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Unveiling Novel Protein Biomarkers for Psoriasis Through Integrated Analysis of Human Plasma Proteomics and Mendelian Randomization

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Background: Current pharmacological treatments for psoriasis are generally non-specific and have significant limitations, particularly in the realm of targeted biologic therapies. There is an urgent need to identify and develop new therapeutic targets to improve treatment options.

Objective: The aim of this study was to explore the proteome associated with psoriasis in large population cohorts to discover novel biomarkers that could guide therapy.

Methods: We analyzed data from 54,306 participants enrolled in the UK Biobank Pharmacological Proteomics Project (UKB-PPP). We investigated the relationship between 2923 serum proteins and the risk of psoriasis using multivariate Cox regression models initially. This was complemented by two-sample Mendelian randomization (TSMR), Summary-data-based Mendelian Randomization (SMR), and coloc colocalization studies to identify genetic correlations with protein targets linked to psoriasis. A protein scoring system was created using the Cox proportional hazards model, and cumulative risk curves were generated to analyze psoriasis incidence variations.

Results: Our study pinpointed 62 proteins significantly linked to the risk of developing psoriasis. Further analysis through TSMR narrowed these down to ten proteins with strong causal relationships to the disease. Additional deep-dive analyses such as SMR, colocalization, and differential expression studies highlighted four critical proteins (MMP12, PCSK9, PRSS8, and SCLY). We calculated a protein score based on the levels of these proteins, with higher scores correlating with increased risk of psoriasis.

Conclusion: This study's integration of proteomic and genetic data from a European adult cohort provides compelling evidence of several proteins as viable predictive biomarkers and potential therapeutic targets for psoriasis, facilitating the advancement of targeted treatment strategies.

Keywords: psoriasis, plasma proteomics, prospective studies, Mendelian randomization

Introduction

The prevalence of psoriasis is notably high.[1] The disease's pathophysiology is complex and not fully understood. Current standard therapies mainly include immunosuppressants and broad anti-inflammatory drugs, which generally provide only symptomatic relief. Although these treatments can reduce symptoms, they often do not prevent disease recurrence, leading to substantial physical, psychological, and financial strain on patients, as well as significant healthcare expenses. While TNF-α inhibitors, IL-23 subunit antagonists, IL-17A and its receptor antagonists, and JAK inhibitors are employed in managing psoriasis, they carry the risk of adverse effects, such as increased susceptibility to recurrent infections.[2] This underscores the critical necessity for discovering and developing new therapeutic targets.[3,4] Enhancing our understanding

Received: 19 August 2024
Accepted: 26 November 2024
Published: 7 December 2024

and treatment strategies for psoriasis is essential to improve patient outcomes, reduce healthcare burdens, and address the shortcomings and risks associated with existing therapies.

In this study, we used a longitudinal cohort of 54,306 participants from the UK Biobank Pharmacological Proteomics Project (UKB-PPP) to perform a comprehensive analysis of observed and genetic correlations between 2923 proteins and psoriasis susceptibility. By leveraging single-cell transcriptome data, we examined the expression patterns of identified drug targets and delved into potential mechanisms driving the pathogenesis of psoriasis.

Methods

Study Design and Participants

The study design is detailed in Figure 1. The UK Biobank is a population-based cohort comprising approximately 502,370 volunteers, who were aged 40 to 69 years at the onset of the study.[5] Recruitment occurred at 22 assessment centers throughout the UK from 2006 to 2010. At enrollment, participants gave informed consent, underwent physical examinations, and provided extensive information about their socio-demographic characteristics, lifestyle factors, medical histories, and medication usage, in addition to donating blood samples. The tracking of participant events was meticulously maintained via electronic health records up to July 2023.

The UKB-PPP, supported by 13 biopharmaceutical companies, is dedicated to generating blood-based proteomic data for a subset of the UK Biobank cohort.[5,6] This subset included 54,306 participants, of whom 46,673 (85.9%) were randomly selected from the initial cohort, 6385 (11.8%) were specifically chosen by consortium members based on criteria such as disease status or genetic lineage, and 1268 (2.3%) were selected due to their participation in multiple

