MMADHC gene

metabolism of cobalamin associated D

Normal Function

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), fat building blocks (fatty acids), 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.

Health Conditions Related to Genetic Changes

Homocystinuria

Variants (also known as mutations) in the *MMADHC* gene cause a condition called homocystinuria, which is characterized by developmental delay, neurological problems, eye defects, and blood abnormalities. The *MMADHC* gene variants 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. Altered levels of homocysteine and methionine lead to the health problems associated with homocystinuria.

Methylmalonic acidemia

Variants in the *MMADHC* gene have been found to cause methylmalonic acidemia, a condition characterized by feeding difficulties, life-threatening episodes of low blood glucose and the build-up of toxic substances in the blood (metabolic crisis), and long-term health problems. The *MMADHC* gene variants 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.

Methylmalonic acidemia with homocystinuria

Variants in the *MMADHC* gene can cause methylmalonic acidemia with homocystinuria, cblD type, which is one form of a condition that has features of both of the two conditions described above. People with this combined condition have developmental delay, eye defects, neurological problems, and blood abnormalities. The *MMADHC* gene variants 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, fatty acids, and cholesterol are not broken down and homocysteine cannot be converted to methionine. This dual defect results in a buildup of toxic compounds, including 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.

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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MMADHC (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=27249[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28MMADHC%5BTIAB%5D%29+OR+%28cblD%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+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- METABOLISM OF COBALAMIN ASSOCIATED D; MMADHC (https://omim.org/entry/611935)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/27249)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=MMADHC[gene])

References

- Coelho D, Suormala T, Stucki M, Lerner-Ellis JP, Rosenblatt DS, Newbold RF, Baumgartner MR, Fowler B. Gene identification for the cblD defect of vitamin B12metabolism. N Engl J Med. 2008 Apr 3;358(14):1454-64. doi: 10.1056/NEJMoa072200. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18385497)
- Froese DS, Kopec J, Fitzpatrick F, Schuller M, McCorvie TJ, Chalk R, Plessl T, Fettelschoss V, Fowler B, Baumgartner MR, Yue WW. Structural Insights into theMMACHC-MMADHC Protein Complex Involved in Vitamin B12 Trafficking. J Biol Chem.2015 Dec 4;290(49):29167-77. doi: 10.1074/jbc.M115.683268. Epub 2015 Oct 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/26483544) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4705923/)
- Miousse IR, Watkins D, Coelho D, Rupar T, Crombez EA, Vilain E, Bernstein JA, Cowan T, Lee-Messer C, Enns GM, Fowler B, Rosenblatt DS. Clinical and molecularheterogeneity in patients with the cblD inborn error of cobalamin metabolism. JPediatr. 2009 Apr;154(4):551-6. doi: 10.1016/j.jpeds.2008.10.043. Epub 2008 Dec5. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19058814)
- Plesa M, Kim J, Paquette SG, Gagnon H, Ng-Thow-Hing C, Gibbs BF, Hancock MA, Rosenblatt DS, Coulton JW. Interaction between MMACHC and MMADHC, two humanproteins participating in intracellular vitamin B(1)(2) metabolism. Mol Genet Metab.2011 Feb;102(2):139-48. doi: 10.1016/j.ymgme.2010.10.011. Epub 2010 Oct 21. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21071249)
- Stucki M, Coelho D, Suormala T, Burda P, Fowler B, Baumgartner MR. Molecularmechanisms leading to three different phenotypes in the cblD defect ofintracellular cobalamin metabolism. Hum Mol Genet. 2012 Mar 15;21(6):1410-8. doi:10.1093/hmg/ddr579. Epub 2011 Dec 8. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22156578)

Genomic Location

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

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