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: **Tyrosinemia, type 1**
Acronym: **FAH deficiency**

This fact sheet contains general information about tyrosinemia 1. 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 tyrosinemia 1?

This condition is one type of **amino acid disorder**. People with tyrosinemia 1 have problems breaking down an amino acid called tyrosine from the food they eat. If not treated, the condition causes severe liver disease and other serious health problems.

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.

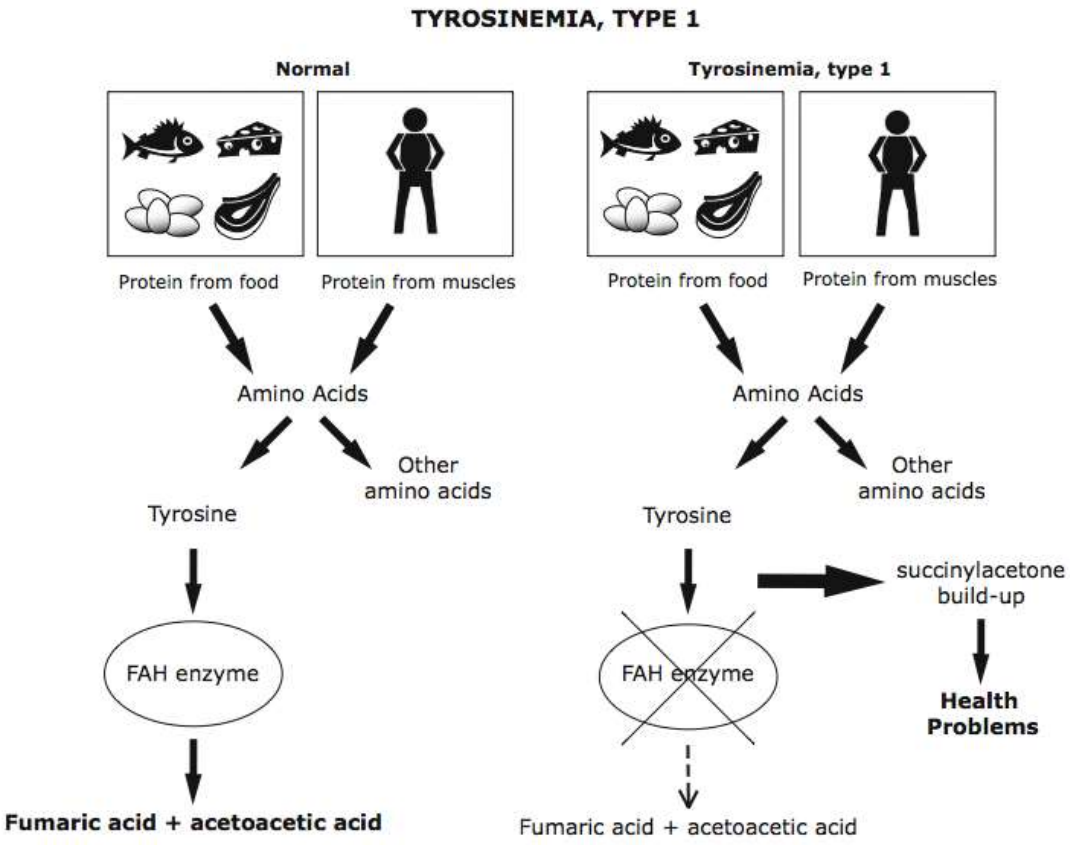
The symptoms and treatment vary between different amino acid disorders. They can also vary from person to person with the same amino acid disorder. See the fact sheets for each specific amino acid disorder.

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

What causes tyrosinemia 1?

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.

Tyrosinemia 1 occurs when an enzyme, called fumarylacetoacetase (FAH), is either missing or not working properly. When FAH is not working, it cannot break down tyrosine. Tyrosine and other harmful substances then build up in the blood. One of these substances is called succinylacetone. When it builds up in the blood, it causes serious liver and kidney damage. It may also cause episodes of weakness or pain.



If tyrosinemia 1 is not treated, what problems occur?

The symptoms can vary a great deal from person to person. There are two types of tyrosinemia 1. The more common type happens in infants. The less common type is seen in older children and adults.

Tyrosinemia 1 in infants:

Babies usually show effects of the condition within the first few months of life. Some of the first symptoms may be:

- diarrhea and bloody stools
- vomiting
- poor weight gain
- extreme sleepiness
- irritability
- “cabbage-like” odor to the skin or urine

Liver problems are common. They can lead to:

- enlarged liver
- yellowing of the skin
- tendency to bleed and bruise easily
- swelling of the legs and abdomen

Kidney problems also happen and can lead to:

- rickets, a bone thinning condition
- delays in walking

Without prompt and careful treatment, babies with severe liver and kidney problems usually die.

Some babies also have episodes that include:

- pain or weakness, especially in the legs
- breathing problems
- rapid heartbeat
- seizures
- coma, sometimes leading to death

Tyrosinemia 1 in children ("chronic" type):

Children with the chronic type usually start having symptoms after two months of age. Some of the first signs may be trouble gaining weight and episodes of vomiting and diarrhea. Over time, the condition can cause liver, kidney, and nerve problems.

