Clinical features, molecular genetics, and pathophysiology of dominant optic atrophy

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Abstract
Inherited optic neuropathies are a significant cause of childhood and adult blindness and dominant optic atrophy (DOA) is the most common form of autosomal inherited (non-glaucomatous) optic neuropathy. Patients with DOA present with an insidious onset of bilateral visual loss and they characteristically have temporal optic nerve pallor, centrocaecal visual field scotoma, and a colour vision deficit, which is frequently blue-yellow. Evidence from histological and electrophysiological studies suggests that the pathology is confined to the retinal ganglion cell. A gene for dominant optic atrophy (OPA1) has been mapped to chromosome 3q28-pter, and studies are under way to refine the genetic interval in which the gene lies, to map the region physically, and hence to clone the gene. A second locus for dominant optic atrophy has recently been shown to map to chromosome 18q12.2-12.3 near the Kidd blood group locus. The cloning of genes for dominant optic atrophy will provide important insights into the pathophysiology of the retinal ganglion cell in health and disease. These insights may prove to be of great value in the understanding of other primary ganglion cell diseases, such as the mitochondrially inherited Leber’s hereditary optic neuropathy and other diseases associated with ganglion cell loss, such as glaucoma. (J Med Genet 1998;35:793–800)

Keywords: dominant optic atrophy; clinical features; molecular genetics; OPA1

Dominant optic atrophy (DOA) is the most common form of autosomal inherited (non-glaucomatous) optic neuropathy. The incidence has been estimated at 1:50,000 and prevalence as high as 1:10,000.1 It is named after the Danish ophthalmologist Poul Kjer,2 who clinically characterised 19 families in 1959. While evidence suggests that its highest prevalence may be in the Danish population, DOA has been described in pedigrees from France,3 the UK,4,5 Cuba,6 and the USA,4 although these pedigrees may all be of European descent. There are currently two known loci, an apparently more common one that maps to chromosome 3q28-pter (all of the pedigrees described above) and a much rarer locus on chromosome 18q12.2-12.37 (see below).

Clinical features

CLINICAL AND PATHOPHYSIOLOGICAL STUDIES OF DOA
Autosomal dominant optic atrophy is an autosomally inherited disorder characterised by optic nerve pallor and reduced visual acuity.8 First described clinically by Batten9 and later by Kjer,2 it typically presents in childhood with bilateral visual loss that is usually symmetrical, temporal optic nerve pallor, centrocaecal visual field scotoma, and colour vision deficit.10-15 The intraocular pressure is normal and the optic disc is not cupped. The clinical profile should be clearly distinguishable from acute Leber’s hereditary optic neuropathy,16 which has a sudden onset of visual loss in two eyes asynchronously and a later age of presentation (typically 18-35 years), although in the atrophic phase it may be very difficult to make this distinction without a family history. It may be more difficult to distinguish clinically dominant optic atrophy from X-linked optic atrophy17,18 without a family history. Recessively inherited optic atrophy is generally much more severe, presenting at the time of birth with nystagmus,19 and is rare in isolation.20 Other primary hereditary optic neuropathies, such as diabetes mellitus and insipidus with optic atrophy and deafness (DIDMOAD)21 and Behr’s syndrome are multisystemic diseases.

Although Kjer2 reported mental retardation in up to 10% of his original patients this would appear to be exceptional.22 Sensorineural deafness has been associated with dominantly inherited optic atrophy in a number of pedigrees,23-28 but in none of these families has the disorder been mapped to the chromosome 3q or 18q loci. Other neurological abnormalities, such as ptosis and ophthalmoplegia28 and peripheral muscle wasting,29 have been reported but these pedigrees probably have a syndromic form of optic atrophy.

DOA has an insidious onset, presenting as young as 1 year of age30 or, more typically, between 4 and 6 years of age, although it may remain subclinical until early adult life.31 Some
children are detected on routine preschool vision testing; 22.6% of the patients of Hoyt and 12.5% of those of Kline and Glaser had mild ophthalmological abnormalities which were only detected by screening, although more recent papers put this figure as low as 3.4%. The best corrected visual acuity ranges from 6/6 to perception of light only, with a median of 6/36. Nystagmus is seen only if the visual acuity is severely impaired. Visual acuity is equal to or better than 6/12 (that is, adequate for driving) in 14% of patients according to a recent study. It is extremely rare (penetrance 0.98) for an affected person to be asymptomatic and to have no optic nerve pallor (around 1%) or colour vision deficit.

