Original Article

The Gut-Brain-Genome Axis in Action: SCN11A and SCN10A Channelopathies as Molecular Drivers of Dual Enteric and Central Nervous System Dysfunction

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Abstract

Objective: The gut–brain axis depends on coordinated neuronal signaling, gastrointestinal motility, and visceral sensory processing, all of which are influenced by ion channels.

Methodology: This narrative review synthesizes clinical and experimental evidence regarding the expression of SCN10A and SCN11A, encoding the voltage-gated sodium channels $Na_v1.8$ and $Na_v1.9$, respectively, and associated phenotypes. $Na_v1.8$ primarily contributes to action-potential firing in peripheral nociceptors, whereas $Na_v1.9$ modulates subthreshold excitability and participates in enteric and visceral sensory signaling.

Results: SCN11A gain-of-function variants are associated with a wide range of phenotypes, ranging from painful neuropathy to congenital insensitivity to pain, and may be accompanied by gastrointestinal disturbances. Conditions involving SCN10A have been shown to include painful small-fiber neuropathy and gastrointestinal dysmotility.

Conclusion: However, despite the number of relevant studies published, small cohorts, incomplete documentation of gastrointestinal disturbances in neurological studies, and reliance on preclinical findings all serve to make drawing definitive conclusions difficult.

Keywords: Gut–brain axis, SCN10A, SCN11A, $Na_v1.8$, $Na_v1.9$, Ion channelopathies. Gastrointestinal symptoms.

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Introduction

In the human body, the Gastrointestinal tract (GIT) and the nervous system communicate with each other and hence are inherently linked together in a duplex connection, commonly known as the Gut-brain axis.[1] Peripheral sensory neurons in the GIT can detect stimuli and transmit them to the CNS (such as visceral pain signals) and the brain, through its emotional and intellectual centres, manipulates the GIT via a network of nerves, the entirety of which is modulated on the molecular level by ion channels.[1,2] Defects in these transmembrane proteins regulating ionic gradients across membranes in the GIT are described in literature as ion channelopathies which lead to functional GI disorders (FGIDs).[2] Among the principal ion-channel families involved in gastrointestinal physiology are voltage-gated sodium (Nav), voltage-gated calcium (Ca_v), voltage-gated and calcium-activated potassium, transient receptor potential (TRP), and epithelial chloride channels such as CFTR.[1,2] Voltage gated sodium (Nav) channels have been functionally categorized into 9 working classes, each with their own organ specific or overlapping locations.[3] For instance, $Na_v1.5$ (encoded by *SCN5A*) contributes to gastrointestinal electrical activity and has been associated with irritable bowel syndrome, while Nav1.7 (*SCN9A*) plays a role in peripheral pain signalling.[1,2,3] Similarly, Nav 1.9 and Nav 1.8, encoded by genes *SCN10A* and *SCN11A* respectively, are the only documented channels distributed selectively in the afferent neurons in the GIT and the dorsal root ganglia of the Peripheral nervous system (PNS), regulating chronic visceral pain, intestinal motility and hyperpathia.[4,5] There exists a vital diagnostic gap among patients presenting with such symptoms of FGIDs due to the absence of genomic screening for neuronal channelopathies.

These channel families fulfill different physiological

functions, with Nav channels supporting action-potential initiation and propagation in enteric and extrinsic sensory neurons, while voltage-gated Ca_v channels mediate calcium entry required for enteric neurotransmitter release and smooth-muscle contraction. Additionally, voltage-gated and calcium-activated potassium channels regulate membrane repolarization, neuronal excitability, and gastrointestinal contractility.[1,2] TRP channels detect chemical and inflammatory stimuli relevant to visceral nociception, while epithelial CFTR channels mediate chloride ions and electrolyte transport.[1,2] PIEZO-family channels, such as PIEZO2, may also participate in detecting gut distension.[1] These activities showcase potential links between altered enteric signalling, neurotransmission and peripheral afferent input to the central nervous system.[1,2]

