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Leber Hereditary Optic Neuropathy

Synonyms: Leber's Disease, Leber's Hereditary Optic Neuropathy, Leber's Optic Atrophy, Leber's Optic Neuropathy, LHON

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Summary

Clinical characteristics

Leber hereditary optic neuropathy (LHON) typically presents in young adults as bilateral, painless, subacute visual failure. The peak age of onset in LHON is in the second and third decades of life, with 90% of those who lose their vision doing so before age 50 years. Very rarely, individuals first manifest LHON in the seventh and eighth decades of life. Males are four to five times more likely to be affected than females, but neither sex nor mutational status significantly influences the timing and severity of the initial visual loss. 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 the general population. Some individuals with LHON, usually women, may also develop a multiple sclerosis-like illness.

Diagnosis/testing

The diagnosis of LHON is established in a proband with a consistent clinical history and/or one of three common mitochondrial DNA (mtDNA) pathogenic variants identified on molecular genetic testing.

Management

Treatment of manifestations: Management of affected individuals remains mostly supportive, and includes provision of visual aids, occupational rehabilitation, and registration with the relevant social services. Idebenone (Raxone®) has been approved for the treatment of LHON by the European Medicines Agency under exceptional circumstances. The current body of evidence indicates some visual benefit in a subgroup of affected individuals treated with idebenone, particularly those treated within the first year of onset of visual loss.

Referral to a cardiologist for individuals with pre-excitation syndrome on EKG is recommended; treatment for symptomatic individuals is per standard practice.

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A multidisciplinary approach for those affected individuals with extraocular neurologic features (ataxia, peripheral neuropathy, nonspecific myopathy, and movement disorders) should be considered to minimize the functional consequences of these complications.

Agents/circumstances to avoid: Individuals in whom a LHON-causing mtDNA variant has been identified should be strongly advised not to smoke and to moderate alcohol intake, avoiding binge-drinking episodes. It would be reasonable to avoid exposure to other putative environmental triggers for visual loss, such as head trauma, industrial toxins, and drugs with mitochondrial toxic effects.

Genetic counseling

LHON is caused by pathogenic variants in mtDNA and is transmitted strictly by maternal inheritance. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have developed visual loss. A male (affected or unaffected) with a primary LHON-causing mtDNA pathogenic variant cannot transmit the variant to any of his offspring. A female (affected or unaffected) with a primary LHON-causing mtDNA variant transmits the variant to all of her offspring. In approximately 60% of families, a history of visual loss affecting maternal relatives is present. Genetic counseling for LHON is complicated by the sex- and age-dependent penetrance of the primary mtDNA LHON-causing pathogenic variants and penetrance can vary markedly in different branches of the same family and between families harboring the same LHON-causing mtDNA pathogenic variant. Once a mtDNA LHON-causing variant in the mother has been identified, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible; however, accurate interpretation of a positive prenatal test result is difficult because the mtDNA mutational load in amniocytes and chorionic villi may not correspond to that of other fetal or adult tissues, and the presence of the mtDNA LHON-causing variant does not predict the occurrence, age of onset, severity, or rate of progression of visual loss.

Diagnosis

No consensus clinical diagnostic criteria for Leber hereditary optic neuropathy (LHON) have been published.

Suggestive Findings

Leber hereditary optic neuropathy (LHON) **should be suspected** in individuals with the following ophthalmologic, extraocular, neuroimaging, and biochemical findings and family history.

Ophthalmologic

- Bilateral, painless subacute visual failure that develops during young adult life
  - Visual acuity is severely reduced to 20/200 or worse in the majority of cases.
  - Visual field testing by kinetic or static perimetry shows an enlarging dense central or centrocecal scotoma.
- Disk hyperemia, edema of the peripapillary retinal nerve fiber layer, retinal telangiectasia, and increased vascular tortuosity

  Note: Approximately 20% of affected individuals show no fundal abnormalities in the acute stage.
- Optic disc atrophy
- Optic nerve dysfunction and absence of other retinal diseases on electrophysiologic studies (pattern electroretinogram and visual evoked potentials)

Extraocular

- Neurologic abnormalities

- Postural tremor
- Peripheral neuropathy
- Movement disorders
- Multiple sclerosis-like illness

- Nonspecific myopathy
- Cardiac arrhythmias

Neuroimaging. MRI is often normal, but may reveal white matter lesions and/or a high signal within the optic nerves [Matthews et al 2015].

