A first letter for dominant optic atrophy on chromosome 22q


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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, centrocical 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 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, oculus 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 Génethon linkage map on the basis of their informativeness—AFM308yf1, AFMa300wa5, AFMb043xe9, and AFM254ve1 at the D3S2748, D3S1311, D3S1601, and D3S3590 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.
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. Electroretinogram 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 (II8) and her healthy brother (II1) allowed us to define a 10.4 cM genetic interval between the D22S1148 and D22S283 loci (family A, fig 1A).

Linkage to the 22q12.1–q13.1 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 I2 (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 θ = 0 was obtained with the marker AFRm043I9 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 optic nerve. 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 most common mendelian cause of primary hereditary optic neuropathies comprises 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. Therefore the exclusion of OSBP2 and C22ORF3 prompted us to screen the genes of the OPA5 interval known to encode proteins involved in the mitochondrial function. The genes encoding the J type co-chaperone HSC20—a 235 amino acid protein involved in the mitochondrial iron-sulphur pathway—and the ubiquinol-cytochrome c reductase 7.2 kDa complex HSPC051 were screened for mutations but no alteration was found.

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


Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/entrez/ (for OPA1 [MIM 165500, 605290], OPA4 [MIM 605293], OPA3 [MIM 606280], LHON [MIM 535000], SDHA [MIM600857]). Therefore the exclusion of OSBP2 and C22ORF3 prompted us to screen the genes of the OPA5 interval known to encode proteins involved in the mitochondrial function. The genes encoding the J type co-chaperone HSC20—a 235 amino acid protein involved in the mitochondrial iron-sulphur pathway—and the ubiquinol-cytochrome c reductase 7.2 kDa complex HSPC051 were screened for mutations but no alteration was found.

Competing interests: none declared

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REFERENCES


