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Exploring new drug treatment targets for immune related bone diseases using a multi omics joint analysis strategy

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In the field of treatment and prevention of immune-related bone diseases, significant challenges persist, necessitating the urgent exploration of new and effective treatment methods. However, most existing Mendelian randomization (MR) studies are confined to a single analytical approach, which limits the comprehensive understanding of the pathogenesis and potential therapeutic targets of these diseases. In light of this, we propose the hypothesis that genetic variations in specific plasma proteins have a causal relationship with immune-related bone diseases through the MR mechanism, and that key therapeutic targets can be accurately identified using an integrated multi-omic analysis approach. This study comprehensively applied a variety of analytical methods. Firstly, the protein quantitative trait locus (pQTLs) data from two large plasma protein databases and the Genome-Wide Association Study (GWAS) data of nine immune-related bone diseases were used for Mendelian randomization (MR) analysis. At the same time, we employed the Summary-based Mendelian Randomization (SMR) method, combined with the Bayesian colocalization analysis method of coding genes, as well as the Linkage Disequilibrium Score Regression (LDSC) analysis method based on genetic correlation analysis, as methods to verify the genetic association between genes and complex diseases, thus comprehensively obtaining positive results. In addition, a Phenome-wide Association Study (PheWAS) was conducted on significantly positive genes, and their expression patterns in different tissues were also explored. Subsequently, we integrated Protein–Protein Interaction (PPI) network analysis, Gene Ontology (GO) analysis. Finally, based on the above analytical methods, drug prediction and molecular docking studies were carried out with the aim of accurately identifying key therapeutic targets. Through a comprehensive analysis using four methods, namely the Mendelian randomization (MR) analysis study, Summary-based Mendelian Randomization (SMR) analysis study, Bayesian colocalization analysis study, and Linkage Disequilibrium Score Regression (LDSC) analysis study. We found that through MR, SMR, and combined with Bayesian colocalization analysis, an association was found between rheumatoid arthritis (RA) and HDGF. Using the combination of MR and Bayesian colocalization analysis, as well as LDSC analysis, it was concluded that RA was related to CCL19 and TNFRSF14. Based on the methods of MR and Bayesian colocalization, an association was found between GPT and Crohn's disease-related arthritis, and associations were found between BTN1A1, EVI5, OGA, TNFRSF14 and multiple sclerosis (MS), and associations were found between ICAM5, CCDC50, IL17RD, UBLCP1 and psoriatic arthritis (PsA). Specifically, in the MR analysis of RA, HDGF (P_ivw = 0.0338, OR = 1.0373, 95%CI = 1.0028—1.0730), CCL19 (P_ivw = 0.0004, OR = 0.3885, 95%CI = 0.2299—0.6566), TNFRSF14 (P_ivw = 0.0007, OR = 0.6947, 95%CI = 0.5634—0.8566); in the MR analysis of MS, BTN1A1 (P_ivw = 0.0000, OR = 0.6101, 95%CI = 0.4813—0.7733), EVI5 (P_ivw = 0.0000, OR = 0.3032, 95%CI = 0.1981—0.4642), OGA (P_ivw = 0.0005, OR = 0.4599, 95%CI = 0.2966—0.7131), TNFRSF14 (P_ivw = 0.0002, OR = 0.4026, 95%CI = 0.2505—0.6471); in the MR analysis of PsA, ICAM5 (P_ivw = 0.0281, OR = 1.1742, 95%CI = 1.0174—1.3552), CCDC50 (P_ivw = 0.0092, OR = 0.7359, 95%CI = 0.5843—0.9269), IL17RD (P_ivw = 0.0006, OR = 0.7887, 95%CI = 0.6886—0.9034), UBLCP1 (P_ivw = 0.0021, OR = 0.6901, 95%CI = 0.5448—0.8741); in the MR analysis of Crohn's disease-related arthritis, GPT (P_ivw = 0.0006, OR = 0.0057, 95%CI = 0.0003—0.1111). In the Bayesian colocalization analysis of RA, HDGF (H4 = 0.8426), CCL19 (H4 = 0.9762), TNFRSF14 (H4 = 0.8016); in the Bayesian colocalization analysis of MS, BTN1A1 (H4 = 0.7660), EVI5 (H4 = 0.9800), OGA (H4 = 0.8569), TNFRSF14 (H4 = 0.8904); in the Bayesian colocalization analysis of PsA, ICAM5 (H4 = 0.9476), CCDC50 (H4 = 0.9091), IL17RD (H4 = 0.9301), UBLCP1 (H4 = 0.8862); in the Bayesian colocalization analysis of

Crohn's disease-related arthritis, GPT (H4 = 0.8126). In the SMR analysis of RA, HDGF (p_SMR = 0.0338, p_HEIDI = 0.0628). In the LDSC analysis of RA, CCL19 (P = 0.0000), TNFRSF14 (P = 0.0258). By comprehensively analyzing plasma proteomic and transcriptomic data, we successfully identified key therapeutic targets for various clinical subtypes of immune-associated bone diseases. Our findings indicate that the significant positive genes associated with RA include HDGF, CCL19, and TNFRSF14; the positive gene linked to Crohn-related arthropathy is GPT; for MS, the positive genes are BTN1A1, EVI5, OGA, and TNFRSF14; and for PsA, the positive genes are ICAM5, CCDC50, IL17RD, and UBLCP1. Through this comprehensive analytical approach, we have screened potential therapeutic targets for different clinical subtypes of immune-related bone diseases. This research not only enhances our understanding of the pathogenesis of these conditions but also provides a solid theoretical foundation for subsequent drug development and clinical treatment, with the potential to yield significant advancements in the management of patients with immune-related bone diseases.

Keywords Immune-related bone diseases, Mendelian randomization, Druggable target genes, Plasma proteins, Genetic correlation

Abbreviations

MR	Mendelian randomization
pQTL	Protein quantitative trait locus
SMR	Mendelian randomization based on summary data
LDSC	LD Score regression
eQTL	Expression quantitative trait loci
mQTL	Methylation quantitative trait locus
GWAS	Genome-wide association studies
SNPS	Single nucleotide polymorphisms
IVS	Instrumental variables
FDR	False discovery rate
IVW	Inverse-variance weighted
PheWAS	Phenome-wide association study
G0	Gene Ontology
PPI	Protein protein interaction
RA	Rheumatoid Arthritis
MS	Multiple Sclerosis
PsA	Psoriatic Arthritis
SP-RA	Seropositive Rheumatoid Arthritis
SN-RA	Seronegative Rheumatoid Arthritis
JRA	Juvenile Rheumatoid Arthritis
AS	Ankylosing Spondylitis
TNFRSF14	Tumor Necrosis Factor Receptor Superfamily Member 14
CCL19	C–C motif chemokine ligand 19
HDGF	Hepatoma-derived growth factor
GPT	Glutamate Aminotransferase
BTN1A1	Butyrophilin Subfamily 1 Member A1
EVI5	Ecotropic Viral Integration Site 5
OGA	O-GlcNAcase
ICAM5	Intercellular Adhesion Molecule 5
CCDC50	Coiled-Coil Domain Containing 50
IL-17RD	IL-17 receptor
UBLCP1	Ubiquitin-like domain containing C-terminal phosphatase 1
OR	Odds ratio
95%CI	95% Confidence interval
DMBA	7,12-Dimethylbenz[a]anthracene
MTZ	Metronidazole
PCB118	3,3',4,4',5-Pentachlorobiphenyl
MMS	Methyl methanesulfonate

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Immune-related bone diseases encompass a range of clinically prevalent conditions that are intricately linked to abnormalities in the immune system. These diseases not only jeopardize the patient's bone health but may also lead to joint dysfunction, significantly impairing the patient's quality of daily life. The clinical manifestations of immune-related bone diseases are diverse, complex, and insidious, rendering diagnosis and treatment particularly challenging. A 2009 report from the United States Coordinating Committee on Autoimmune Diseases estimated that approximately 20 million Americans are affected by autoimmune diseases[1].Furthermore,

according to the 2010 Global Burden of Disease (GBD) data, the global prevalence of RA is approximately 0.24%[2], with the highest rates observed in the United States and Nordic countries, ranging from 0.5% to 1%[3,4]. The most recent GBD data from 2017 indicate that the global prevalence of RA has risen to 0.27%, with North America exhibiting a prevalence of 0.38% and Western Europe 0.35%[5]. Additionally, data from the World Health Organization (WHO) reveal that in 2019, approximately 18 million individuals worldwide were suffering from RA, with women constituting the primary affected demographic[6]. Moreover, clinical studies on inflammatory bowel disease (IBD) indicate that up to 50% of IBD patients may experience extraintestinal manifestations, with osteoarthritis being the most prevalent. It is estimated that between 10 and 39% of IBD patients will develop IBD-related joint complications[7].Another study utilizing the IBM Watson Health commercial database in the United States revealed that the annual all-cause healthcare costs for patients with psoriatic arthritis (PsA) can reach as high as $29,742. This figure represents 2.69 times the costs incurred by patients with ordinary psoriasis and approximately 10% of the costs associated with non-psoriasis patients, indicating a fourfold increase in expenses for PsA patients[8]. Additionally, an assessment of the annual direct and indirect economic costs of axial spondyloarthritis (axSpA) in Singapore estimated the annual direct costs to be approximately US$67,931,457, while indirect costs were around US$6,855,951[9]. The pathogenesis of immune-related bone diseases is complex, potentially involving factors such as genetics, diet, immune regulation, and environmental influences. Given the significant suffering these diseases inflict on patients and the substantial burden they place on society, it is crucial to conduct in-depth and comprehensive research in this area.

