Pediatric erythromelalgia and *SCN9A* mutations: systematic review and single-center case series

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Abbreviations: CBZ, carbamazepine; CYP, children and young people; DRG, dorsal root ganglion; GOSH, Great Ormond Street Hospital; IEM, inherited erythromelalgia; Na_v, voltage-gated sodium channel; NHS, national health service; PEPD, paroxysmal extreme pain disorder; QST, quantitative sensory testing; *SCN*, sodium voltage-gated channel gene family; s-EM, symptomatic erythromelalgia

Abstract

Objectives. To evaluate the clinical features of erythromelalgia in childhood associated with gain-of-function *SCN9A* mutations that increase activity of the $Na_v1.7$ voltage-gated sodium channel we: i) conducted a systematic review of pediatric presentations of erythromelalgia related to *SCN9A* mutations; and ii) compared pediatric clinical presentations of symptomatic erythromelalgia, with or without *SCN9A* mutations.

Study Design PubMed, Embase, and PsycINFO Databases were searched for reports of IEM in childhood. Clinical features, management and genotype were extracted. Case notes of pediatric patients with erythromelalgia from the Great Ormond Street Hospital (GOSH) Pain Service were reviewed for clinical features, patient-reported outcomes and treatments. Children aged over 10 years were recruited for quantitative sensory testing (QST).

Results Twenty-eight publications described erythromelalgia associated with 15 different *SCN9A* gene variants in 25 children. Pain was severe and often refractory to multiple treatments, including non-specific sodium channel blockers. Skin damage or other complications of cold immersion for symptomatic relief were common (60%). *SCN9A* mutations resulting in greater hyperpolarizing shifts in $Na_v1.7$ sodium channels correlated with symptom onset at younger ages (P=.016). Variability in reporting and potential publication bias towards severe cases limit any estimations of overall incidence. At GOSH, reported symptoms in both groups were similar but co-morbidities were more common in *SCN9A*-positive cases. QST revealed marked dynamic warm allodynia.

Conclusions: IEM in children is associated with difficult-to-manage pain and significant morbidity. Standardized reporting of outcome and management in larger series will strengthen

identification of genotype-phenotype relationships. More effective long-term therapies are a significant unmet clinical need.

INTRODUCTION

Erythromelalgia is a rare but difficult-to-manage condition in children.[1] Bilateral episodic pain and redness occur in the feet, hands, and occasionally the ears. Symptoms may also progress proximally to include the legs and arms and rarely the face.[2] Pain is aggravated by heat and relieved by cooling or immersion in iced water. Diagnosis has been based on clinical features,[3, 4] with pathophysiology previously attributed to vascular, inflammatory or neuropathic causes. However, since 2004, cases of inherited erythromelalgia (IEM) have been linked to dominant gain-of-function mutations of the *SCN9A* gene and resultant alterations in function of voltage-gated sodium channel $Na_v1.7$.[5, 6] Additionally, similar symptoms associated with autoimmune or myeloproliferative disorders[4, 7] have been reported in adults and termed 'secondary erythromelalgia', but are extremely rare in children.

Voltage-gated sodium channels ($Na_v1.1$ to $Na_v1.9$) are encoded by a family of *SCN* genes and are differentially distributed throughout the nervous system, heart and muscle. In children, sporadic or inherited mutations that affect different voltage-gated sodium channels have also been associated with epilepsy, cardiac conduction and skeletal muscle abnormalities,[8] with treatment often reliant on non-specific sodium channel blockers such as mexiletine.[9-11] $Na_v1.7$ channels are expressed in peripheral nociceptive sensory neurons within dorsal root ganglia (DRG) and trigeminal ganglia, and in sympathetic ganglion neurons, and play a crucial role in pain sensitivity.[12, 13] Gain-of-function mutations with IEM typically increase excitability of DRG neurons by hyperpolarizing the voltage-dependence of activation of $Na_v1.7$ channels (making the channels easier to activate), slowing channel deactivation (channels remain open longer), and increasing the response to slow ramp-like stimuli (increasing the gain).[13, 14] Importantly, the site of mutation

can influence both the abnormality of $Na_v1.7$ channel function, and age of onset and severity of symptoms.[12, 15-17] While reports in adults have evaluated phenotype-genotype relationships,[18] details of clinical evaluation during childhood and/or results of genetic testing have not been available in all pediatric case series.[1]

We conducted a systematic review to identify cases of *SCN9A*-related IEM reported during childhood. Data for genotype and clinical presentations, complications and management were extracted. Our clinical experience from a tertiary hospital chronic pain clinic managing children with erythromelalgia, in whom SCN9A mutations are present or absent, is summarized to suggest additional questions for future case series.

METHODS

Systematic Literature Review

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.[19] To identify reported symptoms, management and complications of *SCN9A*-positive IEM in children and young people (CYP), we searched PubMed (Jan 2004 to Feb 2017) using erythromelalgia (which also identified 'erythermalgia') AND pediatric search terms (Figure 1; online). Additional hand searches of reference lists and review articles, and a secondary search (erythromelalgia AND *SCN9A*) checked for further manuscripts including clinical details during childhood. Repeat searches in February 2018 identified recent publications fulfilling the inclusion criteria. No additional eligible publications were found from searching PsycINFO, EMBASE or Cochrane databases. Authors were contacted for details of IEM cases in which the *SCN9A* mutation was not reported. Records were screened and restricted to those published in English

since 2004, when erythromelalgia was first associated with mutations in *SCN9A*[6] and alterations in $Na_v1.7$ channel gating and kinetics.[5]

To specifically capture symptoms during childhood, included cases reported: clinical symptoms; age at publication up to 18 years of age; *SCN9A* mutations and/or $Na_v1.7$ substitutions; and individual data that could be extracted from group or family data. Cases in which an *SCN9A* mutation was reported without clinical details during childhood were excluded.

Citations deemed relevant by at least one reviewer underwent full-text screening. Two investigators independently reviewed selected articles. Available demographic data, clinical features, genetic testing results, complications and co-morbidities, and management details were extracted, entered into a database, and cross-checked. Categories for which no details were available were labeled 'Not reported'. Where earlier clinical descriptions were referenced, previous manuscripts were included to group descriptions within the same patient/family.

Data were available as individual case series or case reports, which variably reported clinical details and may be biased to more severe presentations. Data related to symptoms, age at symptom onset and time of report, management, and complications are summarized. Relative frequencies of complications are highlighted within the text. Values for the degree of hyperpolarizing shift in $Na_v1.7$ activation, were extracted for each reported mutation. Additional IEM cases reported in adulthood but with documented onset during childhood are listed, and severe complications summarized.

