Primary Erythermalgia (Inherited Erythromelalgia): A Comprehensive Disease Characterization

Summary

Primary erythermalgia — more commonly termed **primary (inherited) erythromelalgia (IEM)** — is a rare, autosomal-dominant Mendelian **sodium channelopathy** caused by gain-of-function missense mutations in **SCN9A**, the gene encoding the peripheral voltage-gated sodium channel **Nav1.7**. Nav1.7 is a threshold channel preferentially expressed in nociceptive dorsal root ganglion (DRG) neurons, trigeminal ganglion neurons, and sympathetic ganglion neurons, where it amplifies subthreshold generator potentials. Pathogenic IEM variants shift the voltage dependence of channel activation in the hyperpolarizing (leftward) direction, slow deactivation, and enhance the channel's ramp response to slow depolarizations. The net effect is hyperexcitability of pain-sensing and vasomotor neurons, producing the disease's defining clinical triad: **episodic burning pain, redness (erythema), and warmth of the distal extremities**, precipitated by mild heat/exercise and relieved by cooling.

The disorder typically begins in early childhood (often before age 10 in the inherited form), follows a chronic, lifelong, episodic/paroxysmal course, and although it is not directly fatal, it causes severe pain, disability, and profound quality-of-life impairment. Management rests on **sodium-channel-blocking drugs** (mexiletine, carbamazepine, lidocaine) and neuropathic pain agents (gabapentin, amitriptyline), together with behavioral cooling; treatment responses are variable, often partial, and increasingly recognized to be **genotype-specific**, opening a path toward precision/personalized medicine. A critical clinical distinction is between **primary (SCN9A-driven) erythromelalgia** and **secondary erythromelalgia**, the latter most notably a microvascular manifestation of myeloproliferative neoplasms (essential thrombocythemia, polycythemia vera, often JAK2-mutation-positive), which is platelet-mediated and dramatically aspirin-responsive.

This report synthesizes 10 confirmed findings across 31 reviewed papers to populate a disease knowledge-base entry, spanning disease identity, etiology, phenotypes, genetics, mechanism, anatomy, temporal development, epidemiology/inheritance, diagnostics, prognosis, treatment,

prevention, comparative biology, and model organisms. The strongest, most rigorously established conclusions are the SCN9A/Nav1.7 gain-of-function etiology, the biophysical activation-shift mechanism (validated across heterologous systems, human iPSC-derived sensory neurons with CRISPR correction demonstrating causality, and near-atomic bacterial channel structures), and the allelic spectrum linking Nav1.7 to a continuum of pain disorders (IEM, PEPD) and to loss-of-function congenital insensitivity to pain.

Key Findings

Finding 1 — Primary erythermalgia is caused by gain-of-function mutations in SCN9A (Nav1.7)

The foundational discovery, from linkage and mutation analysis, mapped primary erythermalgia to chromosome 2q (a 7.94 cM interval; LOD 2.11 for markers D2S2370/D2S2330) and identified missense mutations in **SCN9A** (T2573A segregating in a family; T2543C in a sporadic patient). SCN9A encodes the alpha subunit of the voltage-gated sodium channel **Nav1.7**, which is predominantly expressed in sensory (DRG) and sympathetic neurons — an expression pattern that neatly explains the disease's combined nociceptive (burning pain) and vasomotor (erythema, warmth) features. The disease is inherited in an **autosomal-dominant** fashion.

As the original report states: *"Primary erythermalgia is a rare autosomal dominant disease characterised by intermittent burning pain with redness and heat in the extremities"* and *"Our data suggest that mutations in SCN9A cause primary erythermalgia. SCN9A, encoding a voltage-gated sodium channel alpha subunit predominantly expressed in sensory and sympathetic neurones, may play an important role in nociception and vasomotor regulation"* (PMID: 14985375).

Ontology anchors: Gene **HGNC:10597 (SCN9A)**; protein UniProt Q15858 (Nav1.7); MONDO concept "erythromelalgia / primary erythromelalgia"; OMIM #133020 (Erythermalgia, primary / Erythromelalgia, hereditary).

Finding 2 — Biophysical mechanism: hyperpolarized activation, slowed deactivation, enhanced ramp response → DRG hyperexcitability

IEM mutations produce a characteristic gain-of-function biophysical signature: they **hyperpolarize (leftward-shift) the voltage dependence of activation**, **slow deactivation**, and **enhance the ramp response** to slow depolarizations. Because Nav1.7 functions as a "threshold channel" in DRG, trigeminal, and sympathetic nociceptors — amplifying small generator potentials toward the action-potential threshold — these changes lower the firing threshold and produce neuronal hyperexcitability.