Currently, the treatment and prevention of immune-related bone diseases present significant challenges in the medical field, characterized by their complexity. While biological agents such as tumor necrosis factor (TNF) antagonists, interleukin-17 inhibitors, interleukin-1 antagonists, and B cell depleting agents can alleviate symptoms and enhance bone and joint function, numerous difficulties persist throughout the treatment process. One major concern is the side effects of these medications, which can include increased neurological complications[10], heightened risk of infections[11], and potential damage to liver and kidney function[12]. Additionally, the long-term use of immunosuppressants may compromise the immune system[13]. Another challenge lies in the variability of treatment response rates; some patients experience limited symptom relief, and their conditions may even deteriorate[14]. This variability is influenced by individual differences, disease heterogeneity, and other factors. To improve the effectiveness of treatments for immune-related bone diseases, it is essential to continue exploring new therapeutic targets. GWAS can identify single nucleotide polymorphisms (SNPs) associated with the risk of these diseases. However, findings from GWAS must be integrated with comprehensive analyses to pinpoint causative genes and facilitate drug development. Without this integration, accurately identifying disease-causing genes or effectively advancing drug development remains challenging. This is partly due to the fact that the associated loci identified by GWAS may reside in intergenic regions, and the mechanisms by which they influence gene expression and function are not yet sufficiently understood. Therefore, further in-depth research is necessary to elucidate the relationship between these loci and disease progression.

MR is a method that employs genetic variation as instrumental variables (IVs) to investigate the causal relationships between exposure factors and disease. Recent technological advancements, such as aptamers and immunoassays from the SomaScan and Olink platforms, have enabled MR analysis to integrate GWAS data with summary results from pQTLs, thereby enhancing its potential to identify novel therapeutic targets. Notably, pQTLs situated within the vicinity of drug-acting genes are particularly valuable, as they can reflect the levels of gene expression—an important indicator of long-term exposure status—and are thus considered alternative biomarkers. Our objective is to provide insights and guidance for the development of more efficient and accurate therapeutic agents through comprehensive analysis, which is anticipated to foster advancements in this area of treatment.

Method

Research design

Figure 1 illustrates the analytical framework of the full text. Initially, we employed the two-sample MR analysis method to identify positive proteins significantly associated with immune-related bone diseases from two large-scale plasma pQTL datasets. Following this, we conducted sensitivity analyses and reproducibility testing to thoroughly investigate the functional roles of these candidate plasma protein targets in immune-related bone diseases. Subsequently, we utilized SMR, Bayesian colocalization analysis, and LDSC analysis based on summary data as validation and supplementary methods for the MR analysis. For the positively identified genes resulting from our comprehensive screening, we performed a PheWAS using all GWAS projects from the 11th version of the FinnGen database, exploring their expression across various tissues to comprehensively examine the potential functions of these genes. Additionally, we investigated the underlying biological mechanisms of the putative protein targets through PPI analysis, GO enrichment analysis. We also carried out drug prediction and molecular docking studies on the positively identified genes, providing a scientific basis for the development of more effective and targeted therapeutic drugs. Finally, we classified and evaluated the evidence from this study based on the results of the MR, SMR, Bayesian colocalization analysis, and LDSC analysis, in conjunction with existing research evidence.

Data sources for plasma proteomics

The Icelandic plasma pQTLs data originates from a study led by Egil Ferkingstad, which analyzed the plasma proteins of 35,559 Icelanders using the SomaScan platform[15]. This investigation revealed 28,191 out of 4,907 protein indicators with genetic links. The study's data were primarily derived from genetic projects associated with the Iceland Cancer Project (ICP) and deCODE Genetics in Reykjavik. Researchers employed recursive conditional analysis to identify the most significant variation within each region (± 1 Mb), designating these as the primary indicators of plasma pQTLs (n = 18,084), while other variations were classified as secondary

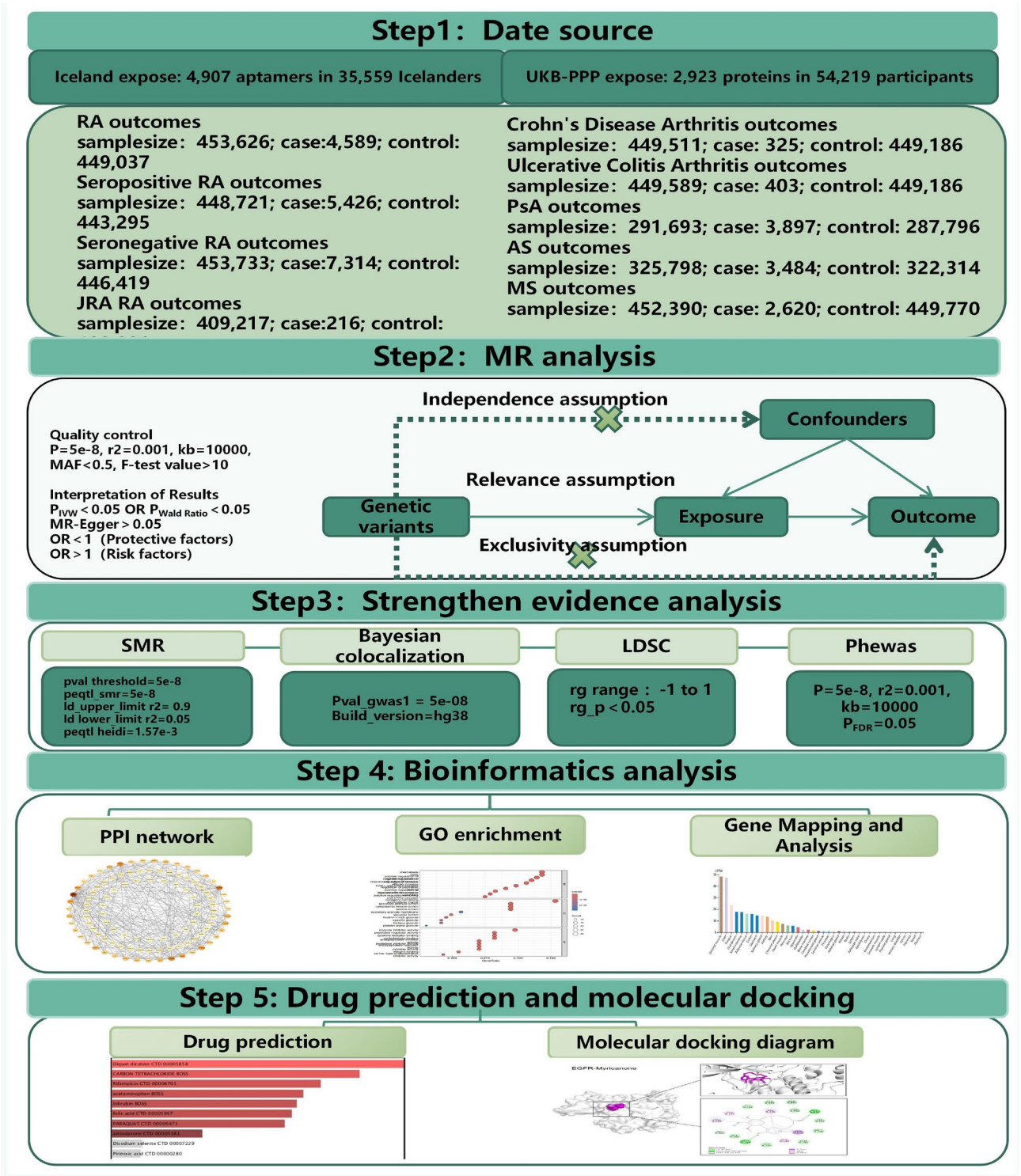

Fig. 1. Flowchart of Article Analysis.MR: Mendelian randomization analysis;SMR: Summary-based Mendelian randomization analysis;LDSC: Linkage disequilibrium score regression;PheWAS: Phenome-wide association study; PPI: Protein-protein interaction;GO: Gene Ontology;KEGG: Kyoto Encyclopedia of Genes and Genomes;DSigDB: Drug Signatures Database.

indicators (n = 10,107). The study successfully replicated 83% of the SomaScan-based plasma pQTLs in the INTERVAL study and 64% of the Olink-based plasma pQTLs in the SCALLOP consortium. The complete GWAS data can be accessed at (https://www.decode.com/summarydata/).

Another sample of plasma pQTLs was obtained from the UK Biobank, with the study published in October 2023[16]. The research team employed the Olink platform to analyze 2,923 proteins from the UK Biobank

Pharmaceutical Proteomics Project (UKB-PPP) and identified 23,588 preliminary genetic associations. The study examined 84% of known pQTLs in antibody studies and 38% of pQTLs in aptamer studies. The complete GWAS dataset is now accessible via the following link: https://www.synapse.org/#!Synapse:syn51364943/files/. It is important to note that all participants in these studies were of European ancestry and provided the necessary informed consent.

