Maple Syrup Urine Disease

Synonyms: BCKD Deficiency, Branched-Chain Ketoacid Dehydrogenase Deficiency, Branched-Chain Ketoaciduria, Maple Syrup Disease, MSUD

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Summary

Clinical characteristics

Maple syrup urine disease (MSUD) is classified as classic or intermediate. Twelve hours after birth, untreated neonates with classic MSUD have a maple syrup odor in cerumen; by 12-24 hours, elevated plasma concentrations of branched-chain amino acids (BCAAs) (leucine, isoleucine, and valine) and allo-isoleucine, as well as a generalized disturbance of plasma amino acid concentration ratios; by age two to three days, ketonuria, irritability, and poor feeding; by age four to five days, deepening encephalopathy manifesting as lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling." By age seven to ten days, coma and central respiratory failure may supervene. Individuals with intermediate MSUD have partial BCKAD enzyme deficiency that only manifests intermittently or responds to dietary thiamine therapy; these individuals can experience severe metabolic intoxication and encephalopathy during sufficient catabolic stress.

Diagnosis/testing

MSUD is diagnosed by the presence of clinical features, elevated BCAAs and allo-isoleucine in plasma, and branched-chain hydroxyacids and ketoacids (BCKAs) in urine. Newborn screening (NBS) programs that employ tandem mass spectrometry detect MSUD by measuring the whole blood combined leucine-isoleucine concentration and its ratio to other amino acids such as alanine and phenylalanine. The three genes in which pathogenic variants are associated with MSUD are BCKDHA, encoding BCKA decarboxylase (E1) alpha subunit (MSUD type 1A); BCKDHB, encoding BCKA decarboxylase (E1) beta subunit (MSUD type 1B); and DBT, encoding dihydrolipoyl transacylase (E2) subunit (MSUD type 2).

Management

Treatment of manifestations: Treatment consists of dietary leucine restriction, BCAA-free medical foods, judicious supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring. Metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to achieve sustained net protein synthesis in tissues. Some
centers use hemodialysis/hemofiltration to remove BCAAs from the extracellular compartment, but this alone does not establish net protein accretion. Brain edema is a common complication of metabolic decompensation and requires careful management in an intensive care setting. Adolescents and adults with MSUD are at increased risk for ADHD, depression, and anxiety disorders and can be treated successfully with standard psychostimulant and antidepressant medications. Orthotopic liver transplantation is an effective therapy for classic MSUD.

Prevention of primary manifestations: Dietary management should allow age-appropriate tolerance of leucine, isoleucine, and valine, and maintain stable plasma BCAA concentrations and BCAA concentration ratios. Use of a "sick-day" formula recipe (devoid of leucine and enriched with calories, isoleucine, valine, and BCAA-free amino acids) combined with rapid and frequent amino acid monitoring allows many catabolic illnesses to be managed in the outpatient setting.

Evaluation of relatives at risk: It can be determined if newborn sibs of an affected individual (who have not been tested prenatally) are affected (1) by molecular genetic testing of umbilical cord blood if the family-specific pathogenic alleles have been identified by prior testing of parents or an affected sib; or (2) by plasma amino acid analysis at approximately 24 hours of life. Early diagnosis may allow management of asymptomatic infants out of hospital by experienced providers.

Pregnancy management: For women with MSUD, metabolic control should be rigorously maintained before and throughout pregnancy by frequent monitoring of plasma amino acid concentrations and dietary adjustments to avoid the likely teratogenic effects of elevated maternal leucine plasma concentration. Fetal growth should be monitored to detect any signs of essential amino acid deficiency.

Genetic counseling

MSUD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being unaffected and a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants have been identified in an affected family member.

Diagnosis

Manifestations of classic maple syrup urine disease (MSUD) in untreated neonates include the following:

- Maple syrup odor in cerumen, the first clinical sign of MSUD, detectable 12 hours after birth
- Elevated plasma concentrations of branched-chain amino acids (BCAAs) (leucine, isoleucine, and valine) and allo-isoleucine, accompanied by a more generalized disturbance of plasma amino acid concentration ratios, detectable by 12-24 hours of age in affected infants on a normal protein intake. Occasionally, plasma concentrations of isoleucine or valine may be low or normal, but plasma concentration of leucine is invariably elevated. Elevated plasma concentration of allo-isoleucine is relatively specific for MSUD [Schadewaldt et al 1999a].
- Ketonuria, irritability, and poor feeding by age two to three days
- Signs of deepening encephalopathy including lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" by age four to five days
- Coma and central respiratory failure that may occur by age seven to ten days, before newborn screening results are available

Rarely, milder variants of MSUD can present as anorexia, poor growth, irritability, or developmental delays later in infancy or childhood [Chuang & Shih 2001]. Such children can present with acute leucinemia, ketonuria, and encephalopathy if stressed by fasting, dehydration, or infectious illness.
Testing

Maple syrup urine disease is caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex (BCKAD), the second enzymatic step in the degradative pathway of the BCAAs.

BCKAD has four subunit components (E1a, E1b, E2, and E3). Pathogenic variants in both alleles encoding any subunit can result in decreased activity of the enzyme complex and the accumulation of BCAAs and corresponding branched-chain ketoacids (BCKAs) in tissues and plasma [Nellis et al 2003, Chuang et al 2004].

Biochemical derangements caused by pathogenic variants in the genes encoding BCKA decarboxylase (E1) alpha subunit (MSUD type 1A); BCKA decarboxylase (E1) beta subunit (MSUD type 1B), and dihydrolipoyl transacetylase (E2) subunit (MSUD type 2) are indistinguishable biochemically.

Note: The E3 subunit (lipoyamide dehydrogenase encoded by DLD) of BCKAD is shared with the pyruvate and alpha-ketoglutarate dehydrogenase complexes, and MSUD type 3 is characterized by increased urinary excretion of BCKAs and alpha-ketoglutarate accompanied by elevated plasma concentrations of lactate, pyruvate, and alanine (Table 2). However, the clinical phenotype of E3 subunit deficiency differs considerably from the classic and intermediate forms of MSUD and is not discussed further in this GeneReview.

Biochemical Testing

Biochemical signs of classic MSUD can be identified by the following testing:

**Quantitative plasma amino acid analysis** performed in a laboratory with experience in testing for MSUD.

- **Increased plasma concentration of leucine.** Plasma isoleucine and valine are also typically elevated, but may be normal or reduced. Elevations of plasma leucine are accompanied by decreased concentrations of other essential and non-essential amino acids, leading to elevated concentration ratios (mol:mol) of leucine to amino acids including alanine, glutamate, glutamine, tryptophan, methionine, histidine, phenylalanine, and tyrosine (Figure 1) [Strauss & Morton 2003, Strauss et al 2010].

- **Plasma concentration of allo-isoleucine (>5 µmol/L),** a distinctive metabolite present in all forms of MSUD [Schadewaldt et al 1999a]
  
  Note: On some chromatographic systems, allo-isoleucine co-elutes with isoleucine, obscuring its detection.

**Tandem mass spectrometry (MS/MS)-based amino acid profiling** of dried blood spots obtained in newborn screening (NBS) programs between age 24 and 48 hours quantifies whole blood concentration ratios of (leucine + isoleucine) to alanine and phenylalanine.

Notes regarding NBS: (1) MS/MS, which is sensitive and specific for MSUD, has made newborn screening with the Guthrie bacterial inhibition assay obsolete [Chace et al 2003, Chace & Kalas 2005]. (2) See National Newborn Screening Status Report (Amino Acid Disorders) for a list of states currently screening for MSUD.

Notes regarding test result interpretation: (1) Individual states set standards for positive or suspected positive screens. (2) Because leucine-isoleucine and hydroxyproline cannot be differentiated by mass spectrometry, neonates with isolated hydroxyprolinemia will test positive for MSUD, but confirmatory amino acid analysis will show only increased hydroxyproline (a false positive newborn screening result). See ACMG ACT Sheet.

**Urinary excretion of branched-chain alpha-hydroxyacids and alpha-ketoacids (BCKAs) occurs in persons older than age 48-72 hours (by which time the plasma concentration of leucine typically exceeds 1,000 µmol/L).** Analysis can be quantitative by gas chromatography-mass spectrometry or non-quantitative by the dinitrophenylhydrazine (DNPH) test.
• **Gas chromatography-mass spectrometry** identifies large quantities of branched-chain ketoacids (BCKAs) and branched-chain hydroxyacids (BCHA) in the urine.

• **The dinitrophenylhydrazine (DNPH) test** is done by mixing equal volumes of urine and DNPH reagent (0.1 g DNPH in 100 ml 2N HCl) and observing for yellow-white precipitate after ten minutes. The DNPH can be scored by clinicians, patients, or parents on a scale of 0 (no precipitate, clear urine) to 4 (strong precipitate, opaque urine).

• **Ketonuria**, which can be detected by standard urine test strips, is a surrogate marker for metabolic instability in persons with MSUD who do not have ready access to DNPH reagent or timely analytic testing. Ketonuria in a newborn should always prompt investigation for metabolic disorders.

  Note: Hypoglycemia and hyperammonemia are unusual in all forms of MSUD.

**BCKAD enzyme activity** can be evaluated in a variety of cells including lymphoblasts.

- Residual enzyme activity is typically less than 3% of control values in persons with the classic MSUD phenotype.
- Residual enzyme activity in fibroblasts varies from 3% to 40% in persons with intermediate MSUD.

