



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](http://www.newbornscreening.info)

Disorder name: Citrullinemia

Acronym: CTLN1

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This fact sheet contains general information about citrullinemia. 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 this condition should be followed by a metabolic doctor in addition to their primary doctor.

What is citrullinemia?

Citrullinemia is one type of amino acid disorder. People with this condition cannot remove ammonia from the body. Ammonia is a harmful substance. It is made when protein and its building blocks, amino acids, are broken down for use by the body.

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.

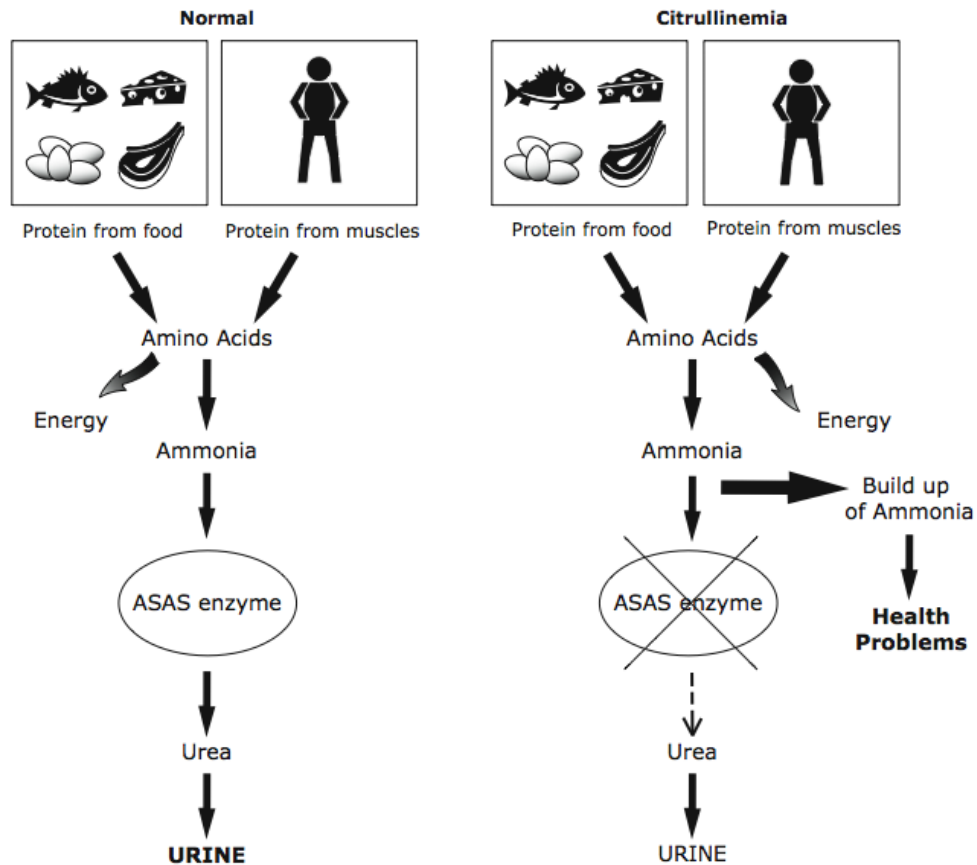
What causes citrullinemia?

This is one of a small number of conditions called "urea cycle disorders" (UCD).

Citrullinemia is caused by problems with the enzyme "argininosuccinate synthetase" (ASS). In people with citrullinemia, the ASS enzyme is either missing or not working properly. This enzyme's job is to help break down certain amino acids and to remove ammonia from the body.

When ASS is not working, an amino acid called citrulline builds up in the blood. Ammonia and other harmful substances also build up. This causes brain damage. If not treated, excess ammonia in the blood can cause death.

CITRULLINEMIA



If citrullinemia is not treated, what problems occur?

