

FGFR3 Gene

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Fibroblast growth factor receptor 3: The *FGFR3* gene provides instructions for making a protein called fibroblast growth factor receptor 3.

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1. Normal Function

This protein is part of a family of four fibroblast growth factor receptors that share similar structures and functions. These proteins play a role in several important cellular processes, including regulation of cell growth and division (proliferation), determination of cell type, formation of blood vessels (angiogenesis), wound healing, and embryo development.

The *FGFR3* protein spans the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with specific growth factors outside the cell and to receive signals that control growth and development. When these growth factors attach to the *FGFR3* protein, the protein is turned on (activated), which triggers a cascade of chemical reactions inside the cell that instruct the cell to undergo certain changes, such as maturing to take on specialized functions (differentiation).

Several versions (isoforms) of the *FGFR3* protein are produced from the *FGFR3* gene. The different isoforms are found in various tissues of the body, and they interact with a variety of growth factors. Many isoforms are found in the cells that form bones. Researchers believe that the *FGFR3* protein regulates bone growth by limiting the formation of bone from cartilage (a process called ossification), particularly in the long bones. One particular isoform of the *FGFR3* protein is found specifically in cells that line the surfaces of the body (epithelial cells), including the cells that form the outermost layer of skin, called the epidermis.

2. Health Conditions Related to Genetic Changes

2.1 Achondroplasia

Two mutations in the *FGFR3* gene cause more than 99 percent of cases of achondroplasia, which is a form of short-limbed dwarfism. Both mutations lead to the same change in the *FGFR3* protein. Specifically, the protein building block (amino acid) glycine is replaced with the amino acid arginine at protein position 380 (written as Gly380Arg or G380R). Researchers believe that this genetic change causes the receptor to be overly active, which leads to the disturbances in bone growth that occur in this disorder.

2.2 Crouzon Syndrome with Acanthosis Nigricans

A single *FGFR3* gene mutation has been identified in people with Crouzon syndrome with acanthosis nigricans. This rare condition causes premature joining of the bones of the skull (craniosynostosis), leading to a misshapen head and distinctive facial features, and a skin abnormality called acanthosis nigricans that is characterized by thick, dark, velvety skin in body folds and creases. The genetic change that causes Crouzon syndrome with acanthosis nigricans replaces the amino acid alanine with the amino acid glutamic acid at position 391 of the *FGFR3* protein (written as Ala391Glu or A391E). The altered receptor is more easily turned on than normal and can trigger signaling pathways even without attachment of growth factors. The resulting overactivity of the *FGFR3* protein disrupts the normal growth of the skull bones and skin, leading to the features of Crouzon syndrome with acanthosis nigricans.

2.3 Epidermal Nevus

Mutations in the *FGFR3* gene have been found in approximately 30 percent of people with a certain type of epidermal nevus (plural: nevi). Specifically, *FGFR3* gene mutations are associated with some keratinocytic epidermal nevi, which are abnormal skin growths that are composed of skin cells called keratinocytes. *FGFR3* gene mutations have not been found in other types of epidermal nevi.

The most common *FGFR3* gene mutation in epidermal nevi changes a single amino acid in the FGFR3 protein. The amino acid arginine is replaced with the amino acid cysteine at position 248 (written as Arg248Cys or R248C). This mutation creates a protein that is turned on without attachment of a growth factor, which means that the FGFR3 protein is constantly active. Studies suggest that cells with this *FGFR3* gene mutation grow and divide more than normal cells. The resulting overgrowth of skin cells leads to epidermal nevi.

The *FGFR3* gene mutations found in epidermal nevi also occur in people with another skin abnormality called seborrheic keratosis and in people with skeletal disorders known as thanatophoric dysplasia, Crouzon syndrome with acanthosis nigricans, and SADDAN (each described in another section on this page). However, in contrast with the skeletal conditions, the mutations associated with epidermal nevi (and seborrheic keratosis) are somatic mutations that arise randomly. In epidermal nevi, the mutations occur during the early stages of development before birth and are present only in the cells of the nevus, not in the normal skin cells surrounding it.

2.4 Hypochondroplasia

More than 25 mutations in the *FGFR3* gene have been identified in people with hypochondroplasia, another form of short-limbed dwarfism that is milder than achondroplasia. Many cases are caused by one of two specific *FGFR3* gene mutations, both of which lead to the same change in the FGFR3 protein. Specifically, the amino acid asparagine is replaced with the amino acid lysine at protein position 540 (written as Asn540Lys or N540K). Other *FGFR3* gene mutations probably cause a small number of cases of hypochondroplasia. Although the effects of these hypochondroplasia-associated mutations have not been explained, they probably cause the receptor to be mildly overactive, which leads to the disturbances in bone growth that occur in this disorder.

2.5 Lacrimo-Auriculo-Dento-Digital Syndrome

At least one mutation in the *FGFR3* gene has been found to cause lacrimo-auriculo-dento-digital (LADD) syndrome. The main features of LADD syndrome are abnormal tear production, malformed ears with hearing loss, decreased saliva production, small teeth, and hand deformities. The *FGFR3* gene mutation that causes LADD syndrome replaces the amino acid aspartic acid with the amino acid asparagine at position 513 in the FGFR3 receptor protein (written as Asp513Asn or D513N). This mutation most likely reduces the ability of the FGFR3 receptor protein to trigger chemical signaling within cells when it is attached to its growth factor. These defects in cell signaling disrupt cell maturation and development, which results in abnormal formation of the ears, skeleton, and glands in the eyes and mouth in people with LADD syndrome.