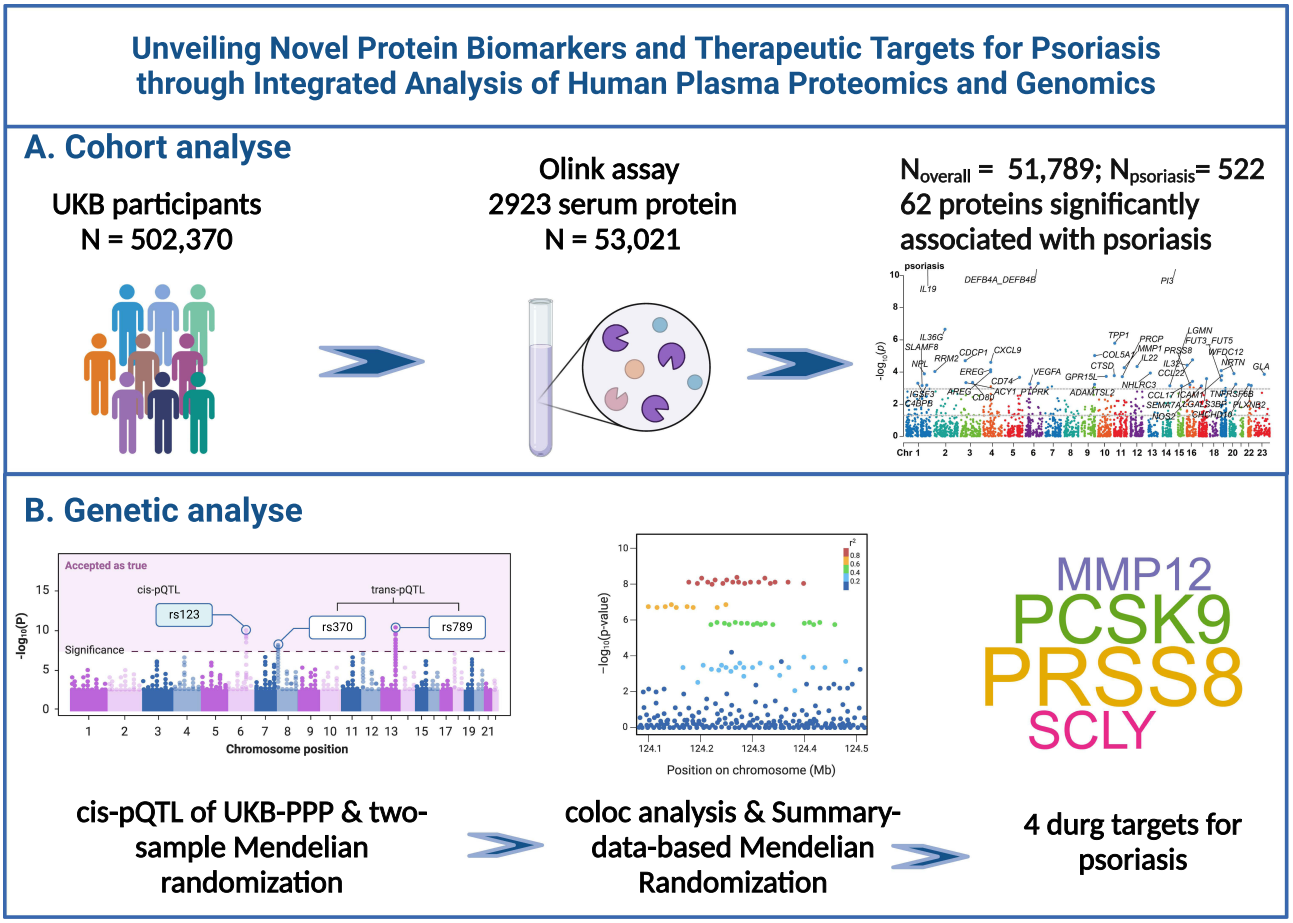

Figure 1 Research Design and Analytical Flowchart. (**A**) Schematic of the Prospective Cohort Analysis Process. (**B**) Schematic Depicting the Processes for Mendelian Randomization, Colocalization, and Supplementary Genetic Analyses.

COVID-19 case-control imaging studies. Following rigorous quality control, data from 51,789 participants were considered suitable for inclusion in our analysis, as shown in Figure 1. Ethical approval was granted by the North West Multicenter Research Ethics Committee, and all study procedures and analyses adhered to the guidelines of UK Biobank Application Number 93810.

Protein Quantification and Proteomic Data Processing Within the UK Biobank

The protocols for protein quantification and data processing utilized in the UKB-PPP are elaborated in earlier publications.[7] In brief, blood samples collected at the start of the UKB-PPP were processed using the Olink Explore 1536 platform (Olink Proteomics, Inc.; Waltham, MA). This system employs proximity extension assay (PEA) technology to measure 2923 protein analytes distributed over four distinct panels (detailed as eTable 1 in Supplement 1). Owing to high data omission rates, three proteins—GLIPR1 (99.7% data omitted), NPM1 (74.0% omitted), and PCOLCE (63.6% omitted)—were excluded from the final cohort analysis. For the evaluation of the remaining proteins, the k-nearest neighbors (k-NN) algorithm was utilized for imputing missing data, with k set at 10.[8] Following this, Z-score normalization was applied to all 2920 protein markers to ensure uniformity before their inclusion in subsequent analyses.

Assessment of Outcome

The identification of outcomes primarily relied on hospital records sourced from the Hospital Episode Statistics in England, the Patient Episode Database for Wales, and the Scottish Morbidity Records. These sources were supplemented with self-reported diagnoses, primary care records, and mortality data from the death registry. Diagnoses of psoriasis were confirmed using the International Classification of Diseases (ICD-10: L40) Coding System. Participants who had self-reported psoriasis or were diagnosed via hospital admissions at the study's start were excluded from the analysis. Follow-up for each participant continued from their initial assessment date up to July 1, 2023, enabling a detailed longitudinal study of health outcomes.

Proteomic Association Analyses

To investigate the relationships between circulating protein levels and the incidence of psoriasis, primary analyses employed Cox proportional hazards models. These models were meticulously adjusted for several covariates to reduce potential confounding effects. Adjustments included body mass index (BMI), race, age, education level, gender, and average annual household gross income. Additionally, the frequency of alcohol consumption was accounted for as a covariate. The Townsend Deprivation Index, serving as a measure of socio-economic status, was included as a continuous variable in the analyses. Physical activity levels were quantified in metabolic equivalent (met-minutes) per week and treated as a continuous variable. The timing of blood collection was categorized by season into winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).

Mendelian Randomization Analysis

This study rigorously adheres to the "Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomisation (STROBE-MR)" guidelines,[9] as specified in eTable 2 of Supplement 1. The datasets used, originating from genome-wide association studies (GWAS) and protein Quantitative Trait Loci (pQTL), were all acquired from open-access databases that had received prior ethical approval. Comprehensive descriptions of all datasets utilized in this analysis are accessible in eTable 3 of Supplement 1. In our analysis, plasma protein levels in the UKB-PPP were defined as the exposure variable, with psoriasis identified as the outcome. The 'TwoSampleMR' package was employed for Mendelian Randomization (MR) analysis. For proteins linked by a single pQTL, the Wald ratio method was used. Conversely, the inverse variance-weighted MR (MR-IVW) method was implemented for proteins with multiple genetic instruments. The odds ratio (OR) indicates the increased risk associated with a one standard deviation (SD) increase in plasma protein levels.

To further validate our findings, summary-level genetic association data from various cohorts were used. This included data from the DECODE study, which involved 35,559 Icelandic participants,[10] and data from Pietzner et al,[11] involving a cohort of 10,708 Finnish participants. Additional validation was performed using the Meta cohort assembled by Zheng et al,[12] which consolidated data from five prior GWAS.[13–17]

Detailed methodologies for analyses such as MR (eFigure 1), SMR, Bayesian co-localization, and Phenome-Wide MR Analysis are outlined in the eMethods section of Supplement 1.[18–32]

Single-Cell RNA Sequencing Data Analysis

Single-cell RNA sequencing (scRNA-seq) datasets relevant to psoriasis were acquired from publicly available databases.[33] Detailed descriptions of each dataset, including origins and characteristics, are provided in eTable 4 of Supplement 1. We utilized the Seurat software package for dataset analysis, beginning with stringent quality control measures. This included the selection of cells with nFeature counts ranging from 200 to 5000 and less than 25% mitochondrial RNA content, effectively excluding low-quality or dying cells. After quality control, dataset integration was carried out using the Harmony package. This method is preferred for its ability to integrate data from various sources effectively while preserving biological variability. Post-integration, the datasets underwent normalization to adjust for technical differences, and dimensionality reduction was performed using Unified Manifold Approximation and Projection (UMAP). This process helps simplify the visualization of complex data in a lower-dimensional space, thereby aiding in the identification of cellular clusters. Following this, clustering was conducted, allowing cells to be categorized into distinct groups based on their gene expression profiles. These groups were subsequently annotated with specific cell markers, facilitating the identification of various cell populations within the datasets.

