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Optic Atrophy Type 1

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Summary

Clinical 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 4 and 6 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). 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).

Visual evoked potentials are typically absent or delayed; pattern electroretinogram shows an abnormal N95:P50 ratio. Tritanopia is the classic feature of color vision defect, but more diffuse nonspecific dyschromatopsia is not uncommon. Ophthalmoscopic examination discloses temporal or diffuse pallor of the optic discs, sometimes associated with optic disc excavation. The neuroretinal rim shows some pallor in most cases, sometimes associated with a temporal pigmentary gray crescent.

Diagnosis

The diagnosis of OPA1 is made based on a combination of clinical findings, electrophysiologic studies, and family history and/or by the identification of a heterozygous pathogenic variant in *OPA1*, the only gene known to be associated with OPA1, by molecular genetic testing.

Management

Treatment of manifestations: Low-vision aids for decreased visual acuity.

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Surveillance: Annual ophthalmologic evaluations (including measurement of visual acuity, visual fields, and optical coherence tomography) and hearing evaluations.

Agents/circumstances to avoid: Smoking, excessive alcohol intake, medications (antibiotics, antivirals) that interfere with mitochondrial metabolism.

Genetic counseling

OPA1 is inherited in an autosomal dominant manner. Most individuals diagnosed with OPA1 have an affected parent; however, *de novo* pathogenic variants have been reported. Each child of an individual with OPA1 has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant has been identified in an affected family member, but genetic counseling remains complicated by the incomplete penetrance and the markedly variable inter- and intrafamilial expressivity of the disease.

Diagnosis

Suggestive Findings

Optic atrophy type 1 (OPA1 or Kjer type optic atrophy) **should be suspected** in individuals with the following clinical, electrophysiologic, and family history findings:

Clinical findings

- Childhood onset
- Bilateral vision loss that is usually symmetric
- Visual field defect that is typically centrocecal, central, or paracentral
- Peripheral field that is usually normal, although 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)
- Opthalmoscopic examination that demonstrates:
  - Optic nerve pallor (the cardinal sign) that is most often bilateral and symmetric, but may be temporal (50% of individuals) and global (50%) [Votruba et al 2003];
  - Profound papillary excavation (21% of eyes with OPA1) [Alward 2003];
  - Neuroretinal rim pallor in most cases, sometimes associated with a temporal pigmentary gray crescent.

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.

Family history is consistent with autosomal dominant inheritance. Absence of a family history of OPA1 does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of optic atrophy type 1 (OPA1) **is established** in a proband with the above clinical findings and/or a heterozygous pathogenic (or likely pathogenic) variant in *OPA1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *OPA1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **genomic testing**.

Single-gene testing

- Targeted analysis for the c.2826delT pathogenic variant can be performed first in individuals of Danish ancestry.
- In individuals who are not of Danish ancestry or if targeted analysis does not identify a pathogenic variant, sequence analysis of *OPA1* is performed, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- If no pathogenic variant is identified, molecular genetic testing of *OPA3* for autosomal dominant optic atrophy type 3 (OPA3) and for the common mitochondrial DNA (mtDNA) single-nucleotide pathogenic variants responsible for Leber hereditary optic neuropathy (LHON) should be considered (see Differential Diagnosis).

A multigene panel that includes *OPA1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of optic atrophy type 1.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method	
		Familial	Simplex [3]
OPA1	Sequence analysis [4]	8/9 [5] 10/14 [6] 17/19 [7]	4/8 [5]
	Gene-targeted deletion/ duplication analysis [8]	Unknown [9]	Unknown
	Targeted analysis for pathogenic variants [10]	Unknown	Unknown
Unknown [11]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Simplex = a single occurrence in a family
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Nakamura et al [2006] found heterozygous *OPA1* pathogenic variants 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 heterozygous *OPA1* pathogenic variants in relatives with a normal or only mildly abnormal phenotype, supporting the notions of variable expressivity and reduced penetrance.
6. Puomila et al [2005]
7. Delettre et al [2001]
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
9. A ~325-bp intronic insertion resulting in exon skipping has been reported [Gallus et al 2010]. See Molecular Genetics.
10. Detects the Danish founder pathogenic c.2826delT variant. Note: Pathogenic variants included in a panel may vary by laboratory.
11. Because the detection rate for pathogenic variants in *OPA1* is less than 100%, it is possible that families in which a pathogenic variant is not detected are not linked to the *OPA1* locus; however, no evidence currently supports this possibility.

Clinical Characteristics

Clinical Description

Vision loss. 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 asymmetric.

