



Genetic Fact Sheets for Parents

Fatty Acid Oxidation 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: Trifunctional protein deficiency

Acronym: TFP deficiency

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This fact sheet contains general information about TFP deficiency. Every child is different and some of this information may not apply to your child specifically. Not all is known about TFP deficiency and, at present, there is no standard treatment plan. Certain treatments may be recommended for some children but not others. Children with TFP deficiency should be followed by a metabolic doctor in addition to their primary doctor.

What is TFP deficiency?

TFP deficiency stands for “trifunctional protein deficiency.” It is one type of fatty acid oxidation disorder. Some people with TFP deficiency have problems breaking down fat into energy for the body.

Fatty Acid Oxidation Disorders:

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

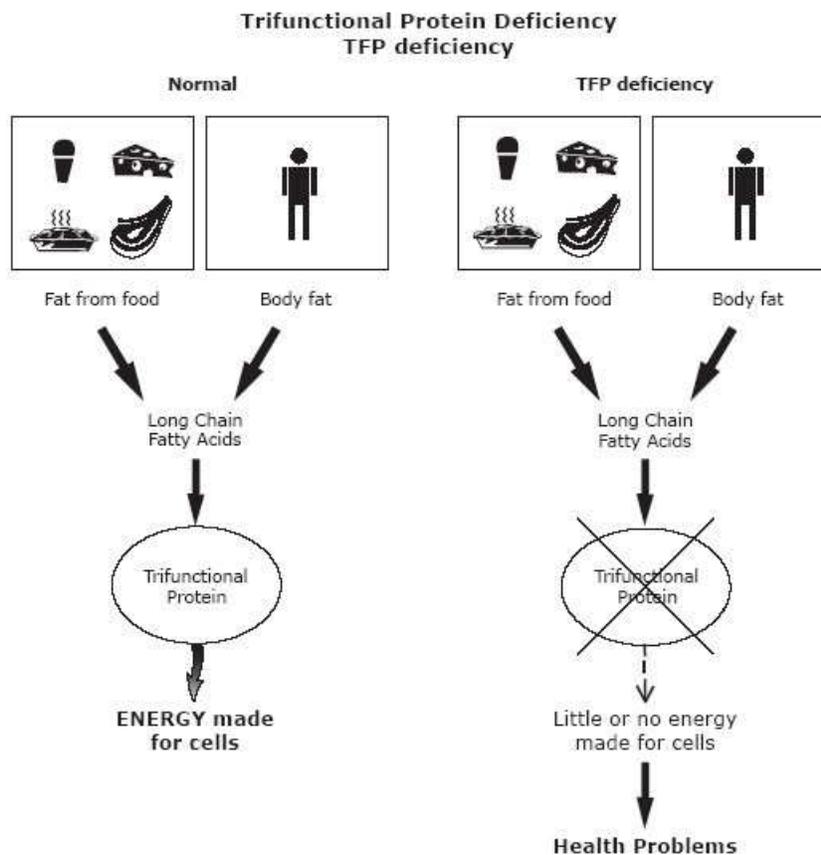
A number of enzymes are needed to break down fats in the body (a process called fatty acid oxidation). Problems with any of these enzymes can cause a fatty acid oxidation disorder. People with FAODs cannot properly break down fat from either the food they eat or from fat stored in their bodies.

The symptoms and treatment vary between different FAODs. They can also vary from person to person with the same FAOD. See the fact sheets for each specific FAOD.

FAODs are inherited in an autosomal recessive manner and affect both males and females.

What causes TFP deficiency?

TFP deficiency occurs when a group of enzymes, called “trifunctional protein” (TFP), is either missing or not working properly. The job of TFP is to break down certain fats from the food we eat into energy. It also breaks down fat already stored in the body.



Energy from fat keeps us going whenever our bodies run low of their main source of energy, a type of sugar called glucose. Our bodies rely on fat when we don't eat for a stretch of time – like when we miss a meal or when we sleep.

When TFP is missing or not working well, the body cannot use fats for energy. Instead, it must rely solely on glucose. Although glucose is a good source of energy, there is a limited amount available. Once the glucose has been used up, the body tries to use fat without success. This leads to low blood sugar, called hypoglycemia, and to the build up of harmful substances in the blood.

