SCN9A (sodium channel protein type 9 subunit alpha) controls a [sodium channels](http://www.uniprot.org/citations/17145499) in neurons that are part of the autonomic (involuntary) nervous system. The channel is controlled by voltage differences across membranes, and they are involved in [feeling pain](http://www.uniprot.org/citations/17145499) and developing [inflammatory pain](http://www.uniprot.org/citations/[17167479](http://www.uniprot.org/citations/17167479)). Numerous diseases are caused by [variants](<https://www.ncbi.nlm.nih.gov/pubmed/23129781>) in SCN9A, such as [congenital insensitivity or indifference to pain (CIP)](https://www.ncbi.nlm.nih.gov/pubmed/20635406), [primary erythromelalgia (PERYTHM)](https://www.ncbi.nlm.nih.gov/pubmed/14985375), [paroxysmal extreme pain disorder (PEPD)](https://www.ncbi.nlm.nih.gov/pubmed/17145499), [generalized epilepsy with febrile seizures](https://www.ncbi.nlm.nih.gov/pubmed/19763161), [fibromyalgia](<https://www.ncbi.nlm.nih.gov/pubmed/29392201>), and [CFS](https://www.ncbi.nlm.nih.gov/pubmed/29392201).

[Congenital indifference to pain (CIP)](<https://www.omim.org/entry/243000>) is a rare disorder where individuals cannot feel pain, although they feel sensations of touch, hot and cold, and pressure. They may have [frequent injuries](https://www.ncbi.nlm.nih.gov/pubmed/17167479) or [recurrent illness](https://www.ncbi.nlm.nih.gov/pubmed/22845492) and [ulcerations which may result in the need for amputation](<https://www.ncbi.nlm.nih.gov/medgen/C2752089>) due to the inability to feel or respond appropriately to pain.

The [opioids](https://www.ncbi.nlm.nih.gov/pubmed/6462379) [naloxone](https://www.ncbi.nlm.nih.gov/pubmed/6085681) and [naltrexone](https://www.ncbi.nlm.nih.gov/pubmed/26634308) may allow patients to feel and respond to pain. Other medicines used to SCN9A variants include [Lacosamide](https://www.drugbank.ca/drugs/DB06218), [Lidocaine](https://www.drugbank.ca/drugs/DB00281), [Ranolazine](https://www.drugbank.ca/drugs/DB00243), [Rufinamide](https://www.drugbank.ca/drugs/DB06201), [Valproic Acid](https://www.drugbank.ca/drugs/DB00313), and [Zonisamide]( https://www.drugbank.ca/drugs/DB00909).

This [variant](<https://www.ncbi.nlm.nih.gov/clinvar/variation/6356/>) causes three distinct diseases. [Hereditary sensory and autonomic neuropathy type II (HSAN2)](<https://www.ncbi.nlm.nih.gov/medgen/C2752089>) causes progressively reduced response to pain, leading eventually to [frequent injuries](https://www.ncbi.nlm.nih.gov/pubmed/17167479) or [recurrent illness](https://www.ncbi.nlm.nih.gov/pubmed/22845492) and [ulcerations which may result in the need for amputation](<https://www.ncbi.nlm.nih.gov/medgen/C2752089>). [Generalized epilepsy with febrile seizures plus, type 7](<https://www.ncbi.nlm.nih.gov/medgen/C2751777>) causes severe seizures beginning between 5 months and 4 years of age. [Paroxysmal extreme pain disorder (PEPD)](<https://www.ncbi.nlm.nih.gov/pubmed/17145499>) causes [rectal, eye, or jaw pain with flushing](https://www.ncbi.nlm.nih.gov/pubmed/1714549).  The pain attacks may last from seconds to hours and is considered a type of [peripheral neuropathy](<https://www.ncbi.nlm.nih.gov/medgen/C1833661>) as it affects the nervous system that connects the brain to sensory cells.