Two forms of dominant optic atrophy have been described, infantile (or congenital) and juvenile. The infantile form was said to present with nystagmus. There was, however, disagreement for a long time as to whether two forms of the disease existed. It is probable that these two conditions are part of a spectrum of clinical presentation, as there is considerable clinical inter- and intrafamilial heterogeneity, both with respect to age at clinical diagnosis and visual acuity. The degree of severity of visual loss in generation does not predict the severity in the next. The visual acuity typically ranges from 6/6 to 6/60 but, exceptionally, may be as poor as 6/120, hand movements, or even perception of light only in very rare cases. There is evidence from longitudinal and cross sectional observations that visual acuity declines slowly with age in some families, but not in others. About one third of patients develop moderate to severe social or occupational handicap. Rapid decline in visual acuity in adult life has been reported, but it is rare. The vision loss is only occasionally asymmetrical.

The visual field defect is classically centrocaecal (fig 1A, B), central or paracentral, and often appears as a large defect (fig 1C) in patients with severe disease. There is a predominance of visual field defects in the superotemporal visual field, but this has not been explained. The peripheral fields are usually full, but an inversion of red and blue isopters is seen, consistent with tritanopia.

The colour vision defect is often reported as an acquired blue-yellow loss or tritanopia, but many people have a generalised non-specific dyschromatopsia. Others have described families with red-green colour defects. More recently, assessment of patients from families that show evidence of linkage to the dominant optic atrophy locus on chromosome 3q28-pter with a battery of tests has shown that no patient examined displayed a truly isolated loss of tritan discrimination. There was even intrafamilial variation in colour axis discrimination. DOA may show some similarities on psychophysical testing to congenital tritanopia, but it should not be confused with the latter disorder.

The optic nerve appearance ranges from complete atrophy (fig 2A, B) through temporal pallor, (fig 2C), to subtle pallor. According to one recent report, 55% of patients have subtle or temporal pallor and 44% have total atrophy of the optic nerve. The appearances are usually symmetrical. Best colour vision and least field loss have been noted in patients with the least degree of clinical optic atrophy. The appearance of the nerve fibre layer in patients with DOA on scanning laser ophthalmoscopy shows a diffuse loss of retinal nerve fibres (unpublished data), which contrasts to the wedge shaped segmental loss of nerve fibres seen in patients with glaucomatous optic atrophy. Magnetic resonance imaging of the optic nerves in patients with dominant optic atrophy shows a reduced optic nerve sheath complex throughout the length of the intraorbital optic nerve with no signal abnormality and a clearly visible cerebrospinal fluid (CSF) space. This contrasts to appearances seen in the atrophic phase of Leber's hereditary optic neuropathy, where there is bright signal and typically no visible surrounding CSF seen, although the optic nerve sheath complex is also small. It also contrasts with the features of tobacco-alcohol neuropathy (where there are normal size optic sheath complexes and no signal abnormality) and optic neuritis (in which during the acute phase there is CSF space loss and signal abnormality, and, in long standing cases, where there are variable, long lesions).

Electrophysiology suggests that the defect is in the ganglion cell layer of the retina. Many patients show an absent or delayed pattern visually evoked potential (PVEP), showing that there is a conduction defect in the optic nerve. The pattern electroretinogram (PERG) shows an abnormal ratio of waveforms (namely the N95:P50 ratio), with reduction in the amplitude of the N95 waveform. Since the PERG N95 component is postulated to be specific for the retinal ganglion cell, this finding supports a ganglion cell origin for dominant optic atrophy.