Normally, the body changes ammonia into a substance called “urea.” Urea is then safely removed in the urine. However, if ammonia is not changed to urea, high levels of ammonia build up in the blood. This can be very harmful. If ammonia levels stay high for too long, severe brain damage can occur.

The symptoms of citrullinemia and the age they start, vary from person to person. There are two main types of this condition. The most common type is called “classic” citrullinemia. It usually starts in infancy. There are milder types that start later in infancy, childhood, or later. Some women with citrullinemia only have symptoms during or after pregnancy.

Classic citrullinemia

Infants seem healthy at birth but quickly develop symptoms. Within a few days of life, babies will have high levels of ammonia in their blood. Some of the first symptoms of high blood ammonia are:

- poor appetite
- extreme sleepiness or lack of energy

- irritability
- vomiting

If not treated, high ammonia levels cause:

- muscle weakness
- decreased or increased muscle tone
- breathing problems
- problems staying warm
- seizures
- swelling of the brain
- coma, and sometimes death

Other effects of citrullinemia can include:

- poor growth
- enlarged liver
- learning delays or intellectual disabilities

Without treatment, most babies die within the first few weeks of life.

Milder types

In the milder types, symptoms start later in infancy or childhood. Symptoms in untreated children can include:

- poor growth
- dry, brittle hair
- hyperactivity
- behavior problems
- learning problems or intellectual disabilities
- avoidance of meat and other high-protein foods
- spasticity
- Cerebral infarction (stroke)
- episodes of high levels of ammonia in the blood
- liver failure

Episodes of high blood ammonia often happen:

- after going without food for long periods of time
- during illness or infection
- after high-protein meals

Some of the first symptoms of high blood ammonia in children are:

- poor appetite
- severe headache
- vomiting
- extreme sleepiness or lack of energy
- slurred speech
- poor coordination or balance problems

If not treated, children with high blood ammonia levels may develop:

- breathing problems
- swelling of the brain
- seizures
- coma, sometimes leading to death

A rare type of citrullinemia occurs during and after pregnancy. Women may experience:

- episodes of vomiting
- lethargy
- seizures
- confusion and hallucinations
- behavioral changes including manic episodes and psychosis
- swelling of the brain

Some people have very mild or no symptoms and are only diagnosed with citrullinemia after their brother or sister is diagnosed.

What is the treatment for citrullinemia?

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

Prompt treatment is needed to prevent the build-up of ammonia. You should start treatment as soon as you know your child has the condition.

The following are treatments often recommended for babies and children with citrullinemia:

1. Low-protein diet and/or special medical foods and formula

Most children need to eat a diet made up of very low-protein foods, special medical foods, and sometimes, a special formula. Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. A special food plan should be continued throughout your child's life.

Low-protein diet

The most effective treatment for citrullinemia is a diet with low amounts of protein. Foods that are high in protein need to be avoided or strictly limited include:

- milk, cheese, and other dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes

- nuts and peanut butter

Eating foods high in protein can cause ammonia to build up, causing severe illness. Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts.

It is important not to remove all protein from your child's diet. Your child still needs a certain amount of protein for normal growth and development. Any changes in the diet should be made under the guidance of a dietician.

Medical foods and formula

There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with amino acid disorders.

Your baby may need to drink a special medical formula that contains the correct amount of amino acids and nutrients. Your metabolic doctor and dietician will decide whether your child needs this treatment. Some states offer help with payment for this special formula and others require private insurance to pay for the formula and other special medical foods.

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

2. Medication

There are certain medications that can help the body get rid of ammonia. These medications are taken by mouth or by tube feeding to prevent high ammonia levels. Your doctor will decide whether your child needs these medications, which ones, and how much to use.

During episodes of high ammonia, children need to be treated in the hospital. Medications to remove ammonia are often given by IV. Dialysis is sometimes needed to remove ammonia from the blood.

An amino acid called arginine is often given by mouth to help prevent ammonia build-up. Your doctor will tell you whether your child needs arginine and how much to use. Do not use any supplements or medications without checking with your doctor.

