



Genetic Fact Sheets for Parents

Fatty Acid Oxidation Disorders

Organic 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: Glutaric acidemia, type 2
Acronym: GA-2

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This fact sheet contains general information about GA-2. 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 GA-2 should be followed by a metabolic doctor in addition to their primary doctor.

What is GA-2?

GA-2 stands for “glutaric acidemia, type 2.” People with GA-2 have problems breaking down fat and protein into energy for the body. GA-2 has symptoms that are part of two different groups of disorders: fatty acid oxidation disorders and organic acid disorders.

Glutaric acidemia, type 2

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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.

Organic Acid Disorders:

Organic acid disorders (OAs) are a group of rare inherited conditions. They are caused by enzymes that do not work properly. A number of enzymes are needed to process protein from the food we eat for use by the body. Problems with one or more of these enzymes can cause an organic acid disorder.

People with organic acid disorders cannot break down protein properly. This causes harmful substances to build up in their blood and urine. These substances can affect health, growth, and learning.

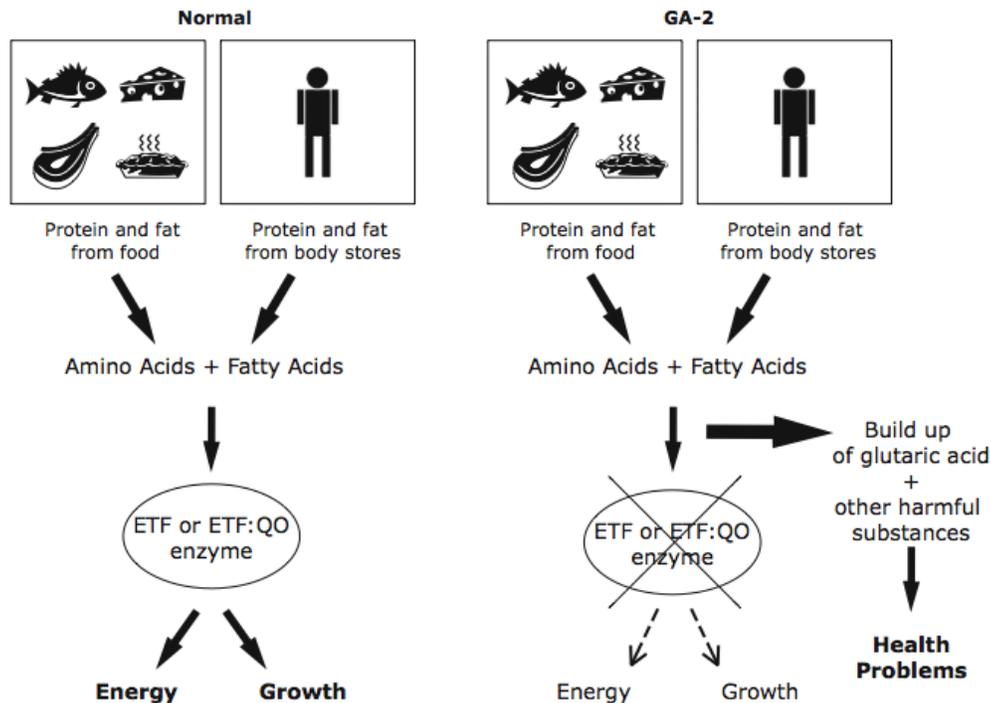
The symptoms and treatment vary between different organic acid disorders. They can also vary from person to person with the same organic acid disorder. See the fact sheets for each specific organic acid disorder.

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

What causes GA-2?

GA-2 occurs when one of two different enzymes is either missing or not working properly. The enzymes responsible for GA-2 are called “electron transfer flavoprotein” (ETF) and “electron transfer flavoprotein dehydrogenase” (ETFDH). The job of these enzymes is to help make energy for the body by breaking down certain fats and proteins from the food we eat. They also break down fat and protein already stored in the body.

Glutaric Acidemia - Type 2 GA-2



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

When either one of these two enzymes is missing, the body cannot break down protein and fat for energy, and must rely on glucose. While 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 and protein with limited success. This leads to the build up of glutaric acid and other harmful substances in the blood. It also causes low blood sugar, called hypoglycemia.

If GA-2 is not treated, what problems occur?

GA-2 can cause bouts 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

Other symptoms then 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 GA-2 can develop:

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

Symptoms can first show up in the newborn period or later in childhood or sometimes even adulthood.

GA-2 in newborns

Some babies have their first symptoms shortly after birth. Rapid breathing and weak muscle tone often happen one to two days after birth. Episodes of metabolic crisis often show up at this time, too.

Many babies with GA-2 have an odor that smells like “sweaty feet.” In addition, they often have serious heart and liver problems.

Without treatment, most babies die within the first few weeks of life. Even with treatment, many babies with GA-2 die of severe heart problems within a few months.

