FGF8 Gene

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Fibroblast growth factor 8: The FGF8 gene provides instructions for making a protein called fibroblast growth factor 8 (FGF8).

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1. Normal Function

This protein is part of a family of proteins called fibroblast growth factors that are involved in many processes, including cell division, regulation of cell growth and maturation, and development before birth. FGF8 attaches (binds) to another protein called fibroblast growth factor receptor 1 (FGFR1) on the cell surface, which triggers a cascade of chemical reactions inside the cell.

Starting before birth, the signals triggered by FGF8 and FGFR1 play a critical role in the formation, survival, and movement (migration) of certain nerve cells (neurons) 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. FGF8 and FGFR1 also 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.

The FGF8 protein is also found in other parts of the developing embryo, including other areas of the brain and the limbs, heart, ears, and eyes. Researchers suspect that it may be involved in the normal formation and development of these structures as well.

2. Health Conditions Related to Genetic Changes

2.1 Kallmann Syndrome

At least seven mutations in the *FGF8* gene have been identified in people with 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 *FGF8* gene account for a small percentage of all cases of Kallmann syndrome.

Most of the *FGF8* gene mutations that cause Kallmann syndrome change single protein building blocks (amino acids) in the FGF8 protein. These mutations reduce or eliminate the protein's function, including its ability to bind to FGFR1. Studies suggest that a shortage of functional FGF8 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 *FGF8* 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), and a condition called bimanual synkinesis, in which the movements of one hand are mirrored by the other hand. It is unclear how mutations in the *FGF8* 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 *FGF8*, and these genetic changes may contribute to the varied features of the condition.

2.2 Nonsyndromic Holoprosencephaly

2.3 Nonsyndromic Holoprosencephaly

2.4 Other Disorders

Several mutations in the *FGF8* 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 most of the *FGF8* gene mutations that cause Kallmann syndrome (described above), the mutations that cause nIHH change single amino acids in the FGF8 protein. These mutations reduce or eliminate the function of FGF8, including its ability to bind to FGFR1. A shortage of functional FGF8 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 *FGF8* gene mutations affect the sense of smell (resulting in Kallmann syndrome) and others do not (resulting in nIHH). At least one mutation has been found to cause Kallmann syndrome in some people and nIHH in others; this genetic change replaces the amino acid arginine with the amino acid glycine at position 127 of the FGF8 protein (written as Arg127Gly or R127G).

3. Other Names for This Gene

- AIGF
- androgen-induced growth factor
- FGF-8
- fibroblast growth factor 8 (androgen-induced)
- HBGF-8
- heparin-binding growth factor 8
- HH6
- KAL6

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