Biochemical studies show respiratory chain defects that are more subtle than those seen in other mitochondrial genetic disorders. The m.3460G>A pathogenic variant in *MT-ND1* is associated with the most severe biochemical phenotype (see Table 1).

Table 1. Respiratory Chain Dysfunction in Leber Hereditary Optic Neuropathy

Mitochondrial DNA Variant	In Vitro		In Vivo
	Complex I activity	Respiratory rate [1]	MRS [1]
m.3460G>A	60%-80% less than controls	30%-35%	0%
m.11778G>A	0%-50% less than controls	30%-50%	75%
m.14484T>C	0%-65% less than controls	10%-20%	50%

See references in Yu-Wai-Man et al [2002].
MRS = magnetic resonance spectroscopy
1. % of decrease relative to controls

Family history is consistent with maternal inheritance (e.g., affected females transmit the disorder to all offspring; affected males do not transmit the disorder). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of LHON **is established** in a proband with the ocular manifestations listed in Suggestive Findings **and/or** by one of three common mtDNA pathogenic variants identified by molecular genetic testing (see Table 2).

Note: Identification of a mtDNA variant of uncertain significance does not by itself establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** methods (i.e., targeted mtDNA analysis for pathogenic variants, multigene panel, and complete mtDNA sequencing).

Step 1

Targeted mtDNA analysis for pathogenic variants. Targeted analysis for the three common mtDNA pathogenic variants observed in approximately 90% of individuals with LHON should be performed first.

- m.3460G>A in *MT-ND1*
- m.11778G>A in *MT-ND4*, present in 60%-70% of affected individuals of northern European descent and approximately 90% of affected individuals of Asian descent [Mackey et al 1996, Mashima et al 1998, Jia et al 2006]
- m.14484T>C in *MT-ND6*, the predominant variant among individuals of French Canadian descent due to a founder effect [Mackey et al 1996, Macmillan et al 1998, Chinnery et al 2001, Yu-Wai-Man et al 2003]

Step 2

A mitochondrial disease multigene panel that includes the mitochondrial genes that encode subunits of NADH dehydrogenase (*MT-ND1*, *MT-ND2*, *MT-ND3, MT-ND4*, *MT-ND4L*, *MT-ND5*, and *MT-ND6*) known to cause LHON, 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. 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*. (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.

Step 3

Complete mtDNA sequencing may be considered if use of targeted testing and/or a multigene panel did not identify a pathogenic variant, clinical suspicion of LHON remains high, and there is no evidence of paternal transmission.

Table 2. Molecular Genetic Testing Used in Leber Hereditary Optic Neuropathy

Gene [1]	Proportion of LHON Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method		
		Targeted analysis for pathogenic variants	Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
MT-ND4 *MT-ND6* *MT-ND1*	~90% [5, 6]	See footnote 7.	90% [6]	None reported [6]
Select mitochondrial genes	~10% [6, 8]		10% [6]	None reported [6]

LHON = Leber hereditary optic neuropathy
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. 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.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Mackey et al [1996]
6. Mitomap
7. The three most common pathogenic variants are: m.11778G>A (in *MT-ND4*), accounting for 60%-70% of cases among northern European populations [Wallace et al 1988, Mackey et al 1996]; m.14484T>C (in *MT-ND6*), most common among French Canadians as a result of a founder effect [Johns et al 1992a, Macmillan et al 1998]; and m.3460G>A (in *MT-ND1*) [Howell et al 1992].
8. Achilli et al [2012]

Interpretation of test results. Heteroplasmy, a mixture of mutated and wild type mtDNA in leukocytes, occurs in approximately 10%-15% of individuals with LHON [Smith et al 1993, Yu-Wai-Man et al 2003].

- Heteroplasmy does not influence the sensitivity of molecular genetic testing for LHON because affected individuals generally have more than 70% mutated mtDNA in leukocytes, which is easily detected by standard techniques.

- It is likely that the level of heteroplasmy may have a bearing on the risk of developing LHON in the asymptomatic individual and on the risk for transmission [Chinnery et al 2001]; however, no rigorous prospective studies have been performed to clarify this possibility.

