



Genetic Fact Sheets for Parents

Amino Acid Disorders

Screening, Technology, and Research in Genetics is a multi-state project to improve information about the financial, ethical, legal, and social issues surrounding expanded newborn screening and genetic testing – <http://www.newbornscreening.info>

Disorder name: Maple Syrup Urine Disease
Acronym: MSUD Type 1A

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This fact sheet has information about MSUD. Every child is different and some of these facts may not apply to your child specifically. Certain treatments may be recommended for some children but not others. All children with MSUD should be followed by a metabolic doctor in addition to their primary doctor.

What is MSUD?

MSUD stands for “maple syrup urine disease.” It is named for the sweet maple syrup smell of the urine in untreated babies. This condition is one type of amino acid disorder. People with MSUD have problems breaking down certain amino acids found in protein.

Amino Acid Disorders:

Amino acid disorders (AAs) are a group of rare inherited conditions. They are caused by enzymes that do not work properly.

Protein is made up of smaller building blocks called amino acids. A number of different enzymes are needed to process these amino acids for use by the body. Because of missing or non-working enzymes, people with amino acid disorders cannot process certain amino acids. These amino acids, along with other toxic substances, then build up in the body and cause problems.

The symptoms and treatment vary between different amino acid disorders. They can also vary from person to person with the same amino acid disorder. See the fact sheets for each specific amino acid disorder.

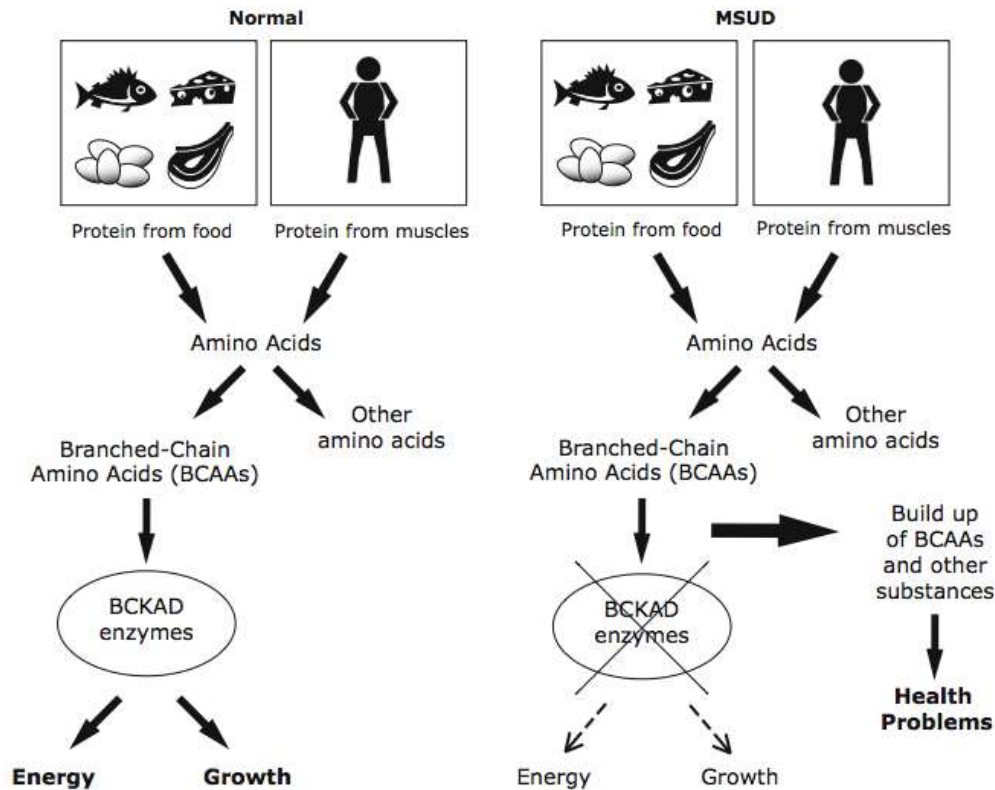
Amino acid disorders are inherited in an autosomal recessive manner and affect both males and females.

What causes MSUD?

In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them.

Classic MSUD, the most common form, is caused by the absence of a group of enzymes called “branched-chain ketoacid dehydrogenase” (BCKAD). The job of this enzyme group is to break down three different amino acids called leucine, isoleucine, and valine. When they cannot be broken down, these amino acids build up in the blood and cause problems.