Single center clinical experience at Great Ormond Street Hospital for Children

A Case Note Review was registered and approved by the Great Ormond Street Hospital (GOSH) National Health Service (NHS) Joint Research and Development Office (R&D No:17NC02; GOSH

NHS Permission 5-5-2017). Previously collected clinical information was extracted from medical records for patients with both symptoms of erythromelalgia and results of *SCN9A* genetic analysis (NHS East Anglian Medical Genetics Laboratories, Cambridge; Accredited Medical Laboratory Ref 1275). For the purposes of this manuscript, Ccases with a confirmed mutation in *SCN9A* are designated as IEM, and those with no *SCN9A* mutation identified on genetic testing are termed symptomatic erythromelalgia (s-EM). Demographic data, clinical and management details were entered into an anonymized spreadsheet. CYP over 8 years attending GOSH Pain Clinic complete a range of patient-reported outcomes, and data were extracted for: current, worst and average pain in the last week (0-100mm Visual Analogue Scale); Pediatric Quality of Life Inventory, Child Report;[20] Pediatric Index of Emotional Distress;[21] and Pain Catastrophizing Scale, Child.[22] A Case Note Review (R&D No:09AR15; GOSH NHS Permission 5-5-2009) in 2009 identified 13 patients clinically diagnosed with erythromelalgia and managed at GOSH prior to availability of clinical genetic testing, and pharmacological management data was extracted.

CYP with erythromelalgia aged 10-18 years were eligible for inclusion in a neuropathic pain cohort study (NHS Research Ethics Committee approval 17/WM/0306, 7-7-2017; Clinicaltrials.gov NCT03312881) that included quantitative sensory testing (QST). Following parental consent and child assent, we measured static thresholds for thermal (cool, warm, cold, heat) and mechanical (detection, pricking, pressure) stimuli, and dynamic allodynia for brush and thermal stimuli using a standardized QST protocol.[23-25]

Statistical Analyses

Correlation between age of symptom onset and $Na_v1.7$ hyper-polarizing shift was assessed (2-tailed Pearson's correlation coefficient)(SPSS® Version 23 IBM, Portsmouth, UK). QST results

were calculated as Z-score comparisons with healthy control data (z=[($X_{patient}$ - $Mean_{controls}$)/$SD_{controls}$]) collected by the same investigator,[23, 24] and sensory profiles were plotted with increased sensitivity as positive values and decreased sensitivity as negative values.[26]

RESULTS

Descriptive Synthesis of Systematic Literature Review

Twenty-eight manuscripts fulfilled the inclusion criteria (Figure 1; online) and reported 25 CYP (<18 years at time of reporting) with clinical features of IEM and confirmed *SCN9A* mutations producing 16 different substitutions of $Na_v1.7$ channels. Six cases included clinical details and/or genetic analyses in sequential manuscripts, and 2 manuscripts included pediatric data for siblings. A positive family history was reported in 12 CYP from 9 families (Table 1; online).[15,27-53] A negative family history suggested a de novo variant, but confirmation by testing other family members was inconsistently reported. The degree of hyperpolarizing shift was obtained from the same or related reports.[2,5,54]

Clinical features. Clinical criteria for erythromelalgia included episodic pain and erythema in feet (*n*=12), feet and hands (*n*=11), or feet, hands and ears (*n*=2). Symptoms were triggered or exacerbated by heat and/or activity, and relieved by cold. In 14 cases reporting pain intensity, it was rated as severe (severe/excruciating/10 out of 10), often with multiple episodes each day, and constant pain was also noted in 4 IEM cases. Fifteen cases (60%) reported significant skin damage or ulceration due to prolonged cold immersion (*n*=11) and/or excessive rubbing or scratching (*n*=4). Cooling for symptomatic relief was associated with severe hypothermia in a 6-year old (p.L858F),[40] and hypothermia, neurological symptoms and pneumonia in a 15 year-old

(p.L823R).[34] Mortality was associated with severe sepsis in one case (p.V1316A)[49] and was also reported in a sibling (p.S241T)[31,55] (Table 1; online).

Additional co-morbidities included: hypertension (p.F1449V)[50] requiring investigation and treatment (p.Q875E);[44] muscle hypotonia and/or joint hypermobility (p.1234T[27,29] and p.L823R[34]) and reduced pain sensitivity (corneal anesthesia, painless fracture in 2 p.I234T cases).[28-30] Impaired growth with under-developed limbs or short stature was associated with normal (p.G856R),[14,37] low (p.Q875E),[44] or unreported (p.L823R)[34] growth hormone levels. Small distal forearms, hands, distal legs and feet were also noted in a 35 year old with symptoms since 10 years of age (p.G856D); growth hormone levels not reported.[56] (Table 2A; online)

Age of onset and genotype. Age of onset of pain and erythema ranged from 1.2 to 14 years (Figure 2A), with some reporting earlier onset of less specific symptoms.[27,29,34,51] Sixteen different amino acid substitutions in $Na_v1.7$ channels resulted in hyperpolarizing shifts in activation ranging from -5.3 to -18mV (Table 1; online). Greater shift tended to correlate with onset of symptoms at a younger age (r=0.47 [95% CI 0.13-0.72], P=.016; Figure 2B) as previously reported.[15]

Pharmacological Management. More than 40 treatments were reported, with details of specific therapy for 15 of 25 cases. All had received agents with predominant but non-specific sodium channel blocking activity (mexiletine, lidocaine, carbamazepine; n=15). Efficacy data were limited, and mexiletine was variably reported to have no or minimal benefit,[15,47,48] partial benefit,[29,34,46] significant initial benefit,[42,57] benefit that reduced after 6 months,[41] or sustained benefit that persisted beyond cessation of treatment.[43,58] Additional treatments included combination therapy with anti-neuropathic drugs (gabapentinoids and anti-depressants; n=9); vasoactive

drugs for symptomatic management and/or hypertension (*n*=5); and other analgesics (opioids, ketamine or procedural interventions; *n*=6) (Table 3; online).

Excluded pediatric cases. Several reports included children as part of group data and/or with limited clinical details (Table 2A online).[2,6,16,33,50,56,59-68] *SCN9A*-related IEM cases in adults reporting onset of symptoms before 18 years are also listed (Table 2B; online).[2,3,6,17,18,33,48,61,63, 69-82] Overall, pediatric onset IEM was associated with 24 different $Na_v1.7$ channel substitutions. As in the systematic review, additional cases reported major complications associated with excessive cooling or ice immersion: skin injury and sepsis resulting in amputations (p.L858F)[78] and mortality (p.F216S);[61,70] and severe hypothermia (p.L858F[78]) with associated cerebral symptoms (p.I848T,[75] p.F216S[70]) (Table 2B; online).

