SCN9A gene

sodium voltage-gated channel alpha subunit 9

Normal Function

The *SCN9A* gene belongs to a family of genes that provide instructions for making sodium channels. These channels, which transport positively charged sodium atoms (sodium ions) into cells, play a key role in a cell's ability to generate and transmit electrical signals.

The *SCN9A* gene provides instructions for making one part (the alpha subunit) of a sodium channel called NaV1.7. NaV1.7 sodium channels are found in nerve cells called nociceptors. Nociceptors are part of the peripheral nervous system, which connects the brain and spinal cord to cells that detect sensations such as touch, smell, and pain. Nociceptors are primarily involved in transmitting pain signals. The cell bodies of nociceptors are located in the spinal cord. Fibers called axons extend from the cell bodies, reaching throughout the body to receive sensory information. Axons transmit the information back to the spinal cord, which then sends it to the brain.

NaV1.7 sodium channels are also found in olfactory sensory neurons, which are nerve cells in the nasal cavity that transmit smell-related signals to the brain.

Health Conditions Related to Genetic Changes

Channelopathy-associated congenital insensitivity to pain

Multiple variants (also called mutations) in the *SCN9A* gene have been found to cause channelopathy-associated congenital insensitivity to pain, a condition that inhibits the ability to perceive physical pain. Most of these *SCN9A* gene variants result in the production of a nonfunctional alpha subunit of the NaV1.7 sodium channel. These nonfunctional subunits do not allow NaV1.7 sodium channels to open, preventing the flow of sodium ions into nociceptors. This lack of sodium ions blocks nociceptors from transmitting pain signals from the site of an injury to the brain.

The loss of NaV1.7 sodium channel activity in olfactory sensory neurons likely prevents smell-related signals from reaching the brain, leading to a complete loss of the sense of smell (anosmia).

Erythromelalgia

Multiple variants in the *SCN9A* gene have been found to cause erythromelalgia, a condition characterized by episodes of pain, redness, and swelling in various parts of the body, particularly the hands and feet. All the identified variants change one protein building block (amino acid) in the NaV1.7 sodium channel. These variants cause cells to produce NaV1.7 sodium channels that opens more easily and stay open longer than normal, increasing the flow of sodium ions. This increase in sodium ions enhances the transmission of pain signals, leading to the signs and symptoms of erythromelalgia.

Paroxysmal extreme pain disorder

Multiple variants in the *SCN9A* gene have been found to cause paroxysmal extreme pain disorder. This condition is characterized by severe pain attacks accompanied by skin redness and warmth (flushing) and, sometimes, seizures and changes in breathing and heart rate. The variants that cause this condition change single amino acids in the alpha subunit of the NaV1.7 sodium channel. As a result, the sodium channel does not completely close when it is turned off, allowing sodium ions to flow abnormally into nociceptors. This increase in sodium ions enhances the transmission of pain signals, leading to the pain attacks experienced by people with paroxysmal extreme pain disorder.

Small fiber neuropathy

Variants in the *SCN9A* gene account for approximately 30 percent of cases of small fiber neuropathy, a condition characterized by severe pain attacks and a reduced ability to differentiate between hot and cold. The variants that cause this condition change single amino acids in the alpha subunit of the NaV1.7 sodium channel. As a result, the sodium channel does not completely close when it is turned off, allowing sodium ions to flow abnormally into nociceptors. This increase in sodium ions enhances the transmission of pain signals. In people with this condition, the axons that extend from the nociceptors and transmit pain signals degenerate over time. The cause of this degeneration is unknown, but it likely accounts for the features of small fiber neuropathy.

Genetic epilepsy with febrile seizures plus

MedlinePlus Genetics provides information about Genetic epilepsy with febrile seizures plus

Hereditary sensory and autonomic neuropathy type II

MedlinePlus Genetics provides information about Hereditary sensory and autonomic neuropathy type II

Other disorders

At least three variants in the *SCN9A* gene have been found in a group of people with febrile seizures, which are seizures that are triggered by a high fever. Febrile seizures are the most common type of seizures in young children, affecting 2 to 5 percent of

children in Europe and North America. Children who have febrile seizures have a 2 to 9 percent chance of developing non-fever-related seizures later in life. When febrile seizures are associated with variants in the *SCN9A* gene, the condition is known as familial febrile seizures 3B. If these individuals go on to develop seizures without fevers, the condition is then known as genetic epilepsy with febrile seizures plus, type 7 (linked above). The variants that cause these conditions change single amino acids in the alpha subunit of the NaV1.7 sodium channel. It is unknown how a change in the sodium channel leads to febrile seizures.

Variants in the *SCN9A* gene, when coupled with variants in another gene called *SCN1A*, alter the progression of a seizure disorder called Dravet syndrome in some individuals. Dravet syndrome is characterized by convulsive seizures in infancy, followed in childhood by absence seizures, which cause loss of consciousness for short periods. In mid-childhood, the seizures change to the generalized tonic-clonic type, which involve muscle rigidity, convulsions, and loss of consciousness. Generalized tonic-clonic seizures are also associated with prolonged episodes of seizure activity known as nonconvulsive status epilepticus. These episodes can cause confusion and a loss of alertness that can last from hours to weeks. *SCN1A* gene variants are the most common cause of Dravet syndrome, but when an affected individual also has a *SCN9A* gene variant, the signs and symptoms of Dravet syndrome are more severe. For example, individuals with both *SCN1A* and *SCN9A* gene changes may have status epilepticus in infancy and experience a variety of seizures at any time. It is unknown how *SCN9A* gene variants contribute to the signs and symptoms of Dravet syndrome.

Other Names for This Gene

- hNE
- Nav1.7
- NE-NA
- NENA
- PN1
- SCN9A_HUMAN
- sodium channel, voltage gated, type IX alpha subunit
- sodium channel, voltage-gated, type IX, alpha
- sodium channel, voltage-gated, type IX, alpha polypeptide
- sodium channel, voltage-gated, type IX, alpha subunit
- voltage-gated sodium channel alpha subunit Nav1.7

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SCN9A (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6335[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SCN9A%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 9; SCN9A (https://omim.org/entry/603415)
- DRAVET SYNDROME; DRVT (https://omim.org/entry/607208)
- GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 7; GEFSP7 (https://omim.org/entry/613863)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6335)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SCN9A[gene])

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Genomic Location

The *SCN9A* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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