- *Liver*: If the condition is not treated, a rare type of liver scarring called nodular cirrhosis can happen. This gets worse over time and can lead to liver failure. If not treated, many children develop liver failure or liver cancer before the age of 10. Medication, when started early, can prevent liver failure in most children.

- *Kidneys*: Serious kidney problems can occur in untreated children. When the kidneys are not working properly, episodes of vomiting, weakness, and fever can happen. Rickets, a bone thinning condition, may happen in children with kidney damage. Medication can prevent kidney problems in most children.

- *Neurologic crises:* Some children have episodes of weakness, pain, or numbness in their arms, legs, or other parts of the body. Breathing problems and rapid heartbeat may also happen. Some children have seizures that can lead to a coma. Medication can stop episodes of neurologic crisis in most children.

- *Other:* A small number of children have had heart problems. Some have had high blood pressure.

What is the treatment for tyrosinemia 1?

Your baby's doctor will work with a metabolic doctor and dietician to care for your child. Lifelong treatment is usually needed to prevent liver and kidney problems.

Treatment consists of medication and a diet low in tyrosine and another amino acid called phenylalanine (phe). The low tyrosine/phenylalanine diet is made up of a special medical formula and carefully chosen foods. The treatment must be started as soon as you know your child has the condition.

The following treatments are often recommended for children with tyrosinemia 1:

1. Medication
A medication called nitisinone (Orfadin®), also known as NTBC, is used to prevent liver and kidney damage. It also stops the neurologic crises. The medication lessens the risk for liver cancer. Your child should start taking Nitisinone as soon as possible. Your doctor will need to write a prescription for this medication.

Nitisinone will increase the level of tyrosine in your child's blood. So, a low-tyrosine diet is a very important part of this treatment.

Vitamin D is sometimes used to treat children who develop bone problems such as osteoporosis or rickets.

Do not take any medication without talking with your doctor.

2. Medical Formula
The special medical formula gives babies and children the nutrients and protein they need while helping keep their tyrosine levels within a safe range. Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

3. Low-tyrosine / phenylalanine diet
The diet is made up of foods that are very low in tyrosine and phenylalanine which come from protein. This means your child will need to limit high-protein foods such as cow's milk and regular formula. He or she will need to avoid meat, eggs, and cheese. Regular flour, dried beans, nuts, and peanut butter contain these amino acids and must also be limited.

Many vegetables and fruits have only small amounts of phenylalanine and tyrosine and can be eaten regularly in carefully measured amounts.

There are other medical foods such as special flours, pastas, and rice that are made especially for people with tyrosinemia 1. Some states offer help with payment for this formula and medical foods, and others require private insurance coverage for 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, general health, and how well the medication is working. Your dietician will fine-tune your child's diet over time.

4. Blood, urine, and other tests
Your child will have regular blood and urine tests to check:

- amino acid levels
- the amount of succinylacetone
- nitisinone level
- liver and kidney function

These tests help your doctor and dietician figure out whether any changes to the medication or diet are needed.

Some experts suggest that children with tyrosinemia 1 have a CT or MRI scan of their liver once a year to check for scarring or cancer.

5. Liver transplantation
Before nitisinone was available, liver transplantation was one of the main treatments for tyrosinemia 1. Now, nitisinone can prevent or reverse many of the liver problems and decreases the risk of developing liver cancer. For most children, nitisinone will delay, and hopefully prevent, the need for a liver transplant.

A liver transplant is still an option for those children that show signs of liver cancer or liver failure. If you have questions, talk to your metabolic doctor or doctor about the benefits and risks of transplantation.

What happens when tyrosinemia 1 is treated?

When treatment is started early, severe liver, kidney, and neurologic symptoms can be prevented. Children who are treated usually have normal growth and intelligence.

If treatment is not started right away, children may have some liver or kidney damage. Rickets may already be present and need to be treated. Delays in growth and development may also be present. The effects of delayed treatment vary from child to child.

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

Genes tell the body to make various enzymes. The FAH gene instructs the body to make the FAH enzyme. Everyone has two copies of the FAH gene. People with tyrosinemia 1 have changes, also called variants, in both copies of their FAH genes that cause them to not work correctly. Because of the variants in the FAH genes, the FAH enzyme either does not work properly or is not made at all.

