STAR-G
Screening, Technology and Research in Genetics

Genetic Fact Sheets for Parents

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: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
Acronym: HMG lyase deficiency

This fact sheet contains general information about HMG lyase deficiency. 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 HMG lyase deficiency?

HMG lyase deficiency is one type of **organic acid disorder**. People with this condition have problems breaking down an amino acid called leucine from the food they eat.

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.

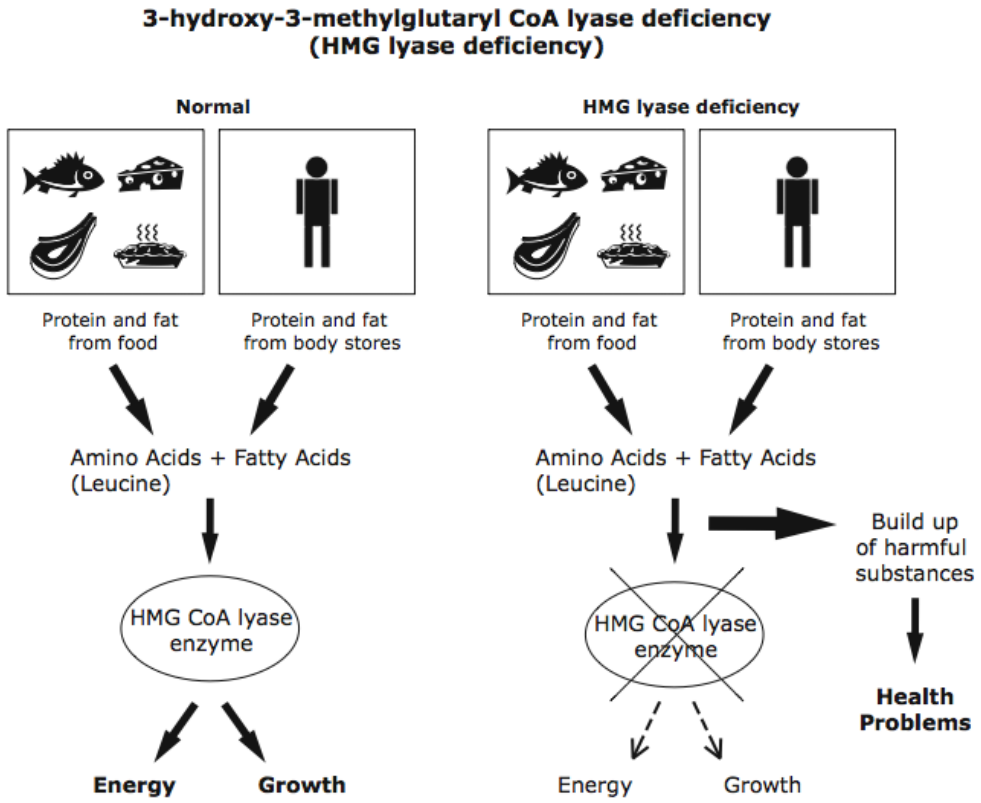
What causes HMG lyase deficiency?

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.

In order for the body to use fat for energy, enzymes break down fatty acids into ketone bodies. Normally, during long periods without eating, ketones are made by the body and used for fuel.

HMG lyase deficiency is caused by problems with the enzyme “HMG CoA lyase.” In people with HMG lyase deficiency, the HMG CoA lyase enzyme is either missing or not working properly. This enzyme has two jobs. The first is to help break down leucine. Leucine is found in all foods that contain protein. The second job is to help the body make ketone bodies from stored fat.

When children with this condition eat food containing leucine, harmful substances build up in the blood. In addition, children with HMG lyase deficiency can’t make ketone bodies from stored fat like most people. So, when they don’t eat for a long period of time, they can develop low blood sugar (hypoglycemia) and serious health problems.



If HMG lyase deficiency is not treated, what problems occur?

Each child with HMG lyase deficiency will have somewhat different effects. Babies with this condition are usually healthy at birth. Most babies start to have symptoms between 3 months and two years of age. A few babies, though, have had their first symptoms just a few days after birth.

HMG lyase deficiency causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite
- extreme sleepiness or lack of energy
- behavior changes
- irritable mood
- muscle weakness

Some or all of these symptoms may also occur:

- fever
- nausea
- diarrhea
- vomiting

- hypoglycemia
- increased levels of acidic substances in the blood, called metabolic acidosis
- high levels of ammonia in the blood
- enlarged liver

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

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

If not treated, many babies with HMG lyase deficiency die during their first metabolic crisis. In surviving babies, repeated episodes of metabolic crisis can cause brain damage. This can result in life-long learning problems or intellectual disabilities.

