GENEReviews

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Optic Atrophy Type 1

[*Kjer Type Optic Atrophy*]

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Summary

Disease characteristics. Optic atrophy type 1 (OPA1, or Kjer type optic atrophy) is characterized by bilateral and symmetric optic nerve pallor associated with insidious decrease in visual acuity usually between ages four and six years, visual field defects, and color vision defects. Visual impairment is usually moderate (6/10 to 2/10), but ranges from mild or even insignificant to severe (legal blindness with acuity <1/20). The visual field defect is typically centrocecal, central, or paracentral; it is often large in those with severe disease. The color vision defect is often described as acquired blue-yellow loss (tritanopia). Spontaneous recovery of vision has not been reported. Other findings can include auditory neuropathy resulting in sensorineural hearing loss that ranges from severe and congenital to subclinical (i.e., identified by specific audiologic testing only).

Diagnosis/testing. The diagnosis of OPA1 is based on a combination of clinical findings, electrophysiologic studies, family history, and molecular genetic testing. Visual evoked potentials (VEPs) are typically absent or delayed; pattern electroretinogram (PERG) shows an abnormal N95:P50 ratio. *OPA1* is the only gene known to be associated with OPA1. Sequence analysis of all exons of *OPA1*, available as a clinical test, detects mutations in 70%-90% of familial cases and about 50% of simplex cases. Deletion/duplication analysis is also available clinically.

Management. *Treatment of manifestations:* low-vision aids for decreased visual acuity. *Surveillance:* annual ophthalmologic and hearing evaluations. *Agents/circumstances to avoid:* smoking, excessive alcohol intake; avoidance of excessive UV exposure to the eyes is a good practice, though no evidence of its effectiveness exists.

Genetic counseling. OPA1is inherited in an autosomal dominant manner. Most individuals diagnosed with OPA1 have an affected parent; however, *de novo* mutations have been reported. Each child of an individual with OPA1 has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Optic atrophy type 1 (OPA1, or Kjer type optic atrophy) is diagnosed in individuals with the following:

- **Bilateral vision loss** that is usually symmetric
- **Optic nerve pallor,** the cardinal sign, usually bilateral and symmetric; temporal in about 50% of individuals and global in about 50% [Votruba et al 2003], particularly in older individuals and those with more severe involvement. In moderate cases, the optic atrophy may not be visible. Profound papillary excavation is reported in 21% of eyes with OPA1 [Alward 2003].
- **Visual field defect** that is typically centrocecal, central, or paracentral; it is often large in individuals with severe disease. The peripheral field is usually normal, but inversion of red and blue isopters may occur.

  Note: The isopters are lines joining points of equal sensitivity on a visual field chart. The red isopter represents the largest/brightest stimulus; the blue isopter represents the smallest/dimmest stimulus. Persons with OPA1 have scotomas (areas of impaired visual acuity) in the central visual fields and sparing of the peripheral visual fields.
- **Color vision defect,** often described as acquired blue-yellow loss (tritanopia)
- **Childhood onset**
- **Family history** consistent with autosomal dominant inheritance

Sensorineural hearing loss may also occur in individuals with OPA1.

Electrophysiology

- **Visual evoked potentials (VEPs)** are typically absent or delayed, indicating a conduction defect in the optic nerve.
- **Pattern electroretinogram (PERG)** shows an abnormal N95:P50 ratio, with reduction in the amplitude of the N95 waveform [Holder et al 1998]. Since the N95 component of the PERG is thought to be specific for the retinal ganglion cell, this finding supports a ganglion cell origin for the optic atrophy.

  Note: The PERG originates from the inner retinal layers, enabling an assessment of ganglion cell function, and is increasingly used in the assessment of anterior visual pathway dysfunction. The normal PERG consists of a prominent positive peak at 50 ms (P50), and a slow, broad trough with a minimum at 95 ms (N95). The positive P50 component is invariably affected in retinal and macular dysfunction, whereas the negative N95 component is principally affected in optic nerve disease. Furthermore, the ratio between N95 and P50 has been shown to be an effective measure of retinal ganglion cell function.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *OPA1* is the only gene known to be associated with optic atrophy type 1 [Alexander et al 2000, Delettre et al 2000].

