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Case Report

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A novel sodium channel gene variant in congenital insensitivity to pain: severe abdominal sequelae from impaired visceral nociception

Abstract

Congenital insensitivity to pain (CIP) comprises a group of rare genetic disorders, classified as hereditary sensory and autonomic neuropathies (HSAN), in which the absence of pain perception exposes patients to unrecognized injury. We report a 21-year-old man with HSAN type IID who showed, in early childhood, no reaction to painful stimuli, anhidrosis and selective hyposmia. In 2005, an episode of acute gastroenteritis whose severity went unrecognized because of the absence of abdominal pain progressed to septic shock, paralytic ileus, intestinal perforation and iliac artery thrombosis, requiring an ileo-ileal anastomosis and a left transtibial amputation. He later had recurrent adhesion-related intestinal obstructions. Clinical exome sequencing identified a homozygous variant of uncertain significance in SCN9A (c.4260+4A>C), predicted to alter splicing and absent from gnomAD and ClinVar. Segregation analysis confirmed that both parents were heterozygous carriers, supporting a likely pathogenic role for the variant; functional studies are still needed to confirm its splicing effect and definitive classification. Despite these sequelae, the patient is fully independent (Barthel Index 100/100), walks and runs with a prosthesis, and reports high quality of life (EQ-5D visual analogue scale 85/100), which may be related to a structured daily body self-examination routine. This clinical trajectory, in which absent visceral nociception leads to severe abdominal complications, has not been previously documented in SCN9A-related HSAN, and it underscores the need for heightened awareness of occult abdominal pathology and for education in structured self-examination in these patients.

Keywords: congenital pain insensitivity, hereditary sensory and autonomic neuropathies, SCN9A gene, gastrointestinal manifestations, self-monitoring

Volume 11 Issue 3 - 2026

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Received: November 14, 2026 | **Published:** November 24, 2026

Abbreviations: 10MWT, 10-meter walk test; ACMG/AMP, American College of medical genetics and genomics/Association for molecular pathology; CIP, congenital insensitivity to pain; CT, computed tomography; EMG, electromyogram; EQ-5D-5L, five-level EuroQol five-dimension questionnaire; HSAN, hereditary sensory and autonomic neuropathies; VAS, visual analogue scale; VUS, variant of uncertain significance

Introduction

Nociception is the ability to sense pain by specialized neurons, called nociceptors, which detect both actual and potential tissue damage.[1] Pain is fundamental for the optimal functioning of the body, aiming to avoid or respond to injuries, so it is easy to understand that being permanently painless results in a significant morbidity and mortality.[1] Congenital insensitivity to pain (CIP), or as suggested by Weisman et al,[2] hereditary sensory and autonomic neuropathies (HSAN), is an infrequent group of genetic disorders characterized by a lack of ability to sense pain of any type associated with varying degrees of autonomic dysfunction.[3–5] The first description of HSAN was made by Dearborn in 1932,[6] while the current classification was suggested by Dyck in 1984.[7] In this classification, HSAN can be categorized into 5 types based on clinical symptoms, pathological findings, age of onset, and affected genes, as shown in Table 1.[5] CIP is a heterogeneous condition, both genetically and clinically,[8] with an assortment of identified mutations on numerous different genes, including NTRK1, NGF, PRDM12, IKBKAP, FAM134B, CLTCL1, SCN9A, SCN11A, and ZFHX2.[1] The most common phenotype, due to a mutated SCN9A gene, primarily presents with the inability to sense pain associated with anosmia.[1] In the following, we present a case report of HSAN type IID in which the absence of visceral nociception led to severe gastrointestinal complications, a clinical trajectory not previously documented in SCN9A-related HSAN.