Paroxysmal extreme pain disorder (PEPD) patients may consider trying [Carbamazepine](https://www.ncbi.nlm.nih.gov/pubmed/17145499). They should also avoid [changes in temperature, emotional distress, spicy food, and cold drinks and food](<https://www.ncbi.nlm.nih.gov/medgen/C1833661>). Hereditary sensory and autonomic neuropathy type II (HSAN2) patients may consider the [opioids](https://www.ncbi.nlm.nih.gov/pubmed/6462379) [naloxone](https://www.ncbi.nlm.nih.gov/pubmed/6085681) and [naltrexone](https://www.ncbi.nlm.nih.gov/pubmed/26634308) that may cause increased sensitivity to pain.

Other medicines used to SCN9A variants include [Lacosamide](https://www.drugbank.ca/drugs/DB06218), [Lidocaine](https://www.drugbank.ca/drugs/DB00281), [Ranolazine](https://www.drugbank.ca/drugs/DB00243), [Rufinamide](https://www.drugbank.ca/drugs/DB06201), [Valproic Acid](https://www.drugbank.ca/drugs/DB00313), and [Zonisamide]( https://www.drugbank.ca/drugs/DB00909).

<https://www.ncbi.nlm.nih.gov/pubmed/29392201>

Severe fibromyalgia is associated with the Nav1.7 rs6754031 GG genotype. However, gain-of-function mutations in sodium channel Nav1.7 are present in 28% of patients with small fiber neuropathy.

<https://www.ncbi.nlm.nih.gov/pubmed/27586831>

https://www.ncbi.nlm.nih.gov/pubmed/21951710/

**Central Sensitivity Syndromes (CSS)**, in which no well-defined peripheral or central disease process can be found are thought to represent a primary dysregulation of the central nervous system leading to pain amplification, and are sometimes termed centralized pain or central sensitization. Examples include somatic pain syndromes such as fibromyalgia and tempromandibular disorder, as well as visceral pain syndromes like interstitial cystitis and irritable bowel syndrome (IBS), and possibly cognitive impairments such as chronic fatigue syndrome

https://www.ncbi.nlm.nih.gov/pubmed/24662556

This review demonstrates that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. This concordance raises the possibility that sympathetic dysfunction could be their common underlying pathogenesis that brings on overlapping clinical features. The recognition of sympathetic predominance in these 4 syndromes may have potential clinical implications. It may be worth exploring the use of nonpharmacological measures as well as drug therapies aimed to regain autonomic balance.

https://www.ncbi.nlm.nih.gov/pubmed/22550986

Although a number of treatment options are available, therapy for chronic pain is less effective than for acute pain, commonly providing significant pain relief for less than 50% of patients

* Many chronic pain syndromes such as fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition.
* Central sensitization appears to be a hallmark of chronic pain, resulting in enhanced function of pain pathways and increased membrane excitability and synaptic efficacy as well as reduced inhibition of neurons.
* reatments designed to reduce the incidence, severity and impact of chronic pain in susceptible individuals are of great clinical importance and include pre-emptive analgesia and/or multidisciplinary pain management programs.

https://www.ncbi.nlm.nih.gov/pubmed/18191990/

Specifically, the presence of central sensitization and other common features including fatigue, insomnia and distress, have resulted in labeling these chronic musculoskeletal conditions as central sensitivity syndromes (CSS)

<https://www.ncbi.nlm.nih.gov/pubmed/14997317/>

he clinical outcome effects of the 20%-30% opioid sparing by non-steroidal anti-inflammatory agents have not been defined, b

<https://www.ncbi.nlm.nih.gov/pubmed/11166973/>

Group comparisons indicated that the cognitive-behavioral group, relative to the comparison group, had significantly better results with regard to fear-avoidance beliefs, number of pain-free days, as well as the key variable of sick leave. Participation in the cognitive behavioral group reduced the risk for long-term sick leave during the follow-up by threefold. Thus, despite the strong natural recovery rate for back pain, the cognitive-behavioral intervention produced a significant preventive effect with regard to disability.

<https://www.ncbi.nlm.nih.gov/pubmed/19410099/>

A stepped care approach based upon existing evidence includes (1) simple analgesics (acetaminophen or nonsteroidal anti-inflammatory drugs); (2) tricyclic antidepressants (if neuropathic, back or fibromyalgia pain) or tramadol; (3) gabapentin, duloxetine or pregabalin if neuropathic pain; (4) cyclobenzaprine, pregabalin, duloxetine, or milnacipran for fibromyalgia; (5) topical analgesics (capsaicin, lidocaine, salicylates) if localized neuropathic or arthritic pain; and (6) opioids.