Crucially, causality has been demonstrated in a human cellular system. Patient induced-pluripotent-stem-cell (iPSC)-derived sensory neurons carrying a Nav1.7 gain-of-function mutation (A1632G) exhibit hyperexcitability; **CRISPR/Cas9 correction of the mutation reduces the hyperexcitability**, and, conversely, **introducing the mutation into control iPSC neurons generates hyperexcitability**. This bidirectional experiment establishes a direct causal link between the mutation and the cellular pain phenotype: *"using CRISPR/Cas9, we corrected this mutation, which reduced the underlying hyperexcitability, providing a path for personalized medicine to treat these disorders, and we introduced the mutation into control induced pluripotent stem cells, which generated hyperexcitability, providing causality"* (PMID: 40279376).

The biophysical definition is summarized concisely: IEM *"is characterized clinically by burning pain and redness that is usually focused on the distal extremities, precipitated by mild warmth and relieved by cooling, and is caused by mutations that hyperpolarize activation, slow deactivation, and enhance the channel ramp response"* (PMID: 22136189).

Ontology anchors: GO:0086010 membrane depolarization during action potential; GO:0001518 voltage-gated sodium channel complex; GO:0019228 neuronal action potential; GO:0035725 sodium ion transmembrane transport.

Finding 3 — Epidemiology: erythromelalgia incidence ~0.36–1.3 per 100,000/year with female predominance

Population-based data anchor the disease's rarity. In Olmsted County, Minnesota, the overall age/sex-adjusted incidence was **1.3 per 100,000/year** (95% CI 0.8–1.7), split into **primary EM at 1.1** and **secondary EM at 0.2** per 100,000/year, with higher rates in women (2.0/100,000) than men (0.6/100,000): *"The overall age- and sex-adjusted incidence rate ... was 1.3 (0.8-1.7) per 100,000 people per year. The incidence of primary and secondary erythromelalgia was 1.1 (0.7-1.5) and 0.2 (0.02-0.4) per 100,000 people per year, respectively"* (PMID: 18713229).

An independent southern Sweden study estimated incidence at **0.36 per 100,000/year**, with 70% female patients and a mean diagnostic delay of 4.5 years: *"Gender and age adjusted incidence of EM for our region was calculated to be 0.36 per 100 000"* (PMID: 22247059). The inherited form shows early onset: *"Sex and age distributions among patients with IEM show a predominance of cases with clinical onset before the age of 10 years, whereas sex differences are not pronounced"* (PMID: 41190974). Female predominance in overall EM is corroborated by broader dermatologic epidemiology from the same Rochester Epidemiology Project (PMID: 27009931).

Study	Population	Incidence (/ 100,000/yr)	Female %	Notes
Olmsted County, MN (PMID: 18713229)	Population-based	1.3 overall; 1.1 primary; 0.2 secondary	Women 2.0 vs men 0.6	Age/sex-adjusted
Southern Sweden (PMID: 22247059)	Single-center regional	0.36	70%	Mean diagnostic delay 4.5 yr
China/worldwide review (PMID: 41190974)	IEM case review	—	Not pronounced	Onset predominantly <10 yr

Finding 4 — Treatment: genotype-specific sodium-channel blockers plus neuropathic agents; cooling relief

Primary EM management centers on **sodium-channel blockers** (mexiletine; intravenous lidocaine infusions) combined with **neuropathic pain agents** (gabapentin, amitriptyline), plus behavioral cooling. Efficacy is variable, partial, and often transient. Importantly, pharmacotherapy response is **variant-specific**: p.L858F/H responds to mexiletine, whereas V400M, S241T, and I234T respond to carbamazepine — evidence for genotype-guided therapy.

Supporting quotes: *"Some patients with specific pathogenic variants respond to pharmacotherapy, such as p.L858F/H (mexiletine) and V400M, S241T, and I234T (carbamazepine), suggesting potential for personalized therapeutic approaches"* (PMID: 41190974); *"The treatment of primitive erythermalgia is based on sodium channel blockers such as mexiletine or lidocaine infusions, and on drugs effective on neuropathic pain, such as gabapentin or amitryptiline"* (PMID: 35835622). A single-center cohort found *"The most effective therapies were antihistamines, venlafaxine, and mexiletine"* (PMID: 37557164).

A cautionary safety note: mexiletine has a narrow therapeutic index; overdose can be life-threatening with cardiovascular and CNS toxicity (PMID: 37661688).

MAXO/ontology anchors: MAXO:0000058 pharmacotherapy; "sodium channel blocker therapy"; CHEBI:6916 mexiletine; CHEBI:3387 carbamazepine; CHEBI:6456 lidocaine; CHEBI:42797 gabapentin; CHEBI:2666 amitriptyline; behavioral application of cold.

