ALK Gene

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ALK receptor tyrosine kinase. The ALK gene provides instructions for making a protein called ALK receptor tyrosine kinase, which is part of a family of proteins called receptor tyrosine kinases (RTKs).

genes

1. Normal Function

Receptor tyrosine kinases transmit signals from the cell surface into the cell through a process called signal transduction. The process begins when the kinase is stimulated at the cell surface and then attaches to a similar kinase (dimerizes). After dimerization, the kinase is tagged with a marker called a phosphate group (a cluster of oxygen and phosphorus atoms) in a process called phosphorylation. Phosphorylation turns on (activates) the kinase. The activated kinase is able to transfer a phosphate group to another protein inside the cell, which is activated as a result. The activation continues through a series of proteins in a signaling pathway. These signaling pathways are important in many cellular processes such as cell growth and division (proliferation) or maturation (differentiation).

Although the specific function of ALK receptor tyrosine kinase is unknown, it is thought to act early in development to help regulate the proliferation of nerve cells.

2. Health Conditions Related to Genetic Changes

2.1 Neuroblastoma

At least 16 mutations in the *ALK* gene have been identified in some people with neuroblastoma, a type of cancerous tumor composed of immature nerve cells (neuroblasts). Neuroblastoma and other cancers occur when a buildup of genetic mutations in critical genes—those that control cell proliferation or differentiation—allows cells to grow and divide uncontrollably to form a tumor. In most cases, these genetic changes are acquired during a person's lifetime and are called somatic mutations. Somatic mutations are present only in certain cells and are not inherited. Less commonly, gene mutations that increase the risk of developing cancer can be inherited from a parent. Both types of mutation occur in neuroblastoma. Somatic mutations in the *ALK* gene occur during the development of some cases of sporadic neuroblastoma, and inherited mutations in the *ALK* gene increase the risk of developing familial neuroblastoma.

Mutations in the ALK gene change single protein building blocks (amino acids) in ALK receptor tyrosine kinase. The most common mutation in neuroblastoma replaces the amino acid arginine with the amino acid glutamine at position 1275 (written as Arg1275Gln or R1275Q). Arg1275Gln has been found in both familial and sporadic neuroblastoma and is the only common *ALK* gene mutation that has been found in both types of the condition.

Occasionally, extra copies of the *ALK* gene are found in people with neuroblastoma. This phenomenon, known as gene amplification, results in overexpression of ALK receptor tyrosine kinase.

Mutated or overexpressed ALK receptor tyrosine kinase no longer requires stimulation from outside the cell to be phosphorylated. As a result, the kinase and the downstream signaling pathway are constantly turned on (constitutively activated). Constitutive activation of ALK receptor tyrosine kinase may increase the proliferation of immature nerve cells, leading to neuroblastoma.

2.2 Lung cancer

Lung cancer

2.3. Other cancers

Rearrangements of genetic material involving the *ALK* gene on chromosome 2 increase the risk of developing several other types of cancer. These rearrangements are somatic mutations, which means they occur during a person's lifetime and are present only in the cells that become cancerous.

One type of rearrangement, called a translocation, exchanges genetic material between chromosome 2 and another chromosome. At least 15 translocations involving the *ALK* gene have been identified in people with anaplastic large cell lymphoma (ALCL), a rare form of cancer involving immune cells called T cells. The most common translocation in ALCL occurs between chromosome 2 and chromosome 5, called t(2;5). This translocation fuses the *ALK* gene to the *NPM* gene and results in a fusion protein called NPM-ALK. In addition, at least seven translocations involving the *ALK* gene have been identified in inflammatory myofibroblastic tumor (IMT). IMT is a rare cancer characterized by a solid tumor composed of inflammatory cells and cells called myofibroblasts that are important in wound healing. About half of people with IMT have a translocation involving the *ALK* gene.

Another type of rearrangement, called an inversion, occurs when chromosome 2 is broken in two places and the resulting piece of DNA is reversed and re-inserted into the chromosome. A small group of people with non-small cell lung cancer, the most common type of lung cancer, have an inversion of chromosome 2. This inversion fuses the *ALK* gene with another gene called *EML4* and results in the EML4-ALK fusion protein.

The fusion proteins created by these rearranged genes have functions of both ALK receptor tyrosine kinase and the partner protein. The presence of the partner protein allows phosphorylation of ALK receptor tyrosine kinase without dimerization. The fusion protein and signaling pathways activated by ALK receptor tyrosine kinase are constitutively activated, which may abnormally increase the proliferation of immature nerve cells, leading to cancer formation.

3. Other Names for This Gene

- ALK tyrosine kinase receptor
- anaplastic lymphoma kinase
- anaplastic lymphoma receptor tyrosine kinase
- CD246
- CD246 antigen
- NBLST3

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