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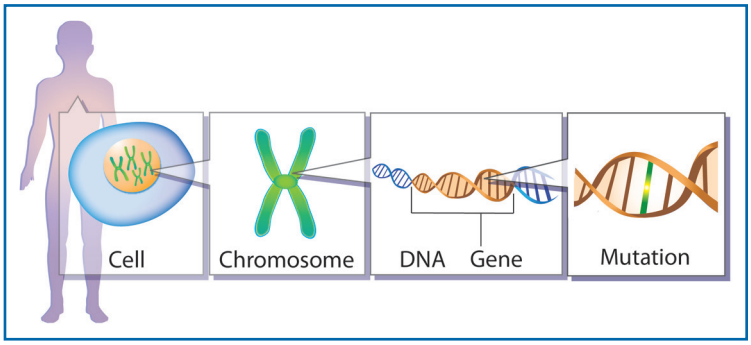
LRBA Deficiency

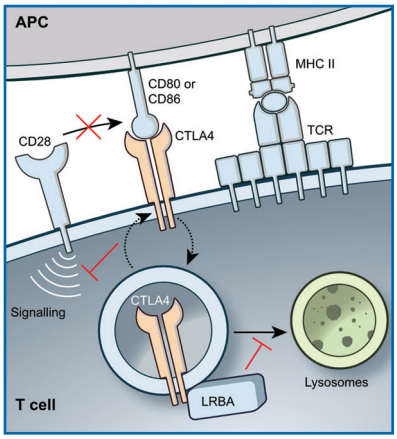
LRBA deficiency is a rare genetic disorder of the immune system caused by mutations in the *LRBA* gene. This disease impairs normal regulation of the immune system and results in excessive numbers of immune cells called lymphocytes (lymphoproliferation), autoimmunity, low levels of antibodies (hypogammaglobulinemia), and recurrent infections. Sometimes the excess lymphocytes enter and accumulate in organs where lymphocytes typically are not present in large numbers, which can cause a variety of symptoms. This infiltration is most common in the gut, lungs, and brain. *LRBA* deficiency also may increase a person's risk of lymphoma, a type of cancer. *LRBA* deficiency is sometimes called LATAIE disease (*LRBA* deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy). *LRBA* deficiency is diagnosed based on clinical symptoms, laboratory findings, and genetic testing.



Genetics primer: All the cells in the body contain instructions on how to do their job. These instructions are packaged into chromosomes, each of which contains many genes. Genes are units of inheritance that are made up of DNA and encode proteins. An error, or mutation, in a gene can cause disorders such as *LRBA* deficiency. Credit: NIAID

Genetics and Function

LRBA deficiency is caused by mutations in the *LRBA* gene, which stands for "lipopolysaccharide-responsive vesicle trafficking, beach- and anchor-containing." The *LRBA* gene provides instructions for production of the large LRBA protein. The LRBA protein participates in recycling specific cellular components, including a "brake" on the immune system called CTLA4. CTLA4 helps slow down or decrease the action of the immune system. A healthy immune system needs to be able to both ramp up and slow down, much like a car controlled by gas and brake pedals. In *LRBA* deficiency, this "brake" is recycled too quickly and does not have sufficient opportunity to keep the immune system's activity under control. *LRBA* defects affect multiple immune cell types and can lead to both autoimmunity and immunodeficiency.



Model depicting the function of CTLA4 and its regulation by LRBA. Credit: NIAID

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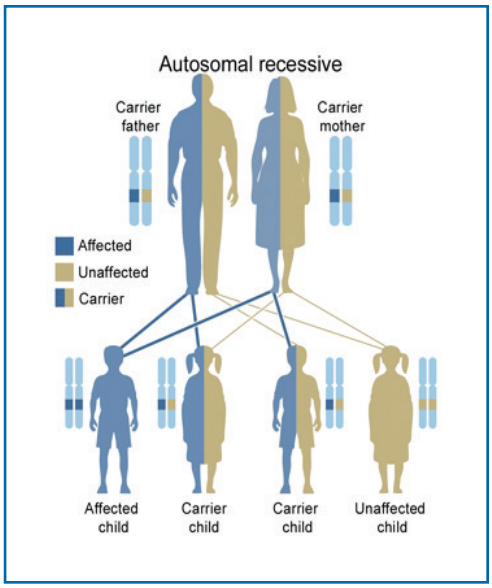
Inheritance

LRBA deficiency is inherited in an autosomal recessive manner. In autosomal recessive inheritance, two copies of an abnormal gene—one copy from each parent—must be present for the disease to develop. Typically, this means that both parents of an affected child carry one abnormal gene and are unaffected by the disease. This also explains why some cases of *LRBA* deficiency have involved homozygosity (identical mutations in the mother and father) related to consanguinity (when parents are related to each other) or geographically isolated communities.

