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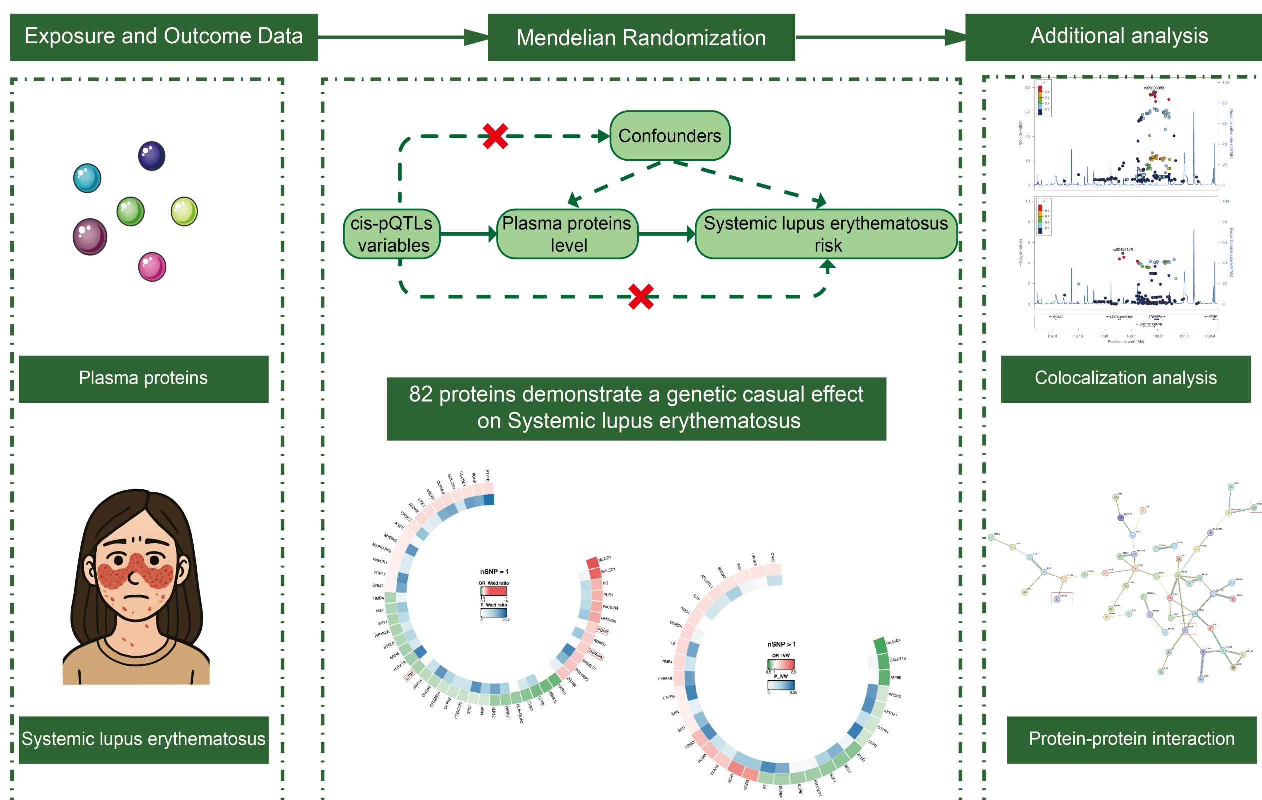
Authors

Xinzhen Zhao, Yinying Chai, Qianran Hong, Yuxuan Song, Yibo He

Correspondence

yuxuan_song2013@163.com (Y. Song), 20173626@zcmu.edu.cn (Y. He)

Graphical Abstract



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Exploring the Causal Relationship Between Plasma Proteins and Systemic Lupus Erythematosus: A Mendelian Randomization Study

Xinzhen Zhao [1†], Yinying Chai [2†], Qianran Hong [2†], Yuxuan Song [3*], Yibo He [1*]

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Abstract

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease that severely impacts patient quality of life. Current treatments primarily manage symptoms rather than cure the disease, emphasizing the need for a deeper understanding of its pathogenesis and the discovery of novel therapeutic targets. Circulating proteins are thought to play a critical role in SLE risk, but their causal relationships remain underexplored.

Methods: This study used pQTL and genome-wide association study (GWAS) data to perform a two-sample Mendelian randomization (MR) analysis to investigate the genetic causal relationships between circulating proteins and SLE. We identified proteins potentially associated with SLE risk and further analyzed their roles in immune regulation and inflammation using Protein-Protein Interaction (PPI) networks. Colocalization analysis was conducted to validate the associations of key proteins with SLE.

Results: Our analysis identified 82 plasma proteins potentially causally linked to SLE risk ($p < 0.05$). Colocalization analysis confirmed the association of proteins such as TNFAIP3, PDHX, and CTSF with SLE, underscoring their critical role in disease pathogenesis. Additionally, PPI network analysis revealed that these proteins are involved in immune modulation and inflammatory pathways, further supporting their relevance as therapeutic targets.

Conclusion: This study identifies 82 plasma proteins that may play a causal role in SLE, with TNFAIP3, PDHX, and CTSF emerging as promising therapeutic targets. These findings provide a foundation for future research aimed at developing precision therapies for SLE.