Some newborns with GA-2 also have birth defects. If this is the case, treatment is usually not helpful. Babies with GA-2 and birth defects usually die within the first weeks of life.

GA-2 in childhood

The symptoms of GA-2 can be very different from person to person. If symptoms do not happen in the newborn period, they may begin anytime from early childhood through adulthood.

Symptoms in childhood can include:

- nausea
- vomiting
- muscle weakness
- periods of hypoglycemia
- full metabolic crisis (described above)

Hypoglycemia, or low blood sugar, can cause a child to feel weak, shaky, or dizzy with clammy, cold skin. Hypoglycemia can occur:

- after strenuous exercise
- after eating too much protein
- after going too long without food
- during illness or infection

Episodes of metabolic crisis can happen for the same reasons.

Other symptoms of GA-2 happen in some people:

- liver problems
- heart problems
- low levels of carnitine, a substance that helps the body use fat for energy
- involuntary movements

Some people with GA-2 never have symptoms and are only found to be affected after a brother or sister is diagnosed.

What is the treatment for GA-2?

Your child's primary doctor will work with a metabolic doctor and dietician familiar with GA-2 to provide your child with medical care.

Certain treatments may be advised for some children but not others. When necessary, treatment is usually needed throughout life. The following are treatments often recommended for children with GA-2:

1. Avoid going a long time without food

Infants and young children with GA-2 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 GA-2 can go without food for up to 12 hours without problems. They may need to continue the other treatments throughout life.

2. Diet

A diet low in fat, low in protein and high in carbohydrates is often advised. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Do not remove all fat and protein from the diet. Children with GA-2 need a certain amount of each to grow properly.

Your dietician can help you create a food plan that meets your child's needs. Any diet changes should be made under the guidance of a dietician experienced with GA-2.

3. Riboflavin, L-carnitine, and Coenzyme Q₁₀

Some children and adults with GA-2 are helped by taking daily riboflavin supplements. Check with your doctor to see whether your child should take riboflavin.

Some children may be helped by taking L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine supplements. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Supplementation with Coenzyme Q₁₀ may also be beneficial. Coenzyme Q₁₀ is a substance this is found in every cell in the body and it helps convert food into energy and it is a powerful antioxidant. Some people with GA-2 may benefit from taking Coenzyme Q₁₀.

Do not use any of these supplements without checking with your doctor.

4. Call your doctor at the start of any illness

Always call your health care provider when your child has any of the following:

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

During illness or infection, children with GA-2 have a much higher chance of developing hypoglycemia or a metabolic crisis. They need to drink fluids and eat extra carbohydrates when they are ill – even if they aren't hungry – or they could have a metabolic crisis.

Children who are sick often don't want to eat. If they can't eat, or if they show signs of hypoglycemia or 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.

What happens when GA-2 is treated?

GA-2 in newborns

A small number of newborns with symptoms of GA-2 have shown benefit from treatment. But, in most cases, treatment has not been helpful. Many newborns with GA-2 die from heart problems within the first few months of life.

GA-2 in children

With prompt and careful treatment, children and adults with GA-2 usually live healthy lives with normal growth and development.

The goal of treatment is to prevent long-term problems. However, children who have repeated metabolic crises may develop life-long learning problems.

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

Genes tell the body how to make enzymes. Three different genes - ETFA, ETFB, and ETFDH – provide the instructions to make electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase enzymes. Everyone has two copies of each of these three genes. People with GA-2 have changes, also called variants, in both copies of either their ETFA, ETFB, or ETFDH genes. Because of the variants in the ETFA, ETFB, or ETFDH genes, the electron transfer flavoprotein or electron transfer flavoprotein dehydrogenase enzyme either does not work properly or is not made at all.

