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ORIGINAL RESEARCH

NMRAL1 as a Causal Factor in Postherpetic Neuralgia: A Proteome-Wide Mendelian Randomization Study

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Background: Postherpetic neuralgia (PHN) is a chronic pain condition following herpes zoster infection, disproportionately affecting elderly and immunocompromised individuals. Despite its significant clinical impact, the underlying mechanisms of PHN remain exclusive, and effective treatments are limited. Circulating plasma proteins offer insights into PHN pathogenesis and serve as potential biomarkers or therapeutic targets.

Methods: We analyzed FinnGen R12 GWAS data (490 PHN cases and 435,371 controls) and protein quantitative trait loci (pQTL) data for 4907 plasma proteins from 35,559 Icelanders. Mendelian randomization (MR) was conducted to investigate causal associations between plasma proteins and PHN risk. Causal effects were assessed using inverse variance weighting (IVW) and MR-Egger methods.

Results: MR analysis identified NMRAL1 as the only plasma protein causally associated with PHN. Genetically predicted higher levels of NMRAL1 were linked to a reduced risk of PHN (IVW odds ratio = 0.553, 95% confidence interval: 0.405–0.755, p = 0.000193). No evidence of heterogeneity or pleiotropy was observed, and sensitivity analyses, including leave-one-out analysis, confirmed the robustness of the findings. No other plasma proteins showed significant associations with PHN.

Conclusion: This study identifies NMRAL1 as a protective factor for PHN and underscores its potential as a biomarker and therapeutic target. The findings highlight the utility of integrating proteomic and genetic data to advance understanding of complex neurological disorders like PHN.

Keywords: postherpetic neuralgia, Mendelian randomization, novel protein biomarkers

Introduction

Postherpetic neuralgia (PHN) is the most prevalent and debilitating complication of herpes zoster (HZ),[1] defined by persistent pain lasting 90 days or more after the resolution of the rash. PHN disproportionately affects elderly individuals and those with compromised immune function, with pain regions often extending beyond the rash-affected area, commonly involving the unilateral chest or trigeminal nerve regions.[2] The pain is heterogenous in nature, manifesting as burning, electric shock-like, stabbing, needle-like, or tearing sensations. Multiple pain modalities often coexist, with one type predominating.[3] Epidemiological data reveal that approximately 13% of individuals aged 50 years or older with HZ develop PHN, with incidence rates increasing markedly with age.[4] Notably, around 60% of HZ patients aged ≥60 years progress to PHN, with this proportion rising to as high as 75% in those aged ≥70 years.[5] PHN is a chronic and refractory condition, characterized by severe, relapsing pain that significantly disrupts patients' sleep, mood, and social interactions, often leading to anxiety, depression, and, in extreme cases, suicide.[6]

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Despite the significant clinical impact of postherpetic neuralgia (PHN), its underlying pathogenesis remains poorly understood, which complicates the identification of high-risk populations and the implementation of effective prevention strategies.[7,8] Furthermore, no single treatment has been shown to consistently alleviate pain in all patients, and existing therapies are limited in their efficacy.[9] Current treatment options include pharmacological interventions, minimally invasive procedures (such as nerve blocks and spinal cord stimulation), acupuncture, and psychotherapy. However, medications often exhibit limited efficacy and are associated with high relapse rates upon discontinuation.[10] Minimally invasive procedures, such as pulsed radiofrequency treatments, typically require CT guidance, which not only increases costs and necessitates specialized equipment but also exposes patients to significant radiation.[11] Additionally, spinal cord stimulation and intrathecal drug delivery carry risks of complications, including physical trauma, cerebrospinal fluid leakage, and infection, and are less tolerable in elderly patients due to their invasive nature and cost.[12] Selective nerve destruction, which involves surgical, chemical, or physical damage to affected nerves, results in irreversible nerve injury. Given the absence of effective, targeted therapies, the outcomes of current treatments remain suboptimal, leading to both poor patient outcomes and inefficient use of healthcare resources. Therefore, the identification of novel biomarkers and therapeutic targets for PHN is imperative for advancing its management and alleviating the considerable burden it imposes on patients and healthcare systems.[13]

