GJC2 gene

gap junction protein gamma 2

Normal Function

The *GJC2* gene provides instructions for making a protein called connexin-47. This protein is a member of the gap junction connexin family, a group of proteins that form channels called gap junctions between cells. Gap junctions allow for the transport of nutrients, charged particles (ions), and small molecules between cells.

Connexin-47 is produced in the brain and spinal cord (central nervous system), specifically in cells called oligodendrocytes, which help coat nerve cells with a protective layer called myelin. Myelin is a fatty substance that insulates nerve fibers and promotes the rapid transmission of nerve impulses.

Connexin-47 forms gap junctions that facilitate communication between oligodendrocytes or between oligodendrocytes and another type of nervous system cell called astrocytes. Communication between these cells is necessary for the formation and maintenance of myelin.

Health Conditions Related to Genetic Changes

Pelizaeus-Merzbacher-like disease type 1

At least 30 mutations in the *GJC2* gene have been found to cause Pelizaeus-Merzbacher-like disease type 1. This condition affects the nervous system's white matter, which consists of nerve fibers covered by myelin. Individuals with Pelizaeus-Merzbacher-like disease type 1 have neurological problems that typically cause movement abnormalities and less frequently, vision problems.

Two *GJC2* gene mutations that appear in up to one-third of people with this condition occur in an area of the *GJC2* gene called the promoter region, which helps control the production of connexin-47. These mutations reduce the production of connexin-47, leading to a decrease in gap junction formation. Other *GJC2* gene mutations prevent the connexin-47 protein from reaching the cell membrane where it is needed to form gap junctions. Still other *GJC2* gene mutations decrease the function of the protein in the gap junction, reducing the overall efficacy of the channel.

All of the *GJC2* gene mutations that cause this condition affect both copies of the gene in each cell. They disrupt the communication between nerve cells that normally occurs

at gap junctions and impair myelin formation. These changes lead to nerve damage that impairs nervous system function, resulting in the signs and symptoms of Pelizaeus-Merzbacher-like disease type 1.

Other disorders

Mutations in the *GJC2* gene are also associated with a neurological disorder called spastic paraplegia type 44 and a form of hereditary lymphedema that causes abnormal swelling of the limbs.

Spastic paraplegia type 44 is characterized by muscle stiffness (spasticity), paralysis of the upper limbs (paraplegia), impaired speech (dysarthria), and mild intellectual disability. These signs and symptoms typically begin in childhood. Spastic paraplegia type 44 is caused by a specific *GJC2* gene mutation that is present in both copies of the gene in each cell. This mutation replaces the protein building block (amino acid) isoleucine with the amino acid methionine at position 33 in the protein (written as Ile33Met or I33M). This change reduces but does not eliminate connexin-47 activity. As a result, gap junctions have some function, which may explain why spastic paraplegia type 44 has similar features to Pelizaeus-Merzbacher-like disease type 1 (described above) but is less severe.

Hereditary lymphedema caused by *GJC2* gene mutations is a condition that affects the normal function of the lymphatic system. The lymphatic system produces and transports lymph fluid and immune cells throughout the body. Impaired transport of lymph fluid resulting in its accumulation can cause swelling (lymphedema). Individuals with hereditary lymphedema can have swelling from birth or develop it later in life. The lymphedema typically begins in the legs and often involves the arms over time. Hereditary lymphedema is caused by mutations in one copy of the *GJC2* gene, but it is unclear what role the *GJC2* gene plays in the lymphatic system and how mutations cause this condition.

Other Names for This Gene

- connexin-46.6
- connexin-47
- CX46.6
- Cx47
- gap junction alpha-12 protein
- gap junction gamma-2 protein
- gap junction protein, gamma 2, 47kDa
- GJA12

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of GJC2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=57165[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28GJC2%5BTIAB%5D%29+OR+%28gap+junction+protein+gamma+2%5BTIAB%5D%29%29+OR+%28%28Cx47%5BTIAB%5D%29+OR+%28connexin-47%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+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- GAP JUNCTION PROTEIN, GAMMA-2; GJC2 (https://omim.org/entry/608803)
- LYMPHATIC MALFORMATION 3; LMPHM3 (https://omim.org/entry/613480)
- SPASTIC PARAPLEGIA 44, AUTOSOMAL RECESSIVE; SPG44 (https://omim.org/entry/613206)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/57165)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=GJC2[gene])

References

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Genomic Location

The *GJC2* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

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