Keywords: Systemic Lupus Erythematosus; Mendelian Randomization; Circulating Proteins; Colocalization Analysis; Protein-Protein Interaction Network

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-system autoimmune disorder characterized by widespread immune dysregulation, autoantibody production, and tissue inflammation that profoundly affects the quality of life and imposes significant socio-economic burdens [1, 2]. The global annual incidence of SLE is approximately 5.14 per 100,000 (1.4 to 15.1 per 100,000), while the prevalence is 43.7 per 100,000 (15.9 to 108.9 per 100,000). The incidence and prevalence rates are significantly higher in females than in males, particularly among women of reproductive age. Additionally, the incidence and prevalence are higher in high-income countries and regions [3]. The conventional treatment regimen for SLE includes nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, corticosteroids, and immunosuppressants [4]. Though effective in many cases, these treatments come with limitations in managing long-term disease progression and preventing irreversible organ damage, leading to ongoing research for better management strategies. Recent advancements have introduced biologic agents, offering new therapeutic avenues for SLE management. For instance, belimumab, approved by the U.S. Food and Drug Administration (FDA), targets the B-lymphocyte stimulator (BLyS) to curtail autoantibody production [5]. Despite the diversity of treatment options, therapeutic outcomes for SLE vary considerably among individuals, and most strategies prioritize symptom management over disease eradication [6]. Moreover, long-term use of existing medications

1 Department of Clinical Lab, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China

2 Department of Traditional Chinese Internal Medicine, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China

3 Department of Urology, Peking University People's Hospital, Beijing, China

† These authors have contributed equally to this work and share first authorship

* Corresponding Author.

can lead to serious adverse effects, including infections, osteoporosis, and retinal disorders [6]. This underscores the need for therapeutic strategies that not only manage symptoms but also target the underlying pathophysiology of SLE, aiming for disease remission and preventing flare-ups.

Proteins play a crucial role in immune regulation and inflammatory responses, both of which are closely associated with the pathophysiological processes of SLE [7]. For example, complement activation is one of the key pathological mechanisms leading to tissue inflammation and damage in SLE [8]. Furthermore, proteins are primary targets for pharmacological interventions [9]. In two Phase III trials, anifrolumab, which blocks the type I interferon receptor 1 (IFNAR1), received approval for treating SLE [10]. This represents a shift toward targeting specific molecular pathways to control disease activity in SLE, highlighting the potential of precision medicine in autoimmune disorders. The circulating proteome, comprising proteins released both actively and passively into the bloods from various tissues and cells [11], has been confirmed its correlation with SLE. Yong Dai's team utilized data-dependent acquisition (DDA) and data-independent acquisition (DIA) proteomics techniques to identify three proteins as potential biomarkers for diagnosing SLE [12]. Liu et al. applied TMT-labeled quantitative proteomics alongside enzyme-linked immunosorbent assays (ELISA) to demonstrate notable differences in the serum levels of SAA1 and CD248 between SLE patients and healthy controls [13]. Nonetheless, current research is constrained by small sample sizes, a limited protein range, and potential confounding factors. Additionally, the variability in patient populations and the complexity of autoimmune diseases like SLE make it challenging to pinpoint universal biomarkers or therapeutic targets. Conducting randomized controlled trials to investigate the potential causal relationships between numerous proteins and SLE is also challenging.

Mendelian Randomization (MR) employs genetic variations as instrumental variables (IVs) to establish causal relationships between exposures and outcomes, effectively mitigating confounding factors and preventing reverse causality [14, 15]. The power of MR lies in its ability to discern causal relationships through genetic instruments, and it has emerged as a robust tool in autoimmune disease research. In this study, we conducted a two-sample MR analysis using pQTL data derived from extensive proteomics studies and genome-wide association study (GWAS) data for SLE to explore the genetic causal relationship between these elements. Additionally, we constructed a protein-protein interaction (PPI) network and performed colocalization analysis for proteins statistically significant in the MR analysis. These analyses enable a more comprehensive understanding of the biological pathways involved in SLE and help to identify proteins that could be targeted for therapeutic interventions. This comprehensive approach is aimed at identifying potential therapeutic targets for SLE and providing valuable insights for future clinical applications (Figure 1).

Methods

Source of Exposure Data

We obtained single nucleotide polymorphisms (SNPs) data associated with plasma protein levels from the Fenland study. The Fenland study provided a robust dataset for understanding the genetic underpinnings of complex diseases, with a large sample size and comprehensive data on genetic variations. This research carried out a genome-wide proteomics association study involving 10,708 participants of European ancestry, assessing 4,775 plasma proteins utilizing the SomaScan v4 assay (http://www.omicscience.org/apps/pgwas) [16].

Source of Outcome Data

The outcome of interest, SLE, was studied using GWAS data obtained from the Finnish Genetic Study (FinnGen), a collaborative research initiative that links genetic data from the Finnish biobank with detailed health records from national registries. This study extracted over 500,000 samples from the Finnish biobank, integrating longitudinal phenotypic data and digital health records from the national health registry [17]. We accessed the publicly available FinnGen R10 dataset (https://r10.finngen.fi/), which included data on 1,083 SLE cases and 306,504 controls [17]. The inclusion of longitudinal data allows for the identification of incident SLE cases, reducing the risk of misclassification bias compared to cross-sectional studies.