Clinical Characteristics

Clinical Description

Leber hereditary optic neuropathy (LHON) typically presents in young adults as bilateral painless subacute visual failure. The peak age of onset in LHON is in the second and third decades of life, with 95% of those who lose their vision doing so before age 50 years. Very rarely, individuals first manifest LHON in the seventh and eighth decades of life [Dimitriadis et al 2014]. Males are four to five times more likely to be affected than females, but neither sex nor mutational status significantly influences the timing and severity of the initial visual loss.

In the **presymptomatic phase**, fundal abnormalities including peripapillary telangiectatic vessels and variable degrees of retinal nerve fiber layer edema have been previously documented; these can vary with time [Nikoskelainen 1994]. Using optical coherence tomography imaging, thickening of the temporal retinal nerve fiber layer was confirmed in clinically unaffected individuals with a LHON-causing mtDNA pathogenic variant, providing further evidence that the papillomacular bundle is particularly vulnerable in LHON [Savini et al 2005]. On more detailed investigation, some individuals with a LHON-causing mtDNA pathogenic variant can also exhibit subtle impairment of optic nerve function including (1) loss of color vision affecting mostly the red-green system, (2) reduced contrast sensitivity, and (3) subnormal electroretinogram and visual evoked potential [Sadun et al 2006].

Affected individuals are usually entirely asymptomatic until they develop visual blurring affecting the central visual field in one eye (**acute phase**); similar symptoms appear in the other eye within weeks or months, with at least 97% of affected individuals having bilateral involvement within one year [Newman et al 2020]. In 25%-50% of individuals, visual loss is bilateral at onset. The most characteristic feature is an enlarging central or centrocecal scotoma, and as the field defect increases in size and density, visual acuity deteriorates to the level of counting fingers or worse.

Broad generalizations with regard to specific LHON-causing pathogenic variants:

- Variants m.3460G>A and m.11778G>A are associated with significant impairment in visual function and poor visual recovery.
- Variant m.14484T>C is associated with the best long-term visual outcome.

Following the nadir, visual acuity may improve. Note, however, that recovery of visual function in LHON – if it does occur – is usually incomplete.

Reported visual recovery rates in persons with LHON are summarized in Table 3.

In a meta-analysis of 12 retrospective and three prospective studies providing visual function information on 695 affected individuals with the m.11778G>A variant, visual recovery occurred in 14% of affected individuals of all ages and 11% of those age 15 years or older [Newman et al 2020].

Table 3. Visual Recovery Rates by Pathogenic Variant in Individuals with Leber Hereditary Optic Neuropathy

Mitochondrial DNA Variant	Visual Recovery [1]	References
m.11778G>A	14% of persons of all ages; 11% of those age ≥15 yrs	Newman et al [2020]
m.14484T>C	37%-64%	Johns et al [1993], Macmillan et al [1998], Spruijt et al [2006]

Table 3. continued from previous page.

Mitochondrial DNA Variant	Visual Recovery [1]	References
m.3460G>A	15%-25% [2]	Johns et al [1992b], Harding et al [1995], Spruijt et al [2006]

1. Different criteria were used to define visual recovery; the range partly reflects this variability.
2. Although published reports would appear to indicate otherwise, the m.3460G>A pathogenic variant is generally accepted among experts as having the worst visual recovery rate [Author, personal communication].

Other predictors of better visual recovery have included an earlier age of onset (≤12 years), a subacute presentation with slow visual deterioration, and a relatively large optic disc [Barboni et al 2006, Ramos et al 2009, Majander et al 2017].

The lifetime risk of visual failure by sex and age in individuals with a homoplasmic primary LHON-causing pathogenic variant is summarized in Table 4.

