

### What is methylmalonic acidemia?

Methylmalonic acidemias are a group of inherited diseases characterized by lethargy, vomiting, developmental delays, hypotonia, and enlargement of the liver. Individuals with methylmalonic acidemia have defects in one of several proteins and enzymes that break down certain amino acids, fatty acids, and cholesterol in the body. Symptoms are due to the toxic build-up of these substances and their metabolites in organs and tissues.<sup>1</sup> Subtypes include cobalamin A type, cobalamin B type, and methylmalonyl CoA mutase deficiency.<sup>2,3,4</sup>

### What are the symptoms of methylmalonic acidemia and what treatment is available?

Methylmalonic acidemia is a disease that varies in age of onset, severity, and responsiveness to vitamin B<sub>12</sub> treatment. The most severe form of the disease is the most common, has onset in early infancy, and is least responsive to vitamin B<sub>12</sub> treatment.<sup>5</sup> Symptoms may include<sup>1,5</sup>:

- Vomiting
- Hypotonia (low muscle tone)
- Lethargy (lack of energy)
- Failure to thrive (not gaining weight or growing well)
- Hepatomegaly (enlarged liver)
- Hypothermia (low body temperature)
- Coma or death, even with aggressive intervention

Some individuals have onset in early childhood or later, and symptoms are often triggered by fasting, illness, or eating large amounts of protein. Symptoms are similar to the severe form; however, these individuals are typically more responsive to vitamin B<sub>12</sub> treatment.<sup>5,6</sup>

Even when treated, long-term complications of methylmalonic acidemia may include<sup>1,6</sup>:

- Feeding problems
- Intellectual disabilities
- Spasticity (abnormally tight muscles)
- Skin rashes and infections
- Kidney disease
- Vision loss

There is no cure for methylmalonic acidemia. Treatment typically includes a low protein diet, nutrition supplements, and vitamin B<sub>12</sub>.<sup>5</sup> Despite treatment, as many as 50% of individuals diagnosed in infancy die in early childhood.<sup>5</sup>

Methylmalonic acidemia is included on all newborn screening panels in the United States.<sup>7</sup>

### How is methylmalonic acidemia inherited?

Methylmalonic acidemia is an autosomal recessive disease caused by mutations in at least five different genes. The majority of individuals have mutations in the *MUT*, *MMAA*, or *MMAB* genes.<sup>5</sup> An individual who has one mutation in any of these genes is a carrier and is not expected to have related health problems. An individual who has two mutations in the same gene, one from each parent, is expected to be affected with methylmalonic acidemia. For example, a child with two *MUT* mutations is expected to be affected, and a child with one *MUT* mutation and one *MMAA* mutation is a carrier.

If both members of a couple are carriers of a mutation in the same gene, the risk of having an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

### Who is at risk for methylmalonic acidemia?

Methylmalonic acidemia can occur in individuals of all races and ethnicities, with an incidence in the United States of approximately 1/91,000 and a calculated carrier frequency of 1 in 151.<sup>5</sup>

Having a relative who is a carrier or who is affected can increase an individual's risk to be a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

### What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

### What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

### Where can I get more information?

Organic Acidemia Association: <http://www.oaaneews.org/mma.htm>

Screening, Technology and Research in Genetics Available at:  
<http://newbornscreening.info/Parents/organicacididorders/MMA.html>

Children Living with Inherited Metabolic Disorders (CLIMB): <http://www.climb.org.uk/>

### References

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