<https://www.ncbi.nlm.nih.gov/pubmed/29123662>

The genes responsible are believed to be involved in the immunological response/inflammatory cytokine expression, glucocorticoid receptor

GR dysfunction is also proposed to play a role in development of chronic fatigue, chronic pain states and the syndrome of fibromyalgia, thus providing a potential link between injury, environmental stressors and severity of chronic pain.

<http://www.uniprot.org/uniprot/Q15858>

**Sodium channel protein type 9 subunit alpha**

Mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na+ ions may pass in accordance with their electrochemical gradient (PubMed:[7720699](http://www.uniprot.org/citations/7720699), PubMed:[17167479](http://www.uniprot.org/citations/17167479), PubMed:[25240195](http://www.uniprot.org/citations/25240195), PubMed:[26680203](http://www.uniprot.org/citations/26680203), PubMed:[15385606](http://www.uniprot.org/citations/15385606), PubMed:[16988069](http://www.uniprot.org/citations/16988069), PubMed:[17145499](http://www.uniprot.org/citations/17145499), PubMed:[19369487](http://www.uniprot.org/citations/19369487), PubMed:[24311784](http://www.uniprot.org/citations/24311784)). It is a tetrodotoxin-sensitive Na+ channel isoform (PubMed:[7720699](http://www.uniprot.org/citations/7720699)). Plays a role in pain mechanisms, especially in the development of inflammatory pain (PubMed:[17167479](http://www.uniprot.org/citations/17167479), PubMed:[17145499](http://www.uniprot.org/citations/17145499), PubMed:[19369487](http://www.uniprot.org/citations/19369487), PubMed:[24311784](http://www.uniprot.org/citations/24311784)).

#### GO - Molecular functioni

* [sodium ion binding](https://www.ebi.ac.uk/QuickGO/term/GO:0031402) Source: Ensembl
* [voltage-gated ion channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0005244) Source: UniProtKB-KW
* [voltage-gated sodium channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0005248) http://www.uniprot.org/citations/17145499

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q15858)

#### GO - Biological processi

* [behavioral response to pain](https://www.ebi.ac.uk/QuickGO/term/GO:0048266) Source: Ensembl
* [inflammatory response](https://www.ebi.ac.uk/QuickGO/term/GO:0006954) Source: Ensembl
* [membrane depolarization during action potential](https://www.ebi.ac.uk/QuickGO/term/GO:0086010) Source: GO\_Central
* [neuronal action potential](https://www.ebi.ac.uk/QuickGO/term/GO:0019228) Source: GO\_Central
* [post-embryonic development](https://www.ebi.ac.uk/QuickGO/term/GO:0009791) Source: Ensembl
* [regulation of ion transmembrane transport](https://www.ebi.ac.uk/QuickGO/term/GO:0034765) Source: UniProtKB-KW
* [response to toxic substance](https://www.ebi.ac.uk/QuickGO/term/GO:0009636) Source: Ensembl
* [sensory perception of pain](https://www.ebi.ac.uk/QuickGO/term/GO:0019233) http://www.uniprot.org/citations/17145499
* [sodium ion transmembrane transport](https://www.ebi.ac.uk/QuickGO/term/GO:0035725) http://www.uniprot.org/citations/17145499
* [sodium ion transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006814) <http://www.uniprot.org/citations/7720699>

###### [**Primary erythermalgia (PERYTHM)**](http://www.uniprot.org/diseases/DI-02201)**11 Publications**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionAutosomal dominant disease characterized by recurrent episodes of severe pain associated with redness and warmth in the feet or hands.

###### [**Indifference to pain, congenital, autosomal recessive (CIP)**](http://www.uniprot.org/diseases/DI-01231)**1 Publication**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionA disorder characterized by congenital inability to perceive any form of pain, in any part of the body. All other sensory modalities are preserved and the peripheral and central nervous systems are apparently intact. Patients perceive the sensations of touch, warm and cold temperature, proprioception, tickle and pressure, but not painful stimuli. There is no evidence of a motor or sensory neuropathy, either axonal or demyelinating.

