

## CLINICAL REPORT

# Pain triangle phenomenon in possible association with SCN9A: A case report

Maurice Sopacua<sup>1,2</sup>  | Janneke G. J. Hoeijmakers<sup>1</sup> | Anneke J. van der Kooi<sup>3</sup> | Ingemar S. J. Merkies<sup>1,4</sup> | Catharina G. Faber<sup>1</sup>

<sup>1</sup>Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, Maastricht, The Netherlands

<sup>2</sup>Department of Rehabilitation Medicine, Libra Revalidatie & Audiologie, Eindhoven, The Netherlands

<sup>3</sup>Department of Neurology, Amsterdam University Medical Center, Amsterdam, The Netherlands

<sup>4</sup>Department of Neurology, Curaçao Medical Center, Willemstad, Curaçao

## Correspondence

Maurice Sopacua, Department of Neurology, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.  
Email: [maurice.sopacua@mumc.nl](mailto:maurice.sopacua@mumc.nl)

## Abstract

**Background:** Voltage-gated sodium channels are essential for the generation and conduction of electrical impulses in excitable cells. Sodium channel Na<sub>v</sub>1.7, encoded by the SCN9A-gene, has been of special interest in the last decades because missense gain-of-function mutations have been linked to a spectrum of neuropathic pain conditions, including inherited erythermalgia (IEM), paroxysmal extreme pain disorder (PEPD), and small fiber neuropathy (SFN).

**Methods:** In this case report, we present a 61-year-old woman who was referred to our tertiary referral center in a standard day care setting with suspicion of SFN. We performed additional investigations: skin biopsy to determine the intra-epidermal nerve fiber density (IENFD), quantitative sensory testing (QST), and blood examination (including DNA analysis) for possible underlying conditions.

**Results:** The patient showed a clinical picture that fulfilled the criteria of IEM, PEPD, and SFN. DNA analysis revealed the heterozygous variant c.554G > A in the SCN9A-gene (OMIM 603415). This variant has already been described in all three human pain conditions separately, but never in one patient having symptoms of all three conditions. Because its pathogenicity has never been functionally confirmed, the variant is classified as a variance of unknown significance (VUS)/risk factor. This suggests that another genetic and/or environmental substrate plays a role in the development of neuropathic conditions like described.

**Conclusion:** We have described this as the SCN9A-pain triangle phenomenon. Treatment should focus on pain management, genetic counseling, and improving/maintaining quality of life by treating symptoms and, if indicated, starting a rehabilitation program.

## KEYWORDS

genotype–phenotype relationships, neurogenetics, SCN9A variant

## 1 | INTRODUCTION

Previous research showed that changes in the expression of voltage-gated sodium channels (VGSC) play a key role in the pathogenesis of neuropathic pain and that drugs that block these channels are potentially therapeutic (de Greef et al., 2016). These channels are found in the peripheral dorsal root ganglion (DRG), trigeminal ganglion, and sympathetic ganglion neurons.

Gain-of-function mutations in VGSC  $\text{Na}_v1.7$ , that promote neuronal hyperexcitability, can cause human pain conditions. These pain syndromes are inherited erythromelgia (IEM), paroxysmal extreme pain disorder (PEPD), and small fiber neuropathy (SFN). IEM is a rare disorder characterized by recurrent attacks of red, warm and painful hands, and/or feet, with the onset of symptoms during the first decade (Arthur et al., 2019; Cheng et al., 2008; Dib-Hajj et al., 2005; Drenth et al., 2005; Estacion et al., 2013; Harty et al., 2006). PEPD is known for its severe pain episodes and skin flushing starting in infancy and induced by perianal probing or bowel movement. The pain progresses to ocular and mandibular areas with age (Dib-Hajj et al., 2008; Jarecki et al., 2009; Meglič et al., 2014; Suter et al., 2015; Yiangou et al., 2007). SFN patients typically manifest neuropathic pain in distal extremities, as well as autonomic dysfunction (Eijkenboom et al., 2019; Sopacua et al., 2019). All these conditions are linked to *SCN9A* missense variants. Pathogenic mutations in *SCN9A*, which encodes the VGSC  $\text{Na}_v1.7$ , have been found. IEM is usually caused by enhanced  $\text{Na}_v1.7$  channel activation, whereas mutations that alter steady-state fast inactivation often lead to PEPD. In SFN, functional variants of  $\text{Na}_v1.7$  impair channel slow inactivation and produce DRG neuron hyperexcitability that contributes to pain. Characteristics of *SCN9A* variants differ between and within the mentioned pain syndromes. Moreover, the same clinical phenotype may be associated with multiple different variants, and a single  $\text{Na}_v1.7$  variant can be associated with a range of clinical phenotypes (Sopacua et al., 2019). In this case report, the patient had a variant of uncertain significance in *SCN9A*, c.554G>A (OMIM 603415), which has been previously reported as a possible cause of pain syndromes.