Note: (1) Although BCKAD enzyme activity can be measured in skin fibroblasts, lymphocytes, or biopsied liver tissue, it is of variable accuracy and may not be necessary [Schadewaldt et al 1998, Schadewaldt et al 2001]. (2) In six persons ages six to 34 years with intermediate MSUD, Schadewaldt et al [2001] found that in vivo measurements of $^{13}$C-leucine oxidation (19%-86% control) were considerably different from estimates of enzyme activity ex vivo (10%-25%), calling into question both the validity and utility of ex vivo enzyme assays for MSUD.

**Molecular Genetic Testing**

**Genes.** The three genes in which biallelic pathogenic variants are associated with MSUD [Nellis & Danner 2001, Nellis et al 2003] are:

- **BCKDHA** encoding BCKA decarboxylase (E1) alpha subunit gene (MSUD type 1A);
- **BCKDHB** encoding BCKA decarboxylase (E1) beta subunit gene (MSUD type 1B);
- **DBT** encoding dihydrolipoyl transacylase (E2) subunit gene (MSUD type 2).

Individuals with MSUD are always homozygous or compound heterozygous for pathogenic variants in the same gene; no individuals with MSUD who are heterozygous for pathogenic variants in two different genes have been identified. Most affected individuals are compound heterozygotes for rare sequence variants; no single pathogenic variant or gene accounts for a significant proportion of pathogenic alleles, except in genetic isolates.

Note: Pathogenic variants in **DLD**, the gene encoding lipoamide dehydrogenase, the fourth component of the branched-chain alpha-ketoacid dehydrogenase complex (BCKAD), produce a different phenotype that is not discussed in this GeneReview.

**Evidence for locus heterogeneity**

- **BCKDK** encodes a regulatory kinase that catalyzes phosphorylation-mediated inactivation of the E1 alpha subunit. Bckdk-/- mice have constitutively elevated BCKAD complex activity, low BCAA levels, stagnant growth of brain and viscera, and neurobehavioral deficits that respond to dietary BCAA supplementation [Joshi et al 2006, Watford 2007]. Inactivating variants of **BCKDK** in humans are associated with BCAA deficiency, autism, epilepsy, and intellectual disability that may respond to dietary treatment [Novarino et al 2012].

- **PPM1K** encodes a regulatory mitochondrial phosphatase (PP2Cm) that interacts with the BCKAD E2 subunit, competes with BCKDK in a substrate-dependent and mutually exclusive manner, and catalyzes
dephosphorylation of the enzyme complex [Lu et al 2009, Zhou et al 2012]. Loss of PP2Cm completely abolished substrate-induced E1alpha dephosphorylation both in vitro and in vivo. Ppm1k−/− mice have impaired BCAA and BCKA metabolism and a metabolic phenotype similar to intermittent or intermediate types of human MSUD [Lu et al 2009]. Defects of PPM1K may account for a subset of human MSUD, but to date no cases have been reported.

Table 1. Molecular Genetic Testing Used in Maple Syrup Urine Disease

<table>
<thead>
<tr>
<th>MSUD Type</th>
<th>Gene 1</th>
<th>Proportion of MSUD Attributed to Pathogenic Variants in This Gene</th>
<th>Test Method</th>
<th>Variants Detected 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSUD type 1A</td>
<td>BCKDHA</td>
<td>45%</td>
<td>Sequence analysis 3</td>
<td>Sequence variants including: c.1312T&gt;A 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Targeted analysis for pathogenic variants 5</td>
<td>c.1312T&gt;A 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deletion/duplication analysis 6</td>
<td>Exon and whole-gene deletions 7, 8</td>
</tr>
<tr>
<td>MSUD type 1B</td>
<td>BCKDHB</td>
<td>35%</td>
<td>Sequence analysis 3</td>
<td>Sequence variants including: c.548G&gt;C c.832G&gt;A c.1114G&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Targeted analysis for pathogenic variants 5</td>
<td>c.548G&gt;C c.832G&gt;A c.1114G&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deletion/duplication analysis 6</td>
<td>Exon and whole-gene deletions 9</td>
</tr>
</tbody>
</table>

Figure 1. Plasma amino values between ages four and 26 months from a child with classic MSUD show a strong reciprocal relationship between leucine (gray diamonds) and alanine (white circles) (Spearman correlation coefficient= -0.86; p<0.0001). From Strauss et al [2010]; republished with permission of Elsevier
### Testing Strategy

#### To Confirm/Establish the Diagnosis in a Proband in the Following Clinical Scenarios

**Newborn with newborn screening (NBS) test that is positive for leucine, isoleucine, and hydroxyproline or signs, symptoms, and/or unexplained ketonuria suggestive of MSUD** (see ACMG ACT Sheet)

- If available, the DNPH reagent or urine ketone test strip can be used as a screening test in infants age >48–72 hours.
- Quantitative plasma amino acid profile to detect elevated BCAAs, including allo-isoalleucine, corroborates the diagnosis of MSUD. Note: (1) In the tandem mass spectroscopy analysis used in expanded NBS leucine, isoleucine, and hydroxyproline are isobaric (i.e., ions with the same mass) and cannot be distinguished from each other. (2) Neonates with isolated hydroxyprolinemia test positive for MSUD but quantitative plasma amino acid analysis shows only increased hydroxyproline (a false positive newborn screening result) (see ACMG Algorithm).
- Analysis of urine by gas chromatography-mass spectrometry to detect BCKAs and branched-chain hydroxyacids corroborates the diagnosis of MSUD.

Note: Neonates and infants suspected of having MSUD should never be challenged with higher than normal protein intake during the diagnostic process. This practice is dangerous; modern diagnostic methods make it unnecessary.

**Newborn from family with previously affected sib and/or high ethnic risk group**

- **If pathogenic alleles are known** based on prior testing of parents or sibs, isolate DNA from umbilical cord blood and proceed to rapid variant detection by high-resolution melting analysis [Olsen et al 2010, Strauss et al 2012], other PCR-based methods [Silao et al 2008], rapid Sanger sequencing, or emerging next-generation sequencing methods [Kingsmore et al 2012].

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Table 1. continued from previous page.

<table>
<thead>
<tr>
<th>MSUD Type</th>
<th>Gene</th>
<th>Proportion of MSUD Attributed to Pathogenic Variants in This Gene</th>
<th>Test Method</th>
<th>Variants Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSUD type 2</td>
<td>DBT</td>
<td>20%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deletion/duplication analysis</td>
<td>Exon and whole-gene deletions</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Examples of pathogenic variants detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. A BCKDHA founder variant in certain Mennonite populations (see Prevalence)
5. Variants detected may vary among testing laboratories.
6. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. Quental et al [2008]
8. Rodríguez-Pombo et al [2006]
9. No deletions or duplications involving BCKDHB have been reported to cause MSUD type 1B. (Note: By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.)
• If specific pathogenic alleles are not known, high-risk newborns should be evaluated as follows:
  ◦ In clinical settings in which the technology is available, obtain umbilical cord blood for next-generation confirmatory sequencing of \textit{BCKDHA}, \textit{BCKDHB}, and \textit{DBT} [Kingsmore et al 2012].
  ◦ Smell cerumen for odor of maple syrup 12-24 hours after birth.
  ◦ Allow ad libitum protein intake after birth and obtain quantitative plasma amino acid analysis between 18 and 24 hours of life.
  ◦ If plasma amino acid profile is equivocal, repeat the test between 24 and 36 hours of life.
  ◦ If quantitative plasma amino acid profile is diagnostic of MSUD, begin dietary therapy and proceed to confirmatory molecular genetic testing of genes encoding BCKAD subunits. When causative allelic variants are unknown, the authors recommend that all three BCKAD subunits be sequenced in each patient.
  ◦ Urine organic acid analysis by gas chromatography-mass spectrometry to detect BCKAs and branched-chain hydroxyacids can be used to corroborate the diagnosis of MSUD.

Note: (1) Obtain newborn screening filter paper card within time window established by the state NBS program. (2) The DNPH reagent test cannot be used as a screening test until age 48-72 hours.

Older child or adult with signs and symptoms suggestive of MSUD
  • If available, the DNPH reagent screening test (mixing equal volumes of DNPH and urine) can be used to detect alpha-ketoacids in urine.
  • Quantitative plasma amino acid analysis that includes quantitation of allo-isoleucine is the most informative analytic test for MSUD.
  • Urine organic acid analysis by gas chromatography-mass spectrometry to detect BCKAs and branched-chain hydroxyacids can be used to corroborate the diagnosis of MSUD.

Note regarding BCKAD enzyme activity: In each of these clinical scenarios, some clinicians prefer to measure BCKAD enzyme activity from lymphocytes or skin fibroblasts. However, in vitro measurements of BCKAD activity do not correlate with measurements of in vivo leucine oxidation [Schadewaldt et al 2001], dietary leucine tolerance [Strauss et al 2010], or in vivo response to BCKAD-activating medications [Brunetti-Pierri et al 2011]. Therefore, the authors do not find measurements of BCKAD enzyme activity clinically useful.

Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the pathogenic variants in the family.

Clinical Characteristics

Clinical Description

Traditionally, the metabolic phenotype of MSUD is termed classic or intermediate on the basis of residual BCKAD enzyme activity. Rarely, affected individuals have partial BCKAD enzyme deficiency that only manifests intermittently or responds to dietary thiamine therapy (Table 2). Phenotypic distinctions are not absolute: individuals with intermediate or intermittent forms of MSUD can experience severe metabolic intoxication and encephalopathy if physiologic stress is sufficient to overwhelm residual BCKAD activity or this activity is
reduced by transient changes in the phosphorylation state of the enzyme complex. Even in persons with relatively high baseline residual BCKAD enzyme activity, episodes of metabolic intoxication can be fatal [Chuang & Shih 2001].