Case description

We report the case of a 21-year-old male born to a healthy, non-consanguineous couple. Pregnancy and delivery were normal. Psychomotor development was reported as normal, with a mild delay in speech. In early childhood, his parents noticed a lack of reaction to painful stimuli, including vaccines, falls, and self-inflicted bites on the fingers. The patient also developed some degree of dysautonomia, with anhidrosis, and hyposmia specifically for food and foul smells, with preserved sense of smell for alcohol and herbs. In 2005, following an episode of acute gastroenteritis whose severity went unrecognized because of the absence of abdominal pain, the patient was hospitalized with septic shock. This led to paralytic ileus, intestinal perforation, and ultimately thrombosis of the iliac arteries (Figure 1A), resulting in acute ischemia of the left lower extremity with irreversible tissue damage. Given the extent of arterial involvement and the patient's hemodynamic instability secondary to septic shock, vascular limb-salvage interventions were not feasible, and a left transtibial amputation was performed (Figures 1B, 1C). An ileo-ileal end-to-end anastomosis was also required for the intestinal perforation. After this episode, an electromyogram (EMG) was performed, which showed normal motor nerve conduction parameters.

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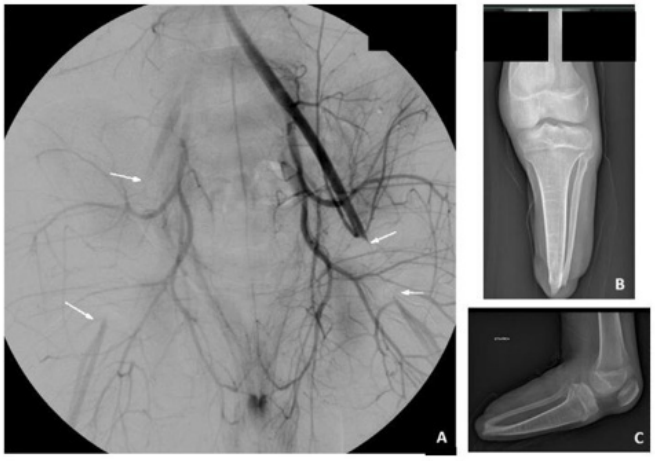


Figure 1 Angiographic and radiographic findings. (A) Pelvic angiography showing bilateral iliac arterial thrombus (arrows), 2005. (B, C) Radiographs of the left lower limb showing the transtibial amputation.

The patient also underwent several intestinal biopsies. The proximal ileum-distal jejunum biopsy showed submucosal edema and congested vessels. In the terminal ileum, the biopsy revealed follicular hyperplasia and prominent germinal centers, consistent with Peyer's patches. The biopsy from the jejunostomy site revealed eroded small intestine mucosa, alongside intense chronic inflammation and a granulomatous reaction attributed to suture material, as well as edema and vascular congestion. Furthermore, the small intestine wall biopsy showed muscular layers with an acute inflammatory infiltrate, predominantly eosinophilic. A colonoscopy performed in the same year identified slight distal anorectal edema, and the ileum presented an ischemic appearance of the mucosa, with corresponding radiological findings shown in Figure 2A. In 2009 and again in 2014 (Figure 2B), the patient had episodes of intestinal obstruction due to adhesions, a recognized complication of prior abdominal surgery, which required surgical intervention. In 2019, he suffered an episode of intestinal pseudo-obstruction caused by an intestinal volvulus, also secondary to adhesions.