Other loci. Because the detection rate for mutations in *OPA1* is less than 100%, it is possible that families in which a mutation is not detected are not linked to the *OPA1* locus; however, no evidence supports this possibility.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis of all exons of *OPA1*** is available clinically.
- **Sequence analysis of RNA.** RT-PCR amplification performed on *OPA1* RNA extracted from blood can identify splice-site mutations and abnormally spliced forms.
- **Deletion/duplication analysis.** *OPA1* deletions involving multiple and single exons, and even the entire gene, have been reported. See HGMD (registration required).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Optic Atrophy Type 1

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method[1]		Test Availability
		Familial	Simplex [2]	
Sequence analysis	*OPA1* sequence variants	8/9 [3] 10/14 [4] 17/19 [5]	4/8 [3]	Clinical Testing
Deletion/duplication analysis [6]	Whole- and partial-gene deletions	Unknown	Unknown	

1. The theoretical possibilities of locus heterogeneity or presence of a large gene deletion not detected by sequence analysis may account for a detection rate less than 100% (see **Interpretation of test results**).

2. Simplex = a single occurrence in a family

3. Nakamura et al (2006) found *OPA1* mutations in 8/9 familial cases and 4/8 simplex cases. Of note, on examination of family members of two apparently simplex cases, Nakamura et al (2006) found *OPA1* mutations in relatives with a normal or only mildly abnormal phenotype, supporting the notions of variable expressivity and reduced penetrance.

4. Puomila et al 2005

5. Delettre et al 2001

6. Testing that identifies duplications/deletions not detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), and array CGH (see Testing) may be used.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

Polymorphisms in *OPA1* may be associated with normal tension glaucoma (NTG), which could be considered a genetically determined optic neuropathy with similarities to both Leber hereditary optic neuropathy (LHON) and OPA1.

Clinical Description

Natural History

Variable expressivity of optic atrophy type 1 (OPA1) is observed both within and between families.

OPA1 usually presents as insidious decrease in visual acuity between ages four and six years; in mild cases visual acuity may remain normal until early adult life. Visual acuity usually declines slowly with age. Although rare, rapid decline in visual acuity has been reported in adults [Kjer et al 1996].

The visual impairment is usually moderate (6/10 to 2/10), but ranges from severe (legal blindness with acuity <1/20) to mild or even insignificant, and consequently can be underestimated.

The vision loss is occasionally asymmetrical.

Spontaneous recovery of vision has not been reported.

Sensorineural hearing loss that ranges from severe and congenital to subclinical (requiring specific testing for detection) has been reported along with optic atrophy in a few families or individuals with the p.Arg445His mutation in *OPA1* [Amati-Bonneau et al 2003, Amati-Bonneau et al 2005]. Amati-Bonneau et al (2005) concluded that the hearing loss resulted from auditory neuropathy. In an individual with the p.Arg445His mutation, auditory brain stem responses (ABRs) were absent and both ears presented normal evoked otoacoustic emissions. Because evoked otoacoustic emissions reflect the functional state of presynaptic elements (the outer hair cells), and the ABRs reflect the integrity of the auditory pathway from the auditory nerve to the inferior colliculus, the presence of evoked otoacoustic emissions and the lack of ABRs support the diagnosis of auditory neuropathy.

Both intra- and interfamilial variation have been observed regarding the presence of hearing loss with optic atrophy. Furthermore, the p.Arg445His mutation was associated with optic atrophy without hearing loss in a 21-year-old Japanese individual; no other family member was clinically affected or had the *OPA1* mutation [Shimizu et al 2003].

- Treft et al (1984) and Meire et al (1985) reported two unrelated families with autosomal dominant optic atrophy, hearing loss, ptosis, and ophthalmoplegia. Subsequent studies revealed the p.Arg445His mutation in *OPA1* in both families [Payne et al 2004].
- Li et al (2005) identified the p.Arg445His mutation in a family with optic atrophy and hearing loss, without ptosis or ocular motility abnormalities. These family members are also myopic, but it is not clear if myopia is part of the phenotype.

Pathology. The cardinal sign of OPA1 is optic atrophy that appears as bilateral and generally symmetric temporal pallor of the optic disc, implying the loss of central retinal ganglion cells.

Histopathology. Histopathology shows a normal outer retina and loss of retinal ganglion cells, primarily in the macula and in the papillo-macular bundle of the optic nerve.

Genotype-Phenotype Correlations

No correlation has been observed between the degree of visual impairment and the location or type of mutation [Puomila et al 2005].