Development of the Protein Scoring System

The initial cohort was randomly segregated into a training set and a test set in a 7:3 ratio. The protein score for each participant in the training set was computed using the Cox proportional hazards model (PH model), expressed as EQN (where exp denotes the level of protein expression; β represents the regression coefficient from the multivariate Cox regression analysis; and EQN is the baseline hazard function). Participants were stratified into high and low protein score groups based on the median protein score. We then assessed the cumulative risk curves for these groups to examine disparities in psoriasis incidence. Utilizing the 'SurvivalROC' package in R software, we generated the receiver operating characteristic (ROC) curve and computed the corresponding area under the curve (AUC).

Statistical Analysis

In our initial analysis to explore the association between the plasma proteome and psoriasis, we utilized the Benjamini-Hochberg (BH) procedure to adjust P-values for multiple testing, effectively controlling the false discovery rate (FDR). We set an FDR threshold of less than 0.05 as the criterion for statistical significance. For the subsequent confirmatory Mendelian Randomization (MR) analysis, we continued to apply a significance threshold of P-values less than 0.05. Details regarding the development of drug targets are systematically categorized into clinical outcomes (Tclin) and chemical outcomes (Tchem). In addition, we extensively gathered information on drug targets, including their assessment in Phase II–IV clinical trials, from the DrugBank and OpenTargets databases. All computational and statistical analyses conducted in this study were performed using R software (version 4.3.1).

Results

The study included 51,789 participants from the UKB-PPP, whose demographics are outlined in Table 1. The majority of the cohort was white, comprising 47,859 participants (92%), with an average age of 56.8 years (standard deviation [SD] = 8.2 years). During the follow-up period, which had a median duration of 14.3 years (interquartile range [IQR] = 13.5–15.0 years), 522 participants (1.01%) developed incident psoriasis.

Observational Associations of Proteins with Psoriasis

The multivariable Cox regression analysis, adjusted for age, body mass index (BMI), gender, educational attainment, the Townsend Deprivation Index, annual household income, smoking status, race, frequency of alcohol consumption, levels of physical activity, and the season of blood collection, revealed significant associations between 62 proteins and the onset of psoriasis. These findings, which account for adjustments for the false discovery rate (FDR) (< 0.05), are illustrated in Figure 2 and detailed in eTable 5 of Supplement 1.

Table 1 Baseline Characterization of Participants in UKB

Variable	Overall, N = 51,789	Psoriasis-Free, N = 51,267	Psoriasis, N = 522	p-Value[a]
Age_when_attended, Mean (SD)	56.79 (8.21)	56.79 (8.22)	57.53 (8.00)	0.044
Sex, n (%)				0.5
Female	27,972 (54%)	27,697 (54%)	275 (53%)	
Male	23,817 (46%)	23,570 (46%)	247 (47%)	
BMI, Median (IQR)	26.78 (24.18, 29.91)	26.77 (24.17, 29.90)	27.40 (24.81, 30.67)	<0.001
Smoking_status, n (%)				<0.001
Current	5488 (11%)	5403 (11%)	85 (16%)	
Previous	18,039 (35%)	17,810 (35%)	229 (44%)	
Never	28,262 (55%)	28,054 (55%)	208 (40%)	
Race, n (%)				0.059
White	47,854 (92%)	47,355 (92%)	499 (96%)	
Asian_or_Asian_British	1872 (3.6%)	1858 (3.6%)	14 (2.7%)	
Black_or_Black_British	312 (0.6%)	309 (0.6%)	3 (0.6%)	
Mixed	963 (1.9%)	960 (1.9%)	3 (0.6%)	
Chinese	150 (0.3%)	149 (0.3%)	1 (0.2%)	
Other ethnic group	638 (1.2%)	636 (1.2%)	2 (0.4%)	
Income, n (%)				0.009
Less_than_18,000	13,485 (26%)	13,313 (26%)	172 (33%)	
18,000_to_30,999	13,673 (26%)	13,548 (26%)	125 (24%)	
31,000_to_51,999	12,660 (24%)	12,539 (24%)	121 (23%)	
52,000_to_100,000	9448 (18%)	9365 (18%)	83 (16%)	
Greater_than_100,000	2523 (4.9%)	2502 (4.9%)	21 (4.0%)	
Alcohol_intake_frequency, n (%)				0.002
Never	4485 (8.7%)	4431 (8.6%)	54 (10%)	
Occasionally	11,794 (23%)	11,688 (23%)	106 (20%)	
Sometimes	25,072 (48%)	24,846 (48%)	226 (43%)	
Daily	10,438 (20%)	10,302 (20%)	136 (26%)	
Summed_MET, Median (IQR)	1798.00 (798.00, 3612.00)	1797.00 (799.10, 3612.00)	1856.25 (773.25, 3531.00)	0.8
Townsend, Median (IQR)	−2.06 (−3.62, 0.77)	−2.06 (−3.62, 0.76)	−1.84 (−3.48, 1.24)	0.035
Education, n (%)				0.3
College or University degree	16,653 (32%)	16,502 (32%)	151 (29%)	
A levels/AS levels or equivalent	5712 (11%)	5660 (11%)	52 (10.0%)	
O levels/GCSEs or equivalent	10,737 (21%)	10,623 (21%)	114 (22%)	
CSEs or equivalent	2763 (5.3%)	2736 (5.3%)	27 (5.2%)	
NVQ or HND or HNC or equivalent	3435 (6.6%)	3406 (6.6%)	29 (5.6%)	
Other professional qualifications	2757 (5.3%)	2728 (5.3%)	29 (5.6%)	
None of the above	9136 (18%)	9022 (18%)	114 (22%)	
Prefer not to answer	596 (1.2%)	590 (1.2%)	6 (1.1%)	
Time, Median (IQR)	14.28 (13.54, 15.04)	14.29 (13.56, 15.05)	5.71 (2.88, 9.03)	<0.001

Note: [a]Wilcoxon rank sum test; Pearson's Chi-squared test.

