HADHA Gene

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Hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha

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1. Introduction

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.

2. Health Conditions Related to Genetic Changes

2.1. 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 sugar (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.

2.2. 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.

2.3. 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.

3. 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

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