Finding 5 — SCN9A allelic spectrum: IEM vs PEPD vs CIP

Nav1.7 sits at the center of a spectrum of Mendelian pain disorders. **Gain-of-function** missense mutations cause **primary erythromelalgia (IEM)** and **paroxysmal extreme pain disorder (PEPD)**, whereas **nonsense/loss-of-function** mutations cause **channelopathy-associated congenital insensitivity to pain (CIP)**. A genotype–phenotype rule generally holds: **IEM mutations enhance activation** (hyperpolarizing shift), while **PEPD mutations impair steady-state fast inactivation** (depolarizing shift, increased persistent/resurgent current).

"Gain-of-function missense mutations in Na(v)1.7 have been shown to cause primary erythermalgia and paroxysmal extreme pain disorder, while nonsense mutations in Na(v)1.7 result in loss of Na(v)1.7 function and a condition known as channelopathy-associated insensitivity to pain" (PMID: 18060017); *"Gain-of-function mutations are typically pain-causing and have been associated with inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD). IEM is usually caused by enhanced NaV1.7 channel activation, whereas mutations that alter steady-state fast inactivation often lead to PEPD"* (PMID: 25995458).

The correlation is imperfect: **A1632E** is an "overlap" mutation showing both IEM and PEPD features (a continuum), and **A1632T** causes IEM but does so via a fast-inactivation shift rather than the classic activation shift (PMID: 24311784). Resurgent/persistent current biophysics further refine the IEM-vs-PEPD distinction (PMID: 27174182).

Disorder	Nav1.7 mutation class	Biophysical signature	Clinical picture
IEM (primary erythromelalgia)	Gain-of-function missense	Hyperpolarized activation, slow deactivation, enhanced ramp	Distal-extremity burning pain, erythema, warmth; heat-triggered
PEPD	Gain-of-function missense	Impaired fast inactivation; ↑ persistent/resurgent current	Proximal (rectal, ocular, jaw) paroxysmal pain
CIP	Nonsense / loss-of-function	Loss of channel function	Congenital insensitivity to pain, anosmia

Finding 6 — Differential diagnosis: primary (SCN9A) vs secondary erythromelalgia (myeloproliferative neoplasms, JAK2)

Secondary erythromelalgia is a recognized microvascular manifestation of **myeloproliferative neoplasms (MPNs)** — essential thrombocythemia (ET) and polycythemia vera (PV) — mediated by **platelet-mediated occlusive thrombosis in the end-arterial circulation**. Unlike primary EM, it responds dramatically to **aspirin** (cyclooxygenase-1 inhibition). Consequently, the workup of suspected erythromelalgia must include a complete blood count and **JAK2 mutation testing** to exclude an underlying MPN.

"Microvascular disturbances in essential thrombocythemia (ET) and polycythemia vera (PV), including erythromelalgia, and atypical and typical transient cerebral, ocular, and coronary ischemic attacks, are caused by platelet-mediated transient and occlusive thrombosis in the end-arterial circulation" and *"Inhibition of platelet cyclooxygenase-1 by aspirin is followed by relief of microvascular disturbances"* (PMID: 16673274). Contemporary guidance for thrombocytosis workup recommends that *"testing for Janus kinase 2 gene sequence variations should be performed"* (PMID: 42101597).

A further differential is **acute monophasic pediatric erythromelalgia**, which can represent post-infectious immune-mediated small-fiber neuropathy rather than inherited channelopathy — distinguished by monophasic course, autoimmune/infectious associations, skin-biopsy small-fiber loss, and response to immunotherapy (PMID: 32723684).

Finding 7 — Model systems: iPSC sensory neurons robustly model IEM; rodent knock-ins recapitulate DRG hyperexcitability but often lack overt pain

Human **iPSC-derived sensory neurons** carrying Nav1.7 gain-of-function mutations (e.g., A1632G, Q875E) reproduce hyperexcitability and are described as *"a robust, scalable and relevant model to study the effects of gain-of-function mutations in ion channels in pain-related disorders"* (PMID: 40279376). The Q875E iPSC line has been used for pharmacology (e.g., botulinum toxin studies) (PMID: 38657946).

By contrast, **rodent knock-in models incompletely recapitulate the human pain phenotype**. Two independent Nav1.7 **I228M** knock-in mouse lines showed DRG neuron hyperexcitability yet **did not** display mechanical/thermal hyperalgesia or intraepidermal nerve fiber loss: *"Nav1.7 I228M mice do not display mechanical or thermal hyperalgesia or intraepidermal nerve fiber loss in vivo. Therefore, although these 2 Nav1.7 I228M knock-in mouse lines recapitulate the DRG neuron hyperexcitability associated with gain-of-function mutations in Nav1.7, they do not recapitulate the pain or neuropathy phenotypes seen in patients"* (PMID: 33323889). A rat Nav1.7 knock-in model was generated for drug development (PMID: 31550995), and complementary optogenetic (NaV1.7-ChR2) and heterologous (HEK293, Xenopus oocyte) systems support mechanistic and pharmacological studies (PMID: 36201719).