Complete deletion of the *OPA1* gene results in typical dominant optic atrophy without predictable severity or other deficits [Marchbank et al 2002]. However, it seems that in-frame deletions involve loss of visual acuity (1/10 on average) that is statistically slightly more severe than that resulting from truncating mutations or missense substitutions (2/10 on average) [Ait Ali et al, unpublished].

Penetrance

The estimated penetrance of 98% in OPA1 has been revised in the light of molecular genetic studies. Penetrance varies from family to family and mutation to mutation. It has been reported as high as 100% (IVS12+1G>T mutation resulting in exon 12 skipping) [Thiselton et al 2002] and as low as 43% (2708delTTAG mutation in exon 27) [Toomes et al 2001]. In these two studies the clinical diagnosis was made on the basis of reduced visual acuity, abnormal color discrimination, fundus examination showing temporal pallor of the optic disc, and electrophysiology studies [Toomes et al 2001, Thiselton et al 2002].

Anticipation

Anticipation is not observed.

Prevalence

OPA1 is believed to be the most common of the hereditary optic neuropathies.

The estimated prevalence of OPA1 is 1:50,000 in most populations, or as high as 1:10,000 in Denmark. The relatively high frequency of OPA1 in Denmark may be attributable to a founder effect [Thiselton et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Leber hereditary optic neuropathy (LHON) is the major differential diagnosis for optic atrophy type 1 (OPA1). LHON typically presents in young adults as painless subacute bilateral visual failure. Males are more commonly affected than females. Women tend to develop the disorder slightly later in life and may be more severely affected. The acute phase begins with blurring of central vision and color desaturation that affect both eyes simultaneously in up to 50% of cases. After the initial symptoms, both eyes are usually affected within six months. The central visual acuity deteriorates to the level of counting fingers in up to 80% of cases. Following the nadir, acuity may improve. Individuals then proceed into the atrophic phase and are usually legally blind for the rest of their lives with a permanent large centrocecal scotoma. Minor neurologic abnormalities (such as a postural tremor or the loss of ankle reflexes) are said to be common in individuals with LHON. Some individuals with LHON, usually women, also have a multiple sclerosis (MS)-like illness.

LHON is inherited by mitochondrial inheritance. In one large study, 95% of individuals with LHON were found to have one of three point mutations of mtDNA: 11778G>A, 14484T>C, 3460G>A.

Two other loci associated with autosomal dominant optic atrophy have been identified:

- OPA4 (OMIM 605293) was mapped to 8q12.2-q12.3 in a single large family by Kerrison et al (1999); however, the locus has not been confirmed and the disease gene is still unknown.
- OPA5 was mapped to 22q12.1-q13.1 by Barbet et al (2005) in two unrelated families.

The phenotype of the three families with OPA4 or OPA5 is comparable to the phenotype seen in OPA1: optic nerve pallor, decreased visual acuity, color vision defects, impaired VEP, and normal ERG. No extraocular findings were described in these families.

Deafness-dystonia-optic neuronopathy syndrome (DDON). Males with DDON have prelingual or postlingual sensorineural hearing impairment, slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from optic atrophy beginning about age 20 years, and dementia beginning at about age 40 years. Psychiatric symptoms such as personality change and paranoia may appear in childhood and progress. The hearing impairment phenotype is a progressive auditory neuropathy, while the neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia.

Inheritance is X-linked. The DDON syndrome occurs as either a single-gene disorder resulting from mutation in *TIMM8A* or a contiguous gene deletion syndrome at Xq22, which also includes X-linked agammaglobulinemia caused by disruption of the *BTK* gene, located telomeric to *TIMM8A*.

WFS1. Mutations in the *WFS1* gene are generally associated with optic atrophy (OPA) as part of the autosomal recessive Wolfram syndrome phenotype (DIDMOAD [**d**iabetes **i**nsipidus, **d**iabetes **m**ellitus, **o**ptic **a**trophy, **d**eafness]) or with autosomal dominant progressive low-frequency sensorineural hearing loss (LFSNHL) without ophthalmologic abnormalities [Cryns et al 2003]. However, Eiberg et al (2006) identified a *WFS1* mutation associated with autosomal dominant optic atrophy, hearing loss, and impaired glucose regulation in one family, supporting the notion that mutations in *WFS1* as well as in *OPA1* may lead to optic atrophy combined with hearing impairment.