Gene mutations leading to modifications in the protein structures of these channels have been described as the molecular origin of these FGIDs.[2] Specifically gain-of-function (GoF) mutations contribute to a hyperexcitable membrane and hence, greater neuronal excitation leading to hypersensitivity.[2] For example, it is well documented that GOF mutations in the SCN11A gene, encoding the Nav 1.9 channel regulating visceral sensitivity, are seen in patients suffering from chronic lower limb pain and numbness (owing to its presence in small diameter pain sensory neurons) together with GI symptoms like diarrhea, constipation or chronic pain.[2] Loss of function (LOF) mutations work in the opposite manner, by decreasing the membrane excitability.[2,5] For instance, certain SCN11A GOF variants have been linked to congenital insensitivity to pain via sustained depolarization and functional neuronal inactivation, and other SCN11A variants have also been reported in patients with chronic diarrhea and pain insensitivity.[12,15] Despite the documentation of genotype–phenotype associations for certain SCN11A variants, evidence for particular gut–brain mechanisms have not been fully established, and evidence ranges from clinical reports to experimental observations.[12,13,14,15,16,17] Although previous reviews have addressed gastrointestinal ion channelopathies and visceral pain signalling, evidence connecting individual SCN10A and SCN11A variants with neurological and gastrointestinal manifestations remains limited. Therefore, this review aims to bring together the reported neurological and gastrointestinal phenotypes associated with SCN10A ($Na_v1.8$) and SCN11A ($Na_v1.9$) variants and to examine the proposed mechanisms linking these manifestations.

Methodology

A detailed literature search was conducted on October 29, 2026, using the PubMed database. Search terms included "SCN10A," "SCN11A," "$Na_v1.8$," "$Na_v1.9$," "ion channelopathies," "gut-brain axis," "visceral pain," "gastrointestinal dysmotility," and "sensory neuropathy," combined using the Boolean operators AND and OR. Studies were considered for inclusion if they investigated SCN10A/SCN11A-associated neurological or gastrointestinal phenotypes, the underlying molecular mechanisms, or diagnostic and therapeutic implications. Studies lacking relevant clinical or mechanistic information were excluded, with the final articles being selected based on their relevance, following title, abstract, and full-text assessment.

Discussion

To clarify the relevance of the included literature, the studies have been categorized as (i) clinical reports documenting gastrointestinal manifestations alongside channelopathy phenotypes;[12, 13, 14, 15, 17] (ii) experimental or mechanistic studies demonstrating effects on enteric neurons, gastrointestinal motility, visceral sensory pathways, autonomic regulation, or related processes;[6, 7, 9] and (iii) studies reporting neurological phenotypes, non-gastrointestinal neuronal physiology, or channel-targeted treatment without documented gastrointestinal involvement or a direct gut–brain link.[8, 10, 11, 16, 21, 22] The third category was added to provide indirect context regarding channel function, variant effects, or therapeutic approaches, not as direct evidence of gastrointestinal dysfunction. Other included experimental findings not directly linked to these genes[23] are also to be regarded as contextual. Importantly, gastrointestinal outcomes that were not reported cannot be interpreted as having been assessed and found absent.

$Na_v1.9$ and $Na_v1.8$, encoded by SCN11A and SCN10A, respectively, occupy a functionally significant position, with $Na_v1.9$ being concentrated in dorsal root ganglion (DRG) nociceptors and in Dogiel type II sensory neurons of both the myenteric and submucosal plexuses. This is consistent with its role in intrinsic enteric sensory signaling.[6] Similarly, $Na_v1.8$ is abundant in peripheral sensory neurons, and studies have shown related afferent fibers terminating within the gastrointestinal mucosa, muscle wall, and myenteric plexus.[7] Thus, evidence for intrinsic primary afferent neuron expression is particularly strong for $Na_v1.9$, whereas $Na_v1.8$ contributes mainly to extrinsic gut–brain afferent pathways.[6,7] Whilst neither are

represented in the sodium channel of skeletal myofibers, functional channels for $Na_v1.8$ have been found in intracardiac neurons.[8] The persistent $Na_v1.9$ current operates near resting membrane potential and amplifies subthreshold depolarization, whereas $Na_v1.8$ serves to provide a major current that supports action-potential firing in nociceptors. These properties make both channels capable of converting mechanical distension and chemical signals from the intestine into neural activity. $Na_v1.9$ is particularly important for colonic mechanosensation and responses to inflammatory mixtures containing prostaglandin E2 and serotonin, while chronic inflammatory signaling factors, such as tumor necrosis factor, can increase SCN10A/SCN11A expression in DRG neurons.[9,10,11] Together, these (predominantly experimental) observations suggest that inflammation may modify somatic and visceral afferent excitability, but do not demonstrate that variants in either gene directly cause gastrointestinal symptoms in humans.

