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Multi-omics analysis reveals novel causal pathways in psoriasis pathogenesis

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Abstract

Background To elucidate the genetic and molecular mechanisms underlying psoriasis by employing an integrative multi-omics approach, using summary-data-based Mendelian randomization (SMR) to infer causal relationships among DNA methylation, gene expression, and protein levels in relation to psoriasis risk.

Methods We conducted SMR analyses integrating genome-wide association study (GWAS) summary statistics with methylation quantitative trait loci (mQTL), expression quantitative trait loci (eQTL), and protein quantitative trait loci (pQTL) data. Publicly available datasets were utilized, including psoriasis GWAS data from the European Molecular Biology Laboratory–European Bioinformatics Institute and the UK Biobank. Heterogeneity in dependent instruments (HEIDI) test and colocalization analyses were performed to identify shared causal variants, and multi-omics integration was employed to construct potential regulatory pathways.

Results Our analyses identified significant causal associations between DNA methylation, gene expression, protein abundance, and psoriasis risk. We discovered two pathways involving the long non-coding RNA *RP11-977G19.11* and apolipoprotein F (APOF). Methylation at sites cg26804944 and cg02705573 was negatively associated with *RP11-977G19.11* expression. Reduced expression of *RP11-977G19.11* was linked to increased APOF levels, which were positively associated with a higher risk of psoriasis. Methylation at sites cg00172967, cg00294382, and cg24773560 was positively associated with *RP11-977G19.11* expression. Elevated expression of *RP11-977G19.11* was associated with decreased APOF levels, reducing the risk of psoriasis. Colocalization analysis highlighted APOF as a key protein in psoriasis pathogenesis. Validation using skin tissue, EBV-transformed lymphocytes data and inflammation-related protein panels confirmed the associations of *RP11-977G19.11* and APOF with psoriasis.

Conclusions Our multi-omics analysis provides preliminary evidence for potential molecular mechanisms in psoriasis pathogenesis. Through the integration of GWAS and molecular QTL data, we identify candidate pathways that may be relevant to disease biology. While these findings require extensive experimental validation, they offer a framework for future investigations into the molecular basis of psoriasis.

Keywords Psoriasis, Multi-omics, Mendelian randomization, DNA methylation, Gene expression, Protein levels, Causal pathways

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Introduction

Psoriasis is a chronic autoimmune disorder characterized by red, scaly plaques on the skin surface, significantly impairing patients' quality of life [1]. Beyond its dermatological manifestations, psoriasis has systemic effects, including an increased risk of depression, psoriatic arthritis, and cardiovascular comorbidities [2]. The global prevalence of psoriasis varies, ranging from 0.14% in East Asia to 1.99% in Australasia, with higher rates observed in Europeans and high-income countries [3]. Despite its prevalence and impact, the pathogenesis of psoriasis remains incompletely understood, limiting the development of effective therapeutic options.

Current evidence highlights the pivotal role of the interleukin-23 (IL-23) and interleukin-17 (IL-17) signaling pathways in psoriasis pathogenesis. IL-23 induces a distinct macrophage phenotype that contributes to inflammatory responses in murine models [4]. IL-17, in particular, has been shown to restore the function of keratinocytes and may play a protective role in psoriasis development under certain conditions [5]. This understanding has spurred rapid advancements in biologic therapies over the past few decades. Biologics—recombinant monoclonal antibodies or receptor fusion proteins—specifically target inflammatory mediators like IL-23 and IL-17, offering substantial clinical benefits [6]. However, these therapies are not universally effective: different agents show various efficacy, some patients exhibit inadequate responses or experience adverse effects [7, 8]. Additionally, the high costs of biologics impose significant economic burdens on patients and healthcare systems [9]. Given these limitations, there is a pressing need to deepen our understanding of psoriasis pathogenesis to identify novel therapeutic targets.

Mendelian randomization (MR) provides a powerful approach to investigate potential causal effects between exposures and outcomes by using genetic variants as instrumental variables (IVs) [10]. Two-sample MR enhances this methodology by estimating the effect of genetic variants on exposure and outcome in separate populations, thereby increasing statistical power and reducing bias [10]. This approach minimizes confounding factors and reverse causation inherent in observational studies [11]. The summary-data-based Mendelian randomization (SMR) technique extends traditional MR by integrating genome-wide association study (GWAS) summary statistics with quantitative trait locus (QTL) data, enabling multi-omics analyses [12].

To date, no studies have comprehensively explored the genetic causal associations between quantitative trait locus and psoriasis risk using a multi-omics approach. Therefore, we employed the SMR technique to investigate the potential associations of DNA methylation, gene expression, and protein abundance with psoriasis. By integrating multi-omics data, we aim to uncover novel insights into the pathogenesis of psoriasis and identify potential targets for therapeutic intervention. This multi-omics approach can provide a more comprehensive understanding of disease mechanisms, facilitating the discovery of new therapeutic targets and biomarkers.

Materials and methods

Study design

An overview of our analytical framework is presented in Fig. 1. Our study integrated three types of molecular quantitative trait loci (QTL) data: methylation QTL (mQTL) from McRae et al. (n = 1980 Europeans) [13], expression QTL (eQTL) from the eQTLGen Consortium (n = 31,684 Europeans) [14], and protein QTL (pQTL) from Ferkingstad et al. (n = 35,559 Icelanders) [15]. For instrument selection, we applied criteria including $p < 5 \times 10^{-8}$, with top-SNPs selected within ± 2000 kb. For psoriasis associations, we utilized two independent datasets: a discovery cohort from EMBL-EBI (5,459 cases and 324,074 controls) and a replication cohort from UK Biobank (5,314 cases and 457,619 controls). For validation, we leveraged tissue-specific data from the GTEx Consortium (V8 release) [16], including both sun-unexposed and sun-exposed skin tissue, as well as EBV-transformed lymphocytes. Additional protein-level validation was conducted using the UK Biobank Pharma Proteomics Project's (UKB-PPP) inflammation panel [17]. All datasets utilized in this study were publicly available and are detailed in Table 1.

