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# Systematic Review of Genetics, Mechanisms, and Pain Management in Erythromelalgia

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## Abstract

This systematic review aims to synthesize current evidence on the genetics, pathophysiological mechanisms, clinical features, and pain management strategies in erythromelalgia, including both inherited and acquired forms. The review will evaluate published data on sodium channel gene mutations (*SCN9A, SCN10A, SCN11A*), neurovascular and inflammatory mechanisms, and clinical outcomes associated with pharmacological, topical, interventional, and non-pharmacological therapies.

Studies published between 2000 and 2025 will be included if they report (1) genetic or mechanistic findings, (2) clinical characteristics or diagnostic features, or (3) treatment outcomes such as pain intensity, frequency of crises, triggers, functional impact, or quality of life. Given the rarity of erythromelalgia and the heterogeneity of interventions, a quantitative meta-analysis is not planned. Instead, this review will provide a structured qualitative synthesis of the available evidence.

This work aims to summarize current knowledge on the genetic and mechanistic aspects of erythromelalgia, identify recurring therapeutic patterns, and highlight gaps in existing evidence, ultimately contributing to improved diagnostic and therapeutic strategies for this rare condition.

## Guidelines

This systematic review protocol follows internationally recognized methodological standards to ensure transparency, reproducibility, and scientific rigor.

The protocol is reported in accordance with the PRISMA-P 2015 (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) guidelines.
The full review will follow the PRISMA 2020 statement to ensure clear and complete reporting of the identification, screening, eligibility, and inclusion processes.
The methodological guide of the Haute Autorité de Santé (HAS) for rare disease protocols was consulted to ensure alignment with standards specific to rare conditions.

**Assessment of methodological quality**
Risk of bias in individual studies will be assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, selected according to the corresponding study design (case report, case series, cohort study, etc.).
The certainty of the evidence for key outcomes will be evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach, when applicable.

**Synthesis methods**
Due to the rarity of erythromelalgia and the expected heterogeneity of interventions and outcomes, no quantitative meta-analysis is planned.
A structured qualitative synthesis will be undertaken, following guidance from the Cochrane Handbook and the Haute Autorité de Santé (HAS) for rare diseases.

**Registration and Peer review**
This protocol will be registered in PROSPERO and adheres to its standards for the prospective registration of systematic review protocols.
The review protocol has undergone  methodological and clinical review to ensure clarity, relevance, and robustness before PROSPERO registration.
The final results of the review will be submitted for peer-reviewed publication in a scientific journal.

## Before start

- Ensure that all team members are familiar with PRISMA-P and PRISMA 2020 guidelines.
- Consult the methodological guide of the Haute Autorité de Santé (HAS) for rare disease protocols to ensure alignment with standards specific to rare conditions.
- Secure access to the required bibliographic databases: PubMed/MEDLINE, Embase, and Scopus.
- Define reviewer roles in advance, including dual independent screening and dual independent data extraction. Identify at least one reviewer with methodological expertise in systematic reviews.

## Population

1 Individuals of any age with a diagnosis of erythromelalgia, whether inherited/primary or acquired/secondary, established on the basis of clinical features and/or genetic testing when available.

## Intervention

2 **Genetic and Mechanistic Investigations**
- sequencing of *SCN9A*, *SCN10A*, and *SCN11A* (encoding Nav1.7, Nav1.8, and Nav1.9);
- neurophysiological assessments;
- microvascular and autonomic evaluations;
- other mechanistic investigations conducted in human studies.

3 **Etiological and Associated Conditions**
Studies reporting conditions known to be associated with secondary erythromelalgia will also be included, such as:
- hematological disorders (e.g., thrombocytosis, polycythemia vera);
- autoimmune or inflammatory diseases;
- neuropathic conditions;
- infectious, metabolic, or drug-related causes;
- other reported comorbidities linked to the onset or worsening of erythromelalgia.

4 **Pain Management Interventions**
- pharmacological treatments (e.g., mexiletine, carbamazepine, lidocaine, gabapentinoids, antidepressants, aspirin in secondary erythromelalgia, prostaglandin inhibitors, biologic agents);
- topical treatments (e.g., lidocaine patches, compounded analgesic creams, capsaicin formulations);
- interventional procedures (e.g., intravenous lidocaine, sympathetic nerve blocks, spinal cord stimulation);
- non-pharmacological approaches, such as:
  - lifestyle adaptations,
  - psychological or supportive interventions,
  - non-invasive neuromodulation techniques

5 **Impact on Quality of Life**
Studies describing the impact of erythromelalgia on quality of life will be included, including:
- functional limitations;
- impact on daily activities or mobility;
- sleep disturbance;
- emotional or social consequences;

- patient-reported outcomes using validated or non-validated measures.