GoF SCN11A conditions demonstrate how this shared sensory architecture can produce varying neurological and gastrointestinal symptoms.[12] Huang et al. identified GoF $Na_v1.9$ variants, such as L1158P, among patients having small-fiber painful neuropathy, with autonomic disturbances including gastrointestinal symptoms present within the wider cohort.[13] Similarly, Han et al. described the R222H variant in a family with early-onset distal extremity and joint pain accompanied by gastrointestinal disturbances, with electrophysiology showing a hyperpolarizing shift in activation, resting-membrane depolarization, and thereby increased firing, while, comparatively, Huang et al. described gastrointestinal complaints within a broader neuropathy cohort.[13,14] While the coexistence of neuropathy and bowel symptoms may reflect a shared sensory-neuron disorder, coincidental gastrointestinal conditions cannot be excluded without systematic assessment.[13,14] These observations showcase that increased $Na_v1.9$ availability simultaneously sensitizes somatic nociceptors and gut-projecting sensory neurons. The co-occurrence of neuropathy and otherwise unexplained gastrointestinal symptoms in several $Na_v1.9$ disorders suggests that "neuropathy" and "functional" bowel symptoms may represent different manifestations of the same sensory-neuron condition rather than independent comorbidities.[13,14]

Distinct from such familial episodic pain variants, Leipold et al. demonstrated that L811P is a GoF mutation, with excessive $Na_v1.9$ activity near resting potential causing sustained neuronal depolarization, creating a functional depolarization block and congenital insensitivity to pain.[12] Subsequent phenotyping of SCN11A-associated congenital pain insensitivity, including families carrying L1302F, documented recurrent painless fractures, self-injury, normal conventional nerve-conduction studies, and chronic diarrhea.[15] Thus, profound enhancement of $Na_v1.9$ activity can silence rather than activate sensory neurons. However, current human literature does not suitably support a separate SCN11A loss-of-function syndrome directly causing congenital insensitivity to pain with life-threatening CIPO or megacolon. Clinically, the combination of unexplained painless fractures, burns or self-injury with chronic diarrhea, constipation, or otherwise refractory dysmotility should raise suspicion for a hereditary sensory channelopathy, particularly when routine large-fiber nerve-conduction testing is normal.[12,15]

The available clinical literature, summarized in the following tables, highlights that SCN11A variants can produce painful syndromes, small-fiber neuropathy, or pain insensitivity depending on the amount of altered $Na_v1.9$ activity.[12,13,14,15] Faber et al. identified GoF $Na_v1.8$ variants in painful small-fiber neuropathy, although gastrointestinal manifestations were not systematically reported in the cohort.[16] In this study, L554P occurred in a father–son pair, and functional testing of L554P and A1304T showcased increased excitability in dorsal root ganglion neurons.[16] By contrast, Dabby et al. reported a single patient with painful small-fiber neuropathy carrying a heterozygous SCN10A D1639N missense variant, demonstrating that a missense mutation in SCN10A can lead to both autonomic and sensory neuropathy.[17] Collectively, these reports are consistent with shared sensory-neuron excitability disorders.

Detection of pure sensory/enteric channelopathies remains difficult using conventional techniques, with gastrointestinal endoscopy primarily identifying mucosal or structural pathology. Therefore, such approaches could increase the risk of yielding incorrect results when symptoms originate from abnormal sensory or enteric electrophysiology.[18,19] Similarly, routine nerve-conduction studies are used to examine large myelinated fibers and can remain normal in disorders caused predominantly by small nociceptive fibers, as illustrated in *SCN11A*-associated congenital pain insensitivity.[15,20] For patients with otherwise unexplained gastrointestinal symptoms accompanied by characteristic sensory findings, targeted next-generation sequencing panels that include SCN11A and SCN10A may be considered, but a detected sequence variant requires careful clinical examination before gastrointestinal causality is inferred. Additionally, emerging channel-specific therapies have become

increasingly attractive as they avoid cardiac or central nervous systemic sedating side effects.[21,22] The $Na_v1.8$-selective inhibitor suzetrigine demonstrated analgesic efficacy in phase III trials of moderate-to-severe acute postoperative pain.[21] Such approaches work to target peripheral excitability rather than broadly depressing the central nervous system.

