International Journal of Rheumatic Diseases

WILEY

International Journal of Rheumatic Diseases

ORIGINAL ARTICLE OPEN ACCESS

Exploration of Circadian Clock-Related Genes in the Pathogenesis of Psoriatic Arthritis to Identify Potential Therapeutic Targets From Multi-Omics Insight: A Mendelian Randomization Study

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Received: 15 October 2024 | **Revised:** 7 February 2025 | **Accepted:** 21 February 2025

Funding: This study was supported by Youth Innovation Research Project of Sichuan Medical Association, Grant/Award Number: Q20006; College Students' Innovative Entrepreneurial Training Plan Program, Grant/Award Number: S202210632171. Medical beauty research of Liyan Workshop, Chengdu Medical College, Grant/Award Number: 23YM14.

Keywords: circadian clock-related genes | multi-omics | psoriatic arthritis | summary-data–based Mendelian randomization | therapeutic targets

ABSTRACT

Background: Circadian rhythms have been shown to play a significant role in the etiology and progression of immune-related morbidities, including cancer and autoimmune diseases. As an autoimmune disorder, psoriatic arthritis (PsA) has been under-explored in the context of circadian rhythms. This study aimed to explore the relationship between circadian rhythm and PsA.

Methods: We conducted a Summary-data–based Mendelian randomization (SMR) analysis, obtaining summary data on gene methylation, expression, and protein abundance levels of circadian clock-related genes (CRGs) from European ancestry individuals, with a total of 1749 genes selected from the GeneCards database using "biological clock" as the search term. The discovery cohort was obtained from the GWAS catalog database, and the replication cohort was obtained from the FinnGen database. Candidate genes related to circadian rhythm and PsA were identified through research, and their pharmacological potential and molecular docking were further validated as drug targets.

Results: After integrating multi-omics data, we identified 11 methylation sites in three genes (*HLA-DQB1*, *ITPR3*, and *GABBR1*) of CRGs that were causally related to PsA, and the effects produced were not consistent. The three gene expressions of CRGs (*IL4*, *HLA-DQB1*, and *OPI-AIS5*) were related to PsA. At the protein level, we identified three proteins (GCKR, STAT3, and CSNK2B) of CRGs related to PsA. The top 20 drug candidates underwent drug prediction screening, resulting in the identification of 12 compounds that demonstrated effective outcomes with three (HLA-DQB1, STAT3, and IL-4) specific therapeutic targets through molecular docking.

Abbreviations: CRGs, circadian clock-related genes; DSigDB, Drug Signatures Database; eQTL, expression quantitative trait loci; FDR, false discovery rate; GTEx, genotype-tissue expression; GWAS, genome-wide association study; HEIDI, heterogeneity in the dependent instrument; IVs, instrumental variants; LD, linkage disequilibrium; MAF, minor allele frequency; mQTL, methylation quantitative trait loci; pQTL, protein quantitative trait loci; PsA, psoriatic arthritis; SMR, Summary-data–based Mendelian randomization; SNP, single nucleotide polymorphism.

Aimei Liu and Wuda Huoshen contributed equally to this study.

Conclusion: This study suggests altered expression of circadian clock genes and proteins, including *HLA-DQB1*, *ITPR3*, *GABBR1*, *IL4*, *OIP5-AS1*, GCKR, CSNK2B, and STAT3, as factors contributing to the increased risk of PsA.

1 | Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthropathy, which occurs in approximately 30% of patients with psoriasis [1], characterized by varying degrees of peripheral and axial joint involvement, and is associated with an increased mortality rate from cardiovascular disease [2]. The pathogenesis of PsA is complex, involving genetic predispositions, immune-mediated inflammation, and environmental factors (such as infection, trauma, stress, obesity, and smoking) [3]. The specific details are not yet clear. Improving our understanding of the pathogenesis of PsA could help to establish effective diagnostic biomarkers, develop precise drugs, and predict which patients will respond to which therapy. A previous study has suggested that circadian rhythms may play a key role in the pathogenesis of psoriasis, as sleep and melatonin may lead to changes in the immune system, leading to the incidence and progression of psoriasis [4]. It has been shown that the circadian clock plays a role in the pathogenesis and clinical manifestations of inflammatory arthritis [5]. In models characterized by significant disruptions in circadian rhythms and melatonin release, such as in night-shift workers or in patients with sleep-related disorders [6], the risk of developing various rheumatic conditions, including psoriasis [4], The circadian rhythm, also referred to as the circadian clock, is an internal clock system that regulates a multitude of biological and behavioral processes, including sleep, hormone production, body temperature, and immune system function. The circadian rhythm has the ability to regulate immune system function by governing the circulation of lymphocytes, natural killer (NK) cells, antibody production, complement levels, cytokine synthesis, host–pathogen interactions, and induction of both innate and adaptive immunity [7]. Therefore, the immune system is affected by the circadian rhythm, and a disruption of the circadian cycle may lead to the occurrence of inflammatory diseases such as PsA. In addition, previous studies have suggested that disruption of the circadian clock may contribute to PsA progression, influence disease severity, and affect DLQI scores [8]. In order to better understand PsA, it is essential to study the relationship between circadian rhythm and PsA.