Maple Syrup Urine Disease MSUD



Leucine, isoleucine, and valine are called “branched-chain amino acids” (BCAAs) because of their “tree-like” structure. They are found in all foods that contain protein. Large amounts are found in meat, eggs, milk, and other dairy foods. Smaller amounts are found in flour, cereal, and in some vegetables and fruits.

If MSUD is not treated, what problems occur?

There are a number of different types of MSUD. The most common type, “classic MSUD,” can be life-threatening and must be treated promptly to prevent serious health problems. Other types, including ‘intermediate’ and ‘intermittent’ forms of MSUD, are less severe. These milder types are less common. This fact sheet contains information on classic MSUD.

Classic MSUD

Symptoms start as soon as a baby is fed protein, usually shortly after birth. Some of the first symptoms are:

- poor appetite
- weak suck
- weight loss

- high-pitched cry
- urine that smells like maple syrup or burnt sugar

Babies with MSUD have episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness
- sluggishness
- irritable mood
- vomiting

If not treated, other symptoms can follow:

- episodes where muscle tone alternates between being rigid and floppy
- swelling of the brain
- seizures
- high levels of acidic substances in the blood, called metabolic acidosis
- coma, sometimes leading to death

Symptoms of a metabolic crisis often happen:

- after going too long without food
- during illness or infection
- during stressful events such as surgery

Without treatment, brain damage can occur. This can cause intellectual disabilities or spasticity. Some babies become blind. If not treated, most babies with classic MSUD die within a few months.

What is the treatment for MSUD?

Your baby's doctor will work with a metabolic doctor and dietician to care for your child.

Prompt treatment is needed to prevent intellectual disabilities and serious medical problems. Most children need to eat a very low-protein diet and drink a special medical formula. You should start the diet and the formula as soon as you know your child has MSUD. Your dietician can create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy.

The following are treatments often recommended for children with MSUD:

1. Medical Formula

In addition to a low-protein diet, children are often given a special medical formula as a substitute for milk. This formula gives them the nutrients and protein they need while helping to keep their BCAA levels in a safe range.

Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

2. Diet low in branched-chain amino acids

The diet is made up of foods that are very low in the BCAAs which are found in protein. This means your child will need to avoid foods that are high in protein such as cow's milk, regular formula, meat, fish, cheese, and eggs. Regular flour, dried beans, nuts, and peanut butter also have BCAAs and must be avoided or strictly limited.

Many vegetables and fruits have only small amounts of the BCAAs and can be eaten in carefully measured amounts.

There are other medical foods such as special low-protein flours, pastas, and rice that are made especially for people with MSUD. Some states offer help with payment for these medical foods, and others require private insurance coverage for medical formula and other special medical foods.

Your metabolic doctor and dietician will decide on the best food plan for your child. The exact plan will depend on many things such as your child's age, weight, and general health. Your dietician will fine-tune the diet over time. Any diet changes should be made under the guidance of a dietician.

Lifelong treatment with the MSUD diet is necessary. Children are at risk for episodes of metabolic crisis when they don't follow the diet.

3. Supplements

Children with a rare type of MSUD, called "thiamine-responsive MSUD," can often be helped by thiamine supplements. Some children with classic MSUD may also benefit from thiamine. Ask your doctor whether your child should take thiamine supplements. Do not use any supplements without checking with your doctor.

4. Tracking BCAA levels

Your child will have regular blood tests to measure amino acid levels. The diet and formula may need to be adjusted based on blood test results.

5. Call your doctor at the start of any illness

For children with MSUD, even minor illness can cause a metabolic crisis. In order to prevent problems, call your doctor right away when your child has any of the following:

- poor appetite
- low energy or extreme sleepiness
- vomiting
- an infection or illness
- a fever

- behavior or personality changes
- difficulty walking or balance problems

Children with MSUD need to eat more carbohydrates and drink more fluids during any illness – even if they’re not hungry – or they could have a metabolic crisis. Children who are sick may not want to eat. If they can’t eat, or if they show signs of a metabolic crisis, they may need to be treated in the hospital.

Ask your metabolic doctor if you should carry a special travel letter with medical instructions for your child’s care.

6. Liver transplantation

Liver transplant surgery is an optional treatment for people with MSUD. The BCKAD enzyme that causes MSUD is located in the liver. Because of this, some children with MSUD have had liver transplantation surgery (removal of their liver and replacement with a donor liver) to treat their MSUD symptoms.