If TFP deficiency is not treated, what problems occur?

TFP deficiency can cause mild symptoms in some people or more serious health problems in others. There are three types of TFP deficiency: early, childhood, and mild.

Babies and children with early and childhood TFP deficiency can have episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness
- behavior changes
- irritable mood
- muscle weakness
- poor appetite

Some of these other symptoms may also follow:

- fever
- nausea
- diarrhea
- vomiting
- hypoglycemia
- increased levels of acidic substances in the blood, called metabolic acidosis

If a metabolic crisis is not treated, a child with TFP deficiency can develop:

- breathing problems
- seizures
- coma, sometimes leading to death

Periods of hypoglycemia can happen without other symptoms of metabolic crisis. Hypoglycemia causes:

- weakness
- shakiness
- dizziness

- clammy, cold skin
- if untreated, coma, and sometimes death

In children with TFP deficiency, either hypoglycemia or a metabolic crisis can happen:

- after going too long without food
- after long periods of exercise
- during illness or infection
- during times of stress, such as surgery

Early TFP deficiency

Babies with early TFP deficiency usually show symptoms anywhere from birth through age two. The first symptoms are often:

- poor appetite
- sluggishness
- extreme sleepiness
- muscle weakness
- absent reflexes
- no response to pain
- delays in walking and learning

Babies with early TFP deficiency often have many episodes of metabolic crisis.

Other effects of early TFP deficiency can include:

- serious heart problems and enlarged heart
- build-up of fat in the liver and other liver problems
- breathing problems

Infants with early TFP deficiency who remain untreated usually die of heart or breathing problems by three years of age.

Childhood TFP deficiency

Childhood TFP deficiency can cause episodes of hypoglycemia and metabolic crisis. Between these episodes, children with TFP deficiency are usually healthy. However, repeated episodes may cause brain damage. This could result in learning problems or intellectual disabilities.

Bouts of muscle weakness and pain happen in some children, especially after heavy exercise, stress, or illness.

Mild/muscle TFP deficiency

The mild type of TFP deficiency has been reported in a small number of people. Symptoms can begin anywhere from age two to adulthood.

Episodes of muscle weakness are common. Breakdown of muscle fibers can occur. This usually happens:

- after strenuous exercise or exertion
- during illness or infection
- after going without food for a long period of time

Signs of muscle breakdown are:

- muscle aches
- cramps
- weakness
- reddish-brown color to the urine
- breathing problems

If muscle symptoms are not treated, kidney failure can occur.

The mild type of TFP deficiency does not cause metabolic crises or heart or liver problems.

What is the treatment for TFP deficiency?

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

Certain treatments may be advised for some children but not others. When necessary, treatment is usually needed throughout life. The following are treatments that may be recommended for children with TFP deficiency:

1. Avoid going a long time without food

Infants and young children with TFP deficiency need to eat frequently to prevent hypoglycemia or a metabolic crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan tailored to your child's needs for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older. When they are well, many teens and adults with TFP deficiency can go without food for up to 12 hours without problems. The other treatments usually need to be continued throughout life.

2. Diet

A diet low in fat and high in carbohydrates is often recommended. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for

children needing this treatment, most foods in the diet should be carbohydrates (bread, pasta, fruit, vegetables, etc.) and protein (lean meat and low-fat dairy foods). Any diet changes should be made under the guidance of an experienced dietician.

People with TFP deficiency cannot use certain building blocks of fat called “long chain fatty acids.” Your dietician can help create a food plan low in these fats. Much of the rest of the fat in the diet will likely be in the form of medium chain fatty acids.

Ask your doctor if your child needs to have any changes in his or her diet.

3. MCT oil and L-carnitine

Medium Chain Triglyceride oil (MCT oil) is often used as part of the food plan for people with TFP deficiency. This special oil has medium chain fatty acids that can be used in small amounts for energy. Your metabolic doctor or dietician can tell you how to use this supplement. You will need to get a prescription from your doctor to get MCT oil.

Some children may be helped by L-carnitine. This is a safe and natural substance that helps body cells create energy. It also helps the body get rid of harmful wastes. Your doctor will decide whether your child needs L-carnitine. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Do not use any medication or supplement without checking with your doctor.

