

GNA11 Gene

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Contributor: Dean Liu

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1. Introduction

The *GNA11* gene provides instructions for making one component, the alpha (α) subunit, of a protein complex called a guanine nucleotide-binding protein (G protein). Each G protein is composed of three proteins called the alpha, beta, and gamma subunits. Specifically, the protein produced from the *GNA11* gene, called $G\alpha_{11}$, is the alpha subunit for a G protein called G_{11} .

In a process called signal transduction, G proteins trigger a complex network of signaling pathways that ultimately influence many cell functions. The G_{11} protein plays many roles in cells. It works with another protein called the calcium-sensing receptor (CaSR) to affect processes that regulate calcium levels in the blood. CaSR proteins in kidney cells and cells of the parathyroid gland sense when a certain concentration of calcium in the blood is reached; the CaSR protein then stimulates the G_{11} subunits, including $G\alpha_{11}$, to send signals that block processes that increase the amount of calcium in the blood. In particular, this signaling blocks the production and release of a hormone called parathyroid hormone. Parathyroid hormone enhances the release of calcium into the blood, so blocking this hormone prevents calcium release. In the kidneys, which filter fluid and waste products in the body and can reabsorb needed nutrients and release them back into the blood, G_{11} signaling blocks the reabsorption of calcium from the filtered fluids.

G_{11} signaling is also involved in the growth and division (proliferation) and self-destruction (apoptosis) of cells in tissues throughout the body, including those in the eyes, skin, heart, and brain.

2. Health Conditions Related to Genetic Changes

2.1. Autosomal dominant hypocalcemia

At least five mutations in the *GNA11* gene have been found in individuals with autosomal dominant hypocalcemia type 2. This condition is characterized by low levels of calcium in the blood (hypocalcemia). The mutations involved in this condition change single protein building blocks (amino acids) in $G\alpha_{11}$. These genetic changes are called activating mutations because the altered alpha subunit is overactive, sending signals to block a rise in calcium levels, even when levels are very low. As a result, calcium levels in the blood remain abnormally low, causing hypocalcemia. Hypocalcemia can cause muscle cramping and seizures, although about half of people with the condition have no associated health problems.

Because overactive $G\alpha_{11}$ signaling blocks the production of parathyroid hormone, the levels of this hormone in the blood can be abnormally low, which is known as hypoparathyroidism. For this reason, autosomal dominant hypocalcemia is sometimes referred to as autosomal dominant hypoparathyroidism.

2.2. Other disorders

Germline mutations in the *GNA11* gene are also involved in a different condition related to abnormal calcium concentrations. Genetic changes that impair $G\alpha_{11}$ signaling cause familial hypocalciuric hypercalcemia type 2. In contrast to autosomal dominant hypocalcemia (described above), this condition is characterized by high levels of calcium in the blood (hypercalcemia) and low levels of calcium in the urine (hypocalciuria). Because $G\alpha_{11}$ signaling to block parathyroid hormone release is impaired, calcium levels in the blood rise, leading to hypercalcemia. Affected individuals typically have no symptoms related to the condition.

2.3. Cancers

The gene mutations that cause autosomal dominant hypocalcemia (described above) are typically inherited and found in every cell in the body (known as germline mutations). However, some gene mutations are not inherited and are instead acquired during a person's lifetime. These changes, which are called somatic mutations, are present only in certain cells. Somatic mutations in the *GNA11* gene have been found in cancerous tumors in the eye known as uveal melanomas. These tumors occur in the colored part of the eye (the iris) or in related tissues known as the ciliary body and the choroid (collectively, these tissues are called the uvea). Less commonly, *GNA11* gene mutations are associated with a type of skin tumor called a blue nevus, so named because of its characteristic bluish appearance. This type of growth is typically noncancerous. *GNA11* gene mutations are activating, leading to production of an overactive $G\alpha_{11}$ protein that stimulates uncontrolled proliferation of the pigment-producing cells (melanocytes) in the uvea or in the skin.

Individuals with uveal melanomas or blue nevi appear to have normal levels of calcium in their blood, and people with an inherited *GNA11*-related calcium concentration disorder do not seem to have an increased risk of developing one of these types of tumors.

3. Other Names for This Gene

- FBH
- FBH2
- FHH2
- guanine nucleotide binding protein (G protein), alpha 11 (Gq class)

References

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