

**Disease Name:**

**HOLOCARBOXYLASE DEFICIENCY**

(HOLOCARBOXYLASE SYNTHETASE DEFICIENCY; MULTIPLE CARBOXYLASE DEFICIENCY, NEONATAL FORM)

**Classification:** Organic Aciduria

**Genetic** **Inheritance:** Autosomal Recessive

**Information:**

**Population Incidence:** 1 in 87,000 live births

**Ethnic Incidence:** No known population at increased risk

**Gene & Location:** 21q22.1- HLCS gene

**Common Mutation:** Some with increased frequency in different populations.

**OMIM #** \*253270

**Disease** **Symptom Onset:** Anytime from birth to 15 months of age.

**Information:**

**Symptoms:** Infants generally present with food refusal, vomiting, breathing problems, hypotonia, seizures, and lethargy. Severe metabolic/lactic acidosis, organic aciduria, mild hyperammonemia and variable hypoglycemia can lead to coma and death if not treated. Survivors can have neurological damage. Patients may have skin rash and alopecia at later stages.

**Physical Findings:** The skin rash and alopecia. Otherwise, no particular dysmorphisms.

**Treatment:** Majority of cases respond readily to biotin supplementation. Biotin increases the functional activation of the carboxylase enzymes.

**Natural History without treatment:** Repeated bouts of acidosis, skin rashes, failure to thrive, coma, developmental delay and death.

**Natural History with treatment:** Children with holocarboxylase synthetase deficiency, treated with biotin have normal growth and development. However, some only partly respond to therapy and one has been reported to be unresponsive to biotin therapy.

**Metabolic**  
**Information:**

**Missing Enzyme & Location:** Holocarboxylase synthetase (HS) attaches biotin to the four carboxylase enzymes (pyruvate carboxylase; propionyl CoA carboxylase; beta-methylcrotonyl CoA carboxylase; acetyl CoA carboxylase) in order to activate them. Deficiency of HS results in functional deficiencies of all the carboxylase enzymes.

**MS/MS profile:** C3 (propionyl carnitine)- elevated  
C5-OH (3-hydroxyisovaleryl carnitine)- elevated

**Prenatal testing:** Enzyme assay of the carboxylase enzymes on amniocytes

**Miscellaneous  
Information:**

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

**References:**

1. Aoki Y, Li X, Sakamoto O, Hiratsuka M, Akaishi H, Xu L, Briones P, Suormala T, Baumgartner ER, Suzuki Y, Narisawa K. "Identification and characterization of mutations in patients with holocarboxylase synthetase deficiency", *Hum Genet.* 1999 Feb;104(2):143-8.
2. Aoki Y, Suzuki Y, Sakamoto O, Li X, Takahashi K, Ohtake A, Sakuta R, Ohura T, Miyabayashi S, Narisawa K. "Molecular analysis of holocarboxylase synthetase deficiency: a missense mutation and a single base deletion are predominant in Japanese patients", *Biochim Biophys Acta.* 1995 Dec 12;1272(3):168-74.
3. Baumgartner ER, Suormala T, Wick H, Bonjour JP. "Biotin-responsive multiple carboxylase deficiency (MCD): deficient biotinidase activity associated with renal loss of biotin", *J Inherit Metab Dis.* 1984;7 Suppl 2:123-5.
4. Brandt NJ. "Symptoms and Signs in Organic Acidurias", *J Inher Metab Dis* 1984; 7(suppl 1): 23-27.
5. Briones P, Ribes A, Vilaseca MA, Rodriguez-Valcarcel G, Thuy LP, Sweetman L. "A new case of holocarboxylase synthetase deficiency", *J Inherit Metab Dis.* 1989;12(3):329-30.
6. Carpenter KH, Wilcken B, Christodoulou J, Thorburn DR. "Holocarboxylase synthetase deficiency: urinary metabolites masked by gross ketosis", *J Inherit Metab Dis.* 2000 Dec;23(8):845-6.
7. Dupuis L, Campeau E, Leclerc D, Gravel RA. "Mechanism of biotin responsiveness in biotin-responsive multiple carboxylase deficiency", *Mol Genet Metab.* 1999 Feb;66(2):80-90.
8. Fuchshuber A, Suormala T, Roth B, Duran M, Michalk D, Baumgartner ER. "Holocarboxylase synthetase deficiency: early diagnosis and management of a new case", *Eur J Pediatr.* 1993 May;152(5):446-9.
9. Gibson KM, Bennett MJ, Nyhan WL, Mize CE. "Late-onset holocarboxylase synthetase deficiency", *J Inherit Metab Dis.* 1996;19(6):739-42.

