FGFR1 gene

fibroblast growth factor receptor 1

Normal Function

The *FGFR1* gene provides instructions for making a protein called fibroblast growth factor receptor 1. This protein is one of four fibroblast growth factor receptors, which are related proteins that are involved in processes such as cell division, regulation of cell growth and maturation, formation of blood vessels, wound healing, and embryonic development.

The FGFR1 protein spans the cell membrane, so that one end of the protein is inside the cell and the other end projects from the outer surface of the cell. This positioning allows the FGFR1 protein to interact with other proteins called fibroblast growth factors (FGFs) outside the cell and to receive signals that help the cell respond to its environment. When an FGF attaches to the FGFR1 protein, the receptor 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. This signaling is thought to play an important role in the development and growth of several parts of the body, including the brain, bones of the head and face (craniofacial bones), bones in the hands and feet, and the long bones in the arms and legs.

Signaling through the FGFR1 protein plays a critical role in the formation, survival, and movement (migration) of nerve cells (neurons) in several areas of in the brain. In particular, this signaling appears to be essential for neurons that produce a hormone called gonadotropin-releasing hormone (GnRH). GnRH controls the production of several other hormones that direct sexual development before birth and during puberty. These hormones are important for the normal function of the ovaries in women and the testes in men. FGFR1 also appears to play a role in a group of nerve cells that are specialized to process smells (olfactory neurons). These neurons migrate from the developing nose to a structure at the front of the brain called the olfactory bulb, which is critical for the perception of odors.

Health Conditions Related to Genetic Changes

8p11 myeloproliferative syndrome

The *FGFR1* gene is involved in a type of blood cancer called 8p11 myeloproliferative syndrome. This condition is characterized by an increased number of white blood cells (

myeloproliferative disorder) and the development of lymphoma, a blood-related cancer that causes tumor formation in the lymph nodes. The myeloproliferative disorder usually develops into another form of blood cancer called acute myeloid leukemia. 8p11 myeloproliferative syndrome results from a rearrangement (translocation) of genetic material between chromosome 8 and another chromosome, which fuses part of the *FGFR1* gene with part of another gene from the other chromosome. The most common partner gene is *ZMYM2* on chromosome 13. These translocations are found only in cancer cells.

Regardless of the partner gene, the protein produced from the fused gene turns on FGFR1 signaling without the need for stimulation from growth factors. The uncontrolled signaling promotes continuous cell growth and division, leading to cancer.

Encephalocraniocutaneous lipomatosis

At least two mutations in the *FGFR1* gene have been identified in people with encephalocraniocutaneous lipomatosis (ECCL), a rare condition characterized by the growth of noncancerous tumors and other abnormalities affecting the brain, eyes, and skin. The mutations that cause ECCL are not inherited from a parent; they arise randomly in one cell during the early stages of development before birth. As cells continue to grow and divide, some cells will have the mutation and other cells will not. This mixture of cells with and without a genetic mutation is known as mosaicism.

The *FGFR1* gene mutations associated with ECCL change single protein building blocks (amino acids) in the FGFR1 protein. These mutations are described as "gain-of-function" because they overactivate the receptor, triggering abnormal signaling that affects cell growth and division. Researchers are studying how these changes in signaling lead to tumor growth and the other features of ECCL.

Hartsfield syndrome

At least seven mutations in the *FGFR1* gene have been identified in people with Hartsfield syndrome, a rare condition characterized by holoprosencephaly, which is an abnormality of brain development, and a malformation of the hands and feet called ectrodactyly.

Some of these mutations affect one of the two copies of the *FGFR1* gene in each cell, causing the autosomal dominant form of the disorder. Researchers believe that these mutations have a "dominant negative" effect, which means that the version of the FGFR1 protein produced from the mutated copy of the gene interferes with the activity of the version of the protein made from the normal copy of the gene. In other cases, mutations occur in both copies of the *FGFR1* gene, causing the autosomal recessive form of the disorder.

All of the mutations associated with Hartsfield syndrome greatly reduce or eliminate the function of the FGFR1 protein, including its ability to bind to FGFs. As a result, the receptor is unable to transmit signals properly, which impairs many aspects of normal development. It is unclear how these changes lead specifically to holoprosencephaly and ectrodactyly, the characteristic features of Hartsfield syndrome.

Kallmann syndrome

Researchers have identified more than 140 *FGFR1* gene mutations that can cause Kallmann syndrome, a disorder characterized by the combination of hypogonadotropic hypogonadism (a condition affecting the production of hormones that direct sexual development) and an impaired sense of smell. This condition can also affect other body systems, and its features vary among affected individuals. Researchers estimate that mutations in the *FGFR1* gene account for about 10 percent of all cases of Kallmann syndrome.

