GENEReviews

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Maple Syrup Urine Disease

[*BCKD Deficiency, Branched-Chain Ketoacid Dehydrogenase Deficiency, Branched-Chain Ketoaciduria, MSUD, Maple Syrup Disease*]

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Summary

Disease characteristics. Maple syrup urine disease (MSUD) in untreated neonates is characterized by maple syrup odor in cerumen at 12-24 hours after birth; elevated plasma branched-chain amino acids (BCAAs, leucine, isoleucine, and valine) and a generalized disturbance of plasma amino acid concentration ratios by 12-24 hours of age; ketonuria, irritablity, and poor feeding by 2-3 days of age; deepening encephalopathy including lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" by 4-5 days of age; and coma and central respiratory failure that may occur by 7-10 days of age. The phenotype is classified as classic or intermediate. Rarely, affected individuals have partial BCKAD enzyme deficiency that only manifests intermittently or responds to dietary thiamine therapy; individuals with intermediate or intermittent forms of MSUD can experience severe metabolic intoxication and encephalopathy under sufficient catabolic stress.

Diagnosis/testing. MSUD is diagnosed by the presence of clinical features and by decreased levels of BCKAD enzyme activity causing accumulation of BCAAs and branched-chain ketoacids (BCKAs) in tissues and plasma. The three genes associated with MSUD are *BCKDHA* (E1a subunit gene, MSUD type 1A), *BCKDHB* (E1b subunit gene, MSUD type 1B), and *DBT* (E2 subunit gene, MSUD type 2). Molecular genetic testing of all three genes is available on a clinical basis.

Management. Treatment of individuals with MSUD includes dietary leucine restriction, high-calorie BCAA-free formulas, and frequent monitoring. Metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine, and in some centers, hemodialysis/hemofiltration, to establish net positive protein accretion. Brain edema, a common potential complication of metabolic decompensation, requires immediate therapy in an intensive care setting. Adolescents and adults with MSUD and ADHD, depression, or anxiety respond to psychostimulant and antidepressent medications. Orthotopic liver transplantation is an effective therapy for classic MSUD. Frequent monitoring of plasma amino acid concentrations and fetal growth may be necessary to avoid essential amino acid deficiencies during pregnancy.

Genetic counseling. Maple syrup urine disease 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. 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. Carrier testing by molecular genetic testing is available on a clinical basis once the mutations have been identified in an affected family member. Prenatal diagnosis by molecular genetic testing for pregnancies at 25% risk is possible if the disease-causing mutations have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

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

- **Maple syrup odor in cerumen** , the first clinical sign of MSUD, at 12-24 hours after birth
- **Elevated plasma branched-chain amino acids (BCAAs, leucine, isoleucine, and valine)** and a more generalized disturbance of plasma amino acid concentration ratios by 12-24 hours of age. Occasionally, plasma isoleucine or valine may be low or normal, but plasma leucine is invariably elevated.
- **Ketonuria, irritablity, and poor feeding** by two to three days of age
- **Signs of deepening encephalopathy** including lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" by 4-5 days of age
- **Coma and central respiratory failure** that may occur by 7-10 days of age, 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 et al 1995, 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 components (E1a, E1b, E2, and E3). Mutations in both alleles of 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 [Chuang et al 1995, Nellis et al 2003, Chuang et al 2004]. The severity of the metabolic phenotype is determined by the amount of residual BCKAD activity relative to dietary BCAA excess and the large demands for BCAA oxidation that accompany fasting, illness, or other catabolic stresses [Morton & Strauss 2002, Strauss & Morton 2003].

BCKAD enzyme activity. BCKAD enzyme activity can be evaluated in a variety of cells including lymphoblasts. In all cases, the assay of enzyme activity should be done with treatments that block endogenous BC-kinase to provide total BCKAD enzyme activity in the tested cell line.

- Residual enzyme activity is typically less than 3% of control values in persons with the classic phenotype.

- Residual enzyme activity in fibroblasts varies from 3-40% in persons with intermittent or intermediate MSUD.

Note: In six persons with intermediate MSUD ages 6-34 years, Schadewalt 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.