MFN2. Charcot-Marie-Tooth (CMT) type 2A2 (see CMT2A) neuropathy with visual impairment resulting from optic atrophy has been designated as hereditary motor and sensory neuropathy type VI (HMSN VI) [Voo et al 2003]. Zuchner et al (2006) described six families with HMSN VI with a subacute onset of optic atrophy and subsequent slow recovery of visual acuity in 60% of affected individuals. In each pedigree a unique mutation in the gene *MFN2*, encoding mitofusin 2, was identified. Inheritance is autosomal dominant.

Other optic neuropathies. The acquired blue-yellow loss (tritanopia) helps differentiate OPA1 from other optic neuropathies in which the axis of confusion is red-green:

- **OPA2.** A gene for X-linked optic atrophy (OPA2) has been mapped to chromosome Xp11.4-p11.21, but to date no gene has been identified.
- ***OPA3.*** The *OPA3* gene consists of two exons and encodes for an inner mitochondrial membrane protein. The function of this protein is not well known. The two disorders associated with *OPA3* mutations are:
  - **Costeff optic atrophy syndrome.** Truncating mutations are responsible for 3-methylglutaconic aciduria type III, also called Costeff optic atrophy syndrome, a neuroophthalmologic syndrome consisting of early-onset bilateral optic atrophy and later-onset spasticity, extrapyramidal dysfunction, and cognitive deficit. Urinary excretion of 3-methylglutaconic acid and of 3-methglutaric acid is increased. Inheritance is autosomal recessive.
  - **Autosomal optic atrophy and cataract (ADOAC).** Reynier et al (2004) have identified two causative mutations, p.Gly93Ser and p.Gln105Glu, that

change one of the amino acids of the optic atrophy 3 protein. Inheritance is autosomal dominant.

- **OPA6.** The first locus for isolated autosomal recessive optic atrophy (ROA1) has been mapped to chromosome 8q. Dyschromatopsia for red-green confusion occurs in OPA6.

Acquired optic neuropathy can be caused by the following:

- Nutritional deficiencies of protein, or of the B vitamins and folate, associated with starvation, malabsorption, or alcoholism
- Toxic exposures. The most common is "tobacco-alcohol amblyopia," thought to be caused by exposure to cyanide from tobacco smoking, and by low levels of vitamin B_{12} caused by poor nutrition and poor absorption associated with drinking alcohol. Other possible toxins include ethambutol, methyl alcohol, ethylene glycol, cyanide, lead, and carbon monoxide.
- Certain medications

Management

Evaluations Following Initial Diagnosis

In order to establish the extent of disease in an individual with optic atrophy type 1 (OPA1), the following evaluations are recommended:

- Visual acuity, color vision, and visual fields
- Assessment of extraocular muscles (the patient is asked to follow the ophthalmoscope with his/her eyes without moving the head)
- Hearing evaluation: auditory brain stem responses (ABRs), auditory evoked potentials (AEPs), and evoked otoacoustic emissions
- Oral glucose tolerance test

Treatment of Manifestations

No treatment is of proven efficacy for OPA1.

Treatment of decreased visual acuity is symptomatic (e.g., low-vision aids).

For treatment of sensorineural hearing loss, see Deafness and Hereditary Hearing Loss Overview.

Surveillance

- Annual ophthalmologic examination
- Annual hearing evaluation

Agents/Circumstances to Avoid

Individuals with an *OPA1* mutation are advised:

- Not to smoke
- To moderate their alcohol intake
- To use sunglasses to limit UV exposure (Note: While limiting UV exposure is a good practice, no evidence for its effectiveness exists.)

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Optic atrophy type 1 (OPA1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with OPA1 have an affected parent.
- A proband with OPA1 may have the disorder as the result of a new gene mutation. Two instances of *de novo* mutations have been reported [Baris et al 2003].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include: (1) ophthalmologic evaluation including an assessment of visual acuity, color vision, and visual fields, (2) audiologic examinations consisting of auditory brain stem responses (ABRs), auditory evoked potentials (AEP) recordings, and study of evoked otoacoustic emissions, and (3) molecular genetic testing of OPA1 if the disease-causing mutation has been identified in the proband.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.

