MMACHC gene

metabolism of cobalamin associated C

Normal Function

The *MMACHC* 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 MMACHC protein plays a role in processing different forms of vitamin B12 so that they can be converted to either of the cofactors, AdoCbl or MeCbl. MMACHC also interacts with another protein called MMADHC (produced from the *MMADHC* gene). Together these proteins transport the processed 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

Methylmalonic acidemia with homocystinuria

Dozens of *MMACHC* gene variants (also known as mutations) have been found to cause methylmalonic acidemia with homocystinuria, cblC type, the most common form of a disorder that causes developmental delay, eye defects, neurological problems, and blood abnormalities. *MMACHC* gene variants lead to production of an abnormal MMACHC protein that is unable to function. A shortage of functional MMACHC protein prevents normal processing and transport of vitamin B12, impairing 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

- cblC
- DKFZP564I122
- methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria
- methylmalonic aciduria and homocystinuria type C protein

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MMACHC (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=25974[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28MMACHC%5BTIAB%5D%29+OR+%28methylmalonic+aciduria+++cblC+type,+with+homocystinuria%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+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- METABOLISM OF COBALAMIN ASSOCIATED C; MMACHC (https://omim.org/entry/609831)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/25974)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=MMACHC[gene])

References

- 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/)

- Hannibal L, Kim J, Brasch NE, Wang S, Rosenblatt DS, Banerjee R, Jacobsen DW. Processing of alkylcobalamins in mammalian cells: A role for the MMACHC (cblC) gene product. Mol Genet Metab. 2009 Aug;97(4):260-6. doi:10.1016/j.ymgme.2009.04.005. Epub 2009 Apr 16. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19447654) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709701/)
- Kim J, Gherasim C, Banerjee R. Decyanation of vitamin B12 by a traffickingchaperone. Proc Natl Acad Sci U S A. 2008 Sep 23;105(38):14551-4. doi:10.1073/pnas.0805989105. Epub 2008 Sep 8. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18779575) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2567227/)
- Lerner-Ellis JP, Anastasio N, Liu J, Coelho D, Suormala T, Stucki M, Loewy AD, Gurd S, Grundberg E, Morel CF, Watkins D, Baumgartner MR, Pastinen T, RosenblattDS, Fowler B. Spectrum of mutations in MMACHC, allelic expression, and evidencefor genotype-phenotype correlations. Hum Mutat. 2009 Jul;30(7):1072-81. doi:10.1002/humu.21001. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19370762)
- Lerner-Ellis JP, Tirone JC, Pawelek PD, Dore C, Atkinson JL, Watkins D, MorelCF, Fujiwara TM, Moras E, Hosack AR, Dunbar GV, Antonicka H, Forgetta V, DobsonCM, Leclerc D, Gravel RA, Shoubridge EA, Coulton JW, Lepage P, Rommens JM, MorganK, Rosenblatt DS. Identification of the gene responsible for methylmalonicaciduria and homocystinuria, cblC type. Nat Genet. 2006 Jan;38(1):93-100. doi:10.1038/ng1683. Epub 2005 Nov 27. Erratum In: Nat Genet. 2006 Aug;38(8):957. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16311595)

Genomic Location

The *MMACHC* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

Last updated August 2, 2022