10. Hoffmann GF, Gibson KM, Trefz FK, Nyhan WL, Bremer HJ, Rating D. "Neurological manifestations of organic acid disorders", *Eur J Pediatr*. 1994;153(7 Suppl 1):S94-100.
11. Larsson A, Therrell BL. "Newborn screening: the role of the obstetrician", *Clin Obstet Gynecol*. 2002 Sep;45(3):697-710; discussion 730-2.
12. Law LK, Lau CY, Pang CP, Lam WY, Sweetman L, Fok TF, Hjelm M. "An unusual case of multiple carboxylase deficiency presenting as generalized pustular psoriasis in a Chinese boy", *J Inherit Metab Dis*. 1997 Mar;20(1):106-7.
13. Leonard JV, Daish P, Naughten ER, Bartlett K. "The management and long term outcome of organic acidurias", *J Inherit Metab Dis*. 1984;7 Suppl 1:13-7.
14. Mardach R, Zempleni J, Wolf B, Cannon MJ, Jennings ML, Cress S, Boylan J, Roth S, Cederbaum S, Mock DM. "Biotin dependency due to a defect in biotin transport", *J Clin Invest*. 2002 Jun;109(12):1617-23.
15. Michalski AJ, Berry GT, Segal S. "Holocarboxylase synthetase deficiency: 9-year follow-up of a patient on chronic biotin therapy and a review of the literature", *J Inherit Metab Dis*. 1989;12(3):312-6.
16. Millington DS. "Interpretation and follow-up of abnormal newborn screening results from MS/MS", 2004 Newborn Screening & Genetics Testing Symposium, May 3, 2004, Atlanta, GA
17. Morita J, Thuy LP, Sweetman L. "Deficiency of biotinyl-AMP synthetase activity in fibroblasts of patients with holocarboxylase synthetase deficiency", *Mol Genet Metab*. 1998 Aug;64(4):250-5.
18. Morrone A, Malvagia S, Donati MA, Funghini S, Ciani F, Pela I, Boneh A, Peters H, Pasquini E, Zammarchi E. "Clinical findings and biochemical and molecular analysis of four patients with holocarboxylase synthetase deficiency", *Am J Med Genet*. 2002 Jul 22;111(1):10-8.
19. OMIM, Online Mendelian Inheritance in Man: MULTIPLE CARBOXYLASE DEFICIENCY; MCD HOLOCARBOXYLASE SYNTHETASE, INCLUDED-\*253270
20. OMIM, Online Mendelian Inheritance in Man: BIOTINIDASE; BTM MULTIPLE CARBOXYLASE DEFICIENCY, LATE-ONSET, INCLUDED-\*253260.
21. Pacheco-Alvarez D, Solorzano-Vargas RS, Del Rio AL. Biotin in metabolism and its relationship to human disease", *Arch Med Res*. 2002 Sep-Oct;33(5):439-47.
22. Pang CP, Law LK, Mak YT, Shek CC, Cheung KL, Mak TW, Lam CW, Chan AY, Fok TF. "Biochemical investigation of young hospitalized Chinese children: results over a 7-year period", *Am J Med Genet*. 1997 Nov 12;72(4):417-21.
23. Roth KS, Yang W, Foremann JW, Rothman R, Segal S. "Holocarboxylase synthetase deficiency: a biotin-responsive organic acidemia", *J Pediatr*. 1980 May;96(5):845-9.