Classic MSUD caused by severe mutations in E1a, E1b, or E2 are indistinguishable biochemically; the biochemical phenotype is as follows:

- **Plasma concentrations of leucine are increased.** 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 such as alanine, glutamate, glutamine, phenylalanine, tyrosine, and methionine [Chace et al 1995, Strauss & Morton 2003].
- **Plasma allo-isoleucine** (>5 µmol/L), a distinctive metabolite present in all forms of MSUD [Schadewaldt, Bodner-Leidecker et al 1999].

  Note: On some chromatographic systems, allo-isoleucine co-elutes with isoleucine, obscuring its detection.
- **BCKAs** of leucine and isoleucine are excreted in large quantity in the urine. **Dinitrophenylhydrazine (DNPH)** added to urine produces a yellow-white precipitate if these BCKAs are present.
- **Ketonuria** can be detected by standard urine test strips; ketonuria in a newborn should always prompt investigation for metabolic disorders.

Hypoglycemia and hyperammonemia are unusual in all forms of MSUD.

Note: The E3 subunit (lipoamide dehydrogenase) 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 classic and variant forms of MSUD caused by mutations in E1a, E1b, or E2 and is not discussed further in this *GeneReview*.

For laboratories offering biochemical testing, see Testing.

Newborn screening. Tandem mass spectrometry (MS/MS)-based amino acid profiling of dried blood spots obtained between 24 and 48 hours of life quantifies whole blood concentration ratios of (leucine + isoleucine) to alanine and phenylalanine [Chace et al 1995].

This test is sensitive and specific for MSUD, and has made newborn screening with the Guthrie bacterial inhibition assay obsolete [Chace et al 2003, Chace & Kalas 2005].

See National Newborn Screening Status Report: Amino Acid Disorders (pdf) for a list of states currently screening for MSUD.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. The three genes associated with MSUD [Nellis & Danner 2001, Nellis et al 2003]:

- MSUD type 1A: BCKA decarboxylase (E1) alpha subunit gene *(BCKDHA)*
- MSUD type 1B: BCKA decarboxylase (E1) beta subunit gene *(BCKDHB)*
- MSUD type 2: Dihydrolipoyl transacylase (E2) subunit gene *(DBT)*

Note: Mutations in *DLD*, the fourth component of the branched-chain alpha-ketoacid dehydrogenase complex (BCKAD), produces a different phenotype and is not discussed in this *GeneReview*.

Other genes. The BCKAD complex contains a regulatory kinase. As yet, no individuals with MSUD have been identified with mutations in the gene encoding the kinase. The existence of a BCKAD complex phosphatase has not been conclusively demonstrated.

Molecular genetic testing: Clinical uses

- Diagnostic confirmation
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis.** Sequence analysis of *BCKDHA*, *BCKDHB*, and *DBT* is clinically available.
  - Individuals with MSUD are always homozygous or compound heterozygous for mutations in the same subunit gene; no individuals with MSUD have been identified who are heterozygous for mutations in two different genes.
  - Most affected individuals are compound heterozygotes for rare sequence variants. No single mutation or locus accounts for a significant proportion of affected alleles, except in genetic isolates.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Sequence analysis	Sequence variants in *BCKDHA*	~95%	Clinical Testing
	Sequence variants in *BCKDHB*		
	Sequence variants in *DBT*		

1. Mutations in each of the three genes account for approximately one-third of MSUD cases.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

If a newborn is suspected of having MSUD based on clinical presentation, ethnic background, or family history, testing should proceed as follows:

- 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 profile by HPLC or MS/MS** 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 diagnostic of MSUD, begin dietary therapy and proceed to **confirmatory DNA sequencing of BCKAD subunits**.
- Analysis of **methoximated urine organic acids by gas chromatography-mass spectrometry** detects BCKAs and corroborates the diagnosis of MSUD, but is not necessary. The DNPH reagent test (mixing equal volumes of DNPH and urine) is rapid and provides similar information, but is not sensitive in the neonate and cannot be used as a screening test until 48-72 hours of life, by which time plasma concentrations of leucine and BCKA typically exceed 1000 µmol/L.
- **BCKAD enzyme activity** can be measured in skin fibroblasts, lymphocytes, or biopsied liver tissue, but is of variable accuracy and may not be necessary [Schadewaldt et al 1998, Schadewalt et al 2001].

