A third locus for dominant optic atrophy on chromosome 22q


A utosomal dominant optic atrophy (ADOA) is the most common form of autosomal inherited optic neuropathy, with an estimated prevalence of 1:50 000 in most populations, though it can reach 1:10 000 in Denmark. The disease typically presents in childhood with variable bilateral slow visual loss, temporal optic nerve pallor, centrocausal visual field scotomas, and abnormalities of colour vision. In most families, the disease is accounted for by mutations in the OPA1 gene, at the OPA1 locus on chromosome 3q28–q29 (MIM165500). The penetrance of the OPA1 disease is highly variable as well as its age of onset, even within the same family.

Some ADOA families have been shown to exclude linkage to the OPA1 locus. In 1999, the genetic study of a large family whose phenotype was similar to the OPA1 phenotype, allowed the mapping of a second ADOA locus on chromosome 18q12.2–q12.3 (OPA4, MIM605293). To date, no report has confirmed this localisation and the disease gene is still unknown.

Here we report the mapping of a third ADOA locus on chromosome 22q12.1–q13.1 (OPA5) in two unrelated families affected with a OPA1-like phenotype.

METHODS

Patients

Two unrelated multiplex families of French origin affected with autosomal dominant optic atrophy were ascertained through the genetic consultation clinic of the Hôpital des Enfants Malades in Paris (family A and family B, fig 1 A and B, respectively). All members of each family underwent ophthalmological examination including visual acuity measurements, visual field testing, colour vision analysis, ocular pressure measurement, examination of the fundi, and electrophysiological recordings. Blood was collected from all family members and the DNA was purified by phenol-chloroform extraction.

Linkage analysis

Linkage to known ADOA loci was studied in both families. Four markers flanking the OPA1 locus on chromosome 3q28–q29 were chosen from the Genéthon linkage map on the basis of their informativeness—AFM308yf1, AFMa300wa5, AFMb043xe9, and AFM254ve1 at the D3S1601, D3S3590, D3S2748, and D3S1311 loci, respectively. For the OPA4 locus, we selected three markers lying in the genetic interval on chromosome 18q12.2–q12.3 as well as two flanking markers: AFM147y12, AFM191vc7, and AFM284ve1 at the D18S1094, D18S540, and D18S542 loci, respectively; and AFMa224wb1 and AFM295xh1 at the D18S1102 and D18S547 loci.

A 10 cM genome-wide search for the disease causing gene was undertaken in family A using fluorescent oligonucleotides flanking the 382 polymorphic markers of the Genescan Linkage Mapping Set, version II (Perkin Elmer Cetus), under conditions recommended by the manufacturer. Amplified fragments were electrophoresed and analysed on an automatic sequencer (ABI 3100, Applied Biosystems, Foster City, California, USA). Linkage analyses were carried out using M-LINK and LINKMAP of the 5.1 version of the Linkage program. All allele frequencies were available from the CEPH database. The gene frequency was estimated to be 1/1000 and the penetrance of the disease to be 100%.

Screening for mutations in candidate genes

The 14 exons encoding the oxysterol binding protein 2 (OSBP2), the five hypothetical exons of the chromosome 22 open reading frame 3 (C22ORF3), the six exons of the ubiquinol-cytochrome c reductase 7.2 kDa complex subunit 2 gene (HSPC051) were amplified using specific primers designed from intronic sequences close to the intron-exon junctions (not shown, available on request). Amplified products were purified by phenol-chloroform extraction, recovered by ethanol precipitation, and directly sequenced using the Big Dye terminator cycle sequencing kit V3 on a 3100 automated sequencer (ABI Prism, Applied Biosystems).

