



3-hydroxy-3-methylglutaryl-CoA lyase deficiency

3-hydroxy-3-methylglutaryl-CoA lyase deficiency (also known as HMG-CoA lyase deficiency) is an uncommon inherited disorder in which the body cannot process a particular protein building block (amino acid) called leucine. Additionally, the disorder prevents the body from making ketones, which are compounds that are used for energy during periods without food (fasting).

The signs and symptoms of HMG-CoA lyase deficiency usually appear within the first year of life. The condition causes episodes of vomiting, diarrhea, dehydration, extreme tiredness (lethargy), and weak muscle tone (hypotonia). During an episode, blood sugar levels can become dangerously low (hypoglycemia), and a buildup of harmful compounds can cause the blood to become too acidic (metabolic acidosis). If untreated, the disorder can lead to breathing problems, convulsions, coma, and death. Episodes are often triggered by an infection, fasting, strenuous exercise, or other types of stress.

HMG-CoA lyase deficiency is sometimes mistaken for Reye syndrome, a severe disorder that develops in children while they appear to be recovering from viral infections such as chicken pox or flu. Most cases of Reye syndrome are associated with the use of aspirin during these viral infections.

Frequency

HMG-CoA lyase deficiency is a rare condition; it has been reported in fewer than 100 individuals worldwide. Most people diagnosed with this disorder have been from Saudi Arabia, Portugal, or Spain.

Causes

Mutations in the *HMGCL* gene cause HMG-CoA lyase deficiency. The *HMGCL* gene provides instructions for making an enzyme known as 3-hydroxymethyl-3-methylglutaryl-coenzyme A lyase (HMG-CoA lyase). This enzyme plays a critical role in breaking down dietary proteins and fats for energy. Specifically, it is responsible for processing leucine, an amino acid that is part of many proteins. HMG-CoA lyase also produces ketones during the breakdown of fats. Ketones are compounds that certain organs and tissues, particularly the brain, use for energy when the simple sugar glucose is not available. For example, ketones are important sources of energy during periods of fasting.

If a mutation in the *HMGCL* gene reduces or eliminates the activity of HMG-CoA lyase, the body is unable to process leucine or make ketones properly. When leucine is not processed normally, a buildup of chemical byproducts called organic acids can result in metabolic acidosis. A shortage of ketones often leads to hypoglycemia. Metabolic

acidosis and hypoglycemia can damage cells, particularly in the brain, resulting in serious illness in children with HMG-CoA lyase deficiency.

Inheritance Pattern

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.

Other Names for This Condition

- 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency
- 3-OH 3-CH3 glutaric aciduria
- 3-OH 3-methyl glutaric aciduria
- 3HMG
- Deficiency of hydroxymethylglutaryl-CoA lyase
- HMG
- HMG-CoA lyase deficiency
- Hydroxymethylglutaric aciduria

Diagnosis & Management

Formal Treatment/Management Guidelines

- New England Consortium of Metabolic Programs: Acute Illness Protocol
https://newenglandconsortium.org/protocols/acute_illness/organic_acid_disorders/3-HMG-CoA-lyase-def.pdf

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetic-testing](#)
- Genetic Testing Registry: Deficiency of hydroxymethylglutaryl-CoA lyase
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268601/>

Other Diagnosis and Management Resources

- Baby's First Test
<https://www.babysfirsttest.org/newborn-screening/conditions/3-hydroxy-3-methylglutaric-aciduria>

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Amino Acid Metabolism Disorders
<https://medlineplus.gov/aminoacidmetabolismdisorders.html>
- Health Topic: Genetic Brain Disorders
<https://medlineplus.gov/geneticbraindisorders.html>
- Health Topic: Newborn Screening
<https://medlineplus.gov/newbornscreening.html>

Genetic and Rare Diseases Information Center

- HMG CoA lyase deficiency
<https://rarediseases.info.nih.gov/diseases/8387/hmg-coa-lyase-deficiency>