GOSH Case Series

Clinical features. Clinical details and genetic analysis were available for 13 patients referred for management or review (*SCN9A* testing positive in 4; negative in 9). Episodic burning pain and erythema occurred in all patients, but skin damage related to immersion injury or repeated rubbing, and hypertension requiring management and investigation was seen only in *SCN9A*-positive cases (Table 4; online). Pain scores varied with time (e.g. exacerbated by hot weather, stress, exams) and tended to be higher and more persistent in IEM cases. Patient-reported outcomes identified impaired quality of life (particularly in the physical function and school domains), emotional distress and increased pain catastrophizing (Table 5; online).

Sensory Testing. QST in 3 patients (two IEM and one S-EM) revealed increased sensitivity to static heat and cold in the s-EM case, but predominantly reduced sensitivity in the 2 IEM cases who also had more prolonged symptoms (11 and 13 years versus 14 months). However, dynamic

warm sensitivity (40^0C rollers) was more intense and extended beyond the hand and into the upper arm in both IEM cases. All had increased digital pressure pain sensitivity, but mechanical detection and pricking pain sensitivity was reduced in one IEM case (p.I234T) (Figure 3, online; Table 6, online).

Management. All patients had multidisciplinary assessment, physiotherapy and/or psychology interventions, and liaison with pediatricians or other medical specialists according to individual need. Mexiletine improved allodynia, activity, and sleep in one IEM (p.I848T) patient. Pain has remained difficult to manage in 3 IEM cases, with partial benefit from higher mexiletine doses at plasma levels below those associated with toxicity (Figure 4; online). Efficacy has not been tested by ceasing mexiletine. Local anesthetic sympathetic and peripheral nerve blocks at another center produced short-term benefit; and a trial of oral opioid was discontinued due to limited efficacy in a separate patient. Inpatient management of skin injury and/or infection has been required in 3 cases (Table 4; online). One IEM (p.I234T) patient has developed a complex phenotype with reduced sensitivity to some forms of acute pain (venipuncture, fracture).[26] For s-EM patients, symptomatic management alone has been used for infrequent pain episodes, One s-EM case initially received mexiletine; changing to an anti-convulsant (once confirmed *SCN9A*-negative) produced similar benefit. Amitriptyline had no benefit in one, but improved pain and/or sleep in two cases. Compared to 13 GOSH cases clinically diagnosed with erythromelalgia prior to availability of genetic testing, pharmacological management has shifted from vasoactive to anti-neuropathic agents (Table 2; online).

DISCUSSION

Erythromelalgia is a rare but severe pain condition in children that can be difficult to diagnose and manage. Identifying effects of *SCN9A* gene mutations on sensory neuron function can improve understanding and identify potential treatment targets. In this study, we report IEM during childhood associated with gain-of-function mutations at multiple sites on the *SCN9A* gene, and a greater degree of hyperpolarizing shift in $Na_v1.7$ channel kinetics tended to correlate with onset of symptoms at younger ages. Pain was often refractory to treatment, and attempts to gain symptomatic relief with excessive cooling or prolonged cold immersion were associated with significant morbidity. Although non-specific sodium channel blockers were commonly used for management, current evidence is limited to uncontrolled case reports with variable reporting of efficacy and follow-up. Preliminary data from our pediatric case series suggests that episodic pain and redness alone do not differentiate *SCN9A*-positive from *SCN9A*-negative cases, which is consistent with a previous small series in adults.[35] However, severe complications and co-morbidities were only seen in *SCN9A*-positive cases. Parent- and patient-reported questionnaires provided further description of the impact of erythromelalgia, and evaluation of somatosensory function with QST may improve evaluation of phenotype-genotype relationships in larger series.

The importance of the *SCN9A* gene for pain sensitivity is reflected by the association between loss-of-function mutations and congenital insensitivity to pain, and gain-of-function mutations with IEM or paroxysmal extreme pain disorder (PEPD).[12,13] Multiple IEM-related mutations of the *SCN9A* gene have now been characterized with more marked shifts in the voltage-dependence of activation (greater than 7.6mV hyperpolarizing shift) of $Na_v1.7$[15] associated with IEM symptom onset at younger ages, as also demonstrated by the significant

negative correlation shown here. Consistent with the distribution of $Na_v1.7$ channels on nociceptive sensory fibres, small fibre but not large fibre dysfunction has been demonstrated in children with IEM.[1,44,50] As also reported with other causes of neuropathic pain,[83,84] QST evaluation of small fiber function in IEM demonstrated mixed patterns of sensory gain and loss in adults,[18,53,76,85-88] and in the 2 pediatric IEM cases reported here. The marked insensitivity to punctate stimuli in our p.I234T case correlated with a high tolerance for clinically required venipunctures,[28] the reduced sensitivity to injury associated with this genotype,[28-30] and a complex pattern that includes marked depolarization and lack of excitability in some DRG neurons expressing $Na_v1.7$-I234T channels.[28]

Erythromelalgia has been associated with significant complications during childhood and later life.[1,89] Sixty percent of children with *SCN9A*-positive IEM identified by systematic review, and 3 of 4 cases at our center, had significant peripheral tissue injury secondary to prolonged cold immersion or rubbing/scratching. Prolonged ice immersion and/or environmental cooling have been associated with severe hypothermia requiring intensive care;[40,70,74,75,79] skin injury with sepsis and significant morbidity;[3,31,48,90,91] and mortality.[49,55,61,90] The extent to which hypertension[50] and increased plasma or urine catecholamines[44,92] in pediatric IEM cases are secondary to uncontrolled pain and stress is difficult to determine. Altered growth has also been noted.[34,37,44,56] Potential mechanisms underlying co-morbidities, and the relationship to sodium channel dysfunction or other genetic conditions, require further study.

The severe and refractory nature of erythromelalgia pain in children is also reflected in the wide range of therapeutic interventions that have been tried for symptomatic relief.[1] Pharmacological management is shifting from vasoactive to anti-neuropathic agents[93] and future

pharmacotherapy for IEM may increasingly be guided by genomic analysis.[14,73,94] While drugs that more selectively target $Na_v1.7$ channels are under development,[72,77] currently available mexiletine and lidocaine are class 1B anti-arrhythmic agents that non-selectively block voltage-gated sodium channels and have been associated with variable efficacy. Laboratory studies have identified beneficial actions of mexiletine specifically against $Na_v1.7$ channels with p.I848T,[48] p.L858F,[95] and p.V872G[43] substitutions, and one study reported reduced axonal excitability and improvement in clinical symptoms with p.I136V, p.I848T, and p.V1316A substitutions.[46] Mexiletine doses for children with erythromelalgia have ranged from 8 to 24mg/kg/day,[42,57,58] but data are insufficient to evaluate efficacy based on genotype.[48,96]

Carbamazepine is effective in patients with PEPD,[97] and specific benefit for some IEM cases is supported by atomic-level structural modeling and in vitro pharmacology.[14,73,98] Carbamazepine normalizes the voltage-dependence of activation of DRG neurons expressing $Na_v1.7$ channels with p.V400M and p.S241T substitutions,[63,94] reduces warmth-evoked firing of p.S241T substitutions,[73] and clinical use reduced the frequency and duration of episodic pain in affected family members with these genotypes.[73] Carbamazepine partially corrects the hyperpolarized activation and reduces sensory neuron firing in $Na_v1.7$ p.I234T channels,[98] and improved symptoms in a child with this substitution,[29] but use can be limited by side-effects. Relative efficacy and side-effects of oxcarbazepine for IEM,[99] and benefit of combinations with other neuropathic agents[36] cannot be determined from the current literature.

