NIAID

ALPS

What Is ALPS?

Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare genetic disorder of the immune system. Most cases of ALPS are caused by mutations in a gene called *FAS*. The disorder can affect both children and adults, although most people with ALPS are diagnosed in childhood and experience a lessening of symptoms in adulthood. Breaking down the name, ALPS, helps explain the syndrome.

Autoimmune is the term that describes how the immune systems of people with ALPS attack their own blood cells and organs. The most common autoimmune problems in ALPS involve blood cells. They include:

- Anemia, which occurs when the body destroys its own red blood cells. Anemia can cause a feeling of weakness and fatigue.
- Thrombocytopenia, which occurs when the body attacks and destroys small blood components called platelets. When platelet levels are low, the blood does not clot well, and bleeding cannot be stopped following minor injuries. Symptoms of thrombocytopenia include nosebleeds, gum bleeds, bruises, and petechiae, or tiny spots that look like a rash and are caused by bleeding under the skin.
- Neutropenia, which occurs when the body destroys infection-fighting immune cells called neutrophils. A decrease in neutrophils increases the risk of infection, which can lead to mouth sores.
- Less often, other autoimmune problems develop, for example, in the skin, liver, kidneys, or eyes.

Lymphoproliferative refers to the buildup of unusually high numbers of immune cells known as lymphocytes in the lymph glands, liver, and spleen. This buildup can cause these organs to enlarge.

Syndrome refers to the collection of symptoms shared by people with ALPS.

Genetics

Most cases of ALPS are caused by mutations in the *FAS* gene. The *FAS* gene produces a receptor that, when activated, leads to programmed cell death, or apoptosis. This is an important part of the normal cell life cycle. When cells do not receive the message that it is time for them to die, an abnormal buildup of cells can result.

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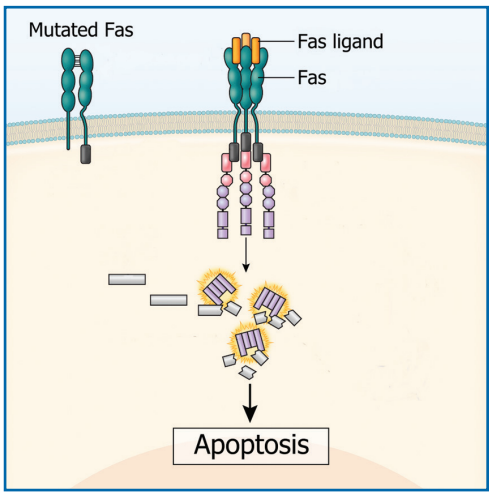
There are two types of *FAS* mutations:

- Germline mutations, which are present in all the body's cells
- Somatic, or acquired, mutations, which are present only in select groups of cells



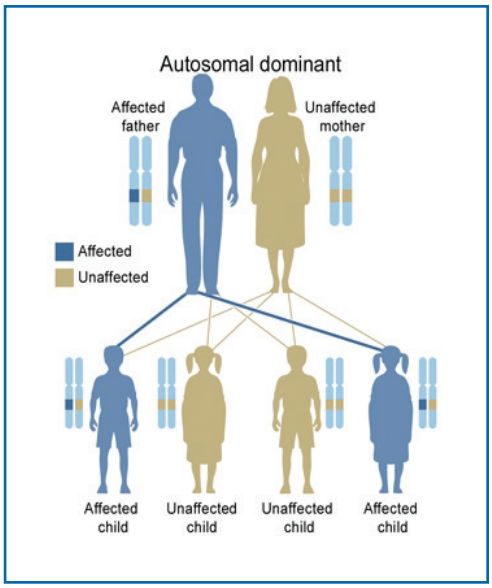
The Fas protein spans the cell membrane. When Fas interacts with an immune system protein called Fas ligand, it signals proteins within the cell to begin the pathway leading to apoptosis. Mutated Fas, found in some ALPS patients, cannot initiate this process. Credit: NIAID

Although germline mutations are more common than somatic mutations, people with germline and somatic *FAS* mutations generally have the same symptoms. Many different types of germline *FAS* mutations have been reported. These include missense, nonsense, insertion, deletion, and splice site mutations (see Glossary).