Note: Metabolic intoxication in untreated infants with MSUD causes brain swelling and can lead to central respiratory failure. If a child is suspected of having the disease, **plasma amino acid analysis should be done without delay**. Referral centers that diagnose and treat children with MSUD should offer quantitative amino acid testing 24 hours every day.

Genetically Related Disorders

No other phenotypes are associated with mutations in *BCKDHA*, *BCKDHB*, and *DBT*.

Clinical Description

Natural History

Traditionally, the metabolic phenotype is classified as classic or intermediate on the basis of residual BCKAD 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 under sufficient catabolic stress [Chuang & Shih 2001].

Table 2. Clinical Phenotypes of Maple Syrup Urine Disease

Type	Age of Onset [1]	Clinical Features [2]	Biochemical Signs [3]	BCKAD Activity, % Normal [4]
Classic	Neonatal	Maple syrup odor of cerumen Poor feeding Irritability, lethargy Opisthotonus Focal dystonia "Fencing," "cycling"	Elevated BCAAs in plasma Elevated plasma allo-isoleucine Elevated BCKAs in urine Positive urine DNPH test Ketonuria	0-2
Intermediate	Variable	Maple syrup odor of cerumen Poor growth Poor feeding Irritability Developmental delays Encephalopathy during illness	Similar to classic phenotype, though quantitatively less severe	3-30
Intermittent	Variable	Normal early growth and development Episodic decompensations can be severe	Normal BCAAs when well Similar to classic biochemical profile during illness	5-20
Thiamine-responsive	Variable	Similar to the Intermediate phenotype	Leucine tolerance and biochemical profile improve with thiamine therapy	2-40

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 neurological manifestations can mimic the classic phenotype if physiological 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 associated with normal growth and plasma leucine 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 is 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, Hammen et al 1999; 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 Dietary Management below).
  - When residual BCKAD enzyme activity exists (i.e., intermediate MSUD), leucine tolerance is higher, and BCKAD enzyme activity is regulated such that ratios of the plasma concentrations among the BCAAs tend to be more stable in both health and illness; individuals with intermediate MSUD are less vulnerable to the large swings in plasma BCAA concentration seen in classic MSUD, and are less likely to experience prolonged essential amino acid deficiencies.
- **The 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 five to seven days of age. In untreated neonates, ketonuria, irritablity, and poor feeding occur within 48 hours of delivery. Lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as "fencing" and "bicycling" are evident by four to five days of age, and are followed by coma and central respiratory failure.

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

Each episode of acute leucinosis is associated with a risk for cerebral edema [Lungarotti et al 1982, Riviello & Rezvani 1991, 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 neurological impairment are more directly related to the rate of change of plasma leucine concentration and concomitant decreases in blood osmolarity. Typically, urine is maximally concentrated and plasma vasopressin levels are elevated (55+/-29 pg/mL; normal <7 pg/mL) when individuals with MSUD present to the hospital. During the evolution of leucinosis, cerebral vasopressin release may be provoked by both acute hyperosmolarity (from the accumulation of BCAAs, ketoacids, ketone bodies, and free fatty acids in the circulation) and vomiting. Renal excretion of BCKAs is accompanied by obligate 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 occurring during the early years of brain development, lead to structural and functional neurological disturbances. Attention deficits, impulsivity, and hyperactivity occur commonly in school-age children and mental illness is prevalent in adolescents and adults with MSUD:

- 29% of the affected individuals between ages six and 12 years (n=21) require psychostimulant medication for core symptoms of **ADHD** [Strauss, Puffenberger, Morton, unpublished observations].
- 37% of affected individuals over 12 years of age (n=35) have been treated with psychotropic medications, singly or in combination, for symptoms of **generalized anxiety, panic, or depression** [Strauss, Puffenberger, Morton, unpublished observations].
- Among drug classes, antidepressants are the most commonly used (47% of all treatment indications) in individuals with classic MSUD over 12 years of age [Strauss, Puffenberger, Morton, unpublished observations].
- Individuals with classic MSUD can reach adulthood with normal intelligence. However, mild to moderate **mental retardation** is common in older persons. In over 80 individuals with classic MSUD, chronic cognitive outcome is more directly related to indices of long-term amino acid homeostasis and cerebral essential amino acid sufficiency, rather than age at diagnosis, residual BCKAD activity, or the number and

severity of metabolic crises [Strauss, Puffenberger, Morton, unpublished observations].