- When the parents are found on the basis of visual acuity study, color vision evaluation, fundus examination, VEP, and PERG to be clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with OPA1 is at a 50% risk of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with OPA1 is found to have the disease-causing mutation or clinical evidence of the disorder based on visual acuity study, color vision evaluation, fundus examination, VEP, and PERG, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as OPA1 that do not affect intellect or life span are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). PGD may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Optic Atrophy Type 1

Gene Symbol	Chromosomal Locus	Protein Name
OPA1	3q28-q29	Dynamin-like 120 kDa protein

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Optic Atrophy Type 1

165500	OPTIC ATROPHY 1; OPA1
605290	OPA1 GENE; OPA1

Table C. Genomic Databases for Optic Atrophy Type 1

Gene Symbol	Entrez Gene	HGMD
OPA1	4976 (MIM No. 605290)	OPA1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Because *OPA1* expression is ubiquitous, and it was recently proposed that neither the pattern nor the abundance of *OPA1* mRNA and dynamin-like 120 kd protein variants are specific to retinal ganglion cell (RGC) [Kamei et al 2005], a plausible hypothesis as to why these neurons may be more vulnerable to OPA1 inactivation could be a particular susceptibility to mitochondrial membrane disorders inducing mitochondrial dysfunction or mislocalization. While the former point is in agreement with reports that describe altered mitochondrial ATP synthesis and respiration in OPA1-inactivated cells [Lodi et al 2004, Amati-Bonneau et al 2005, Chen et al 2005], the latter may relate to the particular distribution of the mitochondria in RGC. These show an accumulation of mitochondria in the cell bodies and in the intraretinal unmyelinated axons, where they accumulate in the varicosities, and a relative paucity of mitochondria in the myelinated parts of axons [Andrews et al 1999, Bristow et al 2002, Wang et al 2003]. Furthermore, the effect of mitochondrial dynamics on the correct intracellular distribution of the mitochondria and its influence on neuronal plasticity and function was recently highlighted by inactivation of *DRP1* in live hippocampal neurons [Li et al 2004]. A link between axonal transport of mitochondria [Hollenbeck & Saxton 2005] and mitochondrial dynamics was also enlightened by a recent study showing that *Drosophila* mutants lacking the ortholog of human DRP1 protein failed to populate the distal axon with mitochondria, affecting the mobilization of the synaptic vesicle reserve pool [Hollenbeck 2005]. Moreover, mutations in the pro-fusion protein encoded by the gene *MFN2*, which causes a peripheral neuropathy (see CMT2A) [Zuchner et al 2006], significantly impaired the transport of mitochondria in axons in neurons expressing disease-mutated forms of *MFN2* [Baloh et al 2007]. These data suggest that proper localization of mitochondria is critical for axonal and synaptic function.

Normal allelic variants: The *OPA1* gene consists of 31 exons spanning more than 114 kb of genomic DNA. Eight isoforms have been described as a result of alternative splicing of exons 4, 4b, and 5b [Delettre et al 2001].

Pathologic allelic variants: There is a wide spectrum of mutations, with over 90 reported to date (see eOPA1, an online database for *OPA1* mutations). The *OPA1* mutations are spread

throughout the gene coding sequence, but most are localized in GTPase domain (exons 8-16) and in the 3' end of the coding region (exons 27-28), whereas few mutations are found in exons 1 to 7. To date no mutations have been found in exons 4 and 4b, which are alternatively spliced. See Genomic Databases table.

Normal gene product: Dynamin-like 120 kd protein (OPA1), encoded by *OPA1*, is a mitochondrial dynamin-related GTP protein of 960 amino acids. This is the first dynamin-related protein found to be involved in human disease. The dynamin-like 120 kd protein comprises a highly basic amino-terminal that provides mitochondrial targeting sequence (MTS), a dynamin-GTPase domain, and a C-terminus of unknown function; the C-terminus differs from that of other dynamin family members in lacking a proline-rich region, a dynamin GTPase effector domain, and a pleckstrin homology domain; the C-terminus may therefore determine the specific functions of the dynamin-like 120 kd protein.

OPA1 appears to exert its function in mitochondrial biogenesis and stabilization of mitochondrial membrane integrity. Downregulation of *OPA1* leads to fragmentation of the mitochondrial network and dissipation of the mitochondrial membrane potential with cytochrome c release and caspase-dependent apoptosis [Olichon et al 2003].