Less commonly, a person with ALPS may have a germline mutation in a gene other than *FAS*, such as *FASLG* or *CASP10*. Less information is available about ALPS due to *FASLG* or *CASP10* mutations because fewer families with these mutations have been identified. Approximately 25 percent of people with ALPS have no detectable mutation in any of these genes, suggesting that other undiscovered genes also are involved in ALPS.

Inheritance

ALPS due to *FAS* mutations is inherited in an autosomal dominant manner, which means that a person needs an abnormal gene from only one parent to have ALPS. The abnormal *FAS* gene dominates the normal *FAS* gene from the other parent. This usually means that a parent or relative from the side of the family with the mutation also has ALPS. Importantly, however, not everyone with an abnormal *FAS* gene develops ALPS. In fact, up to 40 percent of people with a *FAS* mutation show no symptoms of ALPS. This is called incomplete penetrance. Among those with symptoms of ALPS, some are severely affected by their disorder, while others are not. These variations, called variable expressivity, can be striking, even within the same family.



In this example, a man with an autosomal dominant disorder has two affected children and two unaffected children. Women also can pass on the mutation. Credit: U.S. National Library of Medicine

In a family with a parent who has a *FAS* mutation, each child has a 50 percent chance of inheriting the mutated *FAS* gene. The chance of one child inheriting the mutation is independent of whether his or her siblings have the mutation. In other words, if the first three children in a family have the mutation, the fourth child still has a 50 percent chance of inheriting it. Children who do not inherit the abnormal gene will not develop ALPS or pass on the mutation.

Some germline mutations are not inherited but occur as a result of a mutation in the egg or sperm of one of the parents or in the fertilized egg itself. These are called *de novo* mutations. Approximately 10 percent of people with ALPS-FAS have *de novo* mutations. *De novo* mutations can be passed on to children.

Somatic *FAS* mutations are not inherited and cannot be passed on because the mutation is only present in the blood and not in a woman's ovaries or a man's testes.

Symptoms and Management

The major clinical symptoms of ALPS result from lymphoproliferation and autoimmune destruction of blood cells. Many, but not all, people with ALPS experience a lessening or complete resolution of their autoimmune and lymphoproliferative symptoms in adulthood.

Lymphoproliferation

The main lymphoproliferative symptoms are enlarged lymph nodes and spleen. Although the spleen can be massive in some children, the NIH team is aware of only one case of splenic rupture. The swollen lymph nodes in the neck, armpit, and groin are usually most noticeable. Sometimes, these enlarged lymph nodes are confused with cancer of the lymph gland, or lymphoma. Large, visible lymph nodes are normal for many people with ALPS. It is also normal for lymph nodes to change somewhat in size, shape, or feel over time. Such changes usually are not a lymphoma.

Autoimmunity

The main autoimmune issues are related to reactions against components of the blood. Common blood problems in ALPS include anemia, thrombocytopenia, and neutropenia.

In an attempt to control these autoimmune problems, doctors may prescribe immune-suppressing medications such as the corticosteroid prednisone. Low blood counts can recur after a short course of treatment with prednisone, however, requiring repeated doses of corticosteroids or the use of different types of immune-suppressing medications. Chronic low blood counts often can be managed successfully with steroid-sparing approaches, including medications such as mycophenolate mofetil or sirolimus.

Spleen removal, or splenectomy, may be necessary in rare cases of difficult-to-control cytopenias. Unfortunately, many people still struggle with low blood counts after splenectomy. Furthermore, lack of a spleen increases the risk of sepsis, a potentially fatal response to severe infection with common bacteria called pneumococcus.

ALPS-related autoimmunity sometimes targets other organs, leading to conditions such as:

- Hepatitis (inflammation of the liver)
- Glomerulonephritis (inflammation of the kidneys)
- Uveitis (inflammation of the iris in the eye)

In most cases, these rare autoimmune complications can be treated effectively with immune-suppressing medications.