Liver transplantation is a major surgical procedure and has some risks. Individuals who have had a liver transplant must take medication for the rest of their lives to prevent their body from rejecting the donor liver. However, successful liver transplantation cures people of their MSUD symptoms.

Many factors must be considered before surgery and this option should be discussed very thoroughly with your child’s physicians.

What happens when MSUD is treated?

With prompt and lifelong treatment, children with MSUD often have healthy lives with typical growth and development. Early treatment can help prevent brain damage and intellectual disabilities.

However, children with MSUD are at increased risk to have attention deficit hyperactivity disorder (ADHD), anxiety, and depression even if they have had a liver transplant. The reasons for this are not well understood at this time.

Even with treatment, some children still develop swelling of the brain or have episodes of metabolic crisis. Children who have repeated metabolic crises may develop permanent brain damage. This can cause lifelong learning problems, intellectual disabilities, or spasticity.

What causes the BCKAD enzymes to be absent or not working correctly?

Genes tell the body to make various enzymes. There are three genes that can cause MSUD – BCKDHA, BCKDHB, and DBT. Every person has two copies of

each of these genes. People with MSUD have variants (changes) in both of their copies of one of these genes. Because of these genetic variants, the BCKAD enzymes do not work properly or are not made at all.

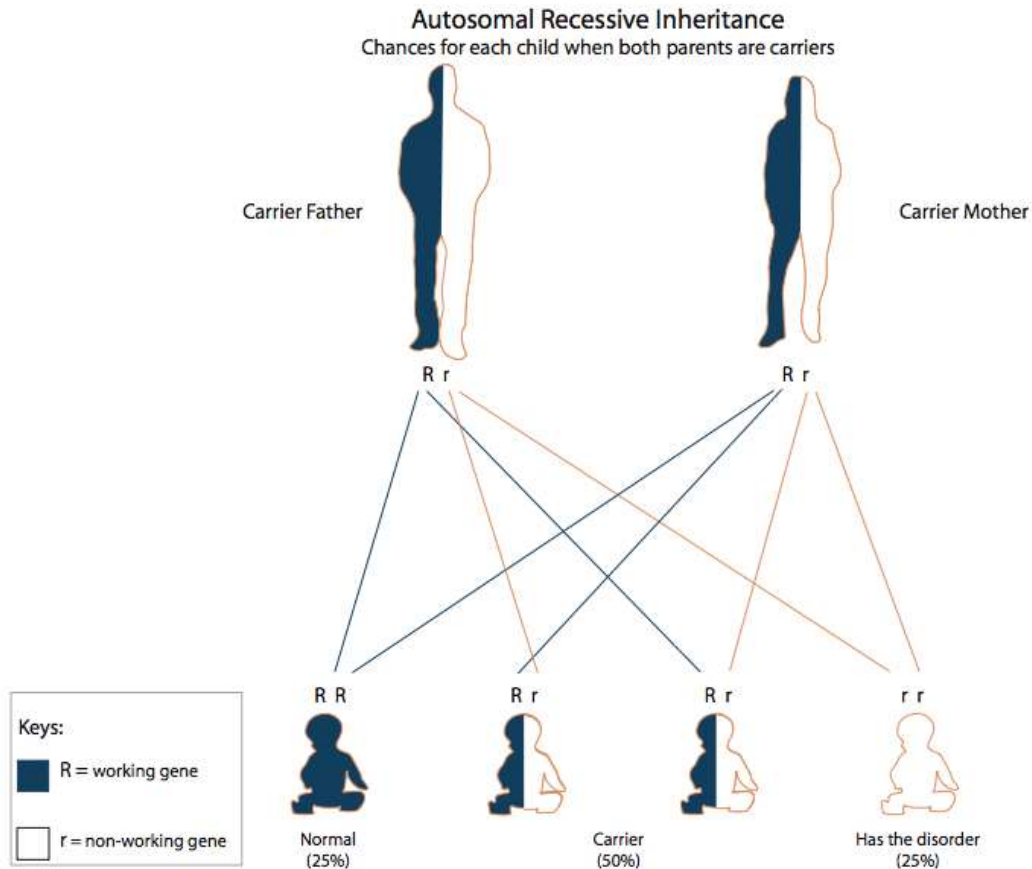
How is MSUD inherited?