Episodes of metabolic crisis can be triggered by:

- illness or infection
- going without food for long periods of time
- eating large amounts of protein

When a child is ill or goes without food for too long, the body breaks down its own protein and fat to use for energy. In people with HMG lyase deficiency, this can trigger a metabolic crisis, as described above.

Between episodes of metabolic crisis, children with this condition are usually healthy.

Long-term effects can happen in some children. These may include:

- enlarged heart
- inflammation of the pancreas, called pancreatitis
- hearing loss
- vision loss
- learning problems or intellectual disabilities

Some people with HMG lyase deficiency never have symptoms and are only found to be affected after a brother or sister is diagnosed. A few individuals have been diagnosed after developing heart conditions in their teens and early twenties.

What is the treatment for HMG lyase deficiency?

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 metabolic crises and the health effects that follow. You need to start treatment as soon as you know your child has HMG lyase deficiency. Certain treatments may be advised for some children but not others. Treatment is usually needed throughout life.

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

1. Avoid going a long time without food

Infants and young children with HMG lyase deficiency need to eat frequently to prevent 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.

2. Low-leucine diet, including medical foods and formula

A food plan low in leucine with limited amounts of fat and protein is often recommended. Most foods in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein and fat can help prevent low blood sugar and metabolic crises.

Foods high in protein and fat that your child may need to avoid or limit:

- milk and dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter
- butter, margarine, oil, lard, and foods made with these fats

Many vegetables and fruits have only small amounts of protein and fat and can be eaten in carefully measured amounts. Do not remove all protein and fat from the diet. Your child needs a certain amount of each to grow properly.

Your dietician will create a food plan that contains the right amount of protein, fat, nutrients, and energy to keep your child healthy. Your child may need to be on a special food plan throughout life.

Medical foods and formula

There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods as part of your child's diet.

Some children are also given a special leucine-free medical formula. Your metabolic doctor and dietician will decide whether your child needs this formula. 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.

3. Medications

Some children may benefit 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. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor. Do not use any medication without checking with your doctor.

Children with symptoms of a metabolic crisis need medical treatment right away. They often need to be treated in the hospital. During a metabolic crisis, children may be given glucose, bicarbonate, and other medications by IV to treat hypoglycemia and other symptoms of a metabolic crisis. Ask your metabolic doctor if you should carry a special travel letter with medical instructions for your child's care.

4. Call your doctor at the start of any illness

In some children, even minor illnesses such as a cold or the flu can lead to a metabolic crisis. In order to prevent problems, call your doctor right away when your child has any of the following:

- loss of appetite
- vomiting
- diarrhea
- infection or illness
- fever

Children with HMG lyase deficiency need to eat more carbohydrates and drink more fluids when they are ill – even if they're not hungry – or they could have a metabolic crisis. Also, they need to avoid eating protein and fat during any illness.

Children who are ill often don't want to eat. If they can't eat, or if they show signs of a metabolic crisis, they may need to be treated in the hospital.

What happens when HMG lyase deficiency is treated?

With prompt and careful treatment, children with HMG lyase deficiency have a good chance to live healthy lives with typical growth and development.

Even with treatment, some children still have repeated bouts of hypoglycemia or metabolic crises. This can cause brain damage and may lead to life-long learning problems or intellectual disabilities.

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

Genes tell the body how to make enzymes. The HMGCL gene instructs the body to make the HMG-CoA lyase enzyme. Everyone has two copies of the HMGCL gene. People with HMG lyase deficiency have changes, also called variants, in both copies of their HMGCL genes. Because of the variants in the HMGCL genes, the HMG-CoA lyase enzyme either does not work properly or is not made at all.