The aforementioned observations support a "gut–brain–genome" model in which a subset of disorders currently categorized as functional gastrointestinal disease may arise from genetically determined abnormalities of sensory-neuron excitability, implying that such conditions are primarily neuro-genomic. The gut microbiome may represent an additional modulator of this process, with experimental exposure to microbial short-chain fatty acid butyrate showing an increase in colonic hypersensitivity.[23] In addition, inflammatory cytokines can increase $Na_v1.8$/$Na_v1.9$ expression in sensory neurons.[10] However, direct evidence that microbial short-chain fatty acids specifically regulate *SCN10A* or *SCN11A* transcription in humans is presently insufficient. Clinically, patients with such conditions should ideally be evaluated through a coordinated pathway involving neuro-gastroenterologists, geneticists, and neurologists for early cohort identification. Such workflow mechanisms may transform apparently unrelated pain and gastrointestinal syndromes into coherent channelopathies and, therefore, can assist in developing targeted treatment mechanisms.

The available literature has several limitations that require consideration. Most human studies involve individual case reports, small cohorts, or affected families, limiting the generalizability of their findings. In addition, gastrointestinal manifestations are often incompletely documented in neurological channelopathy studies, potentially contributing to their underrecognition. As well as this, several proposed mechanisms linking channel dysfunction to gastrointestinal motility and visceral sensitivity rely on preclinical evidence, with limited validation in human populations. Consequently, the clinical significance of individual variants remains uncertain in some cases. Larger studies involving standardized assessments and proper genetic characterization are needed to establish more definitive genotype–phenotype relationships.

Conclusion

SCN11A and SCN10A channelopathies represent a rare and highly selective model of overlapping neurological and gastrointestinal manifestations illustrating how genetically determined alterations in sensory sodium-channel function can influence nociceptive signaling and gastrointestinal motility while largely sparing other organ systems. This potential distinctive gut–brain–genome

Table 1: *Sensory Sodium Channelopathies (SCN11A/SCN10A) in Dual Brain-Gut Dysfunction.*

Study	Gene / channel	Molecular phenotype	CNS/peripheral sensory phenotype	Gastrointestinal phenotype
Leipold et al. (2013)[12]	*SCN11A* ($Na_v1.9$)	Gain-of-Function (L811P)	Congenital insensitivity to pain / pruritogenic pain, recurrent self-inflicted and slow healing wounds, mild muscular weakness and delayed motor development	Severe chronic diarrhea & intestinal hypomotility
Huang et al. (2014)[13]	*SCN11A* ($Na_v1.9$)	Gain-of-Function	Painful Peripheral Neuropathy (small fiber), allodynia, autonomic complaints like dry eyes and hyperhidrosis, cramps, abnormal temperature sensation	Diarrhoea
Han et al. (2016)[14]	*SCN11A* ($Na_v1.9$)	Gain-of-Function	Familial episodic pain involving distal extremities, especially the finger, wrist and ankle joints	Chronic abdominal pain & altered bowel frequency (diarrhoea and urgency to defecate)
Phatarakijnirund et al. (2016)[15]	*SCN11A* / $Na_v1.9$	Gain-of-Function	Congenital pain insensitivity, painless fractures	Chronic diarrhea, Gastroesophageal reflux disease
Faber et al. (2012)[16]	*SCN10A* ($Na_v1.8$)	Gain-of-Function	Small Fiber Neuropathy (burning extremity pain), severe allodynia, paroxysmal itch, redness of soles	NA
Dabby R et al. (2015)[17]	*SCN10A* ($Na_v1.8$)	Missense Variant	Autonomic & Sensory Neuropathy (burning pain and tingling in the periphery and trunk)	Sever, treatment refractory GI dysmotility involving gastroparesis and esophageal hypomotility