Educational Resources

- MalaCards: 3-hydroxy-3-methylglutaryl-coa lyase deficiency
https://www.malacards.org/card/3_hydroxy_3_methylglutaryl_coa_lyase_deficiency
- Newborn Screening Ontario (Canada): C5OH-related Targets
<https://www.newbornscreening.on.ca/en/c5oh-related-targets>
- Orphanet: 3-hydroxy-3-methylglutaric aciduria
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=20
- Screening, Technology, and Research in Genetics
<http://www.newbornscreening.info/Parents/organicacididorders/HMGCoA.html>
- Virginia Department of Health
http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_HMG_English.pdf

Patient Support and Advocacy Resources

- FOD (Fatty Oxidation Disorders) Family Support Group
<https://fodsupport.org/>
- Metabolic Support (UK)
<https://www.metabolicsupportuk.org/>
- Organic Acidemia Association
<https://www.oaanews.org/hmg.html>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28hmg-coa+lyase+deficiency%5BTIAB%5D%29+OR+%283-hydroxy-3-methylglutaryl-coa+lyase+deficiency%5BTIAB%5D%29+OR+%28hydroxymethylglutaric+aciduria%5BTIAB%5D%29%29+AND+human%5Bmh%5D>

Catalog of Genes and Diseases from OMIM

- 3-HYDROXY-3-METHYLGLUTARYL-CoA LYASE DEFICIENCY
<http://omim.org/entry/246450>

Medical Genetics Database from MedGen

- Deficiency of hydroxymethylglutaryl-CoA lyase
<https://www.ncbi.nlm.nih.gov/medgen/78692>

Sources for This Summary

- Bischof F, Nägele T, Wanders RJ, Trefz FK, Melms A. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency in an adult with leukoencephalopathy. *Ann Neurol.* 2004 Nov;56(5):727-30.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15505778>
- Casals N, Gómez-Puertas P, Pié J, Mir C, Roca R, Puisac B, Aledo R, Clotet J, Menao S, Serra D, Asins G, Till J, Elias-Jones AC, Cresto JC, Chamoles NA, Abdenur JE, Mayatepek E, Besley G, Valencia A, Hegardt FG. Structural (betaalpha)8 TIM barrel model of 3-hydroxy-3-methylglutaryl-coenzyme A lyase. *J Biol Chem.* 2003 Aug 1;278(31):29016-23. Epub 2003 May 13.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12746442>
- Gibson KM, Breuer J, Nyhan WL. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: review of 18 reported patients. *Eur J Pediatr.* 1988 Dec;148(3):180-6. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/3063529>
- Mitchell GA, Ozand PT, Robert MF, Ashmarina L, Roberts J, Gibson KM, Wanders RJ, Wang S, Chevalier I, Plöchl E, Mizioro H. HMG CoA lyase deficiency: identification of five causal point mutations in codons 41 and 42, including a frequent Saudi Arabian mutation, R41Q. *Am J Hum Genet.* 1998 Feb;62(2):295-300.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/9463337>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1376904/>
- Pié J, Casals N, Puisac B, Hegardt FG. Molecular basis of 3-hydroxy-3-methylglutaric aciduria. *J Physiol Biochem.* 2003 Dec;59(4):311-21.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15164951>
- Pié J, López-Viñas E, Puisac B, Menao S, Pié A, Casale C, Ramos FJ, Hegardt FG, Gómez-Puertas P, Casals N. Molecular genetics of HMG-CoA lyase deficiency. *Mol Genet Metab.* 2007 Nov;92(3):198-209. Epub 2007 Aug 9. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17692550>
- Yalçinkaya C, Dinçer A, Gündüz E, Fiçicioglu C, Koçer N, Aydın A. MRI and MRS in HMG-CoA lyase deficiency. *Pediatr Neurol.* 1999 May;20(5):375-80. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/10371384>

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/3-hydroxy-3-methylglutaryl-coa-lyase-deficiency>

Reviewed: March 2017

Published: September 10, 2019

Lister Hill National Center for Biomedical Communications

U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services