Emerging evidence indicates that circulating blood factors, including proteins involved in metabolic and inflammatory pathways, may play critical roles in the PHN.[14–16] MR studies leveraging human blood proteome data have provided valuable insights into the genetic underpinnings of complex diseases, particularly those modulated by circulating proteins.[17] Proteins with robust causal associations offer potential as druggable targets. Identifying such proteins in PHN could not only advance our understanding of its genetic architecture but also pave the way for the development of targeted therapeutic interventions.

In this study, we leveraged the largest GWAS dataset for PHN to date, derived from the FinnGen R12 database, encompassing 490 cases and 435,371 controls. By integrating summary statistics from proteomic GWAS data generated by Ferkingstad et al[18] which identified pQTLs for 4907 plasma proteins in 35,559 Icelandic individuals, we conducted a proteome-wide Mendelian randomization (PW-MR) analysis. This approach has identified a novel blood protein, NMRAL1, which may be causally linked to postherpetic neuralgia (PHN), offering new insights into its potential pathogenesis. NMRAL1 functions as a sensor for the NADPH/NADP+ ratio and is involved in regulating inflammatory responses.[19] Inflammatory mediators such as IL-1 and TNF-α activate signaling cascades through the NF-κB pathway. Research has shown that NMRAL1 interacts with this pathway via its modulation of the NADPH/NADP+ ratio. Under conditions of high NADPH/NADP+, NMRAL1 translocates from the nucleus to the cytoplasm, where it forms a complex with NADPH.[20] This complex inhibits NF-κB signaling by interacting with IKKβ (IκB kinase β) and preventing the degradation of its substrate IκBα, thereby blocking the activation of the inflammatory process. This inhibition ultimately leads to enhanced nitric oxide synthase (NOS) activity and increased nitric oxide (NO) production. Concurrently, the NMRAL1-NADPH complex also inhibits the p47phox subunit of NADPH oxidase, reducing superoxide ion production, which contributes to the modulation of immune function and exerts anti-inflammatory effects.[20] The detailed analysis workflow of this study is illustrated in Figure 1.

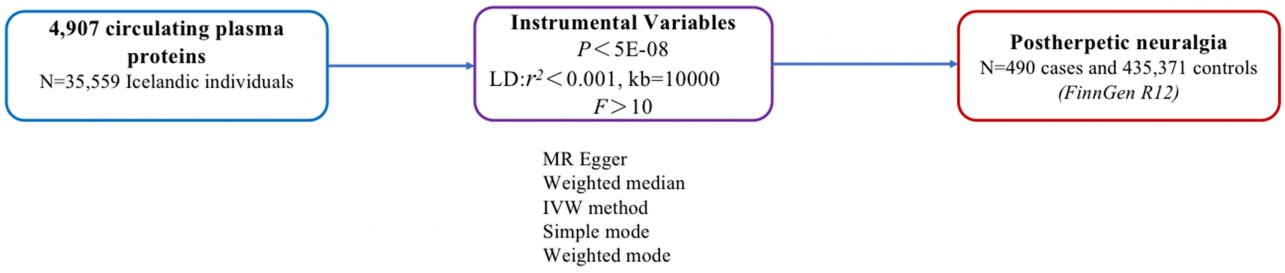

Figure 1 Flowchart of the study design.

This approach uncovered a novel blood protein potentially causally implicated in PHN, offering fresh insights into its underlying pathogenesis. Analysis workflow (Figure 1).

Methods

The data utilized in this study were sourced from existing publications and publicly available databases. In accordance with Article 32, Items 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), no additional ethical approval was required for this analysis.