connection has important clinical implications, as genetic conditions may be mistaken for structural gastrointestinal disease, potentially leading to unnecessary surgical interventions without addressing the underlying pathophysiology. Current evidence showcases associations between specific *SCN11A* variants and distinct sensory phenotypes, including painful neuropathy and congenital pain insensitivity, while gastrointestinal manifestations remain inconsistently characterized. Evidence linking *SCN10A* variants to gastrointestinal dysmotility is similarly limited, and several proposed gut–brain mechanisms mainly rely on experimental findings. Therefore, sensory sodium-channel genes, particularly *SCN11A* and *SCN10A*, should be considered for routine inclusion in genetic diagnostic workups for patients with otherwise unexplained gastrointestinal dysmotility, accompanied by characteristic sensory or pain symptoms, and future investigations should prioritize larger genotype–phenotype correlation studies to clarify the significance of individual variants and to establish potential causal mechanisms.

Table 2: *Literature Summary Table.*

Study author and year	Study design	Genetic variant (where available)	Population or experimental model	Gastrointestinal phenotype or proposed mechanism	Principal findings	Level of evidence
Leipold et al., 2013 [12]	Human genetic case series with knock-in mouse experiments and electrophysiology	*SCN11A* ($Na_v1.9$), L811P; de novo GoF	Two unrelated patients with congenital insensitivity to pain; genetically modified mice and dorsal root ganglion DRG neurons	Diarrhea, constipation, intestinal hypomotility, and enlarged colon; altered neuronal signalling proposed	Excessive $Na_v1.9$ activity caused sustained nociceptor depolarization and impaired action-potential generation, explaining paradoxical pain insensitivity	Direct human GI evidence (two cases), with functional sensory validation; GI mechanism incompletely established
Huang et al., 2014 [13]	Human genetic cohort with functional electrophysiological investigations	*SCN11A* ($Na_v1.9$); multiple missense variants, including I381T and L1158P (GoF)	345 patients sequenced for *SCN11A*; 12 variant carriers; DRG neuron experiments	Diarrhea and autonomic symptoms reported in selected patients; GI outcomes not systematically characterized	Identified eight variants in 12 patients. Functionally investigated mutations enhanced neuronal excitability and were associated with painful small-fiber neuropathy	Human cohort with functional validation; limited GI-specific evidence
Han et al., 2017 [14]	Familial genetic study with segregation analysis and electrophysiology	*SCN11A* ($Na_v1.9$), R222H; heterozygous GoF	Members of a family with early-onset episodic pain; DRG neuron experiments	Gastrointestinal disturbances, including abdominal pain and altered bowel habits; enhanced sensory excitability proposed	R222H facilitated channel activation, depolarized DRG neurons, and increased neuronal firing; the variant was identified in affected family members	Direct familial clinical evidence with functional sensory validation; GI mechanism not directly established
Phatarakijnirund et al., 2016 [15]	Familial case study with genetic and skeletal investigations	*SCN11A* ($Na_v1.9$), L1302F; heterozygous, autosomal dominant; GoF proposed	Mother and two affected children with congenital insensitivity to pain	Chronic diarrhea in affected children; direct enteric mechanism not investigated	Congenital pain insensitivity, painless fractures, and joint hypermobility accompanied gastrointestinal symptoms; skeletal investigations showed no primary skeletal pathology	Direct human GI evidence from a small family; variant-specific functional evidence limited
Faber et al., 2012 [16]	Human neuropathy cohort with genetic screening and functional electrophysiology	*SCN10A* ($Na_v1.8$), L554P and A1304T; GoF	104 patients with painful predominantly small-fiber neuropathy; mouse DRG neuron experiments	Not reported or systematically assessed; no direct GI association established	Seven variants were identified in nine patients. L554P and A1304T increased neuronal excitability, supporting their association with painful neuropathy	Human cohort with functional neurological evidence; indirect GI relevance only
Dabby et al., 2016 [17]	Single-patient clinical case report with genetic and gastrointestinal investigations	*SCN10A* ($Na_v1.8$), D1639N; heterozygous missense variant	37-year-old woman with painful small-fiber neuropathy and gastrointestinal dysmotility	Severe gastroparesis, dysphagia, and esophageal hypomotility; evaluated using gastric scintigraphy and esophageal manometry	Reported coexisting severe gastrointestinal dysmotility and painful neuropathy in a patient carrying a novel *SCN10A* variant	Direct human GI evidence from a single case; causality and functional significance uncertain