Abnormal gene product: The functional consequences of mutations in *OPA1* are unknown. Since almost 50% of mutations result in protein truncation, dominant inheritance of the disease may result from haploinsufficiency of dynamin-like 120 kd protein. However, missense mutations can also cause disease by a dominant-negative mechanism.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Foundation Fighting Blindness
11435 Cronhill Drive
Owings Mill MD 21117-2220
Phone: 888-394-3937 (toll-free); 800-683-5555 (toll-free TDD); 410-568-0150 (local)
Email: info@blindness.org
www.blindness.org

National Eye Institute
Low Vision

National Federation of the Blind (NFB)
1800 Johnson Street
Baltimore MD 21230
Phone: 410-659-9314
Fax: 410-685-5653
Email: nfb@nfb.org
www.nfb.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Alexander C, Votruba M, Pesch UE, Thiselton DL, Mayer S, Moore A, Rodriguez M, Kellner U, Leo-Kottler B, Auburger G, Bhattacharya SS, Wissinger B. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat Genet. 2000;26:211–5. [PubMed: 11017080]

Amati-Bonneau P, Guichet A, Olichon A, Chevrollier A, Viala F, Miot S, Ayuso C, Odent S, Arrouet C, Verny C, Calmels MN, Simard G, Belenguer P, Wang J, Puel JL, Hamel C, Malthiery Y, Bonneau D, Lenaers G, Reynier P. OPA1 R445H mutation in optic atrophy associated with sensorineural deafness. Ann Neurol. 2005;58:958–63. [PubMed: 12488251]

Amati-Bonneau P, Odent S, Derrien C, Pasquier L, Malthiery Y, Reynier P, Bonneau D. The association of autosomal dominant optic atrophy and moderate deafness may be due to the R445H mutation in the OPA1 gene. Am J Ophthalmol. 2003;136:1170–1. [PubMed: 14644237]

Andrews RM, Griffiths PG, Johnson MA, Turnbull DM. Histochemical localisation of mitochondrial enzyme activity in human optic nerve and retina. Br J Ophthalmol. 1999;83:231–5. [PubMed: 10396204]

Baloh RH, Schmidt RE, Pestronk A, Milbrandt J. Altered axonal mitochondrial transport in the pathogenesis of Charcot-Marie-Tooth disease from mitofusin 2 mutations. J Neurosci. 2007;27:422–30. [PubMed: 17215403]

Barbet F, Hakiki S, Orssaud C, Gerber S, Perrault I, Hanein S, Ducroq D, Dufier J-L, Munnich A, Kaplan J, Rozet J-M. A third locus for dominant optic atrophy on chromosome 22q. J Med Genet. 2005;42:el. [PubMed: 15635063]

Baris O, Delettre C, Amati-Bonneau P, Surget M-O, Charlin J-F, Catier A, Dollfus H, Jonveaux P, Bonneau D, Ayuso C, Maumenee I, Lorenz B, Mohammed SN, Tourmen Y, Malthiery Y, Hamel C, Reynier P. Fourteen novel OPA1 mutations in dominant optic atrophy and de novo mutations in isolated cases of optic atrophy. Hum Mut. 2003;21:656. [PubMed: 14961560]

Bristow EA, Griffiths PG, Andrews RM, Johnson MA, Turnbull DM. The distribution of mitochondrial activity in relation to optic nerve structure. Arch Ophthalmol. 2002;120:791–6. [PubMed: 12049585]

Chen H, Chomyn A, Chan DC. Disruption of fusion results in mitochondrial heterogeneity and dysfunction. J Biol Chem. 2005;280:26185–92. [PubMed: 15899901]

Cryns K, Sivakumaran TA, Van den Ouweland JM, Pennings RJ, Cremers CW, Flothmann K, Young TL, Smith RJ, Lesperance MM, Van Camp G. Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. Hum Mutat. 2003;22:275–87. [PubMed: 12955714]

Delettre C, Griffoin JM, Kaplan J, Dollfus H, Lorenz B, Faivre L, Lenaers G, Belenguer P, Hamel CP. Mutation spectrum and splicing variants in the OPA1 gene. Hum Genet. 2001;109:584–91. [PubMed: 11810270]

Delettre C, Lenaers G, Griffoin JM, Gigarel N, Lorenzo C, Belenguer P, Pelloquin L, Grosgeorge J, Turc-Carel C, Perret E, Astarie-Dequeker C, Lasquellec L, Arnaud B, Ducommun B, Kaplan J, Hamel CP. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nat Genet. 2000;26:207–10. [PubMed: 11017079]