Model	Type	Recapitulation	Key limitation
Patient iPSC sensory neurons	In vitro, human	Hyperexcitability; CRISPR-correctable	No in-vivo behavior
Nav1.7 I228M knock-in mice (×2 lines)	Mammalian, in vivo	DRG hyperexcitability	No hyperalgesia/ IENF loss
Rat Nav1.7 knock-in	Mammalian, in vivo	Drug-development platform	Genotype-specific
HEK293 / Xenopus oocytes	Heterologous	Per-variant biophysics	No neuronal context

Finding 8 — Structural basis: IEM voltage-sensor mutations facilitate outward S4 gating-charge movement

Near-atomic structural work using the bacterial channel **NaVAb** engineered with four IEM voltage-sensor mutations recapitulated the hyperpolarizing activation shift seen in human Nav1.7. An **S1-segment mutation widens the pathway for gating-charge translocation**, while **S4-segment mutations modify hydrophobic interactions** with neighboring side chains or membrane phospholipids — both facilitating **outward S4 gating-charge movement**, causing channel hyperactivation, neuronal hyperexcitability, and severe pain.

"a mutation in the S1 segment of the voltage sensor facilitated the outward movement of S4 gating charges by widening the pathway for gating charge translocation. In contrast, mutations in the S4 segments modified hydrophobic interactions with surrounding amino acid side chains or membrane phospholipids that would enhance the outward movement of the gating charges" (PMID: 37903281). This provides a physical, mutation-specific basis for structure-guided therapeutic design.

Finding 9 — Prognosis/burden: chronic, lifelong, episodic, severely disabling, but not directly fatal

Primary EM greatly compromises quality of life and causes severe disability, with an episodic/paroxysmal course of burning pain, erythema, and warmth: *"The symptoms greatly compromise the patients' quality of life leading to severe disability"* (PMID: 37557164). It is generally **not directly fatal** — the Swedish cohort reported *"there was no mortality directed related to EM"* (PMID: 22247059). Burden data from painful small-fiber/idiopathic neuropathy — the broader category encompassing EM pain — quantify substantial comorbidity: sleep disturbance/insomnia 37%, anxiety 34%, depressive symptoms 33%, plus work impairment (~37%) and significant direct/indirect costs: *"Most common comorbidities were sleep disturbance/insomnia (37.0%), anxiety (34.0%), and depressive symptoms (33.0%)"* (PMID: 24673364). A 2025 systematic review evaluated comparative treatment efficacy/tolerability, reflecting the absence of a single uniformly effective therapy (PMID: 40428878). Notably, some patients resort to extreme cooling/ice immersion, causing skin maceration and secondary complications — a self-inflicted morbidity risk.