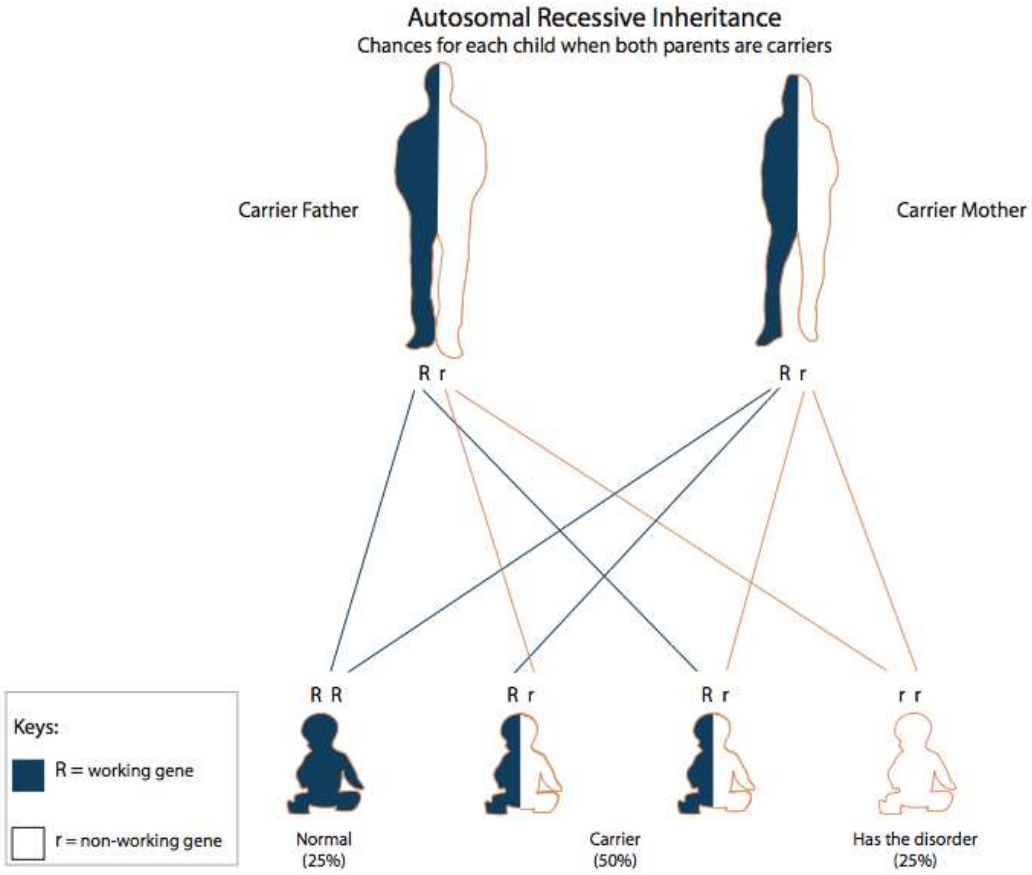
How is tyrosinemia 1 inherited?

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

Everyone has two copies of the FAH genes that make the FAH enzyme. In children with tyrosinemia 1, neither of these FAH genes works correctly. These children inherit one non-working FAH gene for the condition from each parent.

Parents of children with tyrosinemia 1 rarely have the condition themselves. Instead, each parent has a single non-working FAH gene for the condition. They are called carriers. Carriers do not have the condition because their other FAH gene is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have tyrosinemia 1. 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 tyrosinemia 1. 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 tyrosinemia 1 can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes (variants) in the FAH genes that causes this condition.

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?

This condition can be confirmed by measuring the amount of succinylacetone in the urine or by an enzyme test on blood, skin or liver samples. Talk to your metabolic doctor if you have questions about these tests.

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.

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 tyrosinemia type 1. 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 tyrosinemia 1 or be carriers?

Having tyrosinemia 1

If they are healthy and developing normally, older brothers and sisters of a baby with tyrosinemia are unlikely to also have tyrosinemia type 1. However, finding out whether other children in your family have this condition may be important. Early treatment can prevent serious health problems. Ask your metabolic doctor whether your other children should be tested.

Tyrosinemia 1 carriers

Brothers and sisters who do not have the condition 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 tyrosinemia type 1, 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 this condition.

All states offer newborn screening for tyrosinemia 1. 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 immediately – ideally at 24 hours of age.

Can other family members be tested?

Diagnostic testing

If there is a concern, diagnostic testing can be done on brothers and sisters to see if they have tyrosinemia type 1. Talk to your metabolic doctor if you have questions about testing other family members.

Carrier testing

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

How many people have tyrosinemia 1?

About one in every 100,000 babies in the United States is born with this condition.

Does tyrosinemia 1 happen more frequently in a certain ethnic group?

This condition occurs in all ethnic groups around the world. It is found more often in people of French-Canadian background, especially in the Saguenay Lac Saint-Jean region of Quebec. About 1 in 20 French-Canadians in this region are carriers. About one in every 2000 babies in this population is born with the condition. It may also occur more frequently in people from Norway or Finland.

Does tyrosinemia 1 go by any other names?

Tyrosinemia 1 is sometimes also called:

- Hereditary Infantile tyrosinemia
- Hepatorenal tyrosinemia
- Fumarylacetoacetase deficiency
- Fumarylacetoacetate hydrolase deficiency
- FAH deficiency
- Hereditary tyrosinemia type 1

- Tyrosinosis

Two other forms of this condition – tyrosinemia type II and tyrosinemia type III – have different symptoms and are not discussed in this fact sheet.

Where can I find more information?

About Tyrosinemia: New Parents' Guide
http://depts.washington.edu/tyros/abouttyr.htm

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

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

Genetics Home Reference
https://ghr.nlm.nih.gov/condition/tyrosinemia

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