

What is HMG-CoA Lyase Deficiency?

HMG-CoA lyase deficiency is an inherited disease characterized by lethargy, vomiting, and low blood sugar. It can quickly progress to breathing problems, seizures, coma, and death if untreated. It involves defects in the production of enzyme 3-hydroxymethyl-3-methylglutaryl-coenzyme A lyase (HMG-Co A lyase), which the body needs to break down fats and proteins to make energy. The symptoms of HMG-CoA lyase deficiency are due to a reduced energy production in cells and a toxic build-up of metabolites in the body leading to cellular damage—particularly in the brain. HMG-CoA lyase deficiency is also known as hydroxymethylglutaric aciduria.¹

What are the symptoms of HMG-CoA lyase deficiency and what treatment is available?

HMG-CoA lyase deficiency is a disease of variable onset and severity, even within families.² The majority of affected individuals present with symptoms in the form of a metabolic crisis (episode of illness) between infancy and age two; however, some individuals are found to be affected only after a family member is diagnosed.²

Initial symptoms are often triggered by fasting, infection, or strenuous exercise and may include²:

- Lethargy (lack of energy)
- Vomiting
- Irritability
- Poor appetite
- Hypoglycemia (low blood sugar)
- Metabolic acidosis (high levels of acids in the blood)
- Hepatomegaly (enlarged liver)

During an episode, symptoms may progress to breathing problems, seizures, coma, and (possibly) death.² Approximately 20% of affected individuals die in childhood.³

Management includes a low-fat, low-protein diet, nutritional supplements, and avoidance of fasting; however, continued metabolic crises may still occur and cause²:

- Enlarged heart
- Pancreatitis (inflammation of the pancreas)
- Hearing and vision loss
- Learning disabilities or mental retardation

Although HMG-CoA lyase deficiency may be fatal in children, those who survive childhood often experience a remission of symptoms. Most affected adults are symptom-free.³

HMG-CoA lyase deficiency is offered in all newborn screening panels in all states in the United States.²

How is HMG-CoA lyase deficiency inherited?

HMG-CoA lyase deficiency is an autosomal recessive disease caused by mutations in the *HMGCL* gene.¹ An individual who inherits one *HMGCL* gene mutation is a “carrier” and is not expected to have related health problems. An individual who inherits two *HMGCL* gene mutations, one from each parent, is expected to be affected with HMG-CoA lyase deficiency, although clinical severity is highly variable.



If both members of a couple are carriers, the risk for 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 HMG-CoA lyase deficiency?

HMG-CoA lyase deficiency is estimated to occur in fewer than 1 in 100,000 individuals worldwide.³ It has been reported most commonly in individuals of Saudi Arabian, Spanish, and Portuguese descent.¹

Having a relative who is a carrier or who is affected can increase an individual's risk of being 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?

- Screening, Technology and Research in Genetics: www.newbornscreening.info/
- Organic Acidemia Association: www.oaanews.org/hmg.htm
- Fatty Oxidation Disorders Support Group: www.fodsupport.org

References

1. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. *Genetics Home Reference*. Available at: <http://ghr.nlm.nih.gov/condition/3-hydroxy-3-methylglutaryl-coa-lyase-deficiency>. Accessed: March 22, 2012.
2. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. *Screening, Technology and Research in Genetics*. Available at: <http://www.newbornscreening.info/Parents/organicacididorders/HMGCoA.html>. Accessed: March 21, 2012
3. Pié J, *et al.* Molecular genetics of HMG-CoA lyase deficiency. *Molecular Genetics and Metabolism* 2007; 92:198-209.