Mendelian randomization (MR) is not only a reliable method using genetic variants (single-nucleotide polymorphisms [SNPs]) to explain observational bias, but also a quasi-randomized controlled natural trial, due to variants are naturally and randomly allocated during meiosis [9]. MR uses genetic information as instrumental variables (IVs) to analyze the associations between exposures and outcomes. Because the genetic variants are usually unrelated to confounding factors, the difference in outcomes between individuals who carry the mutations and those who do not can be explained by differences in risky factors or disease susceptibility. Therefore, MR overcomes the drawbacks of confusion or reverse causality in traditional observational research [10]. Summary-data–based MR (SMR) is an extension of MR, in which the expression quantitative trait loci (eQTL) or DNA methylation quantitative trait loci (mQTL) for summary analysis, mainly used to analyze the association between genotype, gene expression, and phenotype [11].

To the best of our knowledge, currently, no MR study has investigated the possible causal relationship between circadian rhythm disorders and PsA. Therefore, this study aims to explore the causal association between circadian rhythm disruption and PsA using a comprehensive MR approach, characterized by the genetic susceptibility of circadian rhythm–related genes.

2 | Methods

2.1 | Study Design

We conducted the SMR analysis using publicly available summary-level data of quantitative trait loci (QTLs) and GWAS studies (Figure 1 and Tables S1–S18). All participants provided informed consent, and this study was approved by the ethics committee review board.

2.2 | Data Sources of Circadian Clock-Related Genes (CRGs)

We used "biological clock" as the main search term from the GeneCards (https://www.genecards.org/) to obtain 1749 CRGs (Table S2).

2.3 | Selection of Genetic Instruments

We used publicly available data for research. The eQTL summary-level data were collected from the eQTLGen Consortium (https://www.eqtlgen.org/) and the GTEx Consortium V8 (https:// gtexportal.org/), further details are outlined in the Tables S1–S18. We selected the MR mQTL instruments based on genetic variations that exhibit stable correlations with gene methylation related to circadian rhythm. Using blood mQTL summary data from a meta-analysis of two cohorts totaling 1980 individuals is a solid approach for identifying genetic instruments for studies [12]. We used the file from Price et al. to annotate the closest genes to DNA methylation probes [13]. MR protein QTL (pQTL) instruments were extracted from summary data provided by Ferkingstad E et al. ($n = 35\,559$) [14] and Sun et al. ($n = 54\,219$) [15]. In the analysis of eQTL, mQTL, and pQTL data, only probes that are linked to the expression of circadian clock–related genes and have at least one common cis-QTL (minor allele frequency [MAF] > 2%) surpassing the genome-wide significance threshold ($p < 5.0E\text{-}08$) were considered in the SMR analyses. The cis region was defined as within a 1 Mb range of a probe in both directions.

We conducted another instrument selection method to verify the observed correlation using eQTL as instruments. Specifically,