### Table 2. Clinical Phenotypes of Maple Syrup Urine Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Clinical Features</th>
<th>Biochemical Signs</th>
<th>BCKAD Activity, % Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Neonatal</td>
<td>• Maple syrup odor of cerumen</td>
<td>• Elevated BCAAs in plasma</td>
<td>0%-2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor feeding</td>
<td>• Elevated plasma allo-isoleucine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irritability, lethargy</td>
<td>• Elevated BCKAs in urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Opisthotonus</td>
<td>• Positive urine DNPH test</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Focal dystonia</td>
<td>• Ketonuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &quot;Fencing,&quot; &quot;bicycling&quot;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Obtundation, coma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Central respiratory failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Variable</td>
<td>• Maple syrup odor of cerumen</td>
<td>• Similar to classic phenotype, though quantitatively less severe</td>
<td>3%-30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor growth</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Poor feeding</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Irritability</td>
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<tr>
<td></td>
<td></td>
<td>• Developmental delays</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Encephalopathy during illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>Variable</td>
<td>• Normal early growth &amp; development</td>
<td>• Normal BCAAs when well</td>
<td>5%-20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Episodic decompensations that can be severe</td>
<td>• Similar to classic biochemical profile during illness</td>
<td></td>
</tr>
<tr>
<td>Thiamine-responsive</td>
<td>Variable</td>
<td>• Similar to the intermediate phenotype</td>
<td>• Improvement of leucine tolerance &amp; biochemical profile w/thiamine therapy</td>
<td>2%-40%</td>
</tr>
</tbody>
</table>

1. All infants with classic MSUD present during the neonatal period. For other forms, age of presentation depends on several variables, including dietary protein and calorie intake, growth rate, number and severity of infectious illnesses, and rarely, dietary thiamine intake.

2. In both intermediate and intermittent forms of MSUD, acute biochemical and neurologic manifestations can mimic the classic phenotype if physiologic stress is sufficient to overwhelm residual BCKAD activity or this activity is reduced by transient changes in the phosphorylation state of the enzyme complex. Even in persons with relatively high baseline residual BCKAD activity, episodes of metabolic intoxication can be fatal.

3. Biochemical signs should always be interpreted in the context of dietary leucine tolerance and prevailing clinical circumstances. Dietary leucine tolerance (in mg/kg/day) is defined as the steady-state leucine intake that permits normal growth and maintains plasma leucine concentration within the normal range.

4. The authors do not rely on tissue measurements of decarboxylation activity but classify affected individuals based on their leucine tolerance and metabolic response to illness. Decarboxylation data are from Chuang & Shih [2001].

Metabolic considerations in establishing MSUD phenotype:

- **Dietary leucine intolerance.** Leucine tolerance is defined as the weight-adjusted daily leucine intake sufficient for normal growth that also allows maintenance of steady-state plasma leucine concentration within the normal range.
  - In persons with classic MSUD, the leucine oxidation rate is close to zero and urinary losses of BCAAs are negligible [Schadewaldt et al 1999b, Levy 2001]. Thus, leucine tolerance reflects the sum
of unmeasured protein losses (e.g., sloughed skin, hair, and nails) and net accretion rate of body protein, which in turn is dependent on the growth rate (see Figure 2 and Prevention of Primary Manifestations, **Dietary management**).

- **When residual BCKAD enzyme activity exists in vivo (i.e., intermediate MSUD), leucine tolerance is higher and BCKAD enzyme activity is regulated such that plasma concentration ratios among the BCAAs tend to be more stable in both health and illness. Individuals with intermediate MSUD are less vulnerable to the volatile changes of plasma BCAA concentrations seen in classic MSUD and are less likely to experience prolonged essential amino acid deficiencies.**

- **Rapidity and severity of decompensation during illness.** The risk for metabolic crisis in any ill person with MSUD depends on residual in vivo BCKAD enzyme activity in relation to the net liberation of free leucine from protein catabolism. Thus, individuals with residual in vivo BCKAD enzyme activity enjoy a higher leucine tolerance when well and also tend to have slower and less severe elevations of plasma leucine concentrations during illnesses.

**Classic maple syrup urine disease phenotype.** Maple syrup odor is evident in cerumen soon after birth and in urine by age five to seven days. In untreated neonates, ketonuria, irritability, and poor feeding occur within 48 hours of delivery. Lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" are evident by age four to five days and are followed by coma and central respiratory failure. Preemptive detection of affected newborns, before they exhibit neurologic signs of MSUD, significantly reduces lifetime risk of mental illness and global functional impairment [Strauss et al 2012, Muelly et al 2013].

Following the neonatal period, acute leucine intoxication (leucinosis) and neurologic deterioration can develop rapidly at any age as a result of net protein degradation precipitated by infection, surgery, injury, or psychological stress (Figure 3). In infants and toddlers, leucinosis causes nausea, anorexia, altered level of consciousness, acute dystonia, and ataxia. Neurologic signs of intoxication in older individuals vary and can include cognitive impairment, hyperactivity, sleep disturbances, hallucinations, mood swings, focal dystonia, choreoathetosis, and ataxia. As plasma concentrations of leucine and alpha-ketoisocaproic acid (aKIC) increase, individuals become increasingly stuporous and may progress to coma. In persons of all ages with MSUD, nausea and vomiting are common during crisis and often necessitate hospitalization [Morton et al 2002].

Each episode of acute leucinosis is associated with a risk for cerebral edema (Figure 4) [Levin et al 1993]. Mechanisms of brain edema in MSUD are not completely understood. Plasma leucine concentration correlates only indirectly with the degree of swelling; severe cerebral edema and neurologic impairment are more directly related to the rate of change of plasma leucine and concomitant decreases in blood osmolarity. When individuals with MSUD present to the hospital, urine is typically maximally concentrated and plasma vasopressin levels are elevated (55+/-29 pg/mL; normal <7 pg/mL). During the evolution of leucinosis, cerebral vasopressin release may be provoked by both acute hyperosmolality (from the accumulation of BCAAs, ketoacids, ketone bodies, and free fatty acids in the circulation) and vomiting. Renal excretion of BCKAs is accompanied by obligatory urine sodium loss, and when this coincides with renal free water retention (antidiuresis), administration of hypotonic or even isotonic fluids can result in hyponatremia and critical brain edema [Strauss & Morton 2003].

Transient periods of MSUD encephalopathy appear fully reversible, provided no global or focal ischemic brain damage occurs. In contrast, prolonged amino acid imbalances, particularly if they occur during the early years of brain development, lead to structural and functional neurologic abnormalities that have morbid long-term psychomotor consequences [Carecchio et al 2011, Shellmer et al 2011, Muelly et al 2013].

- **Intelligence and global function.** Compared to age-matched sib controls with mean full scale IQ of 106±15, full scale IQ was lower among individuals with MSUD ages 5-35 years (N=36) who were treated with diet (81±19) or liver transplant (90±15) [Muelly et al 2013]. Neonatal encephalopathy did not affect risk for intellectual disability but was associated with a fourfold higher risk for global functional impairment [Muelly et al 2013]. Measures of intelligence correlated inversely with average lifetime plasma
leucine and its concentration ratio to valine (an indirect index of cerebral valine uptake) (Figure 5) and directly correlated to the frequency of amino acid monitoring.

- **Mood and anxiety.** Relative to age-matched controls, 36 individuals with MSUD had more depression, anxiety, inattention, and impulsivity [Muelly et al 2013]. Together, these conditions reached a cumulative lifetime incidence of 83% by age 36 years (Figure 6). When compared to individuals with MSUD who remained clinically asymptomatic throughout the newborn period, neonates who were encephalopathic at the time of diagnosis were five and ten times more likely, respectively, to later suffer from anxiety and depression (Table 3).

- **Attention and hyperactivity.** Cumulative lifetime incidence of attention deficit and hyperactivity disorder (ADHD) was 54% among individuals with MSUD on dietary therapy, 82% among those treated with liver transplant, and unrelated to the patient’s condition at the time of diagnosis. Younger participants had higher ADHD symptom ratings, as might be expected given the natural course of ADHD.

- **Movement disorders.** Among 17 adults with MSUD (mean age, 27.5 years), 12 (70.6%) had a movement disorder (primarily tremor, dystonia, or a combination of both) on clinical examination [Carecchio et al 2011]. Parkinsonism and simple motor tics were also observed. Pyramidal signs were present in 11 patients (64.7%), and a spastic-dystonic gait was observed in six patients (35.2%). In the authors’ experience, such motor disabilities are rare in patients with MSUD who are managed appropriately from the newborn period.

### Table 3. Lifetime Relative Risks Based on Condition at the Time of Diagnosis

<table>
<thead>
<tr>
<th>Ill vs Well at Diagnosis</th>
<th>Relative Risk</th>
<th>Fisher’s Exact p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>10.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Global assessment of functioning &lt;70</td>
<td>4.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Full scale intelligence quotient &lt;70</td>
<td>2.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Attention-deficit hyperactivity</td>
<td>1.4</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Muelly et al [2013]

Neonatal screening and sophisticated enteral and parenteral treatment protocols have significantly improved neurological outcomes for persons with classic MSUD [Strauss et al 2010, Muelly et al 2013], but risks of acute brain injury or death are always present, and the long-term neuropsychiatric prognosis is guarded.