Eiberg H, Hansen L, Kjer B, Hansen T, Pedersen O, Bille M, Rosenberg T, Tranebjaerg L. Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. J Med Genet. 2006;43:435–40. [PubMed: 16648378]

Holder GE, Votruba M, Carter AC, Bhattacharya SS, Fitzke FW, Moore AT. Electrophysiological findings in dominant optic atrophy (DOA) linking to the OPA1 locus on chromosome 3q 28-qter. Doc Ophthalmol. 1998;95:217–28. [PubMed: 10532406]

Hollenbeck PJ. Mitochondria and neurotransmission: evacuating the synapse. Neuron. 2005;47:331–3. [PubMed: 16055057]

Hollenbeck PJ, Saxton WM. The axonal transport of mitochondria. J Cell Sci. 2005;118:5411–9. [PubMed: 16306220]

Kamei S, Chen-Kuo-Chang M, Cazevieille C, Lenaers G, Olichon A, Belenguer P, Roussignol G, Renard N, Eybalin M, Michelin A, Delettre C, Brabet P, Hamel CP. Expression of the Opa1 mitochondrial protein in retinal ganglion cells: its downregulation causes aggregation of the mitochondrial network. Invest Ophthalmol Vis Sci. 2005;46:4288–94. [PubMed: 16249510]

Kerrison JB, Arnould VJ, Ferraz Sallum JM, Vagefi MR, Barmada MM, Li Y, Zhu D, Maumenee IH. Genetic heterogeneity of dominant optic atrophy, Kjer type: Identification of a second locus on chromosome 18q12.2-12.3. Arch Ophthalmol. 1999;117:805–10. [PubMed: 10369594]

Kjer B, Eiberg H, Kjer P, Rosenberg T. Dominant optic atrophy mapped to chromosome 3q region. II. Clinical and epidemiological aspects. Acta Ophthalmol Scand. 1996;74:3–7. [PubMed: 8689476]

Li C, Kosmorsky G, Zhang K, Katz BJ, Ge J, Traboulsi EI. Optic atrophy and sensorineural hearing loss in a family caused by an R445H OPA1 mutation. Am J Med Genet A. 2005;138:208–11. [PubMed: 16158427]

Li Z, Okamoto K, Hayashi Y, Sheng M. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell. 2004;119:873–87. [PubMed: 15607982]

Lodi R, Tonon C, Valentino ML, Iotti S, Clementi V, Malucelli E, Barboni P, Longanesi L, Schimpf S, Wissinger B, Baruzzi A, Barbiroli B, Carelli V. Deficit of in vivo mitochondrial ATP production in OPA1-related dominant optic atrophy. Ann Neurol. 2004;56:719–23. [PubMed: 15505825]

Marchbank NJ, Craig JE, Leek JP, Toohey M, Churchill AJ, Markham AF, Mackey DA, Toomes C, Inglehearn CF. Deletion of the OPA1 gene in a dominant optic atrophy family: evidence that haploinsufficiency is the cause of disease. J Med Genet. 2002;39:e47. [PubMed: 12161614]

Meire F, De Laey JJ, de Bie S, van Staey M, Matton MT. Dominant optic nerve atrophy with progressive hearing loss and chronic progressive external ophthalmoplegia (CPEO). Ophthalmic Paediatr Genet. 1985;5:91–7. [PubMed: 4058877]

Nakamura M, Lin J, Ueno S, Asaoka R, Hirai T, Hotta Y, Miyake Y, Terasaki H. Novel mutations in the OPA1 gene and associated clinical features in Japanese patients with optic atrophy. Ophthalmology. 2006;113:483–8. [PubMed: 16513463]

Olichon A, Baricault L, Gas N, Guillou E, Valette A, Belenguer P, Lenaers G. Loss of OPA1 perturbates the mitochondrial inner membrane structure and integrity, leading to cytochrome c release and apoptosis. J Biol Chem. 2003;278:7743–6. [PubMed: 12509422]

Payne M, Yang Z, Katz BJ, Warner JE, Weight CJ, Zhao Y, Pearson ED, Treft RL, Hillman T, Kennedy RJ, Meire FM, Zhang K. Dominant optic atrophy, sensorineural hearing loss, ptosis, and ophthalmoplegia: a syndrome caused by a missense mutation in OPA1. Am J Ophthalmol. 2004;138:749–55. [PubMed: 15531309]