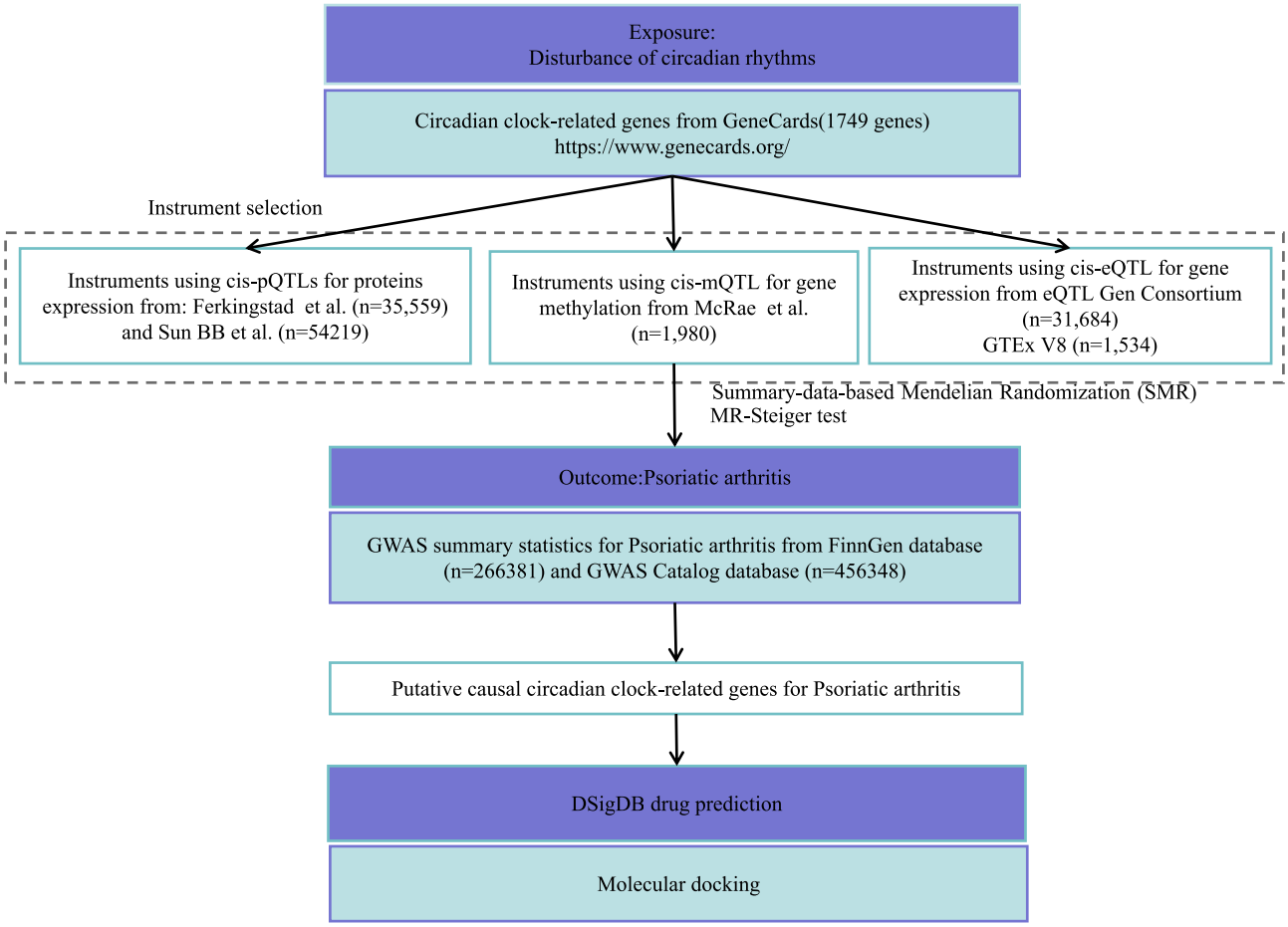

FIGURE 1 | Flowchart of this study. GWAS, genome-wide association studies; IVW-MR, inverse-variance-weighted MR; QTL, quantitative trait loci; SNP, single nucleotide polymorphism.

we selected single nucleotide polymorphisms (SNPs) located within 100 kb windows of the target gene, which had been associated with the circadian clock at a genome-wide significance threshold ($p < 5.0E-08$). These obtained SNPs were considered substitutes for the circadian clock-related exposures.

2.4 | Outcome Sources

GWAS summary statistics for PsA in discovery cohorts were collected from the FinnGen database, which included 266 381 individuals of European ancestry [16]. On the other hand, GWAS summary statistics for PsA in replication cohorts were obtained from the GWAS Catalog database, consisting of 456 348 individuals [17].

2.5 | Statistical Analyses

In our study, the SMR approach was employed using cis-QTLs as instruments to estimate the effect sizes. The SMR method was employed to investigate the association between gene expression and the outcome of interest, utilizing summary-level data from both GWAS and the investigations of cis-QTL [11]. For allele harmonization and analysis, the SMR software (version 1.03, https://yanglab.westlake.edu.cn/software/smr/#Overview) was used. To calculate the odds ratio (OR) estimates of circadian rhythm disorder on the risk of PsA, the following formula was applied: $OR = \exp.(\beta)$, where OR represents the odds ratio estimate per 1-ln increase in circadian clock genome levels, and exp. is the base of the natural logarithm.

The SMR software was used to perform the heterogeneity in the dependent instrument (HEIDI) test for the SMR technique. This test helped to assess whether the observed correlation between gene expression and the outcome of interest can be attributed to a linkage scenario [11]. For the calculation of linkage disequilibrium (LD), Genomes of European ancestry obtained from the 1000 Genomes Project Consortium were used as a reference [18]. The HEIDI test with $p > 0.01$ shows the presence of linkage imbalance [19]. Indeed, horizontal pleiotropy occurs when a single genetic variant is associated with the expression or function of multiple genes. In our study, we identified neighboring genes within a 1 Mb window that exhibited a strong correlation with the instrumental mutation. To investigate the potential presence of horizontal pleiotropy, we performed SMR analysis to examine whether the expression of the genes was also associated with the outcomes related to PsA. In addition, we conducted a direction test through Steiger filtering in MR analysis to ensure the stability of our SMR results. This measure helped to evaluate the direction of causality.

The Benjamini–Hochberg method was used to adjust the p values and control the false discovery rate (FDR) at $\alpha = 0.05$.

2.6 | Integrating Results From Multi-Omics Levels of Evidence

To elucidate the multifaceted relationship between the regulation of clock-related genes and PsA, we synthesized findings from two complementary tiers of gene regulation, providing a comprehensive understanding of their interconnections. Genes exhibiting associations with PsA across multiple omics layers were classified into Tier 1. In contrast, genes showing associations with PsA at a single omics level were classified into Tier 2.

2.7 | Drug Prediction

We utilized protein–drug interactions to investigate whether target genes could be potential drug targets by using the Drug Signatures Database (DSigDB), which is available at http://amp.pharm.mssm.edu/Enrichr. DSigDB contains a large collection of 22 527 gene sets and 17 389 unique compounds that interact with 19 531 genes. By uploading the identified target genes to DSigDB, this study allows for the prediction of potential drug candidates and the assessment of the medicinal properties of these targets. In our study, we uploaded the genes from our SMR results to the DSigDB section of Enrichr. This enabled us to identify candidate drugs and evaluate the therapeutic potential of the target genes based on the enriched gene sets. Default parameter settings were applied throughout the drug prediction. Potential drug targets were then selected based on an adjusted p value of less than 0.05.

2.8 | Molecule Docking

Small molecule ligand drug structures were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), while protein structures were obtained in pdb format from the PDB database (https://www.rcsb.org/). We utilized the CB-Dock2 platform (https://cadd.labshare.cn/cb-dock2/) to validate and visualize the interactions between the small molecule ligands and protein structures, which can help assess the feasibility and potential efficacy of the candidate drugs in targeting specific proteins.

