

GJB2 gene

gap junction protein beta 2

Normal Function

The *GJB2* gene provides instructions for making a protein called gap junction beta 2, more commonly known as connexin 26. Connexin 26 is a member of the connexin protein family. Connexin proteins form channels called gap junctions that permit the transport of nutrients, charged atoms (ions), and signaling molecules between adjoining cells. The size of the gap junction and the types of particles that move through it are determined by the particular connexin proteins that make up the channel. Gap junctions made with connexin 26 transport potassium ions and certain small molecules.

Connexin 26 is found in cells throughout the body, including the inner ear. Because of its presence in the inner ear, especially the snail-shaped structure called the cochlea, researchers are interested in this protein's role in hearing. Hearing requires the conversion of sound waves to electrical nerve impulses. This conversion involves many processes, including maintenance of the proper level of potassium ions in the inner ear. Some studies indicate that channels made with connexin 26 help to maintain the correct level of potassium ions. Other research suggests that connexin 26 is required for the maturation of certain cells in the cochlea.

Connexin 26 is also found in the skin. It is thought to play a role in the growth, maturation, and stability of the skin's outermost layer, the epidermis.

Health Conditions Related to Genetic Changes

Bart-Pumphrey syndrome

At least two *GJB2* gene mutations have been identified in people with Bart-Pumphrey syndrome. This condition is characterized by a white discoloration of the nails (leukonychia), thickened skin on the palms of the hands and soles of the feet (palmoplantar keratoderma), wart-like growths (knuckle pads) on the knuckles of the fingers and toes, and hearing loss. The *GJB2* gene mutations that cause Bart-Pumphrey syndrome replace the protein building block (amino acid) glycine with the amino acid serine at protein position 59 (Gly59Ser or G59S) or replace the amino acid asparagine with the amino acid lysine at protein position 54 (Asn54Lys or N54K). The altered protein probably disrupts the function of normal connexin 26 in cells. This disruption could affect skin growth and also impair hearing by disturbing the conversion

of sound waves to nerve impulses.

Hystrix-like ichthyosis with deafness

At least one *GJB2* gene mutation has been identified in people with hystrix-like ichthyosis with deafness (HID), a disorder characterized by dry, scaly skin (ichthyosis) and hearing loss that is usually profound. This mutation replaces the amino acid aspartic acid with the amino acid asparagine at protein position 50, written as Asp50Asn or D50N. The mutation is thought to result in channels that constantly leak ions, which impairs the health of the cells and increases cell death. Death of cells in the skin and the inner ear may underlie the signs and symptoms of HID.

Because the D50N mutation can also cause keratitis-ichthyosis-deafness (KID) syndrome (described below), many researchers categorize KID syndrome and HID as a single disorder, which they call KID/HID. It is not known why some people with this gene mutation have eye problems while others do not.

Keratitis-ichthyosis-deafness syndrome

At least nine *GJB2* gene mutations have been identified in people with keratitis-ichthyosis-deafness (KID) syndrome, with the most common being the D50N mutation that also occurs in hystrix-like ichthyosis with deafness (described above). KID syndrome is characterized by keratitis, which is inflammation of the front surface of the eye (the cornea); thick, reddened patches of dry and scaly skin (ichthyosis); and deafness.

The *GJB2* gene mutations that cause KID syndrome change single amino acids in connexin 26. The mutations are thought to result in channels that constantly leak ions, which impairs the health of the cells and increases cell death. Death of cells in the skin and the inner ear may underlie the ichthyosis and deafness that occur in KID syndrome. It is unclear how *GJB2* gene mutations affect the eye.

Nonsyndromic hearing loss

Researchers have identified more than 100 *GJB2* gene mutations that can cause nonsyndromic hearing loss, which is loss of hearing that is not associated with other signs and symptoms. Mutations in this gene can cause two forms of nonsyndromic hearing loss: DFNB1 and DFNA3.

DFNB1 is inherited in an autosomal recessive pattern, which means both copies of the *GJB2* gene are mutated in each cell. This form of the condition accounts for about half of all cases of autosomal recessive nonsyndromic hearing loss. It is characterized by mild to profound hearing loss that is present before a child learns to speak (prelingual) and does not become more severe over time.

Some of the mutations that cause DFNB1 delete or insert DNA building blocks (base pairs) within or near the *GJB2* gene. The most common mutation in many populations, particularly in people of northern European descent, deletes one base pair at position 35 in the *GJB2* gene (written as 35delG). In Asian populations, a frequently reported

mutation deletes a base pair at position 235 (235delC). Among people with eastern European (Ashkenazi) Jewish ancestry, the deletion of a single base pair at position 167 (167delT) is a common mutation. Less frequently, *GJB2* gene mutations that cause DFNB1 replace one base pair with an incorrect one or delete a segment of DNA near the gene.

The *GJB2* gene mutations that result in DFNB1 are described as "loss of function" because they lead to an altered or nonfunctional version of connexin 26, which appears to disrupt the assembly or function of gap junctions. In the inner ear, the abnormal or missing gap junctions likely alter the levels of potassium ions, which may affect the function and survival of cells that are needed for hearing.

DFNA3 is inherited in an autosomal dominant pattern, which means only one mutated copy of the *GJB2* gene in each cell is sufficient to cause the condition. This form of hearing loss can be either prelingual or begin after a child learns to speak (postlingual). The hearing loss ranges from mild to profound, becomes more severe over time, and particularly affects the ability to hear high-frequency sounds.

The *GJB2* gene mutations that cause DFNA3 replace one amino acid in connexin 26 with an incorrect amino acid. These mutations are described as "dominant negative," which means that they lead to an abnormal version of connexin 26 that prevents the formation of any functional gap junctions. An absence of these channels probably affects the function and survival of cells in the inner ear that are essential for hearing.

Palmoplantar keratoderma with deafness

At least nine *GJB2* gene mutations have been identified in people with palmoplantar keratoderma with deafness, a condition characterized by hearing loss and unusually thick skin on the palms of the hands and soles of the feet. The *GJB2* gene mutations that cause this condition change single amino acids in connexin 26. The altered protein probably disrupts the function of normal connexin 26 in cells and may interfere with the function of other connexin proteins. This disruption could affect skin growth and also impair hearing by disturbing the conversion of sound waves to nerve impulses.

Vohwinkel syndrome

At least three *GJB2* gene mutations have been identified in people with Vohwinkel syndrome, a condition characterized by hearing loss and skin abnormalities. In addition to abnormal patches of skin, affected individuals develop tight bands of abnormal fibrous tissue around their fingers and toes that may cut off the circulation to the digits and result in spontaneous amputation. The *GJB2* gene mutations that cause Vohwinkel syndrome change single amino acids in connexin 26. The altered protein probably disrupts the function of normal connexin 26 in cells and may interfere with the function of other connexin proteins. These abnormalities could affect skin growth and also impair hearing by disturbing the conversion of sound waves to nerve impulses.

Other Names for This Gene

- CX26
- CXB2_HUMAN
- DFNA3
- DFNB1
- gap junction protein, beta 2, 26kDa
- NSRD1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of GJB2 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2706\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2706[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28GJB2%5BTIAB%5D%29+OR+%28connexin+26%5BTIAB%5D%29+OR+%28DFNB1%5BTI%5D%29+OR+%28DFNA3%5BTI%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

- GAP JUNCTION PROTEIN, BETA-2; GJB2 (<https://omim.org/entry/121011>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/2706>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=GJB2\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=GJB2[gene]))

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Genomic Location

The *GJB2* gene is found on chromosome 13 (<https://medlineplus.gov/genetics/chromosome/13/>).

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