Study Design

In this research, we performed a comprehensive two-sample MR analysis to evaluate the causal relationship between circulating proteins and SLE. MR analysis has become increasingly popular in exploring the causal pathways involved in autoimmune diseases due to its ability to minimize biases inherent in observational studies. To ensure the validity of the results, the MR analysis mandated that the selected IVs satisfy three critical criteria: (1) the IVs must demonstrate a significant direct association with the exposure variable (circulating proteins); (2) the IVs must be independent of any confounders that could affect the exposure-outcome relationship; (3) the influence of the IVs on the outcome must be mediated exclusively through the exposure, with no alternative causal pathways [18].

Selection of Instrumental Variables

Informed by the three assumptions outlined previously and recent research findings, stringent criteria for SNP selection were applied: (1) SNPs must be significantly associated with circulating proteins, adhering to a stringent significance threshold ($P < 5 \times 10^{-8}$) [19]; (2) To ensure the independence of the selected IVs and mitigate the effects of linkage disequilibrium (LD), SNP clustering methods were utilized (r^2 = 0.001, kb = 10,000) [20]; (3) IVs with an F-statistic less than 10, generally considered weak, were excluded to avoid instability and bias in effect estimation [21]; (4) SNPs strongly associated with the ou tcome variable ($P < 5 \times 10^{-8}$) were also excluded to prevent direct causal interference with the outcome [22]; (5) Cis-protein quantitative trait loci (cis-pQTLs) spanning a gene range of ±1Mb were selected. Located at or near the gene encoding the target proteins, cis-pQTLs are favored for their substantial contribution to explaining protein expression by directly regulating transcription, mRNA splicing, or translation, compared to trans-pQTLs, which act at a distance and may have more complex or indirect effects [23]. This selection criterion enhances the power of our study by