Table 4. Lifetime Risk for Visual Failure in Individuals with a Homoplasmic Primary LHON-Causing Mitochondrial DNA Pathogenic Variant by Study

Mitochondrial DNA Pathogenic Variant	Risk of Developing Symptoms		Median Age at Onset (M)	M:F Ratio	Reference
	M	F			
m.3460G>A	32%	15%	20 yrs	4.3:1	Nikoskelainen [1994]
m.3460G>A	49%	28%	22 yrs	1.7:1	Yu-Wai-Man et al [2003]
m.11778G>A	43%	11%	24 yrs	3.7:1	Harding et al [1995]
m.11778G>A	51%	9%	22 yrs	5.1:1	Yu-Wai-Man et al [2003]
m.14484T>C	47%	8%	20 yrs	7.7:1	Macmillan et al [1998]

F = female(s); M = male(s)

The **chronic phase** is characterized by optic atrophy (which typically develops within six weeks of the onset of visual loss), marked thinning of the retinal nerve fiber layer, and a dense central or centrocecal scotoma. Most persons remain severely visually impaired and are within the legal requirements for blind registration [Kirkman et al 2009a].

Other neurologic features associated with LHON. Some neurologic abnormalities (e.g., postural tremor, peripheral neuropathy, nonspecific myopathy, movement disorders, Leigh syndrome) have been reported to be common in individuals with LHON [McFarland et al 2007, Martikainen et al 2016].

A multiple sclerosis (MS)-like illness has been reported in association with all three primary mtDNA LHON-causing pathogenic variants (m.3460G>A, m.11778G>A, and m.14484T>C), but with a female bias [Pfeffer et al 2013].

The pattern of visual loss in LHON-MS appears distinct from classic LHON, being marked by recurrent episodes of visual loss that can be associated with ocular pain, but with incomplete visual recovery and progression to legal blindness in half of all affected persons [Pfeffer et al 2013]. In addition to a severe bilateral optic neuropathy, these individuals manifest disseminated central nervous system demyelination, with characteristic periventricular white matter lesions on neuroimaging and unmatched cerebrospinal fluid oligoclonal bands [Bhatti & Newman 1999, Horváth et al 2000, Palace 2009].

Cardiac conduction defects and LHON. A Finnish study showed an increased incidence of cardiac arrhythmias secondary to accessory pathways in association with LHON [Nikoskelainen 1994]; this finding has not been replicated in other populations [Bower et al 1992].

Genotype-Phenotype Correlations

See Clinical Description.

Penetrance

LHON-causing mtDNA pathogenic variants are characterized by reduced penetrance. An individual can only develop LHON if a pathogenic mtDNA LHON-causing variant is present, but it must be stressed that penetrance can vary markedly in different branches of the same family and between families with the same LHON-causing mtDNA pathogenic variant, which complicates genetic counseling at the individual level.

The two most important risk factors for vision loss are sex and age [Yu-Wai-Man et al 2009].

- **Sex.** Approximately 50% of males and 90% of females with a primary LHON-causing mtDNA pathogenic variant do not develop blindness.
- **Age.** The 95th centile for age at onset in a male is 50 years for all three primary pathogenic variants. Thus, a clinically unaffected male age 50 years has less than a 1/20 chance of losing his vision [Yu-Wai-Man et al 2003] (see also Table 4).

Additional genetic and environmental factors interact with the primary mtDNA pathogenic variant and influence whether an individual ultimately develops optic nerve dysfunction and visual failure.

- **Heteroplasmy.** Many mitochondria (and thus many mtDNA molecules) are present in each cell. Some individuals with a pathogenic LHON-causing mtDNA variant have a mixture of mutated and wild-type species of mtDNA, a finding referred to as heteroplasmy. Heteroplasmy is present in 10%-15% of individuals with a LHON-causing mtDNA variant.
  - In one study, individuals with a m.11778G>A pathogenic variant load of less than 75% in their leukocytes were unaffected [Smith et al 1993].
  - In a retrospective analysis of 17 families heteroplasmic for the m.11778G>A pathogenic variant, males with a mutational load greater than 60% in their leukocytes had a higher frequency of optic neuropathy than those with lower mutational loads [Chinnery et al 2001].

  However, testing to quantify the level of heteroplasmy for the purpose of presymptomatic diagnosis (see Genetic Counseling) is limited, as the majority of individuals with a LHON-causing mtDNA variant are homoplasmic.
- **Smoking** has been associated with an increased risk of vision loss in LHON [Kirkman et al 2009b].

Nomenclature

In the past, LHON was sometimes referred to as Leber hereditary optic neuroretinopathy; this term is outdated and should not be used.