Methylation, expression, and protein quantitative trait loci datasets

Specifically, for mQTL analysis, we utilized whole blood data from McRae et al. [13], which included 417,580 CpG sites genotyped using the Illumina HumanMethylation450 array. The CpG sites were filtered using a detection p-value threshold of 0.01 in at least 95% of samples. Methylation levels were normalized using both beta and M-values, with beta-values used for interpretability and M-values for statistical testing. For eQTL analysis, we used blood-derived data from eQTLGen Consortium [14]. Gene expression levels were quantified using RNA sequencing or gene expression arrays, with subsequent quality control including removal of technical covariates and normalization [14]. Expression data were adjusted for known and hidden confounders using principal component analysis [14]. Blood pQTL data from Ferkingstad et al. [15] measured 4,907 proteins using the SOMAscan platform. Raw protein measurements underwent several quality control steps including hybridization control normalization, median signal normalization, and calibration

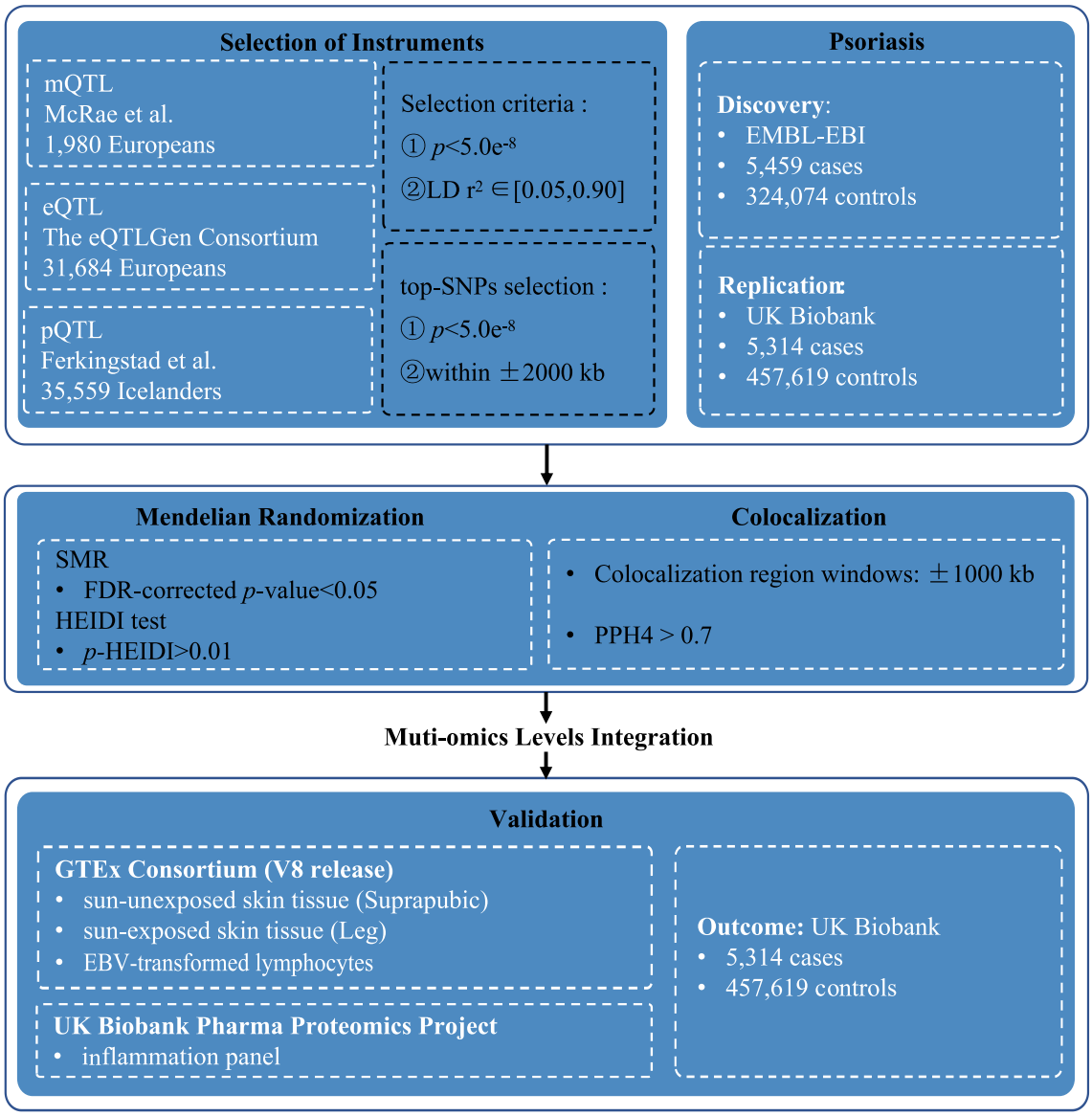


Fig. 1 Study design and workflow for our study. This figure outlines the step-by-step process of our study, including instrument selection, Mendelian randomization analysis, colocalization, multi-omics integration, and validation. The data sources, selection criteria, and analytical methods used at each stage, from initial discovery cohorts to final validation using tissue-specific and proteomic data is included

Table 1 Summary of datasets included in this study

Description	Consortium/First author	Participants
mQTL in whole blood	McRae et al.	1,980 European individuals
eQTL in whole blood	eQTLGen Consortium	31,684 European individuals
Tissue-specific eQTL	The Genotype-Tissue Expression project	838 individuals (majority were European)
pQTL in whole blood	Ferkingstad et al.	35,559 Icelanders
Inflammatory pQTL	UK Biobank Pharma Proteomics Project	54,219 UK Biobank participants
Psoriasis	European Molecular Biology Laboratory -European Bioinformatics Institute	5,459 cases and 324,074 controls
Psoriasis	UK Biobank study	5,314 cases and 457,619 controls

QTL, quantitative trait loci

to remove batch effects. The protein levels were log-transformed and standardized to have a mean of zero and standard deviation (SD) of one. For tissue-specific validation, we utilized GTEx V8 data [16] from sun-exposed (n = 605) and sun-unexposed (n = 517) skin samples, as well as EBV-transformed lymphocytes (n = 147) . Gene expression was quantified using RNA-seq, with reads aligned to GRCh38 reference genome using STAR, followed by gene-level quantification using RNA-SeQC v1.1.9. Expression values were normalized using TMM method and transformed to log2 counts per million [16]. Additional protein-level validation used UKB-PPP data [17], which measured 1,463 proteins using the Olink® Explore platform. The protein levels were normalized using Olink's standard pipeline, including normalization against extension control, inter-plate control, and adjustment for technical variation [17]. The processing and quality control steps for all datasets aligned with established protocols in their respective original publications.