In one longitudinal study of 36 individuals with classic MSUD [Muelly et al 2013], an asymptomatic neonatal course and stringent longitudinal biochemical control proved fundamental to optimizing long-term mental health.

Neuropsychiatric morbidity and neurochemistry are similar among individuals with MSUD who have and have not undergone transplantation [Muelly et al 2013]. However, liver transplantation appears to arrest the progression of neurocognitive impairment [Shellmer et al 2011] and effectively prevent catastrophic brain injuries that can occur during metabolic intoxication [Mazariegos et al 2012].

**Non-central nervous system involvement in MSUD** can include the following:

- **Iatrogenic essential amino acid deficiency.** Anemia, acrodermatitis, hair loss, growth failure, arrested head growth, anorexia, and lassitude are complications of chronic deficiency of leucine, isoleucine, or valine [Puzenat et al 2004]. In resource-poor settings, cerebral deficiency of essential amino acids, particularly valine, is a significant cause of neurologic morbidity in individuals with MSUD [Strauss et al 2010; Strauss, Puffenberger, Morton, unpublished observations].
• **Iatrogenic nutritional deficiencies.** Some commercially available MSUD synthetic formulas provide marginal intakes of certain minerals and micronutrients, and utilize vegetable oils that contain little or no omega-3 fatty acid (linolenic, EPA, DHA). The authors found that zinc, selenium, and omega-3 fatty acid deficiency were common among their patients with classic MSUD [Strauss & Morton 2003]. Other studies have documented deficiencies of folic acid and selenium in persons treated with MSUD formula [Levy et al 1970, Lombeck et al 1980]. Newer medical foods, enriched with vitamins, micronutrients, and essential fatty acids, prevent these nutritional deficiencies in individuals with MSUD [Strauss et al 2010].

• **Osteoporosis.** In 90% of adolescents with classic MSUD (n=10), bone mineral density of the radius and femoral neck, but not lumbar spine, were low compared to unaffected age-matched sibs [Strauss, Puffenberger, Morton, unpublished observations]. Bone fractures commonly cause transient leucinosis. Bone mineral density among individuals with MSUD has not been studied in the era of modern formula design.

• **Recurrent oroesophageal candidiasis.** Candida infections are common in hospitalized persons with MSUD and may result from T-cell inhibitory effects of elevated plasma leucine [Hidayat et al 2003] or iatrogenic immunodeficiency as a result of inadequate BCAA intake.

• **Acute pancreatitis.** During the course of treatment for leucine intoxication, acute pancreatitis may develop on day two or three of hospitalization as the plasma leucine concentration is returning to normal. However, based on the authors’ unpublished observations, the introduction of newer micronutrient- and essential fatty acid-rich medical foods has paralleled a marked decrease in the incidence of pancreatitis among individuals with MSUD [Strauss, Puffenberger, Morton, unpublished observations].

**Intermediate MSUD.** Individuals with residual BCKAD activity (i.e., 3%-30% ex vivo) may appear well during the neonatal period but nevertheless have maple syrup odor in cerumen and a consistently abnormal plasma amino acid profile (Table 2). Individuals with intermediate MSUD can present with feeding problems, poor growth, and developmental delay during infancy, or may present much later in life with nonsyndromic intellectual disability [Chuang & Shih 2001]. The majority of persons with intermediate MSUD are diagnosed between ages five months and seven years. They are vulnerable to the same acute and chronic neurologic sequelae as persons with the classic form of the disease. Severe leucinosis, brain swelling, and death can occur if individuals with intermediate MSUD are subjected to sufficient catabolic stress. Basic management principles for such persons do not differ from those with classic MSUD, and the distinction between classic and intermediate types is not absolute (see Genotype-Phenotype Correlations).

**Intermittent MSUD.** Children with the intermittent form of MSUD have normal growth and intellectual development throughout infancy and early childhood. When they are well, they generally tolerate a normal leucine intake, and plasma amino acid and urine organic acid profiles are normal or show only mild elevations of BCAAs. During infections or other physiologic stress, they can develop the clinical and biochemical features of classic MSUD, in rare cases culminating in coma and death [Chuang & Shih 2001].

**Thiamine-responsive MSUD.** It is not known with certainty if individuals with true thiamine-responsive MSUD exist. In general, such putative individuals have residual ex vivo BCKAD enzyme activity of up to 40% normal and are not ill in the neonatal period, but present later in life with a clinical course similar to intermediate MSUD. To date, no person with “thiamine-responsive” MSUD has been treated solely with thiamine. Rather, they are treated with a combination of thiamine (doses ranging from 10 to 1000 mg per day) and dietary BCAA restriction, making the in vivo contribution of thiamine impossible to discern [Chuang et al 2004]. Based on in vitro data, Chuang et al [2006] provided a biochemical model of thiamine responsiveness linked to specific pathogenic variants in the E2 subunit of BCKAD. It is therefore reasonable to try thiamine supplementation in any individual with MSUD who has verified BCKDHB pathogenic variants.
Figure 2. A. Calorie intake and leucine tolerance correlate tightly (Spearman correlation coefficient = 0.9; p<0.0001) in 15 Mennonite individuals with MSUD from birth to age 4 years. This shows the close connection between energy requirement and the growth process.

B. Similarly, there is a close relationship between leucine tolerance and protein accretion in a Mennonite boy with classic MSUD (assuming body weight is 12.5% protein and 10% of protein weight is leucine).

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Pathophysiology

Leucine and aKIC cause a complex neurochemical syndrome that disturbs brain protein accretion, neurotransmitter synthesis, cell volume regulation, neuron growth, and myelin synthesis (Figure 7). The neurotoxicity of leucine stems in part from its ability to interfere with transport of other large neutral amino acids across the blood-brain barrier, reducing the brain’s supply of tryptophan, methionine, tyrosine, phenylalanine, histidine, valine, and threonine [Gjedde & Crone 1983, Smith & Takasato 1986, Boado et al 1999, Killian & Chikhale 2001]. Cerebral amino acid deficiency has adverse consequences for brain growth and synthesis of neurotransmitter such as dopamine, serotonin, norepinephrine, and histamine [Kamei et al 1992, Araújo et al 2001, Zinnanti et al 2009].

Alpha-ketoisocaproic acid and the other BCKAs may exert toxicity by interfering with transamination reactions in muscle and brain (Figure 7). In tissue culture and perfused brain, extracellular aKIC concentrations greater than 60 µmol/L reverse astrocyte transamination reactions, causing a 50% depletion of glutamate and glutamine, and reduced aspartate and pyruvate [Yudkoff et al 2005, Zinnanti et al 2009]. Severe deficiencies of cerebral glutamate, GABA, and aspartate have been observed in brains of calves with naturally occurring BCKAD deficiency and in postmortem brain of a human infant with MSUD [Prensky & Moser 1966, Dodd et al 1992]. In a murine model of MSUD [Zinnanti et al 2009], leucine and aKIC accumulation in brain tissue is accompanied by depletion of glutamate, GABA, pyruvate, and dopamine, while alpha-ketoglutarate, alanine, and lactate increase. In humans with classic MSUD, quantitative proton magnetic resonance spectroscopy (MRS) reveals brain glutamate levels 69%-79% of normal that vary inversely with plasma leucine concentration and the calculated cerebral leucine uptake (Figure 8) [Muelly et al 2013].

Cerebral lactate is elevated in humans with acute MSUD encephalopathy [Heindel et al 1995, Jan et al 2003] and may be related to reversible inhibition of the respiratory chain by elevated cerebral alpha-ketoisocaproic acid [Sgaravatti et al 2003]. In the mouse model, cerebral ATP and phosphocreatine are low and the ratio of lactate to pyruvate in tissue increases 40-fold, suggesting reduced electron flow through the respiratory chain as reducing equivalents accumulate in mitochondria and cytosol [Zinnanti et al 2009]. The cerebral lactic acidosis associated with MSUD encephalopathy resolves without permanent sequelae, and does not have the same prognostic
Figure 4. A. Coronal T$_2$-weighted MRI from a Mennonite boy age five years during an acute metabolic crisis. Diffuse gray matter swelling and signal hyperintensity (on T$_2$ and FLAIR images) involve the cortical mantle, basal ganglia nuclei, hippocampus, and brain stem. Patches of increased T$_2$ signal are also seen in white matter of the centrum semiovale (yellow arrowhead). Swelling of the pons and medial temporal lobes (red arrows) increases the risk for transtentorial herniation and occlusion of the posterior cerebral circulation, particularly if serum osmolarity decreases. On diffusion-weighted imaging, areas of T$_2$ signal hyperintensity have restricted water diffusion, indicating acute cytotoxic edema. These changes are fully reversible.

B. Comparable coronal slice from a healthy age-matched individual

C. Comparable axial CT image of the brain of an individual with MSUD during crisis. Note indices of cerebral edema: apposition of cerebral tissue to the inner skull table, decreased volume of cerebral ventricles and basal fluid spaces, and reduced gray-white discrimination.