When both parents have one abnormal copy of the *LRBA* gene, each child has a 25 percent, or one in four, chance of being affected by the disease. This risk is independent of prior children's status. For example, if the first two children in a family are affected, the next child has the same 25 percent risk of inheriting the mutation. All affected individuals have two abnormal copies of *LRBA*. Children who inherit only one abnormal copy of *LRBA* will not develop *LRBA* deficiency, although it is possible for them to have affected children, particularly if they marry within the family.

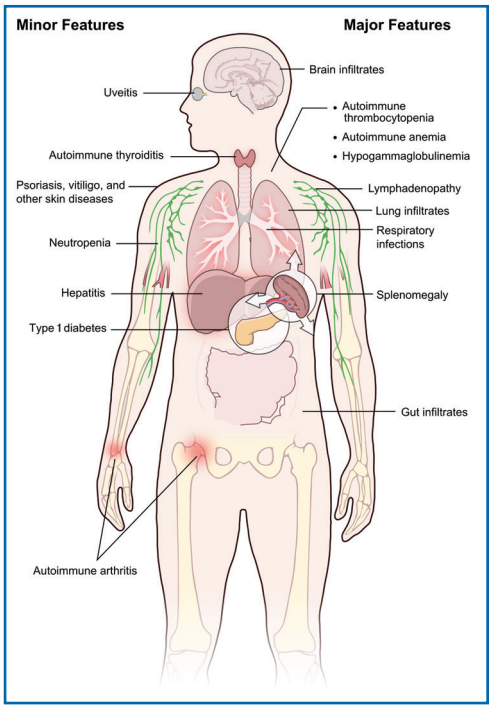


In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation. Credit: U.S. National Library of Medicine

Clinical Symptoms

LRBA deficiency is characterized by lymphocytic infiltration of non-lymphoid organs (such as the gut, lungs, and brain), autoimmunity, hypogammaglobulinemia, and lymphoproliferation. Lymphocytic infiltration of the gut, which causes intestinal disease (enteropathy), is by far the most common. The lymphoproliferation leads to enlargement of the lymph nodes (lymphadenopathy) and liver and spleen (hepatosplenomegaly). Patients with hypogammaglobulinemia are highly susceptible to infections, especially in the upper respiratory tract. Autoimmune problems can affect various organs and tissues, including:

- **Blood:** Blood problems may include thrombocytopenia and hemolytic anemia (see the Glossary). Thrombocytopenia causes poor blood clotting, and bleeding cannot be stopped following minor injuries. Anemia may cause a feeling of weakness or fatigue.
- **Thyroid:** Autoimmune thyroiditis is an inflammation of the thyroid, a small gland at the base of the neck.



Clinical features of *LRBA* deficiency. Credit: NIAID

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- **Skin:** The autoimmune skin disease psoriasis is characterized by red, itchy patches of skin. Alternatively, some people with *LRBA* deficiency have experienced autoimmunity against the pigment in their skin, called vitiligo.
- **Joints:** Autoimmune arthritis causes joint pain and stiffness.
- **Eyes:** Autoimmune uveitis is inflammation of the middle layer of the eye (called the uvea).
- **Pancreas:** Autoimmunity against parts of the pancreas can cause type 1 diabetes.

These symptoms are all related to the immune system not being able to slow down when necessary. Importantly, the symptoms and course of this disease vary widely. Some people are severely affected, whereas others show few symptoms of disease. This "variable expressivity" can be striking, even within the same family, and may be explained by differences in lifestyle, exposure to pathogens, effectiveness of treatment, or other genetic factors.

