

## HADHA gene

hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha

### Normal Function

The *HADHA* gene provides instructions for making part of an enzyme complex called mitochondrial trifunctional protein. This enzyme complex functions in mitochondria, the energy-producing centers within cells. Mitochondrial trifunctional protein is made of eight parts (subunits). Four alpha subunits are produced from the *HADHA* gene, and four beta subunits are produced from the *HADHB* gene. As the name suggests, mitochondrial trifunctional protein contains three enzymes that each perform a different function. The alpha subunits contain two of the enzymes, known as long-chain 3-hydroxyacyl-CoA dehydrogenase and long-chain 2-enoyl-CoA hydratase. The beta subunits contain the third enzyme. These enzymes are essential for fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them to energy.

Mitochondrial trifunctional protein is required to metabolize a group of fats called long-chain fatty acids. Long-chain fatty acids are found in foods such as milk and certain oils. These fatty acids are stored in the body's fat tissues. Fatty acids are a major source of energy for the heart and muscles. During periods of fasting, fatty acids are also an important energy source for the liver and other tissues.

### Health Conditions Related to Genetic Changes

#### Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

Researchers have identified several *HADHA* gene mutations that cause long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. These mutations decrease the long-chain 3-hydroxyacyl-CoA dehydrogenase enzyme activity of mitochondrial trifunctional protein. (The protein's other enzyme activities remain normal or nearly normal.) Many of the *HADHA* mutations change one of the protein building blocks (amino acids) used to make the alpha subunit. The most common mutation replaces the amino acid glutamic acid with the amino acid glutamine at position 474 in the alpha subunit. This mutation is written as Glu474Gln or E474Q. The Glu474Gln mutation and other amino acid replacements probably alter the structure of the alpha subunit, preventing it from functioning normally. Other *HADHA* mutations result in an abnormally short, nonfunctional version of the alpha subunit.

With a shortage (deficiency) of functional alpha subunits, long-chain fatty acids cannot be metabolized and processed. As a result, these fatty acids are not converted to energy, which can lead to some features of LCHAD deficiency, such as lack of energy (lethargy) and low blood glucose (hypoglycemia). Long-chain fatty acids or partially metabolized fatty acids may also build up and damage the liver, heart, muscles, and light-sensitive tissue at the back of the eye (retina). This abnormal buildup causes the other signs and symptoms of LCHAD deficiency.

### Mitochondrial trifunctional protein deficiency

Researchers have identified several *HADHA* gene mutations that cause mitochondrial trifunctional protein deficiency. These mutations reduce all three enzyme activities of mitochondrial trifunctional protein. Some of these mutations result in abnormally short, nonfunctional alpha subunits and lead to decreased levels of mitochondrial trifunctional protein. Other mutations replace one amino acid with another amino acid in the alpha subunit, which probably alters the subunit's structure and disrupts all three functions of the enzyme complex.

When mitochondrial trifunctional protein activity is lost, long-chain fatty acids cannot be metabolized and processed. As a result, these fatty acids are not converted to energy, which can lead to some features of this disorder, such as lethargy and hypoglycemia. Long-chain fatty acids or partially metabolized fatty acids may build up in tissues and damage the liver, heart, and muscles. This abnormal buildup causes the other signs and symptoms of mitochondrial trifunctional protein deficiency.

### Other disorders

In a small number of cases, *HADHA* mutations appear to increase a woman's risk of developing two serious liver disorders during pregnancy, known as acute fatty liver of pregnancy (AFLP) and HELLP syndrome. AFLP begins with abdominal pain and can rapidly progress to liver failure. HELLP stands for hemolysis (the breakdown of red blood cells), elevated liver enzyme levels, and low platelets (cells involved with blood clotting).

A woman is more likely to have AFLP or HELLP syndrome if she has a mutation in one copy of the *HADHA* gene and the fetus she carries has two copies of a *HADHA* mutation, particularly the Glu474Gln mutation. Little is known about the relationship between *HADHA* mutations and liver problems in the mother during pregnancy. One possibility is that partially metabolized long-chain fatty acids produced by the fetus or placenta accumulate in the mother and are toxic to her liver. In very rare cases of maternal liver disease, the mother has one copy of an altered *HADHA* gene and the fetus is not affected. In these cases, the role of the mother's *HADHA* mutation in liver disease is unclear.

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

- ECHA\_HUMAN
- GBP

- hydroxyacyl dehydrogenase, subunit A
- hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit
- hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit
- LCEH
- LCHAD
- long-chain hydroxyacyl-CoA dehydrogenase
- mitochondrial trifunctional protein, alpha subunit
- MTPA

## **Additional Information & Resources**

### Tests Listed in the Genetic Testing Registry

- Tests of HADHA ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3030\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3030[geneid]))

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28HADHA%5BTIAB%5D%29+OR+%28%28LCHAD%5BTIAB%5D%29+OR+%28long-chain+hydroxyacyl-CoA+dehydrogenase%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+2160+days%22%5Bdp%5D>)

### Catalog of Genes and Diseases from OMIM

- HYDROXYACYL-CoA DEHYDROGENASE/3-KETOACYL-CoA THIOLASE/ENOYL-CoA HYDRATASE, ALPHA SUBUNIT; HADHA (<https://omim.org/entry/600890>)

### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/3030>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=HADHA\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=HADHA[gene]))

## **References**

- Angdisen J, Moore VD, Cline JM, Payne RM, Ibdah JA. Mitochondrialtrifunctional protein defects: molecular basis and novel therapeutic approaches.Curr Drug Targets Immune Endocr Metabol Disord. 2005 Mar;5(1):27-40. doi:10.2174/1568008053174796. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/1577720>)

2)

- Blish KR, Ibdah JA. Maternal heterozygosity for a mitochondrial trifunctional protein mutation as a cause for liver disease in pregnancy. *Med Hypotheses*. 2005;64(1):96-100. doi: 10.1016/j.mehy.2004.06.005. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15533621>)
- Choi JH, Yoon HR, Kim GH, Park SJ, Shin YL, Yoo HW. Identification of novel mutations of the HADHA and HADHB genes in patients with mitochondrial trifunctional protein deficiency. *Int J Mol Med*. 2007 Jan;19(1):81-7. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17143551>)
- den Boer ME, Wanders RJ, Morris AA, IJlst L, Heymans HS, Wijburg FA. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. *Pediatrics*. 2002 Jan;109(1):99-104. doi:10.1542/peds.109.1.99. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/11773547>)
- Gutierrez Junquera C, Balmaseda E, Gil E, Martinez A, Sorli M, Cuartero I, Merinero B, Ugarte M. Acute fatty liver of pregnancy and neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency. *Eur J Pediatr*. 2009 Jan;168(1):103-6. doi: 10.1007/s00431-008-0696-z. Epub 2008 Apr 12. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/18408953>)
- Ibdah JA, Bennett MJ, Rinaldo P, Zhao Y, Gibson B, Sims HF, Strauss AW. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med*. 1999 Jun 3;340(22):1723-31. doi:10.1056/NEJM199906033402204. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/10352164>)
- Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab*. 2000 Sep-Oct;71(1-2):182-9. doi:10.1006/mgme.2000.3065. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/11001809>)
- Oey NA, den Boer ME, Wijburg FA, Vekemans M, Auge J, Steiner C, Wanders RJ, Waterham HR, Ruiter JP, Attie-Bitach T. Long-chain fatty acid oxidation during early human development. *Pediatr Res*. 2005 Jun;57(6):755-9. doi:10.1203/01.PDR.0000161413.42874.74. Epub 2005 Apr 21. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15845636>)
- Prasun P, LoPiccolo MK, Ginevic I. Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency. 2022 Sep 1. 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/NBK583531/> Citation on PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/36063482>)
- Shekhawat PS, Matern D, Strauss AW. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. *Pediatr Res*. 2005 May;57(5 Pt2):78R-86R. doi: 10.1203/01.PDR.0000159631.63843.3E. Epub 2005 Apr 6. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15817498>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582391/>)
- Sims HF, Brackett JC, Powell CK, Treem WR, Hale DE, Bennett MJ, Gibson B, Shapiro S, Strauss AW. The molecular basis of pediatric long chain 3-hydroxyacyl-

CoA dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. *Proc Natl Acad Sci U S A*. 1995 Jan 31;92(3):841-5. doi:10.1073/pnas.92.3.841. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/7846063>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC42716/>)

- Spiekerkoetter U, Khuchua Z, Yue Z, Bennett MJ, Strauss AW. General mitochondrial trifunctional protein (TFP) deficiency as a result of either alpha- or beta-subunit mutations exhibits similar phenotypes because mutations in either subunit alter TFP complex expression and subunit turnover. *Pediatr Res*. 2004 Feb;55(2):190-6. doi: 10.1203/01.PDR.0000103931.80055.06. Epub 2003 Nov 19. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/14630990>)
- Spiekerkoetter U, Mueller M, Cloppenburg E, Motz R, Mayatepek E, Bueltmann B, Korenke C. Intrauterine cardiomyopathy and cardiac mitochondrial proliferation in mitochondrial trifunctional protein (TFP) deficiency. *Mol Genet Metab*. 2008 Aug;94(4):428-430. doi: 10.1016/j.ymgme.2008.04.002. Epub 2008 May 15. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/18485779>)
- Tyni T, Pihko H. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. *Acta Paediatr*. 1999 Mar;88(3):237-45. doi: 10.1080/08035259950169954. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/10229030>)
- Yang Z, Yamada J, Zhao Y, Strauss AW, Ibdah JA. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. *JAMA*. 2002 Nov 6;288(17):2163-6. doi: 10.1001/jama.288.17.2163. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12413376>)
- Yang Z, Zhao Y, Bennett MJ, Strauss AW, Ibdah JA. Fetal genotypes and pregnancy outcomes in 35 families with mitochondrial trifunctional protein mutations. *Am J Obstet Gynecol*. 2002 Sep;187(3):715-20. doi:10.1067/mob.2002.125893. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12237653>)

## Genomic Location

The *HADHA* gene is found on chromosome 2 (<https://medlineplus.gov/genetics/chromosome/2/>).

**Last updated July 1, 2009**