2.6 Muenke Syndrome

A single mutation in the *FGFR3* gene has been shown to cause Muenke syndrome, which is a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features. Additional signs and symptoms can include hearing loss, subtle hand and foot abnormalities, and developmental delay. The mutation that causes Muenke syndrome substitutes the amino acid arginine for the amino acid proline at position 250 in the FGFR3 protein (written as Pro250Arg or P250R). This mutation results in the production of a receptor that is overly active, which allows the bones of the skull to fuse sooner than normal.

The Pro250Arg mutation has also been identified in some people with apparently isolated coronal craniosynostosis. This condition is characterized by a premature fusion of the growth line that runs across the top of the head from ear to ear (the coronal suture). People with isolated coronal craniosynostosis do not have the other features that are sometimes associated with Muenke syndrome (such as hand and foot abnormalities).

2.7 SADDAN

One mutation in the *FGFR3* gene has been identified in people with SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans). SADDAN is characterized by short-limb dwarfism (achondroplasia); profound developmental delay; and thick, dark, velvety skin. The genetic change that causes this condition substitutes the amino

acid methionine for the amino acid lysine at position 650 of the FGFR3 protein (written as Lys650Met or K650M). Researchers believe that this mutation strongly overactivates the FGFR3 protein, which leads to severe problems with bone growth. It remains uncertain how the mutation causes developmental delay or acanthosis nigricans.

2.8 Thanatophoric Dysplasia

Mutations in the *FGFR3* gene have been identified in people with thanatophoric dysplasia, which is a severe skeletal disorder characterized by extremely short limbs and a narrow chest. More than 10 *FGFR3* gene mutations have been found to cause type I thanatophoric dysplasia. Most of these mutations change a single amino acid in the FGFR3 protein. The most common mutation substitutes the amino acid cysteine for the amino acid arginine at protein position 248 (written as Arg248Cys or R248C). Other mutations cause the protein to be longer than normal.

Only one mutation has been shown to cause type II thanatophoric dysplasia. This mutation replaces the amino acid lysine with the amino acid glutamic acid at position 650 of the FGFR3 protein (written as Lys650Glu or K650E). This change affects a different part of the FGFR3 protein than the mutations that cause type I thanatophoric dysplasia.

The genetic changes responsible for both types of thanatophoric dysplasia cause the FGFR3 receptor to be overactive, which leads to the severe problems with bone growth that occur in this condition.

2.9 Bladder Cancer

Some gene mutations are acquired during a person's lifetime and are present only in certain cells. These changes, which are called somatic mutations, are not inherited. Somatic mutations in the *FGFR3* 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. Approximately 80 percent of NMIBC tumors have *FGFR3* gene mutations. *FGFR3* gene mutations change single amino acids in the FGFR3 protein, which appears to overactivate protein signaling. As a result, bladder cells are likely directed to grow and divide abnormally. This uncontrolled cell division leads to the formation of bladder cancer.

2.10 Multiple Myeloma

2.11 Other Disorders

At least two *FGFR3* gene mutations have been found to cause a rare disorder called camptodactyly, tall stature, hearing loss syndrome (CATSHL syndrome). Individuals with this condition are taller than average and typically have hearing loss. They can also have permanently bent fingers or toes (camptodactyly) and other skeletal abnormalities. Researchers suggest that the *FGFR3* gene mutations involved in CATSHL syndrome reduce the function of the FGFR3 protein, although it is unclear how the mutations lead to the signs and symptoms of the condition.

Mutations in the *FGFR3* gene have been found in 30 to 70 percent of people with seborrheic keratoses, which are small, dark, noncancerous (benign) tumors of the skin caused by overgrowth of skin cells. Seborrheic keratoses develop in adulthood and are seen in a majority of people older than age 50. The *FGFR3* gene mutations associated with seborrheic keratoses are somatic mutations and are not inherited. At least nine *FGFR3* gene mutations have been identified in people with seborrheic keratoses. These mutations change single amino acids in the FGFR3 protein. The mutated FGFR3 proteins are abnormally active, which results in the overgrowth of skin cells, leading to seborrheic keratosis. It has been suggested that the mutations involved in seborrheic keratosis may be caused by exposure to ultraviolet (UV) light.

The somatic Arg248Cys *FGFR3* gene mutation found in epidermal nevus (described above) can also cause Garcia-Hafner-Happle syndrome (also known as fibroblast growth factor receptor 3 epidermal nevus syndrome). This condition is characterized by a soft, velvety keratinocytic epidermal nevus and neurological problems, such as seizures, intellectual disability, underdevelopment of the tissue that connects the two halves of the brain (corpus callosum), and a loss of brain cells (cortical atrophy). It is thought that the neurological problems occur because the somatic mutation affects brain cells in addition to those in the skin.

2.12 Other Cancers

In addition to bladder cancer, somatic mutations in the *FGFR3* gene have been associated with a cancer of white blood cells (multiple myeloma) and cervical cancer. Some cases of multiple myeloma are related to a rearrangement of genetic material (a translocation) involving chromosome 14 and the region of chromosome 4 containing the *FGFR3* gene. Mutations that have been associated with cervical cancer are changes in single nucleotides in the *FGFR3* gene.

FGFR3 gene mutations that lead to multiple myeloma and cervical cancer are thought to overactivate the FGFR3 protein in certain cells. The mutated receptor directs the cells to grow and divide in the absence of signals from outside the cell. This uncontrolled division can lead to the overgrowth of cancer cells.

3. Other Names for This Gene

- ACH
- CD333
- CEK2
- FGFR-3
- FGR3_HUMAN
- fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)
- HBGFR
- hydroxyaryl-protein kinase
- JTK4
- tyrosine kinase JTK4

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