Parents’ Guide to GA-2
Glutaric Acidemia Type-2

California Department of Health Services
Newborn Screening Program
Genetic Disease Branch
www.dhs.ca.gov/gdb

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*Underlined words in booklet are defined in the Glossary

The information in this booklet is general and is not meant to be specific to each child with GA-2. Certain treatments may be recommended for some children but not others. Children with GA-2 should be followed by a physician specializing in metabolic diseases (metabolic specialist) in addition to their primary doctor. For a list of metabolic centers, see page 16 or visit our website at [www.dhs.ca.gov/gdb](http://www.dhs.ca.gov/gdb).
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.
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 “ETF-ubiquinone oxidoreductase” (ETF:QO). 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.

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 while – such as 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.

**What causes the enzyme to be missing or not working correctly?**

*Genes* tell the body to make various enzymes. People with GA-2 have a pair of genes that do not work correctly. Because of the gene changes, one of the necessary enzymes does not work properly or is not made at all.

**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 and poor appetite. Crises are often set off by an infection so illness may start with symptoms of fever, nausea, diarrhea and vomiting. Low blood sugar and increased levels of acidic substances in the blood, called
metabolic acidosis, then follows. If a metabolic crisis is not treated, a child with GA-2 can develop breathing problems, seizures, and 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 (floppy muscles and joints) usually happen one to two days after birth. Episodes of metabolic crises 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 (later onset form of GA-2)**

There is a milder form of GA-2 that typically presents in childhood. The symptoms of this form 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 low blood sugar
- full metabolic crisis (described earlier)
Low blood sugar can cause a child to feel weak, shaky or dizzy with clammy, cold skin. Low blood sugar 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 after a brother or sister is diagnosed.
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.

**GA-2 in children**
With prompt and careful treatment, children and adults with the milder form of 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 is the treatment for GA-2?
Your child’s primary doctor will work with a metabolic specialist and dietician 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**
   Young children with GA-2 need to eat often to prevent low blood sugar or a metabolic crisis. Most children should not go without food for more than 4 to 6 hours. Some children may need to eat even more often than this.

   When they are well, most 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 low-fat, low-protein, high-carbohydrate diet 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.

3. Riboflavin, L-carnitine and glycine supplements
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.

Some people with GA-2 are helped by taking glycine supplements. Ask your doctor whether your child should take glycine. Do not use any of these supplements without checking with your doctor.
4. **Call your doctor immediately at the sign of any of these symptoms in your child:**
   - 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 low blood sugar 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 or they vomit and cannot keep food down. If they can’t eat, or if they show signs of low blood sugar or a metabolic crisis, they need to be treated in the hospital.
How is GA-2 inherited?

GA-2 affects both boys and girls equally. Everyone has one pair of genes that make the ETF enzyme and another pair that makes the ETF:QO 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. This is called **autosomal recessive** inheritance.

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 are not affected because their other gene of this pair is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have two working genes. This means the child is not a carrier and does not have the disease. There is a 50% chance for the child to be a carrier, just like the parents. There is a 25% chance for the child to have GA-2.

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Chances apply to each pregnancy

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(25% chance) (50% chance) (25% chance)
Genetic counseling is available to families who have children with GA-2. Genetic counselors can answer your questions about how the condition is inherited, options during future pregnancies, and how to test other family members. Other family members can also ask about genetic counseling and testing for GA-2.

Is genetic testing available?

Genetic testing, also called DNA testing, looks for the changes in the pair of genes that cause GA-2. Talk with your genetic counselor or metabolic specialist if you have questions about DNA testing.

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

What other testing is available?

GA-2 can be confirmed by tests done on urine, blood, or skin samples. Ask your metabolic specialist or genetic counselor about testing for GA-2.
Can you test during pregnancy?

Yes, testing can be done during pregnancy. The sample needed for this test is obtained by amniocentesis.

Parents may either choose to have testing during pregnancy or wait until birth to have the baby tested. 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?