4. Call your doctor at the start of any illness

Always call your doctor when your child has any of the following:

- poor appetite
- low energy or excessive sleepiness
- vomiting
- diarrhea
- an infection
- a fever
- persistent muscle pain or weakness
- reddish-brown color to the urine

Children with TFP deficiency need to eat extra starchy food and drink more fluids during any illness - even if they may not feel hungry - or they could develop a metabolic crisis. Children who are sick often don't want to eat. If they won't or can't eat, children with TFP deficiency may need to be treated in the hospital to prevent hypoglycemia or a metabolic crisis. Ask your metabolic doctor if you should carry a special travel letter with medical instructions for your child's care.

5. Avoid heavy exercise and extreme cold

Long periods of heavy exercise can trigger symptoms in people with TFP deficiency. Effects of exercise can include muscle aches, cramps, and weakness. Muscle fibers may break down. This can turn the urine to a reddish-brown color.

If muscle symptoms occur, prompt treatment is needed to prevent kidney damage. Children or adults with muscle symptoms should:

- drink fluids right away
- eat something starchy or sugary
- get to a hospital for treatment

To prevent muscle symptoms:

- avoid prolonged or heavy exercise
- avoid extreme cold
- eat starchy or sugary foods before and during periods of moderate exercise or exertion

What happens when TFP deficiency is treated?

Early TFP deficiency

Most babies with early TFP deficiency die of heart or breathing problems, even when treated. However, treatment may help prolong life in some babies.

Childhood TFP deficiency

With prompt and careful treatment, children with TFP deficiency can often live healthy lives with typical growth and development. However, some children continue to have episodes of hypoglycemia or metabolic crisis, even with treatment. This can cause permanent brain damage and may result in learning problems or intellectual disabilities.

Mild/muscle TFP deficiency

When treated, people with mild/muscle TFP deficiency usually remain healthy. This form does not affect intelligence.

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

Genes tell the body how to make enzymes. The HADHA and HADHB genes instructs the body to make the enzymes in the trifunctional protein. Everyone has two copies of the HADHA and HADHB genes. People with TFP deficiency have changes, also called variants in both copies of either their HADHA genes or their HADHB genes.

Because of the changes in either the HADHA or the HADHB genes, the TFP enzymes do not work properly or are not made at all.

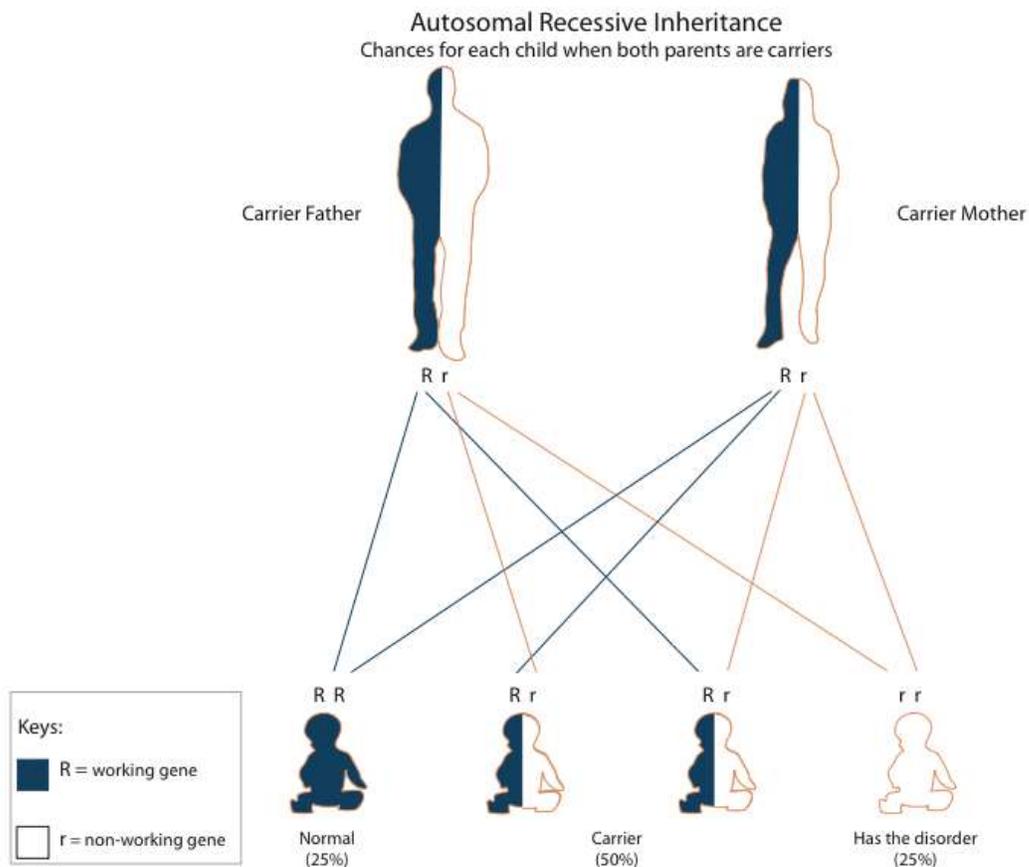
How is TFP deficiency inherited?