Molecular genetics of dominant optic atrophy mapping to chromosome 3q28-pter

MAPPING OF THE OPAI GENE TO CHROMOSOME 3q28-pter AND GENETIC REFINEMENT

Genetic linkage studies in 1994 mapped a dominant optic atrophy gene (OPAI, OMIM No 165500) to chromosome 3q28-pter. The penetrance of the gene is high (0.98). The disease gene was mapped initially to a 10-12 cM interval, but it has since been refined and fine mapped to a critical genetic interval of 1.4 cM flanked by markers D3S3669 and D3S3562 (fig 3A). There is evidence for the overall predominance of one genetic locus, although Seller et al identified a pedigree that does not appear to map to chromosome 3q. Recently, a family has been reported that confirms the existence of genetic heterogeneity (see below).

LINKAGE DISEQUILIBRIUM ANALYSIS

Analysis of pedigrees from the British Isles, unrelated on genealogy, has identified a founder effect. Linkage disequilibrium multipoint analysis suggests that OPAI lies...
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Figure 1 (A) Humphrey 30-2 visual field of right eye of a normal person, showing the physiological blind spot. (B) Humphrey 30-2 visual field of right eye of a patient with dominant optic atrophy mapping to chromosome 3q28-qter, showing a discrete centrocecal scotoma. (C) Humphrey 30-2 visual field of right eye of a patient with dominant optic atrophy mapping to chromosome 3q28-qter, showing an extensive scotoma.
PHYSICAL MAPPING AND CANDIDATE GENES

Physical mapping at the OPA1 locus by the construction of a contig of YACs and PAFS spanning the critical interval is under way.61 72 Several genes and more than 42 ESTs are currently mapped to the wider OPA1 region (between D3S1601 and D3S1265), in the SCIENCE96 database (http://www.ncbi.nlm.nih.gov/SCIENCE96/), and on to the WC3.25 YAC contig (Whitehead Institute/MIT Center for Genome Research).

One of these genes is HRY, the cloned human homologue of the Drosophila segmentation gene, hairy, which maps by in situ hybridisation to 3q28-q29.73 This gene encodes a basic helix-loop-helix transcription factor15 and is a member of a family of mammalian neurodevelopmental genes with Drosophila and rat homologues. Currently, at least 14 transcription factors are known to be required for eye formation and mammalian eye development.75 HRY has been studied in gain of function studies80 and neuronal differentiation has been shown to be suppressed by targeted disruption of the gene in mice homozygous for the mutation.77 HRY has been positioned onto the CEPH YAC 975f4 on a YAC contig that spans the OPA1 region.61 HRY has been genetically mapped to an interval between markers D3S3562 and D3S1305,78 which is outside the critical interval for OPA1. An association has also been excluded by heteroduplex mutation detection (HET) and direct sequencing79 of the gene in its entirety.

An EST (stSG4566) highly similar to the gene for the flavoprotein (fp) subunit of succinate dehydrogenase (SDH2), a complex II mitochondrial respiratory enzyme,79 has also been mapped loosely to the OPA1 interval. SDH deficiency has been reported in phenotypes including Leigh syndrome,77 Kearns-Sayre syndrome,80 hypertrophic cardiomyopathy,81 skeletal myopathy,82 and cerebellar ataxia and optic atrophy.83 However, SDH appears to be represented twice in the human genome, at chromosome 5p15 and 3q29, and there is evidence from human-hamster somatic cell hybrids84 and unpublished data that the SDH2 locus on chromosome 3q is a pseudogene (B Parfait, personal communication).

Three other ESTs corresponding to named genes map to the OPA1 critical interval. They are the gene transferrin receptor (TRP) (stSG13), platelet glycoprotein V (PGV) precursor (L11238), and carboxypeptidase N (SHG-D2002). They are not immediately attractive candidate genes for dominant optic atrophy, but they have yet to be excluded. Lastly, DLG1, the gene for hDlg, encodes a membrane associated guanylate kinase homologue (MAGUK), which belongs to a group of highly related proteins important in controlling epithelial and neuronal cell junctions, especially neuronal synapses. DLG1 has recently been mapped telomeric to the OPA1 critical interval80 and therefore excluded as a candidate gene for dominant optic atrophy.