D. Comparable axial CT image of a normal brain
significance as cerebral lactate accumulation caused by ischemia [Strauss, Puffenberger, Morton, unpublished observation]. Quantitative MRS of individuals with MSUD who are clinically and metabolically stable shows a statistically significant 10%-15% decrease of cerebral N-acetylasparate [Muelly et al 2013], indicating that the

Figure 5. Clinical and neurochemical correlates of intelligence quotient in individuals with classic MSUD

A. More careful attention to valine supplementation is one of several improvements in the dietary management of MSUD over the last two decades. Panel A shows resulting increases in mean plasma concentration ratio of valine to (leucine+isoleucine+allo-isoleucine) at the authors’ clinical center between 1992 and 2006.

B. Among the subgroup of Mennonite patients managed at the authors’ center, there is an inverse correlation between IQ and age, showing improvements in cognitive outcomes as a result of earlier diagnosis, better dietary therapy, and more stringent longitudinal monitoring.

C. The relationship between improved dietary strategies and IQ is illustrated by the inverse correlation between full scale IQ and lifetime plasma leucine/valine ratio, an indirect measure of cerebral valine uptake.

D. Cerebral metabolites, such as basal ganglia N-acetylasparate, also correlated with performance IQ measures.

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biochemical derangement caused by BCKAD deficiency may chronically interfere with neuronal energy metabolism.

**Genotype-Phenotype Correlations**

The severity of the MSUD metabolic phenotype is determined by the amount of residual BCKAD enzyme activity relative to dietary BCAA excess and the large demands for BCAA oxidation that accompany fasting, illness, or other catabolic stresses [Felig et al 1969, Morton et al 2002, Strauss & Morton 2003, Strauss et al 2010]. The distinction between classic and intermediate MSUD provides an example. For individuals with borderline enzyme activity (e.g., 3%-10%), disease expression is influenced by a large number of variables in addition to genotype, including the rate of growth (and net protein synthesis), calorie intake, the quality and quantity of dietary protein, the frequency and severity of precipitating illnesses, and the developmental timing of metabolic disturbances.

As with many Mendelian disorders, strict genotype-phenotype correlations are not easily defined for MSUD [Childs 1999]. Individuals with the same MSUD genotype may vary considerably in their cerebral response to metabolic crisis, some being more vulnerable than others to the complications of leucine encephalopathy, brain edema, and mental illness.

**Prevalence**

Maple syrup urine disease is rare in most populations, with incidence estimates of 1:185,000 live births [Chuang & Shih 2001, Nellis et al 2003].

As a result of a founder variant (c.1312T>A) in BCKDHA (E1a), certain Mennonite populations of Pennsylvania, Kentucky, New York, Indiana, Wisconsin, Michigan, Iowa, and Missouri have a carrier frequency for classic MSUD as high as one in ten and a disease incidence of approximately one in 380 live births [Puffenberger 2003].

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**Figure 6.** A. The cumulative lifetime incidence of mental illness (depression, anxiety disorders, ADHD) among all individuals with MSUD reaches 83% by age 36 years.

B. Neonatal encephalopathy is a strong predictor of mood disorders, but not intellectual disability or ADHD, later in life.

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Differential Diagnosis

Entities to exclude in the encephalopathic neonate include birth asphyxia, hypoglycemia, status epilepticus, kernicterus, meningitis, and encephalitis. The few inborn errors of metabolism that present with neonatal encephalopathy include the following:

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutation of $BCKDHA$, $BCKDHB$, or $DBT$. 
• Hyperketosis syndromes (e.g., beta-ketothiolase deficiency)
• Urea cycle defects (see Urea Cycle Disorders Overview)
• Glycine encephalopathy (non-ketotic hyperglycinemia)
• Propionic or methylmalonic acidemia (rarely)

Among these, MSUD is unique for the sweet odor of cerumen and a positive urine DNPH test. Laboratory testing that includes quantitative plasma amino acids, serum acylcarnitines, urine organic acids, plasma ammonia concentration, and serum lactate concentration distinguishes among these possibilities. In particular, quantitative analysis of plasma amino acids is generally sufficient to diagnosis MSUD expeditiously.

4,5-dimethyl-3-hydroxy-2[5H]-furanone (sotolone), which is thought to be responsible for the characteristic odor of MSUD [Podebrad et al 1999], is also found in maple syrup, fenugreek, and lovage. Maternal ingestion of fenugreek during pregnancy has resulted in false suspicion of MSUD [Korman et al 2001]. Topical benzoin, commonly used in NICUs, also gives off a strong sweet odor.

Note: Pathogenic variants in DLD, the gene encoding the E3 subunit, are associated with lipoamide dehydrogenase (E3) deficiency, which produces a different phenotype since all four complexes that use this protein are dysfunctional. Affected infants have hypotonia, developmental delay, dystonia/chorea, and a Leigh-type encephalopathy. BCKAD enzyme activity is 0%-25% of control activity. Moderate elevations of plasma concentration of BCAAs, lactic acidemia, and hyperalaninemia are observed. In most cases, the disorder is lethal in infants.

Figure 8. Cortical glutamate and plasma leucine levels. Glutamate (in mmol/kg wet weight, ww) in the prefrontal and anterior cingulate cortices (violet) and basal ganglia region (black) inversely correlated with ambient plasma leucine (A) and the calculated cerebral leucine influx (B) in affected individuals on the MSUD diet (circle) or after liver transplantation (diamond). Red asterisks indicate two patients (brothers) on the MSUD diet who demonstrate relatively higher cortical glutamate levels despite having the highest estimated leucine influx.

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Management

Evaluations Following Initial Diagnosis

Establishing the extent of disease in an individual diagnosed with maple syrup urine disease (MSUD). To determine whether an individual has either classic or intermediate MSUD, it is useful to focus on concentration ratios among the BCAAs and between leucine and other essential and non-essential amino acids. Regulated concentration ratios among the full complement of circulating amino acids are one indication of in vivo residual BCKAD enzyme activity. These ratios are normally maintained within a narrow range by balanced transport of branched-chain and other essential amino acids across common carriers (LAT1/2), intracellular transamination equilibria, and coordinated activity of multiple catabolic pathways [Boado et al 1999, Matsuo et al 2000, Killian & Chikhale 2001, Umeki et al 2002, Brosnan 2003].

The following plasma concentration ratios are the most representative of amino acid regulation: leucine:isoleucine, leucine:valine, leucine:tyrosine, leucine:phenylalanine, leucine:glutamate, and leucine:alanine (mol:mol) [Strauss et al 2006, Strauss et al 2010, Mazariegos et al 2012]. In MSUD, plasma leucine concentration has the strongest reciprocal relationship to plasma alanine and glutamine concentrations (Spearman correlation coefficient -0.86 and -0.62, respectively; \( p<0.0001 \); see Figure 1) [Strauss et al 2010].

- Severe BCKAD deficiency (classic MSUD) affects amino acid homeostasis at multiple levels and causes frequent and variable disturbances of plasma amino acid concentration ratios.
- In milder intermediate forms of MSUD, plasma BCAAs may be chronically elevated but plasma amino acid concentration ratios tend to be preserved.

Note: (1) The majority of individuals with MSUD cared for by the authors are known to harbor a classic "Mennonite" variant in BCKDHA (c.1312T>A) and, thus, newly diagnosed children are not routinely tested for residual BCKAD enzyme activity [Strauss et al 2010]. (2) It is often difficult or impossible to establish whether an individual has clinically important residual BCKAD enzyme activity in vivo, even when the precise pathogenic variants are known.

Treatment of Manifestations

The following treatment considerations apply to individuals with MSUD who have pathogenic variants in the E1a, E1b, or E2 subunits of BCKAD complex. Note: Treatment recommendations do not apply to those with disease caused by pathogenic variants in the common E3 subunit.

Home therapy. Dinitrophenylhydrazine (DNPH) reagent allows home detection of high urine BCKAs during metabolic decompensation. With timely detection of mild or moderate illness, many individuals can be managed safely at home by experienced providers using dietary leucine restriction, high-calorie BCAA-free "sick-day" formulas, and frequent outpatient monitoring. Vomiting is the major reason that the sick neonate or child fails home therapy.

Acute decompensation. Dietary indiscretion causes plasma BCAAs to increase but only rarely results in acute decompensation and encephalopathy. In contrast, infections and injuries trigger a large endogenous mobilization of muscle protein and can precipitate metabolic crisis and hospitalization. Leading causes of hospitalization among one cohort of children with MSUD (N=15) are summarized in Table 4 [Strauss et al 2010].

Table 4. Reasons for 28 Hospitalizations in 15 Infants with MSUD

<table>
<thead>
<tr>
<th>Indication for Hospitalization</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting and viral gastroenteritis</td>
<td>11</td>
</tr>
</tbody>
</table>
Correction of metabolic decompensation is predicated on establishing net protein accretion. This is achieved by treating the precipitating stress (e.g., infection, dehydration, pain, fever) while simultaneously delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to stimulate net protein synthesis in muscle and liver. Rapid nutritional correction of leucine intoxication in older children and adults is more challenging than in young rapidly growing infants (see, e.g., Figure 2 and Figure 9) but is, nonetheless, possible with higher weight-adjusted calorie intake (see Methods of achieving these goals) [Strauss, Puffenberger, Morton, unpublished observation].

Simultaneous in-hospital management of metabolic intoxication and brain edema is complex and should be guided by an experienced metabolic specialist. Metabolic physicians may benefit from the expertise of an intensivist when administering medications such as insulin, hypertonic saline, and mannitol. Referral centers that admit individuals with MSUD who are in crisis should be able to provide parenteral BCAA-free amino acid and 1% isoleucine and valine solutions in the hospital pharmacy, as well as 24-hour monitoring of plasma amino acid concentrations.