Genetic Associations of Proteins with Psoriasis

The tow-sample MR was conducted to determine the causal impacts of specific proteins on psoriasis. From the 2920 proteins analyzed within the UKB-PPP, 2030 cis-pQTLs were identified, detailed in eTable 6 of Supplement 1. Out of the 62 proteins highlighted by the Cox analysis, 59 exhibited cis-pQTLs with F statistics exceeding 10, suggesting robust instrumental strength. MR analysis and assessments of causality directions pinpointed 10 proteins as having causal links to psoriasis among the 59 analyzed, as depicted in Figure 2 and detailed in eTable 7 of Supplement 1. Notably, nine proteins were identified as playing a detrimental role in the pathogenesis of psoriasis: CTSE, FAM13A, MMP12, PCSK9, PRSS8, RPA2, SCLY, SEPTIN8, and VEGFA, with AGER exhibiting a protective effect. Steiger filtering confirmed these

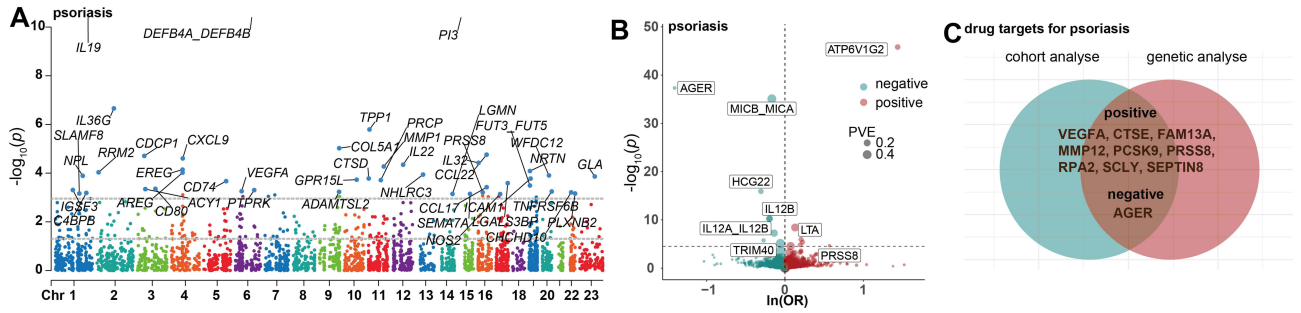

Figure 2 Identification of Potential Drug Targets for Psoriasis via Integrated Cohort and Mendelian Randomization Analyses. This figure provides a detailed visualization of our analytical methodology, beginning with a Manhattan plot (**A**) that illustrates the outcomes of the cohort analysis. Each point on this plot represents a unique protein, with the x-axis indicating the chromosomal location of the gene and the y-axis showing the p-values derived from multivariate Cox regression analysis. The region demarcated by two dotted lines near the x-axis represents the significance threshold ($p < 0.05$). Points surpassing this threshold, which exhibit p-values below 0.05 even after adjusting for the false discovery rate (FDR), are highlighted in blue and labeled with their corresponding protein names. Adjacent to this, a volcano plot (**B**) displays the results from cis-Mendelian Randomization (cis-MR) analysis by plotting each protein according to the effect size derived from MR analysis (x-axis) against its p-value (y-axis). Finally, a Venn diagram (**C**) delineates the overlap of significant findings from both the cohort and cis-MR analyses, with the names of the intersecting proteins detailed within the diagram.

directional associations. Further phenotypic analysis of significant cis-pQTLs associated with proteins causally linked to psoriasis showed no correlation with BMI, body fat percentage, smoking, or other known psoriasis risk factors, as documented in eTable 8 of Supplement 1. Three additional pQTL databases were used to validate the impact of four specific proteins on psoriasis, with consistent findings illustrated in Figure 3.

SMR analysis identified significant causal relationships for eight proteins, excluding CTSE and RPA2 from this subset. Refinement via the HEIDI test led to the exclusion of AGER and SEPTIN8 due to potential horizontal pleiotropy, as detailed in

exposure	cohort	OR(95% CI)	pvalue
AGER	Finland	0.89 [0.82;0.97]	0.011
AGER	UKB−PPP	0.24 [0.20;0.30]	<0.001
CTSE	UKB−PPP	1.06 [1.01;1.13]	0.032
FAM13A	UKB−PPP	1.45 [1.13;1.85]	0.003
MMP12	DECODE	1.06 [1.01;1.12]	0.022
MMP12	Finland	1.06 [1.00;1.12]	0.037
MMP12	meta	1.06 [1.01;1.11]	0.022
MMP12	UKB−PPP	1.05 [1.00;1.11]	0.037
PCSK9	DECODE	1.08 [1.00;1.17]	0.063
PCSK9	Finland	1.09 [1.00;1.18]	0.043
PCSK9	meta	1.07 [1.00;1.16]	0.060
PCSK9	UKB−PPP	1.08 [1.01;1.15]	0.029
PRSS8	DECODE	2.49 [1.63;3.79]	<0.001
PRSS8	UKB−PPP	1.77 [1.36;2.30]	<0.001
RPA2	UKB−PPP	1.37 [1.00;1.88]	0.049
SCLY	UKB−PPP	1.23 [1.04;1.45]	0.017
SEPTIN8	UKB−PPP	1.39 [1.12;1.72]	0.003
VEGFA	DECODE	1.06 [1.03;1.09]	<0.001
VEGFA	Finland	1.04 [1.00;1.07]	0.037
VEGFA	meta	1.04 [1.00;1.09]	0.035
VEGFA	UKB−PPP	1.05 [1.00;1.09]	0.035

Figure 3 Validation of Candidate Protein Causality for Psoriasis Using Three Additional pQTL Databases.

eTable 9 of Supplement 1. Of the six proteins further examined, PRSS8 showed strong genetic co-localization, with a posterior probability for hypothesis 4 (PP.H4) of 0.97, as demonstrated across various priors and analytical windows. This evidence, suggesting a substantial likelihood of shared causal genetic variants affecting both protein levels and the risk of developing psoriasis, is presented in eFigure 2 of Supplement 1 and eTable 10 of Supplement 1.

Phenome-Wide MR Analysis

In recognizing the crucial impact of drugs delivered through the bloodstream, our study investigated the effects of six blood protein expressions on a wide array of health conditions. We conducted a comprehensive Mendelian Randomization (MR) analysis across 1402 conditions and traits cataloged in the UK Biobank. Our findings identified significant associations: PCSK9 is linked with dyslipidemia and cardiovascular diseases, marking it as a significant risk factor. Additionally, PRSS8 was observed to exert a detrimental effect on nasal polyps, as illustrated in eFigure 3 of Supplement 1, with significance determined at a P-value threshold of less than 0.05/1402, equating to 3.57e-5.