Data source of immune-related bone diseases

The GWAS data on immune-related bone diseases are derived from the 11th version of the GWAS dataset released in the FinnGen database on June 24, 2024. This dataset includes the GWAS data for rheumatoid arthritis (RA), which encompasses 453,626 individuals, comprising 4,589 RA patients and 449,037 healthy controls. The GWAS data for seropositive rheumatoid arthritis (SP-RA) involve 448,721 individuals, including 5,426 SP-RA patients and 443,295 healthy controls. In contrast, the GWAS data for seronegative rheumatoid arthritis (SN-RA) cover 453,733 individuals, with 7,314 SN-RA patients and 446,419 healthy controls. Additionally, the GWAS data for Crohn's disease-related arthritis include 449,511 individuals, comprising 325 patients with Crohn's disease-related arthritis and 449,186 healthy controls. The GWAS data for ulcerative colitis-related arthritis involve 449,589 individuals, covering 403 patients with ulcerative colitis-related arthritis and 449,186 healthy controls. The GWAS data for psoriatic arthritis (PsA) encompass 291,693 individuals, including 3,897 PsA patients and 287,796 healthy controls. The GWAS data for ankylosing spondylitis (AS) involve 325,798 individuals, comprising 3,484 AS patients and 322,314 healthy controls. Furthermore, the GWAS data for multiple sclerosis (MS) include 452,390 individuals, with 2,620 MS patients and 449,770 healthy controls. The complete GWAS dataset is available for download at (https://www.finngen.fi/en/access_results). The GWAS data for juvenile rheumatoid arthritis (JRA) originate from the disease-related genetic association map released on September 30, 2021. This dataset covers 409,217 individuals, including 216 JRA patients and 409,001 healthy controls[17]. The complete dataset is accessible for download at (https://www.nature.com/articles/s41588-021–00931-x). All outcome samples included in this study are of European ethnicity.

Mendelian randomization analysis

In MR analysis, three fundamental assumptions must be met[18]: first, the genetic variation should be directly associated with the exposure factor; second, the genetic variation must not correlate with any confounding factors; and finally, if the genetic variation influences the outcome, this effect must be entirely mediated through the exposure factor. In this study, we conducted MR analysis utilizing the "TwoSampleMR" software package (version 0.6.8) within the R programming environment(https://cran.r-project.org/doc/FAQ/R-FAQ.html#Citing-R).Weselected two large plasma pQTLs as exposure data and nine immune-related bone diseases as outcome data. In constructing IVs[19], we screened single nucleotides with a P value less than 5×10^{-8}, as specified by the European 1000 Genomes Project, and located within ± 10,000 kb of the transcription start site (TSS) of each gene's polymorphism (SNP). SNP analysis was conducted with the criterion that the linkage disequilibrium coefficient (r^2) was less than 0.001, and the minor allele frequency (MAF) threshold was set to 0.01. To assess potential weak instrumental variable bias, we calculated the F statistic to quantify the strength of the instrumental variable using the formula: $F = R^2(NK-1)/[K(1-R^2)]$, where R^2, N, and K represent the estimated exposure variance explained by the IV, the sample size, and the number of IVs, respectively. SNPs with an F statistic less than 10 were considered weak IVs and excluded from the analysis to mitigate bias caused by weak instruments[20]. We utilized LDtrait to remove confounding factors (https://ldlink.nih.gov/?tab=home), setting the threshold to 1×10^{-5}[21]. SNPs directly associated with immune-related bone diseases and those traits directly linked to the disease were excluded. Following data reconciliation, MR analysis was performed on the filtered SNPs. When only one SNP was available for analysis, the Wald ratio method was employed[22]; for multiple SNPs, the IVW method with random effects was utilized[23]. Heterogeneity among individual causal effects of SNPs was assessed using Cochran's Q test, and pleiotropy was evaluated with the MR Egger intercept, setting the MR Egger threshold at 0.05. Finally, we applied false discovery rate (FDR) correction to the resulting P values, establishing a significance threshold of $P < 0.05$[24].

Single-gene SMR analysis

To validate the positive plasma pQTLs obtained from the previous MR analysis, we employed the SMR method, which incorporate pooled data and assess heterogeneity through dependent tools (HEIDI). We examined the association between the expression of protein-coding genes and the risk of immune-related bone diseases[25]. For this analysis, we utilized pooled cis-expression quantitative trait loci (eQTLs) summary data and methylation quantitative trait loci (mQTLs) summary data as IVs to support the correlation analysis. In the SMR analysis, a single quantitative trait locus (QTL) significantly associated with the target gene region is selected as the instrumental tool. The default p-value threshold is set at 0.05, with a GWAS window threshold of 1000 kb. Additionally, SMR tools incorporate HEIDI testing to discern whether the association between gene expression and the outcome is attributable to linkage rather than the influence of SNPs on disease through the modulation of gene expression. If the p-value from the HEIDI test is less than 0.05, it is inferred that the association arises from linkage. The primary outcome of the study is reported as the change in disease odds ratio (OR) for each standard deviation (SD) increase in gene expression.

Bayesian colocalization analysis

To determine whether the association between genes and immune-associated bone diseases arises from the same causal variation, we employ the Bayesian colocalization analysis method[26]. This approach allows us to effectively process complex genetic data and accurately evaluate different traits while sharing the potential for identifying causal mutations. Furthermore, due to the complexity and diversity of data concerning immune-related bone

diseases and associated traits, Bayesian colocalization analysis methods can flexibly adapt to this intricate data structure. Simultaneously, this analysis can clearly ascertain whether the associations between genes and immune-related bone diseases are driven by the same causal mutations, while also accurately identifying key genes and causal mutations related to these diseases. The relationships with traits are inferred by calculating five hypothesized posterior probabilities (PPH): (1) H0: There is no association between immune-related bone disease and any trait; (2) H1: Immune-related bone disease is associated only with traits; (3) H2: Immune-related bone disease is specifically related to trait 2; (4) H3: Immune-related bone disease is associated with two traits, but this association is due to different causal mutations; (5) H4: Immune-related bone disease is associated with two traits and is attributed to the same causal variation. During the analysis, we utilized the "coloc.abf" algorithm, adhering to its default parameter configuration. These parameters include: the prior probabilities p1 and p2 of SNPs related to trait 1 or trait 2, set to 1×10^{-4}, and the prior probability p12 for both traits, set to 1×10^{-5}. Our analytical criteria stipulate that when PPH4 exceeds 0.75, a significant colocalization association exists between plasma proteins and immune-associated bone diseases.

LDSC analysis

We employed LDSC analysis to assess potential genetic correlations between genes and immune-related bone diseases[26]. The LDSC tool utilizes genetic linkage disequilibrium (LD) to evaluate the degree of association with complex traits by calculating the LD score for each SNP. This score ranges from −1 to 1, where −1 indicates a perfect negative genetic association and 1 denotes a perfect positive genetic association. LDSC effectively mitigates the influence of sample overlap during the analysis process, thereby ensuring accurate and comprehensive utilization of GWAS data to evaluate genetic correlations. By applying the LDSC method, we can examine the interaction between statistics and linkage disequilibrium, as well as the potential impact of statistical bias on the results.

Phenogroup-wide association analysis

The SNPs associated with plasma pQTLs were identified through comprehensive analysis. Subsequently, a full PheWAS was conducted using the 11th edition of GWAS data published by the FinnGen database (https://www.finngen.fi/en). The aim of this study is to systematically explore the relationships between significant positive findings and broader outcomes, as well as to investigate gene function and comorbidity[27].

Expression status of genes in different tissues

In our analysis of the expression of significantly positive proteins in human tissues, we utilized the Human Protein Atlas (https://www.proteinatlas.org). The mRNA and protein levels were obtained from 44 normal human tissues, encompassing 76% of human genes, which include a total of 15,323 genes[28].

Protein–protein interaction network construction

We utilize PPI networks to illustrate the intricate interactions among proteins encoded by key genes in the context of drug development. In constructing the network, we relied on the STRING database (https://string-db.org/) as our data source and employed a confidence score threshold of 0.7 as the criterion for screening meaningful interactions[29]. All other default parameters of the STRING database were maintained. The protein interaction networks were analyzed and assessed for centrality using CytoNCA to identify significant core genes[30].

GO enrichment analysis

In our analysis of the functional and biological connections of previously screened potential drug target genes, we employed the 'clusterProfiler' package (version 4.12.6) in R software (https://cran.r-project.org/doc/FAQ/R-FAQ.html#Citing-R) to conduct GO enrichment analysis[31]. The GO analysis encompasses three fundamental dimensions: biological process (BP), molecular function (MF), and cellular composition (CC), with the aim of elucidating the activity patterns, functional execution, and cellular localization of these genes within biological systems.

Candidate drug prediction

DSigDB is a large-scale database that encompasses drug compounds and genes (http://dsigdb.tanlab.org/DSigDBv1.0/). It contains 22,527 gene sets and 17,389 compounds, which are associated with 19,531 genes[32]. We conducted a mapping analysis of the druggable genes identified through a comprehensive analysis of the compounds in the DSigDB database, with the objective of predicting potential drug candidates and assessing the pharmacological activity of these target genes.