Neonatal screening and sophisticated enteral and parenteral therapies have dramatically improved outcomes for persons with classic MSUD, but risks of acute brain injury or death are always present, and the long-term neuropsychiatric prognosis is guarded.

Non-central nervous system involvement in MSUD can include:

- **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].
- **Iatrogenic nutritional deficiencies.** Commercially available MSUD synthetic formulas provide marginal intakes of certain minerals and micronutrients, and utilize vegetable oils that contain very little omega-3 fatty acid (linolenic, EPA, DHA). The authors have documented widespread zinc and omega-3 fatty acid deficiency in 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].
- **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 siblings [Strauss, Puffenberger, Morton, unpublished observations].
- **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 [Kahler et al 1994].

Intermediate MSUD. Individuals with residual BCKAD acitivity (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 mental retardation [Chuang & Shih 2001]. The majority of persons with intermediate MSUD are diagnosed between five months and seven years of age. They are vulnerable to the same acute and chronic neurological 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 below).

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 true thiamine-responsive MSUD individuals exist. In general, such putative individuals have residual *ex vivo* BCKAD

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 ten to 1000 mg per day) and dietary BCAA restriction, making the in vivo contribution of thiamine impossible to discern [Bartlett 1983, Chuang et al 2004].

Pathophysiology

Leucine and its corresponding BCKA, alpha-ketoisocaproic acid (aKIC) disturb brain cell volume regulation, neuron growth, myelin synthesis, and cerebral neurotransmitters pools. 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 phenylalanine, tryptophan, methionine, isoleucine, tyrosine, 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 monoamine synthesis [Kamei et al 1992, Araujo et al 2001].

Alpha-ketoisocaproic acid and the other BCKAs may exert toxicity by interfering with transamination reactions in muscle and brain. 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, reduced aspartate, and accumulation of lactate [Yudkoff et al 1994, Yudkoff et al 1996, Yudkoff et al 2005]. Severe depletions of cerebral glutamate, GABA, and aspartate have been observed in brains of calves with naturally occurring BCKAD deficiency and in post-mortem brains of human infants with MSUD [Prensky & Moser 1966, Dodd et al 1992].

Cerebral lactate is elevated in humans with acute MSUD encephalopathy [Felber et al 1993, 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]. The cerebral lactic acidosis associated with MSUD encephalopathy typically resolves without permanent sequelae,and does not have the same prognostic significance as cerebral lactate accumulation caused by ischemia [Strauss, Puffenberger, Morton, unpublished observation].

Genotype-Phenotype Correlations

As with many Mendelian disorders, strict genotype-phenotype correlations are not easily defined for MSUD [Childs 1999]. 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. Furthermore, 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 [Chace et al 1995, Chuang & Shih 2001, Nellis et al 2003].

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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:

- Hyperketosis syndromes (e.g., beta-ketothiolase deficiency)
- Urea cycle defects (see Urea Cycle Disorders Overview)
- Glycine encephalopathy (non-ketotic hyperglycinemia)
- Propionic or methylmalonic academia (rarely) (see Organic Acidemias Overview)

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 and/or urine organic acids, plasma ammonia concentration, and serum lactate concentration distinguishes among these possibilities. In particular, plasma amino acid analysis by HPLC is sufficient to diagnose MSUD and quickly clarifies the clinical situation.

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: Mutations 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.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

The majority of individuals affected by MSUD who are cared for by Strauss, Puffenberger, and Morton are known to harbor a classic "Mennonite" mutation in *BCKDHA* and are not routinely tested for residual BCKAD enzyme activity in a newly diagnosed child [Strauss, Puffenberger, Morton, unpublished observation].