Psoriasis outcome datasets

Summary-level data for psoriasis were obtained from studies by the European Molecular Biology Laboratory–European Bioinformatics Institute (EMBL-EBI) and the UK Biobank. The EMBL-EBI (GCST90014456) dataset included 329,533 individuals of European descent, with 5,459 psoriasis cases and 324,074 controls [18]. For validation, we used the data from UK Biobank, which comprised 462,933 European individuals (5,314 psoriasis cases and 457,619 controls) [19].

Summary data-based mendelian randomization analysis

We employed summary-data-based Mendelian randomization (SMR) analysis to investigate potential causal relationships between molecular traits and psoriasis risk. The SMR approach extends traditional Mendelian randomization by utilizing summary-level data from independent GWAS and QTL studies to examine whether the effect of a SNP on a trait (psoriasis) is mediated through molecular features (such as gene expression, DNA methylation, or protein levels). The SMR method has been described in detail by Zhu et al. [12]. Briefly, the SMR effect size (b_{xy}) was estimated as:

$$bxy = bzy/bzx$$

where b_{zy} represents the SNP's effect on psoriasis from GWAS data, and b_{zx} represents the SNP's effect on molecular traits from QTL studies. The corresponding test statistic (TSMR) was calculated using *z*-statistics from both GWAS and QTL studies:

$$\mathrm{TSMR} = z^2zyz^2zx/\left(z^2zy + z^2zx\right)$$

where z_{zy} and z_{zx} are the *z*-statistics from GWAS and QTL studies, respectively. To implement this analysis, we utilized the SMR software (v1.3.1) [12] with the following criteria: (1) selected top cis-QTLs within ± 2,000 kb of each gene, (2) required p-value $< 5 \times 10^{-8}$ for QTL associations [12], and (3) excluded SNPs with allele frequency differences > 0.2 between datasets. Statistical significance was determined using false discovery rate (FDR)-corrected p-values (threshold < 0.05) via the Benjamini–Hochberg method.

Distinguishing functional association from linkage

To differentiate between pleiotropy and linkage disequilibrium, we implemented the heterogeneity in dependent instruments (HEIDI) test. Under the assumption of a single causal variant, the SMR effect size (b_{xy}) estimated using any SNP in LD with the causal variant should be consistent. The HEIDI test statistic evaluates this consistency by comparing the b_{xy} of the top associated cis-QTL (b_{xy}(top)) with those of other significant SNPs in the cis-QTL region (b_{xy}(i)):

$$di = bxy(i) - bxy(top)$$

where d_i follows a multivariate normal distribution MVN(d,V), with V representing the covariance matrix. The HEIDI test statistic (T_HEIDI) is calculated as:

$$T\_HEIDI = \Sigma z^2 d(i)$$

where $zd(i) = d_i/\sqrt{var(d_i)}$. We excluded SNPs in perfect LD with the top cis-QTL ($r^2 > 0.9$) and those with weak associations ($p > 1.6 \times 10^{-3}$) to ensure robust testing. A p_HEIDI > 0.01 suggests a single causal variant affecting both the molecular trait and the outcome through the same pathway.

Colocalization analysis

To determine whether association signals from separate GWAS at the same locus share a causal variant, we performed colocalization analysis using the "coloc" R package (v5.2.3) [20–22]. Given the significant role proteins play in disease, we focused on genetic associations between psoriasis and corresponding pQTLs. The colocalization analysis tests five hypotheses: (H0) no causal variants for either protein or psoriasis in the locus; (H1) one causal variant for protein only; (H2) one causal variant for psoriasis only; (H3) two distinct causal variants for protein and psoriasis; and (H4) one shared causal variant for both protein and psoriasis. Corresponding posterior probabilities are denoted as PPH0, PPH1, PPH2, PPH3, PPH4, respectively. We defined colocalization

regions as ± 1,000 kb around the locus and considered PPH4 > 0.7 (corresponds to a FDR of < 5%) as strong evidence supporting a shared causal relationship [23].

Integration of multi-omics results

We implemented a systematic approach to integrate multi-omics data. Our analytical framework was guided by the central dogma of molecular biology, where genetic variants influence phenotypes through sequential molecular changes from DNA methylation to gene expression to protein levels. First, we applied SMR analysis with HEIDI tests at each molecular level, requiring both SMR FDR-adjusted p-value < 0.05 and HEIDI p-value > 0.01 to identify significant associations while excluding potential linkage effects. Since proteins represent the functional endpoints of gene regulation, we prioritized our analysis by first identifying proteins showing robust causal associations with psoriasis. We then traced back through the molecular cascade to identify consistent signals at gene expression and DNA methylation levels.

For colocalization analysis, we implemented a PPH4 threshold > 0.7, following established precedents in genomic research. This threshold was chosen based on Foley et al.'s demonstration that it corresponds to a FDR of < 5% [23], and has been successfully applied in multiple recent genomic studies [24–26]. To define regulatory pathways, we required evidence of consistent effects across molecular layers. Specifically, a candidate pathway needed to meet three criteria:1). The protein showed significant causal association with psoriasis (SMR FDR-corrected p-value < 0.05, p-HEIDI > 0.01) and strong colocalization evidence (PPH4 > 0.7); 2). The corresponding gene demonstrated significant expression-level association with psoriasis (SMR FDR-corrected p-value < 0.05, p-HEIDI > 0.01); 3). At least one CpG site in the gene region showed significant methylation-level association with psoriasis (SMR FDR-corrected p-value < 0.05, p-HEIDI > 0.01). For example, if methylation at a CpG site (e.g., cg26804944) showed association with psoriasis through mQTL analysis, and we simultaneously observed consistent associations at both gene expression (through eQTL) and protein levels (through pQTL) for the same gene, we considered this as evidence for a potential regulatory pathway.