## 2 | CASE REPORT

The patient gave informed consent to share her clinical story for educational and/or scientific purposes. The study was conducted according to the ethical policies of Maastricht University Medical Center+ (MUMC+).

A 61-year-old woman was referred to the neurological outpatient clinic because she experienced neuropathic pain in her feet, which started four years ago. The pain in her feet became worse during walking. She described

the pain as a burning and tingling sensation. A couple of months after initiation, the complaints extended to her legs. Furthermore, she developed complaints of itching all over her body, especially in her lower back and lower legs. Dysautonomic symptoms were present, such as hyperhidrosis during the night, hot flashes, and palpitations. Sometimes she had complaints of obstipation.

Furthermore, she described attacks of dull rectal pain, particularly during the nights and after defecation. Sometimes, she has attacks of allodynia in her legs and feet, only present on the left side of her body.

She preferred cold circumstances and walking barefoot at home. She sleeps with air-conditioning on the footboard of her bed; even more, she daily brings cold packs to her working place to put occasionally on her legs in order to reduce the burning sensation. Pressure on her feet during lying or walking with shoes is painful for her. She is not able to use a conventional bike because of the pressure on the pedals and rides more comfortably with an e-bike.

Three years ago, the patient experienced painful feet with attacks of redness. Attacks last for 90 min and disappear with rest. Situational factors such as warm weather and/or exercise worsened these pain attacks. She was diagnosed with primary erythromelalgia. Clonidine was started to reduce the pain; however, it had no effect. Subsequently, amitriptyline was started, up to 25 mg ante noctem. She experienced side effects such as nausea and vertigo. The dosage was lowered to 15 mg which resulted in some pain relief during the night. Yet, she was not able to sleep more than 3–4 h because pain intensity remained relatively high.

The patient has a daughter and three sisters, without similar complaints. Her grandmother had diabetes mellitus type II without neuropathic pain symptoms.

### 2.1 | Level of daily functioning

The patient works for more than 40 years in a factory where she has been exposed to toxic fluids and gases. She still works despite her pain. She is not able to walk longer than 12 min due to painful feet. Driving a car is possible but may lead to dangerous situations if she gets into a pain attack. She and her husband adjusted their lives to the pain by avoiding activities that aggravate the pain, such as long walks, dining out, and city trips. However, they do everything to maintain their Quality of Life.

### 2.2 | Clinical assessment and additional investigations

During the neurological examination, there was no indication of a central nervous system problem or involvement

of large nerve fiber pathology. During the examination, red feet and dry skin on the lower legs were noticed.

Besides a high Vitamin B12 (>1000 pmol/L), other laboratory abnormalities that could be associated with SFN-like symptoms were not found (de Greef et al., 2018).

Nerve conduction studies to test large nerve fibers were normal. Quantitative sensory testing (QST), according to the Levels method, showed an abnormal warmth sensation in both feet. Furthermore, the IENFD was 5.6/mm, which was normal according to the reported normative values (5th percentile: 3.2/mm; median: 8.7/mm) (Lauria et al., 2010).