[See also OMIM:243000](http://www.omim.org/entry/243000)

###### [**Paroxysmal extreme pain disorder (PEPD)**](http://www.uniprot.org/diseases/DI-02140)**3 Publications**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionAutosomal dominant paroxysmal disorder of pain and autonomic dysfunction. The distinctive features are paroxysmal episodes of burning pain in the rectal, ocular, and mandibular areas accompanied by autonomic manifestations such as skin flushing.

[See also OMIM:167400](http://www.omim.org/entry/167400)

###### [**Generalized epilepsy with febrile seizures plus 7 (GEFS+7)**](http://www.uniprot.org/diseases/DI-02931)**1 Publication**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionA rare autosomal dominant, familial condition with incomplete penetrance and large intrafamilial variability. Patients display febrile seizures persisting sometimes beyond the age of 6 years and/or a variety of afebrile seizure types. This disease combines febrile seizures, generalized seizures often precipitated by fever at age 6 years or more, and partial seizures, with a variable degree of severity.

[See also OMIM:613863](http://www.omim.org/entry/613863)

###### [**Febrile seizures, familial, 3B (FEB3B)**](http://www.uniprot.org/diseases/DI-02932)**1 Publication**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionSeizures associated with febrile episodes in childhood without any evidence of intracranial infection or defined pathologic or traumatic cause. It is a common condition, affecting 2-5% of children aged 3 months to 5 years. The majority are simple febrile seizures (generally defined as generalized onset, single seizures with a duration of less than 30 minutes). Complex febrile seizures are characterized by focal onset, duration greater than 30 minutes, and/or more than one seizure in a 24 hour period. The likelihood of developing epilepsy following simple febrile seizures is low. Complex febrile seizures are associated with a moderately increased incidence of epilepsy.

[See also OMIM:613863](http://www.omim.org/entry/613863)

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| Orphaneti | [88642.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=88642) Channelopathy-associated congenital insensitivity to pain.  [33069.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=33069) Dravet syndrome.  [1956.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=1956) Erythromelalgia.  [36387.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=36387) Generalized epilepsy with febrile seizures-plus.  [970.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=970) Hereditary sensory and autonomic neuropathy type 2.  [46348.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=46348) Paroxysmal extreme pain disorder.  [90026.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=90026) Primary erythermalgia.  [306577.](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=306577) Sodium channelopathy-related small fiber neuropathy. |

[DB06218.](https://www.drugbank.ca/drugs/DB06218) Lacosamide.   
[DB00281.](https://www.drugbank.ca/drugs/DB00281) Lidocaine.   
[DB00243.](https://www.drugbank.ca/drugs/DB00243) Ranolazine.   
[DB06201.](https://www.drugbank.ca/drugs/DB06201) Rufinamide.   
[DB00313.](https://www.drugbank.ca/drugs/DB00313) Valproic Acid.   
[DB00909.](https://www.drugbank.ca/drugs/DB00909) Zonisamide.

<https://www.omim.org/entry/243000>

Congenital indifference to pain is a rare autosomal recessive disorder characterized by the complete absence of pain perception typically associated with noxious stimuli. Affected individuals are aware of a stimulus, but have lost the ability to perceive pain. Most patients are hyposmic or anosmic. Other sensory modalities are unaffected, and there is an absence of overt autonomic symptoms. Sural nerve biopsy and nerve conduction velocity studies are normal (summary by https://www.ncbi.nlm.nih.gov/pubmed/17167479; and https://www.ncbi.nlm.nih.gov/pubmed/22845492).

Individuals with congenital indifference to pain have painless injuries beginning in infancy but otherwise normal sensory modalities. Perception of passive movement, joint position, and vibration are normal, as are tactile thresholds and light touch perception. Reflexes and autonomic responses are also normal. The axonal flare response after intradermal injection of histamine is normal, a finding that is in contrast to HSAN ([Nagasako et al., 2003](https://www.omim.org/entry/243000#17) https://www.ncbi.nlm.nih.gov/pubmed/12583863).

