

MT-TL1 gene

mitochondrially encoded tRNA leucine 1 (UUA/G)

Normal Function

The *MT-TL1* gene provides instructions for making a molecule called a transfer RNA (tRNA), which is a chemical cousin of DNA. Transfer RNAs help assemble protein building blocks (amino acids) into functioning proteins. The *MT-TL1* gene provides instructions for making a specific form of tRNA that is designated as tRNA^{Leu(UUR)}. During protein assembly, this molecule attaches to the amino acid leucine (Leu) and inserts it into the appropriate locations in the growing protein.

The tRNA^{Leu(UUR)} molecule is present in cellular structures called mitochondria. These structures convert energy from food into a form that cells can use. Within mitochondria, tRNA^{Leu(UUR)} is involved in the assembly of proteins that carry out a series of chemical steps called oxidative phosphorylation. This process uses oxygen, simple sugars, and fatty acids to create adenosine triphosphate (ATP), the cell's main energy source.

In certain cells in the pancreas, called beta cells, mitochondria also play a role in controlling the amount of sugar (glucose) in the bloodstream. In response to high glucose levels, mitochondria help trigger the release of a hormone called insulin. Insulin regulates blood glucose levels by controlling how much glucose is passed from the blood into cells to be converted into energy.

Health Conditions Related to Genetic Changes

Maternally inherited diabetes and deafness

At least one mutation in the *MT-TL1* gene causes maternally inherited diabetes and deafness (MIDD). People with this condition have diabetes and sometimes hearing loss, particularly of high tones. Less commonly, affected individuals have problems with their eyes, muscles, heart, or kidneys. The *MT-TL1* gene mutation is the most common mutation in MIDD, involved in 85 percent of cases. It changes a single DNA building block (nucleotide) in the *MT-TL1* gene; the nucleotide adenine is replaced by the nucleotide guanine at position 3243 in the gene (written as A3243G).

The A3243G mutation reduces the ability of tRNA^{Leu(UUR)} to add leucine to proteins that are being assembled, which slows protein production. Researchers believe that the A3243G mutation impairs the ability of mitochondria to help trigger insulin release. In

people with MIDD, diabetes results when the beta cells do not produce enough insulin to regulate blood glucose effectively. Researchers have not determined how the A3243G mutation leads to hearing loss or the other features of MIDD.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Several mutations in the *MT-TL1* gene have been identified in people with a condition called mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). This condition is characterized by recurrent severe headaches, muscle weakness (myopathy), hearing loss, stroke-like episodes including a loss of consciousness, seizures, and other problems affecting the nervous system. Most of these mutations change single nucleotides in the gene. The A3243G mutation (described above) is the most common mutation in MELAS. It is responsible for about 80 percent of all MELAS cases. This mutation impairs the ability of mitochondria to make proteins, use oxygen, and produce energy. Researchers have not determined how changes in mtDNA lead to the specific signs and symptoms of MELAS. They continue to investigate the effects of mitochondrial gene mutations in different tissues, particularly in the brain.

Myoclonic epilepsy with ragged-red fibers

Mutations in the *MT-TL1* gene have been found in a few people with features of myoclonic epilepsy with ragged-red fibers (MERRF). These individuals also have some features of MELAS (described above). This combination of signs and symptoms is called MERRF/MELAS overlap syndrome. The features of this syndrome include muscle twitches (myoclonus), muscle weakness (myopathy), difficulty coordinating movement (ataxia), hearing loss, seizures, and diabetes.

Mutations that cause MERRF/MELAS overlap syndrome each change single nucleotides in the *MT-TL1* gene. Researchers have not determined how these genetic changes cause the signs and symptoms of MERRF/MELAS overlap syndrome.

Progressive external ophthalmoplegia

Mutations in the *MT-TL1* gene are responsible for some cases of an eye condition called progressive external ophthalmoplegia. This disorder weakens the muscles that control eye movement and causes drooping eyelids (ptosis).

Some cases of progressive external ophthalmoplegia result from the A3243G mutation, which is the same genetic change that typically causes MELAS and MIDD (described above). It is unclear how the same *MT-TL1* gene mutation can result in different conditions. Researchers have not determined how changes in mtDNA lead to the specific signs and symptoms of progressive external ophthalmoplegia, although the features of the condition may be related to impaired oxidative phosphorylation. It has been suggested that eye muscles are commonly affected by mitochondrial defects because they are especially dependent on oxidative phosphorylation for energy.

Leigh syndrome

MedlinePlus Genetics provides information about Leigh syndrome

Mitochondrial complex I deficiency

MedlinePlus Genetics provides information about Mitochondrial complex I deficiency

Other disorders

About 20 mutations in the *MT-TL1* gene have been reported, most of which change single nucleotides in the gene. These mutations are associated with a variety of signs and symptoms chiefly affecting the muscles and nervous system. People with *MT-TL1* mutations often have muscle weakness, pain, and extreme fatigue, particularly during exercise (exercise intolerance). In some cases, the heart muscle is also weakened, which is known as cardiomyopathy. This abnormality prevents the heart from pumping normally.

A few children with changes in the *MT-TL1* gene have experienced delayed development, psychiatric problems, or autism spectrum disorder (which affects communication and social interaction). *MT-TL1* mutations also have been identified in a small number of cases of sudden infant death syndrome (SIDS), which is a major cause of death in children younger than 1 year.

