

# FGFR2 Gene

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Fibroblast growth factor receptor 2: The FGFR2 gene provides instructions for making a protein called fibroblast growth factor receptor 2 (FGFR2).

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## 1. Normal Function

Fibroblast growth factor receptors are related proteins that are involved in important processes such as cell growth and division (proliferation), cell maturation (differentiation), bone development, formation of blood vessels (angiogenesis), wound healing, and embryonic development.

The FGFR2 protein spans the outer membrane surrounding cells, 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 allows the FGFR2 protein to interact with specific growth factors outside the cell and to receive signals that help the cell respond to its environment. When growth factors attach to the FGFR2 protein, the receptor triggers a series of chemical reactions inside the cell that instruct the cell to undergo certain changes, such as maturing to take on specialized functions.

The FGFR2 protein plays an important role in bone growth, particularly during development before birth (embryonic development). For example, this protein signals certain immature cells in the developing embryo to become bone cells and form the head, hands, feet, and other tissues. The protein is also involved in bone remodeling, a normal process in which old bone is broken down and new bone is created to replace it.

There are several slightly different versions (isoforms) of the FGFR2 protein. Specific patterns of these isoforms are found in the body's tissues, and these patterns may change throughout growth and development.

## 2. Health Conditions Related to Genetic Changes

### 2.1 Apert Syndrome

At least ten mutations in the *FGFR2* gene have been found to cause Apert syndrome. This condition causes premature closure of the bones of the skull (craniosynostosis), leading to a misshapen head, distinctive facial features, and brain abnormalities. Affected individuals often have abnormalities of the fingers and toes, hearing and vision problems, and other signs and symptoms.

More than 98 percent of cases of Apert syndrome are caused by one of two mutations in the *FGFR2* gene. These mutations change single protein building blocks (amino acids) in the FGFR2 protein. One mutation replaces the amino acid serine with the amino acid tryptophan at protein position 252 (written as Ser252Trp). The other mutation replaces the amino acid proline with the amino acid arginine at position 253 (written as Pro253Arg). These changes are described as "gain-of-function" because they increase the activity of the protein, leading to stronger signaling, which causes cells to mature too quickly. As a result, structures in the body develop abnormally, leading to premature fusion of bones in the skull, hands, and feet and other characteristic features of Apert syndrome.

### 2.2 Beare-Stevenson Cutis Gyrate Syndrome

At least three mutations in the *FGFR2* gene have been found to cause Beare-Stevenson cutis gyrate syndrome, a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features, and a skin abnormality called cutis gyrate. The most common mutation replaces the amino acid tyrosine with the amino acid cysteine

at position 375 in the protein (written as Tyr375Cys). The *FGFR2* gene mutations that cause Beare-Stevenson cutis gyrata syndrome appear to overactivate signaling by the FGFR2 protein, which promotes the premature fusion of bones in the skull and alters skin development.

### **2.3 Crouzon Syndrome**

At least 60 mutations in the *FGFR2* gene can cause Crouzon syndrome, a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features. Affected individuals can have vision, hearing, and dental problems related to abnormal skull development. Most of the mutations that cause Crouzon syndrome change single DNA building blocks (nucleotides) in the *FGFR2* gene. Insertions and deletions of a small number of nucleotides are also known to cause the disorder. These mutations in the *FGFR2* gene appear to overactivate signaling by the FGFR2 protein, which promotes premature fusion of bones in the skull.

### **2.4 Jackson-Weiss Syndrome**

At least six mutations in the *FGFR2* gene have been found to cause Jackson-Weiss syndrome. This condition causes craniosynostosis, leading to a misshapen head and distinctive facial features. Affected individuals also have foot abnormalities. Each of the mutations associated with Jackson-Weiss syndrome changes a single amino acid in a region of the FGFR2 protein known as the IgIII domain, which is critical for receiving signals and interacting with growth factors. The mutations appear to overactivate signaling by the FGFR2 protein, which promotes premature fusion of skull bones and affects development of bones in the feet.