Lymphoma

People with ALPS have an increased risk of developing lymphoma. Up to age 40, people with ALPS have an approximately 20 percent risk of developing lymphoma. In other words, about 1 in 5 patients will develop ALPS lymphoma by the time they are 40. The risk continues past age 40, although the data on older age groups are limited. Thus, doctors should monitor patients with ALPS for symptoms of lymphoma, such as night sweats, fever, fatigue, weight loss, loss of appetite, and sudden lymph node enlargement in one area. Although the lymphoma risk for people with ALPS is much higher than that of the general population, most people with ALPS never develop lymphoma.

Laboratory Findings

Laboratory findings can aid ALPS diagnosis. One prominent finding is an elevated level of CD4- and CD8-negative T lymphocytes, called double-negative T cells. Additionally, an increase in serum vitamin B12 can indicate lymphoproliferation in ALPS-FAS. People with ALPS-FAS tend to have B12 levels much higher than those of healthy people.

Doctors may perform additional blood tests to help diagnose ALPS. Other markers that may be elevated in ALPS include immunoglobulin subtypes IgG, IgA, IgM; absolute monocyte count; absolute eosinophil count; anticardiolipin antibody; and antinuclear antibody. See the Glossary for definitions of these markers. In contrast, people with ALPS often have abnormally low levels of HDL (high density lipoprotein) and total cholesterol.

ALPS and Your Family

Living with ALPS can be difficult not only for the person who has it, but for their family members as well. It is important for families to talk openly about ALPS 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 children with ALPS have to work hard to develop their self-confidence and sense of security. Children need 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 ALPS 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 can also help families cope with the challenges of ALPS.

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

Related Disorders

While researching ALPS, scientists have discovered several conditions with overlapping features.

CHAI disease

CTLA4 Haploinsufficiency with Autoimmune Infiltration (CHAI) disease can affect immune responses, leading to accumulation of immune cells in the brain, lungs, and gut and reduced levels of antibodies in the blood (known as hypogammaglobulinemia).

RALD

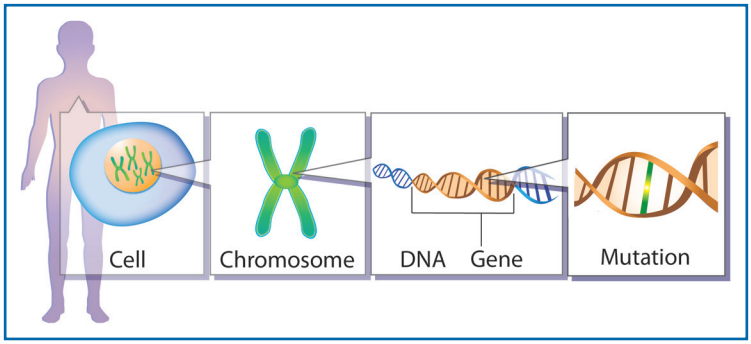
RAS-associated Autoimmune Leukoproliferative Disorder (RALD) is caused by somatic, or acquired, mutations in the *NRAS* or *KRAS* genes. This causes accumulation of cells in the spleen and lymph nodes, increased levels of immune cells called monocytes and lymphocytes, and autoimmunity. Distinguishing RALD from juvenile myelomonocytic leukemia, a rare childhood cancer, can be difficult.

PASLI disease

PASLI disease (PI3K Activating Mutation Causing Senescent T Cells, Lymphadenopathy, and Immunodeficiency) is named after the mutated gene and its symptoms. This disorder causes lymphadenopathy—swelling of the lymph nodes—and recurrent infections starting in childhood. These include bacterial infections of the respiratory system and chronic infections with Epstein-Barr virus (EBV). People with PASLI disease have an increased risk of developing EBV-associated lymphoma.

ALPS Research

Researchers at NIAID focus on gaining a better understanding of the clinical and genetic characteristics of people with ALPS and related disorders. By identifying the genes responsible for symptoms in these people, NIAID researchers not only help affected families, but also increase understanding of how the immune system works. Whole genome sequencing is one of the tools investigators are using to address these research questions. Ultimately, they hope to develop safe and effective treatments targeting the genetic defects in children with ALPS and related disorders.