3. Blood tests

Your child will have regular blood tests to measure ammonia and amino acid levels. Your child's diet and medication may need to be adjusted based on blood test results.

4. Call your doctor at the start of any illness:

For some babies and children with citrullinemia, even minor illnesses can cause high ammonia levels. In order to prevent problems, call your doctor right away when your child has any of the following:

- loss of appetite
- low energy or extreme sleepiness
- vomiting
- fever
- infection or illness
- behavior or personality changes
- difficulty walking or balance problems

Symptoms of high ammonia often 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.

5. Liver transplantation

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

Liver transplant 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 has been reported to improve quality of life and prolong survival in some cases. Liver transplantation does not reverse neurologic problems if they have already occurred.

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

What happens when citrullinemia is treated?

With prompt and lifelong treatment, children with citrullinemia can often live healthy lives with typical growth and learning. Early treatment can help prevent high ammonia levels which decreases the risk for brain damage.

Even with treatment, some children still have episodes of high ammonia. This can result in brain damage. This can cause lifelong learning problems, intellectual disabilities, or spasticity.

What causes the ASS enzyme to be absent or not working correctly?

Genes tell the body to make various enzymes. The ASS1 gene instructs the body to make the ASS enzyme. Everyone has two copies of the ASS1 gene. People with citrullinemia have changes, also called variants, in both copies of their ASS1 genes that cause them to not work correctly. Because of the variants in the ASS1 genes, the ASS enzyme either does not work properly or is not made at all.

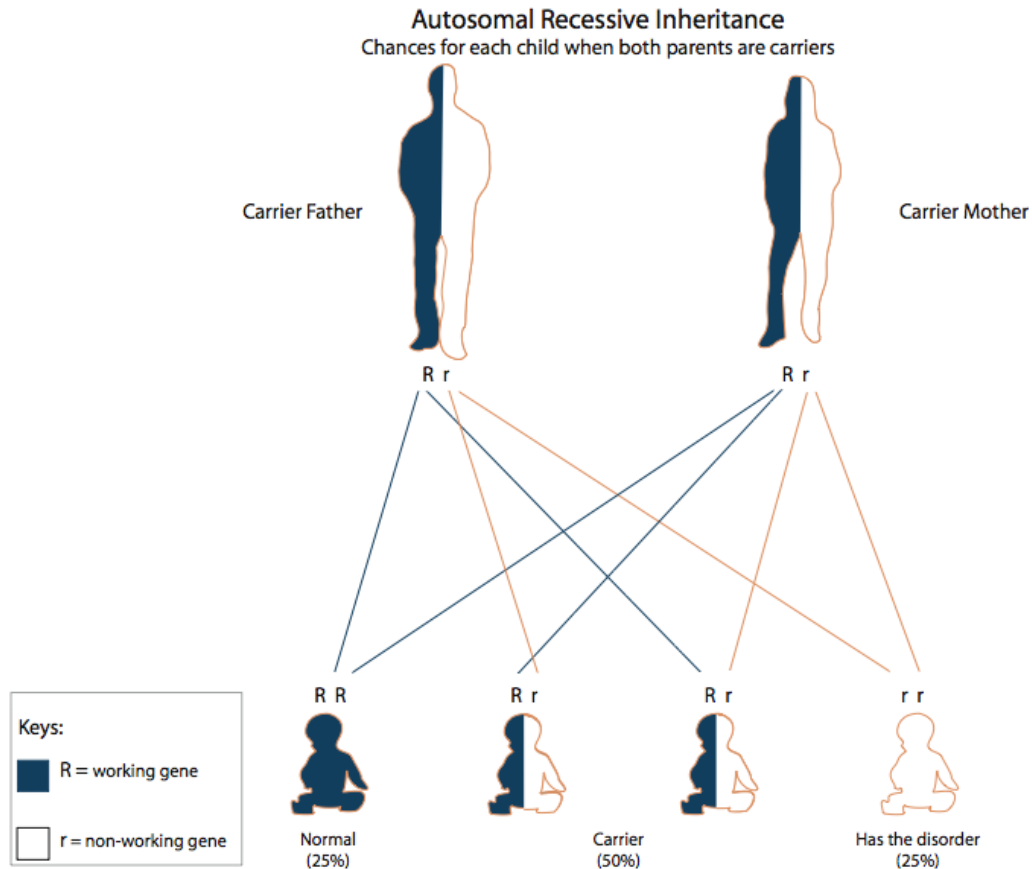
How is citrullinemia inherited?

