**Appendix S1**

**SUPPLEMENTARY MATERIAL**

**Description of medical history and phenotypes for different mutations within the SCN9A gene.**

***I228M variant***

This mutation was found in two female patients. Both of these patients have been active athletes all their lives. Interestingly, out of all of patients included in this study, they are the only patients who describe worsening of EM symptoms after intake of alcohol, particularly red wine.

One of the two (Subject 24) also reports worsening of symptoms after eating chocolate. Her EM symptoms started in her toes at the age of 30 and since 2013 her fingertips have also been involved. The pain is prominent at nighttime and pain level vary from zero to four on a visual analogue scale (VAS) and often disturbs her sleep. Pain is relieved by cooling and pregabalin.

The other patient (Subject 14) experienced hot feet as a child, but the onset of pain began in her early sixties. Using lidocaine patches underneath the soles of her feet controls the pain. She also suffers from restless legs, like her father and brother, but describes these symptoms to be distinctly different from her EM symptoms. This patient reports a possible family history of EM and remembers her mother to have had warm feet.

***I848T variant***

Two related patients (mother and daughter) had an I848T variant in the *SCN9A* gene (Subjects 01 and 02) describe disabling burning pain from their feet.

The mother (Subject 01) experienced periodically warm, burning feet from the age of five. She cooled her feet by walking barefoot on cold floors and outdoors in the winter season. From the age of 13 she started cooling her feet in buckets of cold water. Successively, she had a bucket of iced water continuously available, day and night, intermittently cooling for periods of around 20 minutes with 20 minutes cooling free intervals. At the age of 28 years she developed pitting edema, maceration of the skin, ulcerations, bullae. At the age of 39 the condition eventually led to infection with sepsis, leading to acute need for bilateral knee-joint disarticulation. Prior to amputation she had repeated septic episodes caused by infected skin ulcers and drug induced agranulocytosis. The daughter (Subject 02) has limited cooling with cold water. Neither the mother nor the daughter describes relief from pain killers, including opiates, but misoprostol provides some relief.

The mother describes a maternal aunt known to have had warm feet and intermittent burning pain. This aunt was known to have the habit of cooling her feet in cold water in the summertime or by walking barefoot in snow during winter. A female cousin, the daughter of another maternal aunt, also had symptoms compatible with EM.

***V1820F variant***

One case, a 41-year-old female with a complex history of pain symptoms, including EM since her late teens, and bowel dysfunction since ten years of age. Initially she described burning pain in her feet, progressing over years to pain in both hands and feet combined with hyperemia, warm skin and allodynia. She experiences poor regulation of body temperature and describes intensely hot extremities and cold skin proximal to her umbilicus. At night she keeps her room at a low temperature and sleeps with a wool blanket wrapped around her torso while her feet are outside the blankets. During daytime she experiences less pain from her feet, but sometimes uses wet socks and keeps her feet close to cold surfaces. Treatment with misoprostol (10.4 mg, 2 times daily) relieves some of the EM symptoms.

Apart from EM pain she describes other disabling pain symptoms. In her mid-twenties, the patient started experiencing dreadful rectal cramps, described as *proctalgia fugax*. The pain is so strong that she has fainted twice. These pain attacks are often triggered by diarrhea, but she can also wake from the cramps at night. She also has irritable bowel syndrome (IBS) with diarrhea, bloating and stomachaches as dominating symptoms. Gastroscopy and colonoscopy have revealed discretely inflamed mucous membranes. Biopsies have not revealed helicobacter infection or villus atrophy. Dietary modifications have improved bowel symptoms.

From her early thirties she also experienced continuous extreme vulvar pain for a period of two to three years. An area of around one $cm^2$ underneath the clitoris was especially sensitive and extremely painful. The patient could not wear underwear for more than one year. Biopsy showed chronic inflammation of the mucous membranes. Systemic treatment with amitriptyline relieved some of the symptoms, and at the same time improved her bowl symptoms.

In her early thirties she also experienced an episode of intense acute jaw pain, with some relief from supporting the jaw with her hands. After a couple of hours, the pain gradually subsided. Similar attacks, although less painful, have occurred on a couple of occasions during the past 10 years.

Progressive weakness and disturbed coordination in fingers have caused clumsiness with problems like writing on a pc, holding a cup or using a pen, as well as accidental dropping of objects. Neurological examination has concluded that symptoms are suggestive of small-fiber neuropathy, but neurography and quantitative sensory testing are normal. Her skin reveals multiple cherry angiomas although normal kidney biopsy, eye examination, alfa-galaktosidase and GB3-levels in blood exclude Fabry disease. Chest X-ray shows normal findings. Over the last years she has experienced an “exploding pressure” in her calves. Elevating the extremities relieves the feeling of pressure.

She describes that her mother preferred to walk barefoot indoor, and was observed to have had red hands, cooling them under cold, running water. The mother had hyper-flexible joints and chronic back pain following a trauma. Surgeons allegedly fixated the ileo-sacral joint, but the operation did not provide pain relieve. Post-operatively she was referred to a pain management team but ended up overusing analgesics. She died at the age of 62 due to “liver cancer”. The grandmother, like the patient, also suffered from continuous stomachaches and died from volvulus. Both the mother and her grandmother were diagnosed with rheumatic disease (swollen and painful wrist and finger joints) and the patient herself has positive ANA.

Because of the complex history of disabling pain, the patient was referred to a neurologist and was later diagnosed with Paroxysmal Extreme Pain Disorder (PEPD). PEPD is caused by mutations in the SCN9A gene and is inherited in an autosomal dominant pattern. The condition is characterized by intens episodes of severe pain that last for seconds up to a few minutes. The pain is described as torturous and may affect different parts of the body.

***R1110Q variant***

The R1110Q genetic variant was found in one patient (Subject 26). She describes EM pain from her early twenties located mostly from her palms, but her feet might also be involved. The symptoms tend to peak at nighttime two to three times a week and are alleviated by keeping the burning area on cold surfaces. Warm weather and smoking cigarettes are aggravating factors for EM symptoms. The patient is diagnosed with schizophrenia, which is well managed, and she has not experienced psychotic episodes for many years. There is no familial history of EM.

***P610T variant***

Two patients (Subjects 19 and 28), had P610T variant in the *SCN9A* gene. The male patient (Subject 19) describes continuous EM pain located in the soles of his feet disturbing his sleep and ability to work. The same sense of pain has started to appear in his palms. Gabapentin gave pain relief but had to be discontinued because of side effects. He has periods of vertigo, but Epleys manoeuvre has proved to be effective. He describes unsteadiness caused by decreased sensation to the soles of his feet. Neurography has not demonstrated large-fiber neuropathy. EMG shows unspecific changes in his right leg. Quantitative sensory testing is susceptive of small-fiber neuropathy. He has had periods of depressions since childhood. His diabetes was diagnosed at the age of 36 and is treated with metformin.

The female patient with a P610T variant (Subject 28) has experienced burning pain on the soles of her feet for as long as she can remember. She has no familial history of EM. The burning pain is notable every day and flares up intensely a couple of days a month. Her blood sugar has been irregular for a long period, and she has been on and off metformin for years, depending on the blood sugar levels. This patient experiences recurrent depressive episodes. She tried selective serotonin reuptake inhibitors (SSRI) but had to discontinue this medication due to nightmares. Previous investigations have revealed hypothyreosis, hypercholesterolemia and polycystic ovary syndrome. Both of these relatively young patients have type 2 diabetes, as well as recurrent depressive periods. Neither of them reports a family history of EM.