

Disease Name:

MAPLE SYRUP URINE DISEASE

(BRANCHED-CHAIN KETOACIDURIA; BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE DEFICIENCY; MSUD; KETO ACID DECARBOXYLASE DEFICIENCY)

Classification: Organic aciduria

Genetic **Inheritance:** Autosomal recessive

Information:

Population Incidence: Worldwide frequency is 1:185,000 births

Ethnic Incidence: Old Order Mennonite frequency is 1:176 births
Ashkenazi Jews 1:113 births
Increased incidence among the aboriginal tribes in Taiwan.

Gene & Location: E1 α - located on 19q13.1-q13.2
E1 β - located on 6p21-p22
E2- located on 1p31
E3- located on 7q31-q32

Common Mutation: More than 63 mutations in all four genes
Mennonite population has a common mutation of the Type IA phenotype- Y393N- α
Ashkenazi Jewish common mutation- R183P-E1 β
Austronesian tribes with a common E2 gene 4.7kb deletion
Founder mutation among Filipino population- E2 gene deletion

OMIM # *248600; *248611; *248610; *246900

Disease
Information:

Symptom Onset: Variable onset, usually by 2 years of age.
Neonatal classic disease onset is most severe and most common.

Symptoms: Infants appear normal at birth and develop symptoms between 4-7 days of life. Lethargy and poor suck are first signs followed by alternating hyper and hypotonia, irritability and dystonia. Progress to severe ketoacidosis, hyperammonemia, with seizures and coma leading to death if untreated. Hypoglycemia is not a prominent feature. Pseudotumor cerebri is occasionally observed. Infants with milder forms may only present with episodic acidosis during intercurrent illnesses or other stressors.

Physical Findings: No particular dysmorphism do have prominent neurological findings when ill. Cerumen, urine or sweat may smell faintly of maple syrup.

Treatment:	Dietary management with decreased leucine in diet and limited isoleucine and valine. Aggressive management of acute metabolic events
Natural History without treatment:	The classic form progresses to coma and death if untreated. The intermediate form develops neurological damage and bouts of metabolic decompensation. The intermittent form has normal development with intermittent episodes of metabolic decompensation. Even without metabolic decompensation, chronic high levels of BCAA has been shown to cause demyelination.
Natural History with treatment:	Age of diagnosis and metabolic control are the most important determinants of long-term outcome. Patients with classical disease started on treatment after 14 days of life rarely achieve normal intellect. Early treatment has improved outcome, but there can be complications. Even with treatment some have died from brain edema. Depending on severity of metabolic events, neurological outcome varies.

Metabolic Information:

Missing Enzyme & Location: Branched-chain alpha-keto acid dehydrogenase is a multi-enzyme complex loosely associated with the inner membrane of the mitochondria- responsible for the breakdown of the branched chain amino acids.

MS/MS profile: Leucine- elevated
Leucine to alanine ratio – elevated.

Prenatal testing: Prenatal diagnosis is possible by enzyme assay or if mutations known can do molecular diagnosis

Miscellaneous Information:

E3 gene deficiency causes a defect in dihydrolipoyl dehydrogenase with resultant defects in branched chain metabolism, pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase and typically a more severe, progressive course and later onset of symptoms.

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. Asola MR. “A diver unconscious after gastroenteritis”, *Lancet*. 1995 Nov 18; 346(8986): 1338.
2. Backhouse O, Leitch RJ, Thompson D, Kriss A, Charris D, Clayton P, Russell-Eggitt I. “A case of reversible blindness in maple syrup urine disease”, *Br J Ophthalmol*. 1999 Feb; 83(2): 250-1.
3. Bodamer OA, Leonard JV, Halliday D. “Intermittent maple syrup disease”, *Lancet*. 1996 Jan 20; 347(8995): 191-2.