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).

Typical OPA1 is associated with a progressive and irreversible loss of vision. However, Cornille et al [2008] reported a man age 23 years who developed unexplained isolated, progressive, painless bilateral optic neuropathy as a result of central scotomas (visual acuity 20/200 in the right eye and 20/100 in the left eye) three

months after the first signs of visual loss. Six months later he had spontaneous and durable partial recovery of visual acuity (20/30 in the right eye and 20/25 in the left eye). He was the first affected individual described with a heterozygous pathogenic variant in one of the three alternative *OPA1* exons (see Genotype-Phenotype Correlations).

Extra-ophthalmogic findings. Up to 10% of persons with a heterozgyous *OPA1* pathogenic variant have additional extra-ophthalmologic abnormalities, most commonly sensorineural hearing loss, ataxia, and myopathy, suggesting that pathogenic variants in *OPA1* may be responsible for a continuum of phenotypes ranging from mild disorders affecting only the retinal ganglion cells to a severe and multisystemic disease.

Sensorineural hearing loss that ranges from severe and congenital to subclinical (requiring specific testing for detection) is the most frequently extra-ocular feature observed. Such hearing loss appears to be due to auditory neuropathy [Amati-Bonneau et al 2005]. Seven pathogenic variants in *OPA1* have been found to be associated with optic atrophy and hearing loss (see Genotype-Phenotype Correlations). Both intra- and interfamilial variation in the presence of hearing loss with optic atrophy has been observed.

Ataxia and **myopathy.** Some individuals developed proximal myopathy (35%), a combination of cerebellar and sensory ataxia in adulthood (29%), and axonal sensory and/or motor neuropathy (29%). These features became manifest from the third decade of life onwards.

Muscle biopsy revealed features diagnostic of mitochondrial myopathy. In these individuals approximately 10% of all fibers were deficient in histochemical COX activity and several fibers showed evidence of subsarcolemmal accumulation of abnormal mitochondria.

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 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 pathogenic variant [Puomila et al 2005].

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

Optic atrophy and **hearing loss.** Seven different pathogenic variants in *OPA1* have been reported in individuals with both optic atrophy and hearing loss: p.Arg445His, p.Gly401Asp, p.Leu243Ter, c.983A>G, p.Ile463_Phe464dup, p.Gln437Arg, and p.Ala357LeufsTer4 [Leruez et al 2013].

- In an individual with the p.Arg445His pathogenic variant, auditory brain stem responses (ABRs) were absent and both ears had normal evoked otoacoustic emissions [Amati-Bonneau et al 2005]. 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.

- 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 pathogenic variant in *OPA1* in both families [Payne et al 2004].
- Li et al [2005] identified the p.Arg445His pathogenic variant 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 whether myopia is part of the phenotype.
- In contrast, the p.Arg445His pathogenic variant was associated with optic atrophy **without** hearing loss in a Japanese individual age 21 years; no other family member was clinically affected or had the *OPA1* pathogenic variant [Shimizu et al 2003].

Alternate *OPA1* transcripts. Cornille et al [2008] reported a young man with unexplained isolated, progressive, painless bilateral optic neuropathy as a result of central scotomas (see Clinical Description, **Visual loss**) who harbored a heterozygous pathogenic variant in exon 5b (c.740G>A). This was the first report of a pathogenic variant in one of the three alternative *OPA1* exons, leading to an amino acid change in the N-terminal coiled coil domain (p.Arg247His) from isoform 8. This individual had spontaneous and durable partial recovery of visual acuity (20/30 in the right eye and 20/25 in the left eye) six months later.

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 pathogenic variant to pathogenic variant. It has been reported as high as 100% (variant c.1065+1G>T, resulting in exon 12 skipping) [Thiselton et al 2002] and as low as 43% (variant c.2708_2711delTTAG 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].

Nomenclature

Optic atrophy type 1 was formerly known as Kjer type optic atrophy.

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].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *OPA1*.

Differential Diagnosis

OPA3. *OPA3* consists of three exons and encodes for an inner mitochondrial membrane protein. The function of this protein is not well known. Two disorders are associated with pathogenic variants in *OPA3*:

- **Costeff optic atrophy syndrome (3-methylglutaconic aciduria type 3).** Pathogenic truncating variants are responsible for this 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, OPA3)** (OMIM 165300). Reynier et al [2004] have identified two pathogenic variants in *OPA3* (p.Gly93Ser and p.Gln105Glu) that change one of the amino acids. Inheritance is autosomal dominant.