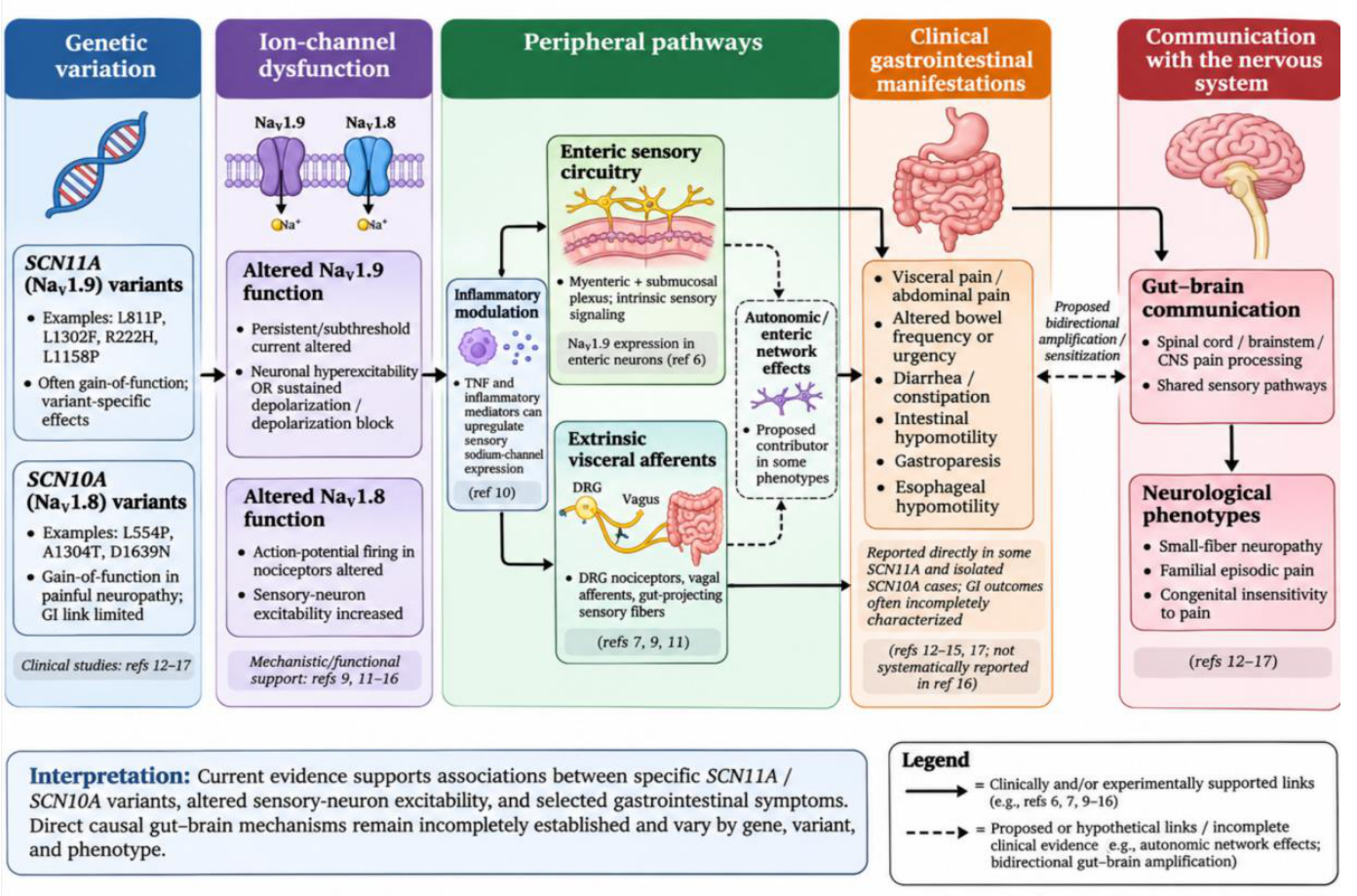


Figure 1: *Conceptual model of sensory sodium-channel variation and gut-brain interactions (Made using assistance from AI models)..*