4. Bodner-Leidecker A, Wendel U, Saudubray JM, Schadewaldt P. "Branched-chain L-amino acid metabolism in classical maple syrup urine disease after orthotopic liver transplantation", *J Inherit Metab Dis*. 2000 Dec; 23(8): 805-18.
5. Brandt NJ. "Symptoms and Signs in Organic Acidurias", *J Inher Metab Dis* 1984; 7(suppl 1): 23-27.
6. Burlina A, Manara R, Calderone M, Catuogno S, Burlina AP. "Early Diagnosis of metabolic Stroke in Branched-Chain Organic Acidurias Without metabolic Decompensation", *J Inherit Metab Dis* 2002; 25(suppl.1): 45.
7. Cavalleri F, Berardi A, Burlina AB, Ferrari F, Mavilla L. "Diffusion-weighted MRI of maple syrup urine disease encephalopathy", *Neuroradiology*. 2002 Jun; 44(6): 499-502. Epub 2002 Apr 24.
8. Chi CS, Tsai CR, Chen LH, Lee HF, Mak BS, Yang SH, Wang TY, Shu SG, Chen CH. "Maple syrup urine disease in the Austronesian aboriginal tribe Paiwan of Taiwan: a novel DBT (E2) gene 4.7 kb founder deletion caused by a nonhomologous recombination between LINE-1 and Alu and the carrier-frequency determination", *Eur J Hum Genet*. 2003 Dec;11(12):931-6.
9. Chuang DT. "Maple syrup urine disease: it has come a long way", *J Pediatr*. 1998 Mar; 132(3 Pt 2): S17-23.
10. Chuang DT, Shih VE. Maple Syrup Urine Disease (Branched-Chain Ketoaciduria) 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
11. Danias J, Raab EI, Friedman AH. "Retinopathy associated with pancreatitis in a child with maple syrup urine disease", *Br J Ophthalmol*. 1998 Jul;82(7):841-2.
12. de Baulny HO, Saudubray JM. "Branched-chain organic acidurias", *Semin Neonatol* 2002; 7: 65-74.
13. Delis D, Michelakakis H, Katsarou E, Bartsocas CS. "Thiamin-responsive maple syrup urine disease: seizures after 7 years of satisfactory metabolic control", *J Inherit Metab Dis*. 2001 Nov;24(6):683-4.
14. Deng C, Deng Y. "Diagnosis of maple syrup urine disease by determination of L-valine, L-isoleucine, L-leucine and L-phenylalanine in neonatal blood spots by gas chromatography-mass spectrometry", *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003 Jul 25;792(2):261-8.
15. Dursun A, Henneke M, Ozgul K, Gartner J, Coskun T, Tokatli A, Kalkanoglu HS, Demirkol M, Wendel U, Ozalp I. "Maple syrup urine disease: mutation analysis in Turkish patients", *J Inherit Metab Dis*. 2002 May;25(2):89-97.
16. Edelman L, Wasserstein MP, Kornreich R, Sansaricq C, Snyderman SE, Diaz GA. "Maple syrup urine disease: identification and carrier-frequency determination of a novel founder mutation in the Ashkenazi Jewish population", *Am J Hum Genet*. 2001 Oct;69(4):863-8. Epub 2001 Aug 16.