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 25% 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 the majority of cases. After the acute phase, the optic discs become atrophic. Significant improvements in visual acuity are rare. Individuals then proceed into the atrophic phase and are usually legally blind for the rest of their lives with a permanent large centrocecal scotoma. Neurologic abnormalities such as postural tremor, peripheral neuropathy, nonspecific myopathy, and movement disorders have been reported to be more common in individuals with LHON than in controls. Some individuals with LHON, usually women, also have a multiple sclerosis (MS)-like illness.

LHON is transmitted by maternal inheritance. In one large study, 90% of individuals with LHON were found to have one of three pathogenic variants in mtDNA: m.11778G>A, m.14484T>C, m.3460G>A.

Autosomal dominant optic atrophy (ADOA). 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 gene in which mutation is causative is unknown.
- OPA5 (OMIM 610708) 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.

Another OPA locus for autosomal dominant optic atrophy (OPA8) was mapped to 16q21-q22 in one Italian family with extraophthalmologic features extending to the auditory system [Carelli et al 2007]. The gene in which mutation is causative is unknown.

Deafness-dystonia-optic neuronopathy syndrome (DDON). Males with DDON have prelingual or postlingual sensorineural hearing impairment in early childhood, 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 pathogenic variants in *TIMM8A* or a contiguous gene deletion syndrome at Xq22, which also includes X-linked agammaglobulinemia caused by disruption of *BTK*, located telomeric to *TIMM8A*.

WFS1. Biallelic pathogenic variants in *WFS1* 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]). Heterozygous pathogenic variants in *WFS1* cause autosomal dominant progressive low-frequency sensorineural hearing loss (LFSNHL) without ophthalmologic abnormalities [Cryns et al 2003]. However, Eiberg et al [2006] identified a *WFS1* heterozygous pathogenic variant associated with autosomal dominant optic atrophy, hearing loss, and impaired glucose regulation in one family, supporting the notion that

heterozygous pathogenic variants in *WFS1* as well as in *OPA1* may lead to optic atrophy combined with hearing impairment (see *WFS1*-Related Disorders).

MFN2. Charcot-Marie-Tooth (CMT) neuropathy type 2A with visual impairment resulting from optic atrophy has been designated as hereditary motor and sensory neuropathy type VI (HMSN VI) [Voo et al 2003]. Züchner 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 heterozygous pathogenic variant in *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** (OMIM 311050). A gene for X-linked optic atrophy (OPA2) has been mapped to chromosome Xp11.4-p11.21; to date no gene has been identified.
- **OPA6** (OMIM 258500). The first locus for isolated autosomal recessive optic atrophy (ROA1) has been mapped to chromosome 8q. Dyschromatopsia for red-green confusion occurs in OPA6.
- **OPA7** (OMIM 612989). Hanein et al [2009] identified an autosomal recessive juvenile-onset optic atrophy in a large multiplex consanguineous Algerian family and subsequently in three other Maghreb families. This form of optic atrophy is caused by biallelic pathogenic variants in *TMEM126A*, which encodes a mitochondrial protein found in higher eukaryotes that has four transmembrane domains and a central domain conserved with the related protein encoded by *TMEM126B*.

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

See OMIM Optic Atrophy Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual with optic atrophy type 1 (OPA1), the following evaluations are recommended:

- Assessment of visual acuity, color vision, and visual fields
- Assessment of extraocular muscles (the affected individual is asked to follow the ophthalmoscope with the eyes without moving the head)
- Hearing evaluation: auditory brain stem responses (ABRs), auditory evoked potentials (AEPs), and evoked otoacoustic emissions
- Oral glucose tolerance test
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No treatment for OPA1 is of proven efficacy.

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

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

For treatment of ataxia, see Ataxia Overview.

Surveillance

Appropriate surveillance includes:

- Annual ophthalmologic examination, including measurement of visual acuity and visual fields and optical coherence tomography (OCT);
- Annual hearing evaluation.

Agents/Circumstances to Avoid

Individuals with an *OPA1* pathogenic variant 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.
- To avoid medications (antibiotics, antivirals) that interfere with mitochondrial metabolism.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

A study using the antioxidant EPI-743 in individuals with autosomal dominant optic atrophy (ADOA), including persons with OPA1, is in preparation in Italy (Dr. Valerio Carelli, University of Bologna).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

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 *de novo OPA1* pathogenic variant.
  - Two instances of *de novo* pathogenic variants have been reported [Baris et al 2003].
  - In a report of molecular genetic testing in 980 persons for suspected hereditary optic neuropathies, about half of those identified as having a heterozygous *OPA1* pathogenic variant were simplex cases (i.e., a single occurrence in a family) [Ferré et al 2009].
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, two possible explanations are *de novo* mutation in the proband or germline mosaicism in a parent. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include: (1) ophthalmologic evaluation including an assessment of visual acuity, color vision, and visual fields; and (2) audiologic examinations consisting of auditory brain stem responses (ABRs), auditory evoked potentials (AEP) recordings, and study of evoked otoacoustic emissions.
- The family history of some individuals diagnosed with OPA1 may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of 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.
- The sibs of a proband with clinically unaffected parents are still at increased risk for OPA1 because of the possibility of reduced penetrance in a parent.