Results

Association between DNA methylation and psoriasis

Our SMR analysis identified 421 CpG sites that have significant causal relationships with psoriasis (Fig. 2A&B). Alternations in methylation levels at these sites can influence gene expression and, consequently, disease risk. Even CpG sites within the same gene region can have differing effects on psoriasis risk. For example, a one SD increase in methylation at site cg04182226 was associated with a higher risk of psoriasis (OR 1.213; 95% CI 1.164–1.264), while an increase at cg15398152 was linked to a reduced risk (OR 0.995; 95% CI 0.992–0.998) (Table S1). Through the replication process, we identified 416 CpG sites significantly associated with psoriasis from the UK biobank GWAS. (Supplementary Fig. 1A&B; Table S2). We observed a substantial overlap between our discovery and replication sets, with 194 CpG sites consistently associated with psoriasis risk in both datasets (Fig. 2C; Table S3). To gain deeper insights into the biological significance of these 194 shared CpG sites, we conducted a trait enrichment analysis using the EWAS Open Platform [27] (Fig. 2D). Our findings showed that aging, smoking, and Down syndrome had the highest number of associated DNA methylation sites among these 194 CpG loci. We also observed significant enrichment for several autoimmune diseases, including primary Sjögren's syndrome, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and psoriasis itself. This overlap with other autoimmune conditions suggests shared epigenetic mechanisms in their pathogenesis. Additionally, our analysis highlighted associations with other relevant traits such as preterm birth, obesity, and allergic conditions. We also found links to chromosomal abnormalities and various types of cancer, indicating the broad implications of these epigenetic markers.

Association between gene expression and psoriasis

We examined the causal effects of gene expression on psoriasis risk and identified 54 significant associations in our initial analysis (Fig. 3A; Table S4). We observed both risk-enhancing and protective effects. For instance, increased expression of *ISYNA1* was associated with a higher risk of psoriasis (OR 1.203; 95% CI 1.094–1.323). Similar risk-enhancing effects were observed for genes such as *MRPL9*, *OAZ3*, *TDRKH*, *SLC27A3*, and *DENND1B* etc. Conversely, elevated expression of some genes appeared to reduce psoriasis risk. An SD increase in *KLRF1* expression corresponded to a 12.7% decrease in risk (OR 0.873; 95% CI 0.810–0.941). Other genes showing protective associations included *VAMP3*, *REL*, *RP11-977G19.11*, *CTD-2260A17.1*, and *HSPA4* etc. Furthermore, we conducted a replication analysis using an independent cohort, which revealed 33 psoriasis-associated genes (Fig. 3B, Table S5). Importantly, we found an overlap of 17 genes between our discovery and validation sets (Fig. 3C).

Association between protein expression and psoriasis

After applying stringent criteria, we identified five proteins with significant associations with psoriasis in the discovery stage: MATN3, ERAP1, APOF, TNFAIP3, and

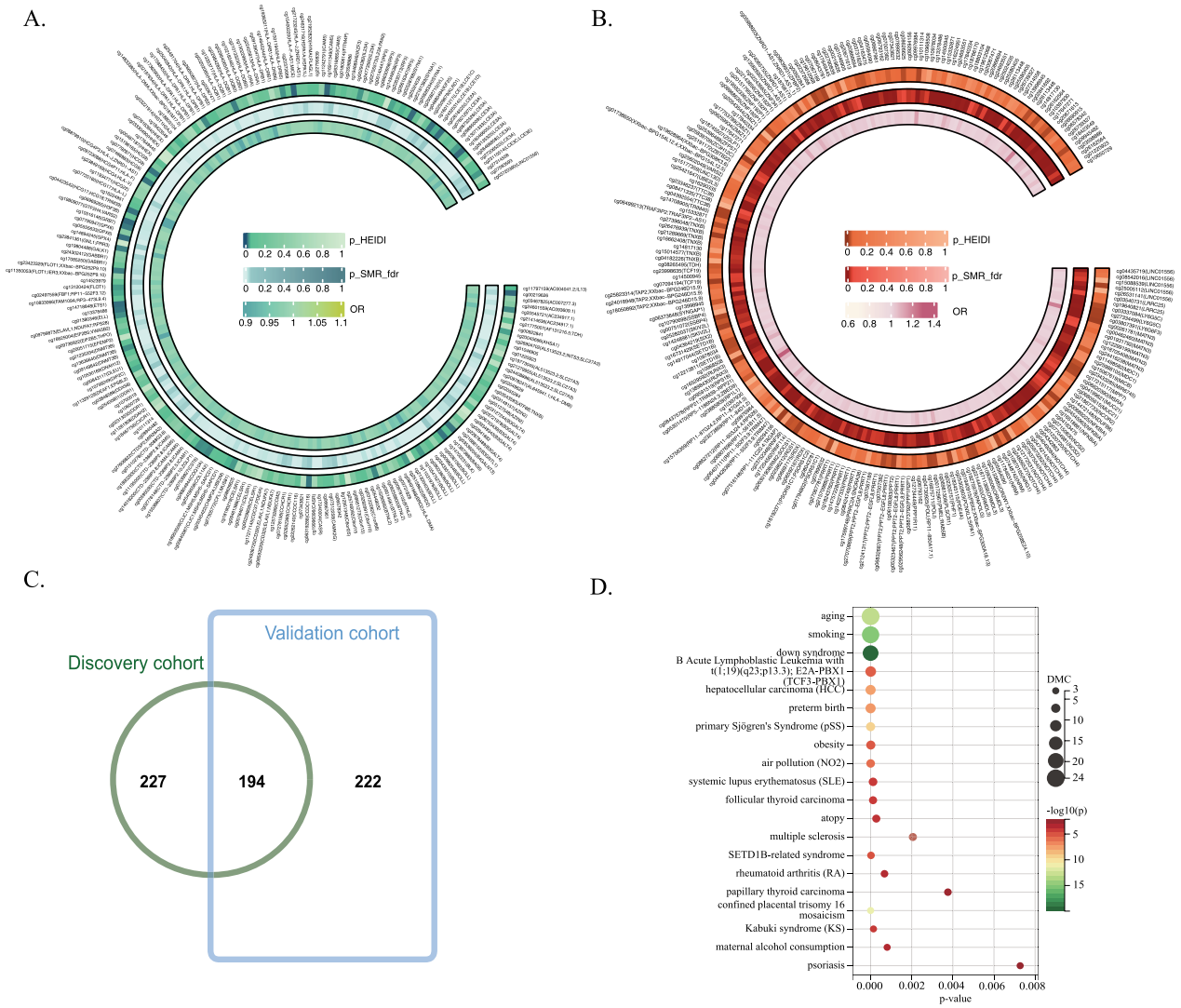


Fig. 2 Multi-omics analysis of methylation quantitative trait loci (mQTLs) and their association with psoriasis. **A**, **B** Circular plot showing mQTLs correlated with psoriasis risk. The outer ring shows individual mQTL sites. Inner rings represent, from outermost to innermost: p-values (p_HEIDI), SMR statistics ($p\_SMR\_b_{xy}$), and odds ratios (OR). Note the different OR scale between **A** and **B**. **C** Venn diagram showing the overlap of mQTLs between the discovery cohort (421 mQTLs) and the validation cohort (416 mQTLs). The intersection reveals 194 mQTLs common to both cohorts, demonstrating robust replication. D. Enrichment analysis of the 194 validated mQTLs. The *y*-axis lists significantly enriched biological processes, traits, or pathways. The *x*-axis shows the enrichment p-value. The size of dots represents the number of genes involved in each process (count), while the color indicates the significance level (adjusted p-value). Key enriched terms include aging, smoking, and various autoimmune and inflammatory conditions