17. Fariello G, Dionisi-Vici C, Orazi C, Malena S, Bartuli A, Schingo P, Carnevale E, Saponara I, Sabetta G. "Cranial ultrasonography in maple syrup urine disease", *AJNR Am J Neuroradiol*. 1996 Feb;17(2):311-5.
18. Green K, Carpenter K, Wilcken B. "Remote Monitoring of Maple Syrup Urine Disease (MSUD) By Tandem-Mass Spectrometry (MS/MS)", *J Inherit Metab Dis* 2002; 25 (Suppl. 1): 25.
19. Grunewald S, Hinrichs F, Wendel U. "Pregnancy in a woman with maple syrup urine disease", *J Inherit Metab Dis*. 1998 Apr;21(2):89-94.
20. Halliday D, Bodamer OA. "Measurement of glucose turnover--implications for the study of inborn errors of metabolism", *Eur J Pediatr*. 1997 Aug;156 Suppl 1:S35-8.
21. Henriquez H, el Din A, Ozand PT, Subramanyam SB, al Gain SI. "Emergency presentations of patients with methylmalonic acidemia, propionic acidemia and branched chain amino acidemia (MSUD)", *Brain Dev*. 1994 Nov;16 Suppl:86-93.
22. Hoffmann GF, Gibson KM, Nyhan WL, Bremer HJ, Rating D. "Neurological manifestations of organic acid disorders", *Eur J Pediatr* 1994; 153(suppl 1): S94-S100.
23. Hong YS, Korman SH, Lee J, Ghoshal P, Wu Q, Barash V, Kang S, Oh S, Kwon M, Gutman A, Rachmel A, Patel MS. "Identification of a common mutation (Gly194Cys) in both Arab Moslem and Ashkenazi Jewish patients with dihydrolipoamide dehydrogenase (E3) deficiency: possible beneficial effect of vitamin therapy", *J Inherit Metab Dis*. 2003;26(8):816-8.
24. Jan W, Zimmerman RA, Wang ZJ, Berry GT, Kaplan PB, Kaye EM. "MR diffusion imaging and MR spectroscopy of maple syrup urine disease during acute metabolic decompensation", *Neuroradiology*. 2003 Jun;45(6):393-9. Epub 2003 May 08.
25. Jouvét P, Kozma M, Mehmet H. "Primary human fibroblasts from a maple syrup urine disease patient undergo apoptosis following exposure to physiological concentrations of branched chain amino acids", *Ann N Y Acad Sci*. 2000;926:116-21.
26. Jouvét P, Jugie M, Rabier D, Desgres J, Hubert P, Saudubray JM, Man NK. "Combined nutritional support and continuous extracorporeal removal therapy in the severe acute phase of maple syrup urine disease", *Intensive Care Med*. 2001 Nov;27(11):1798-806. Epub 2001 Oct 25.
27. Jouvét P, Poggi F, Rabier D, Michel JL, Hubert P, Sposito M, Saudubray JM, Man NK. "Continuous venovenous haemodiafiltration in the acute phase of neonatal maple syrup urine disease", *J Inherit Metab Dis*. 1997 Aug;20(4):463-72.
28. Kahler SG, Sherwood WG, Woolf D, Lawless ST, Zaritsky A, Bonham J, Taylor CF, Clarke JTR, Durie P, Leonard JV. "Pancreatitis in patients with organic acidemias", *J Pediatr* 1994; 124(2): 239-243.
29. Kleopa KA, Raizen DM, Friedrich CA, Brown MJ, Bird SJ. "Acute axonal neuropathy in maple syrup urine disease", *Muscle Nerve*. 2001 Feb;24(2):284-7.

30. Koga Y, Iwanaga T, Yoshida I, Yoshino M, Kaneko S, Kato H. "Maple syrup urine disease: nutritional management by intravenous hyperalimentation and uneventful course after surgical repair of dislocation of the hip", *J Inherit Metab Dis*. 1998 Apr;21(2):177-8.
31. Lebo RV, Shapiro LR, Fenerci EY, Hoover JM, Chuang JL, Chuang DT, Kronn DF. "Rare etiology of autosomal recessive disease in a child with noncarrier parents", *Am J Hum Genet*. 2000 Sep;67(3):750-4. Epub 2000 Jul 27.
32. Losty H, Shortland G, Bradely D, Badminton W, Wassell J. "Treatment and Outcome of Patients with MSUD Identified By Neonatal Screening in Wales (1974-2001)", *J Inherit Metab Dis* 2002; 25 (Suppl. 1): 25.
33. Morris AA, Leonard JV. "Early recognition of metabolic decompensation", *Arch Dis Child*. 1997 Jun;76(6):555-6.
34. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. "Diagnosis and treatment of maple syrup disease: a study of 36 patients", *Pediatrics*. 2002 Jun;109(6):999-1008.
35. Nellis MM, Danner DJ. "Gene preference in maple syrup urine disease", *Am J Hum Genet*. 2001 Jan;68(1):232-7. Epub 2000 Dec 07.
36. Nellis MM, Kasinski A, Carlson M, Allen R, Schaefer AM, Schwartz EM, Danner DJ. "Relationship of causative genetic mutations in maple syrup urine disease with their clinical expression", *Mol Genet Metab*. 2003 Oct;80(1-2):189-95
37. Nyhan WL, Rice-Kelts M, Klein J, Barshop BA. "Treatment of the acute crisis in maple syrup urine disease", *Arch Pediatr Adolesc Med*. 1998 Jun;152(6):593-8.
38. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE IA- *248600.
39. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE IB- *248611.
40. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE II- *248610.
41. OMIM- Online Mendelian Inheritance in Man; LIPOAMIDE DEHYDROGENASE DEFICIENCY, LACTIC ACIDOSIS DUE TO- *246900.
42. Puliyaanda DP, Harmon WE, Peterschmitt MJ, Irons M, Somers MJ. "Utility of hemodialysis in maple syrup urine disease", *Pediatr Nephrol*. 2002 Apr;17(4):239-42.
43. Rousson R, Guibaud P. "Long Term Outcome of Organic Acidurias: Survey of 105 French Cases (1967-1983)", *J Inher Metab Dis* 1984; 7(suppl 1): 10-12.