### **2.5 Lacrimo-Auriculo-Dento-Digital Syndrome**

At least two mutations in the *FGFR2* gene have 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. A mutation that occurs in some people with LADD syndrome replaces the amino acid alanine with the amino acid threonine at position 628 in the FGFR2 protein (written as Ala628Thr or A628T).

The *FGFR2* gene mutations that cause LADD syndrome reduce the FGFR2 protein's ability to trigger chemical signaling within cells when it binds to its growth factor. These defects in cell signaling disrupt cell maturation and development, which results in abnormal formation of glands in the eyes and mouth, the ears, and the skeleton in people with LADD syndrome.

### **2.6 Pfeiffer Syndrome**

More than 25 mutations in the *FGFR2* gene can cause Pfeiffer syndrome, a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features. People with this condition can also have elbow, hand, or foot abnormalities. The severity of this condition varies widely among affected individuals. Several of the mutations that cause this condition change the number of cysteine amino acids in a critical region of the FGFR2 protein known as the IgIII domain. The remaining mutations affect amino acids other than cysteine or result in an FGFR2 protein that is missing one or more amino acids. These mutations appear to overactivate signaling by the FGFR2 protein, which promotes premature fusion of skull bones and affects the development of bones in the hands and feet.

### **2.7 Breast Cancer**

### **2.8 Cholangiocarcinoma**

### **2.9 Epidermal Nevus**

### **2.10 Prostate Cancer**

### **2.11 Other Disorders**

Mutations in the *FGFR2* gene can cause other disorders that affect bone development. *FGFR2* gene mutations have been found in individuals with conditions called bent bone dysplasia syndrome and Antley-Bixler syndrome.

Bent bone dysplasia syndrome is characterized by the underdevelopment of certain bones, bent long bones in the arms and legs, low bone mineral density (osteopenia), and distinctive facial features. Signs and symptoms of Antley-Bixler syndrome typically include craniosynostosis, distinctive facial features, arm and leg malformations, and genitourinary abnormalities.

The *FGFR2* gene mutations that cause these conditions appear to overactivate signaling by the FGFR2 protein, leading to skeletal abnormalities and other characteristic features of the conditions.

The particular condition that results from *FGFR2* gene mutations may be determined by the region of the gene in which the mutation occurs. It is likely that mutations in different regions of the *FGFR2* gene have varied effects on the protein, resulting in a range of protein activity and signaling. Changes in other genes or modifications of DNA that do not alter the DNA sequence (epigenetic changes) may also help determine the resulting signs and symptoms. The different factors lead to similar but distinct features of the many conditions associated with *FGFR2* gene mutations.

## 2.12 Cancers

Alterations in the activity (expression) of the *FGFR2* gene are associated with certain cancers. The altered gene expression may enhance several cancer-promoting cell functions such as cell division (proliferation), cell movement, and the formation of new blood vessels (angiogenesis) that nourish a growing tumor.

The *FGFR2* gene is abnormally active (overexpressed) in certain types of stomach (gastric) cancers, and this amplification is associated with a poor disease outcome. Abnormal expression of the *FGFR2* gene is also found in patients with prostate cancer. A shift in the expression of two specific FGFR2 isoforms, IIIb and IIIc, appears to correlate with prostate cancer progression. This change in expression is complex, however, and varies depending on the type of prostate tumor. More advanced tumors may show an increase in the IIIb isoform, while other prostate tumors show a decrease in IIIb but an increase in IIIc. Altered *FGFR2* gene expression is also associated with ovarian, breast, cervical, endometrial, pancreatic, lung, and head and neck cancers.

## 3. Other Names for This Gene

- bacteria-expressed kinase
  - BEK
  - BEK fibroblast growth factor receptor
  - BEK protein tyrosine kinase
  - BFR-1
  - CD332
  - CEK3
  - CFD1
  - ECT1
  - FGF receptor
  - FGFR2\_HUMAN
  - K-SAM
  - keratinocyte growth factor receptor
  - KGFR
  - protein tyrosine kinase, receptor like 14
  - TK14
  - TK25
  - tyrosylprotein kinase
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