**The primary goals of in-hospital therapy**

- Decrease plasma leucine concentration at greater than 750 µmol/L per 24 hrs.
- Provide isoleucine and valine supplementation sufficient to maintain plasma concentrations of 400-600 µmol/L during the acute phase of illness.
- Maintain serum sodium concentration of 138-145 mEq/L with minimal fluctuation.
- Avoid osmolarity changes of greater than 5 mosm/L per day or 0.25 mosm/L per hour.
- Maintain urine output of 2-4 mL/kg/hr and urine osmolarity of 300-400 mosm/L.
- Minimize exposure to hypotonic fluid sources.
- Anticipate and prevent iatrogenic electrolyte abnormalities associated with intravenous glucose and insulin therapy; the most commonly encountered are hypokalemia and hypophosphatemia.

**Methods of achieving these goals**

- Identify and treat precipitating conditions (e.g., infection, inflammation, and fever).
- Administer antiemetics (e.g., odansetron 0.15 mg/kg/dose) to control nausea and vomiting.
- Provide at least 1.25 times the weight or body surface area-adjusted estimated energy requirement (EER), with 40%-50% of calories as lipid. EER, in kcal/m²/day, is approximately 1,700 for neonates, 1,500 for young children, and 1,200 for adults. In older children and adults with catabolic illness, calorie intakes as high as three times the EER (i.e., 6,000 calories per day) are often necessary to establish net protein anabolism.

Note: Hypercaloric feeding typically requires a total (enteral + parenteral) glucose delivery rate of ≥10 mg/kg/min and can result in hyperglycemia. Regular insulin is typically infused at a continuous rate of 0.05-0.10 units/kg/hour and titrated to maintain euglycemia. Patients with severe illness may require higher rates of insulin infusion to counteract the glycemic effects of circulating glucagon, cortisol, and epinephrine [Strauss, Puffenberger, Morton, unpublished observation].

- Provide BCAA-free essential and non-essential amino acids: 2.0-3.5 g/kg/day.

- Provide specific amino acid supplements during metabolic crisis:
  - **Isoleucine and valine.** 20-120 mg/kg/day each; intake is adjusted as necessary at 12- to 24-hour intervals to achieve the goals for isoleucine and valine plasma concentrations (400-600 µmol/L) and to optimize the rate of plasma leucine correction.
  - **Glutamine and alanine.** Total intake: 150-400 mg/kg/day each, depending on age and clinical circumstances (Table 5). Newer MSUD medical foods are fortified with glutamine and alanine [Strauss et al 2010]; use of such products precludes the need to supply glutamine and alanine separately.
  - **Tyrosine.** During acute metabolic crisis, newborns, infants, and children with MSUD can develop acute focal or generalized dystonic posturing attributed to an increased plasma leucine:tyrosine concentration ratio, restricted brain tyrosine uptake, and reduced cerebral dopamine synthesis [Morton et al 2002, Zinnanti et al 2009]. Tyrosine dissolves poorly in aqueous solution, but when supplied enterally (100-400 mg/kg/day) can rapidly reverse dystonia associated with metabolic crisis [Strauss et al 2010; Strauss & Morton, unpublished observation].

### Table 5. Mean and 25th to 75th Percentile Range Nutrient Intakes (per kg-day) by Age Group

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Age in Months (# of Persons)</th>
<th>Nutrient Intake per kg-day: Mean (25th to 75th Percentile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2 (31)</td>
<td>3-5 (18)</td>
</tr>
<tr>
<td><strong>Leucine (mg)</strong></td>
<td>72 (64-84)</td>
<td>58 (47-68)</td>
</tr>
<tr>
<td><strong>Energy (kcal)</strong></td>
<td>111 (103-119)</td>
<td>99 (94-107)</td>
</tr>
<tr>
<td><strong>Total protein (g)</strong></td>
<td>2.4 (2.1-2.6)</td>
<td>2.3 (1.9-2.6)</td>
</tr>
<tr>
<td><strong>Isoleucine supplement (mg)</strong></td>
<td>4.4 (0.7)</td>
<td>2.3 (0.3-3.6)</td>
</tr>
<tr>
<td><strong>Valine supplement (mg)</strong></td>
<td>11.5 (9.8-14.8)</td>
<td>11.4 (9.0-13.0)</td>
</tr>
<tr>
<td><strong>Alanine intake (mg)</strong></td>
<td>233 (200-262)</td>
<td>209 (197-234)</td>
</tr>
<tr>
<td><strong>Glutamine intake (mg)</strong></td>
<td>416 (361-471)</td>
<td>363 (337-405)</td>
</tr>
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</table>
Table 5. continued from previous page.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Age in Months (# of Persons)</th>
<th>Nutrient Intake per kg-day: Mean (25th to 75th Percentile Range)</th>
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<tbody>
<tr>
<td></td>
<td>0-2 (31)</td>
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<tr>
<td>Iron (mg)</td>
<td>2.2 (1.9-2.5)</td>
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<tr>
<td>Zinc (mg)</td>
<td>4.6 (3.7-4.9)</td>
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<tr>
<td>Selenium (µg)</td>
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<tr>
<td>Omega-3 fatty acids, as 18:3n-3 (mg)</td>
<td>378 (307-401)</td>
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<td>Leucine / energy ratio (mg/kcal)</td>
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<td>3-5 (18)</td>
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<td></td>
<td>2.1 (1.9-2.2)</td>
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<td></td>
<td>4.0 (3.7-4.0)</td>
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<td></td>
<td>6.2 (5.7-7.0)</td>
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<td>330 (307-378)</td>
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<td></td>
<td>0.58 (0.48-0.66)</td>
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<td></td>
<td>0.50 (0.43-0.56)</td>
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<td>3.7 (3.1-4.3)</td>
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<td>5.7 (4.8-6.6)</td>
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<td>0.46 (0.37-0.53)</td>
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<td>13-18 (21)</td>
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<td>2.0 (1.8-2.1)</td>
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<td>3.7 (3.4-4.0)</td>
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<td></td>
<td>5.7 (5.3-6.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>307 (283-330)</td>
<td></td>
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<tr>
<td></td>
<td>0.50 (0.43-0.58)</td>
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<tr>
<td></td>
<td>19-24 (18)</td>
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<tr>
<td></td>
<td>1.8 (1.5-2.1)</td>
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<td>3.4 (2.9-4.0)</td>
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<td>283 (236-330)</td>
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<td>0.48 (0.38-0.58)</td>
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<td>25-36 (32)</td>
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<td></td>
<td>1.3 (1.3-1.6)</td>
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<td>212 (212-260)</td>
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<td></td>
<td>0.54 (0.44-0.55)</td>
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</tbody>
</table>

From Strauss et al [2010]; with permission from Elsevier

Total nutritional goals can be met by combined enteral and parenteral administration. In ill neonates or children otherwise able to tolerate enteral formula, regular feeding (30-60 mL each hour) or continuous nasogastric delivery of a one kcal/mL BCAA-free MSUD formula supplemented with isoleucine and valine is an effective way to manage metabolic crises [Nyhan et al 1998, Morton et al 2002].

**Control of brain edema.** A decrease in blood osmolarity of more than 8 mosm/L per day can precipitate fatal brain herniation in an ill infant or child with MSUD (Figure 4). Close monitoring (preferably in an intensive care unit) is warranted.

Neurologic assessments to be performed on a frequent basis to monitor for brain swelling include the following:

- Measure head circumference and fontanel size in neonates.
- Watch for signs of increased intracranial pressure including the following:
  - Papilledema
  - Disorientation, combativeness
  - Depressed level of consciousness
  - Refractory vomiting
  - Extremity hyperreflexia
  - Bradycardic hypertension
- Watch for signs of impending brain herniation including the following:
  - Hyperactive gag
  - Pupillary asymmetry
  - Ophthalmoplegia
  - Decorticate posturing

Methods to minimize the possibility of brain swelling:

- In appropriate clinical settings, the authors recommend use of a peripherally inserted central catheter (PICC) line in encephalopathic patients with MSUD. This allows sufficient nutritional support to be delivered without an excessive fluid volume and reduces the risk for cerebral edema.
- Elevate the individual’s head.
- Assess total body sodium, potassium, and water balance at 12-hour intervals. The following clinical formula is useful for managing the serum sodium concentration [Rose & Post 1994]:

Serum Na concentration equals ~(total body Na + total body K)/total body water.
Assume total body water equals ~70% body weight, 2/3 of which is intracellular and has sodium and potassium concentrations of 14 mEq/L and 140 mEq/L, respectively [Guyton & Hall 1996].

- Minimize osmotic variation of the extracellular fluid in hospitalized patients by assessing weight trend, urine output, and serum and urine electrolytes every 12 hours and adjusting electrolyte and water intake accordingly [Strauss, Puffenberger, Morton, unpublished observation].

Note: Give furosemide (0.5-1.0 mg/kg/dose) as needed every six to 12 hours to oppose the urinary concentrating action of vasopressin and maintain urine osmolarity at a ceiling value of 300-400 mosm/L. This allows for brisk output of isotonic urine to compensate for the large infused volume associated with hypercaloric feeding.