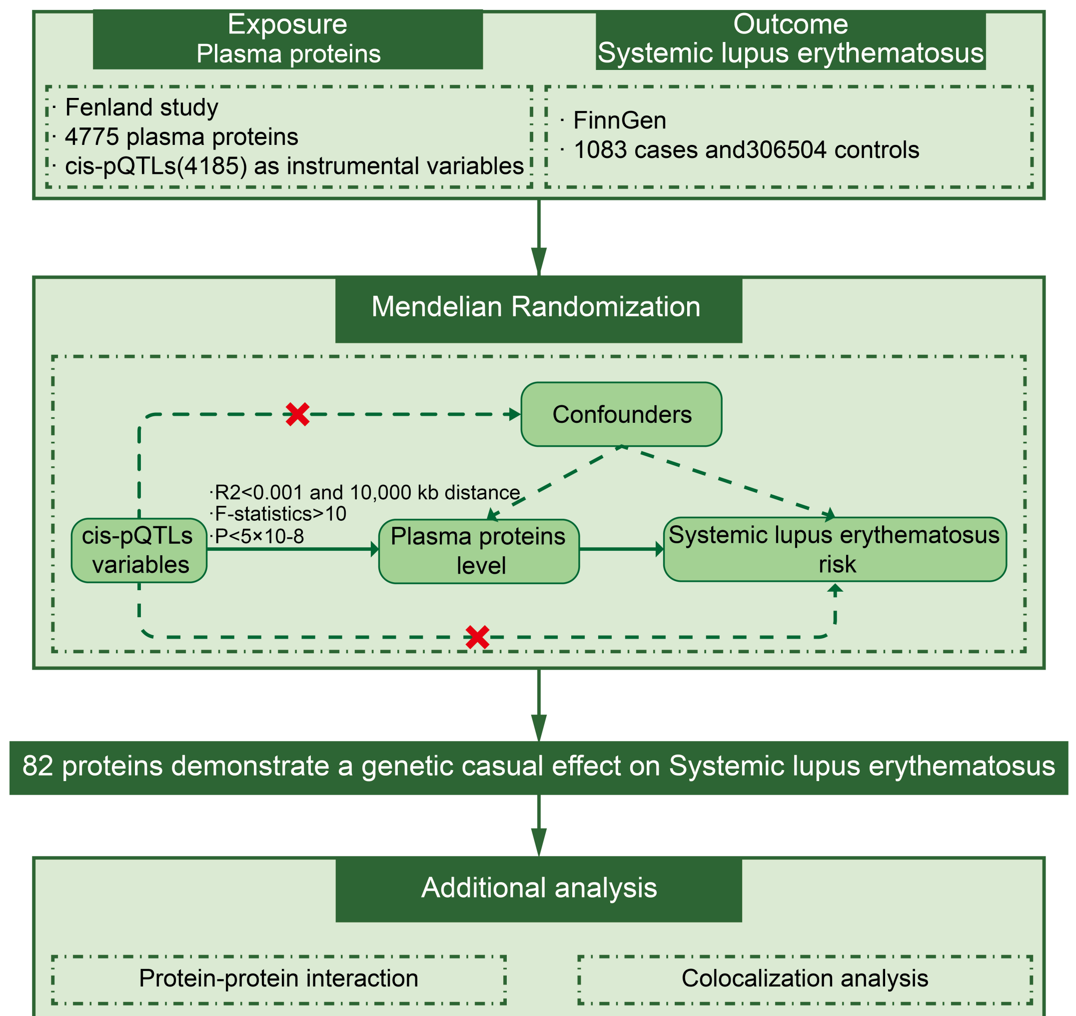


Figure 1. Flow Chart of the Overall Study Design. This study examines the potential genetic causal effects of plasma proteins on the risk of SLE using MR. The exposure (plasma proteins) was assessed using data from the Fenland study, comprising 4,775 plasma proteins. The outcome (SLE) was analyzed using data from the FinnGen study, which included 1,083 cases and 306,504 controls. Cis-pQTLs variables with specific criteria were used to assess the causal relationship. The analysis revealed 82 proteins demonstrating a genetic causal effect on SLE risk. Additional analyses were conducted on protein-protein interaction and colocalization to further validate the findings.

ensuring that the genetic variants selected are likely to have a direct and significant impact on protein expression, reducing the likelihood of bias due to unrelated genetic effects.

MR Analysis and Sensitivity Analysis

In this study, we conducted two-sample MR analysis using R software (version 4.3.3) and the "TwoSampleMR" package, employing various statistical methods to assess the potential causal relationship between circulating proteins and the risk of SLE. We employed the inverse variance weighted (IVW) method as the primary analytical tool when two or more IVs were available. Additionally, when the number of IVs was three or more, the weighted median (WM) and Mendelian randomization-Egger (MR-Egger) methods were also implemented. For proteins represented by a single IV, the Wald ratio method was applied to estimate the change in the log odds ratio of SLE risk per one standard deviation (SD) increase in protein levels [24]. Additionally, we performed sensitivity analysis using Cochran's Q test, MR-Egger, and MR-PRESSO methods. The Cochran's Q statistic was used to assess heterogeneity among the selected IVs, with a $P < 0.05$ indicating significant heterogeneity. A significant intercept in the MR-Egger method suggested potential pleiotropy, which was considered if the $P < 0.05$ [25]. The MR-PRESSO method, utilized via the "MR-PRESSO" package, aimed to identify and remove SNP outliers with horizontal pleiotropy. $P < 0.05$ in the MR-PRESSO global test typically indicates the presence of horizontal pleiotropy in the IVs. However, when the number of SNPs is small (nSNP < 3), this method may be insufficient for effective heterogeneity and pleiotropy analysis [26]. Lastly, the MR-Steiger test was applied to evaluate directional causality by comparing the proportion of variance explained by the IVs in relation to both the exposure and outcome variables, thus assessing the suitability of the IVs [27]. In our analysis, $P < 0.05$ for the MR-Steiger test was considered indicative of a valid causal direction. These multiple sensitivity analyses ensure that our findings are robust to violations of the MR assumptions, minimizing the risk of false-positive causal associations.