The very rare early onset of DOA (clinically detectable in some people as young as 6 months of age) and the very slow progression

MOUSE MODEL

The report of a mouse mutant with optic atrophy offers the possibility that the cloning of the mouse gene may provide candidate genes for the human disorder and lead to the identification of the gene for the human DOA. An autosomal semidominant mouse mutation Bstl+/− shows a variable retinal phenotype, from complete absence of ganglion cells to near wild type numbers.84 86 The ganglion cell numbers appear to be reduced because of a failure of the ganglion cells to reach the optic nerve head in early development.86 The Bst gene is located on mouse chromosome 16 in a region of partial synteny to human chromosome 3q28-qter,87 although the gene order does not appear to be completely conserved. The chromosomal position and phenotype make Bstl+/− the best available model for human DOA.
suggest the possibility that a mutation in a neurodevelopmental gene may be involved. A family of transcription regulators, the POU-IV domain genes, has an important role in determining retinal ganglion cell numbers and is expressed differentially in retinal ganglion cell subtypes. The gene Brn-3b, a member of this class of genes, has been studied by targeted disruption in developing mouse retina. Disruption leads in the homozygous state to a selective loss of 70% of retinal ganglion cells. The POU domain genes are excellent functional candidates for DOA, but to date none map in the OPA1 critical interval.

Genetic heterogeneity within DOA
Recently, linkage has been reported to a second locus on chromosome 18q12.2-12.3 (fig 3B). This linkage confirms the previous report of a large pedigree of German descent resident in the USA, which was linked to the Kidd blood group locus on chromosome 18 in 1983. Studies of the prevalence of the two loci will clarify their relative significance. Although few clinical data describing the chromosome 18 phenotype are available, there is evidence suggesting that the phenotype may be indistinguishable from the highly clinically heterogeneous phenotype of the chromosome 3q28-qter locus. In this respect, there appear to be great similarities to the phenotype of X linked optic atrophy (OPA2) that is closely linked to the Xp11.4-Xp11.2 region of the X chromosome.

Pathophysiology of dominant optic atrophy
The pathophysiology of dominant optic atrophy is only very poorly understood. The site of pathology in dominant optic atrophy is thought to be the retinal ganglion cell, as histopathology shows that the outer retina appears to be normal and that there is a loss of retinal ganglion cells, primarily in the macula and in the papillomacular bundle of the optic nerve. The electrophysiological findings (above) confirm this view. It is far from clear if the disease is present subclinically in some people at the time of birth or if it only develops postpartum. It is possible that the gene for dominant optic atrophy is important in ganglion cell development, but it could also be a gene coding for an enzyme or for a structural protein.

Although few data are available from the direct study of the optic nerve in dominant optic atrophy, it is interesting to consider the parallels with the other major group of inherited optic neuropathies, the mitochondrial optic neuropathy found in Leber’s optic atrophy (LHON). LHON is an inherited form of blindness in which a mutation in the mitochondrial genome (mtDNA) is the primary aetiological factor. More than 95% of the LHON pedigrees of northern European descent have one of the three primary mitochondrial mutations at nucleotides 3460, 11 778, and 14 484. There are other rare primary mutations and mutations that are thought to have a secondary aetiological role. The optic neuropathy involves a loss of central vision owing to degeneration of the retinal ganglion cells and the optic nerve axons of the papillomacular bundle that subserve central vision. Although few histopathological studies of Leber’s optic atrophy have been reported, some data are available. The optic nerve in a patient with genetically proven mutations at nucleotide positions 4160 and 14 484 showed 1.2 μ electron dense, double membrane bound inclusions (found to consist of calcium by electron probe analysis) in retinal ganglion cells. The optic nerve from this patient was homo-
plasmic for mutations 4160 and 14 484.93 These features suggest that the optic nerve and inner retinal atrophy in LHON may be the result of a metabolic mitochondrial dysfunction leading to intramitochondrial calcification. It is hypothesised that the respiratory chain dysfunction leads to axoplasmic stasis and swelling, thereby blocking ganglion cell function and causing vision loss. It is also believed that, in some ganglion cells, this loss of function may be reversible, but in others the apoptotic cell death pathway is activated, leading to extensive degeneration of the retinal ganglion cell layer and optic nerve. It has been suggested that ATP deficiency may be a common mechanism for visual loss in LHON and also in toxic and deficiency optic neuropathies,95 and we believe that a respiratory chain defect may be associated with dominant optic atrophy because of the similarities to LHON. Although the genes for dominant optic atrophy have yet to be cloned, it is possible to speculate that the gene may be a nuclear encoded gene involved in the oxidative phosphorylation (OXPHOS) pathway, given the clinical and morphological similarities between dominant optic atrophy and LHON. Of the many enzymes involved in the OXPHOS chain of reactions, approximately one third are encoded by nuclear genes and two thirds are encoded by mitochondrial genes. Nuclear genes encoding mitochondrial enzymes may be duplicated in the genome. Thus it is possible that a mutation in either of these genomes can lead to a disruption in the OXPHOS cascade.