Differential Expression Analysis and Cell-Type Specificity Expression in Skin Tissue

The differential analysis of protein groups revealed that all six drug targets for psoriasis were significantly overexpressed in the blood of patients with psoriasis, as shown in eFigure 4 in Supplement 1. To explore whether the genes encoding these six circulating proteins exhibit cell type-specific enrichment in dermatological tissues, we carried out a single-cell type expression analysis using scRNA-seq data from the Gene Expression Omnibus (GEO). From the psoriasis dataset GSE173706, 13 distinct cell types were identified, as illustrated in Figure 4A. Expression markers specific to each cell type are displayed in Figure 4B. Proteins such as SCLY, FAM13A, and VEGFA showed uniform expression across various skin cells, including keratinocytes, fibroblasts, and endothelial cells. In contrast, PCSK9 and PRSS8 demonstrated specific expression in keratinocytes, while MMP12 was uniquely expressed in monocytes and macrophages. Further RNA-Seq differential expression analysis indicated that MMP12, PCSK9, PRSS8, and SCLY exhibited significantly elevated expression levels in psoriatic skin lesion tissues compared to normal tissues. Conversely, FAM13A and VEGFA were notably less expressed in psoriatic lesions.

Identification and Stratification of Drug Targets

Our methodology for classifying drug targets is based on the accumulation of evidence from multiple analytical approaches. In our stratification system:

- Tier-1 Drug Targets (n = 10, Table 2): These targets are identified when results from both cohort analysis and Two-Sample Mendelian Randomization (TSMR) analysis are concordant in their directional outcomes. These targets represent the initial level of evidence linking them to potential therapeutic implications.
- Tier-2 Drug Targets (n = 6, Table 2): Targets advance to tier-2 when, in addition to meeting the criteria for tier-1, they also show positive results in either Summary-data-based Mendelian Randomization (SMR) and Heterogeneity in Dependent Instruments (HEIDI) analysis or colocalization tests (coloc). This additional evidence suggests a stronger genetic basis for their role in the disease.
- Tier-3 Drug Targets (n = 4, Table 2): The highest classification, tier-3, is reserved for targets that not only fulfill the criteria for tier-2 but also demonstrate differential expression in both proteomic and single-cell transcriptomic analyses, with the direction of effect consistently aligned. This comprehensive level of evidence supports their potential as highly relevant therapeutic targets, integrating genetic, proteomic, and cellular data.

Evaluating the Druggability of Potential Therapeutic Targets

In terms of druggability assessment, three proteins (MMP12, PCSK9, VEGFA) within this network have been identified as targets in drug development efforts, as detailed in Table 2. Specifically, Marimastat, a drug targeting MMP12, has successfully completed Phase III clinical trials and received approval for treating breast and lung cancers. PCSK9 inhibitors, such as Alirocumab and Evolocumab, have been authorized for managing hyperlipidemia and associated