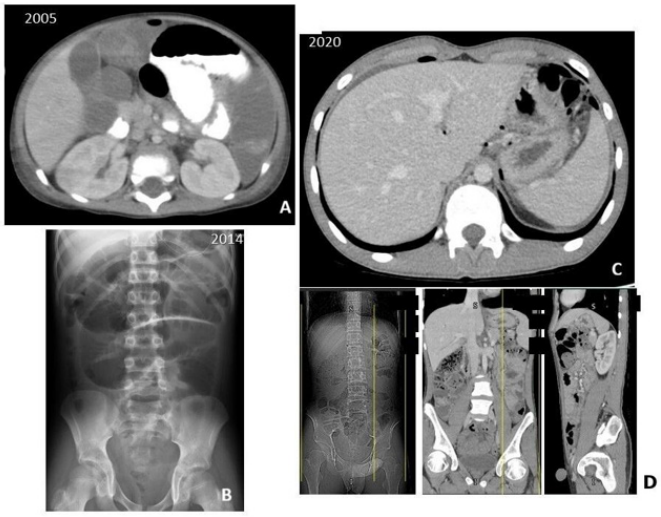


Figure 2 Abdominal imaging. (A) Computed tomography (CT) scan showing moderate intestinal distension with air-fluid levels, 2005. (B) Abdominal X-ray showing severe bowel distension associated with obstipation, 2014. (C) CT scan showing adhesions following surgical procedures, 2020. (D) CT scout view and coronal and sagittal reconstructions from the same 2020 study.

In 2020, a suspected hollow viscus perforation was investigated, although the specific site could not be determined (Figures 2C, 2D). After these recurrent episodes, gastrointestinal transit slowed significantly, leading to chronic constipation, which has recently improved through dietary modifications and increased physical activity. Despite self-inflicted injuries on the digits, he has no current sequelae or amputation of the upper limbs. In the lower limb, he developed a right equinovarus foot deformity, a sequela of multiple painless injuries, which was subsequently corrected surgically through tendon transposition.

Following the clinical suspicion of HSAN, a genetic study was requested. Clinical exome sequencing of genes related to autonomic dysfunction and pain insensitivity identified a homozygous variant of uncertain significance (VUS) in the SCN9A gene (c.4260+4A>C), which could cause a splicing alteration and was potentially associated with HSAN. The variant was absent from gnomAD (v4.1.1) and ClinVar at the time of analysis. In August 2024, a segregation study confirmed that both the father and the mother were heterozygous carriers of the c.4260+4A>C variant, fulfilling the PP1 supporting criterion under the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines. Combined with the clinical phenotype consistent with HSAN IID and the predicted splice-site effect, these findings support a likely pathogenic role for the variant, although formal functional studies are needed for definitive reclassification. The inheritance pattern is autosomal recessive. Currently, the patient is pursuing a degree in veterinary medicine without any aid. He is fully independent in all basic and instrumental activities of daily living, as shown by a perfect Barthel Index score of 100/100. To optimize his gait and strength, he attends private physical therapy and twice-weekly running practice with an athletics coach. His functional performance is objectively demonstrated by the 10-meter walk test (10MWT), in which he achieved times of 4.82 seconds for walking and 2.9 seconds for running (Figure 3A). His high level of functional autonomy and quality of life is further supported by the five-level EuroQol five-dimension (EQ-5D-5L) questionnaire and an overall health state score of 85 on the EQ-5D visual analogue scale (Figures 3B, 3C). He uses his lower limb prosthesis consistently and recently acquired a specialized carbon version for athletic use. Genetic counseling was recommended upon expression of reproductive intent, as all future offspring would be obligate carriers of the variant.

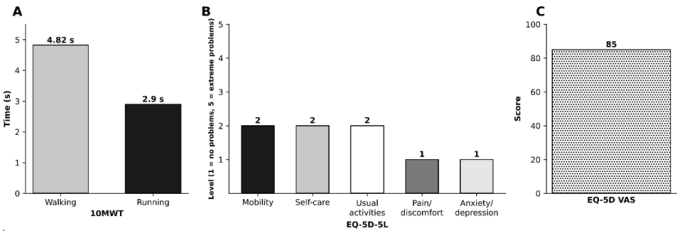


Figure 3 Functional evaluation at the beginning of adulthood. (A) 10-meter walk test (10MWT): walking and running times. (B) Five-level EuroQol five-dimension questionnaire (EQ-5D-5L) levels reported by the patient (1 = no problems; 5 = extreme problems). (C) EQ-5D visual analogue scale (VAS), score 85 out of 100.