Intravenous lidocaine infusion, epidural local anesthetic infusion, or lumbar sympathetic block have been used acutely for management of lower limb immersion injury or as a bridge to oral therapy in children with erythromelalgia, but benefit is often limited in degree and/or

duration.[1,34,42,46] The relative risks and potential degree and duration of benefit need to be carefully considered prior to invasive procedures for children with IEM.

A biopsychosocial formulation and assessment is recommended for all children with chronic pain.[100] While initial diagnosis of erythromelalgia is based on clinical features, confirmation or exclusion of *SCN9A* mutations is important for genetic counselling, informing discussions with families regarding the severity and likely course of symptoms and risk of complications, and in some cases to guide management. As many sporadic or de novo mutations have been associated with IEM, lack of a family history does not preclude a genetic basis. Potential differential diagnoses that have treatment implications, such as Fabry disease, autoimmune disorders and inflammatory arthritides should be excluded,[44,50] and similar symptoms have been associated with mercury ingestion[101] and hydrocarbon exposure.[102] A higher proportion of females with clinically-diagnosed erythromelalgia has been noted in pediatric[1] and adult series,[4,91,103] and some IEM families report worse symptoms in females,[35,36,78] but the degree or mechanisms of sex/gender differences in IEM are unclear. QST may provide a useful non-invasive test for evaluating the degree and distribution of altered small fibre function in children,[104] but potential clinical roles for monitoring disease progression or treatment response require further evaluation. A series of 32 pediatric erythromelalgia cases reported significant impairments of physical activity (in 66%), school attendance (in 34%) and mood (anxiety, depression, or behaviour problems in 28%).[1] Validated parent- and patient-reported outcome measures,[44,105] as reported in our case series, can inform multidisciplinary clinical management and could facilitate standardized evaluation of psychosocial function in multicentre populations. Education for families and patients with IEM is an important component of care,[44]

particularly in relation to symptomatic management and avoidance of aggravating factors, risks of prolonged cold immersion, and the relative benefits and risks of different interventions.

This systematic review has several limitations as data were retrieved from case reports or series with variable reporting of clinical features and management. The potential publication bias towards more severe cases, and the lack of denominator data, limit the ability to estimate the overall incidence of IEM, or the relative proportions of severe complications in *SCN9A*-positive versus *SCN9A*-negative cases. The focus here has been on *SCN9A*-related IEM and mutations of the $Na_v1.7$ channel for which increased activity and hyperpolarizing shifts in voltage-dependent activation have been confirmed in DRG neurons expressing $Na_v1.7$ channels with the related amino-acid substitutions. While some cases show overlap between symptoms of IEM and PEPD,[27] cases specifically reporting PEPD which is associated with different patterns of altered channel kinetics, have not been included.[97,106] We cannot exclude mutations affecting channels other than $Na_v1.7$, such as $Na_v1.8$ or $Na_v1.9$, which may influence pain sensitivity and be associated with small fiber neuropathy.[107-109] Case series for this rare condition are necessarily small, and conclusions from our single centre are limited by sample size, but provide preliminary data and suggest potential additional outcome measures for future series.

Ongoing assessment and standardized reporting in larger series are required to further explore relationships between genotype and phenotype in children with *SCN9A*-related IEM, to confirm the proportion with genetic causes, and identify mechanisms underlying *SCN9A*-negative erythromelalgia. The current findings and significant morbidity associated with IEM highlight the need for mechanism-based therapies to improve outcome.

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FIGURE LEGENDS

FIGURE 1. PRISMA Flowchart of papers included in systematic review.

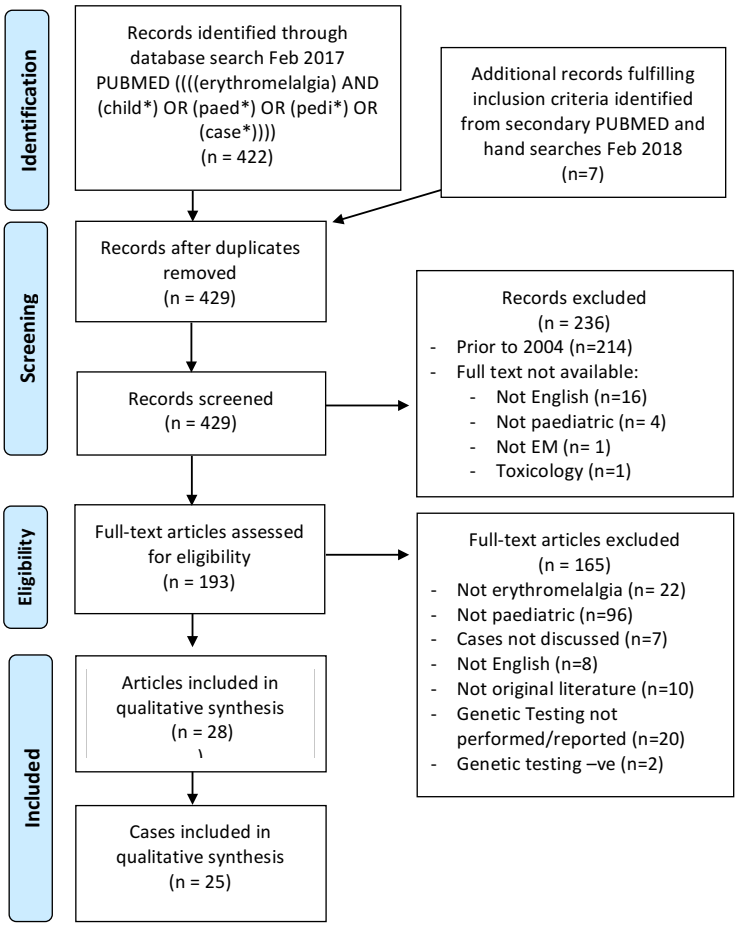

FIGURE 2. Age of onset and shift in voltage dependence of activation. **A:** The age of onset of periodic erythema and pain is shown for subjects with *SCN9A* mutations and inherited erythromelalgia (IEM) identified by systematic review, and for cases at Great Ormond Street Hospital (GOS) with IEM or symptomatic erythromelalgia and negative *SCN9A* testing (s-EM). **B:** Younger age of onset of symptoms is correlated with a more negative shift in voltage dependence of activation (i.e greater hyperpolarizing shift) in DRG neurons expressing $Na_v1.7$ channels with the related amino acid substitution.