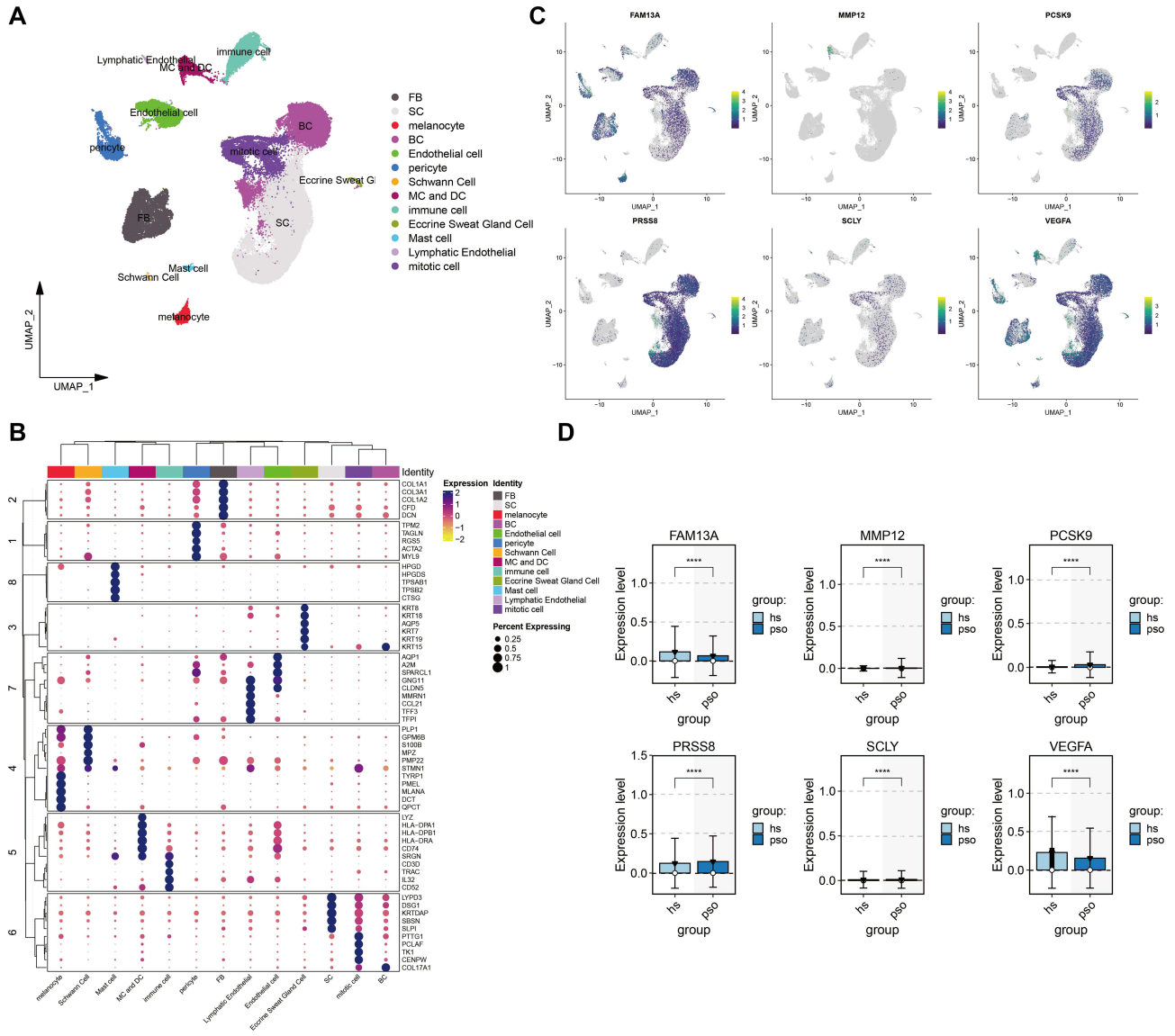

Figure 4 Single-Cell Transcriptomic Profiling of Psoriasis Drug Targets. (**A**) UMAP Visualization: This panel showcases a UMAP (Uniform Manifold Approximation and Projection) dimensionality reduction of the single-cell transcriptome dataset derived from psoriatic tissues. Each point in the visualization represents an individual cell, with distinct colors indicating different cell clusters, providing a visual map of cellular diversity within psoriatic lesions. (**B**) Cell Marker Cluster Heatmap: This heatmap facilitates the categorization of cells by displaying clustering of cell markers. Different color modules represent various cell groups, and the size of each circle within the heatmap reflects the relative abundance of specific genes within these groups. Key cell types are labeled to enhance clarity and understanding of the cellular landscape, including FB (fibroblasts), BC (basal keratinocytes), SC (spinous cells), MC (macrophages), and DC (dendritic cells). (**C**) Feature Plots for Psoriasis Targets: In this section, the expression patterns of genes associated with six identified psoriasis drug targets are depicted. Each point on the plot corresponds to a single cell, with variations in color intensity indicating the level of gene expression. This visual representation helps pinpoint which cells primarily express these target genes, aiding in the identification of potential intervention points. (**D**) Violin Plots of Gene Expression: These plots provide a detailed view of the differential expression of genes linked to the six psoriasis targets between psoriasis patients and normal controls. The shape of the violin plot highlights the distribution of expression levels, while black inverted triangles mark the mean expression levels, offering insights into the upregulation or downregulation of these genes in psoriatic versus normal tissue.

complications. For VEGFA, drugs like Ranibizumab and Pegaptanib have advanced through Phase IV clinical trials for Macular Degeneration treatment.

Development of a Protein Scoring System for Psoriasis

The expression levels of four biomarker proteins were categorized into quartiles, and cumulative risk curve analysis was performed. The results indicated that, with the exception of SCLY, increases in the expression levels of the remaining three proteins significantly elevated both the incidence and risk of psoriasis (Figure 5A–D). Based on these findings, a protein score was developed using the results from a multivariate Cox regression analysis of the four proteins. This

Table 2 Comprehensive Evidence to Identify Drug Targets in Psoriasis

Incident Psoriasis												
Protein	**Cohort Analyse**		**Genetic Analyse**				**Expression**		**Drug Development**			
	HR* (95% CI)	**p-Value/FDR**	**TSMR**		**SMR**	**Coloc**	**ScRNA-seq and Serum Protein**	**Tier**	**Drug Name**	**Outcomes**	**Actions**	**Trial Phase**
			OR (95% CI)	**p-Value**								
AGER	0.91 [0.83;1.00]	4.20e-06/0.00112	0.24 [0.20;0.30]	<0.00001	×	×	×	1				
CTSE	1.10 [1.01;1.20]	3.05e-06/0.00099	1.06 [1.01;1.13]	0.03169	×	×	√	1				
FAM13A	1.09 [1.01;1.19]	3.64e-06/0.00107	1.45 [1.13;1.85]	0.00308	√	×	×	2	/	/	/	/
MMP12	1.14 [1.04;1.25]	5.91e-06/0.00133	1.05 [1.00;1.11]	0.03656	√	×	√	3	Marimastat	Breast/Lung cancer	Inhibitors	III
PCSK9	1.09 [1.00;1.20]	4.88e-06/0.00119	1.08 [1.01;1.15]	0.02887	√	×	√	3	Alirocumab; Evolocumab; Inclisiran	LDL-C	Inhibitors	Approved
PRSS8	1.18 [1.07;1.30]	6.15e-05/0.00819	1.77 [1.36;2.30]	0.00002	√	√	√	3	/	/	/	/
RPA2	1.09 [1.01;1.18]	2.25e-06/0.00097	1.37 [1.00;1.88]	0.04924	×	×	×	1				
SCLY	1.15 [1.05;1.25]	2.31e-06/0.00097	1.23 [1.04;1.45]	0.01687	√	×	√	3	/	/	/	/
SEPTIN8	1.13 [1.04;1.23]	2.96e-06/0.00099	1.39 [1.12;1.72]	0.00258	×	×	×	1				
VEGFA	1.16 [1.07;1.26]	5.50e-05/0.00767	1.05 [1.00;1.09]	0.03466	√	×	×	2	Ranibizumab; Pegaptanib	Macular Degeneration	Inhibitors	IV