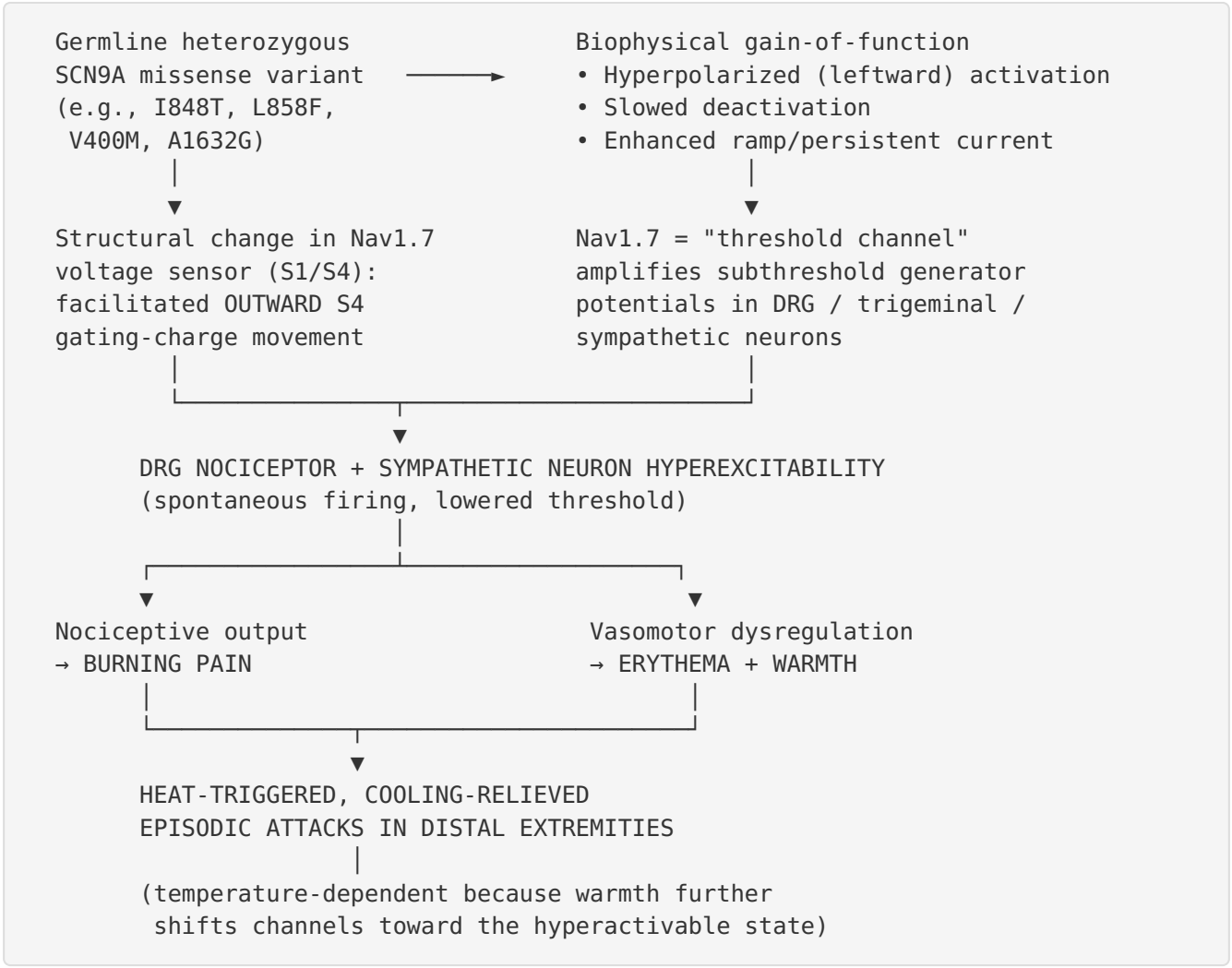
Finding 10 — Variant spectrum and molecular diagnosis: recurrent heterozygous germline SCN9A missense alleles, ultra-rare in population databases

Primary erythermalgia arises from **heterozygous germline missense variants** in SCN9A/Nav1.7. Recurrent/illustrative pathogenic alleles across families and cohorts include **I848T, L858F/H, F1449V, V400M, S241T, I234T, Q875E, I136V, P1308L,** and **A1632G/T/E**, plus novel alleles such as **L1595R (c.4784T>G)** and **F1624S**. Pathogenic alleles are typically **absent from population databases** (e.g., gnomAD) and cosegregate within families, fulfilling ACMG/AMP criteria for pathogenicity: *"The variant was absent from population databases and co-segregated with the phenotype within the family, fulfilling ACMG/AMP criteria for likely pathogenicity"* (PMID: 41997215).

Molecular confirmation uses **single-gene SCN9A sequencing** or **hereditary sensory/autonomic neuropathy gene panels**: *"We conducted a gene-panel sequencing targeting 18 genes associated with hereditary sensory and/or autonomic neuropathy"* (PMID: 37555797); *"We describe a spectrum of SCN9A variants associated with IEM"* (PMID: 41190974). Chromosomal microarray, karyotyping, FISH, mtDNA testing, and repeat-expansion testing are **not indicated** — this is a single-gene point-mutation disorder.

Mechanistic Model / Interpretation

The pathophysiology of primary erythermalgia forms a clean, well-supported causal chain from a single germline point mutation to episodic clinical symptoms:



Upstream vs downstream: The upstream trigger is the germline SCN9A variant and its structural effect on the voltage sensor (outward S4 gating-charge facilitation,).

P 37903281

The proximate downstream mechanism is altered channel gating ( ),

P 22136189

which drives sensory/sympathetic neuronal hyperexcitability (causally proven by CRISPR correction in iPSC neurons,).

P 40279376

The most downstream events are the clinical manifestations — burning pain (nociceptive) and

erythema/warmth (vasomotor), both explicable by Nav1.7's dual expression in sensory and sympathetic neurons ( ).

P 14985375

Cell types and biological processes (ontology anchors): - **CL:0000101** sensory neuron; dorsal root ganglion neuron; **CL:0000198** nociceptor; sympathetic (postganglionic) neuron. - **GO:0019228** neuronal action potential; **GO:0086010** membrane depolarization during action potential; **GO:0035725** sodium ion transmembrane transport; **GO:0001518** voltage-gated sodium channel complex.

