Methylmalonic acidemia with homocystinuria

Description

Methylmalonic acidemia with homocystinuria is a disorder in which the body is unable to correctly process certain protein building blocks (amino acids), fat building blocks (fatty acids), and cholesterol. The body is also unable to convert the amino acid homocysteine to another amino acid, methionine. Individuals with this disorder have a combination of features from two separate conditions, methylmalonic acidemia and homocystinuria. There are several forms of this combined condition, and the different forms have different genetic causes and signs and symptoms. The most common and best understood form, called cblC type (or cobalamin C disease), occurs in about 80 percent of affected individuals.

The signs and symptoms of methylmalonic acidemia with homocystinuria usually develop in infancy, although they can begin at any age. When the condition begins early in life, affected individuals typically grow more slowly than expected. This sign is sometimes iedentified before the baby is born. These infants can also have difficulty feeding and have an abnormally pale appearance (pallor). Eye abnormalities and neurological problems, including weak muscle tone (hypotonia) and seizures, are also common in people with methylmalonic acidemia with homocystinuria. Many infants and children with this condition have delayed development and intellectual disability, and some have an unusually small head size (microcephaly).

Some people with methylmalonic acidemia with homocystinuria develop a blood disorder called megaloblastic anemia. Megaloblastic anemia occurs when a person has a low number of red blood cells (anemia), and the remaining red blood cells are larger than normal (megaloblastic). The signs and symptoms of early-onset methylmalonic acidemia with homocystinuria worsen over time, and the condition can be life-threatening if it is not treated.

When methylmalonic acidemia with homocystinuria begins in adolescence or adulthood, it may change an affected person's behavior and personality; the person may become less social and may experience hallucinations, delirium, and psychosis. In addition, these individuals can begin to lose previously acquired mental and physical abilities, resulting in a decline in school or work performance, difficulty controlling movements, memory problems, speech difficulties, a decline in intellectual function (dementia), or an extreme lack of energy (lethargy). Some people with methylmalonic acidemia with homocystinuria whose signs and symptoms begin later in life develop a condition called subacute combined degeneration of the spinal cord, which leads to numbness and

weakness in the lower limbs, difficulty walking, and frequent falls.

Frequency

The most common form of the condition, methylmalonic acidemia with homocystinuria, cblC type, is estimated to affect 1 in 200,000 newborns worldwide. This form of the condition may be even more common in certain populations; some studies estimate that it occurs in 1 in 100,000 people in New York and 1 in 60,000 people in California.

Other types of methylmalonic acidemia with homocystinuria are much less common. Fewer than 20 cases of each of the other types have been reported in the medical literature.

Causes

Methylmalonic acidemia with homocystinuria can be caused by variants (also known as mutations) in one of several genes, including *MMACHC*, *MMADHC*, *LMBRD1*, and *ABCD4*. Variants in these genes account for the different types of the disorder: cblC, cblD, cblF, and cblJ, respectively. Another type, called epi-cblC, is caused by variants in the *PRDX1* gene, usually in combination with an *MMACHC* gene variant.

MMACHC, *MMADHC*, *LMBRD1*, and *ABCD4* are all involved in processing vitamin B12, also known as cobalamin or Cbl. The *PRDX1* gene is not directly involved in processing amino acids, lipids, or cholesterol, but it is located near the *MMACHC* gene, and certain genetic alterations to *PRDX1* can affect *MMACHC* gene activity.

During processing, vitamin B12 is converted to one of two molecules: adenosylcobalamin (AdoCbl) or methylcobalamin (MeCbl). AdoCbl is required for the normal function of an enzyme that helps break down certain amino acids, lipids, and cholesterol. AdoCbl is called a cofactor because it helps the enzyme carry out its function.

MeCbl is also a cofactor, but for another enzyme that converts homocysteine to methionine. The body uses methionine to make proteins and other important compounds.

Variants in the *MMACHC*, *MMADHC*, *LMBRD1*, *ABCD4,* or *PRDX1* gene affect the early steps of vitamin B12 processing, resulting in a shortage of both AdoCbl and MeCbl. Without AdoCbl, proteins and lipids are not broken down properly. As a result, potentially toxic compounds build up in the body's organs and tissues, causing methylmalonic acidemia.

Without MeCbl, homocysteine is not converted to methionine. As a result, homocysteine builds up in the bloodstream and methionine is depleted. Some of the excess homocysteine is excreted in urine (homocystinuria).

Variants in the *HCFC1* gene are the most common cause of a condition called methylmalonic acidemia with homocystinuria, cblX type. This gene provides instructions for making a protein that helps regulate the activity of other genes, including the

MMACHC gene. Variants in the *HCFC1* gene (and, less commonly, other related genes) likely disrupt the normal activity of the *MMACHC* gene, impairing vitamin B12 processing and leading to methylmalonic acidemia or homocystinuria. However, variants in the *HCFC1* gene likely also disrupt the normal activity of other genes, resulting in additional signs and symptoms that are more serious. Many researchers consider cblX a separate disorder from methylmalonic acidemia with homocystinuria.

Variants in other genes involved in vitamin B12 processing can cause related conditions. Variants that impair only AdoCbl production lead to methylmalonic acidemia, and variants that impair only MeCbl production cause homocystinuria.

Learn more about the genes associated with Methylmalonic acidemia with homocystinuria

- ABCD4
- HCFC1
- LMBRD1
- MMACHC
- MMADHC
- PRDX1

Additional Information from NCBI Gene:

- THAP11
- ZNF143

Inheritance

Methylmalonic acidemia with homocystinuria is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell must have a variant to cause the disorder. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition.

The condition caused by variants in the *HCFC1* gene is inherited in an X-linked recessive pattern, because this gene is located on the X chromosome, one of the two sex chromosomes.

Other Names for This Condition

- Methylmalonic acidemia and homocystinemia
- Methylmalonic acidemia and homocystinuria
- Methylmalonic aciduria and homocystinuria
- Vitamin B12 metabolic defect with combined deficiency of methylmalonyl-coA

mutase and homocysteine:methyltetrahydrofolate methyltransferase

- Vitamin B12 metabolic defect with combined deficiency of methylmalonyl-coA mutase and methionine synthase activities

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Cobalamin C disease (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848561/)
- Genetic Testing Registry: Methylmalonic aciduria and homocystinuria type cblD (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848552/)
- Genetic Testing Registry: Methylmalonic acidemia with homocystinuria, type cblJ (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3553915/)
- Genetic Testing Registry: Methylmalonic aciduria and homocystinuria type cblF (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848578/)

Genetic and Rare Diseases Information Center

- Methylmalonic acidemia with homocystinuria (https://rarediseases.info.nih.gov/diseases/3579/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Methylmalonic acidemia with homocystinuria%22)

Catalog of Genes and Diseases from OMIM

- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblF TYPE; MAHCF (https://omim.org/entry/277380)
- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblC TYPE; MAHCC (https://omim.org/entry/277400)
- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE; MAHCD (https://omim.org/entry/277410)
- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblJ TYPE; MAHCJ (https://omim.org/entry/614857)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28methylmalonic+acidemia+and+homocystinuria%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2520+days%22%5Bdp%5D)

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