PIK3R1 gene

phosphoinositide-3-kinase regulatory subunit 1

Normal Function

The *PIK3R1* gene provides instructions for making a part (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The primary function of the subunit is to regulate the enzyme's activity. Several slightly different versions of this regulatory subunit are produced from the *PIK3R1* gene; the most abundant of these is called p85 alpha (p85α).

PI3K is a kinase, which means that it adds a cluster of oxygen and phosphorus atoms (a phosphate group) to other proteins through a process called phosphorylation. PI3K phosphorylates certain signaling molecules, which triggers a series of additional reactions that transmit chemical signals within cells. PI3K signaling is important for many cell activities, including cell growth and division (proliferation), movement (migration) of cells, production of new proteins, transport of materials within cells, and cell survival.

Studies suggest that PI3K signaling may be involved in how cells regulate several hormones. One of these hormones is insulin, which helps control levels of blood glucose, also called blood sugar. PI3K signaling may also play a role in the maturation of fat cells (adipocytes).

Health Conditions Related to Genetic Changes

Activated PI3K-delta syndrome

Variants (also called mutations) in the *PIK3R1* gene have been found to cause an immune disorder called activated PI3K-delta syndrome. *PIK3R1* gene variants cause a form of the condition called activated PI3K-delta syndrome type 2. People with activated PI3K-delta syndrome type 2 typically have recurrent bacterial infections of the respiratory tract and chronic viral infections.

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 the altered subunit is frequently turned on (overactive).

Studies indicate that overactive PI3K-delta signaling alters the growth of certain immune system cells known as B cells and T cells. T cells mature and die too quickly, and B cells are blocked from maturing at an early stage. The immature B cells cannot respond to foreign invaders and likely self-destruct. The lack of B cells and T cells makes it difficult for people with this disorder to fight off bacterial and viral infections. Overactive PI3K-delta signaling can also stimulate the abnormal proliferation of white blood cells in some affected individuals. Activated PI3K-delta syndrome type 2 is also associated with an increased risk of developing a form of blood cell cancer called lymphoma.

Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay

Variants in the *PIK3R1* gene have also been reported to cause a condition known as short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay (often called SHORT syndrome). This condition is characterized by signs and symptoms affecting many parts of the body, including the skin, eyes, teeth, and joints.

The most common *PIK3R1* gene variant changes a single protein building block (amino acid) in the regulatory subunit of PI3K. Variants in the *PIK3R1* gene alter the structure of the subunit, which reduces the ability of PI3K to participate in cell signaling. Because the variants reduce the enzyme's activity, they are described as loss-of-function variants.

Researchers are working to determine how *PIK3R1* gene variants lead to the specific features of SHORT syndrome. PI3K's role in insulin activity may be related to insulin resistance and diabetes, which are problems with blood glucose regulation that are found in some people with SHORT syndrome. Abnormal adipocyte maturation might contribute to a lack of fatty tissue under the skin (lipoatrophy), which is another common feature of the condition. It is unclear how reduced PI3K signaling is associated with the other signs and symptoms of SHORT syndrome.

Cancers

Some gene variants, called somatic variants, are not inherited and are present only in certain cells. Somatic *PIK3R1* gene variants have been identified in some cancers of the uterine lining (endometrial cancers) and in a form of brain cancer called glioblastoma. Less commonly, somatic variants in the *PIK3R1* gene have been found in cancers of the colon, ovary, and breast.

Cancer-associated changes in the *PIK3R1* gene alter the regulatory subunit such that it can no longer control the activity of PI3K, which increases PI3K signaling dramatically. Because the genetic changes enhance the activity of the enzyme, they are classified as gain-of-function variants. Increased PI3K signaling appears to promote the uncontrolled cell growth and division that is characteristic of cancerous tumors. It is unclear why

these variants seem to be more common in some types of cancer than in others.

Other Names for This Gene

- p85
- p85-ALPHA
- P85A_HUMAN
- phosphatidylinositol 3-kinase 85 kDa regulatory subunit alpha
- phosphatidylinositol 3-kinase regulatory subunit alpha
- phosphatidylinositol 3-kinase-associated p-85 alpha
- phosphoinositide-3-kinase regulatory subunit
- PI3-kinase subunit p85-alpha
- PI3K regulatory subunit alpha

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PIK3R1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5295[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28PIK3R1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 1; PIK3R1 (https://omim.org/entry/171833)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5295)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PIK3R1[gene])

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Genomic Location

The *PIK3R1* gene is found on chromosome 5 (https://medlineplus.gov/genetics/chromosome/5/).

Last updated August 16, 2023