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 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.

Health Conditions Related to Genetic Changes

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).

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.

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.

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.

Genetic epilepsy with febrile seizures plus

Hereditary sensory and autonomic neuropathy type II

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 \textit{SCN9A} gene, when coupled with mutations in another gene called \textit{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. \textit{SCN1A} gene mutations are the most common cause of Dravet syndrome, but when an affected individual also has a \textit{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 \textit{SCN1A} and \textit{SCN9A} gene changes may have status epilepticus in infancy and experience a variety of seizures at any time. It is unknown how \textit{SCN9A} gene changes contribute to the signs and symptoms of Dravet syndrome.

\textbf{Chromosomal Location}

Cytogenetic Location: 2q24.3, which is the long (q) arm of chromosome 2 at position 24.3

Molecular Location: base pairs 166,195,185 to 166,375,987 on chromosome 2 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (NCBI)

\textbf{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

Educational Resources
• Biochemistry (fifth edition, 2002): The Sodium Channel
  https://www.ncbi.nlm.nih.gov/books/NBK22509/figure/A1820/
• Neuroscience (second edition, 2001): Nociceptors
  https://www.ncbi.nlm.nih.gov/books/NBK10965/
• Washington University, St. Louis Neuromuscular Disease Center: Voltage-Gated Sodium Channels
  https://neuromuscular.wustl.edu/mother/chan.html#nachvg

Clinical Information from GeneReviews
• Congenital Insensitivity to Pain Overview
  https://www.ncbi.nlm.nih.gov/books/NBK481553
• SCN9A Neuropathic Pain Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1163

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?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+AND+human%5Bmh%5D+AND+%22last+1800+days%22+AND+human%5Bmh%5D+AND+%22last+1800+days%22

Catalog of Genes and Diseases from OMIM
• EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 6
  http://omim.org/entry/607208
• GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 7
  http://omim.org/entry/613863
• SODIUM CHANNEL, VOLTAGE-GATED, TYPE IX, ALPHA SUBUNIT
  http://omim.org/entry/603415
Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_SCN9A.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SCN9A%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#/hgnc_id/HGNC:10597
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:6335
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/6335
- UniProt
  https://www.uniprot.org/uniprot/Q15858

Sources for This Summary

- Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, Al-Gazali L, Hamamy H, Valente EM, Gorman S, Williams R, McHale DP, Wood JN, Gribble FM, Woods CG. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006 Dec 14;444(7121):894-8. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17167479
- Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. From genes to pain: Na v 1.7 and human pain disorders. Trends Neurosci. 2007 Nov;30(11):555-63. Epub 2007 Oct 22. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17950472
- Dib-Hajj SD, Yang Y, Waxman SG. Genetics and molecular pathophysiology of Na(v)1.7-related pain syndromes. Adv Genet. 2008;63:85-110. doi: 10.1016/S0065-2660(08)01004-3. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19185186
- Doty CN. SCN9A: another sodium channel excited to play a role in human epilepsies. Clin Genet. 2010 Apr;77(4):326-8. doi: 10.1111/j.1399-0004.2009.01366_1.x. Epub 2010 Jan 20. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20095983
- Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest. 2007 Dec;117(12):3603-9. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18060017
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096434/
- Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, Dib-Hajj S, Drenth JP, Waxman SG, Merkies IS. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012 Jan;71(1):26-39. doi: 10.1002/ana.22485. Epub 2011 Jun 22. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21698661
- Fertleman CR, Ferrie CD, Aicardi J, Bednarek NA, Eeg-Olofsson O, Elmslie FV, Griesemer DA, Goutières F, Kirkpatrick M, Malmros IN, Pollitzer M, Rossiter M, Roulet-Perez E, Schubert R, Smith VV, Testard H, Wong V, Stephenson JB. Paroxysmal extreme pain disorder (previously familial rectal pain syndrome). Neurology. 2007 Aug 7;69(6):586-95. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17679678
• Fischer TZ, Waxman SG. Familial pain syndromes from mutations of the NaV1.7 sodium channel. Ann N Y Acad Sci. 2010 Jan;1184:196-207. doi: 10.1111/j.1749-6632.2009.05110.x. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20146699

• Goldberg YP, MacFarlane J, MacDonald ML, Thompson J, Dube MP, Mattice M, Fraser R, Young C, Hossain S, Pape T, Payne B, Radomski C, Donaldson G, Ives E, Cox J, Younghusband HB, Green R, Duff A, Boltshauser E, Grinspan GA, Dimon JH, Sibley BG, Andria G, Toscano E, Kerdraon J, Bowsher D, Pimstone SN, Samuels ME, Sherrington R, Hayden MR. Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. Clin Genet. 2007 Apr;71(4):311-9. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17470132

• Hoeijmakers JG, Merkies IS, Gerrits MM, Waxman SG, Faber CG. Genetic aspects of sodium channelopathy in small fiber neuropathy. Clin Genet. 2012 Oct;82(4):351-8. doi: 10.1111/j.1399-0004.2012.01937.x. Epub 2012 Aug 7. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22803682

• Houlden H. Extending the clinical spectrum of pain channelopathies. Brain. 2012 Feb;135(Pt 2):313-6. doi: 10.1093/brain/aws007. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22345085 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281474/

• Lampert A, O'Reilly AO, Reeh P, Leffler A. Sodium channelopathies and pain. Pflugers Arch. 2010 Jul;460(2):249-63. doi: 10.1007/s00424-009-0779-3. Epub 2010 Jan 26. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20101409

• Meisler MH, O'Brien JE, Sharkey LM. Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects. J Physiol. 2010 Jun 1;588(Pt 11):1841-8. doi: 10.1113/jphysiol.2010.188482. Epub 2010 Mar 29. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20351042 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2901972/

• OMIM: SODIUM CHANNEL, VOLTAGE-GATED, TYPE IX, ALPHA SUBUNIT http://omim.org/entry/603415

• Singh NA, Pappas C, Dahle EJ, Claes LR, Pruess TH, De Jonghe P, Thompson J, Dixon M, Gurnett C, Peiffer A, White HS, Filloux F, Leppert MF. A role of SCN9A in human epilepsies, as a cause of febrile seizures and as a potential modifier of Dravet syndrome. PLoS Genet. 2009 Sep;5(9): e1000649. doi: 10.1371/journal.pgen.1000649. Epub 2009 Sep 18. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19763161 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2730533/

• Waxman SG. Neurobiology: a channel sets the gain on pain. Nature. 2006 Dec 14;444(7121):831-2. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17167466

• Waxman SG. Neuroscience: Channelopathies have many faces. Nature. 2011 Apr 14;472(7342):173-4. doi: 10.1038/472173a. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21490662

• Young FB. When adaptive processes go awry: gain-of-function in SCN9A. Clin Genet. 2008 Jan; 73(1):34-6. Epub 2007 Dec 6. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18070139

Reprinted from Genetics Home Reference: https://ghr.nlm.nih.gov/gene/SCN9A
