MMADHC Gene

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1. Introduction

The *MMADHC* gene provides instructions for making a protein that helps convert vitamin B12 (also called cobalamin) into one of two molecules, adenosylcobalamin (AdoCbl) or methylcobalamin (MeCbl). AdoCbl is required for the normal function of an enzyme known as methylmalonyl CoA mutase. This enzyme helps break down certain protein building blocks (amino acids), fats (lipids), and cholesterol. AdoCbl is called a cofactor because it helps methylmalonyl CoA mutase carry out its function. MeCbl is also a cofactor, but for an enzyme known as methionine synthase. This enzyme converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

Research indicates that the MMADHC protein plays a role in one of the last steps in AdoCbl and MeCbl formation. Together with another protein called MMACHC (produced from the *MMACHC* gene), MMADHC transports vitamin B12 to regions of the cell in which each cofactor is needed: specialized structures that serve as energy-producing centers (the mitochondria), where AdoCbl functions, or the fluid inside the cell (the cytoplasm), where MeCbl functions. Additional chemical reactions then convert vitamin B12 into AdoCbl or MeCbl.

2. Health Conditions Related to Genetic Changes

2.1. Homocystinuria

At least seven mutations in the *MMADHC* gene cause a condition called homocystinuria, which is characterized by skeletal problems and intellectual disability. The *MMADHC* gene mutations that cause homocystinuria result in a protein that cannot transport vitamin B12 to the cytoplasm, where MeCbl is produced. The resulting shortage of MeCbl impairs methionine synthase's conversion of homocysteine to methionine. As a result, homocysteine builds up in the bloodstream and methionine is depleted. Some of the excess homocysteine is excreted in urine. Researchers have not determined how altered levels of homocysteine and methionine lead to the health problems associated with homocystinuria.

2.2. Methylmalonic acidemia

At least three mutations in the *MMADHC* gene have been found to cause methylmalonic acidemia, a condition characterized by feeding difficulties, developmental delay, and long-term health problems. The *MMADHC* gene mutations that cause this condition result in a protein that cannot transport vitamin B12 to mitochondria for the production of AdoCbl. A lack of AdoCbl impairs the function of methylmalonyl CoA mutase. As a result, certain proteins and lipids are not broken down properly. This defect allows toxic compounds to build up in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

2.3. Methylmalonic acidemia with homocystinuria

At least three *MMADHC* gene mutations can cause methylmalonic acidemia with homocystinuria, cblD type, one form of a condition that has features of both of the two previously described conditions. People with this combined condition have developmental delay, eye defects, neurological problems, and blood abnormalities. The *MMADHC* gene mutations that cause this condition result in the production of a protein that cannot transport vitamin B12 to either the mitochondria or the cytoplasm, which disrupts production of both AdoCbl and MeCbl. Because both of these cofactors are missing, the enzymes that require them (methylmalonyl CoA mutase and methionine synthase) do not function normally. As a result, certain amino acids, lipids, and cholesterol are not broken down and homocysteine cannot be converted to methionine.

This dual defect results in a buildup of toxic compounds as well as homocysteine, and a decrease in the production of methionine within the body. This combination of imbalances leads to the signs and symptoms of methylmalonic acidemia with homocystinuria.More About This Health Condition

3. Other Names for This Gene

- C2orf25
- cblD
- CL25022
- methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria
- methylmalonic aciduria and homocystinuria type D protein, mitochondrial
- methylmalonic aciduria and homocystinuria type D protein, mitochondrial precursor
- methylmalonic aciduria and homocystinuria, cblD type
- MMAD_HUMAN

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