Methylmalonic acidemia

Description

Methylmalonic acidemia is a group of inherited disorders that prevent the body from breaking down proteins and fats (lipids) properly. The effects of methylmalonic acidemia, which usually appear in early infancy, vary from mild to life-threatening. Affected infants can experience vomiting, dehydration, weak muscle tone (hypotonia), developmental delays, excessive tiredness (lethargy), an enlarged liver (hepatomegaly), and failure to gain weight and grow at the expected rate (failure to thrive). Long-term complications can include feeding problems, intellectual disabilities, movement problems, chronic kidney disease, and inflammation of the pancreas (pancreatitis). People with methylmalonic acidemia can have frequent episodes of excess acid in the blood (metabolic acidosis) that cause serious health complications.Without treatment, this disorder can lead to coma and death in some cases.

Frequency

Methylmalonic acidemia occurs in an estimated 1 in 50,000 to 100,000 people.

Causes

Variants (also called mutations) in the *MMUT*, *MMAA*, *MMAB*, *MMADHC*, and *MCEE* genes cause methylmalonic acidemia. The long-term effects of methylmalonic acidemia depend on which gene is altered and the severity of the variant.

About 60 percent of individuals with methylmalonic acidemia have variants in the *MMUT* gene. This gene provides instructions for making an enzyme called methylmalonyl-CoA mutase. This enzyme works with vitamin B12 (also called cobalamin) to break down several protein building blocks (amino acids), certain lipids, and cholesterol. Variants in the *MMUT* gene alter the enzyme's structure or reduce the amount of the enzyme, which prevents these molecules from being broken down properly. As a result, a substance called methylmalonic acid and other potentially toxic compounds can accumulate in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

Variants in the *MMUT* gene that prevent the production of any functional methylmalonyl-CoA mutase result in a form of the condition designated mut^0. Mut^0 is the most severe form of methylmalonic acidemia and has the poorest outcomes. Variants that change

the structure of methylmalonyl-CoA mutase but do not eliminate its activity cause a form of the condition designated *mut*$^{-}$. The *mut*$^{-}$ form is typically less severe, with more variable symptoms than the *mut*^{0} form.

Some cases of methylmalonic acidemia are caused by variants in the *MMAA*, *MMAB*, or *MMADHC* gene. Proteins produced from the *MMAA*, *MMAB*, and *MMADHC* genes are required for the proper function of methylmalonyl-CoA mutase. Specifically, these proteins help produce and regulate vitamin B12, which methylmalonyl-CoA mutase needs to function. Variants that affect proteins produced from these three genes can impair the activity of methylmalonyl-CoA mutase, leading to methylmalonic acidemia.

A few other cases of methylmalonic acidemia are caused by variants in the *MCEE* gene. This gene provides instructions for producing an enzyme called methylmalonyl CoA epimerase. Like methylmalonyl CoA mutase, this enzyme also plays a role in the breakdown of amino acids, certain lipids, and cholesterol. Disruption in the function of methylmalonyl CoA epimerase leads to a form of methylmalonic acidemia with varied signs and symptoms.

Because variants in these genes only cause elevations in the levels of methylmalonic acid, this condition is sometimes referred to as isolated methylmalonic acidemia. This helps distinguish it from related conditions, such as methylmalonic acidemia with homocystinuria.

It is possible that variants in other, unidentified genes also cause methylmalonic acidemia.

Learn more about the genes associated with Methylmalonic acidemia

- MCEE
- MMAA
- MMAB
- MMADHC
- MMUT

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the *MMUT*, *MMAA*, *MMAB*, *MMADHC*, or *MCEE* 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.

Other Names for This Condition

- Isolated methylmalonic acidemia
- Methylmalonic aciduria

- MMA

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Methylmalonic acidemia due to methylmalonyl-CoA epimerase deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855100/)
- Genetic Testing Registry: Methylmalonic aciduria, cblA type (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855109/)
- Genetic Testing Registry: Methylmalonic aciduria, cblB type (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855102/)
- Genetic Testing Registry: Methylmalonic acidemia (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268583/)
- Genetic Testing Registry: Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855114/)

Genetic and Rare Diseases Information Center

- Methylmalonic acidemia (https://rarediseases.info.nih.gov/diseases/7033/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%22)

Catalog of Genes and Diseases from OMIM

- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE; MAHCD (https://omim.org/entry/277410)
- METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-CoA MUTASE DEFICIENCY (https://omim.org/entry/251000)
- METHYLMALONIC ACIDURIA, cblA TYPE (https://omim.org/entry/251100)
- METHYLMALONIC ACIDURIA, cblB TYPE (https://omim.org/entry/251110)
- METHYLMALONYL-CoA EPIMERASE DEFICIENCY (https://omim.org/entry/251120)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(Amino+Acid+Metabolism,+Inborn+Errors%5BMAJR%5D)+AND+((methylmalonic+acidemia%5BTIAB%5D)+OR+(methylmalonic+aciduria%5BTIAB%5D)+OR+(mma%5BTIAB%5D)+OR+(methylmalonic acidemia%5BTIAB%5D)+OR+(methylmalonicaciduria%5BTIAB%5D))+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+6000+days%22%5Bdp%5D)

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