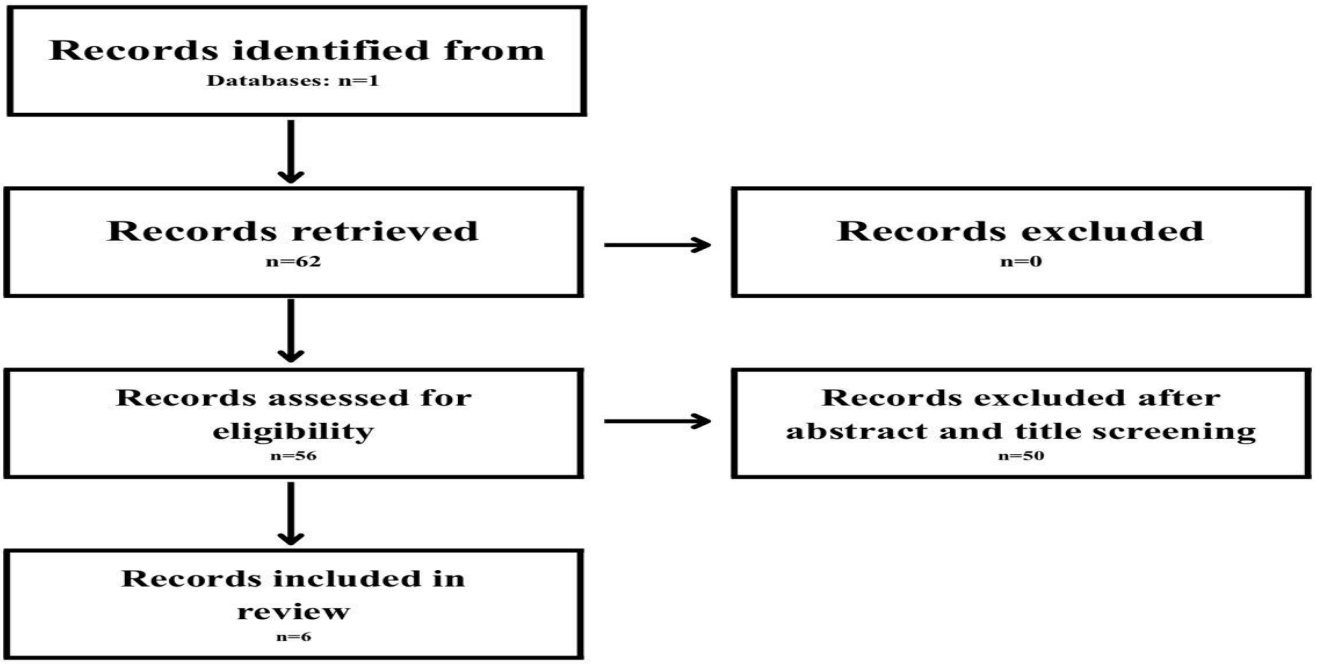


Figure 2: *Literature identification and selection process.*

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Conflict of Interest None

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Authors' Contribution

WQB: Conception.

OBA: Design of the work.

FIK: Data acquisition, analysis, or interpretation.

OBA, FIK: Draft the work.

