

PIK3CD Disorder

Introduction

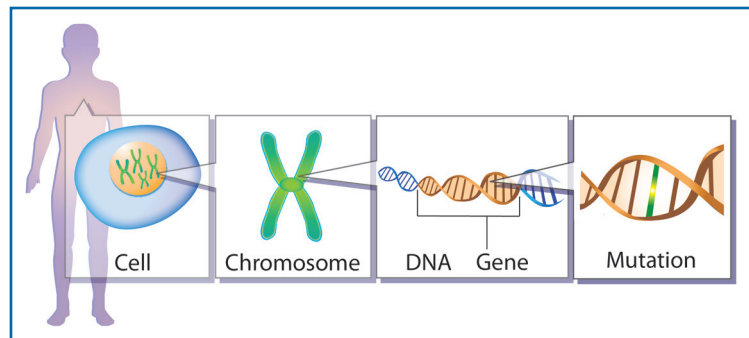
PIK3CD gain-of-function disorder is a rare genetic disorder of the immune system. The disease is named after the genetic mutations that cause it. Sometimes, *PIK3CD* gain-of-function is abbreviated *PIK3CD* GOF or simply referred to as *PIK3CD*. This disorder also is sometimes called PASLI, which stands for p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency, or APS, which stands for activated PI3K syndrome.

People with this disorder have a weakened immune system, which puts them at risk for frequent infections starting in childhood. These include bacterial infections of the respiratory system and chronic viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV). People with *PIK3CD* disorder also have an increased risk of lymphoma, a type of cancer.

Genetics

PIK3CD disorder is caused by “gain-of-function” mutations in the gene *PIK3CD*. This gene produces a protein called p110 delta. These gain-of-function mutations cause the p110 delta protein to become overactive. *PIK3CD* is turned on mainly in white blood cells and plays an important role in the immune system. Mutations in *PIK3CD* appear to affect the immune system by overactivating an important immune system signaling pathway.

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 results in lowered production of memory cells, increasing a person’s susceptibility to infection (see the Glossary for more information about these cell types). Less frequently, mutations in other related genes cause similar versions of this disorder.



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 *PIK3CD* disorder. Credit: NIAID

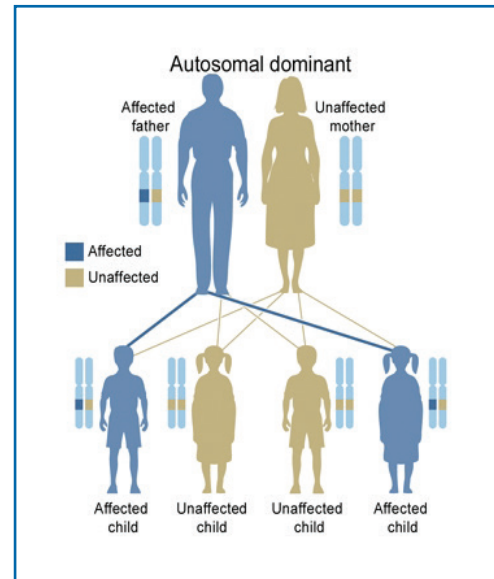


Inheritance

PIK3CD disorder is inherited in an autosomal dominant manner, which means that a person needs an abnormal gene from only one parent to have *PIK3CD* disorder. The abnormal *PIK3CD* gene dominates the normal *PIK3CD* gene from the other parent. Dominant inheritance also means that most families with *PIK3CD* disorder 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 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 *PIK3CD* 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 *PIK3CD* 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 *PIK3CD* disorder 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

PIK3CD disorder ranges in severity and can cause many different symptoms. Most of these symptoms can be successfully treated. *PIK3CD* disorder is characterized by recurrent respiratory infections, which can lead to progressive airway damage. People with *PIK3CD* disorder also may experience the following:

- Lymphoproliferation, or the buildup of immune cells called lymphocytes. This leads to enlarged lymph nodes and an enlarged spleen.
- Chronic viremia, or high levels of viruses such as EBV and CMV in the blood.
- 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 B-cell lymphoma, a type of cancer associated with EBV infection.

Importantly, the severity of *PIK3CD* disorder varies. Some people with *PIK3CD* disorder have many medical problems, whereas others experience minimal symptoms. Some adults with the mutation may outgrow the symptoms that caused them problems as a child. This variation, called variable expressivity, can be striking, even within the same family. It may be explained by differences in lifestyle, exposures, treatments, or other genes.

Laboratory Findings

The clinical symptoms of *PIK3CD* disorder 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 *PIK3CD* disorder typically have too few of a type of memory cells and too many transitional B cells, effector T cells, and old 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 have slightly elevated levels of the IgM subtype and reduced IgA.

Treatment

Once a diagnosis is made, treatment for *PIK3CD* disorder is based on a person's clinical condition. Researchers have had some success treating *PIK3CD* disorder 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), most likely by restoring the normal balance of naïve, effector, and memory cells in the patients' immune systems. More research is needed to determine the most effective timing and dosage of this medication and to investigate other treatment options.

PIK3CD Disorder and Your Family

Living with *PIK3CD* disorder 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 *PIK3CD* disorder 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 *PIK3CD* disorder 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 *PIK3CD* disorder 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 *PIK3CD* disorder.

At the same time, many families say that *PIK3CD* disorder has brought them closer together. Through this disease, 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 *PIK3CD* disorder. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that *PIK3CD* disorder 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.

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.

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.

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.



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