3 | Results

3.1 | Clock Gene Methylation and PsA

In the SMR analysis of the whole genome cis-eqtl of the circadian clock and PsA, we matched 2835 unique genetic loci. To reduce the linkage disequilibrium response and the whole genome type I error, we removed the association of $P_{HEIDI} < 0.01$ and by the marginal significance ($p < 0.05$). Through multiple corrections, after integration with the UK Biobank and the FinnGen data, we determined that 11 CpG loci of the three genes *HLA-DQB1*, *ITPR3*, and *GABBR1* were causal with PsA. CpG loci within the same gene displayed varying effects on PsA risk. Specifically, we found that elevated methylation levels at the *HLA-DQB1* gene loci cg01745539, cg00995368, cg09555323, and cg03202060 were significantly associated with an increased risk of PsA (OR 1.26, 95% CI 1.20–1.33; OR 1.60, 95% CI 1.38–1.86; OR 2.57, 95% CI 1.76–3.74; OR 3.29, 95% CI 1.79–6.06). Reduced methylation at cg22984282 and cg11986643 was associated with an increased risk of PsA (OR 0.82, 95% CI 0.78–0.86; OR 0.74, 95% CI 0.67–0.81). Similarly, an increase in *ITPR3* cg18558423 promoted the risk of PsA (OR 1.26, 95% CI 1.11–1.42), while cg07713849 was just the opposite (OR 0.68, 95% CI 0.55–0.83). Elevated methylation levels at the *GABBR1* locus cg09577455 were associated with an increased risk of PSA (OR 1.02, 95% CI 1.01–1.03) (Figure 2a). The detailed SMR analysis results of clock gene methylation and PsA were presented in Tables S3 and S4. All evaluations successfully passed the Steiger test in gene methylation level and were presented in Table S15.

3.2 | Clock Gene Expression and PsA

eQTL was matched to 585 and 1285 genes from eQTLGen Consortium and GTExV8, respectively. The gene expression of HLA-DQB1, akin to methylation, exhibited a causal association with the manifestation of PsA. After integration, we identified the following three genes: the increased expression of the HLA-DQB1 gene was associated with an increased risk of PsA (OR 1.26, 95% CI 1.18–1.34). There was also strong evidence of a correlation between IL4 and PsA. The decreased expression of IL4 led to an increased risk of PsA (OR 0.28, 95% CI 0.17–0.46). In contrast, the increase of OPI-AIS5 promoted the risk of PsA (OR 1.75, 95% CI 1.31–2.34) (Figure 2b). The results of the SMR analysis examining the relationship between clock gene expression and PsA are presented in Tables S5–S8. All evaluations met the significance threshold according to the Steiger test for gene methylation level, with findings presented in Table S16.

3.3 | Clock Encoded Protein and PsA

PQTL were matched to 625 and 363 proteins from Ferkingstad et al. and Sun et al. respectively. After integration, three proteins were identified: GCKR, CSNK2B, and STAT3. GCKR also had a strong positive correlation with the occurrence of PsA (OR 3.29, 95% CI 1.76–6.06). The increased expression of STAT3 also led to the evaluated risk of PsA (OR 1.18, 95% CI 1.08–1.29). CSNK2B was just the opposite (OR 0.98, 95% CI 0.97–0.99) (Figure 2c). The SMR results of clock-encoded protein and PsA were summarized in Tables S9–S12. All evaluations satisfied the Steiger test criteria for gene methylation level, with results presented in Table S17.

3.4 | Integrating Results From Multi-Omics Level of Evidence

After integrating evidence from multiple omics layers, we identified one gene (*HLA-DQB*1) that was classified into tier 1 based on both gene expression and gene methylation data. The remaining genes (*ITPR3*, *GABBR1*, *IL4*, *OIP5-AS1*, GCKR, CSNK2B, and STAT3) were not classified into Tier 1, as they showed associations with PsA only at a single omics level.

