Combined Malonic and Methylmalonic Mciduria

Subjects: Genetics & Heredity

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Combined malonic and methylmalonic aciduria (CMAMMA) is a condition characterized by high levels of certain chemicals, known as malonic acid and methylmalonic acid, in the body. A distinguishing feature of this condition is higher levels of methylmalonic acid than malonic acid in the urine, although both are elevated.

genetic conditions

1. Introduction

The signs and symptoms of CMAMMA can begin in childhood. In some children, the buildup of acids causes the blood to become too acidic (ketoacidosis), which can damage the body's tissues and organs. Other signs and symptoms may include involuntary muscle tensing (dystonia), weak muscle tone (hypotonia), developmental delay, an inability to grow and gain weight at the expected rate (failure to thrive), low blood sugar (hypoglycemia), and coma. Some affected children have an unusually small head size (microcephaly).

Other people with CMAMMA do not develop signs and symptoms until adulthood. These individuals usually have neurological problems, such as seizures, loss of memory, a decline in thinking ability, or psychiatric diseases.

2. Frequency

CMAMMA appears to be a rare disease. Approximately a dozen cases have been reported in the scientific literature.

3. Causes

Mutations in the *ACSF3* gene cause CMAMMA. This gene provides instructions for making an enzyme that plays a role in the formation (synthesis) of fatty acids. Fatty acids are building blocks used to make fats (lipids). The ACSF3 enzyme performs a chemical reaction that converts malonic acid to malonyl-CoA, which is the first step of fatty acid synthesis in cellular structures called mitochondria. Based on this activity, the enzyme is classified as a malonyl-CoA synthetase. The ACSF3 enzyme also converts methylmalonic acid to methylmalonyl-CoA, making it a methylmalonyl-CoA synthetase as well.

The effects of *ACSF3* gene mutations are unknown. Researchers suspect that the mutations lead to altered enzymes that have little or no function. Because the enzyme cannot convert malonic and methylmalonic acids, they build up in the body. Damage to organs and tissues caused by accumulation of these acids may be responsible for the signs and symptoms of CMAMMA, although the mechanisms are unclear.

3.1. The Gene Associated with Combined Malonic and Methylmalonic Aciduria

- ACSF3

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- CMAMMA

References

1. Alfares A, Nunez LD, Al-Thihli K, Mitchell J, Melançon S, Anastasio N, Ha KC, Majewski J, Rosenblatt DS, Braverman N. Combined malonic and methylmalonicaciduria: exome sequencing reveals mutations in the ACSF3 gene in patients with anon-classic phenotype. J Med Genet. 2011 Sep;48(9):602-5. doi:10.1136/jmedgenet-2011-100230.
2. Gregg AR, Warman AW, Thorburn DR, O'Brien WE. Combined malonic andmethylmalonic aciduria with normal malonyl-coenzyme A decarboxylase activity: acase supporting multiple aetiologies. J Inherit Metab Dis. 1998 Jun;21(4):382-90.
3. Kölker S, Schwab M, Hörster F, Sauer S, Hinz A, Wolf NI, Mayatepek E, HoffmannGF, Smeitink JA, Okun JG. Methylmalonic acid, a biochemical hallmark ofmethylmalonic acidurias but no inhibitor of mitochondrial respiratory chain. JBiol Chem. 2003 Nov 28;278(48):47388-93.
4. Melo DR, Kowaltowski AJ, Wajner M, Castilho RF. Mitochondrial energymetabolism in neurodegeneration associated with methylmalonic acidemia. JBioenerg Biomembr. 2011 Feb;43(1):39-46. doi: 10.1007/s10863-011-9330-2. Review.
5. Sloan JL, Johnston JJ, Manoli I, Chandler RJ, Krause C, Carrillo-Carrasco N,Chandrasekaran SD, Sysol JR, O'Brien K, Hauser NS, Sapp JC, Dorward HM, HuizingM; NIH Intramural Sequencing Center Group, Barshop BA, Berry SA, James PM,Champaigne NL, de Lonlay P, Valayannopoulos V, Geschwind MD, Gavrilov DK, NyhanWL, Biesecker LG, Venditti CP. Exome

sequencing identifies ACSF3 as a cause ofcombined malonic and methylmalonic aciduria. Nat Genet. 2011 Aug 14;43(9):883-6. doi: 10.1038/ng.908.