Methods to manage brain swelling:

- For weight gain, hyponatremia, or deepening encephalopathy, the authors administer the following [Strauss, Puffenberger, Morton, unpublished observation]:
  - Furosemide: 0.5-1.0 mg/kg, followed by
  - Mannitol: 0.5-1.0 g/kg over 60 minutes, followed by
  - Hypertonic (3%-5%) saline: 2.5 mEq/kg over 60 minutes

**Neuroimaging.** During episodes of acute encephalopathy, individuals with MSUD are typically too unstable for magnetic resonance imaging. Cranial CT scan is used to look for major indices of cerebral edema, such as decreased volume of cerebral ventricles and basal fluid spaces, or reduced gray-white discrimination (Figure 4).

If there is clinical evidence of evolving brain herniation, elevate the individual's head, hyperventilate by face mask or endotracheal tube, give mannitol 1-2 g/kg and hypertonic saline 3 mEq/kg, and transfer the individual emergently to a pediatric or neurologic intensive care unit.

**Hemodialysis/hemofiltration.** Nutritional therapy alone can effectively reduce even extremely elevated plasma concentrations of leucine in persons with MSUD of any age and under a wide variety of clinical circumstances [Morton et al 2002, Strauss & Morton 2003]. However, numerous publications have shown that renal replacement methods can achieve rapid corrections of BCAAs and BCKAs during the acute phase of MSUD crisis [Jouvet et al 1997, Schaefer et al 1999, Yoshino et al 1999, Jouvet et al 2001, Puliyanda et al 2002].

As methods of invasive leucine removal, peritoneal dialysis and venovenous hemofiltration are less effective and more dangerous than short courses of continuous hemodialysis [Schaefer et al 1999]. When hemodialysis is used to treat MSUD it must be coupled with effective nutritional management to constrain the catabolic response and prevent recurrent clinical intoxication. A combined approach to therapy, using hemodialysis with simultaneous anabolic nutritional therapy, was shown to be highly effective in one neonate with classic MSUD [Puliyanda et al 2002]. Dialysis without simultaneous management of the underlying disturbance of protein turnover is analogous to treating diabetic ketoacidosis with invasive removal of glucose and ketones rather than insulin infusion. In both conditions, effective treatment depends not only on lowering concentrations of pathologic metabolites, but also on controlling the underlying metabolic derangement.

**Other potential complications** in hospitalized persons with MSUD:

- **Acute pancreatitis.** If clinical signs of pancreatitis (epigastric or mid-back pain, anorexia, vomiting) develop two to three days into the treatment of a metabolic decompensation, stop all enteral feeding and measure serum concentrations of lipase and amylase [Kahler et al 1994]. Treatment is supportive; persons with MSUD with pancreatitis need to be managed with special parenteral nutrition solutions until the condition abates.

- **Infection.** Monitor for and promptly treat hospital-acquired infections. Superficial and invasive *Candida* infections are common. Persons with MSUD are vulnerable to bacterial or fungal infection from central venous catheters.
Prevention of Primary Manifestations

Dietary management. The goals of dietary management for newly diagnosed infants:

- Normal weight gain, linear growth, and head growth

Figure 9. Leucine (A), energy (B), and total protein (C) intakes of 15 stable Mennonite infants with classic MSUD on dietary management

From Strauss et al [2010]; republished with permission of Elsevier
• Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., Denver Developmental Screening Test II, standardized intelligence testing, validated behavioral inventories) [Muelly et al 2013]
• Age-appropriate tolerance of leucine, isoleucine, and valine, with stable plasma BCAA concentrations and BCAA concentration ratios
• Avoidance of essential amino acid, fatty acid, and micronutrient deficiencies

Home formula supplies include BCAA-free powder; breast milk or regular infant formula as a natural protein source; and 10-mg/mL solutions of isoleucine, valine, and leucine in distilled water. If the BCAA-free powder is not already fortified with glutamine and alanine [Strauss et al 2010], these can be given separately as a combined powder (weight ratio 3:2). Parents maintain a record of intake of calories, leucine, isoleucine, and valine and send dried blood spots by overnight mail for monitoring of amino acid concentrations.

The frequency of amino acid monitoring varies by age, metabolic stability, compliance, and regional clinical practice. For rapidly growing infants, monitoring weekly or twice weekly is recommended. Of note, the frequency of amino acid monitoring correlates directly with long-term measures of intelligence [Muelly et al 2013].

Suggested clinical parameters for the asymptomatic infant or young child include the following:

• Normal age- and weight-adjusted energy intake
• Protein as essential and non-essential amino acids: 2-3 g/kg/day
• Appropriate leucine tolerance. The dietary requirement for BCAAs varies as a function of age, growth rate, calorie intake, illness, and residual in vivo BCKAD enzyme activity. In persons with classic MSUD (0%-2% enzyme activity), leucine tolerance in mg/kg/day is 65-85 for neonates, 20-40 for children, and 10-15 for adults (Figure 9) [Strauss et al 2010].
• Isoleucine and valine supplements as needed to maintain a plasma leucine-to-valine concentration ratio (mol:mol) of 0.5 or less and a leucine-to-isoleucine ratio of approximately 2.0. Isoleucine supplements can periodically be suspended based on plasma amino acid monitoring, but continuous valine supplementation is prudent because its low affinity for the blood-brain barrier LAT1 transporter makes it especially vulnerable to competitive inhibition by leucine [Smith & Takasato 1986] and its appropriate fortification is directly related to long-term intellectual outcome [Strauss et al 2010, Muelly et al 2013].
• The authors recently compiled age-specific (birth to age 4 years) nutrient intakes for Mennonite children with classic MSUD under their care. These data are presented in Table 5, which shows mean (and 25th to 75th percentile range) intakes for energy, total protein, supplemental amino acids, omega-3 fatty acids, and select minerals at different age intervals.
• Goals of laboratory monitoring:
  ◦ Plasma leucine concentration: 150-300 µmol/L with an age-appropriate intake
  ◦ Plasma isoleucine concentration approximately equal to plasma leucine concentration
  ◦ Plasma valine concentration at least twofold plasma leucine concentration
  ◦ Indices of calcium, magnesium, zinc, folate, selenium, and omega-3 essential fatty acid sufficiency

Neuropsychiatric morbidity is most effectively addressed by presymptomatic diagnosis followed by strict and consistent metabolic control [Muelly et al 2013]. Adolescents and adults with MSUD and ADHD, depression, or anxiety respond favorably to standard psychostimulant and antidepressant medications.

Thiamine treatment. The existence of “thiamine-responsive” BCKAD mutants is controversial. Nevertheless, for any person with MSUD in whom the functional consequences of the pathogenic variant(s) are unknown, a four-week trial of enteral thiamine (50-100 mg/day, divided 2x a day) is reasonable. However, it should be noted that significant changes in dietary therapy (e.g., BCAA or calorie intake) during the treatment period confounds interpretation of a specific thiamine effect.
Orthotopic liver transplantation (OLT) is an effective therapy for classic MSUD, with removal of dietary restrictions and complete protection from decompensations during illness [Wendel et al 1999, Bodner-Leidecker et al 2000]. Through a collaboration between University of Pittsburgh Children’s Hospital and Clinic for Special Children [Strauss et al 2006], 52 individuals with classic MSUD (age 1.9-20.5 years) underwent elective orthotopic liver transplantation between 2004 and 2013. Plasma leucine, isoleucine, and valine concentrations were normal within six hours after transplantation in all individuals and remained so on an unrestricted diet. Metabolic cure was reflected by a sustained increase in weight-adjusted leucine tolerance from 10-40 mg/kg/day to more than 140 mg/kg/day, normalization of plasma concentration relationships among branched-chain and other essential and non-essential amino acids, and metabolic and clinical stability during protein loading and intercurrent illnesses [Strauss et al 2006, Mazariegos et al 2012].

Risks associated with surgery and immune suppression were similar to those in other pediatric liver transplant populations and one person developed EBV-associated post-transplant lymphoproliferative disease. Currently, disease-free survival and graft survival are 100% in this cohort of 52 patients [Mazariegos et al 2012]; however, deaths and graft failures have been reported among individuals with MSUD transplanted elsewhere during the same time period [Mazariegos, unpublished observations].

Although liver transplantation does not reverse cognitive disability or psychiatric illness in individuals with MSUD [Muelly et al 2013], it does appear to arrest progression of neurocognitive impairment [Shellmer et al 2011] and prevent life-threatening cerebral edema associated with metabolic crisis [Mazariegos et al 2012].

Prevention of Secondary Complications

Any trauma care or surgical procedures should be approached in consultation with a metabolic specialist.

Surveillance

The authors recommend that infants with MSUD be evaluated by a pediatrician and metabolic specialist once monthly and have a full amino acid profile measured (either from plasma or filter paper) at least once a week. At the authors’ center, strict adherence to these guidelines by 15 Mennonite infants managed between 2005 and 2008 was associated with a 64% reduction in the overall hospitalization rate to 0.14 admissions per patient per year [Strauss et al 2010].

Children, adolescents, and adults also need to be followed closely and should ideally have amino levels monitored once per week. This is usually not practical without a "send-in" filter paper method.

The Denver Developmental Screening Test II or a comparable tool is useful for monitoring development of infants and young children with MSUD.

School-age children, adolescents, and adults should have neurocognitive testing if indicated by school performance or behavioral problems [Shellmer et al 2011, Muelly et al 2013]. Referral to a psychiatrist is appropriate for individuals who show signs of ADHD, anxiety, or depression.

Evaluation of Relatives at Risk

Early diagnosis of at-risk sibs of an affected individual may allow asymptomatic infants to be managed out of hospital by experienced providers.