Data Source

A large-scale pQTL study involving 35,559 Icelandic individuals provided genetic association data for 4907 circulating proteins. Proteomic profiling was performed using a modified, multiplexed aptamer-based binding assay (SOMAscan version 4). Protein level variations were normalized for age- and sex-specific effects, followed by rank-inverse normal transformation to standardize residuals. These normalized values were then utilized as phenotypes in GWAS conducted with BOLT-LMM linear mixed models. Supplementary GWAS data were obtained from the original publication. Proteins associated with genome-wide significant pQTLs ($P < 5 \times 10^{-8}$) were included in two-sample MR analyses. Significant SNPs linked to PHN were identified based on a genome-wide significance threshold ($P < 5 \times 10^{-8}$). To ensure independence of IVs, SNPs in linkage disequilibrium ($r^2 > 0.001$) within a 10,000-kb window were excluded. The strength of SNP-exposure associations was assessed using F statistics, calculated as F=b2/SD2, where b represents the effect size of the SNP on the exposure and SD is the standard deviation. SNPs with F values < 10, indicative of weak instruments, were excluded to minimize bias and improve the reliability of causal effect estimates.

The primary outcome data, including summary statistics for PHN, were obtained from the largest GWAS dataset to date, encompassing 490 PHN cases and 435,371 healthy controls.

MR Analysis

For the primary MR analysis, plasma proteins served as the exposure factor, with PHN as the outcome. Causal relationships were assessed using the Wald ratio (WR) method for proteins with a single pQTL as the IV.[21] For proteins with multiple IVs, the IVW method was employed.[22] Results were reported as ORs with 95% CIs and a nominal significance threshold of $p < 0.05$.

To ensure robustness and reliability, Cochran's Q test and MR-Egger intercept test were conducted to assess potential heterogeneity and horizontal pleiotropy, respectively ($p > 0.05$ indicated absence of heterogeneity or pleiotropy). For IVW analysis, a fixed-effects model was used when no significant heterogeneity was detected; otherwise, a random-effects model was applied.

Results

MR analysis identified a significant association between NMRAL1 and the risk of PHN. Across multiple analytical approaches, NMRAL1 consistently demonstrated strong causal relevance. Key results include: IVW: OR = 0.553, 95% CI: 0.405–0.755, p = 0.000193. β-values across the five MR methods were directionally consistent (Figure 2). Importantly, no evidence of heterogeneity or horizontal pleiotropy was observed ($p > 0.05$; Table S1), supporting the

Exposure	Method	nSNP	OR(95%CI)	P−value
NMRAL1	MR Egger	13	0.521(0.327−0.829)	1.89e−02
NMRAL1	Weighted median	13	0.604(0.400−0.913)	1.67e−02
NMRAL1	Inverse variance weighted	13	0.553(0.405−0.755)	1.93e−04
NMRAL1	Simple mode	13	0.553(0.271−1.126)	1.28e−01
NMRAL1	Weighted mode	13	0.578(0.376−0.887)	2.76e−02

Figure 2 Forest plot for MR results between plasma pQTLs and PHN.

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robustness and reliability of these findings. Figure S1 presents a scatter plot depicting the causal relationship between NMRAL1 and PHN, while leave-one-out analysis (Figure S2) revealed no SNP outliers, further confirming the stability of the results.

Notably, NMRAL1 was the only plasma protein identified as causally associated with PHN in both the primary IVW analysis and secondary methods. No other proteins showed significant associations, underscoring the critical role of NMRAL1 in PHN pathogenesis.

Comprehensive visualizations and datasets for all plasma proteins, including forest plots, scatter plots, funnel plots, leave-one-out sensitivity analysis plots, heterogeneity test result tables, and OR tables for SNP effects with associated statistical details, as well as single SNP analysis results, are provided.

