HRAS Gene

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1. Introduction

The *HRAS* gene provides instructions for making a protein called H-Ras that is involved primarily in regulating cell division. Through a process known as signal transduction, the H-Ras protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow or divide. The H-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP. The H-Ras protein acts like a switch, and it is turned on and off by GTP and GDP molecules. To transmit signals, the protein must be turned on by attaching (binding) to a molecule of GTP. The H-Ras protein is turned off (inactivated) when it converts GTP to GDP. When the protein is bound to GDP, it does not relay signals to the cell's nucleus.

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

2. Health Conditions Related to Genetic Changes

2.1. Costello Syndrome

At least 15 mutations in the *HRAS* gene have been identified in people with Costello syndrome, a rare condition that affects many parts of the body and increases the risk of developing cancerous and noncancerous tumors. The mutations change single protein building blocks (amino acids) in a critical region of the H-Ras protein. The most common mutation accounts for more than 80 percent of all cases of Costello syndrome; it replaces the amino acid glycine with the amino acid serine at protein position 12 (written as Gly12Ser or G12S).

The *HRAS* gene mutations that cause Costello syndrome lead to the production of an H-Ras protein that is abnormally turned on (active) in cells throughout the body. Instead of triggering cell growth in response to signals from outside the cell, the overactive protein directs cells to grow and divide constantly. This uncontrolled cell division can result in the formation of noncancerous and cancerous tumors. Researchers are uncertain how mutations in the *HRAS* gene cause the other features of Costello syndrome (such as intellectual disability, distinctive facial features, and heart problems), but many of the signs and symptoms probably result from cell overgrowth and abnormal cell division.

2.2. Epidermal Nevus

Mutations in the *HRAS* gene are involved in the development of abnormal, noncancerous patches of skin called epidermal nevi (singular: nevus). These patches are caused by an overgrowth of cells in the outer layer of skin (the epidermis). *HRAS* gene mutations have been found in a majority of people with a certain type of epidermal nevus called a nevus sebaceous. This type is classified as an organoid epidermal nevus because it involves cells that make up structures (or organs) in the skin, usually the hair follicles, the sweat glands, or the sebaceous glands (glands in the skin that produce a substance that protects the skin and hair). Additional tumors often develop in the region of the nevus sebaceous. In rare cases, these tumors are cancerous. *HRAS* gene mutations are less commonly found in keratinocytic epidermal nevi, a type of epidermal nevus that involves a particular type of epidermal cell called a keratinocyte. Keratinocytic epidermal nevi are not typically associated with additional tumors.

Epidermal nevi are caused by gene mutations that are acquired during the early stages of development before birth. The mutations are present only in the cells of the nevus and not the normal skin cells surrounding it. These changes, which are called somatic mutations, are not inherited. The somatic *HRAS* gene mutations involved in epidermal nevi, change single amino acids in the H-Ras protein. The most common mutation replaces the amino acid glycine with the amino acid valine at protein position 12 (written as Gly12Val or G12V). These mutations lead to production of an H-Ras protein that is always turned on. The affected skin cells grow and divide more than normal cells, resulting in epidermal nevi.

2.3. Other Disorders

Somatic *HRAS* gene mutations are also involved in development of Schimmelpenning syndrome, which is a type of epidermal nevus syndrome. Affected individuals have a type of epidermal nevus called nevus sebaceous (described above) in addition to abnormalities of the brain, eyes, or bones. Problems with these other systems can include seizures, intellectual disability, extra or missing pieces of tissue in eye structures (choristomas or colobomas), underdeveloped bones, and a disorder called rickets that leads to softening and weakening of the bones. Schimmelpenning syndrome is caused by the same gene mutations involved in epidermal nevus. It is thought that the additional signs and symptoms occur because the somatic mutation affects other tissues in addition to the skin.

2.4. Other Cancers

Somatic mutations in the *HRAS* gene are probably involved in the development of several additional types of cancer. These mutations lead to a version of the H-Ras protein that is always active and can direct cells to grow and divide without control. Studies suggest that *HRAS* gene mutations may be common in thyroid and kidney cancers. Increased activity (expression) of the *HRAS* gene has also been reported in other types of cancer.

3. Other Names for This Gene

- C-H-RAS
- Harvey murine sarcoma virus oncogene
- Harvey rat sarcoma viral oncogene homolog
- HRAS1
- Oncogene, G-RAS
- RASH1
- RASH_HUMAN
- Transformation gene: Oncogene HaMSV
- Transforming protein P21/H-RAS-1 (C-H-RAS)
- v-Ha-ras Harvey rat sarcoma viral oncogene homolog

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