WQB: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work

References

1. Meerschaert KA, Chiu IM. The gut-brain axis and pain signalling mechanisms in the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2025;22(3):206–21.
2. Beyder A, Farrugia G. Ion channelopathies in functional GI disorders. Am J Physiol Gastrointest Liver Physiol. 2016;311(4)–G586.
3. England S, de Groot MJ. Subtype-selective targeting of voltage-gated sodium channels. Br J Pharmacol. 2009;158(6):1413–25.
4. Heinle JW, Dalessio S, Janicki P, Ouyang A, Vrana KE, Ruiz-Velasco V, et al. Insights into the voltage-gated sodium channel, $Na_v1.8$, and its role in visceral pain perception. Front Pharmacol. 2024;doi: 10.3389/fphar.2024.1398409
5. Zhao C, Zhou X, Shi X. The influence of $Na_v1.9$ channels on intestinal hyperpathia and dysmotility. Channels (Austin). 2023;17(1):2212350.
6. Padilla F, Couble ML, Coste B, Maingret F, Clerc N, Crest M, et al. Expression and localization of the $Na_v1.9$ sodium channel in enteric neurons and in trigeminal sensory endings: implication for intestinal reflex function and orofacial pain. Mol Cell Neurosci. 2007;35(1):138–52.
7. Gautron L, Sakata I, Udit S, Zigman JM, Wood JN, Elmquist JK. Genetic tracing of $Na_v1.8$-expressing vagal afferents in the mouse. J Comp Neurol. 2011;519(15):3085–101.
8. Verkerk AO, Remme CA, Schumacher CA, Scicluna BP, Wolswinkel R, de Jonge B, et al. Functional $Na_v1.8$ channels in intracardiac neurons: the link between SCN10A and cardiac electrophysiology. Circ Res. 2012;111(3):333–43.
9. Hockley JRF, Boundouki G, Cibert-Goton V, McGuire C, Yip PK, Chan C, et al. Multiple roles for $Na_v1.9$ in the activation of visceral afferents by noxious inflammatory, mechanical, and human disease-derived stimuli. Pain.2014;155(10):-1962–75.
10. Fischer BD, Ho C, Kuzin I, Bottaro A, O'Leary ME. Chronic exposure to tumor necrosis factor in vivo induces hyperalgesia, upregulates sodium channel gene expression and alters the cellular electrophysiology of dorsal root ganglion neurons. Neurosci Lett. 2017;653:195–201. doi: 10.1016/j.neulet.2017.05.004
11. Osorno T, Stewart RG, Fujita A, Jo S, Bean BP. Functional role of $Na_v1.8$ channels in action potentials of mouse CGRP-lineage dorsal root ganglion neurons. J Physiol. 2026;604(14):6104–27.
12. Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, et al. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet. 2013;45(11):1399–404.
13. Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JGJ, Gerrits MM, et al. Gain-of-function mutations in sodium channel $Na_v1.9$ in painful neuropathy. Brain. 2014;137(Pt 6):1627–42.
14. Han C, Yang Y, Te Morsche RH, Drenth JPH, Politei JM, Waxman SG, et al. Familial gain-of-function $Na_v1.9$ mutation in a painful channelopathy. J Neurol Neurosurg Psychiatry. 2017;88(3):233–40.
15. Phatarakijnirund V, Mumm S, McAlister WH, Novack DV, Wenkert D, Clements KL, et al. Congenital insensitivity to pain: fracturing without apparent skeletal pathobiology caused by an autosomal dominant, second mutation in SCN11A encoding voltage-gated sodium channel 1.9. Bone. 2016;doi: 10.1016/j.bone.2015.11.022
16. Faber CG, Lauria G, Merkies ISJ, Cheng X, Han C, Ahn HS, et al. Gain-of-function $Na_v1.8$ mutations in painful neuropathy. Proc Natl Acad Sci U S A. 2012;109(47):19444–9.
17. Dabby R, Sadeh M, Broitman Y, Yosovich K, Dickman R, Leshinsky-Silver E. Painful small fiber neuropathy with gastroparesis: a new phenotype with a novel mutation in the SCN10A gene. J Clin Neurosci. 2016;doi: 10.1016/j.jocn.2015.05.071

18. Lacy BE, Crowell MD, Cangemi DJ, Lunsford TN, Simren M, Tack J. Diagnostic evaluation of gastric motor and sensory disorders. Am J Gastroenterol. 2021;116(12):2345–56.
19. Ang D, Fock KM, Law NM, Ang TL. Current status of functional gastrointestinal evaluation in clinical practice. Singapore Med J. 2015;56(2):69–79.
20. Krarup C. Pitfalls in electrodiagnosis. J Neurol. 1999;246(12):1115–26.
21. Bertoch T, D'Aunno D, McCoun J, Solanki D, Taber L, Urban J, et al. Suzetrigine, a nonopioid $Na_v1.8$ inhibitor for treatment of moderate-to-severe acute pain: two phase 3 randomized clinical trials. Anesthesiol. 2025;142(6):1085–99.
22. Osteen JD, Immani S, Tapley TL, Indersmitten T, Hurst NW, Healey T, et al. Pharmacology and mechanism of action of suzetrigine, a potent and selective $Na_v1.8$ pain signal inhibitor for the treatment of moderate to severe pain. Pain Ther. 2025;14(2):655–74.
23. Xu D, Wu X, Grabauskas G, Owyang C. Butyrate-induced colonic hypersensitivity is mediated by mitogen-activated protein kinase activation in rat dorsal root ganglia. Gut. 2013;62(10):1466–74.