A third locus for dominant optic atrophy on chromosome 22q


Autosomal 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, centrocaecal visual field scotoma, 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 mutations in the OPA1 gene, at the OPA1 locus on chromosome 3q28–q29 were chosen from the Genethon 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 (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 Genethon 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: AFM1457y2, AFM191vc7, and AFM284ve1 at the D18S1094, D18S540, and D18S472 loci, respectively; and AFM224wb1 and AFM295xh1 at the D18S110 and D18S474 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 Geneset 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 J type co-chaperone HSC20 gene, and the two exons of the ubiquinol-cytochrome c reductase 7.2 kDa complex (HSCPC051) 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...
differed (in the first and the third decades), the phenotype was similar in both families. When examined, the fundus of patients constantly showed optic nerve pallor. Visual acuity decreased slowly, perhaps related to a central scotoma. Colour vision was moderately impaired, varying from normal to blue-yellow dyschromatopsia. After several years of evolution, the patients show a severe dyschromatopsia without axis. Electoretinogram 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).

**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–q13.1 (family A, fig 1A). Obligatory recombination events in the affected individual (III) and her healthy brother (II) allowed us to define a 10.4 cM genetic interval between the D22S1148 and D22S283 loci (family A, fig 1).

Linkage to the 22q12.1–q13.1 ADOA locus was sought in family B. Interestingly, all affected patients of this family and D22S283 loci (family A, fig 1).

**Figure 1** Haplotype of families A and B at the OPA5 locus on chromosome 22q12.1–q13.1, respectively. The disease haplotype is squared in each patient.
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. 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 22q12.1–q13.1, in two unrelated families of French origin, both affected with a phenotype similar to the chromosome 22q12.1–q13.1 chromosomal region (OPA5).

Mapping of the OPA5 locus on 22q

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

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Maximum pairwise lod score >3 at h=0 were obtained at the D22S275, D22S1176, D22S280, and D22S1158 loci.

Electronic database information


UCSC Human Genome Project working draft, http://genome.ucsc.edu (for marker order and genetic distance between markers).


Acknowledgements

This work was supported by the Association Retina France and the Association Valentin Haüy.

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Competing interests: none declared

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References


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*J Med Genet* 2005 42: e1
doi: 10.1136/jmg.2004.025502

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