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

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 affected or has an *OPA1* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with optic atrophy type 1 has the *OPA1* pathogenic variant or clinical evidence of the disorder based on visual acuity study, color vision evaluation, fundus examination, VEP, and PERG, the *OPA1* pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *OPA1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for OPA1 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Optic Atrophy Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

OPA1	3q29	Dynamin-like 120 kDa protein, mitochondrial	OPA1 database	OPA1	OPA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Optic Atrophy Type 1 (View All in OMIM)

165500	OPTIC ATROPHY 1; OPA1
605290	OPA1 MITOCHONDRIAL DYNAMIN-LIKE GTPase; OPA1

Molecular 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 retinal ganglion cells. 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, pathogenic variants in the pro-fusion protein encoded by *MFN2*, which cause a peripheral neuropathy (see CMT2A) [Züchner et al 2006], significantly impaired the transport of mitochondria in axons in neurons expressing disease-causing forms of *MFN2* [Baloh et al 2007]. These data suggest that proper localization of mitochondria is critical for axonal and synaptic function.

Gene structure. *OPA1* 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]. For details see Table A, **Gene**.

Pathogenic variants. There is a wide spectrum of pathogenic variants, with more than 213 reported to date (see Table A, **Locus-Specific Databases** and **ClinVar**). The *OPA1* pathogenic variants are distributed throughout the coding sequence, but most are localized in exons 8-16 encoding the GTPase domain and in the last two coding exons: 27 and 28); fewer pathogenic variants are found in exons 1 to 7. To date no pathogenic variants have been found in exons 4 and 4b, which are alternatively spliced. However, a heterozygous pathogenic variant in exon 5b (c.740G>A) has been described in one affected individual [Cornille et al 2008].

An ~325-bp Alu-element insertion located in intron 7 of *OPA1* [NM_015560.2] has been described as causing an in-frame deletion of exon 8 in a family with autosomal dominant optic atrophy (ADOA) [Gallus et al 2010].

Table 2. *OPA1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.740G>A [2]	p.Arg247His	NM_130837.2 NP_570850.2 (isoform 8)
c.1065+1G>T (IVS12+1G>T)	--	NM_015560.2
c.728T>A	p.Leu243Ter	NM_015560.2 NP_056375.2 (isoform 1)
c.983A>G [3]	--	NM_015560.2
c.1067_1068dup	p.Ala357LeufsTer4	NM_015560.2 NP_056375.2 (isoform 1)
c.1202G>A	p.Gly401Asp	
c.1310A>G	p.Gln437Arg	
c.1334G>A	p.Arg445His	
c.1387_1392dup	p.Ile463_Phe464dup	
c.2708_2711delTTAG	p.Val903GlyfsTer3	
c.2826delT	p.Arg943GlufsTer25	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. In exon 5b of alternative transcript that encodes isoform 8 (Table A, **Gene**)
3. Substitution in the antepenultimate nucleotide position of exon 9, which modifies the consensus sequence of the 5' donor splice site of intron 9, resulting in an in-frame skipping of exon 9 [Baris et al 2003]

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]. Mitochondrial DNA (mtDNA) deletions have been identified in families with autosomal dominant optic atrophy who have complex multisystem involvement in addition to the optic neuropathy [Amati-Bonneau et al 2008, Ferraris et al 2008, Hudson et al 2008] suggesting a role of OPA1 in mtDNA maintenance.

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

Interestingly, evidence for a dominant-negative mechanism has been reported in all the multisystemic forms of the disease (ADOAD and "ADOA plus"). These disease forms have pathogenic missense variants affecting the GTPase domain [Amati-Bonneau et al 2008]. In addition, one person with ADOA, who had biallelic pathogenic

OPA1 missense variants located in exon 8, was severely affected by the disease [Pesch et al 2001], whereas her heterozygous parents and sibs were less severely affected, suggesting a semi-dominant mode of inheritance in this family.

Chapter Notes

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