<https://www.ncbi.nlm.nih.gov/pubmed/17167479>

https://www.omim.org/entry/603415#0005

#### ****.0005****  ****INSENSITIVITY TO PAIN, CHANNELOPATHY-ASSOCIATED https://www.ncbi.nlm.nih.gov/pubmed/17167479****

SCN9A, SER459TER    homozygous

[dbSNP:rs121908908](http://www.ensembl.org/Homo_sapiens/Variation/Summary?v=rs121908908;toggle_HGVS_names=open) [RCV000006725](https://www.ncbi.nlm.nih.gov/clinvar?term=RCV000006725)

In a consanguineous northern Pakistani family segregating autosomal recessive congenital insensitivity to pain ([243000](https://www.omim.org/entry/243000)), [Cox et al. (2006)](https://www.omim.org/entry/603415#3) identified homozygosity for a 1376C-G transversion in exon 10 of the SCN9A gene, resulting in a ser459-to-ter (S459X) substitution. The mutation was not found in 300 northern Pakistani control chromosomes.

<http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=88642>

<https://www.ncbi.nlm.nih.gov/clinvar/variation/6353/>

<https://www.omim.org/entry/243000>

<https://www.ncbi.nlm.nih.gov/pubmed/17167479>

https://www.omim.org/entry/603415#0007

#### ****.0007****  ****INSENSITIVITY TO PAIN, CHANNELOPATHY-ASSOCIATED****

SCN9A, TRP897TER

[dbSNP:rs121908909](http://www.ensembl.org/Homo_sapiens/Variation/Summary?v=rs121908909;toggle_HGVS_names=open) [RCV000006727](https://www.ncbi.nlm.nih.gov/clinvar?term=RCV000006727)

In a consanguineous northern Pakistani family segregating autosomal recessive congenital insensitivity to pain ([243000](https://www.omim.org/entry/243000)), [Cox et al. (2006)](https://www.omim.org/entry/603415#3) identified homozygosity for a 2691G-A transition in exon 15 of the SCN9A gene, resulting in a trp897-to-ter (W897X) substitution. The mutation was not found in 300 northern Pakistani control chromosomes.

<https://www.ncbi.nlm.nih.gov/clinvar/variation/6355/>

Indifference to pain, congenital, autosomal recessive

<https://www.ncbi.nlm.nih.gov/clinvar/variation/6356/>

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| ikely pathogenic (Mar 9, 2017) | criteria provided, single submitter   * [Invitae Variant Classification Sherloc (09022015)](https://www.ncbi.nlm.nih.gov/pubmed/28492532) | clinical testing | * Hereditary sensory and autonomic neuropathy type IIA[[MedGen](https://www.ncbi.nlm.nih.gov/medgen/C2752089" \t "_blank) | [OMIM](http://www.omim.org/entry/201300)] * Generalized epilepsy with febrile seizures plus, type 7[[MedGen](https://www.ncbi.nlm.nih.gov/medgen/C2751777" \t "_blank) | [OMIM](http://www.omim.org/entry/613863)] | germline |  | [Invitae](https://www.ncbi.nlm.nih.gov/clinvar/submitters/500031/) | SCV000649307.1 |
| Pathogenic (Dec 7, 2006) | no assertion criteria provided | literature only | * Paroxysmal extreme pain disorder |  |  |  |  |

<https://www.ncbi.nlm.nih.gov/medgen/C2752089>

Hereditary sensory and autonomic neuropathy type II (HSAN2) is characterized by progressively reduced sensation to pain, temperature, and touch. Onset can be at birth and is often before puberty. The sensory deficit is predominantly distal with the lower limbs more severely affected than the upper limbs. Over time sensory function becomes severely reduced. Unnoticed injuries and neuropathic skin promote ulcerations and infections that result in spontaneous amputation of digits or the need for surgical amputation. Osteomyelitis is common. Painless fractures can complicate the disease. Autonomic disturbances are variable and can include hyperhidrosis, tonic pupils, and urinary incontinence in those with more advanced disease.