Newborn at-risk sibs who have not undergone prenatal testing can be tested in one of two ways:

- Plasma amino acid analysis of a sample obtained at approximately 24 hours of life. In some laboratories, samples obtained earlier can yield false negative results.
- If the pathogenic variants have been identified in the family, a cord blood sample can be used for molecular genetic testing.
See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

**Pregnancy Management**

With the advent of newborn screening and preventive care, more women with MSUD are surviving to childbearing age. Successful delivery of a healthy baby is possible for women with classic MSUD. Reports include Van Calcar et al [1992] and Grünewald et al [1998].

Elevated maternal leucine plasma concentration, like elevated maternal phenylalanine plasma concentration, is likely teratogenic. If a woman with MSUD is planning a pregnancy, metabolic control should be maintained in a rigorous fashion preceding and throughout the gestation. Keeping the maternal plasma levels of the branched-chain amino acids between 100 and 300 μmol/L is compatible with delivery of a normal infant [Grünewald et al 1998].

During the development of the placenta and fetus, maternal BCAA and protein requirements increase, and frequent monitoring of plasma amino acid concentrations and fetal growth may be necessary to avoid essential amino acid deficiencies [Grünewald et al 1998].

The postpartum period is dangerous for the mother. Catabolic stress of labor, involutional changes of the uterus, and internal sequestration of blood are potential sources of metabolic decompensation [Chuang & Shih 2001]. Appropriate monitoring at a metabolic referral center is advised at the time of delivery.

**Therapies Under Investigation**

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

**Genetic Counseling**

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.*

**Mode of Inheritance**

Maple syrup urine disease is inherited in an autosomal recessive manner.

**Risk to Family Members**

*Parents of a proband*

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutated allele).
- Heterozygotes (carriers) are asymptomatic.

*Sibs of a proband*

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.
Offspring of a proband. The offspring of an individual with maple syrup urine disease are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members of a proband. Each sib of the proband’s parents is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing is possible once the pathogenic variants have been identified in the family.

Biochemical testing. Quantitative plasma amino acids and fibroblast enzymatic analyses are not indicated for detection of heterozygotes.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the BCKDHA, BCKDHB, or DBT pathogenic variants have been identified in an affected family member, prenatal diagnosis and preimplantation genetic diagnosis for a pregnancy at increased risk for MSUD are possible.

Biochemical testing. If only one or neither pathogenic variant is known within a family, BCKAD enzyme activity can be measured from cultured amniocytes obtained by amniocentesis (usually performed at ~15 -18 weeks' gestation) or chorionic villus cells obtained by CVS (usually performed at ~10-12 weeks' gestation).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- MSUD Family Support Group
  
  The MSUD Family Support Group is a non-profit 501 (c)(3) organization for those with MSUD and their families and includes health-care professionals and others interested in MSUD.
  
  Phone: 740-972-5619
  
  Email: sandybulcher@gmail.com
Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Maple Syrup Urine Disease: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus-Specific Databases</th>
<th>HGMD</th>
<th>ClinVar</th>
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</thead>
<tbody>
<tr>
<td>BCKDHA</td>
<td>19q13.2</td>
<td>2-oxoisovalerate dehydrogenase subunit alpha, mitochondrial</td>
<td>BCKDHA database</td>
<td>BCKDHA</td>
<td>BCKDHA</td>
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<tr>
<td>BCKDHB</td>
<td>6q14.1</td>
<td>2-oxoisovalerate dehydrogenase subunit beta, mitochondrial</td>
<td>BCKDHB database</td>
<td>BCKDHB</td>
<td>BCKDHB</td>
</tr>
<tr>
<td>DBT</td>
<td>1p21.2</td>
<td>Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex, mitochondrial</td>
<td>DBT database</td>
<td>DBT</td>
<td>DBT</td>
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</tbody>
</table>

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.
**Molecular Genetic Pathogenesis**

Maple syrup urine disease is caused by decreased activity of human branched-chain alpha-ketoacid dehydrogenase complex (BCKAD), a multi-enzyme complex found in the mitochondria. It catalyzes the oxidative decarboxylation of the branched-chain keto acids (alpha-ketoisocaproate, alpha-keto-beta-methyl valerate, and alpha-ketoisovalerate) in the second step in the degradative pathway of the branched chain amino acids (leucine, isoleucine, and valine).

BCKAD has four subunit components (E1a, E1b, E2, and E3). Biallelic pathogenic variants in one of the four unlinked genes encoding any subunit can result in decreased activity of the enzyme complex and the accumulation of BCAAs and corresponding branched-chain ketoacids (BCKAs) in tissues and plasma [Nellis et al 2003, Chuang et al 2004].

Biochemical derangements caused by pathogenic variants in the genes encoding BCKA decarboxylase (E1) alpha subunit (MSUD type 1A); BCKA decarboxylase (E1) beta subunit (MSUD type 1B), and dihydrolipoyl transacylase (E2) subunit (MSUD type 2) are indistinguishable biochemically.

Note: The E3 subunit (lipoamide dehydrogenase encoded by DLD) of BCKAD is shared with the pyruvate and alpha-ketoglutarate dehydrogenase complexes, and MSUD type 3 is characterized by increased urinary excretion of BCKAs and alpha-ketoglutarate accompanied by elevated plasma concentrations of lactate, pyruvate, and alanine (Table 2). However, the clinical phenotype of E3 subunit deficiency differs considerably from the classic and intermediate forms of MSUD and is not discussed further in this GeneReview.

BCKAD complex consists of three catalytic components:

- The E1 decarboxylase, which is a heterotetramer of alpha and beta subunits (alpha2, beta2)
- The E2 transacylase, which is a homo-24-mer
- The E3 dehydrogenase, which is a homodimer

The complete functional BCKAD complex contains a cubic E2 core surrounded by the following:

- 12 E1 components
- Six E3 components
- A single kinase

BCKAD colocalizes with branched-chain amino acid transaminases in mitochondria of diverse tissues and is regulated by a kinase-phosphatase pair. In humans, skeletal muscle is the major site for both transamination and oxidation of BCAAs. The liver and kidney each mediate an estimated 10%-15% of whole-body BCAA transamination-oxidation [Suryawan et al 1998]. BCKAD is expressed in brain, where BCAA transamination-oxidation may contribute to cerebral glutamate and GABA production [Yudkoff et al 2005].

**BCKDHA**

**Gene structure.** The gene spans nearly 28 kb and comprises nine exons. For a detailed summary of gene and protein information, see Table A, Gene.
Pathogenic variants. The pathogenic BCKDHA sequence variants identified in individuals with MSUD known at the time are summarized in Chuang & Shih [2001]. Additional variants identified in research laboratories remain unpublished.

No pathogenic variants occur in especially high frequency in the overall population. In isolated populations, specific pathogenic variants occur at high frequency, including the BCKDHA c.1312T>A variant in Old Order Mennonites of southeastern Pennsylvania. See Table 6.

Table 6. BCKDHA Pathogenic Variants Discussed in This GeneReview

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change (Alias 1)</th>
<th>Reference Sequences</th>
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<tr>
<td>c.1312T&gt;A</td>
<td>p.Tyr438Asn 2 (Tyr393Asn)</td>
<td>NM_000709.2</td>
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<td>NP_000700.1</td>
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Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions
2. BCKDHA founder variant in certain Mennonite populations (see Prevalence)

Normal gene product. The gene encodes the E1-alpha subunit of the BCKAD complex (see Molecular Genetic Pathogenesis).

Abnormal gene product. See Molecular Genetic Pathogenesis.

BCKDHB

Gene structure. The gene spans roughly 240 kb and comprises 11 exons (a shorter isoform contains 10 exons). For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. The pathogenic BCKDHB sequence variants identified in individuals with MSUD known at the time are summarized in Chuang & Shih [2001]. Additional pathogenic variants identified in research laboratories remain unpublished.

No pathogenic variants occur in especially high frequency in the overall population. In isolated populations, specific variants occur at high frequency, including the BCKDHB c.548G>C variant in Ashkenazi Jews. See Table 7.

Table 7. BCKDHB Pathogenic Variants Discussed in This GeneReview

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
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<tr>
<td>c.832G&gt;A</td>
<td>p.Gly278Ser</td>
<td></td>
</tr>
<tr>
<td>c.1114G&gt;T</td>
<td>p.Glu372Ter</td>
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</table>

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The gene encodes the E1-beta subunit of the BCKAD complex (see Molecular Genetic Pathogenesis).
Abnormal gene product. See Molecular Genetic Pathogenesis.

**DBT**

Gene structure. The gene covers approximately 56 kb and comprises 11 exons. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. The pathogenic DBT sequence variants identified in individuals with MSUD known at the time are summarized in Chuang & Shih [2001]. Additional pathogenic variants identified in research laboratories remain unpublished. No variants occur in especially high frequency in the general population.

A higher-than-expected percentage of DBT pathogenic variants are deletions (both large and small). These appear to be mediated by non-homologous recombination between repetitive elements within DBT. However, these elements are not more abundant in DBT and there is, to date, no adequate explanation for the increased frequency of deletions.

Normal gene product. The gene encodes the E2 subunit of the BCKAD complex (see Molecular Genetic Pathogenesis).

Abnormal gene product. See Molecular Genetic Pathogenesis.

References

**Literature Cited**


Chapter Notes

Revision History

- 9 May 2013 (me) Comprehensive update posted live
- 15 December 2009 (me) Comprehensive update posted live
- 30 January 2006 (me) Review posted live
- 22 November 2004 (ep) Original submission

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