FGFR3 gene

fibroblast growth factor receptor 3

Normal Function

The *FGFR3* gene provides instructions for making a protein called fibroblast growth factor receptor 3. 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 allows the protein to interact with specific growth factors outside the cell and receive signals that control growth and development. When these growth factors attach to the FGFR3 protein, the protein is turned on (activated). This 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. Cartilage is a tough but flexible tissue that makes up much of the skeleton during early development. The process of converting cartilage to bone is called ossification. 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.

Health Conditions Related to Genetic Changes

Achondroplasia

Two variants (also called mutations) in the *FGFR3* gene cause more than 99 percent of cases of achondroplasia, which is the most common form of short-limbed dwarfism. Both variants lead to the same change in the FGFR3 protein. This change replaces the protein building block (amino acid) glycine with the amino acid arginine at a specific location within the FGFR3 protein. This genetic change causes the receptor to be overly

active, which leads to the disturbances in bone growth that occur in people with this disorder.

Crouzon syndrome with acanthosis nigricans

A single *FGFR3* gene variant 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. It also causes 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 a specific position in the FGFR3 protein (known as A391E). The altered protein is activated more easily than normal, and this overactivity disrupts the normal growth of the skull bones and skin, leading to features of Crouzon syndrome with acanthosis nigricans.

Epidermal nevus

Variants 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 variants are associated with some keratinocytic epidermal nevi, which are abnormal skin growths that are composed of skin cells called keratinocytes. *FGFR3* gene variants have not been found in people with other types of epidermal nevi.

The most common *FGFR3* gene variant in people with epidermal nevi changes a single amino acid in the FGFR3 protein. This variant creates a protein that turns on without the help of a growth factor, which means that the FGFR3 protein is constantly active. Studies suggest that cells with this *FGFR3* gene variant grow larger and divide more often than normal cells. The resulting overgrowth of skin cells leads to epidermal nevi.

The *FGFR3* gene variant found in people with 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 severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN). However, in contrast to the skeletal conditions, the variants associated with epidermal nevi (and seborrheic keratosis) are somatic variants. Somatic gene variants are not inherited; they are acquired during a person's lifetime and are present only in certain cells. In epidermal nevi, the variants occur during the early stages of development and are present only in the cells of the nevus, not in the normal skin cells surrounding it.

Hypochondroplasia

Multiple variants 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 variants,

both of which lead to the same change in the FGFR3 protein. This change replaces the amino acid asparagine with the amino acid lysine at a specific position in the FGFR3 protein (known as N540K). Other *FGFR3* gene variants probably cause a small number of cases of hypochondroplasia. These hypochondroplasia-associated variants probably cause the receptor to be mildly overactive, which leads to the disturbances in bone growth that occur in people with this disorder.

Lacrimo-auriculo-dento-digital syndrome

At least one variant 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 variant that causes LADD syndrome replaces the amino acid aspartic acid with the amino acid asparagine at a specific position in the receptor protein (known as D513N). When a growth factor attaches to this modified version of FGFR3 receptor protein, the protein has difficulty triggering the normal chemical signals within the cell. These defects in cell signaling disrupt cell maturation and development, which results in abnormal formation of the ears, the skeleton, and the glands in the eyes and mouth in people with LADD syndrome.

Muenke syndrome

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

The *FGFR3* gene variant that causes Muenke syndrome has also been identified in some people with 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).

SADDAN

One variant 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 a specific position in the FGFR3 protein (known as K650M). Researchers believe that this variant strongly overactivates the FGFR3 protein, which leads to severe problems with bone growth. It remains uncertain how the variant causes developmental delays or acanthosis nigricans.

Thanatophoric dysplasia

Variants 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. Most individuals with thanatophoric dysplasia are stillborn or die shortly after birth.

Most of these *FGFR3* gene variants change a single amino acid in the FGFR3 protein or create a protein that is longer than normal. These variants cause type I thanatophoric dysplasia.

Only one *FGFR3* gene variant has been shown to cause type II thanatophoric dysplasia. This variant affects a different part of the FGFR3 protein than the variants 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 people with this condition.

Bladder cancer

Somatic variants 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 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 variants. *FGFR3* gene variants 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 bladder cancer.

Multiple myeloma

MedlinePlus Genetics provides information about Multiple myeloma

Other disorders

At least two *FGFR3* gene variants have been found to cause a rare disorder called camptodactyly, tall stature, hearing loss (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 variants involved in CATSHL syndrome reduce the function of the FGFR3 protein, although it is unclear how the variants cause the signs and symptoms of the condition.

Variants 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 variants associated with seborrheic keratoses are somatic variants, which means that they are only found in the tumors and are not inherited. These variants change single amino acids in the FGFR3 protein. The altered FGFR3 proteins are abnormally active, which results in the overgrowth of skin cells. It has been suggested that the variants involved in seborrheic keratosis may be caused by exposure to ultraviolet light.

A somatic *FGFR3* gene mutation that causes epidermal nevus 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 variant affects brain cells in addition to cells in the skin.

Other cancers

In addition to bladder cancer, somatic variants 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 rearrangements (translocations) of genetic material between chromosome 14 and the region of chromosome 4 that contains the *FGFR3* gene. Variants that have been associated with cervical cancer are changes in single DNA building blocks (nucleotides) in the *FGFR3* gene.

FGFR3 gene variants 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.

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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of FGFR3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2261[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28FGFR3%5BTI%5D%29+OR+%28fibroblast+growth+factor+receptor+3%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3 (https://omim.org/entry/134934)
- KERATOSIS, SEBORRHEIC (https://omim.org/entry/182000)
- MYELOMA, MULTIPLE (https://omim.org/entry/254500)
- CERVICAL CANCER (https://omim.org/entry/603956)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2261)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=FGFR3[gene])

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Genomic Location

The *FGFR3* gene is found on chromosome 4 (https://medlineplus.gov/genetics/chromosome/4/).

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