<https://www.ncbi.nlm.nih.gov/medgen/C2751777>

Mutations in the SCN9A gene cause a spectrum of seizure disorders, ranging from early-onset isolated febrile seizures to generalized epilepsy with febrile seizures plus, type 7, which represents a more severe phenotype. Patients with isolated febrile seizures usually have onset between ages 5 months to 4 years and show spontaneous remission by age 6 years (summary by Singh et al., 2009), whereas patients with GEFS+ continue to have various types of febrile and afebrile seizures later in life (summary by Singh et al., 1999). Mutations in certain genes can cause a phenotypic spectrum of overlap between the isolated febrile phenotype and the GEFS+ phenotype. For a general phenotypic description and a discussion of genetic heterogeneity of GEFS+, see 604233. For a phenotypic description and a discussion of genetic heterogeneity of familial febrile seizures, see 121210.

https://www.ncbi.nlm.nih.gov/pubmed/17145499

Paroxysmal extreme pain disorder (PEPD), previously known as familial rectal pain (FRP, or OMIM 167400), is an inherited condition characterized by paroxysms of rectal, ocular, or submandibular pain with flushing.  Carbamazepine, a drug that is effective in PEPD, but not PE, showed selective block of persistent current associated with PEPD mutants, but did not affect the negative activation threshold of a PE mutant. PEPD and PE are allelic variants with distinct underlying biophysical mechanisms and represent a separate class of peripheral neuronal sodium channelopathy.

<https://www.ncbi.nlm.nih.gov/medgen/C1833661>

Paroxysmal extreme pain disorder is a condition characterized by skin redness and warmth (flushing) and attacks of severe pain in various parts of the body. The area of flushing typically corresponds to the site of the pain. The pain attacks experienced by people with paroxysmal extreme pain disorder usually last seconds to minutes, but in some cases can last hours. These attacks can start as early as infancy. Early in life, the pain is typically concentrated in the lower part of the body, especially around the rectum, and is usually triggered by a bowel movement. Some children may develop constipation, which is thought to be due to fear of triggering a pain attack. Pain attacks in these young children may also be accompanied by seizures, slow heartbeat, or short pauses in breathing (apnea).As a person with paroxysmal extreme pain disorder ages, the location of pain changes. Pain attacks switch from affecting the lower body to affecting the head and face, especially the eyes and jaw. Triggers of these pain attacks include changes in temperature (such as a cold wind) and emotional distress as well as eating spicy foods and drinking cold drinks.Paroxysmal extreme pain disorder is considered a form of peripheral neuropathy because it affects the peripheral nervous system, which connects the brain and spinal cord to muscles and to cells that detect sensations such as touch, smell, and

https://www.omim.org/entry/603415#0008

#### ****.0008****  ****PAROXYSMAL EXTREME PAIN DISORDER****

SCN9A, ARG996CYS

[dbSNP:rs121908910](http://www.ensembl.org/Homo_sapiens/Variation/Summary?v=rs121908910;toggle_HGVS_names=open)[RCV000006728...](https://www.ncbi.nlm.nih.gov/clinvar?term=RCV000006728%20OR%20RCV000559164)

In 2 families segregating paroxysmal extreme pain disorder ([167400](https://www.omim.org/entry/167400)), [Fertleman et al. (2006 https://www.ncbi.nlm.nih.gov/pubmed/17145499)](Fertleman%20et%20al.%20(2006%20https://www.ncbi.nlm.nih.gov/pubmed/17145499)) identified a C-to-T transition in exon 16 of the SCN9A gene resulting in an arginine-to-cysteine substitution at codon 996 (R996C). Affected members of 1 family who carried this mutation in heterozygosity had a less severe phenotype not requiring medication. In another family, the R996C mutation was found in the proband in compound heterozygosity with a V1298D mutation ([603415.0009](https://www.omim.org/entry/603415#0009)) and in his affected father in heterozygosity. The proband was more severely affected than his father.

https://www.omim.org/entry/603415#0014

#### ****.0014****  ****INSENSITIVITY TO PAIN, CHANNELOPATHY-ASSOCIATED****

SCN9A, ARG277TER

[dbSNP:rs121908916](http://www.ensembl.org/Homo_sapiens/Variation/Summary?v=rs121908916;toggle_HGVS_names=open) [RCV000006734](https://www.ncbi.nlm.nih.gov/clinvar?term=RCV000006734)

In affected members of 2 unrelated Swiss families with congenital insensitivity to pain ([243000](https://www.omim.org/entry/243000)), [Goldberg et al. (2007)](https://www.omim.org/entry/603415#11) <https://www.ncbi.nlm.nih.gov/pubmed/17470132> identified a homozygous 829C-T transition in exon 6 of the SCN9A gene, resulting in an arg277-to-ter (R277X) substitution.