DNA analysis of the *SCN9A*, *SCN10A*, and *SCN11A*, by means of the molecular inversion Probes-next-generation sequencing (MIPs-NGS) (Almmani et al., 2020), showed the following variant: c.554G>A (version number AB839087.1) in the *SCN9A* gene, which is a gain-of-function variant which enhanced re-surgent currents within the DRG neurons and renders DRG neurons hyperexcitable (Faber et al., 2012; Han, Hoeijmakers, Liu, et al., 2012). The variant is classified as a variant of unknown significance(VUS)/risk factor (Eijkenboom et al., 2019), according to the Practice Guidelines by the Association for Clinical Genetic Science (ACGS) and recommendations by Waxman et al. (2014).

## 2.3 | Diagnosis

The patient was diagnosed with the combination of IEM, PEPD, and SFN, based on clinical symptoms and an abnormal QST, and could be associated with the variant c.554G>A in the *SCN9A*-gene.

## 3 | DISCUSSION

In literature, the *SCN9A*-variant c.554G>A is known to cause several pain syndromes, namely IEM (Goldberg et al., 2012), PEPD (Meglič et al., 2014) and SFN (Han, Hoeijmakers, Ahn, et al., 2012). This patient presented an unusual combination of signs and symptoms of three pain syndromes, IEM, PEPD, and SFN. Situational factors such as warm weather and/or exercise worsened the total package of her complaints. Therefore, this concept could be described as a “pain triangle phenomenon” (see Figure 1).

Interestingly, the patient was found to carry an *SCN9A* missense variant, c.554G>A. This variant has been previously reported to cause all three pain syndromes in different case reports. However, some doubt about its pathogenicity could be raised due to its relatively high frequency in the general population (0.3% in the total population, 0.24% in the European-non Finnish population,

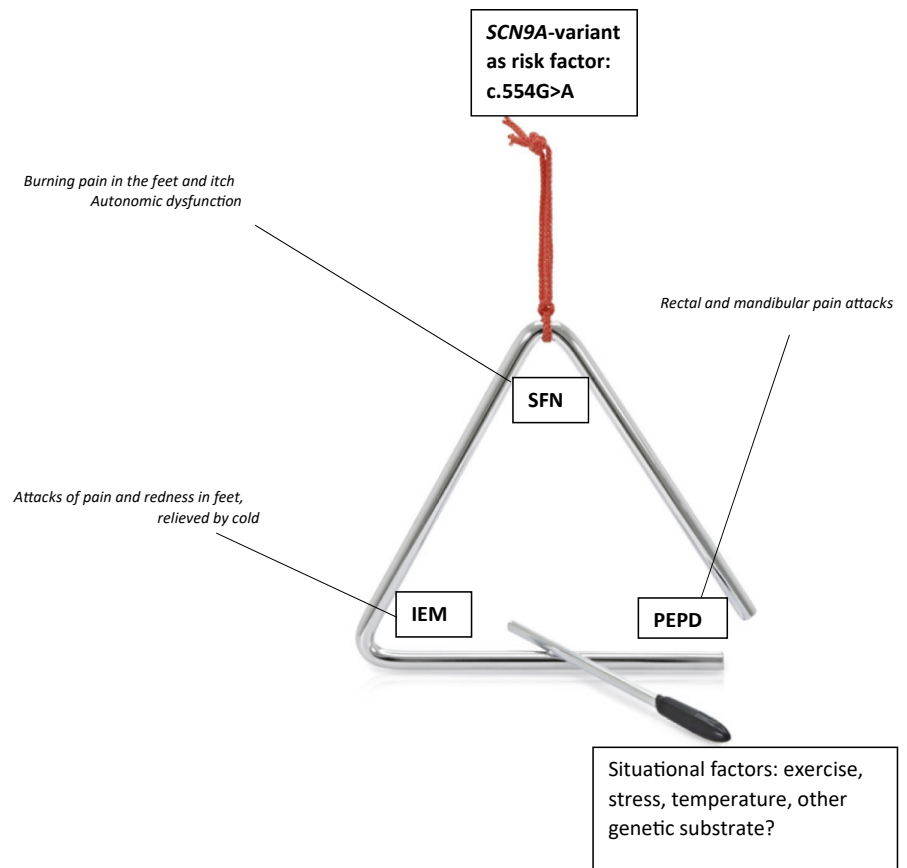


FIGURE 1 The *SCN9A*-pain triangle phenomena

and 1.4% in the African/African-American population in GnomADv2.1.1) and in healthy heterozygous carriers. Moreover, it is still an open question how the same genetic variant could cause early-onset diseases, like EM and PEPD, as well as a late-onset condition, like SFN.

