MT-ND6 gene

mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 6

Normal Function

The *MT-ND6* gene provides instructions for making a protein called NADH dehydrogenase 6. This protein is part of a large enzyme complex known as complex I, which is active in mitochondria. Mitochondria are structures within cells that convert the energy from food into a form that cells can use. These cellular structures produce energy through a process called oxidative phosphorylation, which uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source.

Complex I is one of several enzyme complexes necessary for oxidative phosphorylation. Within mitochondria, these complexes are embedded in a tightly folded, specialized membrane called the inner mitochondrial membrane. During oxidative phosphorylation, mitochondrial enzyme complexes carry out chemical reactions that drive the production of ATP. Specifically, they create an unequal electrical charge on either side of the inner mitochondrial membrane through a step-by-step transfer of negatively charged particles called electrons. This difference in electrical charge provides the energy for ATP production.

Complex I is responsible for the first step in the electron transport process, the transfer of electrons from a molecule called NADH to another molecule called ubiquinone. Electrons are then passed from ubiquinone through several other enzyme complexes to provide energy for the generation of ATP.

Health Conditions Related to Genetic Changes

Leber hereditary optic neuropathy

Several mutations in the *MT-ND6* gene have been identified in people with Leber hereditary optic neuropathy. Each of these mutations changes a single protein building block (amino acid) in the NADH dehydrogenase 6 protein. One common *MT-ND6* mutation is responsible for about 14 percent of all cases of Leber hereditary optic neuropathy, and it is the most common cause of this disorder among people of French Canadian descent. This genetic change, written as T14484C or Met64Val, replaces the amino acid methionine with the amino acid valine at protein position 64. The T14484C mutation is associated with a good long-term prognosis; affected people with this genetic change have a 37 percent to 65 percent chance of some visual recovery.

Researchers are investigating how mutations in the *MT-ND6* gene lead to Leber hereditary optic neuropathy. These genetic changes appear to prevent complex I from interacting normally with ubiquinone, which may affect the generation of

ATP. *MT-ND4* mutations may also increase the production within mitochondria of potentially harmful molecules called reactive oxygen species. It remains unclear, however, why the effects of these mutations are often limited to the nerve that relays visual information from the eye to the brain (the optic nerve). Additional genetic and environmental factors probably contribute to the vision loss and other medical problems associated with Leber hereditary optic neuropathy.

Leigh syndrome

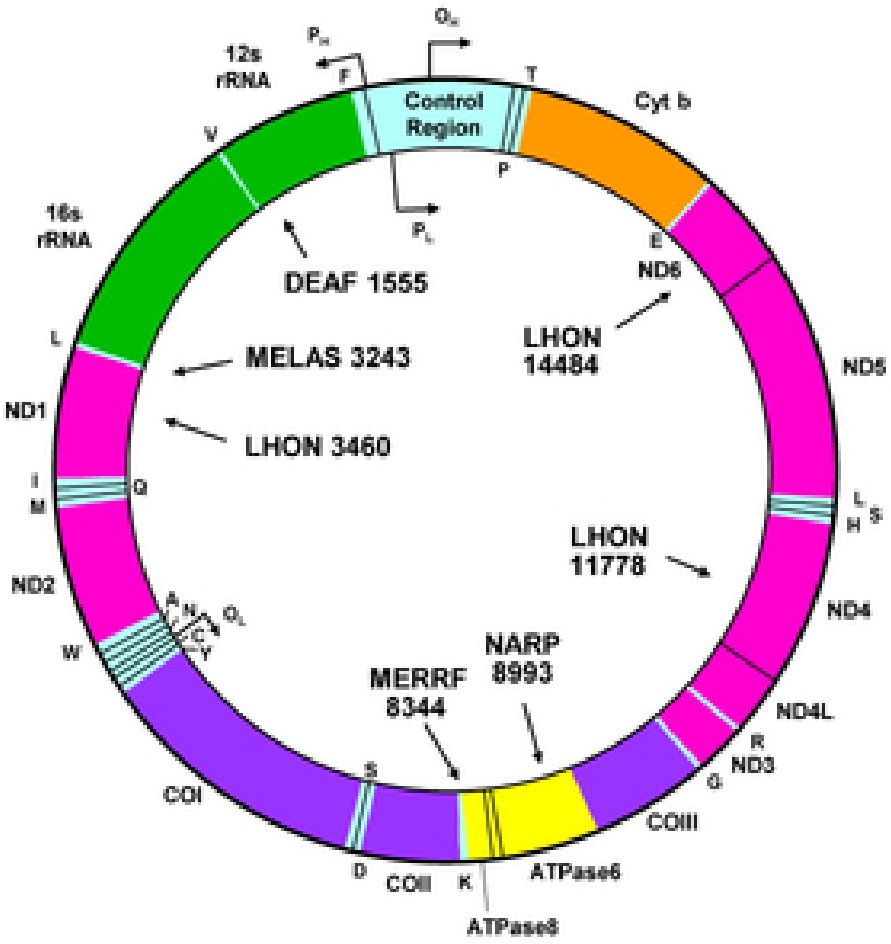
Mitochondrial complex I deficiency

Other disorders

A mutation in the *MT-ND6* gene also has been identified in a small number of people with Leigh syndrome, a progressive brain disorder that typically appears in infancy or early childhood. Affected children may experience vomiting, seizures, delayed development, muscle weakness, and problems with movement. Heart disease, kidney problems, and difficulty breathing can also occur in people with this disorder.

