

SCN9A Gene

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sodium voltage-gated channel alpha subunit 9

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1. 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 that transmit pain signals. 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 centers of nociceptors, known as the cell bodies, are located in a part of the spinal cord called the dorsal root ganglion. Fibers called axons extend from the cell bodies, reaching throughout the body to receive sensory information. Axons transmit the information back to the dorsal root ganglion, 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.

2. Health Conditions Related to Genetic Changes

2.1. Congenital insensitivity to pain

At least 13 mutations in the *SCN9A* gene have been found to cause congenital insensitivity to pain, a condition that inhibits the ability to perceive physical pain. The *SCN9A* gene mutations that cause congenital insensitivity to pain create a premature stop signal in the instructions for making the alpha subunit of the NaV1.7 sodium channel. As a result, a shortened, nonfunctional subunit is produced which cannot be incorporated into the channel, leading to a loss of functional NaV1.7 sodium channels. The loss of these channels impairs the transmission of pain signals from the site of injury to the brain, causing those affected to be insensitive to pain. Loss of this channel in olfactory sensory neurons likely impairs the transmission of smell-related signals to the brain, leading to a complete loss of the sense of smell (anosmia).

2.2. Erythromelalgia

More than 10 mutations 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 identified mutations change one protein building block (amino acid) in the NaV1.7 sodium channel. These mutations result in a NaV1.7 sodium channel that opens more easily than usual and stays open longer than normal, increasing the flow of sodium ions that produce nerve impulses within nociceptors. This increase in sodium ions enhances transmission of pain signals, leading to the signs and symptoms of erythromelalgia.

2.3. Paroxysmal extreme pain disorder

Approximately 10 mutations 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 mutations 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 transmission of pain signals, leading to the pain attacks experienced by people with paroxysmal extreme pain disorder.

2.4. Small fiber neuropathy

Mutations 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 mutations that cause this condition change single amino acids in the alpha subunit of the Nav1.7 sodium channel. As a result of the altered alpha subunit, 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 transmission of pain signals. In this condition, the small fibers that extend from the nociceptors and transmit pain signals (axons) degenerate over time. The cause of this degeneration is unknown, but it likely accounts for signs and symptoms such as the loss of temperature differentiation.

2.5. Other disorders

At least three mutations in the *SCN9A* gene have been found in a group of people affected 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 mutations 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 generalized epilepsy with febrile seizures plus, type 7. The mutations 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 mutations 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 lasting from hours to weeks. *SCN1A* gene mutations are the most common cause of Dravet syndrome, but when an affected individual also has a *SCN9A* gene change, which might not otherwise cause health problems, 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 changes contribute to the signs and symptoms of Dravet syndrome.

3. 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

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