

Lysosomal Acid Lipase Deficiency (LAL-D)

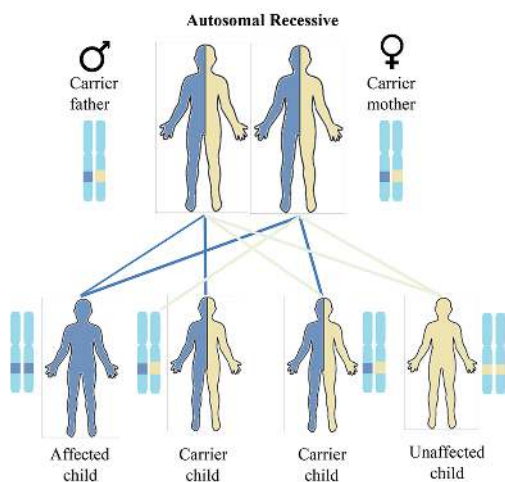


Your Liver. Your Life.

What is LAL-D?

Lysosomal acid lipase deficiency (LAL-D) is a rare, chronic, progressive inherited disorder. It affects the body's ability to produce an enzyme called lysosomal acid lipase (LAL). This enzyme is needed for the breakdown of fats (lipids) and cholesterol in your cells. When the LAL enzyme is missing or deficient, fats accumulate in organs and tissues throughout the body, primarily leading to liver disease and high "bad cholesterol," which is linked to cardiovascular disease.

How is LAL-D inherited?



LAL-D is an autosomal recessive inherited disorder, meaning that both parents must pass on a defective gene to the affected child. The disorder is usually passed on by two parents that are carriers – meaning their health is not affected – but both parents have one abnormal gene (recessive gene) and one normal gene (dominant gene) for the condition. When both parents are

carriers, there is a 25% chance of having an affected child with each pregnancy.

LAL-D is caused by abnormalities in the *LIPA* gene, which is responsible for the production of the enzyme LAL. Abnormalities in this gene result in little to no LAL enzyme activity.

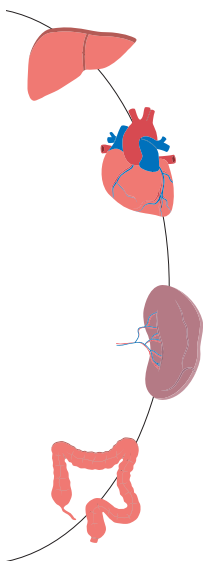
How does LAL-D affect the body?

The LAL enzyme plays a major role in breaking down certain lipids and cholesterol, including low density lipoproteins (LDL), the type of cholesterol referred to as “bad cholesterol.” When there is a decrease or loss of the LAL enzyme, lipids and cholesterol do not get processed; they build up in cells and organs throughout the body, including the spleen, liver, and blood vessel walls.

High levels of LDL, or bad cholesterol, are associated with cardiovascular complications, such as heart attack and stroke. Lipid accumulation in the liver can lead to fibrosis (first stage of liver scarring), cirrhosis (more advanced stage of scarring), and eventually liver failure.

What are the complications of LAL-D?

LAL-D can affect many systems throughout the body. Potential complications of LAL-D include damage to the:



Liver: Enlarged liver, fibrosis, cirrhosis, liver failure

Cardiovascular System: Low amounts of good cholesterol, high amounts of bad cholesterol, heart attack and stroke

Spleen: Enlarged spleen, low platelet count leading to bleeding problems

Gastrointestinal System: Pain, bleeding, diarrhea, poor absorption of nutrients leading to malnutrition and poor growth

Who gets LAL-D?

LAL-D is an ultra-rare disease, which is defined as a disease that affects fewer than 20 people per one million of the general population. It can affect individuals of any gender or ethnic background, with the incidence being higher for people of Persian-Jewish descent.

