

## MT-ND4 gene

mitochondrially encoded NADH dehydrogenase 4

### Normal Function

The *MT-ND4* gene provides instructions for making a protein called NADH dehydrogenase 4. 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 variants (also called mutations) in the *MT-ND4* gene are known to cause Leber hereditary optic neuropathy. This condition is an inherited form of vision loss. Each of these variants changes a single protein building block (amino acid) in the NADH dehydrogenase 4 protein.

One *MT-ND4* gene variant is the most common cause of Leber hereditary optic neuropathy; it is responsible for about 70 percent of all cases worldwide. This variant, which can be written as G11778A or Arg340His, replaces the amino acid arginine with the amino acid histidine at protein position 340. This variant tends to cause severe

vision loss, with little chance of recovery.

Researchers are investigating how variants in the *MT-ND4* 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* gene variants may also increase the production within mitochondria of potentially harmful molecules called reactive oxygen species. It remains unclear, however, why the effects of these variants 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

A variant in the *MT-ND4* 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-ND4* variant that can cause Leigh syndrome, written as C11777A or Arg340Ser, replaces the amino acid arginine with the amino acid serine at protein position 340. This genetic change appears to disrupt the normal function of complex I in mitochondria. It is not known, however, how this *MT-ND4* gene variant is related to the specific features of Leigh syndrome.

### Mitochondrial complex I deficiency

MedlinePlus Genetics provides information about Mitochondrial complex I deficiency

### **Other Names for This Gene**

- mitochondrially encoded NADH dehydrogenase 4
- MTND4
- NADH dehydrogenase 4
- NADH dehydrogenase subunit 4
- NADH-ubiquinone oxidoreductase chain 4
- NADH-ubiquinone oxidoreductase, subunit ND4
- ND4
- NU4M\_HUMAN

### **Additional Information & Resources**

Tests Listed in the Genetic Testing Registry

- Tests of MT-ND4 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4538\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4538[geneid]))

## Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28MT-ND4%5BTIAB%5D%29+OR+%28mitochondrially+encoded+NADH+dehydrogenase+4%5BTIAB%5D%29%29+OR+%28%28MTND4%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+subunit+4%5BTIAB%5D%29+OR+%28NADH+dehydrogenase+4%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase+chain+4%5BTIAB%5D%29+OR+%28NADH-ubiquinone+oxidoreductase,+subunit+ND4%5BTIAB%5D%29+OR+%28ND4%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 ND4; MTND4 (<https://omim.org/entry/516003>)
- LEIGH SYNDROME; LS (<https://omim.org/entry/256000>)

## Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/4538>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=MT-ND4\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=MT-ND4[gene]))

## References

- Baracca A, Solaini G, Sgarbi G, Lenaz G, Baruzzi A, Schapira AH, Martinuzzi A, Carelli V. Severe impairment of complex I-driven adenosine triphosphatase in leber hereditary optic neuropathy cybrids. *Arch Neurol*. 2005 May;62(5):730-6. doi: 10.1001/archneur.62.5.730. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15883259>)
- Bugiani M, Invernizzi F, Alberio S, Briem E, Lamantea E, Carrara F, Moroni I, Farina L, Spada M, Donati MA, Uziel G, Zeviani M. Clinical and molecular findings in children with complex I deficiency. *Biochim Biophys Acta*. 2004 Dec;1659(2-3):136-47. doi: 10.1016/j.bbabi.2004.09.006. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15576045>)
- Huoponen K. Leber hereditary optic neuropathy: clinical and molecular genetic findings. *Neurogenetics*. 2001 Jul;3(3):119-25. doi: 10.1007/s100480100115. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/11523562>)
- Komaki H, Akanuma J, Iwata H, Takahashi T, Mashima Y, Nonaka I, Goto Y. A novel mtDNA C1177A mutation in Leigh syndrome. *Mitochondrion*. 2003 Mar;2(4):293-304. doi: 10.1016/S1567-7249(03)00003-5. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16120329>)

- Lenaz G, Baracca A, Carelli V, D'Amico A, Sgarbi G, Solaini G. Bioenergetics of mitochondrial diseases associated with mtDNA mutations. *Biochim Biophys Acta*. 2004 Jul 23;1658(1-2):89-94. doi: 10.1016/j.bbabi.2004.03.013. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/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. doi: 10.1136/jmg.2005.032474. Epub 2005 Jun 21. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15972314>) or Free article on PubMed Central (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564640/>)
- Phasukkijwatana N, Chuenkongkaew WL, Suphavilai R, Suktitipat B, Pingsuthiwong S, Ruangvaravate N, Atchaneeyasakul LO, Warrasak S, Poonyathalang A, Sura T, Lertrit P. The unique characteristics of Thai Leber hereditary optic neuropathy: analysis of 30 G11778A pedigrees. *J Hum Genet*. 2006; 51(4):298-304. doi:10.1007/s10038-006-0361-1. Epub 2006 Feb 14. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16477364>)
- Yu-Wai-Man P, Chinnery PF. Leber Hereditary Optic Neuropathy. 2000 Oct 26 [updated 2021 Mar 11]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews*(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1174/> Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20301353>)
- Zhou X, Wei Q, Yang L, Tong Y, Zhao F, Lu C, Qian Y, Sun Y, Lu F, Qu J, Guan MX. Leber's hereditary optic neuropathy is associated with the mitochondrial ND4G11696A mutation in five Chinese families. *Biochem Biophys Res Commun*. 2006 Feb 3;340(1):69-75. doi: 10.1016/j.bbrc.2005.11.150. Epub 2005 Dec 6. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16364244>)

## Genomic Location

The *MT-ND4* gene is found on mitochondrial DNA (<https://medlineplus.gov/genetics/chromosome/mitochondrial-dna/>).

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