https://doi.org/10.2147/PTT.S492205 DovePress

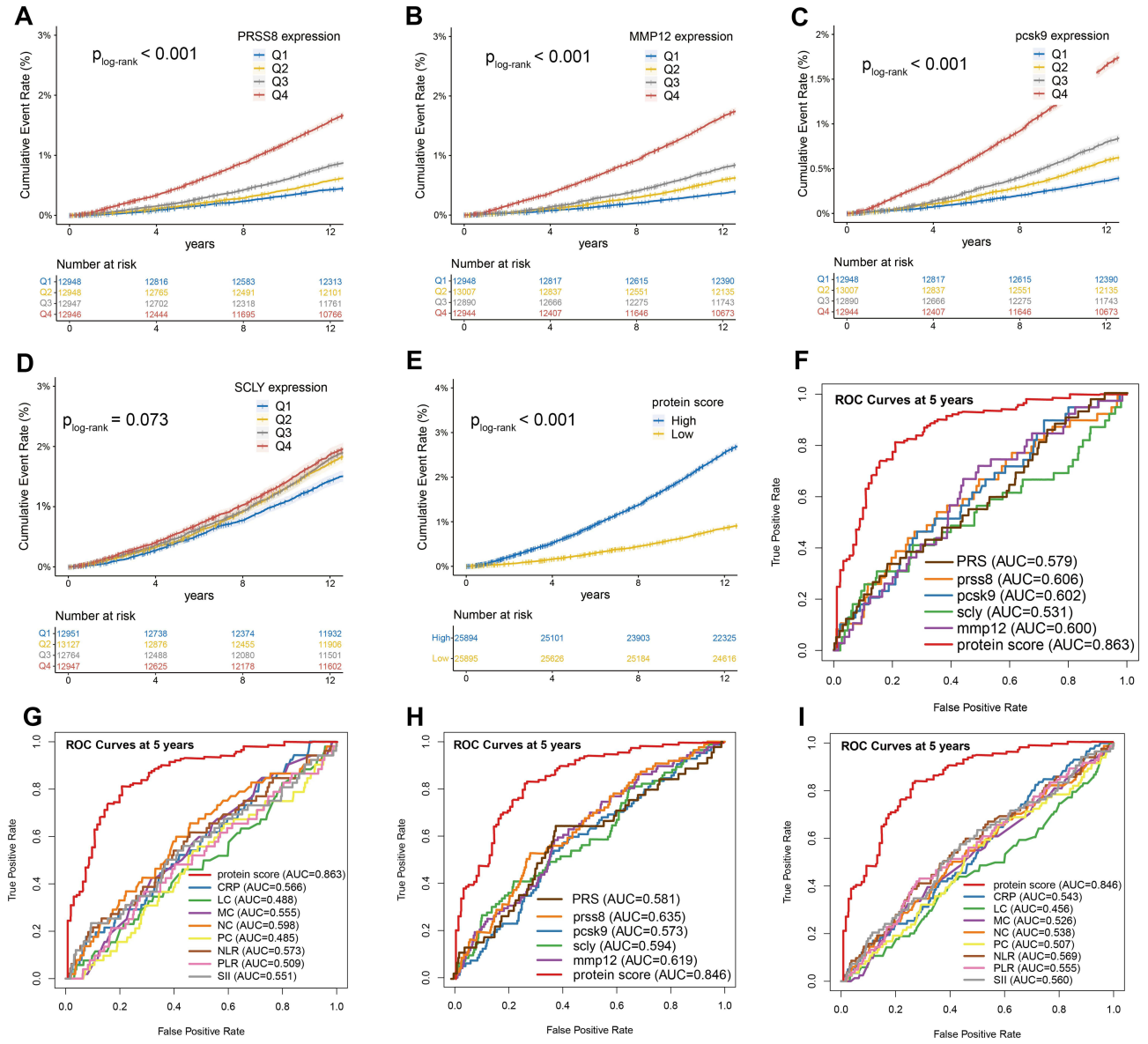

Figure 5 Development of a Protein Scoring System for Psoriasis. (**A–E**) Results of cumulative risk curve analysis of PRSS8, MMP12, PCSK9, SCLY and risk score. (**F** and **G**) ROC curves of 4 protein markers, protein scores, and multiple systemic inflammatory markers for predicting the onset of psoriasis in the training set. (**H** and **I**) ROC curves of 4 protein markers, protein scores, and multiple systemic inflammatory markers for predicting the onset of psoriasis in the test set.

analysis revealed that individuals with higher protein scores demonstrated markedly increased incidence and risk of psoriasis compared to those with lower scores (Figure 5E). Additionally, the AUC for these proteins and protein scores, along with polygenic risk score of psoriasis (Supplement 1) and common inflammatory biomarkers such as C-reactive protein (CRP), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil count, was calculated to predict the onset of psoriasis within a five-year period. The AUC values of the protein score for predicting the 5-year incidence of psoriasis were 0.863 in the training cohort and 0.846 in the test cohort (Figure 5F–I).

Discussion

Utilizing data from the UKB-PPP, which includes 53,016 participants and spans 2923 plasma proteins, we conducted an integration of proteomic and genomic data to investigate the longitudinal associations and causal relationships between the proteome and psoriasis. This extensive analysis led to the identification of four proteins as potential therapeutic

targets for psoriasis. Notably, two of these proteins, PRSS8 and SCLY, have not previously been the focus of drug development efforts. Further verification through single-cell transcriptomics confirmed the cell-specific expression of these proteins, reinforcing their significance in relation to psoriasis and highlighting their potential as novel drug targets for the treatment of this chronic skin condition.

MMP12, also known as human macrophage metalloelastase (HME), was initially characterized as an elastolytic metalloproteinase secreted by inflammatory macrophages. Functionally, MMP12 facilitates macrophage-driven proteolysis and matrix invasion in vivo and has been shown to suppress angiogenesis.[34] Specifically, in the context of psoriasis, MMP12 expression is markedly observed in macrophages and various immune cells within the papillary dermis, demonstrating pronounced expression in immune cells infiltrating this region.[35] Research conducted by Starodubtseva et al[36] revealed that MMP12 mRNA levels in psoriatic lesions are 17-fold higher compared to unaffected skin. In our analysis, an increase of one SD in blood MMP12 levels corresponded to a 14% elevated risk of developing psoriasis. Furthermore, both the protein levels of MMP12 in the blood and its mRNA expression levels in psoriatic skin lesions were significantly elevated when compared to those in the normal control group. This evidence underscores the significant association of MMP12 with psoriasis.

PCSK9, belonging to the proprotein convertase family, has been observed to have elevated circulating levels in psoriasis patients compared to healthy individuals. In hyperlipidemic mouse models, PCSK9 knockout was shown to diminish IL-17 levels in the circulation and the differentiation of IL-17-producing cells.[37] Additionally, human recombinant PCSK9 has been found to activate macrophages in vitro, elevating tumor necrosis factor and IL-6 expression,[38] whereas PCSK9 inhibition can attenuate inflammation in stimulated macrophages by suppressing nuclear factor-κB activity.[39] Recent research by Luan et al[40] further corroborates PCSK9's role in psoriasis, demonstrating elevated PCSK9 expression in keratinocytes and dermal vascular endothelial cells within psoriatic plaques compared to normal skin, aligning with findings from our single-cell transcriptome analysis. PCSK9 knockout mice exhibited a reduced response to imiquimod, and small interfering RNAs aimed at lowering PCSK9 expression similarly inhibited the imiquimod response. These collective findings underscore PCSK9's significant involvement in psoriasis pathophysiology. Our cohort study indicated that with every one SD increase in blood PCSK9 protein levels, the risk of developing psoriasis rises by 9%.

The relationship between PRSS8 and psoriasis has not been studied. Previous study found that PRSS8 plays a crucial role in epidermal barrier function and skin homeostasis.[41] The transgenic expression of PRSS8 in mouse skin has been shown to induce epidermal hyperplasia, inflammation, ichthyosis, and pruritus.[42] In our study, we observed that the expression levels of both PRSS8 are notably elevated in the blood and skin lesions of psoriasis patients compared to healthy controls. For each one SD increase in the blood expression level of PRSS8, the risk of psoriasis escalates by 18%. The increased risk associated with PRSS8 may potentially arise through mechanisms involving inflammatory responses and the disruption of skin homeostasis. These findings may further contribute to a deeper understanding of the pathogenesis of psoriasis.