pQTL-GWAS Co-localization Analysis

To determine whether protein expression levels and SLE risk share causal variants within the same genomic region, we performed a colocalization analysis using the "coloc" R package with default prior probabilities [28]. Bayesian methods were applied to each cis-gene locus of the proteins to evaluate five mutually exclusive hypotheses: (1) No significant association with either trait (H0); (2) Associated only with protein levels (H1); (3) Associated only with SLE risk (H2); (4) Association

with both traits, driven by distinct causal variants (H3); (5) Both traits driven by the same causal variant (H4). In our analysis, co-localization was deemed supported when the posterior probability of sharing pathogenic variants (pph4) exceeded 0.6 [29].

PPI Network

To enhance our understanding of the interactions between proteins, we constructed a PPI network using the STRING database (version 11.5, https://cn.string-db.org/), a comprehensive resource that integrates experimental data, computational predictions, and text mining to catalog protein-protein interactions [30]. We developed the PPI network with a minimum interaction threshold of 0.4 (medium confidence), maintaining other parameters at their default settings. The PPI network is essential for visualizing protein interactions and uncovering potential signaling pathways involved in SLE.

Results

Circulating proteins and SLE risk mendelian analysis results

In this study, due to the stringent selection criteria for IVs, only 1581 of the 4,775 circulating proteins assessed in the Fenland study were included in the analysis. This rigorous filtering ensures that the remaining proteins are associated with high-quality, independent genetic instruments, minimizing the risk of bias. MR analysis revealed that 82 plasma proteins were potentially causally associated with SLE risk ($P < 0.05$) as shown in Figure 2. This substantial number of proteins offers valuable insights into the complex interplay of molecular factors contributing to SLE. Specifically, high expression of 46 proteins and low expression of 36 proteins are positively correlated with an increased risk of SLE. Additionally, for proteins with at least three SNPs (nSNP ≥ 3), 13 proteins were further validated by the WM method as being associated with SLE risk ($P < 0.05$) (Table S1).

The minimum F-statistic for the selected IVs for each protein was 23.926, far exceeding the threshold of 10, confirming their strength as robust instruments. The p-values of the Steiger test ranged from 0 to 9.01E-06, affirming that the directionality of the IVs is consistent with the fundamental assumptions of the MR analysis. Additionally, the MR-Egger intercept tests for each protein indicated no evidence of horizontal pleiotropy ($P > 0.05$), with further details available in Table S1, supporting the validity of our causal inferences.