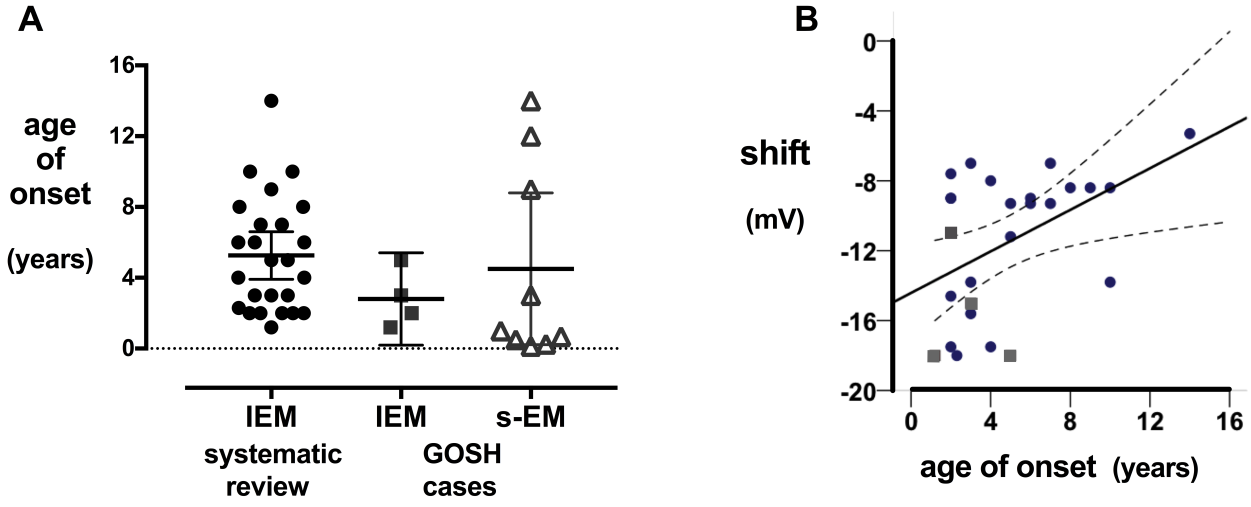

FIGURE 3. Quantitative sensory testing profiles in adolescents with erythromelalgia.

A: Somatosensory measures on the thenar eminence expressed as *Z*-score comparisons to healthy control data (capped at a maximum of 2 standard deviation difference) for individual cases with inherited erythromelalgia and p.I234T or p.I848T substitutions (*n*=2), or symptomatic erythromelalgia with no *SCN9A* mutation (*n*=1). Positive values represent increased sensitivity and negative values decreased sensitivity compared to control data. **B:** Dynamic allodynia was assessed by moving a hand-held brush, cool (25^{0}C) or warm (40^{0}C) rollers distally from the upper arm, and graded on a verbal report scale (VRS) of 0-10. All subjects reported marked allodynia to warm, with one also reporting allodynia to brush and cool. *Legend:* CDT, cool detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; WUR, wind-up ratio; MDT, mechanical detection threshold

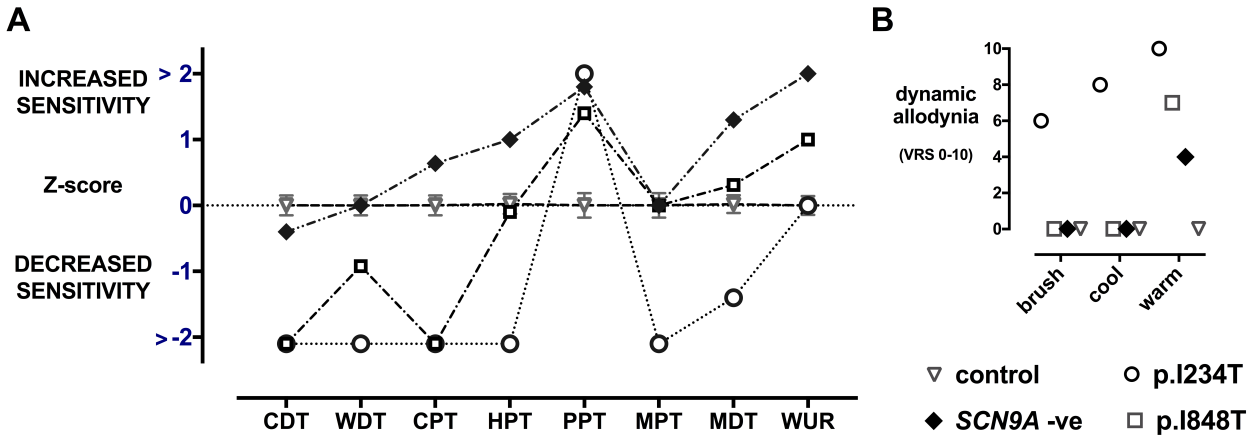

FIGURE 4. Mexiletine dosing and plasma levels. A: Daily mexiletine dose (mg/kg/day; given in divided doses) varies across individuals. To more clearly demonstrate dose titration in earlier phases of follow-up, time is represented on a $\log_{10}$ scale. **B:** Mexiletine plasma levels are monitored to confirm levels remain below those associated with toxicity (2 mg/L).

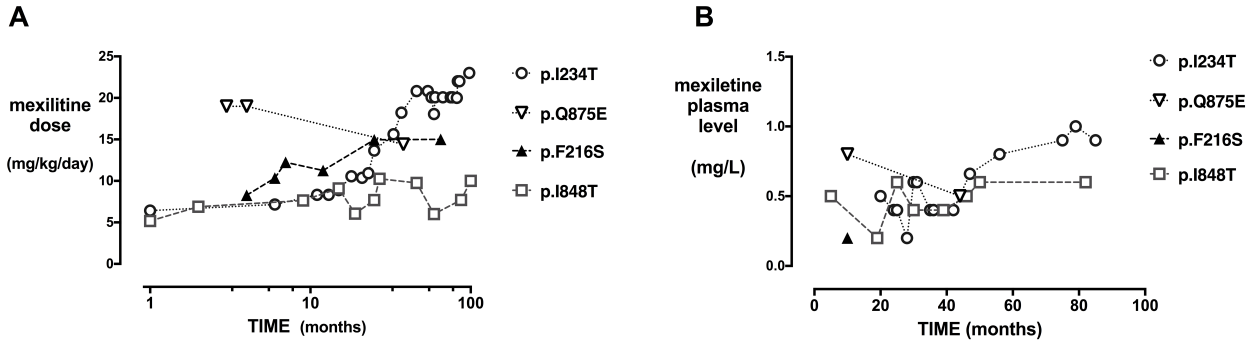

Table 1. Pediatric reports of IEM: genotype, clinical features, co-morbidities and treatments

