

KRAS Gene

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1. Introduction

The *KRAS* gene provides instructions for making a protein called K-Ras that is part of a signaling pathway known as the RAS/MAPK pathway. The protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate). The K-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP. In this way the K-Ras protein acts like a switch that is turned on and off by the GTP and GDP molecules. To transmit signals, it must be turned on by attaching (binding) to a molecule of GTP. The K-Ras protein is turned off (inactivated) when it converts the GTP to GDP. When the protein is bound to GDP, it does not relay signals to the cell's nucleus.

The *KRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. The *KRAS* gene is in the Ras family of oncogenes, which also includes two other genes: *HRAS* and *NRAS*. These proteins play important roles in cell division, cell differentiation, and the self-destruction of cells (apoptosis).

2. Health Conditions Related to Genetic Changes

2.1. Cardiofaciocutaneous Syndrome

Mutations in the *KRAS* gene are an uncommon cause of cardiofaciocutaneous syndrome, accounting for less than 5 percent of cases. Several mutations in the *KRAS* gene have been identified in people with characteristic features of the disorder, which include heart defects, distinctive facial features, and skin abnormalities. These mutations are present in all of the body's cells and are known as germline mutations. The mutations change single protein building blocks (amino acids) in the K-Ras protein. The altered protein shows increased GTP binding and a decreased ability to convert GTP to GDP. These effects lead to prolonged activation of the K-Ras protein, which alters tightly regulated RAS/MAPK signaling during development. The altered signaling interferes with the development of organs and tissues throughout the body, leading to the varied signs and symptoms of cardiofaciocutaneous syndrome.

2.2. Lung Cancer

At least three mutations in the *KRAS* gene have been associated with lung cancer. Lung cancer is a disease in which certain cells in the lungs become abnormal and multiply uncontrollably to form a tumor. Lung cancer may not cause signs or symptoms in its early stages. These *KRAS* gene mutations are somatic, which means they are acquired during a person's lifetime and are present only in tumor cells. Somatic mutations are not inherited. Nearly all of the *KRAS* gene mutations associated with lung cancer change the amino acid glycine at position 12 or 13 (Gly12 or Gly13) or change the amino acid glutamine at position 61 (Gln61) in the K-Ras protein. These mutations result in a K-Ras protein that is constantly turned on (constitutively activated) and directing cells to proliferate in an uncontrolled way, which leads to tumor formation. When these genetic changes occur in cells in the lungs, lung cancer can develop.

KRAS gene mutations are found in 15 to 25 percent of all lung cancer cases but are more frequent in white populations than in Asian populations; 25 to 50 percent of whites with lung cancer have *KRAS* gene mutations, whereas 5 to 15 percent of Asians with lung cancer have *KRAS* gene mutations.

KRAS gene mutations are much more common in long-term tobacco smokers with lung cancer than in nonsmokers. Lung cancers with *KRAS* gene mutations typically indicate a poor prognosis and are associated with resistance to several cancer treatments.

2.3. Other Cancers

Somatic mutations in the *KRAS* gene are involved in the development of several types of cancer, particularly pancreatic and colorectal cancers. These mutations lead to a K-Ras protein that is more strongly overactivated than the mutations that cause cardiofaciocutaneous syndrome (described above). The abnormal K-Ras protein is always active and can direct cells to proliferate in an uncontrolled way.

2.4. Other Disorders

Germline mutations in the *KRAS* gene also cause a disorder whose major features overlap with those of cardiofaciocutaneous syndrome (described above) and two related disorders called Noonan syndrome and Costello syndrome. This condition has been described as the *KRAS* mutation-associated phenotype. People with this condition have variable signs and symptoms that include mild to moderate intellectual disability, distinctive facial features, short stature, an unusually large head (macrocephaly), and hair that is sparse and thin.

At least nine mutations in the *KRAS* gene have been reported in people with this disorder. Each of these mutations changes single amino acids in the K-Ras protein. These genetic changes abnormally activate the protein, which alters chemical signaling in cells throughout the body. The altered signaling interferes with the normal development of many organs and tissues, resulting in the characteristic features of the *KRAS* mutation-associated phenotype.

3. Other Names for This Gene

- C-K-RAS
- c-K-ras protein
- c-K-ras2 protein
- c-Kirsten-ras protein
- cellular c-Ki-ras2 proto-oncogene
- K-ras p21 protein
- KI-RAS
- Kirsten rat sarcoma viral oncogene homolog
- KRAS1
- PR310 c-K-ras oncogene
- RASK2
- RASK_HUMAN
- transforming protein p21
- v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

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