Co-localization Analysis

Bayesian co-localization analysis was conducted on 82 circulating proteins that showed statistically significant associations, encompassing both upstream and downstream regions (detailed results are presented in Table S2). Co-localization analysis is a crucial step in understanding the genetic mechanisms that may underlie both the exposure (protein levels) and the outcome (SLE). The analysis revealed co-localization between SLE and several proteins, namely PDHX (pph4 = 0.67), CTSF (pph4 = 0.64), and TNFAIP3 (pph4 = 0.66), suggesting that these proteins may share common genetic variants with SLE (Figure 3).

PPI networks

A total of 82 proteins ($P < 0.05$) were entered into the STRING database to construct a protein network. Given the study's threshold for minimum interaction strength of 0.4, only 50 imported proteins successfully formed a network with other supplementary proteins, collectively comprising 82 nodes and 54

Figure 2. Mendelian Randomization Analysis Identified 82 Plasma Proteins Potentially Causally Linked to SLE Risk (p < 0.05). (A) Presents the analysis for proteins with a single associated SNP (nSNP = 1) using the Wald ratio test in the Mendelian Randomization (MR) analysis. (B) Depicts proteins with multiple associated SNPs (nSNP > 1) using the Inverse Variance Weighted (IVW) method in the MR analysis.

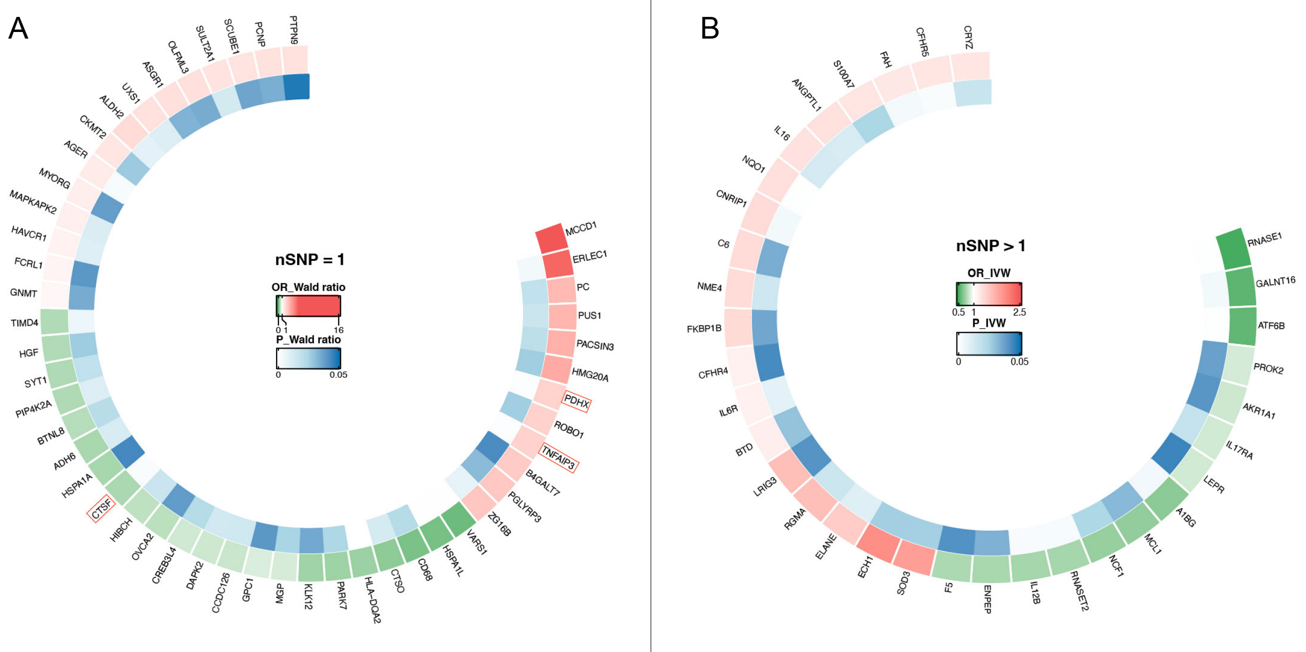
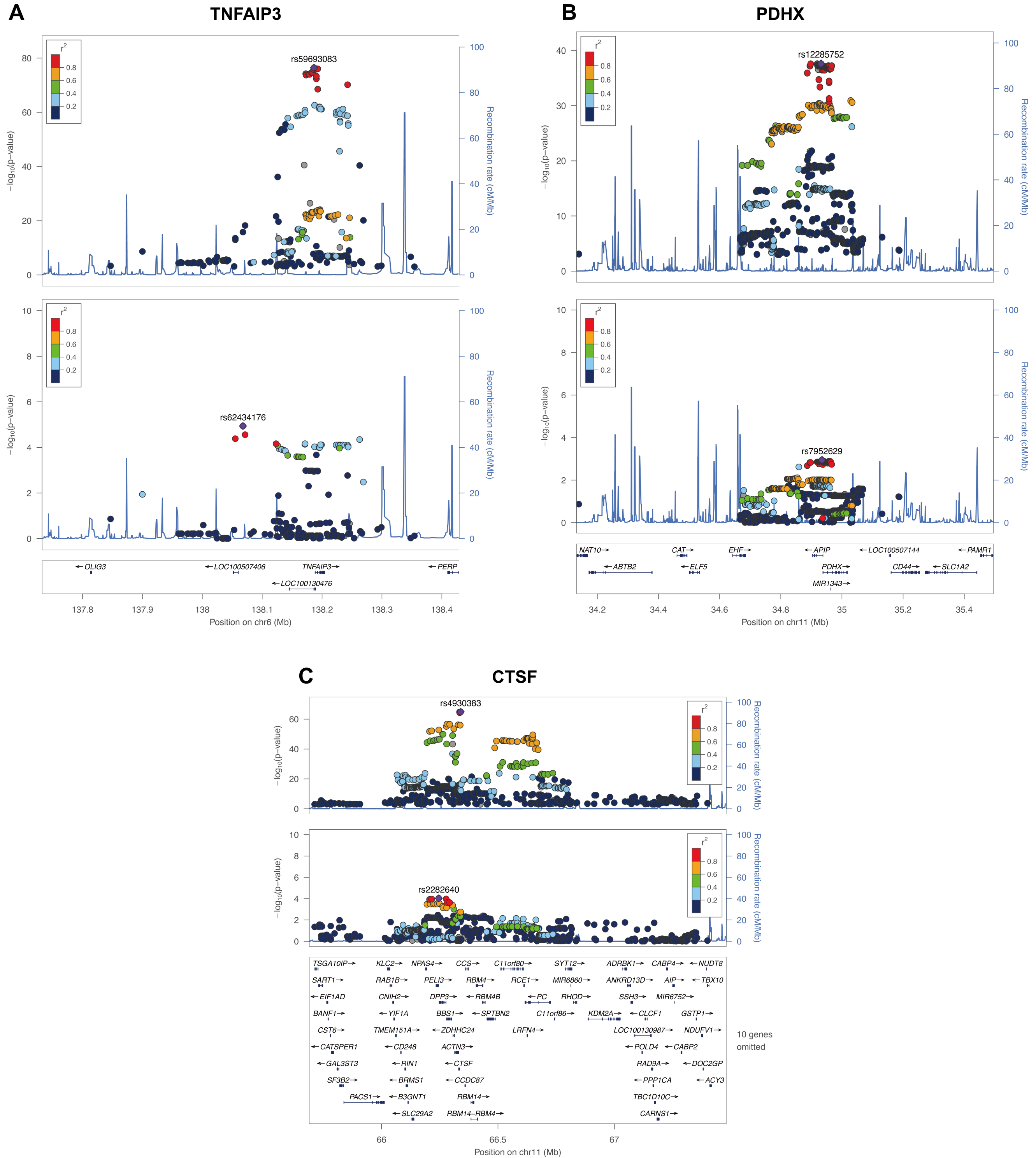