Prevalence

In northeast England, 1:8,500 individuals were found to have a pathogenic LHON-causing variant; 1:31,000 had experienced visual loss as a result of LHON [Yu-Wai-Man et al 2003, Gorman et al 2015].

Fairly similar figures have been reported in other northern European populations, with a disease prevalence of 1:39,000 in the Netherlands and 1:50,000 in Finland [Spruijt et al 2006, Puomila et al 2007].

Genetically Related (Allelic) Disorders

Mitochondrial DNA pathogenic variants are responsible for a heterogeneous group of inherited diseases (see Mitochondrial Disorders Overview) that often cause a progressive neurologic disorder in association with multiorgan involvement (e.g., diabetes mellitus, cardiomyopathy) [McFarland et al 2010, Lightowlers et al 2015].

- In a few families, mtDNA complex I pathogenic variants cause optic atrophy in association with severe neurologic deficits including ataxia, dystonia, and encephalopathy [Jun et al 1994, De Vries et al 1996, Gropman et al 2004, Tarnopolsky et al 2004, Watanabe et al 2006].
- Two mtDNA complex I single-nucleotide variants, m.3376G>A and m.3697G>A, have also been identified in individuals with a LHON-like optic neuropathy and clinical features of MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*trokelike episodes) [Blakely et al 2005, Spruijt et al 2007].

Differential Diagnosis

Unilateral optic nerve involvement in Leber hereditary optic neuronopathy (LHON) is exceptionally rare; if it is present, another underlying pathologic process should be actively excluded.

If the ophthalmologic assessment (including an assessment of visual acuity, color vision, visual fields, and electrophysiology) and molecular genetic testing leave any uncertainty about the diagnosis of LHON, further investigations are appropriate to exclude other potentially reversible causes of bilateral optic neuropathy and to allow for the initiation of prompt treatment before visual loss becomes irreversible.

Depending on the clinical presentation and evolution, the following could be considered:

- Autoantibody testing and an infectious or vasculitic screen
- A lumbar puncture to evaluate for unmatched oligoclonal bands when demyelination is suspected or to exclude infection and neoplasia
- Use of the appropriate neuroimaging modality, ideally reviewed with an experienced neuroradiologist

Acute phase. A wide range of non-genetic causes of bilateral visual failure must be excluded during the acute phase.

Chronic phase. If an individual is only seen at this stage, it can be difficult to exclude other possible causes of optic atrophy, especially if there is no clear maternal family history. In these instances, neuroimaging of the anterior visual pathways is mandatory while awaiting the results of molecular genetic testing.

Management

An international consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy (LHON) has been published [Carelli et al 2017].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Leber hereditary optic neuropathy (LHON), the evaluations summarized below (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Measurement of best corrected visual acuity
- Assessment of visual fields with static or kinetic perimetry
- Measurement of retinal nerve fiber layer thickness with optical coherence tomography imaging
- EKG. Although a relatively rare finding, an EKG may reveal a pre-excitation syndrome in both symptomatic and asymptomatic individuals who have a LHON-causing mtDNA variant. Even when

present, such an EKG finding does not necessitate further intervention in the absence of cardiac symptoms.
- Screening for possible associated neurologic complications, which can further compound the visual impairment in individuals with LHON
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of LHON in order to facilitate medical and personal decision making

Treatment of Manifestations

Management of affected individuals remains mostly supportive and includes provision of visual aids, occupational rehabilitation, and registration with the relevant local social services.

Idebenone (Raxone®) has been approved for the treatment of LHON under exceptional circumstances by the European Medicines Agency [Carelli et al 2017]. The current body of evidence indicates some visual benefit in a subgroup of affected individuals treated with idebenone, in particular those treated within the first year of disease onset [Klopstock et al 2011, Carelli et al 2011, Catarino et al 2020].

There is evidence that increased intraocular pressure could be a risk factor triggering visual loss in individuals at risk for developing LHON. Until further evidence becomes available, it is reasonable to set a lower threshold for initiating treatment for increased intraocular pressure in individuals with a LHON-causing variant given the possible deleterious consequences for mitochondrial function and retinal ganglion cell survival [Thouin et al 2013].