Genetic counselling in dominant optic atrophy

Although the penetrance of dominant optic atrophy is high (0.98),96 there is considerable intra- and interfamilial phenotypic heterogeneity. The majority of patients present in early to mid childhood and the clinical diagnosis is generally reliable from 6 years of age and above, except in rare cases. As there are some people who may only be very mildly affected, it is advisable to include colour vision assessment and even electrodiagnostic testing in cases where there is any doubt, in addition to the full clinical examination. A multidisciplinary approach to the diagnosis and management of these patients is helpful, involving both clinical ophthalmologists and geneticists, electrodiagnostic services, low vision specialists, and educational advisors.

The clinician may be faced with one of two difficult situations: either an apparently sporadic person who presents with non-progressive optic atrophy and normal neuroimaging, or a person uncertain of his clinical status from a family known to be affected by dominant optic atrophy. In the first situation, it is important to examine all family members fully, as relatives may be only mildly affected, and establish if there is a disease pedigree and, if so, what the mode of transmission is. In the second situation, one may need to include colour vision and electrophysiology in the full clinical assessment of the patient in order to be able to make a diagnosis.

Genetic counselling in this condition currently relies on conventional risk assessment, in the absence of a diagnostic test. Linkage and haplotype analysis in larger pedigrees can provide evidence of a strong likelihood that a person carries the disease gene, but may be inconclusive, than the presence of a problem if there is genetic heterogeneity, as hereditary diseases resulting from mutations at different loci may be indistinguishable phenotypically. In this respect, the position of dominant optic atrophy is akin to the situation in autosomal dominant polycystic kidney disease, where PKD1 is said to account for 85% of patients, PKD2 for 10%, and an as-yet-unlinked locus (PKD3) for a few remaining families.96 Therefore, at present, the assignment of status in most families must rely upon clinical findings.

It is not possible to predict with any certainty the degree of severity of visual handicap and long term prognosis of a member of a family from one generation to the next. However, it is true to say that the severity of the condition by the age of adolescence reflects the overall level of visual function to be expected throughout most of the patient's adult life. There is evidence for slow deterioration in visual acuity, particularly reported by patients as they approach later middle age, which is not entirely explained by refractive changes. This deterioration has been documented to be particularly marked in some families. The reasons for this are not known, but may relate to the nature or type of mutation in those families.

Future prospects

The gene that causes dominant optic atrophy, OPA1, mapping to chromosome 3q28-qter, is likely to be cloned within the next few years. Given the abundant clinical heterogeneity of the condition, both within and between families, it will be fascinating to assess the genotype-phenotype correlations once mutations in the gene have been identified. While different mutations in the OPA1 gene in unrelated families (allelic heterogeneity) would account for interfamilial variation, intrafamilial variation could not be explained in this manner. Other factors, including age, genetic background, the modifying effects of other genes involved in retinal and ganglion cell development, physiological and environmental factors, may be relevant. The presence of a second locus on chromosome 18, so far reported in one pedigree, has recently been confirmed, but no data on genotype-phenotype correlations are yet available. This second locus is likely to account for a smaller proportion of cases affected by autosomal dominant optic atrophy than the chromosome 3q locus, because it has not been reported so far in the large collections of families studied by other workers to date, who have generally found that all the families studied mapped to chromosome 3q.

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