This condition is inherited in an autosomal recessive manner. It affects both boys and girls.

Everyone has two copies of the ASS1 genes that make the ASS enzyme. In children with citrullinemia, neither of these genes works correctly. Children with citrullinemia inherit one non-working gene for the condition from each parent.

Parents of a child with citrullinemia rarely have the condition themselves. Instead, each parent has a single non-working ASS1 gene for citrullinemia. They are called carriers. Carriers do not have the condition because their other ASS1 gene is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have citrullinemia. 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 this condition. Genetic counselors can answer your questions about how it 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 can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes (variants) in the ASS1 genes that cause the condition.

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

What other testing is available?

Special tests on blood, urine, or skin samples can be done to confirm citrullinemia. Talk to your metabolic doctor or genetic counselor if you have questions about this type of testing.

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.

Although prenatal testing is possible, many parents choose to 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 citrullinemia. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing after birth.

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

Having citrullinemia

The brothers and sisters of a baby with citrullinemia have a chance of being affected, even if they haven't had symptoms. Finding out whether other children in your family have the condition is important because early treatment can prevent serious health problems. Talk to your metabolic doctor or genetic counselor about testing your other children.

Citrullinemia carriers

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

If you are a parent of a child with citrullinemia, 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 chance they are also at risk to have children with citrullinemia.

All states offer newborn screening for citrullinemia. 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.

Can other family members be tested?

Diagnostic testing

Brothers and sisters of a child with citrullinemia can be tested using blood, urine, or skin samples to see if they also have this disorder.

Carrier testing

If both gene changes in the ASS1 genes have been found in your child, other family members can have genetic testing to see if they are carriers.

If DNA testing would not be helpful, other methods of carrier testing may be available. Your metabolic doctor or genetic counselor can answer your questions about carrier testing.

How many people have citrullinemia?

This is a rare condition. About one in every 57,000 babies in the United States is born with citrullinemia.

Does citrullinemia happen more frequently in a certain ethnic group?

The classic form of citrullinemia occurs in all ethnic groups around the world.

Does citrullinemia go by any other names?

Citrullinemia is sometimes also called:

- Citrullinemia, type 1 (classic form)
- Argininosuccinate synthetase deficiency
- Argininosuccinic acid synthetase deficiency
- ASS deficiency
- Citrullinuria
- CTLN I

The adult-onset form of citrullinemia is also called:

- Late-onset citrullinemia

A disorder which was originally thought to be related to Citrullinemia but is now known to be a separate disorder is called:

- Citrullinemia, Type II
- Citrin Deficiency

Where can I find more information?

National Urea Cycle Disorders Foundation
<http://www.nucdf.org/>

Metabolic Support UK
<https://www.metabolicsupportuk.org>

Baby's First Test
<http://www.babysfirsttest.org>

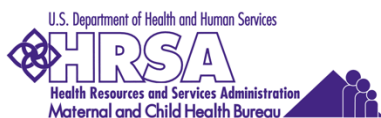
Urea Cycle Disorders Consortium
<http://rarediseasesnetwork.epi.usf.edu/ucdc/>

[MedlinePlus](#)
<https://medlineplus.gov/genetics/condition/citrullinemia/>

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