Discussion

With this case report, we aim to highlight that this infrequent condition can present with clinical trajectories that extend beyond Dyck's classification (Table 1), making diagnosis and management a challenge. The SCN9A gene plays a pivotal role in our ability to perceive pain, as it encodes the NaV1.7 voltage-gated sodium channel, present in all sensory neurons and highly expressed in

nociceptors.[8,9] The NaV1.7 channel acts at the cell membrane, allowing sodium ions to flow into the cell, which amplifies small voltage changes and is essential for initiating and propagating pain signals throughout the nervous system.[1,10] Mutations in SCN9A can cause autosomal dominant conditions of excess pain, such as congenital erythromelalgia and familial paroxysmal extreme pain disorder, with episodic severe neuropathic pain,[11,12] as well as autosomal recessive congenital insensitivity to pain, associated with non-functional changes to the NaV1.7 channel that prevent the generation of action potentials in response to painful stimuli.[1,3] From a clinical standpoint, besides the absence of pain sensation, patients with SCN9A-related HSAN typically present with hyposmia or anosmia, self-inflicted oral and digit lesions, and orthopedic deformities from untreated fractures and repeated joint injuries, which frequently lead to Charcot joints.[10,13–15] Notably, as detailed above, the amputation in our patient resulted from acute limb ischemia secondary to iliac artery thrombosis in the context of septic shock, rather than from typical HSAN-related bone or joint complications. It is important to emphasize that the gastrointestinal complications observed in our patient are best understood as secondary consequences of delayed medical intervention due to the inability to perceive visceral pain, rather than as a primary phenotypic feature of the SCN9A mutation itself. Primary gastrointestinal dysfunction has been described in association with gain-of-function SCN11A (NaV1.9) mutations, but not with loss-of-function SCN9A mutations.[16] Nevertheless, this clinical trajectory, in which the absence of visceral nociception leads to severe abdominal sequelae, has not been previously documented in the literature on SCN9A-related HSAN, and it underscores the importance of heightened awareness of occult abdominal pathology in these patients.

Table 1 Types of hereditary sensory and autonomic neuropathy (HSAN) according to the Dyck classification[5]

	HSAN I	HSAN II	HSAN III	HSAN IV	HSAN V
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Age of onset	20–40 years	Infancy	Infancy	Infancy	Infancy
Pain insensitivity	++	++	+	++	++
Other clinical manifestations		Anosmia	Hyperhidrosis, alacrimia, postural hypotension, recurrent pyrexia	Anhidrosis, pyrexia, intellectual disability	Anhidrosis
Genes	SPTLC1, SPTLC2, ATL1, DNMT1	SCN9A, WNK1	IKBKAP	NTRK1, PRDM12	NGF, NTRK1

++, severe pain insensitivity; +, mild pain insensitivity

The diagnosis of HSAN is often made during infancy or early childhood by observing abnormal or absent emotional responses to tissue damage,[17] with genetic sequencing for confirmation.[3] In our patient, clinical exome sequencing identified a homozygous SCN9A variant (c.4260+4A>C), initially classified as a VUS and absent from gnomAD (v4.1.1) and ClinVar at the time of analysis. A subsequent segregation study confirmed biparental inheritance, with both parents being heterozygous carriers, fulfilling the PP1 supporting criterion under ACMG/AMP guidelines. Combined with the clinical phenotype consistent with HSAN IID and the predicted splice-site effect, these findings support a likely pathogenic role for the variant, although formal functional studies are needed for definitive reclassification. Several other SCN9A mutations have been identified previously, but, to our knowledge, the c.4260+4A>C variant has not been reported, thereby broadening the genetic spectrum of HSAN IID. Two clinical features of our patient deserve specific comment. First, anhidrosis is listed in the Dyck classification for HSAN types IV and V (Table 1), which are related to NTRK1 and NGF and to a failure of sweat gland development,[1] whereas anosmia is listed for HSAN II. In SCN9A-related disease, by contrast, the core phenotype is pain insensitivity with anosmia, and autonomic involvement is not constant: the patients of the original description sweated normally,[10] while anhidrosis or other autonomic dysfunction together with hyposmia has been reported in SCN9A-related HSAN IID.[18] NaV1.7 is highly enriched in nociceptive and also in sympathetic neurons,[19] so loss of its function may reduce the excitability of sympathetic neurons, including those that drive sweating. Anhidrosis in our patient could therefore reflect the autonomic expression of NaV1.7 deficiency, rather than a mechanism shared with HSAN IV and V. This remains a hypothesis: the anhidrosis was identified clinically, and no quantitative sudomotor testing is reported here.