RESULTS

Clinical evaluation

We report two unrelated multiplex families of French origin affected with ADOA. Although the age of onset of the disease

Abbreviations: ADOA, autosomal dominant optic atrophy

Key points

- Autosomal dominant optic atrophies (ADOA) are by far the most common mendelian cause of primary hereditary optic neuropathy. A major locus has been mapped to chromosome 3q28–q29 and the OPA1 gene identified. The penetrance of the disease accounted for by mutations in this gene is reported to be highly variable. A second locus, OPA4, has been mapped on chromosome 18q12.2–q12.3 in a family whose phenotype was similar to that of OPA1 patients.
- We report the mapping of a third locus of ADOA, OPA5, on chromosome 22q12.1–q13.1 in two unrelated families of French origin. The phenotype of affected patients of the two families was similar to that of patients harbouring OPA1 mutations.
- The OPA5 locus lies in a 10.4 Mb interval flanked by the D22S1148 and D22S283 loci. To date, 73 known genes and as many predicted genes are contained in this interval. Screening of OSBP2, C22ORF3, HSC20 and HSPC051 failed to identify any mutation.
The disease haplotype is f of Barbet, Hakiki, Orssaud, et al. Linkage studies at the OPA1 and OPA4 loci allowed the exclusion of the OPA1 and OPA4 loci while visual evoked potential recordings were moderately impaired, varying from normal to severe dyschromatopsia without axis. Electrophoretic recordings were normal while visual evoked potential recordings were moderately altered in the early stages and severely impaired in the later stages. In both families, the phenotype of affected patients was similar to that of patients harbouring mutations in the OPA1 gene.

**Exclusion of the OPA1 and OPA4 loci**

Linkage studies at the OPA1 and OPA4 loci allowed the exclusion of the two loci in both families (not shown, available on request).

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**Mapping of a third locus for ADOA (OPA5)**

A genome-wide search was undertaken to map the disease gene in family A. All eight affected patients were found to share a common haplotype on chromosome 22q12.1–q13.31 (family A, fig 1A). Obligatory recombination events in the affected individual (1B) and her healthy brother (11) allowed us to define a 10.4 cM genetic interval between the D22S1148 and D22S283 loci (family A, fig 1B).

Linkage to the 22q12.1–q13.31 ADOA locus was sought in family B. Interestingly, all affected patients of this family were found to harbour the same haplotype, inherited from the affected grandfather 12 (family B, fig 1B). No recombination event was found with the markers of the region.

When the two families were taken into account, a maximum lod score of Zmax = 3.75 at 0 = 0 was obtained with the marker AFM0403F9 at the D22S1176 locus (table 1). For this calculation, the penetrance was set at 100% (12 of 12 individuals with a disease haplotype were affected with ADOA).
Candidate genes study

Three known genes—OSBP2, HSC20, and HSPC051—which encode the oxysterol binding protein 2, the J-type co-chaperone HSC20, and the ubiquinol-cytochrome c reductase 7.2 kDa complex, respectively, as well as the hypothetical chromosome 22 open reading frame 3 (C22ORF3), were screened for mutations. No disease causing alteration was found in any of the two families. Only already reported single nucleotide polymorphisms (Human Genome Project working draft at UCSC) were identified in the two families (not shown, available on request).

DISCUSSION

The primary hereditary optic neuropathies comprise a group of disorders in which there is cell death confined to the retinal ganglion cells. Dominant optic atrophies are by far the most common mendelian cause of primary hereditary optic neuropathy;¹ A major locus has been mapped to chromosome 3q28–q29 and the OPA1 gene identified (MIM 165500). A neuropathy.⁹ A major locus has been mapped to chromosome 22q telomeric of the OPA5 genetic interval (MIM 605290), which is centromeric boundary of the OPA5 genetic interval at the D22S283 loci encompasses 10.4 Mb on chromosome 22q 3o f 4. We report here the mapping of a third locus, OPA5, on chromosome 22q13.1 chromosomal region (OPA5) between the disease and the markers of the 22q12.1–q13.1 chromosomal region (OPA5).

Further studies are required to identify the causative ADOA gene in these two families and to delineate the role of this locus.

ELECTRONIC DATABASE INFORMATION


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REFERENCES


Table 1 Two point lod score values for the two families between the disease and the markers of the 22q12.1–q13.1 chromosomal region (OPA5)

<table>
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<th>Locus</th>
<th>Family 1</th>
<th>Family 2</th>
<th>Total</th>
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<tr>
<td>D22S1148</td>
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<td>0.18</td>
<td>0.14</td>
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<td>D22S283</td>
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</table>

Maximum pairwise lod score >3 at 0.00 were obtained at the D22S275, D22S1176, D22S280, and D22S283 loci.


