Activated PI3K-delta syndrome

Description

Activated PI3K-delta syndrome (also known as APDS) is a disorder that impairs the immune system. Individuals with this condition often have low numbers of white blood cells (lymphopenia), particularly B cells and T cells. Normally, these cells recognize and attack foreign invaders, such as viruses and bacteria, to prevent infection. The severity of activated PI3K-delta syndrome varies widely. Some people may have multiple, severe infections while others show mild symptoms to none at all.

Most commonly, people with activated PI3K-delta syndrome develop recurrent infections that begin in childhood, particularly in the lungs, sinuses, and ears. Over time, recurrent respiratory tract infections can lead to a condition called bronchiectasis, which damages the passages leading from the windpipe to the lungs (bronchi) and can cause breathing problems. People with activated PI3K-delta syndrome may also have chronic active viral infections, such as Epstein-Barr virus, herpes simplex virus, or cytomegalovirus infections.

Another possible feature of activated PI3K-delta syndrome is abnormal clumping of white blood cells. These clumps can lead to enlarged lymph nodes (lymphadenopathy) or an enlarged spleen (splenomegaly). The white blood cells can also build up to form solid masses (nodular lymphoid hyperplasia), usually in the moist lining of the airways or intestines. While nodular lymphoid hyperplasia is not cancerous (benign), activated PI3K-delta syndrome increases the risk of developing forms of blood cancer called Hodgkin lymphoma and non-Hodgkin lymphoma.

Some people with activated PI3K-delta syndrome develop autoimmunity, which occurs when the body attacks its own tissues and organs by mistake.

There are two types of activated PI3K-delta syndrome, each with different genetic causes.

Frequency

Activated PI3K-delta syndrome is considered a rare disorder, but its exact prevalence is unknown.

Causes

Activated PI3K-delta syndrome is caused by variants (also called mutations) in the *PIK3CD* gene and the *PIK3R1* gene. Activated PI3K-delta syndrome type 1 is caused by variants in the *PIK3CD* gene, which provides instructions for making a protein called p110 delta (p110δ). Activated PI3K-delta syndrome type 2 is caused by variants in the *PIK3R1* gene. This gene provides instructions for making slightly different versions of another protein; the most common version is called p85 alpha (p85α).

Both p110δ and p85α are pieces (subunits) of an enzyme called phosphatidylinositol 3-kinase (PI3K), which turns on signaling pathways within cells. The version of PI3K that contains the p110δ and p85α subunits is called PI3K delta. PI3K delta is found in white blood cells, including B cells and T cells. PI3K-delta signaling is involved in the growth and division (proliferation) of white blood cells, and it helps direct B cells and T cells to mature (differentiate) into different types, each of which has a distinct function in the immune system.

The *PIK3CD* gene variants that cause activated PI3K-delta syndrome lead to the production of an altered p110δ protein. *PIK3R1* gene variants lead to an altered p85α protein, sometimes causing it to be abnormally short. These variants are classified as gain-of-function variants because a PI3K-delta enzyme that contains either of the altered subunits is frequently turned on (overactive).

Studies indicate that overactive PI3K-delta signaling alters the differentiation of B cells and T cells, producing cells that cannot respond to infections and that die earlier than usual. The lack of functioning B cells and T cells makes it difficult for people with activated PI3K-delta syndrometo fight off bacterial and viral infections. Overactive PI3K-delta signaling can also stimulate the abnormal proliferation of white blood cells, leading to lymphadenopathy and nodular lymphoid hyperplasia in some affected individuals. An increase in B cell proliferation in combination with reduced immune system function may contribute to the development of lymphoma in people with activated PI3K-delta syndrome.

Learn more about the genes associated with Activated PI3K-delta syndrome

- PIK3CD
- PIK3R1

Inheritance

Activated PI3K-delta syndrome is inherited in an autosomal dominant pattern, which

means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition

- APDS
- Immunodeficiency 14
- Immunodeficiency 36
- P110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency
- PASLI

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Immunodeficiency 14 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3714976/)
- Genetic Testing Registry: Immunodeficiency 36 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4014934/)

Genetic and Rare Diseases Information Center

- Activated PI3K-delta syndrome (https://rarediseases.info.nih.gov/diseases/11983/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Activated PI3K-delta syndrome%22)

Catalog of Genes and Diseases from OMIM

- IMMUNODEFICIENCY 36 WITH LYMPHOPROLIFERATION; IMD36 (https://omim.org/entry/616005)
- IMMUNODEFICIENCY 14A WITH LYMPHOPROLIFERATION, AUTOSOMAL DOMINANT; IMD14A (https://omim.org/entry/615513)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(activated+pi3k-delta+syndrome%5BTIAB%5D)+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+6000+days%22%5Bdp%5D)

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