Discussion

In this study, we leveraged genome-wide association summary data to conduct a comprehensive MR analysis, evaluating the causal relationship between 4907 plasma proteins and PHN. MR analysis provided a powerful framework to disentangle upstream and downstream factors in the disease pathway, effectively eliminating the potential for reverse causation. Our findings revealed that genetically predicted elevated levels of NMRAL1 were significantly associated with a reduced risk of PHN, while no other plasma proteins demonstrated a causal relationship with the disease. Previous proteomic studies have identified several proteins associated with PHN, including HNRNPK, RPS10, interferons α and γ, GM-CSF, and IL-6 in blood,[16,23] as well as PLG, APOA1, and APOE in cerebrospinal fluid,[24] which are involved in processes such as infection and inflammation. These proteins hold potential as therapeutic targets. However, in this MR analysis, none of the aforementioned proteins demonstrated a causal relationship with PHN. Further exploration in larger and more diverse populations, as well as through the use of additional databases, will be necessary to better understand their role in PHN pathogenesis.

The pathophysiological mechanisms underlying PHN are highly complex and not yet fully elucidated.[7] Current evidence suggests that PHN is closely associated with diminished varicella-zoster virus (VZV)-specific cellular immunity and structural and functional plasticity of the nervous system. Following initial infection, VZV causes chickenpox and subsequently enters a dormant state within sensory ganglia, including cranial nerves and posterior roots of the spinal cord. When host immunity is compromised due to factors such as fatigue or malignancy, the virus reactivates, replicates, and spreads, triggering immune responses in the affected ganglia. This immune activity leads to ganglionic degeneration, necrosis, and the onset of neuralgia. Reactivated VZV travels via peripheral sensory nerve fibers to the skin and bloodstream, inducing local skin inflammation and damaging peripheral fibers through immune responses.[25] Nerve damage initiates an immune cascade, characterized by macrophage infiltration and elevated expression of pro-inflammatory cytokines, such as TNF-α and IL-1β. These cytokines sensitize primary sensory neurons, thereby amplifying neuropathic pain and driving the progression of PHN.[26,27]

Emerging evidence highlights the critical role of central nervous system (CNS) inflammatory responses and glial cell activation in the development and maintenance of peripheral neuropathic pain, including PHN. Cytokines and inflammatory mediators released during these processes contribute to brain edema, axonal degeneration, and glial proliferation, thereby driving the initiation and progression of PHN.[28,29] Microglia and astrocytes, key glial cells in the CNS, become activated following central injury and play a pivotal role in central sensitization and persistent pain.[30] These activated glial cells amplify neuroinflammation by releasing pro-inflammatory cytokines such as IL-1 and TNF-α, further exacerbating neuropathic pain.[31] This interplay between glial activation and neuroinflammation underscores the importance of targeting these pathways to mitigate PHN-associated pain.[32]

NMRAL1 serves as a negative regulator of innate immunity, playing a critical role in modulating antiviral responses. Following RNA virus infection, RIG-I-like receptors recognize cytoplasmic viral RNA, activating the Cardif-TRAF3-TBK1 /IKKε-IRF3 axis to induce type I interferon (IFN) production.[33,34] Studies have demonstrated that NMRAL1 overexpression impairs IKKε recruitment, reduces IRF3 phosphorylation and nuclear translocation, and downregulates IFN-β levels in response to viral infection.[35] Furthermore, NMRAL1 inhibits TNF and IL-1-induced NF-κB activation, a key pathway in cytokine-mediated transcriptional regulation. In the canonical NF-κB signaling pathway, membrane receptors recognize cytokines such as TNF or IL-1, initiating a ubiquitination cascade that modulates transcriptional activity.[36] NMRAL1

regulates this pathway by inhibiting IκB phosphorylation and degradation, thereby suppressing NF-κB activity and reducing the expression of antiviral genes, including TNF-α and MX1.[37] Knockdown of HSCARG, an NMRAL1-related factor, enhances antiviral responses and reduces viral replication, highlighting the protein's involvement in antiviral signaling. Although no studies have directly linked NMRAL1 to PHN, its role in regulating antiviral responses and viral replication through the NMRAL1-NF-κB axis suggests a potential connection. By inhibiting TNF- and IL-1-induced NF-κB activation, NMRAL1 may exert a protective effect against PHN. Lower NMRAL1 levels could increase susceptibility to PHN, although the specific pathological mechanisms require further investigation and validation.