Molecular docking

Based on our analysis of the DSigDB database, we subsequently performed the molecular docking step to evaluate the binding energy and interaction modes between drug candidates and their corresponding targets. Protein structure data were retrieved from the Protein Data Bank (PDB) at http://www.rcsb.org/, while drug structure data were obtained from the U.S. National Library of Medicine Chemical Substance Database (https://pubchem.ncbi.nlm.nih.gov/). In the molecular docking process, we selected the top five key drugs along with the proteins encoded by their respective target genes, utilizing the computerized protein–ligand docking software AutoDock 4.2.6 (http://autodock.scripps.edu/) for the docking procedure. The results were subsequently visualized using PyMol 3.0.5 software (https://www.pymol.org/).

Result

Mendelian randomization analysis results

In the MR analysis, we utilized plasma pQTLs as exposure factors and examined nine immune-related bone diseases as outcome factors. The results of the two-sample MR analysis of plasma proteins and the nine immune-related bone diseases are presented in Appendix Tables S1-S9, while Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10 display the correlation analysis via volcano plots. In our MR analysis of plasma pQTLs from Iceland, we identified a total of 137 plasma proteins associated with RA, 150 plasma proteins associated with SP-RA, 95 plasma proteins associated with SN-RA, 69 plasma proteins associated with JRA, and an additional 70 plasma proteins also associated with JRA. Furthermore, plasma proteins were found to be associated with Crohn's disease-associated arthritis, with 83 proteins linked to ulcerative colitis-associated arthritis, 92 proteins associated with AS, 88 proteins associated with PsA, and 88 proteins associated with MS. After applying FDR correction, we identified several significantly positive proteins in relation to RA: PPA2, JUND, AGER, F2, and PMEL. In the SP-RA analysis, TGFBR3, FCGR3B, TIMP4, and PMEL emerged as significant positive proteins, while CRH was identified as a significant positive protein in ulcerative colitis-related arthritis. Additionally, GCKR was noted as a significant positive protein in the PsA analysis, and STAT3 was recognized as a significant positive protein in the MS analysis.

In the MR analysis of pQTLs in the UK Biobank, we identified a total of 156 plasma proteins associated with RA, 167 plasma proteins related to SP-RA, 106 plasma proteins linked to SN-RA, and 81 plasma proteins connected to JRA. Additionally, 106 plasma proteins were associated with AS, 116 with PsA, and 122 with MS. After applying FDR correction, we found that AIF1, ARG2, ATP5IF1, CCL19, CDSN, CEP43, MXRA8, PADI2, RPA2, SLC16A1, TNF, and TNFRSF14 were significant positive proteins in the RA-related analysis. In the SP-RA correlation analysis, AIF1, APOBR, ATP6V1G2, BCL2L15, C1QTNF6, CCL19, CD40, CDSN, CEP43, CX3CL1, FCGR2B, FCRL1, IL6R, MXRA8, TGFBR3, TNF, and TNFRSF14 emerged as significantly positive proteins. For SN-RA, AIF1, CEP43, and TNF were identified as significantly positive proteins. In the AS analysis, ACOT13, AGER, FKBPL, NFKB1, and TNF were significant, while in the PsA-related analysis, APOF, ATP6V1G2, IFNLR1, PTPRF, and TNF were significantly positive proteins. Lastly, in the MS-related analysis, AGER, AIF1, BTN1A1, CD58, DSG4, EVI5, TNF, and TNFRSF14 were identified as significantly positive proteins.

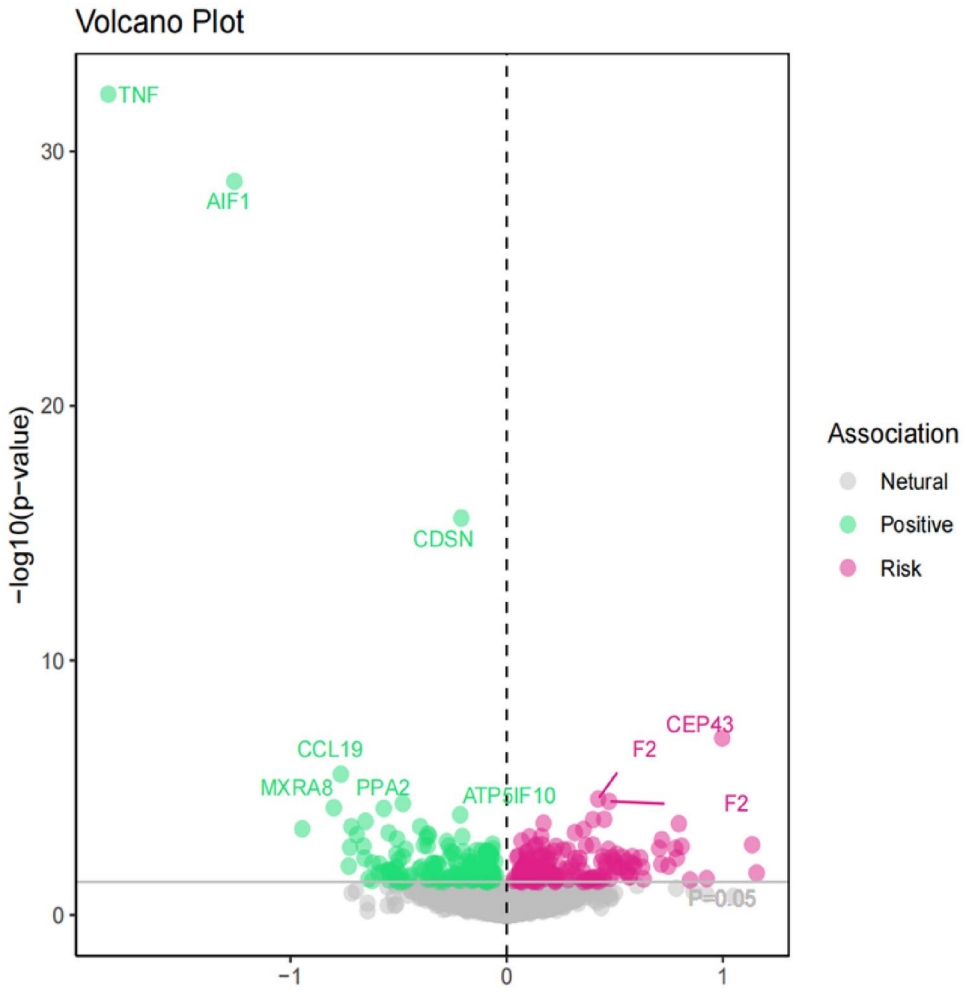

Fig. 2. Volcano plot of MR analysis for rheumatoid arthritis.

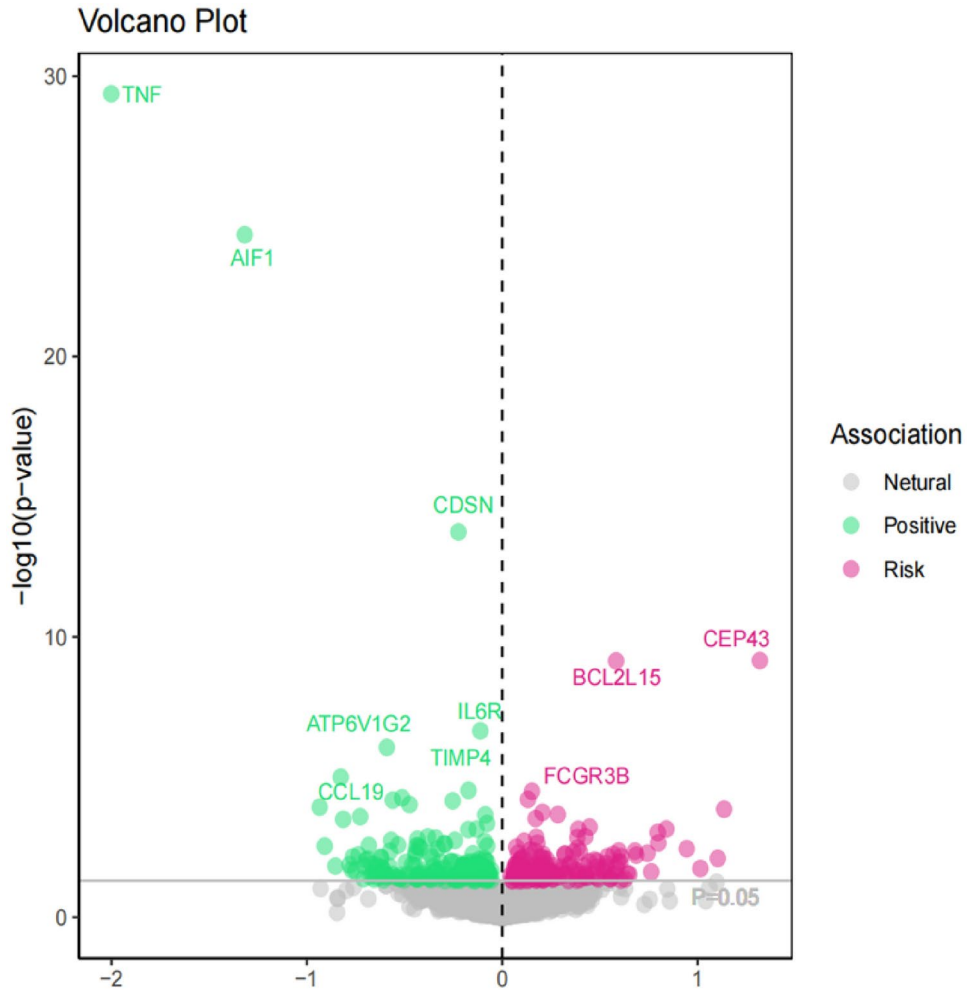

Fig. 3. Volcano plot of MR analysis for seropositive rheumatoid arthritis.