A minority of individuals with LHON develop neurologic features including ataxia, peripheral neuropathy, nonspecific myopathy, and movement disorders [Yu-Wai-Man et al 2016]. This group of affected individuals should be managed by a multidisciplinary team of physicians and allied professionals to minimize the functional consequences of these neurologic complications.

In those individuals who are found to have pre-excitation syndrome on EKG, referral to a cardiologist should be considered. Treatment for symptomatic individuals with pre-excitation syndrome is the same as for the general population.

Surveillance

Ongoing surveillance of asymptomatic individuals with a LHON-causing mtDNA variant is not necessary; however, they should be advised to seek immediate medical attention if they experience any visual disturbance.

The frequency of follow up for affected individuals varies depending on the individual's personal circumstances and the availability of health care locally.

Agents/Circumstances to Avoid

Individuals with established LHON-causing mtDNA variants should be strongly advised not to smoke and to moderate their alcohol intake, avoiding binge-drinking episodes [Kirkman et al 2009b].

Although based largely on anecdotal evidence, avoidance of other environmental factors that have been implicated in precipitating visual loss in LHON (e.g., head trauma, industrial toxins, drugs with mitochondrial toxic effects) is reasonable [Yu-Wai-Man et al 2011].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Gene therapy. Promising preclinical data based on in vitro and rodent models have resulted in the launch of pivotal clinical trials for affected individuals with the m.11778G>A pathogenic variant. The intervention involves the intravitreal injection of a modified adeno-associated virus (AAV2) vector carrying the replacement *MT-ND4* subunit with a mitochondrial targeting sequence (see ClinicalTrials.gov). The published results from ongoing gene therapy programs indicate significant visual improvement in treated individuals beyond what would be expected based on the natural history of LHON [Guy et al 2017, Yuan et al 2020, Yu-Wai-Man et al 2020, Newman et al 2021].

Hormone therapy. The marked male bias in LHON could reflect a protective influence of female sex hormones; this hypothesis was recently investigated using LHON cybrid cell lines. Treatment with estrogens was found to reduce reactive oxygen species levels in these LHON cybrids, with increased activity of the antioxidant enzyme superoxide dismutase. These beneficial estrogenic effects translated into more efficient mitochondrial oxidative phosphorylation [Giordano et al 2011, Pisano et al 2015].

Mitochondrial replacement. In vitro fertilization (IVF) techniques aimed at preventing the maternal transmission of mtDNA pathogenic variants from mother to child are being developed. Pronuclear transfer and metaphase II spindle transfer are the two approaches that are being investigated, and further experimental work to validate the safety of these IVF strategies is currently ongoing [Tachibana et al 2009, Craven et al 2010, Chinnery et al 2014]. Mitochondrial replacement to prevent the transmission of mtDNA disease with pronuclear transfer has recently been licensed by the Human Fertilisation and Embryology Authority for clinical use in the United Kingdom [Craven et al 2020]. An ongoing research study will look at the outcome at age 18 months for children in whom this novel reproductive technology was used.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

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

Leber hereditary optic neuropathy (LHON) is caused by pathogenic variants in mitochondrial DNA (mtDNA) and is transmitted strictly by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the mtDNA pathogenic variant.
- The mother of a proband usually has the mtDNA pathogenic variant and may or may not have developed visual loss.
- In approximately 60% of families, a history of visual loss affecting maternal relatives is present.
- Up to 40% of individuals with LHON have no known family history of LHON. The explanation for apparently simplex cases may be absence of a comprehensive and/or reliable family history or, in rare cases, a *de novo* mtDNA pathogenic variant in the proband.

- Maternal testing is not considered necessary for recurrence risk counseling as the mtDNA LHON-causing variant is usually homoplasmic or present at high levels in the proband [Carelli et al 2017].

Sibs of a proband

- All sibs of a proband will inherit the mtDNA LHON-causing variant and may or may not have symptoms (see **Offspring of a proband**). If the mother of the proband is heteroplasmic for the mtDNA LHON-causing variant, she may transmit a lower level of mutated mtDNA to sibs of the proband, conferring a lower disease risk [Chinnery et al 2001].
- Penetrance can vary markedly between sibs with the same LHON-causing mtDNA pathogenic variant (see Penetrance).