Figure 3. Colocalization Analysis of TNFAIP3, PDHX, and CTSF with SLE Risk. (**A**) Illustrates the co-localization pattern of TNFAIP3 with SLE; the upper image shows pQTLs for TNFAIP3 plasma protein levels, and the lower image displays genetic associations with SLE, with key variant rs59693083 exhibiting significant colocalization. (**B**) Depicts the co-localization pattern of PDHX with SLE; the upper image presents pQTLs for PDHX plasma protein levels, and the lower image shows genetic associations with SLE, with key variant rs12289762 demonstrating significant colocalization. (**C**) Presents the co-localization pattern of CTSF with SLE; the upper image displays pQTLs for CTSF plasma protein levels, and the lower image illustrates genetic associations with SLE, with key variant rs4920540 showing significant colocalization, indicating shared causal variants for protein expression and SLE across all panels.



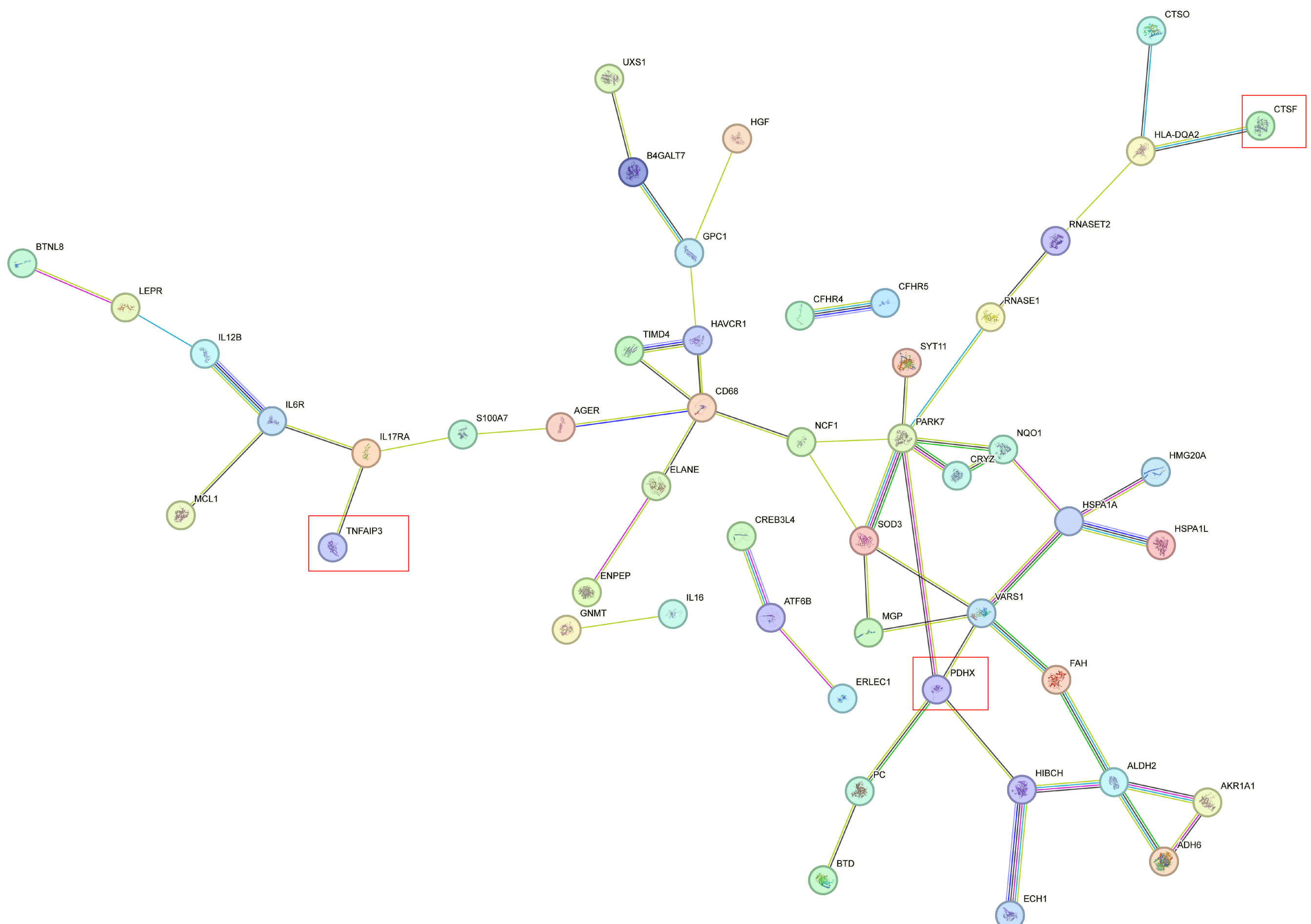
edges (Figure 4). Subsequent network functional enrichment analysis (Figure S1) identified several proteins significantly involved in biological processes such as inflammatory response and immune system regulation, with PFDR values of 1.1e-04 and 4.8e-04, respectively. These processes are intimately connected to the pathophysiology of SLE [31, 32], as chronic inflammation and immune dysregulation are hallmarks of the disease.

Discussion

This proteomics MR study investigated the causal relationships between 4775 plasma proteins and the risk of SLE, leveraging large-scale pQTL and GWAS datasets to overcome limitations of previous observational studies. Employing stringent selection criteria, we identified 82 plasma proteins significantly associated with SLE risk. Notably, proteins such as TNFAIP3, PDHX, and CTSF appear to share the same causal variants as the disease, as evidenced by colocalization analysis. The identification of these proteins highlights their potential as novel therapeutic targets and biomarkers for early diagnosis of SLE, addressing the unmet need for more effective and personalized treatments.

TNFAIP3 is an ubiquitin-editing enzyme extensively documented to act as an endogenous negative feedback regulator of inflammatory responses by inhibiting NF-κB signaling pathway activity [33, 34]. However, TNFAIP3 also promotes the phosphorylation of receptor-interacting protein 3 (RIP3) through deubiquitination [35], thereby activating the NLRP3 inflammasome pathway, which contributing to the development of lupus nephritis [36]. This dual role of TNFAIP3 as both an anti-inflammatory and pro-inflammatory mediator highlights its complex role in SLE pathogenesis. Additionally, various GWAS studies across different populations have demonstrated that SNPs at the TNFAIP3 locus are associated with susceptibility to SLE [37]. For instance, the rs2230926 SNP alters the amino acid sequence of the A20 protein (from phenylalanine to cysteine), diminishing its capacity to inhibit TNF-induced NF-κB activation. This alteration compromises the inflammatory control in individuals carrying this risk allele, thereby heightening their susceptibility to SLE [38, 39]. Additionally, cohort studies have associated the TNFAIP3 rs5029939 genetic polymorphism with SLE susceptibility and potential impacts on its clinical phenotype [39]. Notably, this study identifies for the first time that rs59693083 (located in the TNFAIP3 promoter [40]) escalates the risk of SLE, offering new insights into the pathogenesis and clinical treatment of the disease.

Figure 4. Protein-Protein Interaction (PPI) Network Illustrating Relationships Between Plasma Proteins ($p < 0.05$) Associated with Systemic Lupus Erythematosus (SLE) Risk. Each node represents a plasma protein, and edges between the nodes indicate direct interactions. The greater the number of edges, the stronger the interactions between the proteins. Notable proteins such as TNFAIP3, PDHX, and CTSF are highlighted in red.