The late onset of IEM and PEPD is rare. Both conditions have been linked to symptoms that start in childhood (Arthur et al., 2019; Fertleman et al., 2007). In this case, symptoms started with the clinical picture of SFN (burning feet after walking) and probably triggered the IEM and PEPD symptoms. Interestingly, no family members were known with identical clinical symptoms. For this reason, co-segregation research has not been conducted. However, it would be interesting to investigate whether other genetic factors (by whole exome sequencing) could be involved in the possible missing heritability in healthy carriers of this *SCN9A* variant and provide novelty in the explanation of genotype–phenotype correlation.

Nevertheless, it is important as a consultant to recognize (parts of) this triangle in order to put in the appropriate additional investigations and discuss treatment options. Genetic counseling is important to find out the underlying cause and/or get informed about the future perspective and inheritance pattern of patients and their families with a pathogenic *SCN9A* mutation. Furthermore, clinical studies with Na<sub>v</sub>1.7-selective blockers have started to test pain relief (de Greef et al., 2016), but its clinical use is still scarce. Nowadays, the treatment of neuropathic pain should follow an algorithm not focusing on the physical aspects but also psychological and social aspects (Brouwer et al., 2015).

### 3.1 | Patients' perspective

Our patient was complimented and encouraged to keep her lifestyle as active as possible. She accepted the illness as it is. Another pain medication such as pregabalin and carbamazepine was offered, but she was reluctant in taking pain medication due to its side effects. She tries to focus on activities that give her relaxation and energy such as playing the piano, reading books, and working in the garden. She was informed to contact a rehabilitation consultant when she experienced significant limitations in her daily activities within her household and/or on a society level.

## 4 | MAIN CONCLUSION AND RELEVANCE

This is the first case that describes a combination of signs and symptoms of IEM, PEPD, and SFN. With genetic

diagnostic screening, a missense variant in the *SCN9A* gene was found, which is classified as VUS/risk factor. This means that other genetic factors might play a role in this genotype–phenotype correlation. Previously, these three pain conditions have been linked separately to the same variant. In complicated pain conditions, it is evident to focus on the sound and loudness that the triangle produces. Perhaps more importantly, attention to factors that determine its tone and volume and its position in the societal orchestra is important.

### AUTHOR CONTRIBUTIONS

All authors contributed equally to this article, from case description to discussion.

### CONFLICT OF INTEREST

There are no conflicts of interest.

### ETHICS STATEMENT

Our patient signed informed consent for the publication of her clinical picture in an international scientific journal.

### ORCID

Maurice Sopacua  <https://orcid.org/0000-0001-8132-1532>

### REFERENCES

- Almomani, R., Marchi, M., Sopacua, M., Lindsey, P., Salvi, E., Koning, B., Santoro, S., Magri, S., Smeets, H. J. M., Martinelli Boneschi, F., Malik, R. R., Ziegler, D., Hoeijmakers, J. G. J., Bönhof, G., Dib-Hajj, S., Waxman, S. G., Merkies, I. S. J., Lauria, G., Faber, C. G., ... on behalf on the PROPANE Study Group. (2020). Evaluation of molecular inversion probe versus TruSeq(R) custom methods for targeted next-generation sequencing. *PLoS One*, 15(9), e0238467.
- Arthur, L., Keen, K., Verriotis, M., Peters, J., Kelly, A., Howard, R. F., Dib-Hajj, S. D., Waxman, S. G., & Walker, S. M. (2019). Pediatric erythromelalgia and *SCN9A* mutations: Systematic review and single-center case series. *The Journal of Pediatrics*, 206, 217–224 e9.
- Brouwer, B. A., de Greef, B. T. A., Hoeijmakers, J. G. J., Geerts, M., van Kleef, M., Merkies, I. S. J., & Faber, C. G. (2015). Neuropathic pain due to small fiber neuropathy in aging: Current management and future prospects. *Drugs & Aging*, 32(8), 611–621.
- Cheng, X., Dib-Hajj, S. D., Tyrrell, L., & Waxman, S. G. (2008). Mutation I136V alters electrophysiological properties of the Na(v)1.7 channel in a family with onset of erythromelalgia in the second decade. *Molecular Pain*, 4, 1.
- de Greef, B. T., Merkies, I. S., Geerts, M., Faber, C. G., & Hoeijmakers, J. G. (2016). Efficacy, safety, and tolerability of lacosamide in patients with gain-of-function Nav1.7 mutation-related small fiber neuropathy: Study protocol of a randomized controlled trial—the LENSS study. *Trials*, 17(1), 306.
- de Greef, B. T. A., Hoeijmakers, J. G. J., Gorissen-Brouwers, C. M. L., Geerts, M., Faber, C. G., & Merkies, I. S. J. (2018). Associated conditions in small fiber neuropathy—A large cohort study and