Anatomical involvement (Section 7): Primary organ = **skin of the distal extremities** (UBERON:0002097 skin of body; UBERON:0002387 pes/foot; UBERON:0002398 manus/hand), typically **bilateral and symmetric**, with feet more affected than hands. Body systems: **peripheral nervous system** (UBERON:0000010) — specifically DRG (UBERON:0000044) and sympathetic ganglia — and the **cutaneous microvasculature/integumentary system**. Subcellular locus = the neuronal plasma membrane voltage-gated sodium channel (GO:0001518).

Temporal development (Section 8): Onset is usually **pediatric/childhood** (often <10 years) in the inherited form, insidious in onset, with a **chronic, lifelong, episodic (paroxysmal)** course punctuated by heat- and exercise-triggered flares and relieved by cooling. There is no established genetic anticipation, and the disorder is not self-limited (contrasting with the acute monophasic post-infectious pediatric form).

Inheritance and population (Section 9): Autosomal dominant, single-gene (SCN9A), with recurrent private missense alleles that are ultra-rare/absent in gnomAD and cosegregate in families. Both familial and de novo/sporadic cases occur. Penetrance is high but expressivity is variable, including striking intra- and interfamily phenotypic diversity for the same variant ( ).

P 22136189

Female predominance is seen in overall EM epidemiology, though sex differences are less pronounced in the inherited subtype.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
14985375	Mutations in SCN9A cause primary erythermalgia	Human genetic (linkage/mutation)	F1: causal gene, AD inheritance, Nav1.7 expression
22136189	Phenotypic diversity of a Nav1.7 GoF variant	Human clinical + biophysics	F2: IEM biophysical signature; variable expressivity
40279376	CRISPR correction in iPSC sensory neurons	In vitro human iPSC	F2, F7: causality; iPSC model validation
18713229	Incidence in Olmsted County	Population epidemiology	F3: incidence, primary vs secondary
22247059	EM in Sweden	Population/single-center	F3, F9: incidence, female %, no EM mortality
41190974	IEM review (China/ worldwide)	Review	F3, F4, F10: onset <10 yr; genotype-specific therapy; variant spectrum
35835622	Paroxysmal vascular acrosyndromes	Clinical review	F4: first-line drug classes
37557164	Single-center primary EM experience	Clinical cohort	F4, F9: effective therapies; QoL/disability
37661688	Mexiletine overdose	Clinical case	F4: treatment safety/narrow index
18060017	SCN9A spectrum of pain disorders	Review	F5: IEM/PEPD/CIP allelic spectrum
25995458	Novel SCN9A mutations, phenotype correlations	Human + electrophysiology	F5: IEM vs PEPD biophysical rule
24311784	A1632T causes IEM via fast-inactivation shift	In vitro electrophysiology	F5: imperfect genotype-phenotype correlation
27174182	Slow inactivation & open-channel block	In vitro biophysics	F5: resurgent/persistent current distinctions
16673274		Clinical/mechanistic	

PMID	Title (abbrev.)	Evidence type	Supports
	Platelet-mediated thrombosis in ET/PV		F6: secondary EM mechanism, aspirin response
42101597	Thrombocytosis evidence review	Clinical guideline	F6: JAK2 testing
32723684	Pediatric acute monophasic EM = SFN	Clinical case series	F6: immune-mediated differential
33323889	Two Nav1.7 I228M knock-in mouse lines	Mouse model	F7: incomplete pain-phenotype recapitulation
31550995	Rat Nav1.7 knock-in	Rat model	F7: drug-development platform
36201719	NaV1.7-ChR2 optogenetic mice	Mouse model	F7: nociceptor activation tool
38657946	BoNT/A in Q875E iPSC neurons	In vitro human iPSC	F7: iPSC pharmacology model
37903281	Structural basis (NaVAb) of IEM voltage-sensor mutations	Structural biology	F8: S4 gating-charge mechanism
24673364	Burden of painful small-fiber neuropathy	Survey/chart review	F9: comorbidity/cost burden
40428878	Comparative treatment efficacy (systematic review)	Systematic review	F9: no single uniformly effective therapy
41997215	Germline SCN9A variant, unilateral erythema	Human clinical/ genetic	F10: ultra-rare, cosegregating, ACMG classification
37555797	Gene-panel study of SCN9A pain disorders	Human genetic	F10: gene-panel diagnostic approach
27009931	Sex differences in skin diseases (REP)	Epidemiology	F3: female predominance in EM

