HADHB gene

hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta

Normal Function

The *HADHB* 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 beta subunits contain one of the enzymes, known as long-chain 3-keto-acyl-CoA thiolase. The alpha subunits contain the other two enzymes. 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

Mitochondrial trifunctional protein deficiency

Researchers have identified at least 26 mutations in the *HADHB* gene that cause mitochondrial trifunctional protein deficiency. These mutations reduce all three enzyme activities of mitochondrial trifunctional protein. Most mutations change one of the protein building blocks (amino acids) used to make the beta subunit. A change in amino acids probably alters the subunit's structure, which disrupts all three activities of the enzyme complex. Some mutations produce abnormally short, nonfunctional beta subunits and lead to decreased levels of mitochondrial trifunctional protein.

With a loss of mitochondrial trifunctional protein activity, 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 a 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, and muscles. This abnormal

buildup causes the other signs and symptoms of mitochondrial trifunctional protein deficiency.

Other disorders

A few mutations in the *HADHB* gene have been found to decrease only the long-chain 3-keto-acyl-CoA thiolase enzyme activity of mitochondrial trifunctional protein. These mutations change single amino acids used to make the beta subunit. The signs and symptoms of isolated long-chain 3-keto-acyl-CoA thiolase deficiency are similar to those of mitochondrial trifunctional protein deficiency. These features include feeding difficulties, lethargy, hypoglycemia, weak muscle tone (hypotonia), and liver problems. Infants with this disorder are also at high risk for serious heart problems, breathing difficulties, coma, and sudden death.

HADHB 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 small percentage of women who have a mutation in one copy of the *HADHB* gene and carry a fetus with mutations in both copies of the *HADHB* gene develop one of these maternal liver diseases. Little is known about the relationship between *HADHB* 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 the liver.

Other Names for This Gene

- ECHB_HUMAN
- HADH
- hydroxyacyl dehydrogenase, subunit B
- hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
- hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), beta subunit
- MTPB
- TFPB
- TP-beta

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of HADHB (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3032[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28HADHB%5BTIAB%5D%29+OR+%28%283-ketoacyl-Coenzyme+A+thiolase%5BTIAB%5D%29+OR+%28trifunctional+protein%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29+NOT+%28G1528C%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- HYDROXYACYL-CoA DEHYDROGENASE/3-KETOACYL-CoA THIOLASE/ENOYL-CoA HYDRATASE, BETA SUBUNIT; HADHB (https://omim.org/entry/143450)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/3032)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=HADHB[gene])

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Genomic Location

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

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