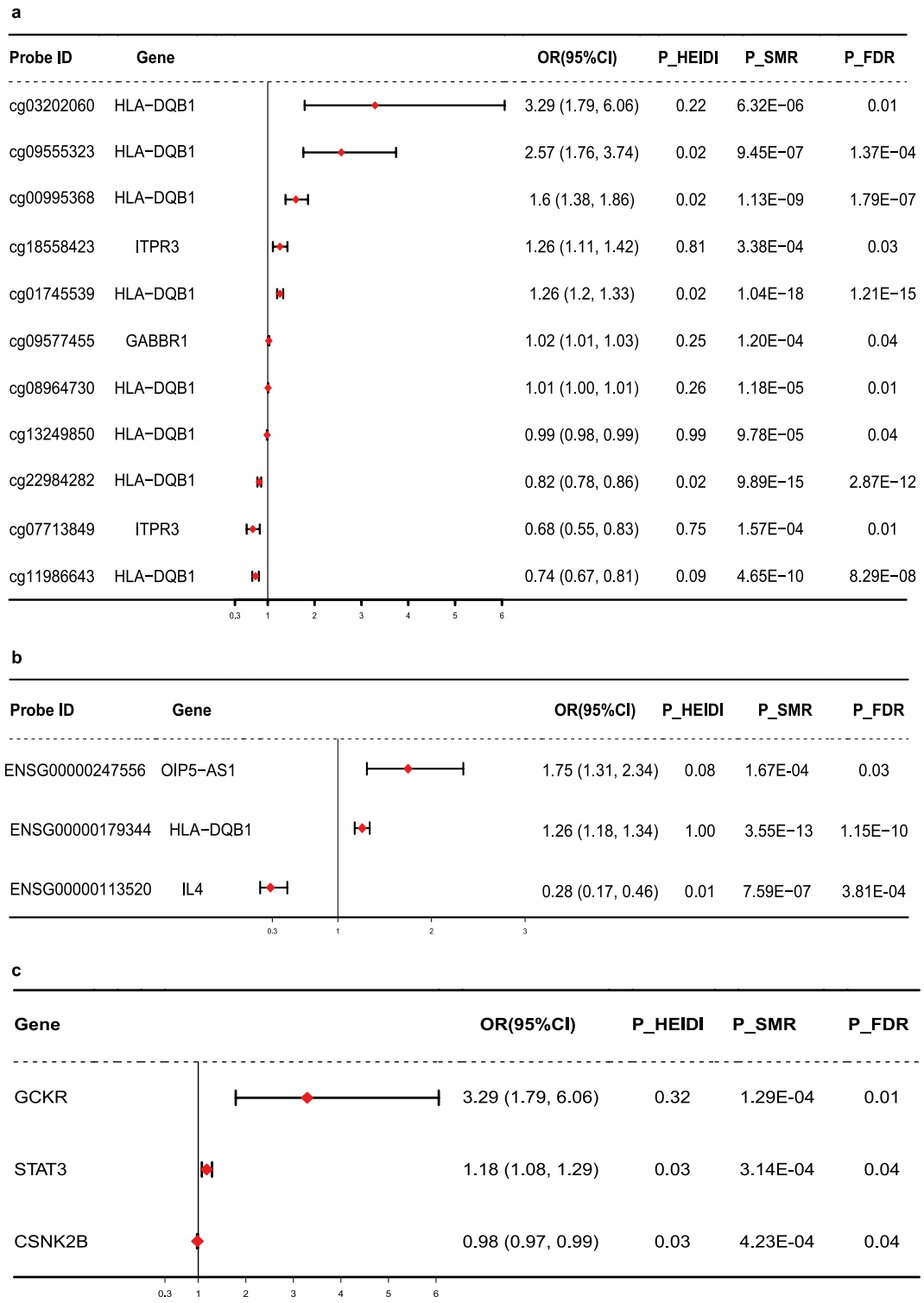

FIGURE 2 | Summary-data–based Mendelian randomization (SMR) results for the association between the multi-omic level of circadian clock-related genes and PsA. OR, odds ratio; PsA, psoriatic arthritis; SMR, Summary-data–based Mendelian randomization. (a) The SMR results for the association between the methylation of circadian clock–related genes and PsA. (b) SMR results for the association between the expression of circadian clock-related genes and PsA. (c) SMR results for the association between the encoded protein of circadian clock–related genes and PsA.

3.5 | Drug Candidate Prediction

The DsigDB database was used to predict the possible effective intervention drugs. According to the adjusted *p* value, the top 20 potential compounds were listed (Table S18 and Table 1). Results showed that DL-Phenylalanine BOSS and L-glutamine BOSS affected IL4, STAT3, and ITPR3 (Table 1). IL4 was linked to 2,4-Diisocyanato-1-methylbenzene CTD 00006908 and HLA-DQB1 (Table 1). Ouabain BOSS was linked to STAT3 and ITPR3. Trichloroethylene CTD 00006932 was linked to IL4 and GABBR1. The rest were linked to IL4 and STAT3.

TABLE 1 | Candidate drug predicted using DSigDB.

Drug names	*p*	Adjusted *p*	Genes
DL-Phenylalanine BOSS	5.90E-06	0.003	IL4; STAT3
L-glutamine BOSS	4.56E-05	0.008	IL4; STAT3
Cladribine CTD 00007175	5.65E-05	0.008	IL4; STAT3
2,4-Diisocyanato-1-methylbenzene CTD 00006908	6.47E-05	0.008	IL4; HLA-DQB1
Pulmicort Nebuamp BOSS	7.35E-05	0.008	IL4; STAT3
Kynurenine BOSS	1.20E-04	0.01	IL4; STAT3
124020-07-1 CTD 00007038	1.20E-04	0.01	IL4; STAT3
Azathioprine CTD 00005457	2.06E-04	0.012	IL4; STAT3
Ferrous sulfate CTD 00001009	2.21E-04	0.012	IL4; STAT3
105156–22-7 CTD 00005867	2.21E-04	0.012	IL4; STAT3
Ouabain BOSS	2.53E-04	0.013	STAT3; ITPR3
Sodium sulfate BOSS	2.88E-04	0.013	IL4; STAT3
2-Fluoroadenosine BOSS	4.25E-04	0.016	IL4; STAT3
Trichloroethylene CTD 00006932	4.46E-04	0.016	IL4; GABBR1
Pentadecane BOSS	4.69E-04	0.016	IL4; STAT3
Acetoacetic acid BOSS	4.92E-04	0.016	IL4; STAT3
Etretinate BOSS	5.39E-04	0.016	IL4; STAT3
Dichloromercury CTD 00006273	5.39E-04	0.016	IL4; STAT3
Chlorophenothane CTD 00005755	5.51E-04	0.016	IL4; STAT3
Eicosapentaenoic acid BOSS	5.63E-04	0.016	IL4; STAT3
Eicosapentaenoic acid BOSS	5.63E-04	0.016	IL4; STAT3