The *MT-ND6* mutation that can cause Leigh syndrome, written as G14459A or Ala72Val, replaces the amino acid alanine with the amino acid valine at protein position 72. This genetic change also has been found in people with Leber hereditary optic neuropathy and a movement disorder called dystonia, which involves involuntary muscle contractions, tremors, and other uncontrolled movements. This mutation appears to disrupt the normal assembly or activity of complex I in mitochondria. It is not known, however, how this *MT-ND6* gene alteration is related to the specific features of Leigh syndrome, Leber hereditary optic neuropathy, or dystonia. It also remains unclear why a single mutation can cause such varied signs and symptoms in different people.

Chromosomal Location



Other Names for This Gene

- mitochondrially encoded NADH dehydrogenase 6
- MTND6
- NADH dehydrogenase 6
- NADH dehydrogenase subunit 6
- NADH-ubiquinone oxidoreductase chain 6
- NADH-ubiquinone oxidoreductase, subunit ND6

- ND6
- NU6M_HUMAN

Additional Information & Resources

Educational Resources

- Mayo Clinic: North American Mitochondrial Disease Consortium Patient Registry and Biorepository (NAMDC)
  https://www.mayo.edu/research/clinical-trials/cls-20409244
- Oxidative Phosphorylation (Biochemistry, Fifth Edition, 2002)
  https://www.ncbi.nlm.nih.gov/books/NBK21208/
- The Neuromuscular Disease Center at Washington University: Complex I
  https://neuromuscular.wustl.edu/pathol/diagrams/mito.htm#complexI

Clinical Information from GeneReviews

- Leber Hereditary Optic Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1174
- Mitochondrial Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1224
- Mitochondrial DNA-Associated Leigh Syndrome and NARP
  https://www.ncbi.nlm.nih.gov/books/NBK1173

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28MT-ND6%5BTIAB%5D%29+OR+%28mitochondrially+encoded+NADH+dehydrogenase+6%5BTIAB%5D%29%29+OR+%28%28MTND6%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+subunit+6%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+6%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase+chain+6%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase,+subunit+ND6%5BTIAB%5D%29+OR+%28ND6%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- COMPLEX I, SUBUNIT ND6
  http://omim.org/entry/516006
- LEIGH SYNDROME
  http://omim.org/entry/256000

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_ND6.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MT-ND6%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:7462
- Mitomap: Leber Hereditary Optic Neuropathy Disease Mutation Database
  https://www.mitomap.org/MITOMAP/MutationsLHON
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:4541
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4541
- UniProt
  https://www.uniprot.org/uniprot/P03923

Sources for This Summary

- Baracca A, Solaini G, Sgarbi G, Lenaz G, Baruzzi A, Schapira AH, Martinuzzi A, Carelli V. Severe impairment of complex I-driven adenosine triphosphate synthesis in leber hereditary optic neuropathy cybrids. Arch Neurol. 2005 May;62(5):730-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15883259
- Carelli V, Ghelli A, Bucchi L, Montagna P, De Negri A, Leuzzi V, Carducci C, Lenaz G, Lugaresi E, Degli Esposti M. Biochemical features of mtDNA 14484 (ND6/M64V) point mutation associated with Leber's hereditary optic neuropathy. Ann Neurol. 1999 Mar;45(3):320-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10072046
- Chinnery PF, Andrews RM, Turnbull DM, Howell NN. Leber hereditary optic neuropathy: Does heteroplasmy influence the inheritance and expression of the G11778A mitochondrial DNA mutation? Am J Med Genet. 2001 Jan 22;98(3):235-43.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11169561
- Fauser S, Leo-Kottler B, Besch D, Luberichs J. Confirmation of the 14568 mutation in the mitochondrial ND6 gene as causative in Leber's hereditary optic neuropathy. Ophthalmic Genet. 2002 Sep;23(3):191-7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12324878
- Gropman A, Chen TJ, Perng CL, Krasnewich D, Chernoff E, Tifft C, Wong LJ. Variable clinical manifestation of homoplasmic G14459A mitochondrial DNA mutation. Am J Med Genet A. 2004 Feb 1;124A(4):377-82.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14735585
- Huoponen K. Leber hereditary optic neuropathy: clinical and molecular genetic findings. Neurogenetics. 2001 Jul;3(3):119-25. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11523562
- Kirby DM, Kahler SG, Freckmann ML, Reddihough D, Thorburn DR. Leigh disease caused by the mitochondrial DNA G14459A mutation in unrelated families. Ann Neurol. 2000 Jul;48(1):102-4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10894222

- Lenaz G, Baracca A, Carelli V, D'Aurelio M, Sgarbi G, Solaini G. Bioenergetics of mitochondrial diseases associated with mtDNA mutations. Biochim Biophys Acta. 2004 Jul 23;1658(1-2):89-94. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15282179
- Mitchell AL, Elson JL, Howell N, Taylor RW, Turnbull DM. Sequence variation in mitochondrial complex I genes: mutation or polymorphism? J Med Genet. 2006 Feb;43(2):175-9. Epub 2005 Jun 21.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15972314
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564640/
- Tarnopolsky MA, Baker SK, Myint T, Maxner CE, Robitaille J, Robinson BH. Clinical variability in maternally inherited leber hereditary optic neuropathy with the G14459A mutation. Am J Med Genet A. 2004 Feb 1;124A(4):372-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14735584
- Valentino ML, Avoni P, Barboni P, Pallotti F, Rengo C, Torroni A, Bellan M, Baruzzi A, Carelli V. Mitochondrial DNA nucleotide changes C14482G and C14482A in the ND6 gene are pathogenic for Leber's hereditary optic neuropathy. Ann Neurol. 2002 Jun;51(6):774-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12112086

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/MT-ND6

Reviewed: August 2006
Published: June 25, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services