MX1 (Table 2). Higher levels of MATN3 (OR 1.011; 95% CI 1.005–1.017), ERAP1 (OR 1.006; 95% CI 1.002–1.009), and APOF (OR 1.029; 95% CI 1.016–1.041) were linked to an increased risk of psoriasis. In contrast, higher levels of TNFAIP3 (OR 0.976; 95% CI 0.966–0.985) and MX1 (OR 0.982; 95% CI 0.972–0.992) were associated with a decreased risk. Colocalization analysis strengthened these findings by highlighting the significance of TNFAIP3 (posterior probability PPH4 = 0.97), APOF (PPH4 = 0.89), and MX1 (PPH4 = 0.71) (Table 2; Table S6). In the replication cohort, the associations of TNFAIP3 (OR 0.992; 95% CI 0.989–0.996; PPH4 = 0.87), APOF (OR 1.007; 95% CI 1.004–1.010; PPH4 = 0.87), and MX1 (OR 0.997; 95% CI 0.996–0.999; PPH4 = 0.84) were confirmed. However, proteins such as FGF2, ERAP1, UBLCP1, and PNLIPRP2 did not pass the colocalization analysis (Table S7).

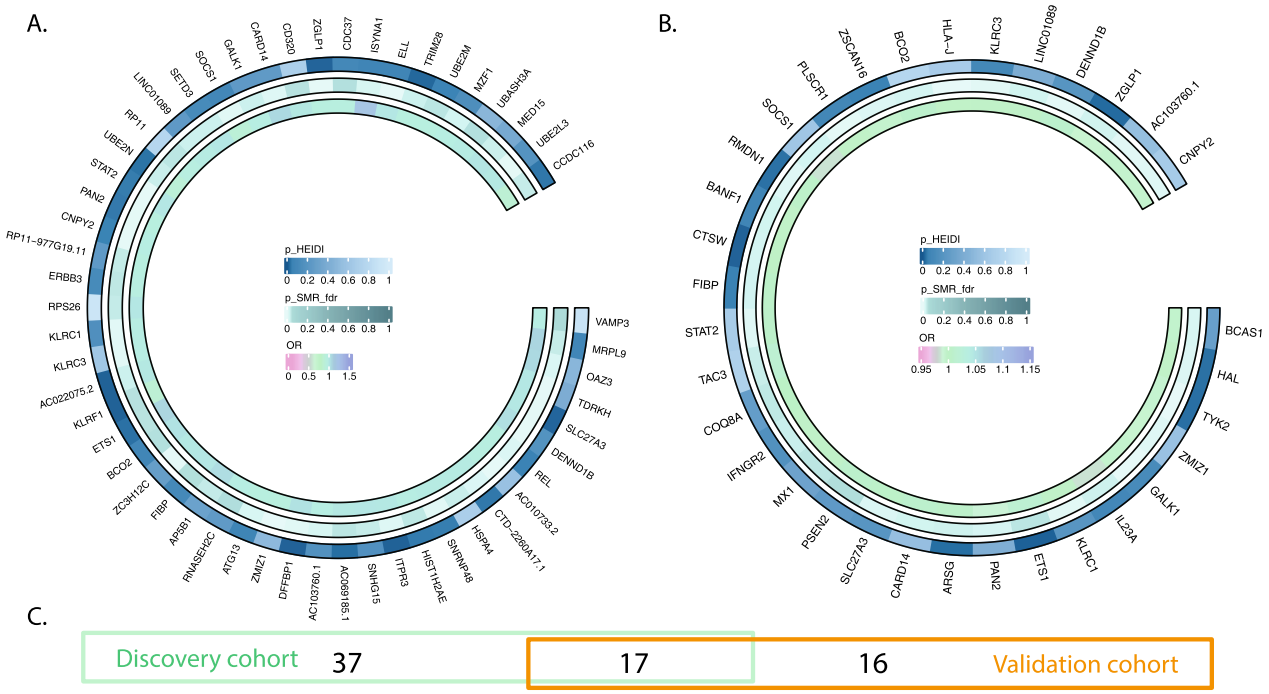


Fig. 3 Expression quantitative trait loci (eQTLs) associated with psoriasis risk and their replication. **A** Circular plot depicting eQTLs associated with psoriasis risk in the discovery cohort. The outer ring shows individual gene names. Inner rings represent, from outermost to innermost: p-values (p_HEIDI), SMR statistics (p_SMR_b$_{xy}$), and odds ratios (OR). **B** Circular plot showing eQTLs associated with psoriasis risk in the replication cohort. The layout is identical to **A.** Note the different OR scale compared to **A**. **C** Venn diagram-style representation of overlapped eQTL between discovery and replication cohorts. The discovery cohort identified 54 eQTLs, while the replication cohort identified 33 eQTLs. The Venn diagram shows 17 eQTLs that were successfully replicated in both cohorts

Table 2 Summary data-level Mendelian randomization analysis for association between protein abundance and psoriasis in discovery cohort

Gene	topSNP	b_SMR	OR (95% CI)	nsnp_HEIDI	p_SMR	p_HEIDI	FDR-corrected p-value	PPH4
MATN3	rs2670634	0.0112137	1.011 (1.005,1.017)	20	0.000215503	0.383171	0.019803546	0.038481532
ERAP1	rs30185	0.00550688	1.006 (1.002,1.009)	20	0.000436539	0.05006876	0.033138996	0.00031427
TNFAIP3	rs5029939	-0.0246981	0.976 (0.966,0.985)	19	1.51487E-06	0.2021788	0.000264496	0.965285122
APOF	rs2020854	0.0284272	1.029 (1.016,1.041)	20	4.7082E-06	0.04332918	0.000747319	0.893422503
MX1	rs464138	-0.0184196	0.982 (0.972,0.992)	20	0.000579	0.1475849	0.03888207	0.708369724

CI, confidence interval. FDR, false dicovery rate. HEIDI, heterogeneity in dependent instruments. SNP, single nucleotide polymorphsim. OR odds ratio. PPH4, posterior probabilities of H4

* Only presented the association with FDR-corrected p-value < 0.05 and p-HEIDI test > 0.01

Multi-omics evidence

We conducted a multi-layered analysis to explore the relationships between DNA methylation, gene expression, and protein levels in the context of psoriasis risk. This approach involved two stages of analysis: mQTLs and eQTLs (Table S8), and second, between eQTLs and pQTLs (Table S9). This multi-omics approach highlighted APOF as a central factor in the pathogenesis of psoriasis (Fig. 4).