The disease affects individuals of all ages from infancy through adulthood; however, manifestations of the disease vary across the lifespan. Infants with LAL-D begin to show severe symptoms about one month of age that rapidly progress to life-threatening complications, with death typically occurring before six months of age. Historically, LAL-D in infants was called Wolman disease.

In children and adults, symptoms may appear early or the disease may go unrecognized because the individual feels well and has no symptoms. If initial signs and symptoms are mild, patients and healthcare providers may not suspect a progressive disease and the person may not be diagnosed until later in life. Historically, late onset LAL-D was known as cholesteryl ester storage disease (CESD). However, researchers now recognize that CESD and Wolman disease are simply different presentations along a continuum of just one disease – LAL-D.

What are the signs and symptoms of LAL-D?

Infants, children, and adults who suffer from LAL-D experience a wide range of symptoms.

Some of the more common signs and symptoms of LAL-D in infants include:

- Failure to grow
- Enlarged abdomen

- Persistent vomiting and diarrhea
- Jaundice (yellowing of the skin and whites of the eyes)

Children and adults may not experience symptoms. An enlarged liver may be detected on a routine physical exam. Adolescents may have an abnormal lipid profile on routine screening. The first sign in adults may be elevated liver enzymes seen on a blood test. As liver damage progresses, signs and symptoms may include:

- Easy bruising or bleeding
- Ascites (enlarged abdomen due to accumulation of fluid)
- Jaundice (yellowing of the skin and whites of the eyes)
- Liver fibrosis or cirrhosis
- Premature cardiovascular events, for example, heart attack and stroke



How is LAL-D diagnosed?

A diagnosis of LAL-D may sometimes be delayed by months or even years since many of the signs and symptoms associated with the disorder are similar to

those of other more common conditions, like nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Additionally, patients can look and feel healthy until the condition is advanced.

LAL-D is diagnosed by a blood test that measures the activity of the LAL enzyme. Other supportive tests that your healthcare provider may order include genetic testing and a liver biopsy. Biopsy results can help assess liver damage, but cannot be used to diagnose LAL-D, since similar liver damage can occur from other diseases.

How is LAL-D treated?

In December 2015, the U.S. Food and Drug Administration (FDA) approved an enzyme replacement protocol, the first therapy that treats the underlying cause of the disease. Previously, there were only supportive therapies available for LAL-D.

Supportive treatments used to manage LAL-D include the following:

- Low-fat diet
- Statins and other lipid-lowering agents
- Stem cell transplant
- Liver transplant

What resources are available?

Additional resources for information and support regarding LAL-D include:

- National Organization for Rare Disorders (NORD): Provides rare disease information, resources, and financial assistance. Call 1-800-999-6673 or visit www.rarediseases.org
- LAL Solace: An online patient community for people with LAL-D. Visit www.lalsolace.org
- American Liver Foundation's National Helpline: The National ALF Helpline is available to answer



questions about liver disease and liver wellness. This resource provides emotional support to patients at their point of crisis and information on local resources including where to find physicians in your area. To reach our Helpline, call 1-800-GO-LIVER or 1-800-465-4837.

Facts-at-a-Glance

- LAL-D is a rare, genetic disorder that affects the body's ability to produce lysosomal acid lipase (LAL), an enzyme needed for the breakdown of fats and cholesterol.
- Having little or no LAL enzyme results in fat accumulation in a number of organs leading to liver damage, an increased risk of heart attack and stroke, and other symptoms.
- LAL-D affects people of all ages from infancy through adulthood.
- The signs and symptoms of LAL-D vary considerably in both severity and presentation across the lifespan.
- There is considerable overlap in clinical presentation and laboratory findings between LAL-D and fatty liver disease (NAFLD/NASH).
- In children and adults, a diagnosis of LAL-D is often delayed since symptoms associated with the disorder are similar to those of other more common conditions, and patients can look and feel healthy until the condition is advanced.
- LAL-D can be diagnosed by a simple blood test that measures LAL enzyme activity.
- LAL-D can be treated with enzyme replacement therapy, given intravenously (IV), along with other supportive therapies.



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