## Types of Studies

6 The review will include:
– randomized controlled trials;
– non-randomized interventional studies;
– prospective and retrospective cohort studies;
– case–control studies;
– analytical cross-sectional studies;
– case series ;
– individual case reports.

Excluded: animal studies, expert opinions, narrative reviews, editorials, and non-extractable conference abstracts.

## Search strategy

7 A comprehensive search will be conducted in PubMed/MEDLINE, Embase, and Scopus using a combination of controlled vocabulary and free-text terms related to erythromelalgia, sodium channelopathies, pain mechanisms, and treatment.

Key terms will include:
“erythromelalgia”, “erythromelalgia syndrome”, “SCN9A”, “SCN10A”, “SCN11A”, “Nav1.7”, “Nav1.8”, “Nav1.9”, “sodium channel”, “genetic”, “physiopathology”, “treatment”, “therapy”, “analgesic” ; "quality of life" ; "interventional procedures" ; "topical treatment" ; "pharmacotherapy" ;" secondary erythromelalgia"

Search terms will be combined using Boolean operators (AND/OR) and adapted to the indexing system and syntax of each database.

## Screening Strategy

8 All records identified through database searches will be imported into a screening platform, where duplicates will be automatically removed and manually checked if needed.

Titles and abstracts of unique records will be screened by two independent reviewers using predefined inclusion and exclusion criteria.

Full-text articles deemed potentially eligible will then undergo a thematic assessment, with each article reviewed by two reviewers according to its domain

(genetics/mechanisms, associated conditions, pain management, or quality of life). Discrepancies will be resolved through discussion or by a third reviewer if necessary.

The selection process will be documented using a PRISMA 2020 flow diagram, and reasons for exclusion at the full-text stage will be recorded.

## Data management

9 All references will be imported into a single reference management system.
A standardized data extraction form will be developed to collect:

- study characteristics;
- participant demographics;
- genetic findings;
- mechanistic or physiological insights;
- details of interventions;
- reported outcomes.

Data extraction will be performed independently by two reviewers to ensure accuracy. Study authors will be contacted when clarification or missing information is needed.

## Outcomes

10 **Primary Outcome**
Treatment response, defined as complete, partial, or no improvement, as reported in the original studies.
When available, treatment response may encompass changes in:

- pain intensity (e.g., VAS, NRS);
- cutaneous lesions or skin manifestations described in erythromelalgia;
- frequency and duration of crises;
- functional impairment.

11 **Secondary Outcomes**

- Genetic findings, including results of sequencing (*SCN9A, SCN10A, SCN11A*) and any other reported molecular analyses;
- Mechanistic insights, such as neurophysiological findings, microvascular or autonomic abnormalities, and other human mechanistic investigations;
- Etiological classification, including identification of primary (inherited) or secondary (acquired) causes and associated comorbidities;
- Characteristics of treatments used, including type of intervention (pharmacological, topical, interventional, or non-pharmacological), dosage, modality, and duration when available;

- Treatment-related adverse events or side effects;
- Quality-of-life impact, including functional limitations, sleep disturbance, emotional or social consequences, and other patient-reported outcomes;
- Clinical features, including temperature triggers, autonomic symptoms, and any reported skin manifestations (e.g., cutaneous lesions);
- Diagnostic information, such as reported diagnostic pathways or diagnostic delays.

## Statistical Methods

12 A quantitative meta-analysis is not planned due to:

- heterogeneity of interventions (no standard treatment),
- variability of populations (genetic vs acquired forms),
- predominance of case reports and small case series,
- non-standardized outcome measures (VAS, subjective improvement, crisis frequency),
- lack of comparable effect estimates.

A structured qualitative synthesis will be conducted, focusing on:

- treatment effects;
- patterns of therapeutic response;
- reported mechanisms (sodium channel, neurovascular, inflammatory);
- etiological classification and clinical features;
- methodological strengths, limitations, and evidence gaps.

If unexpectedly two or more studies report comparable outcomes for a single intervention, a small exploratory pooled analysis may be discussed, but none is anticipated.

## Risk of Bias and Quality Assessment

13 The following JBI Critical Appraisal Tool will be used according to study design.
Two reviewers will independently assess methodological quality. Discrepancies will be resolved through discussion or adjudication.

Given the expected number and heterogeneity of included studies, publication bias will be described narratively rather than statistically.

## Certainty of Evidence

14 The certainty of evidence for each key outcome will be assessed using the GRADE approach.
Certainty will be rated as: high, moderate, low, or very low.

Two reviewers will independently evaluate certainty, resolving disagreements through consensus or third-party arbitration.

## Support and Funding

15 This review is conducted by the Rare Pain Diseases Working Group of the French Society for the Study and Treatment of Pain (SFETD). No external funding was received for its development.