MSUD is inherited in an autosomal recessive manner. It affects both boys and girls equally.

In children with MSUD, both copies of a gene needed to make the BCKAD enzymes is not working correctly. These children inherit one non-working gene for MSUD from each parent.

Parents of children with MSUD rarely have the condition themselves. Instead, each parent has a single non-working gene for MSUD. They are called carriers. Carriers do not have MSUD because their other copy of this gene is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have MSUD. There is a 50% chance for the child to be a carrier, just like the parents. And, there is a 25% chance for the child to have two working genes.



Genetic counseling is available to families who have children with MSUD. Genetic counselors can answer your questions about how the condition is inherited, choices during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

Is genetic testing available?

Genetic testing for MSUD can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes, also called variants, in the genes that causes MSUD.

DNA testing is not necessary to diagnose your child. It can be helpful for carrier testing or prenatal testing, discussed below.

What other testing is available?

MSUD can be confirmed by measuring the amount of the branched chain amino acids in a blood sample. It can also be diagnosed by an enzyme test using a

blood or skin sample. Talk to your doctor or genetic counselor if you have questions about testing for MSUD.

Can you test during a future pregnancy?

If both gene changes (variants) have been found in your child, DNA testing can be done during future pregnancies. The sample needed for this test is obtained by either CVS or amniocentesis.

If DNA testing would not be helpful, an enzyme test can be done on cells from the fetus. Again, the sample needed for this test is obtained by either CVS or amniocentesis.

Parents may choose to have testing during pregnancy or wait until birth to have the baby tested. Parents may also choose to use assisted reproductive techniques to decrease the chance that their future children would have MSUD. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

Can other members of the family have MSUD or be carriers?

Having MSUD

If they are healthy and growing normally, older brothers and sisters of a baby with MSUD are unlikely to have the condition. If you have questions about testing your other children, talk with your metabolic doctor or genetic counselor.

MSUD Carriers

Brothers and sisters who do not have MSUD still have a chance to be carriers like their parents. Except in special cases, carrier testing should only be done on people over 18 years of age.

If you are a parent of a child with MSUD, your brothers and sisters have a 50% chance to be a carrier. It is important for other family members to be told that they could be carriers. There is a small chance they are also at risk to have children with MSUD.

All states offer newborn screening for MSUD. However, when both parents are carriers, newborn screening results are not sufficient to rule out the condition in a newborn baby. In this case, special diagnostic testing should be done in addition to newborn screening. It is very important that this testing be done shortly – ideally at 24 hours of age.

Can other family members be tested?

Diagnostic testing

If there is concern about whether they have the condition, diagnostic testing can be done on brothers or sisters to see if they also have this disorder. Talk to your metabolic doctor if you have questions about testing for MSUD.

Carrier testing

If both genetic variants have been found in your child, other family members can have DNA testing to see if they are carriers.

If DNA testing is not helpful, other methods of carrier testing may be available. If you have questions about carrier testing, ask your genetic counselor or metabolic doctor.

How many people have MSUD?

About one in every 200,000 babies in the United States is born with MSUD.

Does MSUD happen more frequently in a certain ethnic group?

MSUD occurs in all ethnic groups. It is more common in Mennonite people in certain parts of the United States. In the U.S., about one in 380 babies of Mennonite background is born with MSUD. It is also more common in people of French-Canadian ancestry.

Does MSUD go by any other names?

MSUD is sometimes also called:

- branched chain ketoaciduria
- branched chain alpha-keto dehydrogenase deficiency
- BDKD deficiency
- Maple Syrup Disease
- Branched Chain Ketoacid Dehydrogenase deficiency
- BCKD deficiency

There are a number of other forms of MSUD that are less common than the classic type. These other forms are not discussed in this fact sheet.

- Intermittent branched-chain ketoaciduria
- Intermediate branched-chain ketoaciduria
- Thiamine responsive MSUD
- MSUD Type 1B
- MSUD Type II

Where can I find more information?

The MSUD Family Support Group

<http://www.msud-support.org/>

Metabolic Support UK

<https://www.metabolicsupportuk.org>

Genetic Alliance

<http://www.geneticalliance.org>

Baby's First Test

<http://www.babysfirsttest.org>

Genetics Home Reference

<https://ghr.nlm.nih.gov/condition/maple-syrup-urine-disease>

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