<https://www.ncbi.nlm.nih.gov/clinvar/variation/6362/>

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| athogenic (Apr 1, 2007) | no assertion criteria provided | literature only | * Indifference to pain, congenital, autosomal recessive |

<https://www.ncbi.nlm.nih.gov/pubmed/17470132>

Congenital indifference to pain (CIP) is a rare condition in which patients have severely impaired pain perception, but are otherwise essentially normal.

<https://www.ncbi.nlm.nih.gov/clinvar/variation/6363/>

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| Pathogenic (Apr 1, 2007) | no assertion criteria provided | literature only | * Indifference to pain, congenital, autosomal recessive |

https://www.omim.org/entry/603415#0015

#### ****.0015****  ****INSENSITIVITY TO PAIN, CHANNELOPATHY-ASSOCIATED****

SCN9A, TYR328TER

[dbSNP:rs121908917](http://www.ensembl.org/Homo_sapiens/Variation/Summary?v=rs121908917;toggle_HGVS_names=open) [ExAC:rs121908917](http://exac.broadinstitute.org/awesome?query=rs121908917)[RCV000006735](https://www.ncbi.nlm.nih.gov/clinvar?term=RCV000006735)

In affected members of a large Canadian family with congenital insensitivity to pain ([243000](https://www.omim.org/entry/243000)), [Goldberg et al. (2007)](https://www.omim.org/entry/603415#11) <https://www.ncbi.nlm.nih.gov/pubmed/17470132> identified a homozygous 984C-A transversion in exon 8 of the SCN9A gene, resulting in a tyr328-to-ter (Y328X) substitution.

<https://www.ncbi.nlm.nih.gov/pubmed/29392201>

Severe fibromyalgia is associated with the Nav1.7 rs6754031 GG genotype. However, gain-of-function mutations in sodium channel Nav1.7 are present in 28% of patients with small fiber neuropathy.

<https://www.ncbi.nlm.nih.gov/pubmed/27586831>

https://www.ncbi.nlm.nih.gov/pubmed/21951710/

**Central Sensitivity Syndromes (CSS)**, in which no well-defined peripheral or central disease process can be found are thought to represent a primary dysregulation of the central nervous system leading to pain amplification, and are sometimes termed centralized pain or central sensitization. Examples include somatic pain syndromes such as fibromyalgia and tempromandibular disorder, as well as visceral pain syndromes like interstitial cystitis and irritable bowel syndrome (IBS), and possibly cognitive impairments such as chronic fatigue syndrome [106](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012312/#R106). Attempts to diagnose these disorders based on their “central” component include self-reported symptom questionnaires such as the **Central Sensitization Inventory (CSI)**[**106**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012312/#R106)**,**[**112**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012312/#R112) and **Fibromyalgia Criteria and Severity Scales**[**154**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012312/#R154), which have the patient evaluate and grade a wide array of symptoms, including somatic and visceral pain, mood, energy, sleep, cognitive function, among others.

https://www.ncbi.nlm.nih.gov/pubmed/24662556

This review demonstrates that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. This concordance raises the possibility that sympathetic dysfunction could be their common underlying pathogenesis that brings on overlapping clinical features. The recognition of sympathetic predominance in these 4 syndromes may have potential clinical implications. It may be worth exploring the use of nonpharmacological measures as well as drug therapies aimed to regain autonomic balance.

https://www.ncbi.nlm.nih.gov/pubmed/22550986

Although a number of treatment options are available, therapy for chronic pain is less effective than for acute pain, commonly providing significant pain relief for less than 50% of patients