Reference	$Na_v1.7$ AA Substit-ution	Hyper-polarizing shift	DNA	FHx	Age of onset (years)	Age of report (years)	Sex	Site	Trigger H,heat; A, activity	Relief with cool	Skin injur y	Co-morbidity	Na blocking agent	Neuropathic agent	Vaso-dilator therapy	Other analgesic intervention
Han et al., 2009[15]	p.Q10R	-5.3mV	c.29A>G	No	14	17	Male	F	H/A	NR	NR		Mexiletine (NB)			Aspirin (NB)
Ahn et al., 2010,[27] Huang et al, 2018[28]	p.I234T	-18mV	c.701T>C	No	1.2	5 & 12	Female	F/H	H	Yes	Yes	Breath holding and flexion to warm water from 11 mths; joint hypermobility, reduced sensitivity and painless injury	CBZ (side-effects) Mexiletine (PB)	Gabapentin Amitriptyline	SNP Atenolol	
Meijer et al., 2014[29] Kim et al., 2015[30]	p.I234T	-18mV	c.701T>C	No	2.3	3 & 6	Female	F/H	H/A	NR	Yes	Irritability from 3 mths; hypotonia; corneal anaesthesia; painless injury	CBZ (B) Mexiletine (B; side-effects)	Gabapentin (added B)		
Michiels et al., 2005[31] Lampert et al., 2006[32]	p.S241T	-8.4mV	c.721T>A	Yes	Siblings 10, 9, 8	Siblings 14,15, 18	1 Female 2 Males	F	H/A	Yes	Yes	One death due to sepsis [54]	NR	NR	NR	Analgesics & multidisciplinary pain team Implanted lumbar neurostimulator in one
Choi et al., 2010[33]	p.G616R		c.1846G>A	Yes	Siblings 6, 8	14, 10	2 Males	F	NR	Yes	NR		NR	NR	NR	NR
Takahashi et al., 2007[34]	p.L823R	-14.6mV [55]	c.2468T>G	No	2	~16	Male	F/H	H	Yes	Yes	Behavior change 12mths; Hypermobility, hypotonia; Short stature, Immune dysfunction; Hypothermia	CBZ (PB) Mexiletine (PB)	NR	NR	Sympathetic block (temporary benefit)
Drenth et al., 2008[35]	p.I848T	-13.8mV [5]	c.2543T>C	Yes	10	13	F	F/H	H	Yes	NR		NR	NR	NR	NR
Natkunaraja h et al., 2009[36]	p.I848T	-13.8mv	c.2543T>C	Yes	3	14	Female	F/H	H/A	Yes	Yes		CBZ	Gabapentin (initial B)		
Tanaka et al., 2017[37]	p.G856R	-11.2mV	c.2567G>C	Yes	5	11	Male	F/H	H/A	Yes	Yes	Underdevelopment of limbs (GH normal in affected sibling)	CBZ (NB)	Gabapentin pregabalin, venlaflaxine (all NB)	Propran-olol (NB)	Aspirin (NB)
Han et al., 2006[38]	p.L858F	-9mV	c.2572T>C	Yes	2	15	Male	F	H/A	Yes	NR		NR	NR	NR	"refractory to Rx"
Li et al., 2009[39]	p.L858F	-9mV	c.2572C>T	No	6	8	Male	F/H	H/A	Yes	Yes	Prurigo and itch (hyperpigmented, hyperkeratotic pruritic nodules)	NR	NR	NR	NR

Tham et al., 2017[40]	p.L858F	-9mV	c.2572C>T	Yes	<4	6	F	F	H	Yes	Yes	Severe hypothermia requiring ICU admission; associated bradycardia and organ dysfunction	Lidocaine IV (PB)			Ketamine (sedation in ICU); topical ketamine & amitriptyline (NB); Hydromorphone (NB); Pain coping beneficial
Harty et al., 2006[41] Nathan et al., 2005[42]	p.A863P	-8mV	c.2587G>C	No	4	11 & 14	Male	F/H	H/A	Yes	Yes		Lidocaine IV, Mexiletine (B initial)	Amitriptyline Gabapentin	Clonidine	Opioids NSAID Epidural at 11 yrs
Choi et al., 2009[43]	p.V872G	-9.3mV	c.2616T>G	adop-ted	5	7	Female	F/H	H	Yes	NR		Mexiletine (B)			Paracetamol, aspirin (NB)
Skeik et al., 2012[44] Stadler et al., 2015[45]	p.Q875E	-17.5mV	c.2623C>G	No	4	15	Female	F	H/A	Yes	Yes	HTN, short stature, GH deficiency	Lidocaine IV & patch (NB)	Gabapentin (SB)	SNP Atenolol	Opioids Aspirin Topical ketamine/amitriptyline
Farrar et al., 2017[46]	p.Q875E	-17.5mV	c.2623C>G	No	2	6	Female	F	H	Yes	Yes		Mexiletine (PB) CBZ (NB)	Amitriptyline Gabapentin Pregabalin (all NB)	Phenoxy-benzamine	Anti-histamine, aspirin (NB) Lumbar sympathy-ectomy (NB)
Estacion et al., 2013[47]	p.V1316A	-9.3mV	c.3947T>G	No	6	9	Female	F	H/A	Yes	NR		Mexiletine (NB) CBZ (initial B)	NR	NR	NR
Wu et al., 2013[48] Huang et al., 2016[49]	p.V1316A	-9.3mV	c.3947T>C	No	7	16 & 18	Female	F	H	Yes	Yes	Neurogenic shock following debridement & death	CBZ (MB) Mexiletine (MB)	Gabapentin Imipramine	Propran-olol	
Novella et al., 2007[50]	p.F1449V	-7.6mV[2]	c.4345T>G	Yes	2 infant	15	Male	F/H ears	H/A	Yes	Yes	HTN	No	No	No	"no pharmacological Rx"
Estacion et al., 2008[51]	p.A1632**E**	-7mV	c.4895C>A	No	3	10	Female	F/H face	H	Yes		Initial cardiorespiratory instability; PEPD	NR	NR	NR	NR
Yang et al., 2016[52]	p.A1632G	-7mV	c.4895C>G	Yes	7	14	Female	F/H	H/A	Yes	NR		Lidocaine patch (PB)	Gabapentin (NB) Amitriptyline (s-effects)		
Cregg et al., 2013[53]	p.A1746G	-15.6mV	c.5237C>G	No	3	7	Male	F/H	H/A	Yes	NR		Mexiletine (B) Lidocaine patch			Capsaicin cream

Legend: FHx, family history; mths, months of age; NR, not reported; HTN, hypertension; GH, growth hormone; MSK, musculoskeletal; CBZ, carbamazepine; SNP, sodium nitroprusside infusion; B, benefit; PB, partial benefit; MB, marginal benefit; NB, no benefit