Our analysis suggests that methylation at specific CpG sites influences the expression of *RP11-977G19.11*, which in turn affects APOF protein levels and modulates psoriasis risk. Specifically, at the first level, we found that methylation at the cg26804944 site was associated with reduced expression of the gene *RP11-977G19.11* (OR 0.753; 95% CI 0.657–0.863) (Table S8). The second level of analysis revealed that lower expression of *RP11-977G19.11* was linked to higher levels of APOF protein (OR 0.240; 95% CI 0.145–0.398) (Table S9). Previous

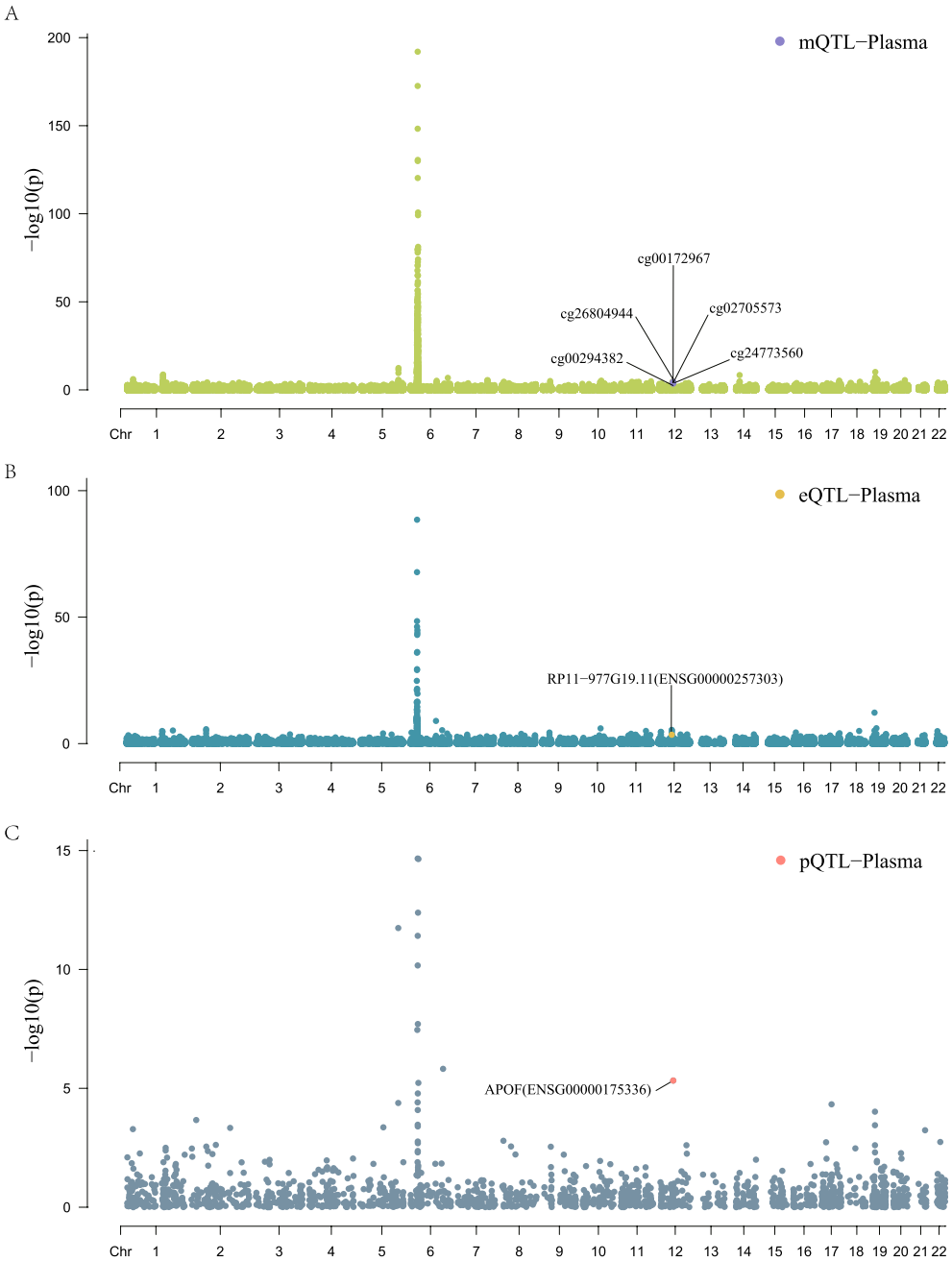


Fig. 4 Multi-omics Manhattan plots for mQTL, eQTL, and pQTL associations with psoriasis risk in plasma. **A** Manhattan plot of mQTL associations. The *x*-axis represents chromosomal positions, and the *y*-axis shows the -log10(p) values. Significant mQTLs are highlighted, with key CpG sites labeled (cg00172967, cg26804944, cg02705573, cg00294382, cg24773560). **B** Manhattan plot of eQTL associations. The plot follows the same format as **A**. The gene *RP11-977G19.11* (*ENSG00000257303*) is highlighted as a significant eQTL. **C** Manhattan plot of pQTL associations. The plot maintains the same structure as **A** and **B**. The APOF is identified as a significant pQTL

studies have associated increased APOF levels with a higher risk of psoriasis (OR 1.029; 95% CI 1.016–1.041) (Table 2). These findings align with our earlier observation that methylation at cg26804944 is associated with increased psoriasis risk (OR 1.014; 95% CI 1.007-1.020) (Table S1). We observed similar effects for methylation at cg02705573, which was negatively associated with *RP11-977G19.11* expression (OR 0.806; 95% CI 0.728–0.891).