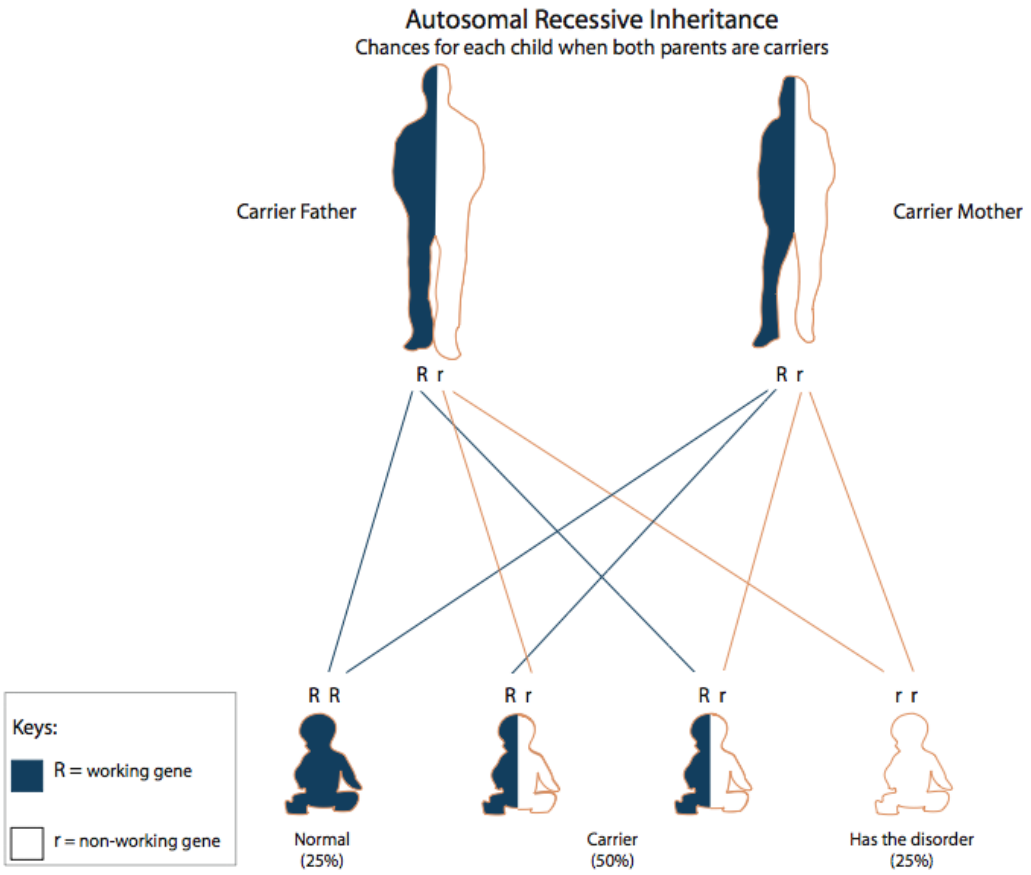
How is HMG lyase deficiency inherited?

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

Everyone has two copies of the HMGCL gene that make the HMG CoA lyase enzyme. In children with HMG lyase deficiency, neither of their HMGCL genes works correctly. These children inherit one non-working HMGCL gene for the condition from each parent.

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

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have HMG lyase 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 HMG lyase deficiency. 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 this condition is available. Genetic testing, also called DNA testing, looks for changes (variants) in the HMGCL genes that cause HMG lyase deficiency. Talk with your genetic counselor or metabolic doctor if you have questions about DNA testing.

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

What other testing is available?

Special tests on blood, urine, or skin samples can be done to help confirm if your child has HMG lyase deficiency. Talk to your metabolic doctor or genetic counselor if you have questions about testing for this condition.

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.

It may also be possible to do an enzyme test using cells from the fetus. The sample needed for this test is obtained by either CVS or amniocentesis. Testing has also been done in late pregnancy (after 23 weeks) using a urine sample from the mother.

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 HMG lyase 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 HMG lyase deficiency or be carriers?

Having HMG lyase deficiency

The brothers and sisters of a baby with HMG lyase deficiency 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 may prevent serious health problems. Talk to your metabolic doctor or genetic counselor about testing your other children.

HMG lyase deficiency carriers

Brothers and sisters who do not have HMG lyase 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 HMG lyase deficiency, 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 HMG lyase deficiency.

All states offer newborn screening for HMG lyase deficiency. However, when both parents are carriers for HMG lyase deficiency, 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 HMG lyase deficiency can be tested using blood, urine, or skin samples to see if they also have HMG lyase deficiency.

Carrier testing

If both gene changes (variants) have been found in the child with HMG lyase deficiency, other family members can have DNA testing to see if they are carriers.

If DNA testing is not possible or is not 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 HMG lyase deficiency?

This condition is very rare. The actual incidence is unknown.

Does HMG lyase deficiency happen more often in a certain ethnic group?

HMG lyase deficiency happens in all ethnic groups throughout the world. It happens more often in people from Saudi Arabia, Portugal, and Spain.

Does HMG lyase deficiency go by any other names?

This condition is sometimes also called:

- HMG-CoA lyase deficiency
- hydroxymethylglutaric aciduria
- HMGCL deficiency
- HL deficiency
- HMG
- 3-OH 3-CH3 glutaric aciduria
- 3-OH 3-methyl glutaric aciduria

Where can I find more information?

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

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

MedlinePlus
https://medlineplus.gov/genetics/condition/3-hydroxy-3-methylglutaryl-coa-lyase-deficiency/

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

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