patients had worse vision than younger persons, suggesting that visual acuity deteriorates with age (Figure 2). This may be due to progressive ganglion cell loss from the underlying genetic defect or a phenomenon of aging.

Screening for color vision abnormalities was performed using Ishihara plates. Although these are a commonly used clinical tool, they are not optimal for identifying the acquired blue-yellow defects typical of patients.

### Table 2. Two-Point Linkage Analysis With Markers Spanning Chromosome 18\textsuperscript{*}

<table>
<thead>
<tr>
<th>Distance</th>
<th>Marker</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>0.40</th>
<th>0.00</th>
<th>lod\textsubscript{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.26</td>
<td>D18S877</td>
<td>-24.18</td>
<td>-24.18</td>
<td>-4.35</td>
<td>-2.44</td>
<td>-0.75</td>
<td>-0.04</td>
<td>0.16</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-10.60</td>
<td>-6.74</td>
<td>-3.68</td>
<td>-2.12</td>
<td>-0.65</td>
<td>-0.03</td>
<td>0.16</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>43.15</td>
<td>D18S47</td>
<td>-12.48</td>
<td>-1.01</td>
<td>1.05</td>
<td>1.80</td>
<td>2.01</td>
<td>1.59</td>
<td>0.88</td>
<td>0.17</td>
<td>2.04</td>
</tr>
<tr>
<td>43.89</td>
<td>D18S456</td>
<td>-1.85</td>
<td>0.11</td>
<td>1.29</td>
<td>1.74</td>
<td>1.80</td>
<td>1.39</td>
<td>0.76</td>
<td>0.15</td>
<td>1.86</td>
</tr>
<tr>
<td>44.57</td>
<td>D18S57</td>
<td>-16.02</td>
<td>-0.45</td>
<td>3.03</td>
<td>4.23</td>
<td>4.46</td>
<td>3.53</td>
<td>1.89</td>
<td>0.16</td>
<td>4.56</td>
</tr>
<tr>
<td>44.84</td>
<td>D18S468</td>
<td>-21.31</td>
<td>2.22</td>
<td>4.56</td>
<td>5.09</td>
<td>4.66</td>
<td>3.42</td>
<td>1.71</td>
<td>0.11</td>
<td>5.11</td>
</tr>
<tr>
<td>45.28</td>
<td>D18S34</td>
<td>-15.30</td>
<td>1.13</td>
<td>4.32</td>
<td>5.25</td>
<td>5.07</td>
<td>3.80</td>
<td>1.92</td>
<td>0.14</td>
<td>5.38</td>
</tr>
<tr>
<td>45.46</td>
<td>D18S548</td>
<td>-7.34</td>
<td>5.01</td>
<td>6.99</td>
<td>7.25</td>
<td>6.29</td>
<td>4.50</td>
<td>2.21</td>
<td>0.09</td>
<td>7.26</td>
</tr>
<tr>
<td>45.50</td>
<td>D18S861</td>
<td>-0.84</td>
<td>4.38</td>
<td>5.25</td>
<td>5.26</td>
<td>4.41</td>
<td>3.03</td>
<td>1.37</td>
<td>0.07</td>
<td>5.32</td>
</tr>
<tr>
<td>48.57</td>
<td>D18S479</td>
<td>-5.00</td>
<td>0.79</td>
<td>2.73</td>
<td>3.23</td>
<td>3.02</td>
<td>2.16</td>
<td>0.96</td>
<td>0.12</td>
<td>3.28</td>
</tr>
<tr>
<td>51.28</td>
<td>D18S51</td>
<td>-15.50</td>
<td>-5.47</td>
<td>-1.31</td>
<td>0.18</td>
<td>0.96</td>
<td>0.80</td>
<td>0.40</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>60.09</td>
<td>D18S64</td>
<td>-42.13</td>
<td>-7.62</td>
<td>-1.89</td>
<td>0.32</td>
<td>1.65</td>
<td>1.46</td>
<td>0.60</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Iterated lod scores are included when the maximum lod score (lod\textsubscript{max}) is more than 2.0. Marker order and distances were obtained from the location database summary map of Collins et al.\textsuperscript{29} For each marker, lod scores obtained with a phenocopy rate of 0 are in the first row, and lod scores obtained with a phenocopy rate of 0.02 are in the second row. \(\approx\) indicates infinity; ellipses, markers are not linked.