Single-gene SMR analysis results

In the SMR analysis of RA, we identified a total of 39 positive genes, which include ACOT13, ADAM15, ATXN2L, CD6, CHCHD6, DPP4, EPHB6, FCRL1, HDGF, LSP1, PARK7, PFKFB2, RABEP1, RARRES2, RELT, RPA2, SEMA4D, SERPINB1, ST13, STX4, TEF, TNFRSF4, UROD, USP8, ACADVL, ARPC1B, CBL, CFL2, CHI3L2, CRAT, GHR, HIBCH, JUND, KLKB1, NMB, OAF, PDE4A, PPID, TAGLN2, and TNFAIP3. In the SMR analysis of SP-RA, we found a total of 42 positive genes, including ADAM15, CCL5, CD6, DOK2, DTNB, FCRL3, FDX1, IMMT, KIAA0319, LSP1, PADI2, PARK7, PFKFB2, RABEP1, RPA2, ST13, STX4, TEF, TOR1AIP1, ACADVL, C5, CD14, CD48, CHI3L2, CYTL1, FCRL3, HIBCH, IL15RA, ISOC1, MDH1, OAF, PDE4A, POMGNT2, PPID, PSMB4, QPCTL, ROBO1, SERPINB1, SH3BGRL2, ST13, TAGLN2, TNFAIP3, TPI1, ULK3, and ZG16B. In the SMR analysis of SN-RA, we identified a total of 30 positive genes, namely BAG3, CASP10, CD300E, FCRL1, FCRL3, GZMB, LSP1, MAPKAPK2, PDCD1, PFKFB2, PKD1, RNASET2, SEMA4D, SERPINB1, SHISA5, ST13, B3GNT8, C4BPA, CBL, CHI3L2, CRAT, DLK2, G3BP1, KLKB1, LRP4, MAPKAPK2, MTHFD1, OAF, PPID, SARS2, TAGLN2, and TCEA2. In the JRA SMR analysis, we found a total of 24 positive genes, which include AIF1, ASAH2, BCAM, CD59, COQ7, HS6ST1, SLAMF6, SORBS1, SPINK8, STX4, STX8, ABLIM3, BCL10, BPNT1, CCS, CD59, HEXIM2, JUND, PTPN7, SLAMF6, SPOCK2, STX8, TBCE, TNFSF8, TXNDC12, and UBE2F.

In the SMR analysis of MS, we identified a total of 18 positive genes: ATOX1, CA2, CD79B, CD160, DPP4, EHBP1, ERP44, FKBP4, HPCAL1, IFIT3, IFNGR2, ITGB7, MFGE8, MITD1, PFKFB2, SESTD1, VCAM1, and ZFYVE19. In the SMR analysis of ulcerative colitis-related arthritis, we found 17 positive genes: ARG1, C1orf198, DNAJB6, ECHS1, EVA1C, GATM, KCNAB2, MGP, MST1, PDLIM1, POMGNT2, RAB6B, TDGF1, CA2, NCF2, and TGFA. In the SMR analysis of ulcerative colitis-related arthritis, we identified 23 positive genes: ADAM15, CEP112, EGF, IGSF8, ITGB2, KHK, MCEE, PSTPIP2, SPINK8, TEF, TMEM106A, TNFRSF17, TXNDC15, UROD, VAT1, BIN1, DECR2, ERAP2, GNMT, MAPKAPK2, PMM1, SERPINH1, SUB1, SYK, and YWHAB. In the SMR analysis of AS, we found 30 positive genes: ABO, CCL5, CD200R1, CD209, FIS1, JUND, KPNA6, MDH1, MGAT4B, MUC16, NUDCD3, TNFRSF1A, UBE2C, ACTA2, EHD3, FUCA1, GPC5, GPIHBP1, KHK, LMNB1, PCSK7, PGF, PRKD2, RAB44, RTN4IP1, SIRPA, SLC16A1, and SNX15. In the SMR analysis of PsA, we identified 21 positive genes: CPNE1, DNAJB12, FN1, GNMT, IFI16, MAPKAPK2, NRBP1,

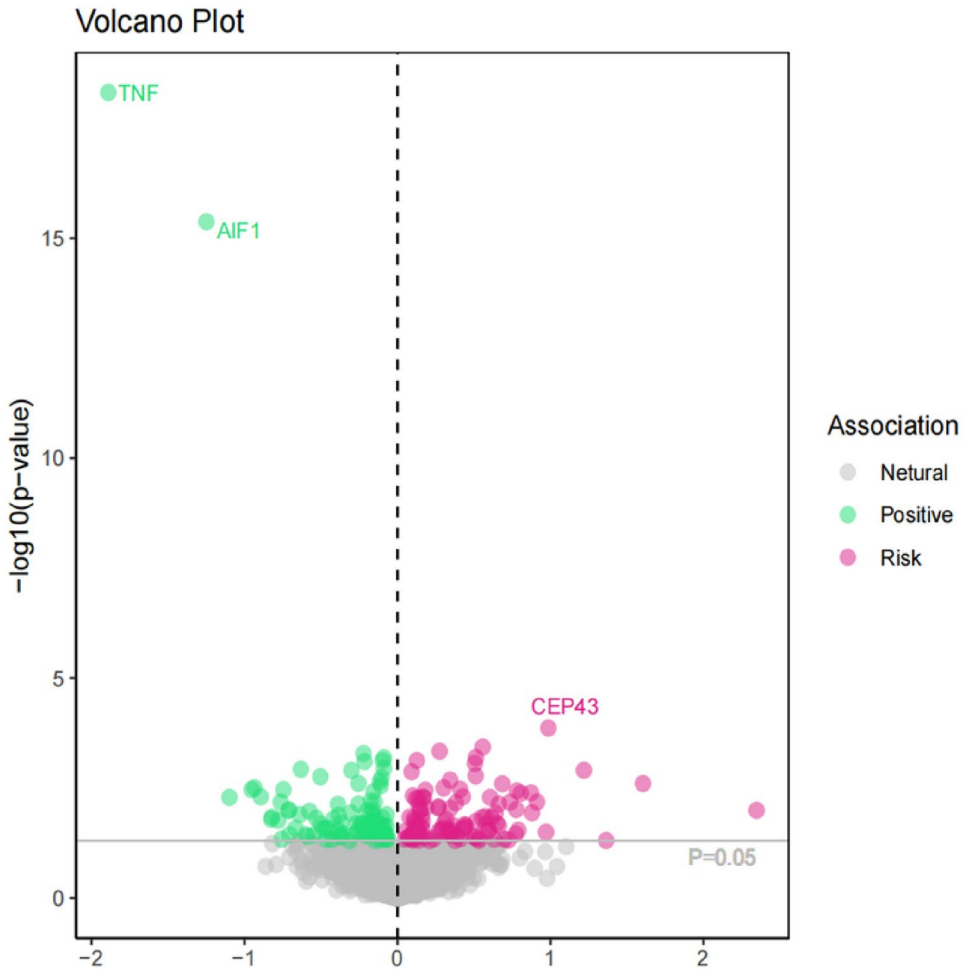

Fig. 4. Volcano plot of MR analysis for seronegative rheumatoid arthritis.

POR, SARS2, TAGLN2, TBCB, TXNL4B, ACTA2, ATOX1, CTSF, DBI, EDN1, HSPB1, IL1R2, IL10, MET, and PTPRF. Appendix Tables S10-S18 present the results of the SMR analysis of plasma pQTLs and nine immune-related bone diseases.

Bayesian colocalization analysis results

In our Bayesian co-localization analysis, we identified several genes significantly associated with various conditions. For RA, the positively correlated genes include F2 (PPH4 = 0.7678), ATP5IF1 (PPH4 = 0.9298), CCL19 (PPH4 = 0.9762), CX3CL1 (PPH4 = 0.9463), HDGF (PPH4 = 0.8426), MXRA8 (PPH4 = 0.7889), and TNFRSF14 (PPH4 = 0.8016). For SP-RA, the significant genes are FCGR3A (PPH4 = 0.9822), ADAM15 (PPH4 = 0.9721), CCL19 (PPH4 = 0.9766), CX3CL1 (PPH4 = 0.9837), NFKBIE (PPH4 = 0.7643), and TNFRSF14 (PPH4 = 0.9552). GPT (PPH4 = 0.8126) is identified as a significant positive gene for Crohn's disease-related arthritis. Additionally, for PsA, ICAM5 (PPH4 = 0.9476), IL17RD (PPH4 = 0.9301), UBLCP1 (PPH4 = 0.8862), and CCDC50 (PPH4 = 0.9091) are significant positive genes. In MS, the significant positive genes include BTN1A1 (PPH4 = 0.7660), EVI5 (PPH4 = 0.9800), OGA (PPH4 = 0.8569), and TNFRSF14 (PPH4 = 0.8904). The results of the Bayesian co-localization analysis for nine immune-related bone diseases are detailed in Appendix Tables S19-S27, while Figs. 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 present scatter plots illustrating the co-localization results for the significant positive genes.

