

Disease Name	
MAPLE SYRUP URINE DISEASE (MSUD)	
<i>(BRANCHED-CHAIN KETOACIDURIA; BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE DEFICIENCY; MSUD; KETO ACID DECARBOXYLASE DEFICIENCY)</i>	
Classification:	Organic aciduria
Genetic Information	
Inheritance:	Autosomal recessive..
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 two years of age. Neonatal classic disease onset is most severe and most common.
Symptoms:	Classic form infants appear normal at birth and develop symptoms between four to seven 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 and labs may be normal between episodes.
Physical Findings:	No particular dysmorphisms 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, a chronic high level 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.	
Credit:	<i>Prepared by the North West Regional Newborn Screening Program Judith Tuerck, RN, MS, and Lorinda Paradise at Oregon Health Services University in Portland, Oregon and by Sara Copeland MD, Iowa Neonatal Metabolic Screening Program.</i>	
Sites of Reference:	<p>Dietary Specialties - Low Protein Foods www.dietspec.com/</p> <p>Maple Syrup Urine Disease (MSUD) www.doh.wa.gov/EHSPHL/PHL/Newborn/msud.htm</p> <p>MUMS - National Parent-to-Parent Network www.netnet.net/mums/</p> <p>Organization For Endocrine & Metabolic Diseases www.niddk.nih.gov/health/endo/pubs/endorg/endorg.htm</p> <p>National Library of Medicine Genetics Home Reference <u>Maple syrup urine disease</u> http://ghr.nlm.nih.gov/condition=maplesyrupurinedisease</p> <p>NCBI Genes and Disease <u>Maple syrup urine disease</u> http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.section.253</p>	
Support Groups:	<p>MSUD Family Support Group 24806 SR119 Goshen, IN 46526 www.msud-support.org/ (219) 862-2992 Fax: (219) 862-2012 Contact: Joyce Brubacher msud-support@juno.com</p> <p>Children Living with Inherited Metabolic Diseases (CLIMB) Climb Building 176 Nantwich Road Crewe, CW2 6BG United Kingdom (+44) 0870 7700 326 Fax: (+44) 0870 7700 327 steve@climb.org.uk www.climb.org.uk</p>	<p>National Coalition for PKU & Allied Disorders P.O. Box 1244 Mansfield, MA 02048 www.pku-allieddisorders.org/ Contact: Trish Mullaley (877) 996-2723 coalition4pkvad@aol.com</p> <p>Save Babies Through Screening Foundation, Inc 4 Manor View Circle Malvern, PA 19355-1622 888-454-3383 Fax: 610-993-0545 email@savebabies.org www.savebabies.org www.savebabies.org/MSUD</p>