Other Names for This Gene

- MTTL1
- tRNA leucine 1 (UUA/G)

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MT-TL1 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4567\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4567[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28MT-TL1%5BTIAB%5D%29+OR+%28%28MTTL1%5BTIAB%5D%29+OR+%28tRNA+leucine+1%5BTIAB%5D%29%29+OR+%28A3243G%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D%29>)

Catalog of Genes and Diseases from OMIM

- TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 1; MTTL1 (<https://omim.org/entry/590050>)
- SUDDEN INFANT DEATH SYNDROME (<https://omim.org/entry/272120>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/4567>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=MT-TL1\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=MT-TL1[gene]))

References

- Betts J, Jaros E, Perry RH, Schaefer AM, Taylor RW, Abdel-All Z, Lightowlers RN, Turnbull DM. Molecular neuropathology of MELAS: level of heteroplasmy in individual neurones and evidence of extensive vascular involvement. *Neuropathol Appl Neurobiol*. 2006 Aug;32(4):359-73. doi: 10.1111/j.1365-2990.2006.00731.x. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16866982>)
- Brackmann F, Abicht A, Ahting U, Schroder R, Trollmann R. Classical MERRF phenotype associated with mitochondrial tRNA(Leu) (m.3243A>G) mutation. *Eur J Pediatr*. 2012 May;191(5):859-62. doi: 10.1007/s00431-011-1662-8. Epub 2012 Jan 25. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22270878>)
- Chinnery PF, Howell N, Lightowlers RN, Turnbull DM. Molecular pathology of MELAS and MERRF. The relationship between mutation load and clinical phenotypes. *Brain*. 1997 Oct;120 (Pt 10):1713-21. doi: 10.1093/brain/120.10.1713. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/9365365>)
- Choi BO, Hwang JH, Cho EM, Jeong EH, Hyun YS, Jeon HJ, Seong KM, Cho NS, Chung KW. Mutational analysis of whole mitochondrial DNA in patients with MELAS and MERRF diseases. *Exp Mol Med*. 2010 Jun 30;42(6):446-55. doi:10.3858/emm.2010.42.6.046. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20440095>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892598/>)
- Kirino Y, Goto Y, Campos Y, Arenas J, Suzuki T. Specific correlation between the wobble modification deficiency in mutant tRNAs and the clinical features of a human mitochondrial disease. *Proc Natl Acad Sci U S A*. 2005 May 17;102(20):7127-32. doi: 10.1073/pnas.0500563102. Epub 2005 May 3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15870203>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1129107/>)
- Liu K, Zhao H, Ji K, Yan C. MERRF/MELAS overlap syndrome due to the m.3291T>C mutation. *Metab Brain Dis*. 2014 Mar;29(1):139-44. doi:10.1007/s11011-013-9464-5. Epub 2013 Dec 12. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24338029>)
- Maassen JA, Jahangir Tafrechi RS, Janssen GM, Raap AK, Lemkes HH, & Hart LM. New insights in the molecular pathogenesis of the maternally inherited diabetes and deafness syndrome. *Endocrinol Metab Clin North Am*. 2006 Jun;35(2):385-96, x-xi. doi: 10.1016/j.ecl.2006.02.014. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16632100>)
- Moraes CT, Ciacchi F, Bonilla E, Jansen C, Hirano M, Rao N, Lovelace RE, Rowland

LP, Schon EA, DiMauro S. Two novel pathogenic mitochondrial DNA mutations affecting organelle number and protein synthesis. Is the tRNA(Leu(UUR)) gene an etiologic hot spot? J Clin Invest. 1993 Dec;92(6):2906-15. doi:10.1172/JCI116913. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/8254046>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC288494/>)

- Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. Diabet Med. 2008 Apr;25(4):383-99. doi: 10.1111/j.1464-5491.2008.02359.x. Epub 2008 Feb 18. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/18294221>)
- Opdal SH, Rognum TO, Torgersen H, Vege A. Mitochondrial DNA point mutations detected in four cases of sudden infant death syndrome. Acta Paediatr. 1999 Sep;88(9):957-60. doi: 10.1080/08035259950168441. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/10519336>)
- Palecek T, Tesarova M, Kuchynka P, Dytrych V, Elleder M, Hulkova H, Hansikova H, Honzik T, Zeman J, Linhart A. Hypertrophic cardiomyopathy due to the mitochondrial DNA mutation m.3303C>T diagnosed in an adult male. Int Heart J. 2012;53(6):383-7. doi: 10.1536/ihj.53.383. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23258140>)
- Sotiriou E, Coku J, Tanji K, Huang HB, Hirano M, DiMauro S. The m.3244G>A mutation in mtDNA is another cause of progressive external ophthalmoplegia. Neuromuscul Disord. 2009 Apr;19(4):297-9. doi: 10.1016/j.nmd.2009.01.014. Epub 2009 Mar 13. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/19285865>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699630/>)
- Yarham JW, Blakely EL, Alston CL, Roberts ME, Ealing J, Pal P, Turnbull DM, McFarland R, Taylor RW. The m.3291T>C mt-tRNA(Leu(UUR)) mutation is definitely pathogenic and causes multisystem mitochondrial disease. J Neurol Sci. 2013 Feb 15;325(1-2):165-9. doi: 10.1016/j.jns.2012.12.003. Epub 2012 Dec 27. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23273904>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3560033/>)
- Yu Wai Man CY, Chinnery PF, Griffiths PG. Extraocular muscles have fundamentally distinct properties that make them selectively vulnerable to certain disorders. Neuromuscul Disord. 2005 Jan;15(1):17-23. doi:10.1016/j.nmd.2004.10.002. Epub 2004 Nov 26. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15639116>)

Genomic Location

The *MT-TL1* gene is found on mitochondrial DNA (<https://medlineplus.gov/genetics/chromosome/mitochondrial-dna/>).

Last updated May 1, 2014