The brothers and sisters of a baby with GA-2 have a chance also having GA-2 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 specialist or genetic counselor about testing your other children for GA-2.
Brothers and sisters who do not have GA-2 still have a chance to be carriers like their parents. Carriers do not have the disorder and will never develop it.

Each of the parents’ brothers and sisters has a 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.

When both parents are known GA-2 carriers or have had a baby with GA-2, subsequent newborns should have special diagnostic testing in addition to the newborn screen to test for GA-2.

**How many people have GA-2?**

The incidence of GA-2 is unknown. 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 aciduria-II
- ETF/ETF QO deficiency
- Ethylmalonic adipic aciduria (later onset form)
- MADD (multiple acyl-CoA dehydrogenase deficiency)
- Electron transfer flavoprotein dehydrogenase deficiency

RESOURCES

Organic Acidemia Association
13210 35th Avenue North
Plymouth, MN 55441
(763) 559-1797
www.oaanews.org

Fatty Oxidation Disorders (FOD)
Family Support Group
1559 New Garden Road, 2E
Greensboro, NC 27410
(336) 547-8682
www.fodsupport.org

United Mitochondrial Disease Foundation
8085 Saltsburg Road, Suite 201
Pittsburgh, PA 15239
(412) 793-8077
www.umdf.org

Genetic Alliance
4301 Connecticut Ave. NW, Suite 404
Washington, DC 20008-2369
(202) 966-5557
www.geneticalliance.org
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<td>Cedars-Sinai Medical Center, Los Angeles</td>
<td>Los Angeles</td>
<td>(310) 423-9914</td>
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<tr>
<td>Children’s Hospital Central California, Madera</td>
<td>Madera</td>
<td>(559) 353-6400</td>
</tr>
<tr>
<td>Children’s Hospital &amp; Research Center, Oakland</td>
<td>Oakland</td>
<td>(510) 428-3550</td>
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<tr>
<td>Children’s Hospital Los Angeles</td>
<td>Los Angeles</td>
<td>(323) 660-2450</td>
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<tr>
<td>Children’s Hospital of Orange County, Orange</td>
<td>Orange</td>
<td>(714) 532-8852</td>
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<tr>
<td>Children’s Hospital San Diego Health Center, La Jolla</td>
<td>La Jolla</td>
<td>(619) 543-7800</td>
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<tr>
<td>Harbor/UCLA Medical Center Torrance</td>
<td>Torrance</td>
<td>(310) 222-3756</td>
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<td>Kaiser Permanente - No. Cal.</td>
<td>No. Cal.</td>
<td>(510) 752-7703</td>
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<td>Kaiser Permanente - So. Cal.</td>
<td>So. Cal.</td>
<td>(323) 783-6970</td>
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<td>LAC/USC Medical Center Los Angeles</td>
<td>Los Angeles</td>
<td>(323) 226-3816</td>
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<tr>
<td>Lucile Salter Packard Children’s Hospital at Stanford</td>
<td>Stanford</td>
<td>(650) 723-6858</td>
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<tr>
<td>Sutter Medical Center Sacramento</td>
<td>Sacramento</td>
<td>(916) 733-6023</td>
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<td>UC Davis Medical Center</td>
<td>Sacramento</td>
<td>(916) 734-3112</td>
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<td>UC San Francisco Medical Center</td>
<td>San Francisco</td>
<td>(415) 476-2757</td>
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<td>UCLA Medical Center</td>
<td>Los Angeles</td>
<td>(310) 206-6581</td>
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<tr>
<td>UCI Medical Center, Orange</td>
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<td>(714) 456-8513</td>
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Amniocentesis - Test done during pregnancy (usually between 16 and 20 weeks). A needle is used to remove a small sample of fluid from the sac around the fetus. The sample can be used to test for certain genetic disorders in the fetus.