PDHX, a crucial component of the pyruvate dehydrogenase complex (PDC), primarily facilitates the conversion of pyruvate into acetyl-CoA, bridging glycolysis to the Krebs cycle [41]. Research indicates that the 11p13 locus, situated between PDHX and CD44, is linked to genetic susceptibility to SLE. This region contains multiple regulatory sites, which potentially affect the expression and function of both PDHX and CD44, consequently influencing immune regulation and inflammatory responses in SLE [42]. This aligns with our MR results. Intriguingly, high PDHX expression has also been associated with diminished immune cell infiltration in the tumor microenvironment [43], suggesting that PDHX's role in SLE pathogenesis might be more complex than previously understood. These insights necessitate further basic and clinical studies to elucidate the underlying mechanisms.

CTSF is a lysosomal cysteine protease that plays a role in various physiological processes, including antigen processing [44]. In clear cell renal carcinoma (ccRCC) studies, CTSF expression has been found to inversely correlate with the infiltration of immune cells and the expression of MHC molecules such as TAP1 and TAP2 [45]. Our MR results show a negative correlation between CTSF and SLE risk, suggesting that CTSF may influence SLE susceptibility. Additionally, cysteine cathepsins (Cts) have been implicated in the hydrolysis of the extracellular matrix (ECM), processing cytokines, chemokines, and cell adhesion molecules, which are critical in inflammatory responses [46]. Cts may mitigate inflammation triggered by cellular debris by degrading damaged organelles and proteins. Although the link between CTSF and SLE risk has not been widely studied, the causal relationship identified in this study warrants further investigation into CTSF's specific role and mechanisms in SLE, which could uncover new therapeutic targets.

This study employed a large-scale dataset for MR analysis to enhance result reliability. In the initial phases, we selected cis-pQTLs for inclusion due to their typical proximity to or within genes encoding proteins, thus directly regulating protein expression by affecting transcription, translation, degradation, stability, or activity. This reduces the likelihood of pleiotropy compared to trans-pQTLs, strengthening the validity of our causal inferences. Additionally, our team utilized various statistical methods such as the Wald ratio, IVW, WM, and MR-Egger to bolster the robustness of the MR analysis, with sensitivity analyses confirming no evidence of horizontal pleiotropy or weak instrument bias. Finally, we performed PPI network analysis to validate the links between protein-related biological processes and the disease's pathological processes.

Despite the strengths of our study, several limitations must be acknowledged. Firstly, it relies on population data from individuals of European ancestry, which may limit the generalizability of the findings to other ancestral groups, as genetic associations and protein levels can vary by ethnicity. Future studies should replicate these findings in diverse populations, including African, Asian, and Hispanic cohorts, to ensure global applicability. Secondly, while the Fenland study included a broad range of circulating proteins, our stringent selection criteria for IVs might have excluded other potentially relevant target proteins. Moreover, protein expression and function are influenced by various factors, such as environmental interactions and epigenetic modifications, which were not comprehensively accounted for in our analysis. Furthermore, there is limited research on CTSF and its relationship with SLE, and much of the proposed mechanisms discussed in this paper are primarily based on inference from related cathepsins or other diseases. Therefore, further research —including in vitro studies with SLE patient samples and in vivo murine models—is needed to establish the direct relationship between CTSF and SLE, elucidate its specific mechanisms, and evaluate its potential as a therapeutic target.

Conclusion

Overall, this study offers a comprehensive assessment of the causal relationships between circulating proteins and SLE, further confirming their critical roles in the initiation and progression of the disease. By combining MR, colocalization, and PPI network analyses, we identified 82 proteins with potential causal associations with SLE. Notably, proteins such as TNFAIP3, PDHX, and CTSF are identified as likely candidates for new therapeutic targets. These findings contribute to the growing body of knowledge on the molecular mechanisms underlying autoimmune diseases, offering promising directions for the development of precision therapies for SLE. However, additional research is essential to unravel the complex mechanisms linking these candidate proteins with SLE risk, a crucial step in validating their potential clinical relevance.

Abbreviations

B-lymphocyte stimulator: BLyS; cysteine cathepsins: Cts; Cis-protein Quantitative Trait Loci: cis-pQTLs; data-dependent acquisition: DDA; data-independent acquisition: DIA; Extracellular Matrix: ECM; enzyme-linked immunosorbent assays: ELISA; Food and Drug Administration: FDA; Genome - Wide Association Study: GWAS; I interferon receptor 1: IFNAR1; Instrumental Variables: IVs; Inverse Variance Weighted: IVW; Linkage Disequilibrium: LD; Mendelian Randomization: MR; Mendelian Randomization-Egger: MR-Egger; protein Quantitative Trait Loci: pQTL; Protein-Protein Interaction: PPI; Receptor-Interacting Protein 3: RIP3; Single Nucleotide Polymorphisms: SNPs; Systemic Lupus Erythematosus: SLE; Trans-protein Quantitative Trait Loci: trans-pQTLs; Weighted Median: WM.

Author Contributions

Xinzhen Zhao: Writing – review & editing, Writing – original draft, Conceptualization, Visualization, Formal analysis. Yinying Chai: Writing – review & editing, Validation, Supervision, Data curation, Formal analysis. Qianran Hong: Writing – review & editing, Writing – original draft, Validation, Funding acquisition, Formal analysis. Yuxuan Song: Writing – review & editing, Validation, Funding acquisition, Data curation. Yibo He: Writing – review & editing, Conceptualization, Supervision. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

Not Applicable.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

The data that supports the findings of this study are available in the supplementary material of this article.

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