It is often difficult or impossible to establish whether or not an individual has clinically important residual BCKAD enzyme activity in vivo, even when the precise mutations are known. To determine whether an individual has either classic or variant (i.e., intermediate) MSUD, it is useful to focus on concentration ratios among BCAAs and between BCAA 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 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, valine:leucine, leucine:tyrosine, leucine:phenylalanine, leucine:glutamate, and leucine:alanine (mol:mol) [Strauss, Puffenberger, Morton, unpublished observation].

- 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 variant forms of MSUD, plasma BCAAs may be chronically elevated but plasma amino acid concentration ratios tend to be preserved.

Treatment of Manifestations

The following treatment considerations apply to individuals with MSUD who have mutations in the E1a, E1b, or E2 subunits of BCKAD complex. **Treatment recommendations do not apply to those with disease caused by mutations 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 illnesses, 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.

Correction of metabolic decompensation is predicated on establishing net positive 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, but is nonetheless possible with higher weight-adjusted calorie intake (see below) [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 have parenteral BCAA-free amino acid and 1% isoleucine and valine solutions available for preparation in the hospital pharmacy, as well as 24-hour-a-day capability for monitoring 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 less 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

- Minimize painful or invasive procedures

Methods of achieving these goals:

- Identify and treat precipitating events (e.g., infection, inflammation, and fever)
- Administer antiemetics (e.g., odansetron 0.15 mg/kg/dose) to control nausea and vomiting
- Provide at least 1.5 times the weight or body surface area-adjusted estimated energy requirement (EER), with 40-50% of calories as lipid. EER, in kcal/m^2/day, is approximately 1700 for neonates, 1500 for young children, and 1200 for adults. In older children with severe catabolic illness, calorie intake as high as three times the EER may be necessary to establish rapid net protein anabolism. Note: Hypercaloric feeding typically requires a total (enteral + parenteral) glucose delivery rate of 10-15 mg/kg/min and can result in hyperglycemia. Regular insulin is infused at a continuous rate of ten units per 12.5 grams of glucose delivered or using a sliding scale to maintain euglycemia [Strauss, Puffenberger, Morton, unpublished observation].
- Provide BCAA-free essential and non-essential amino acids: 2.5-3.5 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 12-24 hour intervals to achieve the goals for isoleucine and valine plasma concentrations noted above and to optimize the rate of correction of plasma leucine concentration.
  - Glutamine and alanine: 100-150 mg/kg/day each

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 & Strauss 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. 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:
  - Papilledema
  - Disorientation, combativeness
  - Depressed level of consciousness
  - Refractory vomiting
  - Extremity hyperreflexia
  - Bradycardic hypertension
- Watch for signs of impending brain herniation including:
  - Hyperactive gag

- Pupillary asymmetry
- Ophthalmoplegia
- Decorticate posturing

Methods to minimize the possibility of brain swelling include the following:

- 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 1994; Strauss, Puffenberger, Morton, unpublished observation]:
  - 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].
- 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 include the following:

- For weight gain, hyponatremia, or deepening encephalopathy, administer [Strauss, Puffenberger, Morton, unpublished observation]:
  - Lasix™: 1 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 or basal fluid spaces or reduced gray-white discrimination [Strauss, Puffenberger, Morton, unpublished observation].

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 neurological 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 [Hammersen et al 1978, Gortner et al 1989, Sherbotie 1995, 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 [Sherbotie 1995, 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, has been 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 pathological 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

Dietery management. The goals of dietary management of newly diagnosed infants:

- Normal weight gain, linear growth, and head growth
- Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., DDST II)
- 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; breastmilk or regular infant formula as a natural protein source; 10 mg/mL solutions of isoleucine, valine, and leucine; and glutamine and alanine as a combined powder (weight ratio 1:1). 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 1-2 times per week twice is recommended.

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: 2.5-3.0 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 activity. In persons with classic MSUD (0-2% enzyme activity), leucine tolerance in

mg/kg/day is 50-80 for neonates, 15-40 for children, and 5-15 for adults [Strauss, Puffenberger, Morton, unpublished observations].