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

Everyone has two copies of the HADHA and HADHB genes that make the enzymes in the TFP enzyme group. In children with TFP deficiency, one set of these genes – either HADHA or HADHB – does not work correctly. These children inherit one non-working gene for the TFP deficiency from each parent.

Parents of children with TFP deficiency rarely have the disorder. Instead, each parent has a single non-working gene for TFP deficiency. They are called carriers. Carriers do not have TFP deficiency because their other HADHA or HADHB gene is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have TFP deficiency. 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 TFP deficiency. Genetic counselors can answer your questions about how TFP deficiency 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 TFP deficiency can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes, also called variants, in the HADHA and HADHB genes that cause TFP deficiency. In some affected children, both variants can be found. However, in other children, neither or only one of the two gene changes can be found, even though we know they are present.

DNA testing is not necessary to diagnose your child. It can be helpful for carrier testing or prenatal diagnosis, discussed below. Ask your metabolic doctor or genetic counselor if you have questions about DNA testing for TFP deficiency.

What other testing is available?

TFP deficiency can be confirmed by special enzyme tests using a skin or muscle sample. Talk to your doctor or your genetic counselor if you have questions about testing for TFP deficiency.

Can you test during a future pregnancy?

If both gene changes have been found in your child with TFP deficiency, 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, special enzyme tests can be done during pregnancy using cells from the fetus. Again, the sample needed for this test is obtained by either CVS or amniocentesis.

Parents may either 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 TFP deficiency. 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 TFP deficiency or be carriers?

Having TFP deficiency

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

TFP deficiency carriers

Brothers and sisters who do not have TFP deficiency 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 TFP deficiency, your brothers and sisters have a 50% chance to be a TFP deficiency 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 TFP deficiency.

All states offer newborn screening for TFP deficiency. 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.

During pregnancy, women carrying fetuses with TFP deficiency are at risk to develop serious medical problems. There is a small risk of:

- excessive vomiting
- abdominal pain
- high blood pressure
- jaundice
- severe bleeding
- abnormal fat storage in the liver

All women with a family history of TFP deficiency should share this information with their obstetricians and other health care providers before and during any future pregnancies. Knowing about these risks allows early treatment.

Can other family members be tested?

Diagnostic testing

Brothers and sisters can be tested for TFP deficiency by DNA testing or special enzyme tests to determine if they also have TFP deficiency.

Carrier testing

If both gene changes have been found in your child with TFP deficiency, other family members can have DNA testing to see if they are carriers.

How many people have TFP deficiency?

TFP deficiency is a very rare disorder. The actual incidence is unknown.

Does TFP deficiency happen more often in a certain ethnic group?

TFP deficiency does not happen more often in any specific race, ethnic group, geographical area, or county.

Does TFP deficiency go by any other names?

TFP deficiency is sometimes also called:

- mitochondrial trifunctional protein deficiency

Where can I find more information?

Fatty Oxidation Disorders (FOD) Family Support Group
<http://www.fodsupport.org>

Organic Acidemia Association
<http://www.oaanews.org>

United Mitochondrial Disease Foundation
<http://www.umdf.org>

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

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

Genetic Home Reference
<https://ghr.nlm.nih.gov/condition/mitochondrial-trifunctional-protein-deficiency>

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