* This view is supported by the fact that many chronic pain syndromes (e.g., fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome) are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition. Many chronic pain syndromes such as fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, headache and chronic fatigue syndrome are associated with hypersensitivity to painful stimuli and reduced endogenous pain inhibition.
* Central sensitization appears to be a hallmark of chronic pain, resulting in enhanced function of pain pathways and increased membrane excitability and synaptic efficacy as well as reduced inhibition of neurons.
* Accumulating evidence suggests that endogenous pain inhibition depends on activation of the prefrontal cortex, periaqueductal gray and rostral ventral medulla.
* Quantitative sensory test paradigms have been designed to acquire detailed information of each individual’s endogenous pain inhibition and facilitation.
* Pain inhibition and facilitation can be assessed by testing temporal summation of pain, which is mostly used for testing of facilitatory pain modulation and conditioned pain modulation, which tests pain inhibition by utilizing two simultaneously applied painful stimuli (pain inhibits pain paradigm).
* Treatments designed to reduce the incidence, severity and impact of chronic pain in susceptible individuals are of great clinical importance and include pre-emptive analgesia and/or multidisciplinary pain management programs.

https://www.ncbi.nlm.nih.gov/pubmed/18191990/

Specifically, the presence of central sensitization and other common features including fatigue, insomnia and distress, have resulted in labeling these chronic musculoskeletal conditions as central sensitivity syndromes (CSS)

<https://www.ncbi.nlm.nih.gov/pubmed/14997317/>

he clinical outcome effects of the 20%-30% opioid sparing by non-steroidal anti-inflammatory agents have not been defined, b

<https://www.ncbi.nlm.nih.gov/pubmed/11166973/>

Group comparisons indicated that the cognitive-behavioral group, relative to the comparison group, had significantly better results with regard to fear-avoidance beliefs, number of pain-free days, as well as the key variable of sick leave. Participation in the cognitive behavioral group reduced the risk for long-term sick leave during the follow-up by threefold. Thus, despite the strong natural recovery rate for back pain, the cognitive-behavioral intervention produced a significant preventive effect with regard to disability.

<https://www.ncbi.nlm.nih.gov/pubmed/19410099/>

A stepped care approach based upon existing evidence includes (1) simple analgesics (acetaminophen or nonsteroidal anti-inflammatory drugs); (2) tricyclic antidepressants (if neuropathic, back or fibromyalgia pain) or tramadol; (3) gabapentin, duloxetine or pregabalin if neuropathic pain; (4) cyclobenzaprine, pregabalin, duloxetine, or milnacipran for fibromyalgia; (5) topical analgesics (capsaicin, lidocaine, salicylates) if localized neuropathic or arthritic pain; and (6) opioids.

<https://www.ncbi.nlm.nih.gov/pubmed/29123662>

he genes responsible are believed to be involved in the immunological response/inflammatory cytokine expression, glucocorticoid receptor

GR dysfunction is also proposed to play a role in development of chronic fatigue, chronic pain states and the syndrome of fibromyalgia, thus providing a potential link between injury, environmental stressors and severity of chronic pain.

<https://www.ncbi.nlm.nih.gov/pubmed/23129781>

Mutations in SCN9A have been reported in (1) congenital insensitivity to pain (CIP); (2) primary erythromelalgia; (3) paroxysmal extreme pain disorder; (4) febrile seizures and recently (5) small fibre sensory neuropathy. We sought to investigate for SCN9A mutations in a clinically well-characterised cohort of patients with CIP and erythromelalgia.

<https://www.ncbi.nlm.nih.gov/pubmed/29172294>

xaliplatin is a platinum drug active against digestive tract cancers. Among its side effects, peripheral neuropathy is one of the dose-limiting toxicities. This affects around 50 to 70% of patients but the pathophysiology of development of oxaliplatin-induced peripheral neuropathy (OXAIPN) remains unclear. Sodium channels (SCNAs) play major role in neuronal electrical signaling processes and mutations in SCNAs lead to various neuronal diseases involving the central and peripheral nervous systems. In this study, we evaluated whether SCNA genetic variants might be associated with risk of chronic OXAIPN in patients with digestive tract cancers treated with oxaliplatin. e found that the rs6746030 polymorphic variant of SCN9A was significantly associated with a higher incidence of chronic OXAIPN (GA+AA vs GG: OR=1.8, 95% CI=1.04-3.4, P=0.04; dominant model) while the rs6754031 variant was linked with a lower incidence (OR=0.45, 95% CI=0.22-0.77, P=0.005; dominant model).