- Specific dietary supplements that include:
  - Isoleucine and valine each: neonates 10-40 mg/kg/day, children and adults 2-10 mg/kg/day
  - Glutamine and alanine each: 50-100 mg/kg/day
  - Omega-3 polyunsaturated fatty acids as alpha-linolenic acid: 100-150 mg/kg/day (flaxseed oil is 50% alpha-linolenate by weight)
  - Iodized sodium chloride in formula (17 mEq sodium per gram): 3.5-5.0 mEq/kg/day
  - Age-appropriate intake for vitamins, minerals, and micronutrients; may require a complete pediatric multivitamin for some individuals
- Goals of laboratory monitoring:
  - Plasma leucine concentration: 150-300 5mol/L with an age-appropriate intake
  - Plasma isoleucine concentration approximately equal to plasma leucine concentration
  - Plasma valine concentration approximately twofold plasma leucine concentration
  - Indices of calcium, magnesium, zinc, folate, selenium, and omega-3 essential fatty acid sufficiency

Neuropsychiatric morbidity is first addressed with strict and consistent metabolic control. Adolescents and adults with MSUD and ADHD, depression, or anxiety respond favorably to standard psychostimulant and antidepressent medications.

Thiamine treatment. As noted above, the existence of "thiamine-responsive" BCKAD mutants is controversial. Nevertheless, for any person with MSUD in whom the functional consequences of the mutation(s) are unknown, a four-week trial of enteral thiamine (50-100 mg/day, divided twice 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 & Saudubray 1999, Bodner-Leidecker et al 2000]. Through a collaboration between University of Pittsburgh Children's Hospital and Clinic for Special Children, 14 individuals with classic MSUD (ages 1.9-20.5 years) underwent elective orthotopic liver transplantation from 2004-2005 [Strauss, Mazariegos et al, manuscript in preparation]. 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. Preliminary observations suggest improvements in ability to concentrate, attention, and mood stability after surgery, but these outcomes have not been formally assessed. Risks associated with surgery and immune suppression were similar

to other pediatric liver transplant populations and one person developed EBV-associated post-transplant lymphoproliferative disease.

Management of pregnancy. Successful delivery of a healthy baby is possible for women with classic MSUD. Reports include Van Calcar et al 1992 and Grunewald et al 1998. With the advent of newborn screening and preventative care, more women with MSUD are surviving to child-bearing age.

Elevated maternal leucine plasma concentration, like elevated maternal phenylalanine plasma concentration, is probably teratogenic [Gardiner 1990]. If a woman with MSUD is planning for a pregnancy, metabolic control should be maintained in rigorous fashion preceding and throughout the gestation.

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 [Grunewald et al 1998].

The post-partum 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.

Agents/Circumstances to Avoid

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

Testing of Relatives at Risk

Newborn sibs of an affected individual who have not undergone prenatal testing can be tested by 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. Early diagnosis may allow asymptomatic infants to be managed out of hospital by experienced providers.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 and therefore carry one mutant 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 symptomatic 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 disease-causing mutation.

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

Carrier Detection

Molecular genetic testing. Carrier testing is available on a clinical basis once the mutations have been identified in the proband.

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

Related Genetic Counseling Issues

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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both pathogenic alleles of an affected family member or of the carrier parents must be identified before prenatal testing can be performed.

Biochemical testing. If both mutant alleles are not known within a family, BCKAD enzyme activity can be measured from cultured amniocytes (obtained by amniocentesis usually performed at about 15-18 weeks' gestation) or chorionic villus cells (obtained by CVS usually performed at about 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.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Maple Syrup Urine Disease

Gene Symbol	Chromosomal Locus	Protein Name
BCKDHA	19q13.1-q13.2	2-oxoisovalerate dehydrogenase alpha subunit
BCKDHB	6p22-p21	2-oxoisovalerate dehydrogenase beta subunit
DBT	1p31	Lipoamide acyltransferase component of branched-chain alpha-keto acid dehydrogenase complex
GCSL	7q31-q32	Dihydrolipoyl dehydrogenase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Maple Syrup Urine Disease