3.6 | Molecular Docking

The assessment of the affinity between drug candidates and their targets is essential for evaluating the efficacy of drug intervention on the target. Molecular docking was performed in this study. Using the binding sites and interactions of the top 20 drug candidates with the corresponding gene-encoded proteins, each drug candidate was connected to its protein target through visible hydrogen bonds and strong electrostatic interactions. By calculating the binding energy of each interaction, a total of 12 drug candidates were found to have effective docking results with their drug targets (Table 2). Specifically, 2,4-Diisocyanato-1-methylbenzene CTD 00006908 was found to be associated with HLA-DQB1 and IL-4, while several other drugs were connected to IL-4 and STAT3. Notably, Pulmicort Nebuamp BOSS, Etretinate, Cladribine CTD 00007175, and 2-Fluoroadenosine exhibited stronger associations. Among the compounds targeting STAT3 gene expression, ouabain demonstrated the most significant association (Figure 3). A lower binding energy corresponds to a more favorable binding interaction and increased affinity.

4 | Discussion

In our study, we leveraged multi-omics data integration to analyze GWAS signals and perform molecular docking in order to explore the relationship between genetic prediction of CRGs methylation, expression, protein, and PsA. The following causative genes or proteins were identified: *HLA-DQB1*, *ITPR3*, *GABBR1*, *IL4*, *OIP5-AS1*, GCKR, CSNK2B, and STAT3. Molecular docking was performed on the corresponding gene-encoded proteins, which further proves the value of these gene-targeted drug developments.

Circadian clock–related gene HLA-DQB1 belongs to the HLA-II antigen β para-system, which is composed of β chains and forms a functional complex protein with DQA1 composed of α chains [20]. Its primary role is to process and present exogenous antigens for CD4 + T lymphocytes, facilitating immune regulation [20]. The involvement of HLA-DQB1 in the pathogenesis of various diseases, including rheumatoid arthritis, has been demonstrated by previous studies [21], and different gene loci also play different roles. The DQB1*06:02 allele is considered to confer susceptibility to multiple sclerosis [22]. HLA-DQB1*05:03 and DQB1*03:02 are substantially increasing the incidence of pemphigus; HLA-DQB1*02, DQB1*06:01, and DQB1*03:03 are negatively correlated [23]. HLA-DQB1*02 is a risk factor for psoriasis, and DQB1*0202 is an important allele for the response to Acitretin drug therapy in patients with psoriasis [24]. Participants with the HLA-DQB1*06 allele produced more antibodies in their bodies after Coronavirus disease 2019 (COVID-19) vaccination [25]. The aforementioned studies have demonstrated that HLA-DQB1 plays a pivotal role in immune

TABLE 2 | Docking results of available proteins with small molecules.

Target	PDB ID	Drug	PubChem ID	Binding energy
HLA-DQB1	2NNA	2,4-Diisocyanato-1-methylbenzene CTD 00006908	11443	−5.5
IL4	1BBN	Pulmicort Nebuamp BOSS	5281004	−6.4
IL4	1BBN	Cladribine CTD 00007175	20279	−6.1
IL4	1BBN	Kynurenine BOSS	846	−6
IL4	1BBN	124020-07-1 CTD 00007038	12133445	−6
IL4	1BBN	Azathioprine CTD 00005457	2265	−5.9
IL4	1BBN	DL-Phenylalanine BOSS	994	−5.6
IL4	1BBN	2,4-Diisocyanato-1-methylbenzene CTD 00006908	11443	−5.6
IL4	1BBN	Etretinate	5282375	−7.1
IL4	1BBN	2-Fluoroadenosine	8975	−6.6
IL4	1BBN	Eicosapentaenoic acid	446284	−5.8
IL4	1BBN	Chlorophenothane	3036	−5.7
STAT3	6NJS	Ouabain	439501	−9.0
STAT3	6NJS	Pulmicort Nebuamp BOSS	5281004	−7.7
STAT3	6NJS	2-Fluoroadenosine	8975	−7.1
STAT3	6NJS	Cladribine CTD 00007175	20279	−6.8
STAT3	6NJS	Etretinate	5282375	−6.4
STAT3	6NJS	Azathioprine CTD 00005457	2265	−6.3
STAT3	6NJS	Kynurenine BOSS	846	−6.2
STAT3	6NJS	Chlorophenothane	3036	−6.1
STAT3	6NJS	124020-07-1 CTD 00007038	12133445	−5.8
STAT3	6NJS	Eicosapentaenoic acid	446284	−5.4
STAT3	6NJS	DL-Phenylalanine BOSS	994	−5.2

activity. The aforementioned studies have demonstrated that the role of HLA-DQB1 in immune activity is well documented. Our study revealed a significant association between HLA-DQB1 gene methylation and gene expression with the occurrence of PSA. Specifically, increased methylation at cg01745539, cg00995368, cg09555323, and cg03202060 was linked to an elevated risk of PsA, whereas decreased methylation at cg22984282 and cg11986643 was associated with a reduced risk.