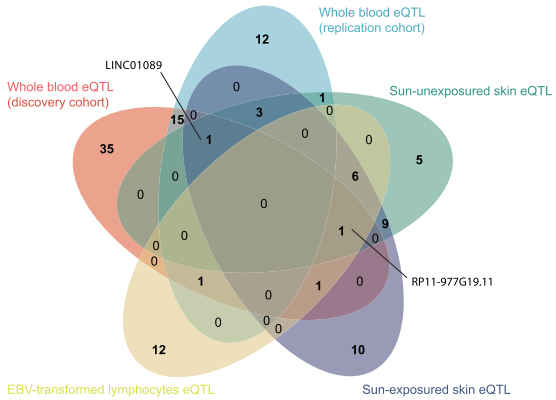
Conversely, methylation at three other sites—cg00172967 (OR 1.155; 95% CI 1.077–1.238), cg00294382 (OR 1.710; 95% CI 1.342–2.179), and cg24773560 (OR 1.853; 95% CI 1.389–2.473)—showed positive associations with *RP11-977G19.11* expression. These findings suggest that these three CpG sites might have a protective effect against psoriasis through their influence on gene expression. This integrated analysis provides insights into the potential molecular pathway from DNA methylation to protein expression in the context of psoriasis risk.

Tissue-specific and protein-level analyses

Recognizing the unique characteristics of psoriasis as a skin condition affected by environmental factors and an autoimmune disease, we conducted analyses using tissue-specific data from the GTEx project. We specifically focused on both sun-exposed, sun-unexposed skin and EBV-transformed lymphocytes to account for potential differences in gene expression patterns related to sun exposure, a factor known to influence psoriasis, and inflammation. Our analysis of gene expression in sun-unexposed skin (Table S10) and sun-exposed skin (Table S11) revealed a consistent association between *RP11-977G19.11* expression and psoriasis risk across both tissue types. In sun-unexposed skin, increased expression of *RP11-977G19.11* was associated with a slight increase in psoriasis risk (OR 1.002; 95% CI 1.001–1.003). A similar, slightly stronger association was observed in sun-exposed skin (OR 1.003; 95% CI 1.001–1.004). Besides, considering that this pathway, especially the identified methylation sites were mostly associated with inflammatory pathways, we also extracted eQTL data in EBV-transformed lymphocytes (Table S12). The positive association between *RP11-977G19.11* and psoriasis was indicated again (OR 1.002; 95% CI 1.001–1.003). Together with our eQTL results from whole blood (Fig. 3), suggest that the effect of *RP11-977G19.11* expression on psoriasis risk is consistent regardless of sun exposure, underscoring its potential importance in inflammation mechanism of psoriasis (Fig. 5A).

We also examined inflammation-related protein data from the UKB-PPP to validate our findings and explore additional associations. This protein-level analysis confirmed the positive association between APOF protein levels and psoriasis risk (OR 1.006; 95% CI 1.003–1.009) (Table S13, Fig. 5B), corroborating our earlier findings (Table 2; Table S6, Table S7). Additionally, we identified potential associations between psoriasis and several other inflammation-related proteins, including FGF2, PNLIPRP2, and MFAP4 (Table S13). These proteins may offer new insights into psoriasis pathogenesis and represent potential therapeutic targets.

A.



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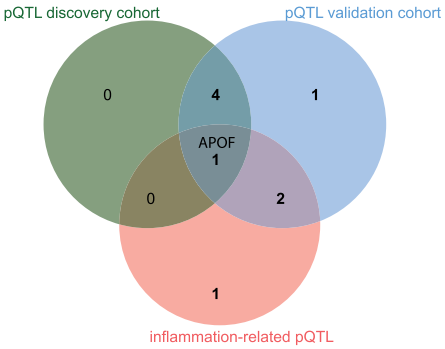

Fig. 5 Tissue-specific eQTL and pQTL analysis for psoriasis-associated genes and proteins. **A** Venn diagram showing the overlap of eQTLs across different tissue types: sun-exposed skin (10 unique eQTLs, dark blue), sun-unexposed skin (5 unique eQTLs, green, with 20 overlapping with sun-exposed skin), whole blood eQTL in replication cohort (12 unique eQTLs, light blue), whole blood eQTL in discovery cohort (35 unique eQTLs, pink), and eQTLs from EBV-transformed cell (12 unique eQTLs, yellow). Both gene *RP11-977G19.11* and gene *LINC01089* were replicated four times. **B** Venn diagram illustrating the overlap of pQTLs across different datasets: pQTL discovery cohort (5 pQTLs, green), pQTL replication cohort (8 pQTLs, blue), and inflammation-related pQTL (4 pQTLs, pink). APOF is highlighted as the single pQTL common to all three datasets

Discussion

Psoriasis is a chronic inflammatory skin disease with significant health impacts. While *HLA-C*06:02* is an established genetic risk locus that has led to successful biologic therapies targeting TNF-α, IL-23, and IL-17 pathways [28, 29], clinical heterogeneity in genetic profiles and treatment responses suggests additional pathogenic mechanisms remain to be uncovered [30, 31]. Recent transcriptome-wide analysis has identified novel gene associations, including *RP11-977G19.11* [32], highlighting the potential for discovering new therapeutic

targets. However, a comprehensive understanding of causal molecular mechanisms through integrated multi-omics analysis is still lacking.

In this study, we implemented a systematic multi-omics approach using SMR coupled with HEIDI tests and colocalization analysis to investigate causal molecular mechanisms in psoriasis pathogenesis, following the established biological cascade from DNA methylation to gene expression to protein levels. Our analysis identified significant associations with psoriasis across multiple molecular layers, including 643 methylation sites, 112 genes, and 9 proteins (3 of them passed the colocalization analysis). Through this integrative approach, we detected two potential regulatory pathways involving *RP11-977G19.11* and APOF.

The first pathway (cg26804944/cg02705573–*RP11-977G19.11*–APOF) involves two CpG sites, with cg02705573 located in the *PAN2* gene previously associated with environmental exposure responses [33], while cg26804944 represents a novel methylation site. Our findings suggest that decreased methylation at these sites correlates with reduced expression of *RP11-977G19.11*, ultimately leading to increased APOF levels and elevated psoriasis risk.