238331	DIHYDROLIPOAMIDE DEHYDROGENASE; DLD
248600	MAPLE SYRUP URINE DISEASE
248610	DIHYDROLIPOAMIDE BRANCHED-CHAIN TRANSACYLASE; DBT
248611	BRANCHED-CHAIN KETO ACID DEHYDROGENASE E1, BETA POLYPEPTIDE; BCKDHB
608348	BRANCHED-CHAIN KETO ACID DEHYDROGENASE E1, ALPHA POLYPEPTIDE; BCKDHA

Table C. Genomic Databases for Maple Syrup Urine Disease

Gene Symbol	Locus Specific	Entrez Gene	HGMD
BCKDHA	BCKDHA	593 (MIM No. 608348)	BCKDHA
BCKDHB	BCKDHB	594 (MIM No. 248611)	BCKDHB
DBT	DBT	1629 (MIM No. 248610)	DBT
GCSL		1738 (MIM No. 238331)	DLD

For a description of the genomic databases listed, click here.

Note: Links related to GSCL are included in the above tables, even though MSUD type 3 is not discussed in this *GeneReview*.

Molecular Genetic Pathogenesis

Maple syrup urine disease is caused by decreased activity of human BCKD, 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). The BCKD is a large complex consisting 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 three subunits of the BCKD complex (E1, E2, and E3) are encoded by four unlinked genes. The complete functional BCKD complex contains a cubic E2 core surrounded by:

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

BCKAD co-localizes 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

Normal allelic variants: The gene spans nearly 28 kb and comprises nine exons.

Pathologic allelic variants: Over 60 separate pathogenic sequence variants in the four genes encoding the subunits of the BCKD complex have been identified in individuals with MSUD (see Human Gene Mutation Database links, above) [Chuang & Shih 2001). Additional mutations identified in research laboratories remain unpublished. No mutations occur in especially high frequency in the overall population. In isolated populations, specific mutations occur at high frequency, including the *BCKDHA* 1312T↓A (Y438N) in Old Order Mennonites of southeastern Pennsylvania. See also MSUD mutation identification table, polymorphism table.

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

BCKDHB

Normal allelic variants: The gene spans roughly 240 kb and contains 11 exons (a shorter isoform contains ten exons).

Pathologic allelic variants: Over 60 separate pathogenic sequence variants in the four genes encoding the subunits of the BCKD complex have been identified in individuals with MSUD (see Human Gene Mutation Database links, above) [Chuang & Shih 2001]. Additional mutations identified in research laboratories remain unpublished. No mutations occur in especially high frequency in the overall population. In isolated populations, specific mutations occur at high frequency, including the *BCKDHB* 548G↓C (R183P) mutation in Ashkenazi Jews. See also MSUD mutation identification table, polymorphism table.

Normal gene product: The gene encodes the E1-beta subunit of the BCKD complex (see Molecular Genetic Pathogenesis).

DBT

Normal allelic variants: This gene covers about 56 kb and contains 11 exons.

Pathologic allelic variants: Over 60 separate pathogenic sequence variants in the four genes encoding the subunits of the BCKD complex have been identified in individuals with MSUD (see Human Gene Mutation Database links, above) [Chuang & Shih 2001]. Additional

mutations identified in research laboratories remain unpublished. No mutations occur in especially high frequency in the general population. A higher-than-expected percentage of *DBT* mutations are deletions (both large and small), and there is to date no adequate expectation for this. These deletions can make mutation identification by PCR and sequencing difficult. See also MSUD mutation identification table, polymorphism table.

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

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Maple syrup urine disease

NCBI Genes and Disease
Maple syrup urine disease

Save Babies Through Screening Foundation, Inc
4 Manor View Circle
Malvern, PA 19355-1622
Phone: 888-454-3383
Fax: 610-993-0545
Email: email@savebabies.org
Maple Syrup Urine Disease (MSUD)

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe, CW2 6BG
United Kingdom
Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

Organic Acidemia Association
13210 - 35th Avenue North
Plymouth, MN 55441
Phone: 763-559-1797
Fax: 763-694-0017
Email: oaanews@aol.com
www.oaanews.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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