LDSC analysis results

To assess the genetic correlates of complex diseases and intricate genetic signatures, we conducted an LDSC analysis of the Bayesian colocalization of significantly positive genes associated with nine immune-related bone diseases. The results indicated a significant positive genetic correlation between CCL19 and RA (rg_p = 0.0000), as well as between TNFRSF14 and RA (rg_p = 0.0258). Additionally, a significant positive genetic correlation was observed between CCL19 and SP-RA (rg_p = 0.0000), and between TNFRSF14 and SP-RA (rg_p = 0.0105). Appendix Table S28 presents the LDSC analysis results for the significantly positive genes.

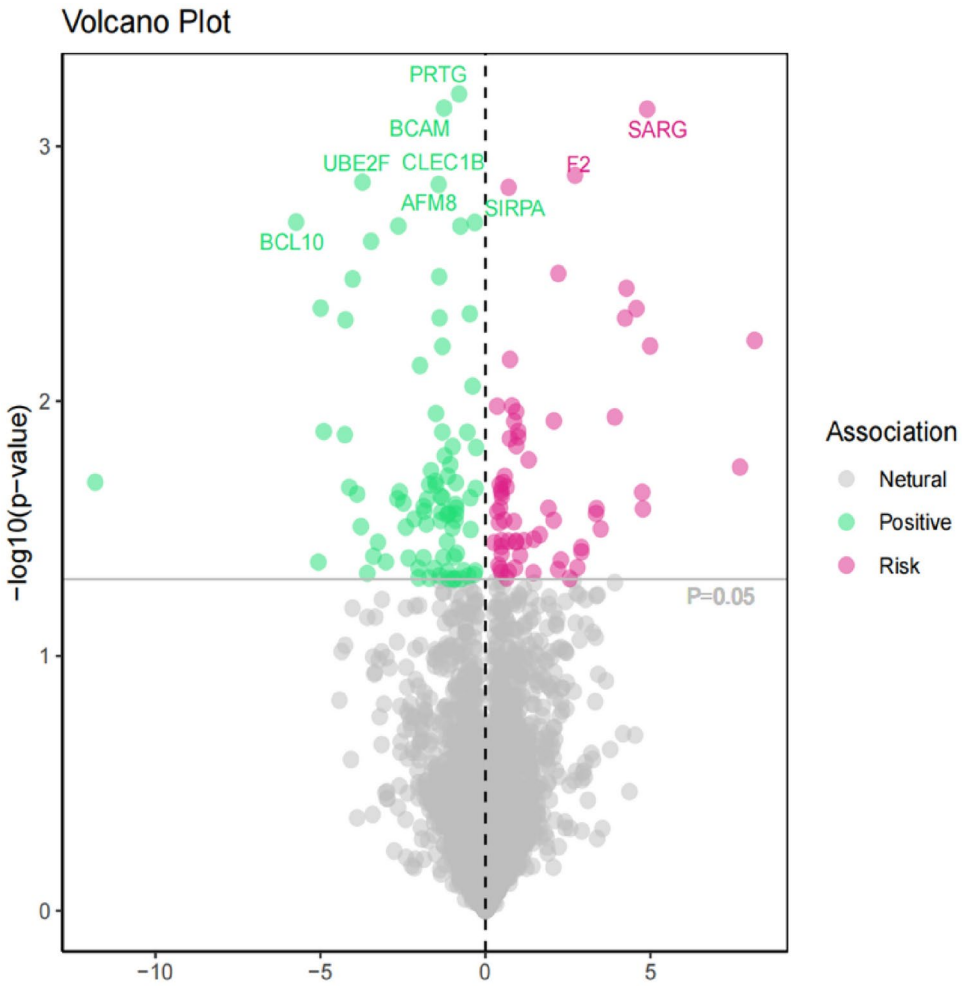

Fig. 5. Volcano plot of MR analysis for juvenile rheumatoid arthritis.

Results of whole-phenome group association analysis

We conducted a PheWAS analysis on the significantly positive genes identified from our comprehensive analysis, utilizing the latest version 11 GWAS data released by the Finngen database. The results indicated that CCL19 was associated with 195 diseases or phenotypes. Following FDR correction, it was determined that the gene CCL19 is strongly linked to RA. HDGF was associated with 120 diseases or phenotypes, and after FDR correction, it was found to have a significant relationship with cranial nerve diseases and hypertensive heart disease. TNFRSF14 was connected to 203 diseases or phenotypes, and post-FDR correction, it was identified as being highly relevant to various allergic diseases, autoimmune diseases, and RA. GPT was correlated with 188 diseases or phenotypes, and after FDR correction, it was found to be significantly associated with abnormal uterine and vaginal bleeding. ICAM5 was linked to 137 diseases or phenotypes, and following FDR correction, it was established that ICAM5 has a strong correlation with chronic diseases of the tonsils and adenoids, as well as oral leukoplakia. The gene IL17RD was associated with 127 diseases or phenotypes, and after FDR correction, it was found to be significantly correlated with diaphragmatic hernia. UBLCP1 was linked to 101 diseases or phenotypes, and after FDR correction, it was identified as being highly correlated with psoriasis. Additionally, CCDC50 was associated with 103 diseases or phenotypes.The gene BTN1A1 is associated with 271 diseases or phenotypes. Following FDR correction, BTN1A1 was found to be related to sexually transmitted infections, body mass index, immune mechanism diseases, thyroid diseases, skin diseases, lumbar spine issues, sciatica, and conditions affecting the female reproductive system. Additionally, developmental abnormalities and lesions are strongly associated with this gene. The gene EVI5 is correlated with 163 diseases or phenotypes, and after FDR correction, it was identified as being highly correlated with MS. The gene OGA is linked to 216 diseases or phenotypes, and after FDR correction, it was determined that OGA is significantly correlated with arrhythmia, cervical and lumbar spine diseases, and ovarian endometriosis. Appendix Table S29 and Fig. 23 present the results of the MR-PheWas analysis and the Manhattan plot of significantly positive proteins.

Expression status of genes in different tissues

We utilized the Human Protein Atlas to identify variations in the expression of significantly positive genes across human tissues. Previous studies have indicated that CCL19 is predominantly expressed in lymph nodes, bone

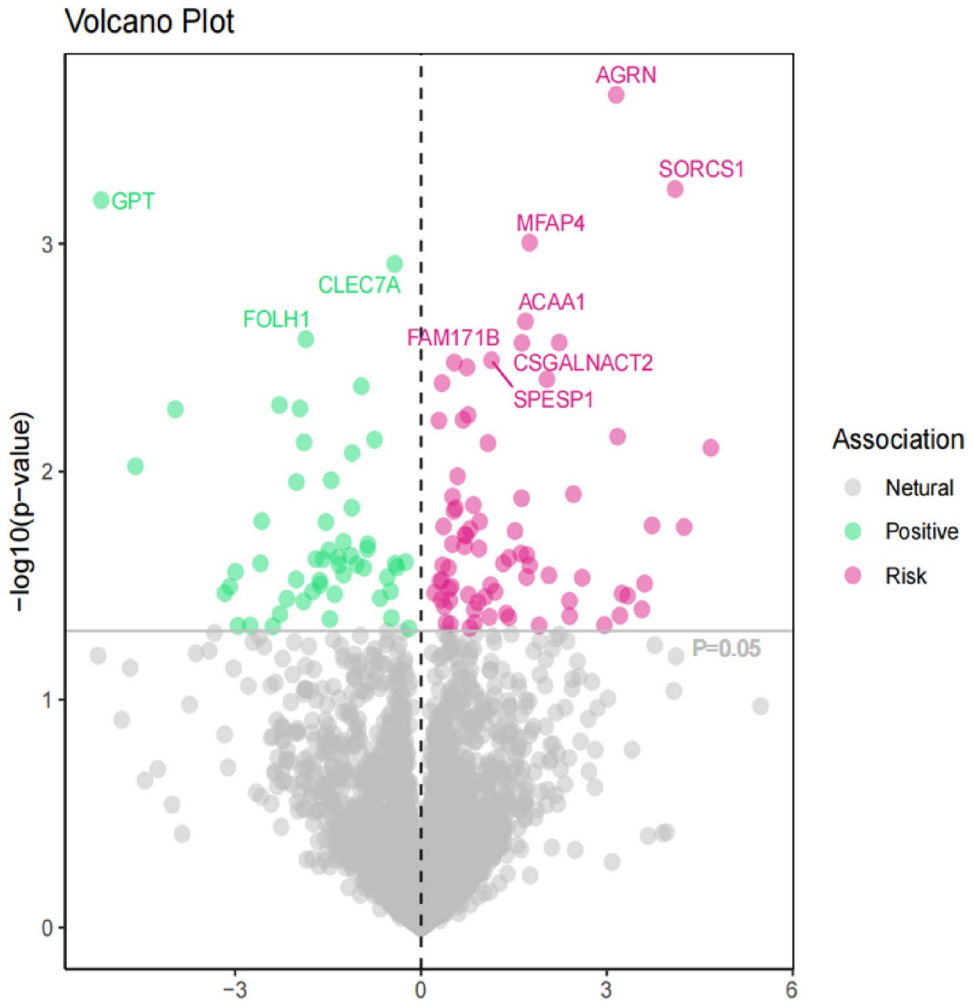

Fig. 6. Volcano plot of MR analysis for Crohn's disease-related arthropathy.