The *FGFR1* gene mutations that cause Kallmann syndrome change single amino acids in the FGFR1 protein or result in the production of an abnormally small, nonfunctional version of the protein. Because these mutations reduce or eliminate the function of FGFR1, preventing it from transmitting signals properly, they are described as "loss-of-function" mutations. Studies suggest that a shortage of functional FGFR1 disrupts the migration and survival of olfactory neurons and GnRH-producing neurons in the developing brain. If olfactory nerve cells do not extend to the olfactory bulb, a person's sense of smell will be impaired or absent. Misplacement or premature loss of GnRH-producing neurons prevents the production of sex hormones, which interferes with normal sexual development and causes puberty to be delayed or absent.

Some people with Kallmann syndrome resulting from *FGFR1* gene mutations have additional features, such as a split in the lip (cleft lip) with an opening in the roof of the mouth (a cleft palate), abnormal tooth development, and abnormalities of the hands and feet. It is unclear how mutations in the *FGFR1* gene lead to these other signs and symptoms. Because these features vary among individuals, researchers suspect that other genetic and environmental factors may be involved. Some affected individuals have mutations in one of several other genes in addition to *FGFR1*, and these genetic changes may contribute to the varied features of the condition.

Osteoglophonic dysplasia

At least three mutations in the *FGFR1* gene can cause a rare condition called osteoglophonic dysplasia. This condition is characterized by abnormal bone growth that leads to head and face (craniofacial) abnormalities and dwarfism. *FGFR1* gene mutations that cause osteoglophonic dysplasia change single amino acids in the FGFR1 protein. The altered FGFR1 protein appears to cause prolonged signaling, which promotes premature fusion of bones in the skull and disrupts the regulation of bone growth in the arms and legs, leading to craniofacial abnormalities and shortened limbs. Because the *FGFR1* gene mutations that cause osteoglophonic dysplasia abnormally increase FGFR1 signaling, they are described as "gain-of-function" mutations.

Pfeiffer syndrome

Another "gain-of-function" mutation in the *FGFR1* gene can cause Pfeiffer syndrome. This condition is characterized by premature fusion of certain bones in the skull (craniosynostosis), which leads to a misshapen head and distinctive facial features.

Affected individuals also have hand and foot abnormalities. The *FGFR1* gene mutation that causes this condition changes a single amino acid in the FGFR1 protein; the amino acid proline is replaced with the amino acid arginine at protein position 252 (written as Pro252Arg or P252R). The altered FGFR1 protein appears to cause prolonged signaling, which promotes early fusion of the skull bones and affects the development of bones in the hands and feet.

Other disorders

Several mutations in the *FGFR1* gene have been found to cause a form of hypogonadotropic hypogonadism that occurs without an impaired sense of smell. This condition is often called normosmic isolated hypogonadotropic hypogonadism (nIHH). Like the *FGFR1* gene mutations that cause Kallmann syndrome (described above), these mutations reduce or eliminate the function of the FGFR1 protein, preventing it from transmitting signals properly.

A shortage of functional FGFR1 disrupts the migration of GnRH-producing nerve cells in the developing brain, which affects the production of sex hormones and leads to delayed or absent puberty. It is unclear why some *FGFR1* gene mutations affect the sense of smell (resulting in Kallmann syndrome) and others do not (resulting in nIHH). A few mutations have been found to cause Kallmann syndrome in some people and nIHH in others.

Other cancers

Changes involving the *FGFR1* gene have been found in certain cancers. These genetic changes are somatic, which means they are not inherited but instead occur in cells that give rise to the tumor. Gene amplification, which results in an abnormally large number of copies of the *FGFR1* gene, occurs in several forms of cancer. These include some cancers of the lung, esophagus, breast, and oral cavity. Additionally, mutations that change single amino acids in the *FGFR1* gene have been identified in several types of brain tumor.

Studies suggest that the genetic changes in *FGFR1* that are associated with cancer abnormally increase the activity of the FGFR1 protein and enhance its ability to trigger chemical reactions within the cell. The resulting uncontrolled signaling can promote continuous cell growth and division, which is a hallmark of cancer. Amplification of the *FGFR1* gene has been associated with a poorer prognosis for some cancers and an increased likelihood that the tumor will spread (metastasize) to other parts of the body.

Other Names for This Gene

- BFGFR
- C-FGR
- CD331
- CEK
- FGFR1_HUMAN

- fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)

- FLG
- FLJ14326
- FLT2
- FMS-like gene
- FMS-like tyrosine kinase 2
- heparin-binding growth factor receptor 1
- hydroxyaryl-protein kinase
- KAL2
- N-SAM tyrosine kinase
- protein-tyrosine kinase
- tyrosyl protein kinase

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of FGFR1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2260[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28FGFR1%5BTIAB%5D%29+OR+%28fibroblast+growth+factor+receptor+1%5BTIAB%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+360+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- FIBROBLAST GROWTH FACTOR RECEPTOR 1; FGFR1 (https://omim.org/entry/136350)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2260)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=FGFR1[gene])

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Genomic Location

The *FGFR1* gene is found on chromosome 8 (https://medlineplus.gov/genetics/chromosome/8/).

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