Offspring of a proband

- A male (affected or unaffected) with a primary LHON-causing mtDNA variant **cannot** transmit the variant to any of his offspring.
- A female (affected or unaffected) with a primary LHON-causing mtDNA variant will transmit the variant to all of her offspring.
- The presence of the mtDNA pathogenic variant does not predict the occurrence, age of onset, severity, or rate of progression of visual loss. See Clinical Description and Penetrance for information regarding the risk to individuals with a primary LHON-causing mtDNA variant of being affected.
- If a female proband is heteroplasmic for the mtDNA LHON-causing variant, she may transmit a lower level of mutated mtDNA to her offspring, conferring a low disease risk [Chinnery et al 2001].

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the proband's mother has a mtDNA pathogenic variant, her sibs and mother are also at risk.

Related Genetic Counseling Issues

Penetrance. Genetic counseling for LHON is complicated by the sex- and age-dependent penetrance of the primary LHON-causing mtDNA variants.

- Large studies have established accurate risks for the m.11778G>A and m.14484T>C pathogenic variants (reviewed in Yu-Wai-Man et al [2009]). Confirming the genetic status of an individual at risk for one of these pathogenic variants who is seeking counseling allows for an accurate estimation of the risks, based on established age- and sex-specific penetrance data (see Clinical Description). Data for the m.3460G>A pathogenic variant are more limited. Similarly, counseling for the other pathogenic variants requires cautious extrapolation.
- The identification of the familial LHON-related pathogenic variant confers a lifetime risk; however, such testing is not useful in predicting the age of onset or the visual outcome in family members. The most important factors determining risk are sex and age (see Clinical Description and Penetrance). For example, a male age 18 years has a lifetime risk of approximately 50% for LHON **after** a positive test result. The risk declines with age but (because loss of sight can occur at any age) never falls to zero. In large, multigenerational LHON pedigrees, these risks were known **before** the advent of molecular genetic testing.
- It must be stressed that the penetrance can vary markedly in different branches of the same family and between families with the same LHON-causing mtDNA pathogenic variant.

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, allelic variants, 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 genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once a mtDNA LHON-causing variant in the mother has been identified, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing [Sallevelt et al 2013] are possible.

Accurate interpretation of a positive prenatal test result is difficult for the following reasons:

- The majority of mothers will be homoplasmic for the mtDNA LHON-causing variant. For mothers who are heteroplasmic, the mtDNA mutational load in amniocytes and chorionic villi may not correspond to that of other fetal or adult tissues due to mitotic segregation.
- The presence of the mtDNA LHON-causing variant does not predict the occurrence, age of onset, severity, or rate of progression of visual loss in this mitochondrial genetic disorder. See Clinical Description for information regarding the risk to individuals with a primary LHON-causing mtDNA variant of being affected.

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. For more information, see the National Society of Genetic Counselors position statement on prenatal testing for adult-onset conditions.

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.

- **LHON**
  www.lhon.org
- **LHON Society**
  United Kingdom
  www.lhonsociety.org
- **MedlinePlus**
  Leber hereditary optic neuropathy
- **International Foundation for Optic Nerve Disease (IFOND)**
  NY
  Phone: 845-534-8606
  Email: ifond@aol.com
  www.ifond.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org

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. Leber Hereditary Optic Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
MT-ATP6	Mitochondrion	ATP synthase subunit a	MT-ATP6
MT-CO3	Mitochondrion	Cytochrome c oxidase subunit 3	MT-CO3
MT-CYB	Mitochondrion	Cytochrome b	MT-CYB
MT-ND1	Mitochondrion	NADH-ubiquinone oxidoreductase chain 1	MT-ND1
MT-ND2	Mitochondrion	NADH-ubiquinone oxidoreductase chain 2	MT-ND2
MT-ND3	Mitochondrion	NADH-ubiquinone oxidoreductase chain 3	MT-ND3
MT-ND4	Mitochondrion	NADH-ubiquinone oxidoreductase chain 4	MT-ND4
MT-ND4L	Mitochondrion	NADH-ubiquinone oxidoreductase chain 4L	MT-ND4L
MT-ND5	Mitochondrion	NADH-ubiquinone oxidoreductase chain 5	MT-ND5
MT-ND6	Mitochondrion	NADH-ubiquinone oxidoreductase chain 6	MT-ND6