ITPR3 encodes the inositol 1,4,5-triphosphate receptor, which is a widely existing endoplasmic reticulum calcium channel protein related to apoptosis [26]. The upregulation of this receptor is implicated in the development of various tumors, including cervical squamous cell carcinoma and cholangiocarcinoma [27]. The expression in the salivary glands of Sjogren's syndrome and autoimmune extra-glandular diseases related to secretion defects is observed to be reduced [28]. The upregulation of methylation levels at the ITPR3 locus cg18558423 may be associated with an increased risk of PsA. The human genes that encode IL-4 and IL-13 are situated at chromosome 5q31. Both IL-4 and IL-13 belong to the T helper cytokine 2 family and share a receptor known as the type II receptor [29]. The cytokine IL-4 plays a crucial role in both the initiation and therapeutic management of psoriasis. Notably, IL-4 has been identified as a psoriasis-associated gene in the CASP (Collaborative Association Study of Psoriasis) through a comprehensive GWAS study involving individuals of European descent [30]. The skin treated with dupilumab, an antibody that targets the IL-4 and IL-13 receptors in the treatment of atopic dermatitis, exhibited psoriasis-like alterations [31]. Our study suggests that the decrease of IL4 gene expression may lead to the occurrence of PsA. The long non-coding transcript OIP5-AS1 exhibits high expression in the nervous system as a pivotal role in tumor transformation. The involvement of this lncRNA in the regulation of cell cycle transformation at various stages is evident. OIP5-AS1 is elevated in almost all types of tumor tissues except for multiple myeloma [32]. Further, it was found that OIP5-AS1 is associated with the occurrence and development of rheumatoid arthritis; the knockdown of RNA OIP5-AS1 can inhibit the proliferation and inflammation of FLSs [33]. The overexpression of OIP5-AS1 may be associated with the occurrence of PsA.

GCK is a key liver enzyme for glucose metabolism. The expression of glucose kinase regulatory protein (GCKR) is primarily

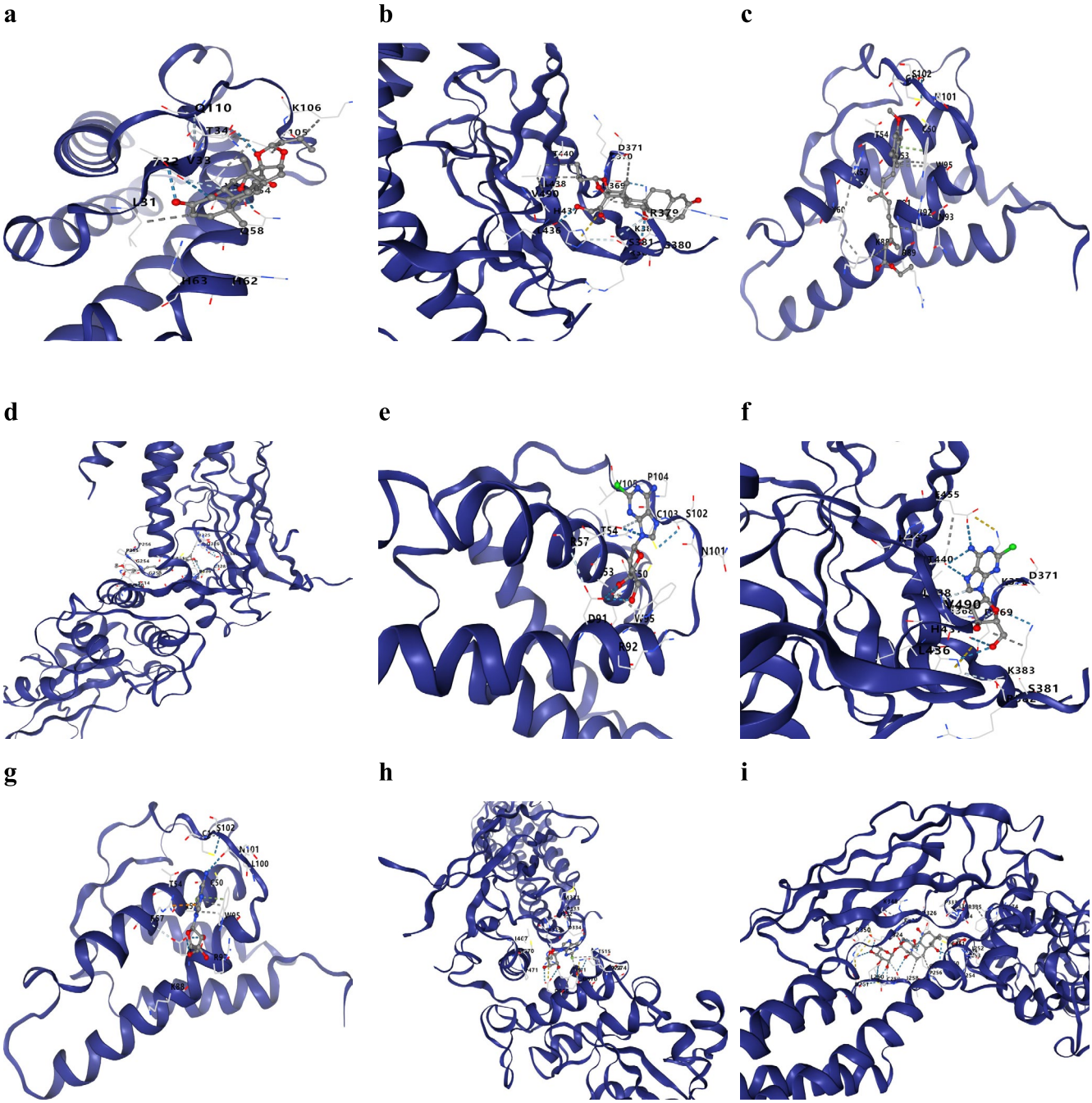

FIGURE 3 | Docking results of protein-small molecule interactions. (a) IL4 docking Pulmicort Nebuamp BOSS, (b) STAT3 docking Pulmicort Nebuamp BOSS, (c) IL docking etretinate, (d) STAT3 docking etretinate, (e) IL4 docking Cladribine CTD 00007175, (f) STAT3 docking Cladribine CTD 00007175, (g) IL4-2 docking fluoroadenosine, (h) STAT3 docking 2-fluoroadenosine, (i) STAT3 docking ouabain.