- review of the literature. *European Journal of Neurology*, 25(2), 348–355.
- Dib-Hajj, S. D., Estacion, M., Jarecki, B. W., Tyrrell, L., Fischer, T. Z., Lawden, M., Cummins, T. R., & Waxman, S. G. (2008). Paroxysmal extreme pain disorder M1627K mutation in human Nav1.7 renders DRG neurons hyperexcitable. *Molecular Pain*, 4, 37.
- Dib-Hajj, S. D., Rush, A. M., Cummins, T. R., Hisama, F. M., Novella, S., Tyrrell, L., Marshall, L., & Waxman, S. G. (2005). Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons. *Brain*, 128(Pt 8), 1847–1854.
- Drenth, J. P., te Morsche, R. H., Guillet, G., Taieb, A., Kirby, R. L., & Jansen, J. B. (2005). SCN9A mutations define primary erythromelalgia as a neuropathic disorder of voltage gated sodium channels. *The Journal of Investigative Dermatology*, 124(6), 1333–1338.
- Eijkenboom, I., Sopacua, M., Hoeijmakers, J. G. J., de Greef, B. T. A., Lindsey, P., Almomani, R., Marchi, M., Vanoevelen, J., Smeets, H. J. M., Waxman, S. G., Lauria, G., Merkies, I. S. J., Faber, C. G., & Gerrits, M. M. (2019). Yield of peripheral sodium channels gene screening in pure small fibre neuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 90(3), 342–352.
- Estacion, M., Yang, Y., Dib-Hajj, S. D., Tyrrell, L., Lin, Z., Yang, Y., & Waxman, S. G. (2013). A new Nav1.7 mutation in an erythromelalgia patient. *Biochemical and Biophysical Research Communications*, 432(1), 99–104.
- Faber, C. G., Hoeijmakers, J. G. J., Ahn, H. S., Cheng, X., Han, C., Choi, J. S., Estacion, M., Lauria, G., Vanhoutte, E. K., Gerrits, M. M., Dib-Hajj, S., Drenth, J. P. H., Waxman, S. G., & Merkies, I. S. J. (2012). Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. *Annals of Neurology*, 71(1), 26–39.
- Fertleman, C. R., Ferrie, C. D., Aicardi, J., Bednarek, N. A. F., Eeg-Olofsson, O., Elmslie, F. V., Griesemer, D. A., Goutieres, F., Kirkpatrick, M., Malmros, I. N. O., Pollitzer, M., Rossiter, M., Roulet-Perez, E., Schubert, R., Smith, V. V., Testard, H., Wong, V., & Stephenson, J. B. P. (2007). Paroxysmal extreme pain disorder (previously familial rectal pain syndrome). *Neurology*, 69(6), 586–595.
- Goldberg, Y. P., Price, N., Namdari, R., Cohen, C. J., Lamers, M. H., Winters, C., Price, J., Young, C. E., Verschoof, H., Sherrington, R., Pimstone, S. N., & Hayden, M. R. (2012). Treatment of Na(v)1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker. *Pain*, 153(1), 80–85.
- Han, C., Hoeijmakers, J. G. J., Ahn, H. S., Zhao, P., Shah, P., Lauria, G., Gerrits, M. M., te Morsche, R. H. M., Dib-Hajj, S. D., Drenth, J. P. H., Faber, C. G., Merkies, I. S. J., & Waxman, S. G. (2012). Nav1.7-related small fiber neuropathy: Impaired slow inactivation and DRG neuron hyperexcitability. *Neurology*, 78(21), 1635–1643.