marrow, and lymphoid tissues. TNFRSF14 is primarily expressed in the duodenum, small intestine, fallopian tube, and lymph nodes. BTN1A1 shows significant expression in the breast, tonsils, lymph nodes, and bone marrow. EVI5 is notably expressed in the placenta, liver, testis, parathyroid gland, adrenal gland, smooth muscle, and skeletal muscle. OGA is mainly found in the bone marrow, lymph nodes, thymus, and tonsils. ICAM5 demonstrates significant expression in the cerebral cortex, lung, testis, and bone marrow. CCDC50 is significantly expressed in adipose tissue, liver, ovary, smooth muscle, and spleen. IL17RD is notably expressed in the endometrium, choroid plexus, smooth muscle, and testis. UBLCP1 shows significant expression in the tonsils, thymus, lymph nodes, and testes. GPT is highly expressed in skeletal muscle and is also significantly expressed in the liver, tongue, duodenum, and small intestine.

Protein–protein interaction network construction results

Based on SMR analysis and Bayesian co-localization analysis, we imported the positively identified genes into the STRING database to construct a PPI network. This network comprises 276 nodes and 262 edges. The results of the PPI interaction network are presented in Appendix Table S30 and Fig. 24, while Fig. 25 illustrates the core gene results derived from CytoNCA analysis.

GO enrichment analysis results

To investigate the characteristics of potential drug targets, we employed the GO framework for a systematic analysis. This analysis revealed that these targets are widely distributed across 511 biological pathways. Following an integrated analysis, it was determined that these genes are primarily involved in a series of key biological processes (BP). Specifically, they are significantly associated with the positive regulation of cytokine production (GO:0,001,819), the regulation of immune effector processes (GO:0,002,697), chemotaxis (GO:0,006,935), tropism (GO:0,042,330), negative regulation of response to external stimuli (GO:0,032,102), leukocyte-mediated immunity (GO:0,002,443), and positive regulation of cell adhesion (GO:0,045,785). Additionally, these targets exhibit specific molecular functions (MF), predominantly encompassing cytokine receptor binding (GO:0,005,126), amide binding (GO:0,033,218), and enzyme inhibitor activity (GO:0,004,857). At the cellular

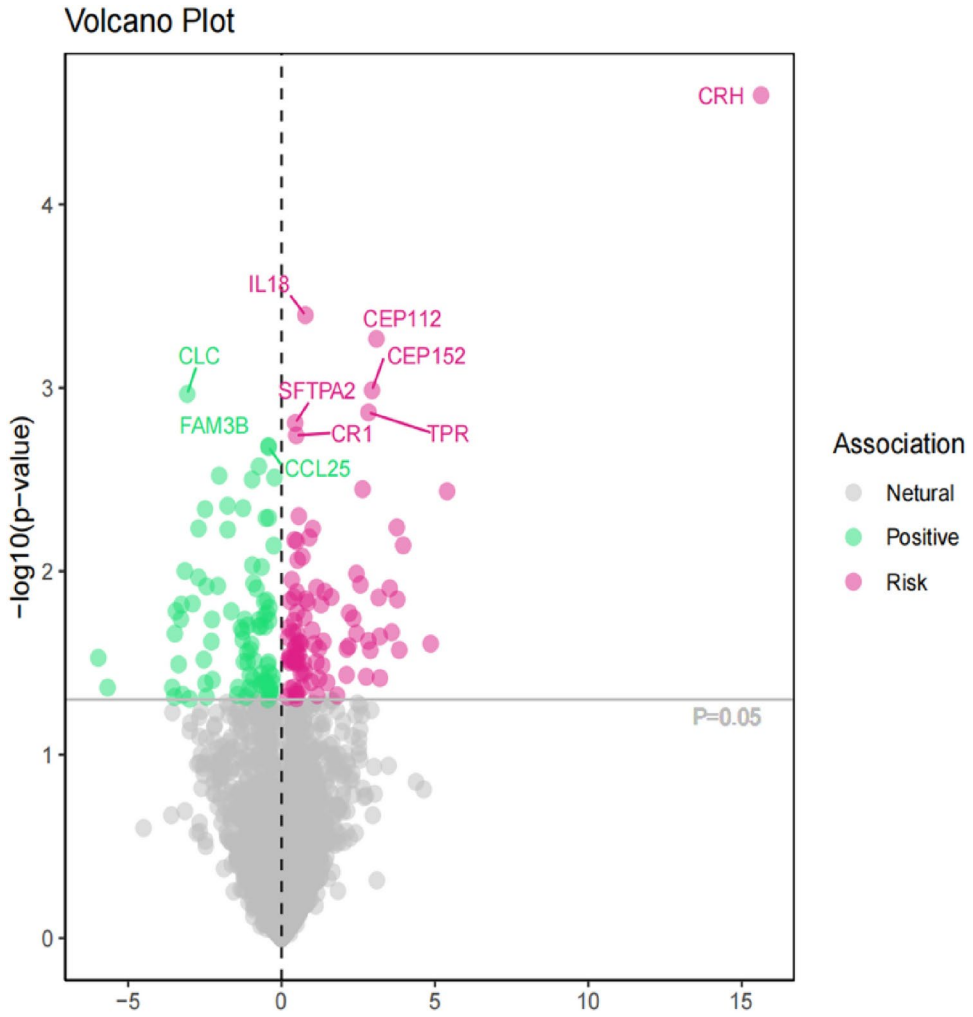

Fig. 7. MR analysis volcano map of ulcerative colitis related joint diseases.

component (CC) level, they are localized to the exterior of the plasma membrane (GO:0,009,897), the lumen of the endoplasmic reticulum (GO:0,005,788), and the collagen-containing extracellular matrix (GO:0,062,023). Appendix Table S31 and Fig. 26 present the histogram and bubble chart of the GO enrichment analysis.

Candidate drug prediction outcomes

To predict potentially effective intervention drugs, we utilized the Drug Signatures Database (DSigDB) to generate a list of the top ten candidate drugs based on P values and adjusted P values. The results indicated that methotrexate (CTD 00,006,299), paraquat (CTD 00,006,471), cyclosporine A (CTD 00,007,121), tamibarotene (CTD 00,002,527), and dexamethasone (CTD 00,005,779) emerged as the five most significant drugs. Specifically, methotrexate is associated with 28 genes, including CDKN1A, ACADVL, and ECHS1; paraquat is linked to 17 genes, such as IL10, CDKN1A, and NOS2; cyclosporine A is related to 100 genes, including EPHB6, NCF2, and ICAM3; tamibarotene is associated with 25 genes, including CDKN1A, ITGB2, and ICAM3; and dexamethasone is connected to 22 genes, including IL10, CDKN1A, and EDN1. Appendix Table S32 presents the prediction results for single-gene drug candidates linked to significantly positive genes, while Appendix Table S33 displays the prediction results for disease candidate drugs related to immune-mediated bone diseases.

Molecular docking results

In this study, we utilized positive genes identified through Bayesian co-localization as significantly positive target genes. We employed AutoDock 4.2.6 software to analyze candidate drugs associated with the top five significantly positive genes and calculated the binding sites and interactions between these drug candidates and the proteins encoded by their corresponding genes. We assessed the binding energy of each interaction and successfully obtained effective docking results for 16 genes and their respective drugs. Among all docking results, CCL19 and 1-Nitropyrene exhibited the lowest binding energy of −7 kcal/mol, while EVI5 and sanguinarine demonstrated a binding energy of −8.3 kcal/mol. The combination of TNFRSF14 and 7,12-dimethylbenzanthracene yielded the lowest binding energy value of −8.8 kcal/mol, and the pairing of UBLCP1 and indomethacin also showed a low binding energy of −8.4 kcal/mol. Additionally, the combination of GPT and rifampicin had a binding energy of