limited to hepatocytes. GCKR is a glucose kinase regulatory protein that can act as an inhibitor of glucose kinase (GCK) activity [34]. By influencing metabolism, GCKR has been linked to many metabolic diseases, most notably NAFLD [35], which is considered to be a predictor of the transformation of asymptomatic hyperuricemia to gout and a genetic marker for end-stage and high-risk kidney disease (ESKD) population in type 2 diabetes patients [36]. GCKR has not been studied in relation to psoriasis and PsA for the time being. The findings of our study suggest that the upregulation of the protein encoded by the GCKR gene may potentially contribute to the pathogenesis of PsA. In summary, we can see that among the genes affecting circadian rhythm, the genes associated with PsA include immunity, cell proliferation, and metabolism. CSNK2B and STAT3 have been implicated in the pathogenesis of PsA, although the relationship between these genes and the disease remains modest.

Furthermore, this study successfully predicted and conducted molecular docking for drugs targeting the identified genes, providing additional evidence to support their potential as therapeutic targets in disease treatment. Pulmicort Nebuamp BOSS contains Budesonide as its active ingredient, which has been shown in studies to improve clinical scores and cell proliferation in psoriasis when used for a duration of 1–3 weeks

[37]. The pharmacologically active metabolite of Etretinate is Acitretin, which has been widely utilized for treating PsA [38, 39]. Cladribine CTD 00007175 (2-chlorodeoxyadenosine) is currently extensively employed in multiple sclerosis treatment [40], there was one clinical case report demonstrating relief from PsA after oral administration of this drug [41]. Therefore, it can be inferred that these aforementioned drugs may exert their effects on treating psoriasis or PsA by modulating the expression of IL-4 and STAT3 genes. Previous studies have demonstrated the potential of ouabain as an effective anti-psoriasis medication due to its capacity to induce cytotoxicity in psoriatic keratinocytes [42]. However, there have been no clinical trials conducted thus far to investigate the efficacy of ouabain in treating PsA. These pharmaceuticals influence genes associated with the circadian rhythm and have therapeutic potential for PsA or psoriasis. Consequently, our study is reciprocally validated, suggesting that genetic alterations in the circadian clock may influence psoriatic arthritis.

This study boasts several strengths. Notably, it is the first to explore the causal relationship between circadian rhythm and the onset of PsA using SMR, integrating multi-omics data to elucidate GWAS signals. This approach effectively mitigates confounding variables and reverse causality, thereby enhancing the precision of our findings. Furthermore, the GWAS data utilized for IV selection feature a large sample size and high accuracy. Additionally, we employed molecular docking and drug prediction analyses to uncover the therapeutic potential of the identified genes.

To minimize the impact of confounding factors, we utilized a MR study design. Furthermore, we implemented rigorous measures to optimize the validity of our instrumental variables, thereby mitigating potential biases to the greatest extent possible. However, some sources of inaccuracy and bias may still exist. Unconsidered potential factors may still significantly impact the research outcomes. First, the generalizability of the study is limited by its predominant inclusion of individuals of European descent. Second, the existing eQTL and mQTL datasets lack information on genetic variation associated with gene expression or methylation levels in the X and Y chromosomes. In addition, in order to explore more potential relationships between PsA and CRGs as an exploratory study, we included the CRGs verified in only one cohort. In future studies, we plan to extend our research to more diverse racial and ethnic populations to address the limitation that the current data are predominantly derived from individuals of European descent.

Nevertheless, we provide a comprehensive catalog of potential therapeutic agents that merit further validation through experimental and population-based studies.

5 | Conclusion

Multi-omics studies have revealed altered expression of circadian clock genes and proteins, including HLA-DQB1, ITPR3, GABBR1, IL4, OIP5-AS1, GCKR, CSNK2B, and STAT3, which are associated with an increased risk of PsA. Notably, these genes and proteins also emerge as potential therapeutic targets. Furthermore, in silico drug prediction indicates a potential therapeutic prospect and significance.

Author Contributions

Zhen Qin, Aimei Liu, Yifei Wang, and Wuda Huoshen contributed to the conception and design of the study. Zhen Qin, Aimei Liu, and Wuda Huoshen conducted data analysis. Zhen Qin and Yifei Wang drafted the manuscript, and Aimei Liu performed editing. Sha Yi provided valuable guidance on writing style. All authors reviewed and approved the final manuscript.

Acknowledgments

We all really appreciate being involved in the McRae et al. the eQTLGen consortium, GTEx Consortium V8, Ferkingstad et al. Sun et al. the FinnGen study, and the GWAS Catalog database for generously sharing data.

Ethics Statement

This study draws on published studies and coalitions that have made their publicly accessible summary statistics, which have obtained approval from their respective ethical review boards. So, a new ethical review and approval was not required in our study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets presented in this study can be found in online repositories. The names of the repositories can be found in the article or Supporting Information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.