

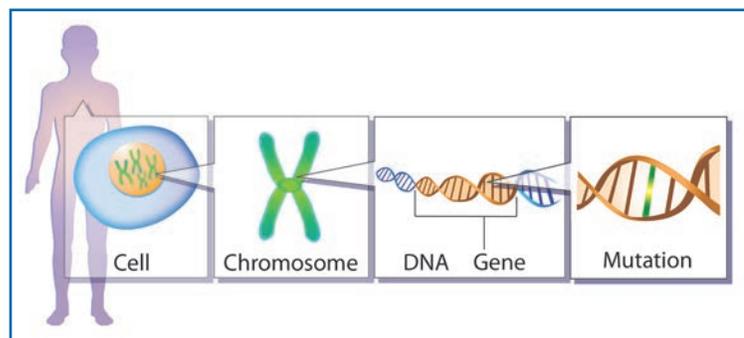
Activated PI3K Syndrome: *PIK3R1* Disease

PIK3R1 disease is a rare genetic disease of the immune system that was first described in 2013. The disease goes by several names, including activated PI3K syndrome. It is sometimes called PASLI, which stands for PI3K-activating mutation causing senescent T cells, lymphadenopathy, and immu-nodeficiency, or APDS2, which stands for activated PI3K delta syndrome 2. It also is referred to by the affected protein, p85a.

People with *PIK3R1* disease have a weakened immune system, which puts them at risk for frequent infections starting in childhood and continuing through adulthood. These include recurrent infections of the upper respiratory tract and lungs. *PIK3R1* disease also is characterized by autoimmunity and chronic lymphoproliferation (buildup of unusually high numbers of immune cells). The lymphoproliferation can cause swelling of the lymph nodes and spleen and upper respiratory tract lymphoid hyperplasia (proliferation of cells that make up lymphoid tissue). Some people also have smaller stature and experience mild developmental delay. Most people with this disease receive immunoglobulin replacement therapy because they have low levels of immunoglobulin-producing B cells. People with *PIK3R1* disease also have an increased risk of lymphoma, a type of cancer.

Genetics

PIK3R1 disease is caused by mutations in the *PIK3R1* gene, specifically mutations that affect a region called exon 11. The *PIK3R1* gene produces a protein called p85a. *PIK3R1* mutations affecting exon 11 cause the p85a protein to be shortened, which leads to overactivation of the important PI3K delta signaling pathway in immune cells. This leads to disruptions in the normal development of immune T cells, causing too many naïve T cells to become effector cells. These effector cells undergo a burst of proliferation and then become senescent, which means they stop growing and dividing. This skew toward senescence results in lowered production of B memory cells, increasing a person's susceptibility to infection (see the Glossary for more information about these cell types). Mutations in related genes, like *PIK3CD*, cause similar versions of this disease.



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 *PIK3R1* disease. Credit: NIAID

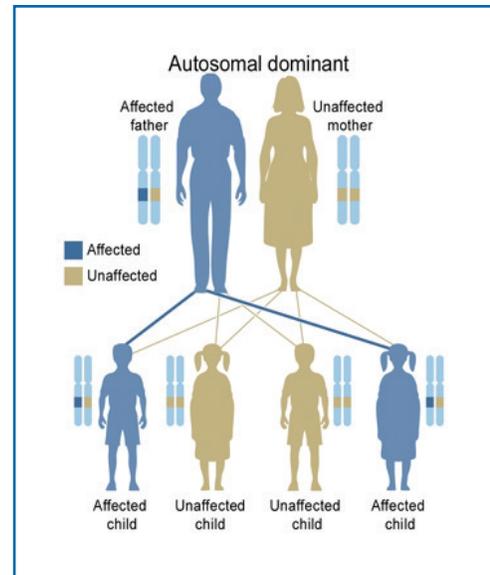


Inheritance

PIK3R1 disease is inherited in an autosomal dominant manner, which means that a person needs an abnormal gene from only one parent to have the disease. The abnormal *PIK3R1* gene dominates the normal *PIK3R1* gene from the other parent. Dominant inheritance also means that most families with *PIK3R1* disease have affected relatives in each generation on the side of the family with the mutation. Importantly, however, not all people with the mutation have severe disease.

Unlike mutations that run in a family, some *PIK3R1* mutations 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*, which means “new,” mutations. In these cases, the patient does not have a family history of similar symptoms. *De novo* mutations can be passed on to children.

Children of a parent who carries a *PIK3R1* mutation have a 50 percent chance of inheriting the mutation. This means that, within a given family, each child’s risk of inheriting the mutated gene is independent of whether or not siblings have the mutation. For example, if the first three children in a family have the mutation, the fourth child has the same 50 percent risk of inheriting the mutation. Children who do not inherit the abnormal gene will not develop *PIK3R1* disease or pass on the mutation.



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

Clinical Symptoms

PIK3R1 disease ranges in severity and can cause many symptoms. Most of these symptoms can be treated successfully. People with *PIK3R1* disease may experience the following:

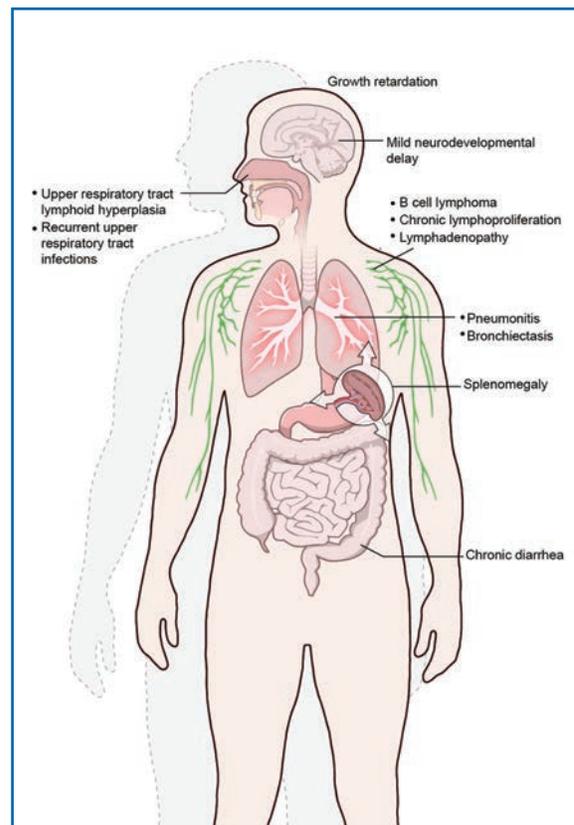
- Recurrent infections, particularly of the respiratory tract, which can lead to airway damage (e.g., pneumonitis, bronchiectasis).
- Lymphoproliferation, or the buildup of immune cells called lymphocytes, which leads to enlarged lymph nodes (lymphadenopathy) and an enlarged spleen (splenomegaly).
- Chronic viremia, or high levels of viruses such as Epstein-Barr virus (EBV) and cytomegalovirus in the blood.
- Lymphoid hyperplasia, or development of distinctive lymphoid nodules—small collections of lymph tissue—on mucosal surfaces such as the airways or gastrointestinal tract.
- Cytopenias, or reductions in the number of blood cells. Autoimmune cytopenias occur when the immune system attacks and destroys the body’s blood cells. Cytopenias can cause fatigue, increased risk of bleeding, and slow wound healing.

- EBV-driven lymphoma, a type of cancer associated with EBV infection.
- Small stature or growth retardation.
- Developmental delays (when a child does not meet his or her developmental milestones at expected times).

Importantly, the severity of *PIK3R1* disease varies. Some people with *PIK3R1* disease have many medical problems while others experience minimal symptoms. This variation in disease severity, called variable expressivity, can be striking, even within the same family. Symptoms also may change over time. This variation may be explained by differences in lifestyle, exposures, treatments, or other genes.

Laboratory Findings

The clinical symptoms of *PIK3R1* disease are caused by immune system abnormalities. These include too few of some immune cell types and too many of other types. For example, people with *PIK3R1* disease typically have too few of a type of memory cells and too many transitional B cells, effector T cells, and senescent T cells (see the Glossary for more information about these cell types). Many patients also have differences in their immunoglobulin, or antibody, concentrations. For example, most people with *PIK3R1* disease have slightly elevated levels of the IgM subtype and reduced levels of IgA and IgG.



Clinical features of *PIK3R1* disease. Credit: NIAID

Treatment

Once a diagnosis is made, treatment for *PIK3R1* disease is based on a person's clinical condition. Some symptoms can be managed with immunoglobulin replacement and preventive use of antibiotics. Some patients have been treated with a medication that targets and reduces B cells to minimize lymphoproliferation or autoimmune cytopenias. Researchers have had some success treating *PIK3R1* disease with medications that inhibit the immune system pathway that is overactivated in people with the disease. In early studies, this strategy reduced swelling of the lymph nodes (lymphadenopathy). More research is needed to determine the most effective timing and dosage of this medication and to investigate other treatment options. In rare and severe cases, bone marrow transplantation may be an option.

PIK3R1 Disease and Your Family

Living with *PIK3R1* disease 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 the disease 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 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, because of enlarged lymph nodes in the neck).

Some children who have siblings with this disease worry about their brother or sister being in pain or dying. 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 or similar diseases. Counseling also can help families cope with the challenges of a chronic illness.

At the same time, many families say that *PIK3R1* disease has brought them closer together. Through this disease, 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 *PIK3R1* disease. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that this chronic illness presents helps children develop resilience.

Glossary

Antigen—Any substance that causes the immune system to produce antibodies against it. An antigen may be a foreign substance from the environment. Examples of antigens include chemicals, bacteria, viruses, or pollen.

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.

Bronchiectasis—A chronic condition in which the walls of the bronchi are thickened due to inflammation and infection. People with bronchiectasis have periodic flareups of breathing difficulties, called exacerbations.

Cancer-causing virus—Any virus that can cause cancer, such as Epstein-Barr virus or human papillomavirus. Also known as "oncovirus."

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.

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

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

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 system cell that performs the functions of an immune response such as cell killing and cell activation. There are several different subtypes, each with a specific role.

Gene—A unit of heredity that is transferred from parent to child. Genes are made up of DNA.

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 falls under a general subtype. Examples of the subtypes include IgG, IgA, and IgM.

Inheritance—The passing of genetic traits to offspring.

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.

Lymphadenopathy—A condition in which lymph nodes are abnormal in size, number, or consistency. The term is often used to refer to enlarged or swollen lymph nodes.

Lymphoid hyperplasia—Proliferation of cells that make up lymphoid tissue.

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.

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

Memory cells—These cells create immunological "memory." They are very sensitive to antigens they have seen before and respond rapidly to re-exposure.

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

Naïve T cells—Immune system cells that have never encountered their specific antigen and thus have not responded to it. This is in contrast to other types of T cells, such as effector or memory T cells, which are primed to a specific antigen.

Pneumonitis—A general term that refers to inflammation of lung tissue.

Respiratory system—A biological system consisting of the lungs and structures, such as the trachea, used for the process of respiration or breathing.

Senescent—Growing old. A senescent cell is one that has stopped growing and dividing.

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

Transitional B cells—The link between immature B cells developing in the bone marrow and the mature types of B cells circulating in the blood.

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

Viremia—The presence of viruses in the blood.