The second pathway (cg00172967/cg00294382/cg24773560–*RP11-977G19.11*–APOF) features three CpG sites. The CpG sites cg00294382 and cg24773560, both associated with *IL23A*, are particularly noteworthy given IL-23's central role in psoriasis pathogenesis. IL-23 drives the differentiation and activation of pathogenic Th17 cells [34], and the IL-23/IL-17 axis is now a well-established therapeutic target with several approved biologics [35]. These methylation sites have been previously implicated in various inflammatory conditions: cg00294382 has shown associations with systemic inflammation markers including blood C-reactive protein levels and inflammatory diseases such as Crohn's disease [36–42], while cg24773560 has been linked to similar inflammatory conditions [39–41, 43–45]. Additional associations of these sites with cancer susceptibility, aging, and metabolic responses suggest their broader role in inflammatory regulation [39–41, 43–45]. The convergence of our findings with these previous observations strengthens the biological plausibility of these methylation sites as regulatory elements in psoriasis pathogenesis through IL-23 signaling.

Our analysis also revealed causal relationship between *RP11-977G19.11* (*CNPY2-AS1*), a long non-coding RNA on chromosome 12q13.3, and APOF. APOF, present in both HDL and LDL [46], functions as a key regulator of lipid metabolism by inhibiting cholesteryl ester transfer protein activity [47]. This association has been demonstrated through animal studies, where APOF manipulation directly affects cholesterol distribution between lipoproteins [48, 49]. Particularly relevant to psoriasis pathogenesis is the finding that *APOF* deletion affects *STAT2* expression and type I interferon signaling [50]. Given that dysregulated interferon signaling is a hallmark of psoriasis [51], this connection suggests a potential mechanism linking lipid metabolism to inflammatory pathways in psoriasis through APOF-mediated regulation.

Additionally, our analysis revealed two additional proteins with potential causal roles in psoriasis pathogenesis. TNFAIP3 (A20), a critical negative regulator of inflammation, suppresses NF-κB signaling, with recent evidence showing that its reduced expression in psoriatic skin enhances NF-κB activation and promotes disease progression [52, 53]. MX1, an interferon-stimulated gene, functions in the type I interferon pathway [54, 55], which is notably dysregulated in psoriasis. These protein-level findings complement our methylation data, particularly the *IL23A*-associated sites (cg00294382 and cg24773560). The involvement of these regulatory elements in the IL-23/IL-17 axis [34, 35], together with TNFAIP3 and MX1's roles in inflammatory signaling, suggests a coordinated network of epigenetic and inflammatory regulation in psoriasis.

We confirmed the *RP11-977G19.11*-APOF finding using independent eQTL data from skin tissue and EBV-transformed lymphocytes, and pQTL data from an inflammation panel. The consistency of these associations across different tissue types and independent datasets enhances the reliability of our identified pathways.

Clinical and therapeutic implications

Our multi-omics findings provide potential insights into both established and novel therapeutic strategies for psoriasis. The identification of APOF as a mediator in psoriasis pathogenesis aligns with existing clinical evidence, where meta-analyses have demonstrated the efficacy of lipid-modulating therapies in reducing PASI (psoriasis area and severity index) scores [56]. The newly identified *RP11-977G19.11*-APOF regulatory axis may offer additional therapeutic possibilities. This pathway could potentially inform the development of more targeted approaches to lipid regulation in psoriasis, complementing current broad-spectrum treatments. The validation of TNFAIP3 and MX1's involvement provides molecular context for existing therapeutic approaches while suggesting new directions. Current JAK inhibitors effectively target the type I interferon pathway [57], where MX1 plays a crucial role. Our identification of specific methylation sites regulating these proteins may help explain the variable treatment responses observed in clinical practice. These findings suggest the potential utility of

considering both inflammatory and lipid-related pathways in treatment strategies, though further clinical validation is needed.

Limitations

Our study has several important limitations that should be considered when interpreting the results. First, due to the limited availability of large-scale GWAS data from non-European populations, our analysis was primarily confined to European cohorts. While this reflects current data availability rather than study design, we acknowledge the importance of validating these findings across diverse ethnic groups. Future studies incorporating multi-ethnic populations will be crucial as more genomic data becomes available from different populations. Second, the inherent complexity of biological systems presents analytical challenges. Our pathway analysis relies on QTL-based causal inference and directional consistency across methylation, expression, and protein levels. Although this approach offers a systematic framework for pathway identification, it may not fully capture the intricate regulatory networks and feedback mechanisms present in vivo. Methylation patterns, in particular, can be highly tissue-specific and dynamically influenced by environmental factors [58–60]. Third, regarding the protein-level validation, while both exposure and outcome data were derived from the UK Biobank, the potential for substantial overlap between datasets is limited. The psoriasis GWAS from EMBL-EBI includes participants from multiple European cohorts beyond the UK Biobank, and the substantial differences in both case numbers (5,459 psoriasis cases in EMBL-EBI vs. 5,314 cases in UK Biobank) and control group sizes (324,074 vs. 457,619) indicate distinct participant pools. Furthermore, only a small portion of EMBL-EBI data originates from UK Biobank, minimizing potential overlap with UKB-PPP participants. Regarding our colocalization analysis threshold, we followed established statistical guidelines. Foley et al. demonstrated that a PPH4 threshold of >0.7 corresponds to a FDR of $<5\%$ [23], providing statistical rigor to this cutoff. This threshold has been widely implemented in recent genomic studies [24–26]. While we acknowledge that more stringent thresholds might be applied, our chosen threshold tries to strike a balance between sensitivity and specificity in identifying genuinely colocalized loci. To address these limitations and strengthen our findings, we are initiating follow-up studies involving experimental validation in relevant tissue samples and diverse patient populations. Our current findings, while preliminary, provide a well-supported framework for these targeted investigations.

Conclusion

Our study investigated the potential causal relationships among DNA methylation, gene expression, and protein abundance in psoriasis using SMR and colocalization analysis. Through replication and validation, we identified a potential causal pathway involving APOF and several significant associations at the multi-omics level. These findings enhance our understanding of psoriasis pathogenesis and may help identify targets for pharmacological intervention, potentially leading to more effective treatments for this chronic autoimmune disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06099-w.

Supplementary material 1: Supplement Figure 1. Multi-omics analysis of methylation quantitative trait loci (mQTLs) and their association with psoriasis (validation cohort).

Supplementary material 2.

Author contributions

Hua Guo: Data curation, Software, Visualization, Methodology, original draft preparation. Jinyang Gao: Visualization. Liping Gong: Methodology, Revision, Funding acquisition. Yanqing Wang: Conceptualization, Supervision, Funding acquisition, Writing and Editing.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

We have no potential conflicts of interest to disclose.

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