PIK3CA Gene

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phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

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1. Introduction

The *PIK3CA* gene provides instructions for making the p110 alpha (p110α) protein, which is one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The p110α protein is called the catalytic subunit because it performs the action of PI3K, while the other subunit (produced by a different gene) regulates the enzyme's activity.

Like other kinases, PI3K 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 the regulation of several hormones and may play a role in the maturation of fat cells (adipocytes).

2. Health Conditions Related to Genetic Changes

2.1. Klippel-Trenaunay syndrome

At least five mutations in the *PIK3CA* gene have been found to cause Klippel-Trenaunay syndrome. This condition is characterized by a red birthmark called a port-wine stain, abnormal overgrowth of soft tissues (such as skin and muscles) and bones, and vein malformations. The *PIK3CA* gene mutations associated with this condition arise randomly in one cell during the early stages of development before birth. These changes, which are called somatic mutations, are not inherited. As cells continue to divide during development, cells arising from the first abnormal cell will have the mutation, and other cells will not. This mixture of cells with and without a genetic mutation is known as mosaicism.

The *PIK3CA* gene mutations associated with Klippel-Trenaunay syndrome change single protein building blocks (amino acids) in the p110α protein. These changes lead to production of an altered p110α subunit that makes PI3K abnormally active. The altered enzyme triggers unregulated chemical signaling in cells, which allows cells to grow and divide continuously. Increased cell proliferation leads to abnormal growth of the bones, soft tissues, and blood vessels.

Despite the involvement of *PIK3CA* gene mutations in cancer (described below) and the overgrowth of cells caused by changes in this gene, individuals with Klippel-Trenaunay syndrome do not appear to have an elevated risk of developing cancer.

2.2. Megalencephaly-capillary malformation syndrome

At least 15 mutations in the *PIK3CA* gene have been found to cause a condition known as megalencephaly-capillary malformation syndrome (MCAP), which is characterized by overgrowth of the brain (megalencephaly) and abnormalities caused by enlargement of small blood vessels in the skin (capillary malformations). The mutations that cause MCAP overlap with those that cause Klippel-Trenaunay syndrome (described above). These mutations are not inherited from a parent; they arise randomly in one cell during the early stages of development before birth and lead to mosaicism. The presence of the mutation in different tissues helps explain why multiple conditions can be caused by the same gene mutations.

Most *PIK3CA* gene mutations involved in MCAP change single amino acids in the p110α protein. These mutations lead to the production of an altered p110α subunit that makes PI3K abnormally active. The resulting unregulated signaling allows cells to grow and divide continuously. Increased cell proliferation in the brain and other tissues and organs leads to the overgrowth characteristic of MCAP.

Despite the involvement of the *PIK3CA* gene mutations in many cancers (described below) and the overgrowth of cells caused by changes in this gene, individuals with MCAP do not appear to have an elevated risk of developing cancer.

2.3. Bladder cancer

Somatic mutations in the *PIK3CA* gene have been found in some cases of bladder cancer. Bladder cancer is a disease in which certain cells in the bladder become abnormal and multiply uncontrollably to form a tumor. Bladder cancer may cause blood in the urine, pain during urination, frequent urination, the feeling of needing to urinate without being able to, or lower back pain.

Bladder cancer is generally divided into two types, non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), based on where in the bladder the tumor is located. A *PIK3CA* gene mutation has been found in about half of NMIBC tumors. These mutations change single amino acids in the p110α protein. The altered p110α subunit appears to allow PI3K to become overactive. The increased signaling by PI3K likely contributes to uncontrolled cell growth and division and the formation of bladder cancer.

2.4. Epidermal nevus

Mutations in the *PIK3CA* gene have been found in up to a quarter of people with a certain type of epidermal nevus (plural: nevi). Specifically, *PIK3CA* gene mutations are associated with some keratinocytic epidermal nevi, which are abnormal skin growths that are composed of skin cells called keratinocytes. *PIK3CA* gene mutations have not been found in other types of epidermal nevi.

The most common *PIK3CA* gene mutation found in epidermal nevi replaces the amino acid glutamic acid with the amino acid glycine at position 545 of the p110α protein (written as Glu545Gly or E545G). Studies suggest that this mutation causes cells to grow and divide more than normal. The resulting overgrowth of skin cells leads to formation of epidermal nevi. The genetic changes associated with this condition are somatic mutations and are present only in the cells of the nevus.

Despite the involvement of *PIK3CA* gene mutations in many cancers (described above) and the overgrowth of cells caused by changes in this gene, individuals with an epidermal nevus do not appear to have an elevated risk of developing cancer.

2.5. More About This Health Condition

Head and neck squamous cell carcinoma

Lung cancer

Ovarian cancer

2.6. Other disorders

Mutations in the *PIK3CA* gene, including those found in some cancers, have been found to cause several other conditions related to overgrowth of tissues. These conditions include hemimegalencephaly; fibroadipose hyperplasia; and a condition called congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal or spinal abnormalities (CLOVES) syndrome. Hemimegalencephaly is characterized by enlargement of one side of the brain and can cause seizures and intellectual disability. Fibroadipose hyperplasia causes overgrowth of fibrous and fatty (adipose) tissues in various regions of the body, which leads to enlargement of different portions of the body, such as the lower body, an individual arm or leg, or one or more fingers or toes. CLOVES syndrome has multiple features, including an overgrowth of adipose tissue in the abdomen that is often associated with a reddish birthmark on the skin over it, in addition to blood vessel, skin, and bone abnormalities. It is unknown whether individuals with these disorders have an elevated risk of developing cancer.

As in Klippel-Trenaunay syndrome, MCAP, and epidermal nevus (each described above), the genetic changes involved in these disorders occur early in development and are found in only some of the body's cells. This mosaicism helps explain why different conditions involving different parts of the body can be caused by the same gene mutations. Together, the overgrowth disorders caused by *PIK3CA* gene mutations are known as the *PIK3CA*-related overgrowth spectrum (PROS).

2.7. Cancers

Somatic mutations in the *PIK3CA* gene are found in many other types of cancer, including cancer of the ovary, breast, lung, brain, and stomach. These mutations are also involved in cancer of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. These mutations change single amino acids in the p110α protein. Two common mutations occur in the same region and change the amino acid glutamate at position 542 or at position 545 of the p110α protein to the amino acid lysine (written as Glu542Lys and Glu545Lys, respectively). Two other common mutations occur in another region, changing the amino acid histidine at position 1047 of p110α to the amino acid arginine or leucine (written as His1047Arg and His1047Leu, respectively).

Cancer-associated *PIK3CA* gene mutations result in production of an altered p110α subunit that allows PI3K to signal without regulation. The increased signaling can contribute to an uncontrolled proliferation of cells, leading to the development of cancer. However, *PIK3CA* gene mutations may not cause cancer by themselves. Researchers suspect that some cases of cancer likely result from a combination of mutations in *PIK3CA* and mutations in other genes that influence cancer risk.

3. Other Names for This Gene

- p110-alpha
- phosphatidylinositol 3-kinase, catalytic, 110-KD, alpha
- phosphatidylinositol 3-kinase, catalytic, alpha polypeptide
- phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform
- phosphatidylinositol-4,5-bisphosphate 3-kinase 110 kDa catalytic subunit alpha
- phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
- phosphoinositide-3-kinase, catalytic, alpha polypeptide
- PI3-kinase p110 subunit alpha
- PI3K
- PI3K-alpha
- PK3CA_HUMAN
- ptdIns-3-kinase subunit p110-alpha
- serine/threonine protein kinase PIK3CA

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