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, which are made up of DNA. Errors, or mutations, in the genes can cause diseases such as ALPS. Credit: NIAID

Glossary

The glossary that follows provides ALPS-related terms and their definitions.

Absolute eosinophil count—A blood test that measures the number of white blood cells called eosinophils. Certain allergic diseases, infections, and other conditions cause eosinophils to become active.

Absolute monocyte count—A blood test that measures the number of white blood cells called monocytes. High monocyte levels can be a sign of abnormal immune responses, chronic inflammatory disease, infection, or blood cancer.

Anticardiolipin antibody—An antibody found in some autoimmune conditions, including ALPS, which is directed against the lipid (fat) cardiolipin.

Antinuclear antibody—An antibody found in some autoimmune conditions, including ALPS, which is directed against contents of the cell nucleus.

Apoptosis—The process of programmed cell death. Apoptosis is a normal part of the cell life cycle.

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

Autosomal dominant—A pattern of inheritance in which an affected person has one mutated copy of a gene and one normal copy.

Cytopenia—A general term for a reduction in the number of blood cells.

***De novo* mutations**—A gene mutation that occurs in the egg or sperm of one of the parents or in the fertilized egg itself.

Deletion mutation—A type of mutation in which part of the DNA sequence is missing. This results in a loss of genetic material.

Double-negative T cells—A type of immune cell that expresses neither CD4 nor CD8 on its surface. CD4 and CD8 are two of many markers used to characterize cells. The presence of double-negative T cells is a hallmark of ALPS.

Genotype—A term that refers to a person's genetic makeup, usually in reference to a specific characteristic.

Germline—Part of a person's genetic makeup that is present in every cell of the body and can be transmitted to offspring.

Hypogammaglobulinemia—A type of immune deficiency that is characterized by a reduction in all types of gammaglobulins, 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.

Immunoglobulins—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.

Incomplete penetrance—Penetrance refers to the degree to which a particular variant of a gene is expressed in a population. Incomplete penetrance means that not everyone who carries the variant expresses the trait.

Inheritance—The passing of genetic traits to offspring.

Insertion mutation—A type of mutation in which one or more nucleotide base pairs is added into the DNA sequence. This results in a gain of genetic material.

Lymph node—An oval-shaped organ of the lymphatic system, distributed throughout the body. Large nodes are located in the neck, armpit, and groin. These nodes are linked by lymphatic vessels, and the lymph system collects and transports lymph fluid around the body.

Lymphocytes—A class of white blood cells that are part of the immune system.

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

Lymphoproliferative—Refers to diseases in which lymphocytes are produced in excessive quantities or do not properly undergo programmed cell death.

Missense mutation—A type of mutation in which a single nucleotide change results in a change in an amino acid. Amino acids are the building blocks of proteins.

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

Neutrophils—A type of white blood cell that defends against infection.

Nonsense mutation—A mutation that results in a premature "stop" signal for the manufacture of a protein from DNA.

Phenotype—A person's observable characteristics.

Platelet—A small, disk-shaped cell fragment that helps blood clot.

Polymorphism—A relatively common variation in a particular area of a gene that may or may not be associated with disease.

Receptor—A protein found on the surface of a cell that receives chemical messages from outside the cell.

Sepsis—A potentially fatal whole-body inflammation caused by severe infection.

Serum vitamin B12—A vitamin level that can be tested in a person's blood.

Somatic mutation—A mutation acquired after conception and present in select groups of cells. Somatic mutations cannot be passed to offspring.

Spleen—A fist-sized organ that sits above the stomach and is part of the lymphatic system.

Splenectomy—Surgical removal of the spleen.

Splenic rupture—A medical emergency in which the outermost layer of the spleen ruptures, spilling blood into the abdomen.

Splice site mutation—A mutation that changes or removes the specific sequence that marks the site at which the joining, or splicing, of different gene segments will occur. Such mutations result in one or more segments of a gene being left out of the final gene product.

Variable expressivity—A term used in genetics to refer to variations in phenotype among people carrying a particular genotype, or genetic characteristic.

Whole genome sequencing—The analysis of one's entire genome, or all genetic material. This includes about 20,000 genes and numerous unknown regions between genes.

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