Puomila A, Huoponen K, Mantyjarvi M, Hamalainen P, Paananen R, Sankila EM, Savontaus ML, Somer M, Nikoskelainen E. Dominant optic atrophy: correlation between clinical and molecular genetic studies. Acta Ophthalmol Scand. 2005;83:337–46. [PubMed: 15948788]

Reynier P, Amati-Bonneau P, Verny C, Olichon A, Simard G, Guichet A, Bonnemains C, Malecaze F, Malinge MC, Pelletier JB, Calvas P, Dollfus H, Belenguer P, Malthiery Y, Lenaers G, Bonneau D. OPA3 gene mutations responsible for autosomal dominant optic atrophy and cataract. J Med Genet. 2004;41:110. [PubMed: 15342707]

Shimizu S, Mori N, Kishi M, Sugata H, Tsuda A, Kubota N. A novel mutation in the OPA1 gene in a Japanese patient with optic atrophy. Am J Ophthalmol. 2003;135:256–7. [PubMed: 12566046]

Thiselton DL, Alexander C, Taanman JW, Brooks S, Rosenberg T, Eiberg H, Andreasson S, Van Regemorter N, Munier FL, Moore AT, Bhattacharya SS, Votruba M. A comprehensive survey of mutations in the OPA1 gene in patients with autosomal dominant optic atrophy. Invest Ophthalmol Vis Sci. 2002;43:1715–24. [PubMed: 12036970]

Toomes C, Marchbank NJ, Mackey DA, Craig JE, Newbury-Ecob RA, Bennett CP, Vize CJ, Desai SP, Black GC, Patel N, Teimory M, Markham AF, Inglehearn CF, Churchill AJ. Spectrum, frequency and penetrance of OPA1 mutations in dominant optic atrophy. Hum Mol Genet. 2001;10:1369–78. [PubMed: 11440989]

Treft RL, Sanborn GE, Carey J, Swartz M, Crisp D, Wester DC, Creel D. Dominant optic atrophy, deafness, ptosis, ophthalmoplegia, dystaxia, and myopathy. A new syndrome. Ophthalmology. 1984;91:908–15. [PubMed: 6493699]

Voo I, Allf BE, Udar N, Silva-Garcia R, Vance J, Small KW. Hereditary motor and sensory neuropathy type VI with optic atrophy. Am J Ophthalmol. 2003;136:670–7. [PubMed: 14516807]

Votruba M, Thiselton D, Bhattacharya SS. Optic disc morphology of patients with OPA1 autosomal dominant optic atrophy. Br J Ophthalmol. 2003;87:48–53. [PubMed: 12488262]

Wang L, Dong J, Cull G, Fortune B, Cioffi GA. Varicosities of intraretinal ganglion cell axons in human and nonhuman primates. Invest Ophthalmol Vis Sci. 2003;44:2–9. [PubMed: 12506048]

Zuchner S, De Jonghe P, Jordanova A, Claeys KG, Guergueltcheva V, Cherninkova S, Hamilton SR, Van Stavern G, Krajewski KM, Stajich J, Tournev I, Verhoeven K, Langerhorst CT, de Visser M, Baas F, Bird T, Timmerman V, Shy M, Vance JM. Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. Ann Neurol. 2006;59:276–81. [PubMed: 16437557]

Suggested Readings

Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res. 2004;23:53–89. [PubMed: 14766317]

Chinnery PF, Griffiths PG. Optic mitochondriopathies. Neurology. 2005;64:940–1. [PubMed: 15781804]

Delettre C, Lenaers G, Pelloquin L, Belenguer P, Hamel CP. OPA1 (Kjer type) dominant optic atrophy: a novel mitochondrial disease. Mol Genet Metab. 2002;75:97–107. [PubMed: 11855928]

Howell N. LHON and other optic nerve atrophies: the mitochondrial connection. Dev Ophthalmol. 2003;37:94–108. [PubMed: 12876832]

Newman NJ. Hereditary optic neuropathies: from the mitochondria to the optic nerve. Am J Ophthalmol. 2005;140:517–23. [PubMed: 16083845]

Newman NJ, Biousse V. Hereditary optic neuropathies. Eye. 2004;18:1144–60. [PubMed: 15534600]

Votruba M. Molecular genetic basis of primary inherited optic neuropathies. Eye. 2004;18:1126–32. [PubMed: 15534598]

Chapter Notes

Author Notes

Web site: Institut des Neurosciences de Montpellier

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