This study has several notable strengths. First, by employing MR to assess the association between plasma proteins and PHN, we minimized the influence of reverse causality and potential confounders, ensuring robust causal inferences. Second, we utilized SNPs from the largest GWAS datasets available for plasma proteins and PHN, enhancing the statistical power and reliability of our findings.

However, our study also has limitations. MR analysis is constrained by its reliance on existing genetic data and cannot account for non-genetic factors, such as lifestyle, that may influence PHN risk or progression. Furthermore, we cannot ascertain whether comorbidities or other underlying conditions in the studied population affected plasma protein levels, potentially confounding the results. Additionally, while MR allows for causal inference, it does not provide insights into the mechanisms linking plasma proteins to PHN severity or duration, which requires further investigation. Another limitation is the restricted population diversity in our analysis, as the study was conducted entirely within European cohorts. Consequently, the generalizability of our findings to other ethnicities remains uncertain. Future studies should validate these results in more diverse populations and incorporate non-genetic factors to provide a more comprehensive understanding of PHN pathogenesis. Expanding these efforts will be critical for translating our findings into clinical applications across global populations. Furthermore, in this study, we identified NMRAL1 as a potential protective factor for PHN. However, while our findings suggest a causal relationship, the underlying biological mechanisms remain speculative and require experimental validation. To address this, several future experimental approaches are proposed. Firstly, in vitro studies will be conducted using neuronal and immune cell lines, where NMRAL1 expression will be modulated through RNA interference or CRISPR-Cas9 technology. We will assess the activation of NF-κB pathway markers (such as phosphorylated IκBα and p65) and cytokine release (eg, TNF-α, IL-1β, IL-6) using ELISA or qPCR. Secondly, animal models of PHN, such as herpes zoster virus-induced neuralgia or spinal nerve injury models, will be employed to evaluate the role of NMRAL1 in vivo. NMRAL1 expression will be altered using viral vectors or genetic manipulation, and behavioral assessments (eg, mechanical withdrawal threshold, heat sensitivity) will be used to evaluate changes in neuropathic pain. Additionally, tissue analysis of dorsal root ganglia and spinal cord will be performed to measure inflammatory markers, immune cell infiltration, and NMRAL1 levels. Further studies will focus on pathway analysis in immune cells, particularly microglia and macrophages, to understand how NMRAL1 influences NF-κB signaling and oxidative stress pathways. Finally, human cohort studies will analyze NMRAL1 expression in plasma and cerebrospinal fluid from PHN patients, correlating these levels with clinical parameters such as pain severity and inflammatory markers. These future studies are crucial for validating the role of NMRAL1 in PHN and exploring its potential as a therapeutic target.

Conclusion

Our study systematically evaluated the causal relationship between circulating plasma proteins and the risk of PHN using two-sample MR. The findings revealed that genetically predicted elevated levels of NMRAL1 were associated with a reduced risk of PHN. By employing an innovative approach and a rigorous validation process, this study establishes a robust framework for identifying causal protein biomarkers and therapeutic targets for PHN. Beyond advancing the understanding of PHN pathogenesis, our work highlights the potential of integrating proteomic MR with conventional MR analyses to uncover novel insights into complex diseases.

Data Sharing Statement

The data underpinning the findings of this study are presented in the figures and tables within the manuscript, as well as the raw data, which are accessible at https://doi.org/10.7910/DVN/OR6YYI. The analysis code can be obtained from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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