Table 2. Pediatric onset SCN9A-positive IEM : not fulfilling inclusion criteria for the systematic review

Table 2A: Pediatric onset of IEM limited clinical details or only group data

$Na_v1.7$ substitution	**Number of cases**	**Age of onset (years)**	**Age at reporting (years)**	**Additional features**	**Reference**
p.S211P	1	NR	15-year old male	No family history or pain disorder Additional clinical details: NR	59
p.F216S	family	NR	father and daughter	Additional clinical details: NR	60, 61
p.N395K	family; n=2	Age of onset: NR	Father & son (11 yrs)	"fulfilled diagnostic criteria…refractory to routine pharmacotherapy"	62
p.V400M	family; n=5 in 3 generations	Father: before 1 yr age 2 children: age onset NR	Father 37 yrs 2 children (age NR)	Response to carbamzepine: reduced frequency attacks; improved tolerance shoes, socks and exercise	63
p.G616R	family; n=4 in 3 generations	Father: 24 yrs 2 sons: 6 and 8 yrs	Father 51 yrs 2 sons: 10 and 14 yrs	Children: increasing pain in feet, limiting mobility	33
p.I848T	family	NR	Age: NR	Additional clinical details: NR	61
p.I848T	2 sporadic cases	NR	13 yr girl; 10 yr boy	"fulfilled diagnostic criteria…refractory to routine pharmacotherapy"	62
p.G856D	family; n=3 in 2 generations	10 yrs, childhood	35 yr male brother 32 yrs father 68 yrs (resolved by 20 yrs)	Autonomic symptoms (atypical[16]); reduced growth of hands and feet; small fiber peripheral neuropathy	56
p.L858H	family; n=7 in 3 generations	2 probands : 4-8 yrs	adulthood	"Refractory to treatment"	6
p.F1449V	family; n=36 in 6 generations[54]; n=29 in 5 generations[55]	Mean onset 3 years (all before 6th birthday)	3 to 75 years	Distribution of symptoms in 16 subjects: all in hands and feet; 10 include other areas (face, ears, elbows, knees; one include perineum)[54] Skin injury associated with scratching[55] 15 yr male: mild decrease pinprick to ankles; MRI, skin biopsy, nerve conduction studies normal[48]	2, 50, 64
SCN9A	3 unrelated cases		5, 15, 17 years	Reported as primary erythromelalgia but no details of genetic analysis or family history; initial response to sympathetic blocks	65
R1150W polymorphism	family; n=2 (father asymptomatic)[66] family; n=6 in 4 generations[67]	NR)[66] Infant, 37, 40, 41 [67]	15 year daughter [66] Adults; 2 year-old brother [67]	Response to sympathetic block in 15 year old[66] same polymorphism in unaffected family members[66] (may not be pathogenic of IEM[68])	66, 67

Legend: NR, not reported; yrs, years

Table 2B: IEM reported in adults with onset of symptoms before 18 years of age

$Na_v1.7$ substitution	**Number of cases**	**Age of onset (years)**	**Age at reporting (years)**	**Additional features / complications**	**Reference (same patient/family)**
p.I136V	13 (3 generation family)	Proband: pain in feet from 11yrs, hands from 19 yrs (range 9-22 yrs in family)	21		17, 48, 69
p.F216S	1	NR	19 (sister, father)	Hypothermia, hypercalcemia, ataxia, and encephalopathy (19 yrs) Sister died uncontrolled sepsis Father less severe symptoms	61, 70
p.F216S	1	3	49	Nerve conduction study, EMG: normal; sudomotor function reduced	71
p.S241T	2	Teens: initially feet, then hands, knees, elbows, shoulders, ears	adult	Response to carbamazepine [73] Minimal response to single dose PF-05089771 in sibling with onset at 17yrs [72]	72, 73
p.S241T	2 (family)	17, 17	15-77 yrs	Comorbidities: hypertension (n=6/13), diabetes (n=3/13), hypothyroidism (n=3/13) QST: increased detection thresholds at pain sites	18
p.V400M	3 (family)	4, <10, 1.5 [63, 72]			
p.I848T	1	4			
p.F1449V	7 (family)	4-5, 7, 6, 6, <2, <6, 5 [2]			
p.G616R	3 (family)	6, 8, 24	14,10, 51	Adult onset in some family members	33
p.I848T	3 (family)	childhood	19, 24, 45	Excessive ice immersion, non-healing ulcers, insomnia and cachexia (24 yrs) [74] Hypothermia, hypoglycaemia, hypotension, seizure [75]	61, 74, 75
p.I848T	1	4	ave. 40.2 yrs		72
p.I848T	1	5	adult		76
p.I848T	1	8	33		48
p.I848T	1	age not reported; 'unaffected parents'			6
p.G856D	1	10: initially hands, later feet, cheeks, ears	35		77
p.L858F	3 (family)	3 years, or since birth	43, 48, 49	Sepsis and amputations in 2 siblings (13 yrs, 20 yrs) Excessive cooling and hypothermia	3, 61, 78, 79
p.L858F	1	since birth	32	Excessive cooling and ulceration; epidural at 16 yrs; QST: increased thresholds	80
p.L858H	7 (3 generation family)	7 to 15 yrs	3 yrs to adult		6
Del-L955	2 (family)	15: initially hands and feet, by 21 yrs included face and ears	22, mother		81
p.F1449V	1	5	46		77
p.F1449V	1	<2	ave. 40.2		72
p.A1632T	2 (family)	17, 3	22, 50		82

Legend: yrs, years; NR, not reported

Table 3. Treatments used for erythromelalgia

		Na channel block	Neuropathic	Vasodilator	Other	Multiple	Source
Systematic Review (treatment details in 15 of 25 cases)*		**15** (100%) mexiletine (10) CBZ (8) lidocaine (5)	**8** (62%) anti-convulsant (7) anti-depressant (5)	**5** (38%) symptoms (5) HTN (1)	**7** (46%) opioid (3) invasive (4)** ketamine (2)	**15** (100%)	**10** (limited details in case report) refractory to Rx (1) analgesics and pain team (3) no medication (1) not recorded (5)
GOSH	IEM (n=4)	**4** (100%) mexiletine (4) CBZ (3)	**3** (75%) anti-convulsant (3) anti-depressant (1)	**3** (75%) symptoms (1) HTN (3)	**2** (50%) opioid (1) LA blocks (1)***	**3** (75%)	Retrospective review of patients managed by Chronic Pain Service (2017): data prospectively entered in database
	s-EM (n=9)	**2** (22%) mexiletine (1) lidocaine patch (1)	**4** (44%) anti-convulsant (1) anti-depressant (3)	**0**	**0**	**2** (22%)	
	EM pre 2009 (n=13)	**4** (31%) mexiletine (1) CBZ (3) lidocaine (1)	**11** (85%) anti-convulsant (3) anti-depressant (8)	**9** (69%) symptoms (9)	**6** (46%) opioid (5) epidural (1) ketamine (2)	**8** (62%)	Retrospective case note review of GOSH records (2009)