44. Saudubray JM, Ogier H, Charpentier C, Depondt E, Coude FX, Munnich A, Mitchell G, Rey F, Rey J, Frezal J. "Neonatal Management of Organic Acidurias. Clinical Update", *J Inher Metab Dis* 1984; 7(suppl 1): 2-9.
45. Schadewaldt P, Bodner-Leidecker A, Hammen HW, Wendel U. "Significance of L-alloisoleucine in plasma for diagnosis of maple syrup urine disease", *Clin Chem*. 1999 Oct;45(10):1734-40.
46. Schadewaldt P, Bodner-Leidecker A, Hammen HW, Wendel U. "Whole-body L-leucine oxidation in patients with variant form of maple syrup urine disease", *Pediatr Res*. 2001 May;49(5):627-35.
47. Schadewaldt P, Hammen HW, Ott AC, Wendel U. "Renal clearance of branched-chain L-amino and 2-oxo acids in maple syrup urine disease", *J Inher Metab Dis*. 1999 Aug;22(6):706-22.
48. Schadewaldt P, Wendel U. "Metabolism of branched-chain amino acids in maple syrup urine disease", *Eur J Pediatr*. 1997 Aug;156 Suppl 1:S62-6.
49. Schonberger S, Schweiger B, Schwahn B, Schwarz M, Wendel U. "Dysmyelination in the brain of adolescents and young adults with maple syrup urine disease", *Mol Genet Metab*. 2004 May;82(1):69-75.
50. Seashore M. "The Organic Acidemias: An Overview", www.geneclinics.org
51. Sgaravatti AM, Rosa RB, Schuck PF, Ribeiro CA, Wannmacher CM, Wyse AT, Dutra-Filho CS, Wajner M. "Inhibition of brain energy metabolism by the alpha-keto acids accumulating in maple syrup urine disease", *Biochim Biophys Acta*. 2003 Nov 20;1639(3):232-8.
52. Silao CL, Padilla CD, Matsuo M. "A novel deletion creating a new terminal exon of the dihydrolipoyl transacylase gene is a founder mutation of Filipino maple syrup urine disease", *Mol Genet Metab*. 2004 Feb;81(2):100-4.
53. Skladal D, Grissenauer G, Konstantopoulou V, Felber S, Sperl W. "Very high plasma leucine concentrations without neurological symptoms in a patient with classical maple syrup urine disease", *J Inher Metab Dis*. 2000 Jul;23(5):513-4.
54. Van Calcar SC, Harding CO, Davidson SR, Barness LA, Wolff JA. "Case reports of successful pregnancy in women with maple syrup urine disease and propionic acidemia", *Am J Med Genet*. 1992 Nov 15;44(5):641-6.
55. Wajner M, Coelho DM, Barschak AG, Araujo PR, Pires RF, Lulhier FL, Vargas CR. "Reduction of large neutral amino acid concentrations in plasma and CSF of patients with maple syrup urine disease during crises", *J Inher Metab Dis*. 2000 Jul;23(5):505-12.
56. Wajner M, Vargas CR. "Reduction of plasma concentrations of large neutral amino acids in patients with maple syrup urine disease during crises", *Arch Dis Child*. 1999 Jun;80(6):579.

57. Wendel U, Saudubray JM, Bodner A, Schadewaldt P. "Liver transplantation in maple syrup urine disease", *Eur J Pediatr*. 1999 Dec;158 Suppl 2:S60-4.
58. Wynn RM, Chuang JL, Sansaricq C, Mandel H, Chuang DT. "Biochemical basis of type IB (E1beta) mutations in maple syrup urine disease. A prevalent allele in patients from the Druze kindred in Israel", *J Biol Chem*. 2001 Sep 28;276(39):36550-6. Epub 2001 Jul 11.
59. Yoshida S, Tanaka T. "Postpartum death with maple syrup urine disease", *Int J Gynaecol Obstet*. 2003 Apr;81(1):57-8.