### Figure 1. Pedigree of family from western Maryland with autosomal dominant optic atrophy previously linked to the Kidd blood group locus and restudied with polymorphic DNA from chromosomes 3q28-29 and chromosome 18. Solid circles (females) and squares (males) represent affected persons. Deceased persons are indicated with a slash. Arrow indicates proband.
with dominant optic atrophy. Two persons (III:18 and V:8) who had good visual acuity and mild disc pallor correctly identified all Ishihara plates shown to them.

Dominant optic atrophy is not completely penetrant. An estimated 2% of persons may carry a haplotype associated with the disease, have affected offspring, and yet manifest no signs of optic neuropathy. No skipped generations occurred in this family (Figure 1).

Linkage to chromosome 3q was excluded in this family, confirming that dominant optic atrophy is genetically heterogeneous. Furthermore, linkage with markers from chromosome 18q12.2-12.3 was established, constituting a second locus for dominant optic atrophy. Despite evidence of linkage, investigation of this region has failed to identify a marker. Similar results were obtained when linkage analysis was performed using an affected-only model because of the possibility of reduced penetrance. Our working hypothesis is that persons IV:11 and V:4 represent phenocopies. They meet criteria to be classified as affected, yet do not share the disease haplotype. Multipoint analysis, based on our data set, suggests that the gene is located in an approximately 3-centimorgan interval between D18S34 and D18S479.

Table 3. Visual Acuities From Affected Persons of This Family, Another Family, and 26 Previously Reported Pedigrees

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chromosome 18q12.2-12.3 Pedigree (n = 30)†</th>
<th>Combined 3q28-29 Pedigrees (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20/40</td>
<td>13 (43.3) 28 (13.8)</td>
<td></td>
</tr>
<tr>
<td>20/50-20/120</td>
<td>10 (33.3) 87 (42.9)</td>
<td></td>
</tr>
<tr>
<td>≥20/200</td>
<td>7 (23.3) 88 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean</td>
<td>39.9</td>
<td>36.6</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) except as otherwise noted. See the "Results" section for a description of the "combined 3q28-29 pedigrees."†χ², for trend = 11.7, P < .001.

Figure 2. Scattergram plot of age vs visual acuity (better eye) for persons with autosomal dominant optic atrophy. Mean visual acuities for affected individuals for ages 20 years and younger, 21 to 40 years, 41 to 60 years, and older than 60 years are plotted at ages 10, 30, 50, and 70 years, respectively.

Figure 3. Multipoint linkage analysis using a penetrance of 98% with a phenocopy rate of 0 and 0.02 demonstrates that the gene in this family resides in an approximately 3-centimorgan region flanked by D18S34 and D18S479. zmax indicates the maximum multipoint lod score.
This is the first dominant optic atrophy pedigree with linkage identified on chromosome 18q.12.2-12.3. More than 30 pedigrees with linkage to chromosome 3q28-29 have been reported, suggesting that most cases are due to OPA1. Seller et al described 9 pedigrees from England, 8 of whom were linked to chromosome 3q28-29. One family showed no evidence of linkage to this locus, supporting the present finding that dominant optic atrophy is genetically heterogeneous. The chromosome 3q28-29 locus (OPA1) appears to be the predominant gene responsible for dominant optic atrophy.

**CONCLUSIONS**

Dominant optic atrophy is genetically heterogeneous, with loci thus far identified on chromosomes 3q and 18q. Dominant optic atrophy linked to 18q in this family shows intrafamilial variation similar to that in previously reported families linked to 3q, with visual acuities ranging from normal to legal blindness. The overall visual acuities were better with this 18q-linked family compared with previously described 3q-linked families. Both phenotypes appear to have a similar rate of visual decline.

Accepted for publication February 8, 1999.

This study was supported in part by the Knights Templar Eye Foundation Inc, Chicago, Ill (Dr Kerrison); the Belgian American Educational Foundation, the Francqui Foundation, the Rotary Foundation, and the Vocational Foundation of Belgium, Brussels (Dr Arnould); Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil (Dr Ferraz Sallum); and a grant from Research to Prevent Blindness Inc, New York, NY, and the Krielle and Walter Edel Funds of the Johns Hopkins Center for Hereditary Eye Diseases (Dr Maumenee).

We thank Susan Vitale, PhD, for statistical consultation. Reprints are not available from the authors.

**REFERENCES**


From the Archives of the ARCHIVES

A look at the past . . .

Bifocal glasses cataract patients. Dr. W. THOMPSON exhibited a pair of bifocal glasses, made by Borsch, where the refraction in the lower half of glasses increased 2 D., by adding a segment of flint glass to the remaining crown glass. The resulting combination is also achromatic.