Consistency and conflicts. The genetic etiology (SCN9A/Nav1.7 gain-of-function) is corroborated by convergent evidence types — human linkage/mutation studies, in-vitro electrophysiology, human iPSC causality experiments, and channel structural biology — with

no contradicting evidence in the reviewed literature. The main internal tension is genotype–phenotype: while IEM generally maps to activation-enhancing mutations and PEPD to inactivation-impairing mutations (P 25995458), overlap variants (A1632E) and exceptions (A1632T causing IEM via an inactivation shift, P 24311784) show the rule is a useful heuristic rather than an absolute law. The second key tension is model fidelity: iPSC neurons faithfully model human hyperexcitability, but mouse knock-ins reproduce cellular hyperexcitability without overt pain behavior (P 33323889), a species/context gap important for preclinical drug development.

Section-by-Section Knowledge-Base Annotations

1. Disease information. Rare AD Mendelian sodium channelopathy; synonyms: primary/inherited/familial erythromelalgia, IEM, primary erythermalgia, Mitchell disease (historical, for EM broadly), "man on fire" syndrome. Identifiers: **OMIM #133020**; **Orphanet ORPHA:90026 (primary erythromelalgia)**; MeSH "Erythromelalgia"; ICD-10 I73.81; MONDO erythromelalgia concept. Information is derived from aggregated disease-level resources and published case/family cohorts (not primarily EHR).

2. Etiology. Primary cause = heterozygous germline gain-of-function SCN9A missense variants (F1, F5, F10). Genetic risk = the causal variant itself (dominant); no established environmental risk factors cause the disease, though **heat, exercise, and warm environments** are potent symptom **triggers**. No robust protective genetic/environmental factors identified; **cooling** is the principal symptom-relieving intervention. Gene–environment interaction is temperature-dependent channel gating: warmth further biases already-hyperactivable channels toward opening.

3. Phenotypes (HPO). Core: burning extremity pain (**HP:0012531 Pain**), **erythema** (**HP:0500252 Erythema**), local **skin warmth/increased temperature**, **episodic/paroxysmal** course, heat-triggered, cooling-relieved, distal and typically **bilateral**. Onset childhood (**HP:0011463 Childhood onset**). Severity moderate–severe, variable; progression episodic/fluctuating. QoL impact severe (F9).

4. Genetic/molecular. Causal gene **SCN9A (HGNC:10597; OMIM *603415)**, protein Nav1.7 (UniProt Q15858). Variant class: missense, heterozygous, germline, gain-of-function (F1, F5, F10). Illustrative alleles: I848T, L858F/H, F1449V, V400M, S241T, I234T, Q875E, I136V, P1308L, A1632G/T/E, L1595R, F1624S. Allele frequency: absent/ultra-rare in gnomAD; ACMG-classified pathogenic/likely pathogenic via cosegregation and functional data. No causal chromosomal abnormalities or established epigenetic drivers.

5. Environmental. No toxic/infectious cause of the primary form; heat/warmth and physical activity are triggers; a distinct **acute post-infectious/immune-mediated pediatric erythromelalgia** exists as a phenocopy (P 32723684).

6. Mechanism. See Mechanistic Model above (F2, F5, F8). Molecular pathway = voltage-gated sodium channel gating / neuronal excitability; cellular process = altered action-potential threshold and firing; protein dysfunction = gain-of-function voltage-sensor defect. No primary immune/metabolic/fibrotic mechanism.

7. Anatomy. Skin of distal extremities (feet > hands), bilateral/symmetric; peripheral sensory (DRG) and sympathetic neurons; cutaneous microvasculature. UBERON/CL/GO anchors listed above.

8. Temporal. Childhood onset, insidious, chronic lifelong, episodic/paroxysmal; heat-triggered flares; cooling-induced transient remission.

9. Inheritance/epidemiology. AD; incidence ~0.36–1.3/100,000/yr (F3); high penetrance, variable expressivity; female predominance overall.

10. Diagnostics. Clinical triad + provocation/relief pattern; CBC and **JAK2 testing** to exclude secondary MPN-associated EM (F6); molecular confirmation by **SCN9A single-gene sequencing** or **HSAN gene panel** (F10). Skin biopsy for small-fiber neuropathy in atypical/acquired presentations. CMA/karyotype/FISH/mtDNA/repeat-expansion testing NOT indicated.

11. Prognosis. Chronic, disabling, non-fatal (F9); high psychiatric/functional comorbidity; risk of self-inflicted cooling injury.

12. Treatment (MAXO). Sodium-channel blockers (mexiletine, carbamazepine, lidocaine), neuropathic agents (gabapentin, amitriptyline), antihistamines, venlafaxine; behavioral cooling; genotype-guided selection (F4). Emerging: selective Nav1.7 blockers, structure-guided and gene/CRISPR-based precision approaches.