Laboratory Findings

The clinical symptoms of *LRBA* deficiency are caused by immune system abnormalities. Most people with *LRBA* deficiency develop reduced levels of immunoglobulins. People with *LRBA* deficiency also may have low LRBA protein expression in regulatory T cells, overactivation of effector T cells, low levels of a certain type of B cell called a switched memory B cell, and progressive loss of circulating B cells (see the Glossary for more information about these cell types).

Treatment

Once a diagnosis is made, treatment is based on a person's clinical condition and may include standard therapies for autoimmune problems and immunoglobulin deficiencies. Some patients have been treated with medications that inhibit the immune system pathway that is overactivated in people with the disease, medications that impact the recycling of cellular components, or medications that mimic the "CTLA4 brake" on the immune system. More research is needed to determine the most effective timing and dosage of these medications and to investigate other treatment options. In rare and severe cases, bone marrow transplantation also may be an option.

LRBA Deficiency and Your Family

Living with *LRBA* deficiency can be difficult not only for the person who has it but also for their family members. It is important for families to talk openly about *LRBA* deficiency and about how the family is dealing with it so misconceptions can be identified and corrected and children can learn to identify and cope with their reactions. Some people with *LRBA* deficiency have to work hard to develop their self-confidence and sense of security. Everyone needs to be reminded that they have many positive characteristics, especially when their appearance attracts attention (for example, due to large lymph nodes).

Some children who have siblings with *LRBA* deficiency worry about their brother or sister being in pain or dying from the disease. Some think that they may develop symptoms because they look or

act like a sibling who has the disease or that the disease is contagious. Some children struggle with how much time their parents spend with their sick sibling. Many families benefit from meeting or talking to other families affected by the same rare disease. Counseling also can help families cope with the challenges of *LRBA* deficiency.

At the same time, many families say that *LRBA* deficiency has brought them closer together. Through their experiences with the disease and its treatment, family members learn about controllable and uncontrollable aspects of life. Although certain aspects of the disease cannot be controlled, how a family responds to the stress of any illness is controllable and an important aspect of managing *LRBA* deficiency. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that *LRBA* deficiency presents helps children develop resilience.

Glossary

Arthritis—Painful inflammation and stiffness of the joints.

Autoimmune—Describes a process during which a person's immune system attacks healthy cells, organs, and tissues.

B cells—Immune cells that present antigens to T cells and produce antibodies, or immunoglobulins.

Cell—The basic unit of living organisms. Human cells consist of a nucleus (control center) and cellular organs, called organelles, enclosed by a membrane. Groups of cells with similar structure and function form tissues.

Chromosome—A thread-like structure made up of DNA that is tightly coiled around supporting proteins. Chromosomes reside in the control center, or nucleus, of a cell.

DNA (deoxyribonucleic acid)—A self-replicating material present in nearly all living organisms. It is the carrier of genetic information.

Effector T cell—A type of immune cell that performs the functions of an immune response such as cell killing and cell activation.

Enteropathy—Disease of the intestines.

Hemolytic anemia—A condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

Hypogammaglobulinemia—A type of immune deficiency that is characterized by a reduction in all types of gamma globulins, or infection-fighting antibodies.

Immune system—A system of biological structures and processes within the body that protects it against "foreign" threats such as bacteria or viruses.

Immunodeficiency—A state in which the immune system's ability to fight disease is compromised or entirely absent.

Immunoglobulin—Large Y-shaped proteins, also known as antibodies, produced by immune cells called B cells. The immune system uses immunoglobulins to identify and neutralize foreign objects such as bacteria. Each immunoglobulin is unique, but they fall under general subtypes. Examples of the subtypes include IgG, IgA, and IgM.

Lymphoma—A type of blood cancer that occurs when certain immune cells start dividing uncontrollably and no longer behave like normal immune cells.

Lymphoproliferation—The excessive production or buildup of immune cells called lymphocytes.

Mutation—A change in the DNA sequence that is associated with disease or susceptibility to disease.

Pathogen—A bacterium, virus, or other microorganism that can cause disease.

Psoriasis—A skin disease marked by red, itchy, scaly patches.

Regulatory T cell—A type of immune T cell that monitors and regulates the activity of other T cells.

Thrombocytopenia—An abnormally low number of platelets in the blood.

Thyroiditis—A condition in which the thyroid is inflamed, often due to being attacked by a person's own immune system. The thyroid is a small gland at the base on the neck, below the Adam's apple.

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