Legend: CBZ, carbamazepine; HTN, treatment for hypertension; LA, local anesthetic

* available data; missing data and/or no specific information in 10 cases listed in final column

** invasive procedures: sympathectomy (2), dorsal column stimulator (1), epidural local anesthetic (1)

***LA blocks: sympathetic, epidural, sciatic nerve

Table 4. Great Ormond Street Hospital cases of erythromelalgia: genotype and clinical features

	Na_v 1.7 substit-ution	**Hyper-polarizing shift**	**Family History***	**Age of onset (years)**	**Age of report (years)**	**Sex** (F, female, M, male)	**Site of pain & erythema** (F,feet; H,hands; E,ears)	**Frequency**	**Trigger** (H=heat; A=activity/ exercise)	**Clear relief with cold**	**Immersion or skin damage**	**Co-morbidity**
IEM-1	I234T	-18mV[25]	no	1.2	13	**3** female **1** male	F/H	multiple daily	H/A	Yes	Yes	Hypermobility; MSK pain; HTN; Low GH
IEM-2	I848T	-15mV[3]	yes	3	16		F/H/E	multiple daily	H/A	Yes	No	
IEM-3	F216S	-11mV[57]	no	2	4		F	multiple daily	H	Yes	Yes	HTN
IEM-4	Q875E	-18mV[43]	no	5	8		F	multiple daily	H/A	Yes	Yes	HTN
s-EM (**n**=9)	**9** (100%) negative		**9** (100%) no	mean 4.5 [range: 0.13-14]		**5** female **4** male	**2** F **6** F/H **1** F/H/E	**1** constant **4** daily **3** $\leq$ 3 per wk **1** <weekly	**6** (67%) H or H/A	**6** (67%) relief with cooling	**0** (0%) skin injury	

Legend: IEM, inherited erythromelalgia (*SCN9A*-positive); s-EM, symptomatic erythromelalgia (*SCN9A* negative); HTN, hypertension; GH, growth hormone.
*A positive family history was based on similar symptoms and genetic testing in other family members; a negative family history was based on lack of symptoms rather than confirmatory negative genetic testing in family members.

Table 5. Patient-Reported Outcomes

	Genetic analysis	**Pain Score (VAS 0-100mm)**			**Pediatric Quality of Life (PedsQL)*** [17]				**Pediatric Index Emotional Distress (PI-ED)**** [18]	**Pain Catastrophizing Scale (PCS-C)***** [19]			
		Worst in last week	Average in last week	Current	Physical	Emot-ional	Social	School		Total	Rumin-ation	Magnif-ication	Helpless-ness
IEM-1 mean (range over 4 years)	I234T-Nav1.7	88 (64-100)	78 (67-91)	57 (49-71)	21 (6-15)	44 (25-45)	76 (40-60)	56 (35-50)	17 (14-20)	28 (14-22)	12 (12-12)	4.5 (3-6)	11.5 (7-16)
IEM-2 mean (range over 5 years)	I848T-Nav1.7	38 (5-79)	14 (6-28)	22 (0-67)	68 (56-84)	66 (50-75)	75 (65-90)	38 (25-50)	18 (16-20)	17 (7-26)	8.5 (4-14)	3 (1-6)	5 (2-10)
Symptomatic EM (n=5) mean (range)	SCN9A negative	39 (0-100)	48 (0-94)	24 (0-59)	42 (12-93)	44 (0-95)	55 (0-80)	40 (10-70)	15 (2-35)	30 (27-50)	11 (6-16)	6 (5-6)	13 (12-14)
Pediatric control data					84 [17]	81 [20]	87 [17]	79 [21]	<20	16 [9] low 0-14 high >26	7.2 [3.6]	3.6 [2.6]	6.1 [4.1]

Data: mean(range); mean [SD]

References include details of outcome tool and source of healthy control data.

* higher scores (>75) represent better function (maximum score 100); **higher scores represent increased distress (14 items; maximum score 42); ***higher scores represent increased catastrophizing (total 13 items, maximum total score 52; rumination 4 items, maximum 16; magnification 3 items, maximum 12; helplessness 6 items, maximum 24)

Table 6. Quantitative Sensory Testing (raw data)

	CDT (^{0}C)	WDT (^{0}C)	CPT (^{0}C)	HPT (^{0}C)	PPT (kPa)	MPT (mN)	WUR	MDT (g)	DMA (VRS 0-10)	COOL ALLODYNIA (VRS 0-10)	WARM ALLODYNIA (VRS 0-10)
IEM-1	25.5±2.7	42.7±6.1	16.1±2.1	49.0±1.3	57±13	>512	0	0.25	6	8	10
IEM-2	25.7±1.3	35.9±0.3	12.1±1.4	38.5±0.4	144±73	64	+1	0.05	0	0	7
s-EM	28	34.8	29.1±1.8	34.5±0.7	73±11	64	+3	0.02	0	0	4
Control	29.6±1	34.7±1.3	27±3.3	38.2±3.8	246±95	64	0	0.09±0.05	0	0	0

Legend: CDT, cool detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; WUR, wind-up ratio; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VRS verbal report scale intensity of allodynia rated 0 to 10

A standardized QST protocol[20,21] included : i) cool (CDT) and warm detection (WDT), cold (CPT) and heat pain (HPT) thresholds using a handheld 18x18mm contact thermode (baseline 32°C, 1°C/s, limits 10°C and 50°C)(Senselab MSA Thermal Stimulator; Somedic, Sosdala, Sweden); ii) mechanical detection threshold (MDT) with von Frey hairs (geometric mean of 10 appearance and disappearance thresholds); iii) mechanical pricking pain threshold (MPT) with ascending PinPrick Stimulators (8-512mN) until discomfort/pain experienced (single measure is threshold) and rated 0-10 (verbal rating scale, VRS_1) followed by a 1/sec train of 10 repeated stimuli (VRS_{10}) to calculate wind-up ratio ($WUR=VRS_{10}-VRS_1$); iv) pressure pain threshold (PPT; mean±SD 3 measures) on middle phalanx of middle finger using hand-held 1cm^2 algometer and optical feed-back (ramp 40kPa/sec, maximum 1000kPa)(SENSEBox; Somedic, Sosdala, Sweden). Dynamic allodynia was mapped using: i) mechanical brush stimulus (SENSELab Brush-05; Somedic, Sosdala, Sweden); and ii) thermal hand-held rollers at predetermined temperatures of 25^{0}C (cool) and 40^{0}C (warm)(Somedic RollTemp®; Somedic, Sosdala, Sweden). Stimuli were moved distally from the upper arm towards the hand until any allodynia/discomfort was reported (VRS 0-10).