13. Prevention. No primary prevention (Mendelian). Genetic counseling for AD 50% recurrence risk; cascade family testing; prenatal/preimplantation options where applicable. Tertiary prevention = trigger avoidance (heat, exertion) and avoidance of cooling-related skin damage.

14. Other species / natural disease. Human disease (NCBI Taxon 9606). Ortholog **Scn9a** in mouse (NCBI Gene 20274) and rat; no well-documented naturally occurring companion-animal/wildlife equivalent identified; engineered rodent orthologs used experimentally (F7).

15. Model organisms. Human iPSC-derived sensory neurons (preferred, robust; F7); mouse and rat Nav1.7 knock-in lines (cellular hyperexcitability, incomplete pain behavior); optogenetic NaV1.7-ChR2 mice; HEK293/Xenopus oocyte heterologous systems; bacterial NaVAb for structural studies. Resources: MGI, RGD, Cellosaurus/iPSC repositories.

Limitations and Knowledge Gaps

1. **Model fidelity gap.** Mouse Nav1.7 I228M knock-ins recapitulate DRG hyperexcitability but not pain behavior or nerve-fiber loss (P 33323889), limiting preclinical predictive validity; iPSC neurons capture excitability but lack in-vivo behavioral read-outs.
2. **Imperfect genotype–phenotype mapping.** The IEM (activation shift) vs PEPD (inactivation shift) dichotomy has documented exceptions and overlap variants (A1632E/T), complicating variant interpretation and prognostication.
3. **Sparse population genetics.** Because pathogenic alleles are private/ultra-rare, formal penetrance estimates, carrier frequencies, and founder effects are not well quantified from population databases.
4. **Epidemiology heterogeneity.** Incidence estimates (0.36 vs 1.3/100,000/yr) mix primary and secondary EM and different ascertainment methods; primary-EM-specific, molecularly confirmed incidence/prevalence is uncertain.
5. **Treatment evidence quality.** Most therapeutic data are from small single-center cohorts and case reports; the 2025 systematic review (P 40428878)

underscores the lack of a uniformly effective, high-evidence therapy. Genotype-specific responses are promising but not yet validated in prospective randomized trials.

6. **No omics depth.** Transcriptomic/proteomic/metabolomic profiling of patient tissue is limited; QoL is documented qualitatively and via proxy small-fiber-neuropathy burden data rather than EM-specific validated instruments.
7. **Comparative/veterinary biology** for a naturally occurring animal counterpart is essentially absent.

Proposed Follow-up Experiments / Actions

1. **Prospective, genotype-stratified pharmacology trial.** Test the mexiletine-responsive (L858F/H) vs carbamazepine-responsive (V400M, S241T, I234T) hypothesis in a controlled, biophysically phenotyped patient cohort to validate genotype-guided prescribing (extends F4/F5).
2. **iPSC pharmacology panel.** Build an isogenic, CRISPR-engineered iPSC-sensory-neuron library spanning the recurrent allelic spectrum (F10) and screen selective Nav1.7 blockers and existing sodium-channel drugs against multielectrode-array excitability to prioritize variant-specific therapies (extends F7).
3. **Structure-guided drug design.** Leverage the NaVAb/Nav1.7 voltage-sensor structures (F8) to design mutation-specific state-dependent inhibitors that preferentially stabilize the resting (deactivated) voltage sensor.
4. **Improved in-vivo model.** Develop humanized-SCN9A or higher-impact knock-in/conditional models that reproduce pain behavior and intraepidermal nerve-fiber changes, closing the mouse-model gap (addresses F7 limitation).
5. **Molecularly confirmed natural-history registry.** Establish a genotyped primary-EM registry to quantify penetrance, expressivity, incidence/prevalence, progression, and EM-specific QoL with validated instruments (addresses epidemiology and prognosis gaps).
6. **Diagnostic standardization.** Formalize a diagnostic flow-chart combining clinical triad + CBC/JAK2 exclusion of secondary EM + SCN9A/HSAN panel confirmation + skin biopsy for atypical acquired cases (operationalizes F6/F10).

Evidence source types are indicated throughout: human clinical/genetic (e.g., PMIDs 14985375, 22136189, 25995458, 41190974, 41997215, 37555797), in-vitro human iPSC (40279376, 38657946), heterologous/electrophysiology (24311784, 27174182), model organism (33323889, 31550995, 36201719), structural/computational (37903281), and epidemiologic/clinical-review (18713229, 22247059, 16673274, 42101597, 24673364, 40428878, 35835622, 37557164, 27009931).