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 Leber Hereditary Optic Neuropathy (View All in OMIM)

516000	COMPLEX I, SUBUNIT ND1; MTND1
516001	COMPLEX I, SUBUNIT ND2; MTND2
516003	COMPLEX I, SUBUNIT ND4; MTND4
516004	COMPLEX I, SUBUNIT ND4L; MTND4L
516005	COMPLEX I, SUBUNIT ND5; MTND5
516006	COMPLEX I, SUBUNIT ND6; MTND6
516020	CYTOCHROME b OF COMPLEX III; MTCYB
516050	CYTOCHROME c OXIDASE III; MTCO3
516060	ATP SYNTHASE 6; MTATP6
535000	LEBER OPTIC ATROPHY

Molecular Pathogenesis

See Mitochondrial Disorders Overview.

The ocular pathology in Leber hereditary optic neuropathy (LHON) is limited to the retinal ganglion cell layer with sparing of the retinal pigment epithelium and photoreceptor layers. There is marked cell body and axonal degeneration, with associated demyelination, extending to the lateral geniculate bodies. A number of pathologic factors have been implicated, including a reduction in the amount of ATP being produced by the mitochondrial respiratory chain (Table 1), impaired glutamate transport, and increased levels of reactive oxygen species production, all of which ultimately trigger retinal ganglion cell death via an apoptotic mechanism [Danielson et al 2002, Beretta et al 2004, Zanna et al 2005, Levin 2015, Yu-Wai-Man et al 2017].

Although LHON has a well-defined clinical and molecular genetic phenotype, the pathophysiology is complex and the selective vulnerability of retinal ganglion cells in this mitochondrial disorder remains unexplained [Yu-Wai-Man et al 2011].

Table 5 includes a complete list of mitochondrial DNA variants identified in individuals with LHON [Jurkute et al 2019].

Table 5. Mitochondrial DNA Variants Identified in Individuals with LHON

Reference Sequence	Gene	Mitochondrial DNA Variant [1]
NC_012920.1	*MT-ND4* [2]	**m.11778G>A** m.11696G>A m.11253T>C
	MT-ND6 [2]	**m.14484T>C** m.14325T>C m.14459G>A [3] m.14729G>A m.14482C>G [3] m.14482C>A [3] m.14495A>G [3] m.14498C>T m.14568C>T [3] m.14596A>T
	MT-ND1 [2]	**m.3460G>A** m.3376G>A m.3635G>A [3] m.3697G>A m.3700G>A [3] m.3733G>A [3] m.4025C>T m.4160T>C [3] m.4171C>A [3]
	MT-ND2	m.4640C>A m.5244G>A
	MT-ND3	m.10237T>C
	MT-ND4L	m.10663T>C [3]
	MT-ND5	m.12811T>C m.12848C>T m.13637A>G m.13730G>A
	MT-ATP6	m.9101T>C
	MT-CO3	m.9804G>A
	MT-CYB	m.14831G>A

From Jurkute et al [2019], Table 1

1. **Bolded** variants are the three most common causes of LHON.

2. Core genes

3. Mitochondrial DNA variants that affect function. They have been identified in at least two independent LHON pedigrees and segregate with affected disease status.

Chapter Notes

Revision History

- 11 March 2021 (bp) Comprehensive update posted live
- 23 June 2016 (ma) Comprehensive update posted live
- 19 September 2013 (me) Comprehensive update posted live
- 19 April 2012 (cd/pc) Revision: prenatal testing no longer listed in GeneTests Laboratory Directory; addition to therapies (EPI-743)
- 7 July 2011 (me) Comprehensive update posted live
- 10 March 2008 (me) Comprehensive update posted live
- 3 October 2005 (pc) Revision: mitochondrial gene *MT-ND2* added
- 12 April 2005 (me) Comprehensive update posted live
- 7 March 2003 (me) Comprehensive update posted live
- 14 January 2002 (pc) Author revisions
- 27 August 2001 (pc) Author revisions
- 26 October 2000 (me) Review posted live
- May 2000 (pc) Original submission

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Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 3-15-21.

National Society of Genetic Counselors. Position statement on prenatal testing for adult-onset conditions. Available online. 2019. Accessed 3-15-21.

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