- Han, C., Hoeijmakers, J. G. J., Liu, S., Gerrits, M. M., te Morsche, R. H. M., Lauria, G., Dib-Hajj, S. D., Drenth, J. P. H., Faber, C. G., Merkies, I. S. J., & Waxman, S. G. (2012). Functional profiles of SCN9A variants in dorsal root ganglion neurons and superior cervical ganglion neurons correlate with autonomic symptoms in small fibre neuropathy. *Brain*, 135(Pt 9), 2613–2628.
- Harty, T. P., Dib-Hajj, S. D., Tyrrell, L., Blackman, R., Hisama, F. M., Rose, J. B., & Waxman, S. G. (2006). Na(V)1.7 mutant A863P in erythromelalgia: Effects of altered activation and steady-state inactivation on excitability of nociceptive dorsal root ganglion neurons. *The Journal of Neuroscience*, 26(48), 12566–12575.
- Jarecki, B. W., Sheets, P. L., Xiao, Y., Jackson, J. O., & Cummins, T. R. (2009). Alternative splicing of Na(V)1.7 exon 5 increases the impact of the painful PEPD mutant channel I1461T. *Channels (Austin, Tex.)*, 3(4), 259–267.
- Lauria, G., Bakkers, M., Schmitz, C., Lombardi, R., Penza, P., Devigili, G., Smith, A. G., Hsieh, S. T., Mellgren, S. I., Umaphathi, T., Ziegler, D., Faber, C. G., & Merkies, I. S. J. (2010). Intraepidermal nerve fiber density at the distal leg: A worldwide normative reference study. *Journal of the Peripheral Nervous System*, 15(3), 202–207.
- Meglić, A., Perkovič-Benedik, M., Trebušak Podkrajšek, K., & Bertok, S. (2014). Painful micturition in a small child: an unusual clinical picture of paroxysmal extreme pain disorder. *Pediatric Nephrology*, 29(9), 1643–1646.
- Sopacua, M., Hoeijmakers, J. G. J., Merkies, I. S. J., Lauria, G., Waxman, S. G., & Faber, C. G. (2019). Small-fiber neuropathy: Expanding the clinical pain universe. *Journal of the Peripheral Nervous System*, 24(1), 19–33.
- Suter, M. R., Bhuiyan, Z. A., Laedermann, C. J., Kuntzer, T., Schaller, M., Stauffacher, M. W., Roulet, E., Abriel, H., Decosterd, I., & Wider, C. (2015). p.L1612P, a novel voltage-gated sodium channel Nav1.7 mutation inducing a cold sensitive paroxysmal extreme pain disorder. *Anesthesiology*, 122(2), 414–423.
- Waxman, S. G., Merkies, I. S. J., Gerrits, M. M., Dib-Hajj, S. D., Lauria, G., Cox, J. J., Wood, J. N., Woods, C. G., Drenth, J. P. H., & Faber, C. G. (2014). Sodium channel genes in pain-related disorders: Phenotype-genotype associations and recommendations for clinical use. *Lancet Neurology*, 13(11), 1152–1160.
- Yiangou, Y., Facer, P., Chessell, I. P., Bountra, C., Chan, C., Fertleman, C., Smith, V., & Anand, P. (2007). Voltage-gated ion channel Nav1.7 innervation in patients with idiopathic rectal hypersensitivity and paroxysmal extreme pain disorder (familial rectal pain). *Neuroscience Letters*, 427(2), 77–82.

**How to cite this article:** Sopacua, M., Hoeijmakers, J. G. J., van der Kooi, A. J., Merkies, I. S. J., & Faber, C. G. (2022). Pain triangle phenomenon in possible association with SCN9A: A case report. *Molecular Genetics & Genomic Medicine*, 10, e2026. <https://doi.org/10.1002/mgg3.2026>