Second, the patient reports hyposmia limited to food and foul smells, with preserved perception of alcohol and herbs, instead of complete anosmia. NaV1.7 is expressed along the axons of olfactory sensory neurons and is required for synaptic transmission to the olfactory bulb, so complete loss of function typically causes anosmia.[13] A partial olfactory phenotype is compatible with residual NaV1.7 function. This would be plausible for a variant at position +4 of a donor splice site, which may only partially impair normal splicing, but this has not been demonstrated. The preserved perception of selected odorants may also reflect interindividual variability in the olfactory phenotype or compensation by other sodium channels in olfactory neurons. As in the anhidrosis, these explanations are speculative, and the olfactory function was based on the patient's report, without standardized olfactory testing. Knowledge of HSAN has been built mostly on case reports focused on clinical aspects, and data on functional impact and overall quality of life, both equally important for understanding the long-term burden of HSAN, are scarce. In our case, despite life-threatening complications and substantial sequelae, the patient has reached adulthood with a high level of functional independence and quality of life. This may be attributable to an increased awareness of his own body, developed to compensate for the absence of nociception. Specifically, the patient performs a structured daily self-examination protocol that includes: (1) systematic visual inspection of the skin of all extremities, particularly the feet and residual limb, for wounds, blisters, erythema, or signs of infection; (2) palpation of joints for swelling or deformity; (3) monitoring of bowel habits and abdominal distension as a surrogate for occult visceral pathology; and (4) assessment of skin temperature by touch to detect localized warmth suggestive of infection or inflammation. This approach is analogous to the structured foot care protocols recommended for patients with diabetic neuropathy and has been advocated for HSAN management.[20] We suggest that structured education in daily body self-examination may represent a protective strategy to reduce the risk of major complications in patients with congenital pain insensitivity.

This report has the inherent limitations of a single case, and the pathogenicity of the novel variant has not been confirmed by functional studies. The splicing effect of c.4260+4A>C is inferred

from its position and from in silico prediction, and has not been demonstrated experimentally. Position +4 lies within the donor splice-site consensus, where a substitution may weaken donor recognition and lead to exon skipping, intron retention or use of a cryptic splice site; whether this occurs here, and whether the resulting transcript causes loss of NaV1.7 function, is unknown. For this reason, the variant is considered likely pathogenic, on the basis of co-segregation in the family (PP1), its absence from population databases and a compatible phenotype, but it cannot be classified as definitively pathogenic. Future validation should include a splicing assay (for example, a minigene assay in cultured cells or analysis of patient-derived RNA), and electrophysiological characterization of the resulting channel, for instance in patient-derived induced pluripotent stem cell nociceptors.[19] Until then, the findings should be interpreted with caution.

Conclusion

We describe a novel homozygous SCN9A variant (c.4260+4A>C) in a patient with HSAN type IID in whom the inability to perceive visceral pain led to severe abdominal complications and a left transtibial amputation, a clinical trajectory not previously documented in SCN9A-related HSAN. Clinicians should maintain a high index of suspicion for occult abdominal pathology in patients with congenital pain insensitivity. Despite significant sequelae, our patient achieved a high level of functional independence, and structured daily body self-examination may serve as a protective strategy. Genetic counseling is recommended upon expression of reproductive intent.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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