Autosomal recessive - Autosomal recessive conditions affect both boys and girls equally. How autosomal recessive inheritance works: Everyone has a pair of genes responsible for making each enzyme in the body. A person with a metabolic disorder has one enzyme that is either missing or not working properly. The problem is caused by a pair of "recessive" genes that are not working correctly. They do not make the needed enzyme. A person has to have two non-working "recessive" genes in order to have an autosomal recessive metabolic disorder. A person with an autosomal recessive disorder inherits one non-working gene from their mother and the other from their father.

Carrier - A person who has a gene mutation in one of their genes that cause a disease, but does not have any symptoms of the disease. The mutation is often recessive, which means that both copies of the gene have to be mutated in order for disease symptoms to develop. Carriers are able to pass the mutation onto their children and therefore have an increased chance of having a child with the disease.
**DNA** - Deoxyribonucleic acid (DNA) is a molecule that makes up chromosomes. It is composed of four units (called bases) that are designated A, T, G, and C. The sequence of the bases spell out instructions for making all of the proteins in an organism. The instructions set for each individual protein is a gene. A change in one of the DNA letters making up a gene is a mutation. In some cases, these mutations can alter the protein instructions and lead to disease. Each individual passes their chromosomes on to their children, and therefore pass down the DNA instructions. It is these instructions that cause certain traits, such as eye or hair color, to be inherited.

**Enzyme** - A molecule that helps chemical reactions take place. For example, enzymes in the stomach speed up the process of breaking down food. Each enzyme can participate in many chemical reactions without changing or being used up.

**Fatty Acid Oxidation Disorders (FAODs)** - A group of rare inherited conditions. FAODs are caused by missing or non-working enzymes. Normally, many enzymes are used by the body to break down fat into energy. In people with FAODs, one of these enzymes is not working and fat cannot be used for energy. If these conditions are not treated, they can lead to serious health problems.
Gene - A segment of DNA that contains the instructions to make a specific protein (or part of a protein). Genes are contained on chromosomes. Chromosomes, and the genes on those chromosomes, are passed on from parent to child. Errors in the DNA that make up a gene are called mutations and can lead to diseases.

Genetic Counseling - Genetic counseling gives patients and their families education and information about genetic-related conditions and helps them make informed decisions. It is often provided by Genetic Counselors or Medical Geneticists who have special training in inherited disorders.

Glutaric acid - A harmful waste product made when certain amino acids (lysine, tryptophan and hydroxylysine) are broken down in the body.

Glycine - One of 20 amino acids that make up protein. It has many functions, one of which is helping cells create energy for the body. It is make by the body and does not need to be eaten in the diet. It is also available as a supplement.

Metabolic Crisis - A serious health condition caused by low blood sugar and the build-up of toxic substances in the blood. Symptoms of a metabolic crisis are: poor appetite, nausea, vomiting, diarrhea, extreme sleepiness, irritable mood and behavior changes. If not treated, breathing problems, seizures, coma, and
sometimes even death can occur. Metabolic crises happen more often in people with certain metabolic disorders (some fatty acid oxidation disorders, amino acid disorders, and organic acid disorders). They are often triggered by things like illness or infection, going without food for a long time, and, in some cases, heavy exercise.

**Organic Acid Disorders (OA)** - A group of rare inherited conditions. OA disorders are caused by one or more enzymes that do not work properly. People with these conditions cannot digest certain parts of protein from the food they eat. This causes harmful substances to build up in their blood and urine. This can cause serious effects on health, growth, and learning.

**Riboflavin** - One type of B vitamin (vitamin B2). It helps change carbohydrates, protein, and fat into energy for the body. Some foods high in riboflavin are dairy products, yogurt, cheese, meats, poultry, whole and enriched grains, and green vegetables. Some children with metabolic disorders may be helped by taking riboflavin supplements.

**Seizure** - Also called “convulsions” or “fits”. During a seizure, a person loses consciousness and control of their muscles. It may also cause involuntary movements. Seizures can happen for many reasons. Some causes are metabolic disorders, a metabolic crisis, brain injury, and infection.
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