24. Sakamoto O, Suzuki Y, Li X, Aoki Y, Hiratsuka M, Holme E, Kudoh J, Shimizu N, Narisawa K. "Diagnosis and molecular analysis of an atypical case of holocarboxylase synthetase deficiency", *Eur J Pediatr*. 2000 Jan-Feb;159(1-2):18-22.
25. Sakamoto O, Suzuki Y, Aoki Y, Li X, Hiratsuka M, Yanagihara K, Inui K, Okabe T, Yamaguchi S, Kudoh J, Shimizu N, Narisawa K. "Molecular analysis of new Japanese patients with holocarboxylase synthetase deficiency", *J Inherit Metab Dis*. 1998 Dec; 21(8): 873-4.
26. Santer R, Muhle H, Suormala T, Baumgartner ER, Duran M, Yang X, Aoki Y, Suzuki Y, Stephani U. "Partial response to biotin therapy in a patient with holocarboxylase synthetase deficiency: clinical, biochemical, and molecular genetic aspects", *Mol Genet Metab*. 2003 Jul; 79(3): 160-6.
27. Sherwood WG, Saunders M, Robinson BH, Brewster T, Gravel RA. "Lactic acidosis in biotin-responsive multiple carboxylase deficiency caused by holocarboxylase synthetase deficiency of early and late onset", *J Pediatr*. 1982 Oct;101(4):546-50.
28. Solorzano-Vargas RS, Pacheco-Alvarez D, Leon-Del-Rio A. "Holocarboxylase synthetase is an obligate participant in biotin-mediated regulation of its own expression and of biotin-dependent carboxylases mRNA levels in human cells", *Proc Natl Acad Sci U S A*. 2002 Apr 16; 99(8): 5325-30.
29. Sovik O. "Inborn errors of amino acid and fatty acid metabolism with hypoglycemia as a major clinical manifestation", *Acta Paediatr Scand*. 1989 Mar;78(2):161-70.
30. Squires L, Betz B, Umfleet J, Kelley R. "Resolution of subependymal cysts in neonatal holocarboxylase synthetase deficiency", *Dev Med Child Neurol*. 1997 Apr;39(4):267-9.
31. Stigsby B, Yarworth SM, Rahbeeni Z, Dabbagh O, de Gier Munk C, Abdo N, Brismar J, Gascon GG, Ozand PT. "Neurophysiologic correlates of organic acidemias: a survey of 107 patients", *Brain Dev*. 1994 Nov;16 Suppl:125-44.
32. Suormala T, Fowler B, Jakobs C, Duran M, Lehnert W, Raab K, Wick H, Baumgartner ER. "Late-onset holocarboxylase synthetase-deficiency: pre- and post-natal diagnosis and evaluation of effectiveness of antenatal biotin therapy", *Eur J Pediatr*. 1998 Jul;157(7):570-5.
33. Suzuki Y, Aoki Y, Sakamoto O, Li X, Miyabayashi S, Kazuta Y, Kondo H, Narisawa K. "Enzymatic diagnosis of holocarboxylase synthetase deficiency using apo-carboxyl carrier protein as a substrate", *Clin Chim Acta*. 1996 Jul 15;251(1):41-52.
34. Tang NL, Hui J, Law LK, To KF, Mak TW, Cheung KL, Vreken P, Wanders RJ, Fok TF. "Overview of common inherited metabolic diseases in a Southern Chinese population of Hong Kong", *Clin Chim Acta*. 2001 Nov;313(1-2):195-201.
35. Tang NL, Hui J, Yong CK, Wong LT, Applegarth DA, Vallance HD, Law LK, Fung SL, Mak TW, Sung YM, Cheung KL, Fok TF. "A genomic approach to mutation analysis of holocarboxylase synthetase gene in three Chinese patients with late-onset holocarboxylase synthetase deficiency", *Clin Biochem*. 2003 Mar;36(2):145-9.

36. Thuy LP, Belmont J, Nyhan WL. "Prenatal diagnosis and treatment of holocarboxylase synthetase deficiency", *Prenat Diagn.* 1999 Feb;19(2):108-12.
37. Thuy LP, Jurecki E, Nemzer L, Nyhan WL. "Prenatal diagnosis of holocarboxylase synthetase deficiency by assay of the enzyme in chorionic villus material followed by prenatal treatment", *Clin Chim Acta.* 1999 Jun 15;284(1):59-68.
38. Touma E, Suormala T, Baumgartner ER, Gerbaca B, Ogier de Baulny H, Loiselet J. "Holocarboxylase synthetase deficiency: report of a case with onset in late infancy", *J Inherit Metab Dis.* 1999 Apr;22(2):115-22.
39. Wolf B. Disorders of Biotin Metabolism In: C. Scriver, A.L. Beaudet, W. Sly and D. Valle, Editors, *The Metabolic and Molecular Basis of Inherited Disease* (eighth ed.), McGraw-Hill, New York (2001), [www.genetics.accessmedicine.com](http://www.genetics.accessmedicine.com)
40. Wolf B. "Biotinidase Deficiency", [www.genetests.org](http://www.genetests.org)
41. Wolf B. "Children with profound biotinidase deficiency should be treated with biotin regardless of their residual enzyme activity or genotype", *Eur J Pediatr.* 2002 Mar;161(3):167-8; author reply 169.
42. Wolf B, Hsia YE, Sweetman L, Feldman G, Boychuk RB, Bart RD, Crowell DH, Di Mauro RM, Nyhan WL. "Multiple carboxylase deficiency: clinical and biochemical improvement following neonatal biotin treatment", *Pediatrics.* 1981 Jul;68(1):113-8.
43. Yang X, Aoki Y, Li X, Sakamoto O, Hiratsuka M, Gibson KM, Kure S, Narisawa K, Matsubara Y, Suzuki Y. "Haplotype analysis suggests that the two predominant mutations in Japanese patients with holocarboxylase synthetase deficiency are founder mutations", *J Hum Genet.* 2000;45(6):358-62.
44. Yang X, Aoki Y, Li X, Sakamoto O, Hiratsuka M, Kure S, Taheri S, Christensen E, Inui K, Kubota M, Ohira M, Ohki M, Kudoh J, Kawasaki K, Shibuya K, Shintani A, Asakawa S, Minoshima S, Shimizu N, Narisawa K, Matsubara Y, Suzuki Y. "Structure of human holocarboxylase synthetase gene and mutation spectrum of holocarboxylase synthetase deficiency", *Hum Genet.* 2001 Nov;109(5):526-34. Epub 2001 Oct 05.
45. Zempleni J, Mock DM. "Bioavailability of biotin given orally to humans in pharmacologic doses", *Am J Clin Nutr.* 1999 Mar;69(3):504-8.