Additionally, transcriptome analysis demonstrated that expression levels of SCLY in skin lesions of psoriasis patients are also higher than in unaffected skin, with specific expression noted in keratinocytes. SCLY has been proposed as a crucial regulator in the pathway of selenocysteine biosynthesis for the efficient production of selenoproteins.[43] In patients with severe psoriasis, Baran et al observed a significant increase in selenoprotein P levels prior to treatment, which subsequently decreased significantly post-treatment.[44] This observation implies that selenoprotein P could potentially function as a valuable biomarker for psoriasis. Meanwhile, our results demonstrated that SCLY, as a key player in selenium metabolism, is closely associated with the pathogenesis of psoriasis. These findings suggested that selenium metabolism may play a crucial role in the development of psoriasis, and SCLY could potentially serve as a significant predictive factor. There have been reports linking decreased selenium levels with the severity of psoriasis.[45] However, research on the selenium regulation of SCLY indicated that its activity was not dependent on selenium levels, and its expression differed based on cell type-specific responses to selenium levels.[46] Further elucidation is required to understand the mechanism underlying the elevated levels of SCLY in the blood and skin lesions in individuals with psoriasis.

Among the four significant proteins we identified, two proteins, MMP12 and PCSK9, have corresponding inhibitors.[47] Marimastat is an effective MMP inhibitor that has been previously used in the treatment of pancreatic and gastric cancers. The most common side effects are musculoskeletal symptoms.[48,49] Abnormal proliferation and migration of keratinocytes play a significant role in the progression of psoriasis. One study found that a broad-spectrum MMP inhibitor significantly reduced

keratinocyte migration.[47] PCSK9 inhibitors, including alirocumab and evolocumab, are commonly used in the treatment of hyperlipidemia-related disorders.[50,51] Abnormal lipid metabolism is closely related to the inflammatory response in psoriasis.[52] Our results further provide evidence for the use of lipid-lowering drugs in the prevention and treatment of psoriasis, and may help guide the selection of lipid-lowering medications for patients with psoriasis. However, the efficacy of these treatments for psoriasis still needs to be validated in clinical studies.

Psoriasis is a chronic inflammatory skin condition associated with elevated levels of common inflammatory biomarkers.[53] Studies have suggested that the PLR and NLR may serve as potential predictors for both the onset and severity of psoriasis.[54] In our study, we identified four key proteins and created a scoring system based on their expression. We found that individuals with higher scores had a significantly increased risk of incident psoriasis. Additionally, this scoring system demonstrated superior predictive ability compared to commonly used inflammatory biomarkers such as PLR and NLR, as well as polygenic risk score based on the largest GWAS to date on psoriasis.[55] Proteins can reflect ongoing biological processes, and the protein-based scoring system has been utilized for predicting both occurrence and prognosis of cardiovascular disease.[56,57] Based on our results, this evaluative system holds promise for improving the predictive capabilities of psoriasis onset and prognosis by integrating a broader range of psoriasis-associated proteins.

The strength of this study lies in its integrative approach that combines proteomic and genomic data to systematically explore the relationship between plasma protein biomarkers and psoriasis risk through cohort analysis and Mendelian Randomization. The substantial sample size, extensive proteome coverage, and capability to control for reverse causation with minimal confounding significantly enhance the credibility of our results. Consistency across various analytical methods further supports the robustness of our findings. However, the study is not without its limitations. Primarily, the cohort consists mostly of white participants, limiting the generalizability of the findings to other racial and ethnic groups. Additionally, the study does not directly measure protein levels within psoriatic skin lesions. To address this gap, single-cell RNA sequencing was employed to assess gene expression levels of associated proteins in disease-specific tissues. Furthermore, not every protein identified in our preliminary cohort analysis was backed by robust cis-pQTLs, limiting our ability to perform comprehensive cis-MR analyses for all proteins. The variability in the strength of the genetic instruments, where instruments with more variants tended to show statistically significant associations, may lead to an underestimation of associations for proteins represented by fewer genetic variants. This variability underscores the need for cautious interpretation of the results and suggests areas for further research to validate and extend these findings.

Conclusion

In our investigation utilizing a large cohort from the UK Biobank-PPP, along with Mendelian randomization and proteome analysis, we have identified four novel biomarkers for psoriasis: MMP12, PCSK9, PRSS8, and SCLY. Among these, PRSS8 and SCLY are novel discoveries in the context of psoriasis and present new opportunities for therapeutic exploration. Marimastat, which targets MMP12, has shown potential relevance to psoriasis, suggesting an extended utility beyond its current indications. Similarly, PCSK9 inhibitors like Alirocumab and Evolocumab, approved for hyperlipidemia, also hold promise for psoriasis management. Furthermore, we have developed a protein scoring system that effectively predicts both the incidence and the associated risk of developing psoriasis, leveraging these biomarkers. This scoring system could significantly enhance the precision of psoriasis diagnosis and prognosis.

Data Sharing Statement

Data underpinning the conclusions of this research can be accessed via the UKB Resource, application number 93810, which contains a comprehensive range of data. Researchers wishing to use the UK Biobank dataset should start the application process by registering and applying through the official UK Biobank website at [http://ukbiobank.ac.uk/register-apply/]. This paper has been uploaded to SSRN as a preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4797649.

Ethics Statement

The study was approved by the Institutional Review Board (IRB) of Xiangya Hospital, Central South University (Approval No. 202001007). The GWAS and pQTL data employed in our research were obtained from publicly accessible databases that have secured the required ethical clearances. Notably, a significant amount of this data originated from the

UK Biobank study, which received its ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference number: 21/NW/0157; IRAS project ID: 299116). It is essential to acknowledge that the UK Biobank obtained informed consent from all its participants before including them in the study.

Acknowledgments

We are profoundly grateful to the many researchers who have shared their GWAS datasets, enabling us to conduct this study. We also extend special thanks to the participants and the committed staff of the UK Biobank, whose unwavering dedication to scientific progress and their provision of invaluable resources have significantly contributed to the advancement of our research.

Author Contributions

Rui Mao: Writing an original draft, Software, Investigation, Visualization, Methodology, and Conceptualization. Tongtong Zhang: Software, Data Source, Methodology. Ziye Yang: Investigation, Methodology, Writing an original draft. Ji Li: Supervision, Conceptualization, Writing –review & editing, Funding acquisition. 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.

Funding

This research was funded by the National Natural Science Foundation of China under grant numbers 82273557, 82221002, 82173448, and 81874251.

Disclosure

The authors report no conflicts of interest in this work.

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