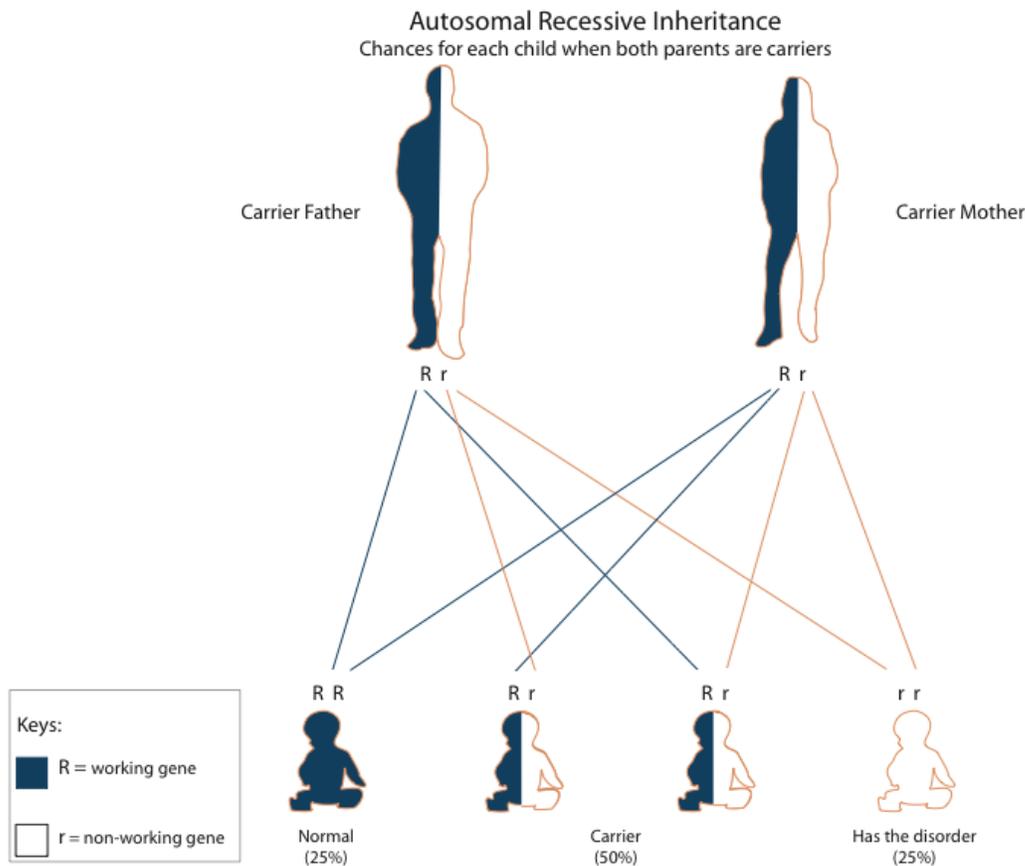
How is GA-2 inherited?

GA-2 is inherited in an autosomal recessive manner. It affects both boys and girls equally.

Everyone has two copies of the ETFA and ETFB genes that make the ETF enzyme, and two copies of the ETFHD genes that makes the ETFDH enzyme. In children with GA-2, the pair of genes for one of these enzymes does not work correctly. These children inherit one non-working gene for the condition from each parent.

Parents of children with GA-2 rarely have the disorder. Instead, each parent has a single non-working gene for GA-2. They are called carriers. Carriers do not have GA-2 deficiency because their other gene is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have GA-2. 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 GA-2. 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 GA-2 can be done on a blood sample. Genetic testing, also called DNA testing, looks for the changes (variants) in the pair of genes that cause GA-2. Talk with your genetic counselor or metabolic doctor if you have questions about DNA testing.

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

What other testing is available?

GA-2 can be confirmed by tests done on urine, blood, or skin samples. Ask your metabolic doctor or genetic counselor about testing for GA-2.

Can you test during a future pregnancy?

If both gene changes 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 GA-2. 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 GA-2 or be carriers?

Having GA-2

The brothers and sisters of a baby with GA-2 have a chance of being affected, even if they haven't shown symptoms. Finding out if other children in the family have GA-2 is important because early treatment may prevent serious health problems. Talk to your metabolic doctor or genetic counselor about testing your other children for GA-2.

GA-2 carriers

Brothers and sisters who do not have GA-2 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 GA-2, your brothers and sisters have a 50% chance to be a GA-2 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 GA-2.

Some states do not provide newborn screening for GA-2. However, expanded newborn screening through private labs is available for babies born in states that do not screen for this condition. Your healthcare provider or genetic counselor can help you obtain expanded newborn screening.

When both parents are carriers, newborn screening results are not sufficient to rule out GA-2 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

GA-2 can be confirmed by special tests using urine, blood, or skin samples.

Carrier testing

Carrier testing for GA-2 may be available. Ask your genetic counselor or metabolic doctor whether carrier testing is possible for your family.

How many people have GA-2?

GA-2 is very rare. The actual incidence is unknown.

Does GA-2 happen more often in a certain ethnic group?

GA-2 does not happen more often in any specific race, ethnic group, geographical area, or country.

Does GA-2 go by any other names?

GA-2 is sometimes also called:

- glutaric acidemia-II
- glutaric aciduria-II
- multiple acyl-CoA dehydrogenase deficiency (MADD)
- electron transfer flavoprotein dehydrogenase deficiency
- ETF/ETF QO 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>

MedlinePlus

<https://medlineplus.gov/genetics/condition/glutaric-acidemia-type-ii/>

Baby's First Test

<http://www.babysfirsttest.org>

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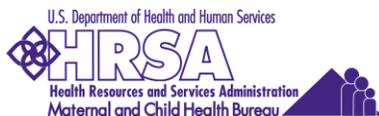
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