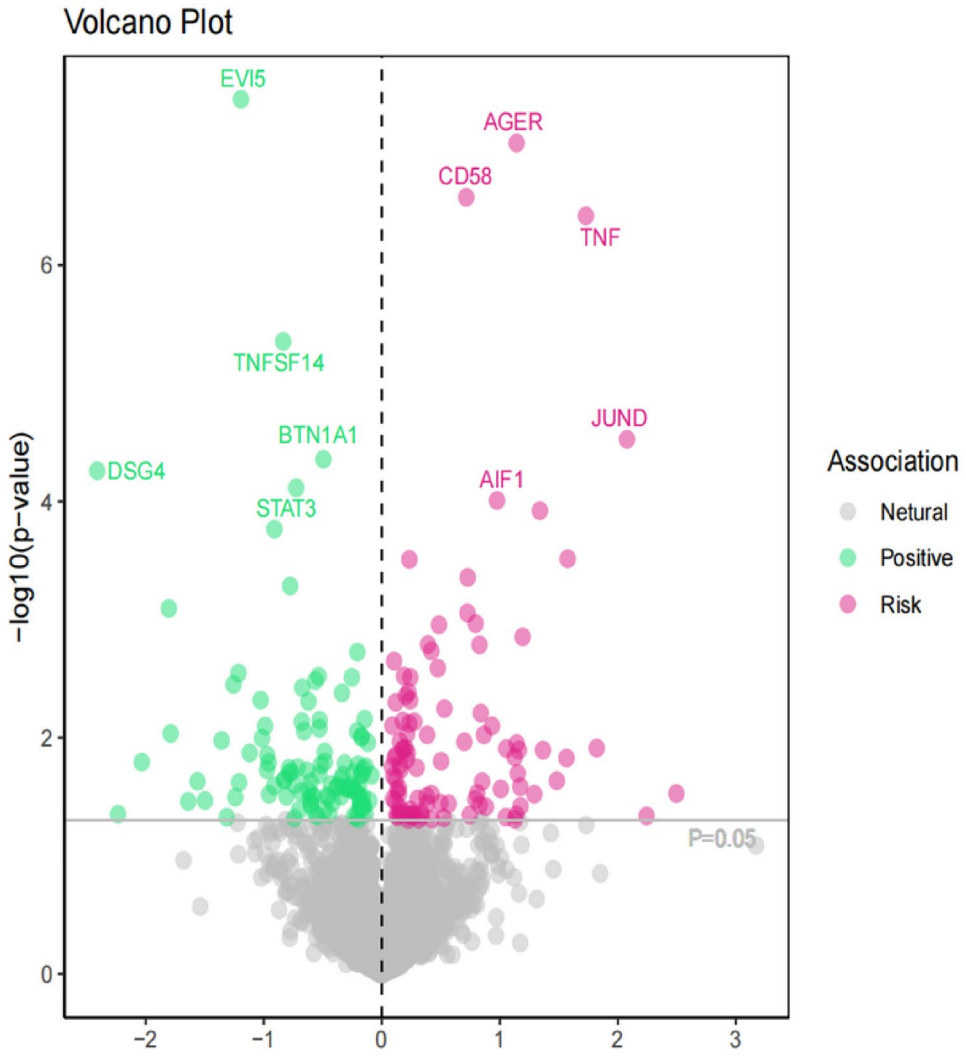

Fig. 8. Volcanic diagram of MR analysis results of multiple sclerosis.

−8.1 kcal/mol, while IL17RD and ketone showed a binding energy of −7.8 kcal/mol. The interaction between HDGF and troglitazone resulted in a binding energy of −7.5 kcal/mol, and the combination of CCDC50 and indomethacin exhibited a binding energy of −7.4 kcal/mol, indicating the stability of their binding efficiency. Appendix Table S34 presents the binding energy scores from the molecular docking analysis, and Figs. 27, 28, 29, 30, 31, 32, 33, 34, 35, 36 illustrate the most significant results of molecular binding energies,Table 1 shows the comprehensive analysis results of significantly positive genes.

Discussion

Immune-related bone diseases encompass a range of conditions associated with disorders of the immune system, characterized by abnormalities in the bone remodeling process that can lead to osteoporosis, fractures, and other skeletal complications. The pathogenesis of these diseases is complex and involves intricate interactions among immune cells, cytokines, and bone cells. Comprehensive research utilizing various methodologies has identified specific genes and proteins closely associated with the pathogenesis and treatment of these diseases. Notably, BTN1A1, EVI5, OGA, and TNFRSF14 are recognized as key therapeutic targets for MS; HDGF, CCL19, and TNFRSF14 may play critical roles in the treatment of RA; ICAM5, CCDC50, IL17RD, and UBLCP1 are significantly linked to the onset and management of PsA; and GPT is identified as a crucial therapeutic target for arthritis related to Crohn's disease. These findings offer new directions and insights for research into immune-related bone diseases. By focusing on these key targets, it is anticipated that more effective and personalized treatment options will be developed in the future, thereby enhancing treatment outcomes and improving the quality of life for patients.

Association of TNFRSF14 with RA and MS

TNFRSF14, also known as HVEM, is a member of the tumor necrosis factor receptor superfamily. The protein it encodes plays a central role in regulating immune responses. TNFRSF14 is associated with multiple immune

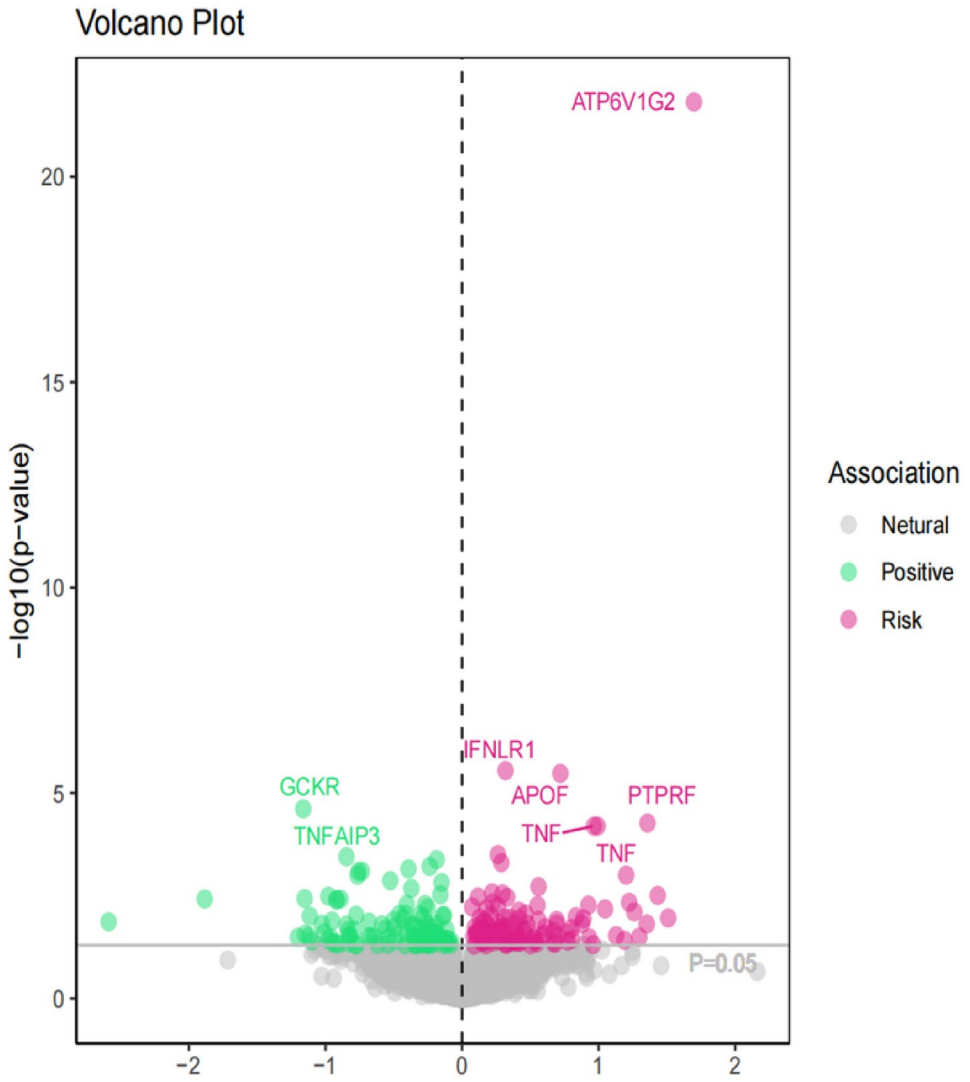

Fig. 9. Volcanic diagram of MR analysis results of psoriatic arthritis.

mechanisms, including those involving T cells and B cells. Studies have demonstrated that TNFRSF14 can effectively regulate T cell immune responses by both promoting inflammatory responses and transmitting inhibitory signals[33,34]. Furthermore, TNFRSF14 interacts with receptors on the surface of B cells and T cells, inhibits T cell activation, and plays a crucial role in maintaining immune balance and preventing excessive immune responses.

RA as an autoimmune disease, significantly contributes to the abnormal activation of B cells and T cells. Relevant studies have indicated that the role of B cells in RA extends beyond the production of autoantibodies; they also activate T cells through antigen presentation and directly engage in the inflammatory response by producing cytokines. These mechanisms are closely associated with the onset and progression of RA[35]. T cells are similarly crucial in RA, participating in the disease's pathological processes by releasing pro-inflammatory cytokines or directly damaging joints. The function of TNFRSF14 in regulating immune responses may be linked to the pathogenesis of RA. Research has demonstrated that HVEM exhibits distinctive expression and distribution in the synovium of RA patients, potentially influencing the disease's development[36]. Furthermore, bioinformatics studies have identified the TNFRSF14-MMEL1 gene as having the strongest correlation with RA[37]. Genetic studies have also established that TNFRSF14 plays a significant role in the genetic susceptibility to RA[38]. Collectively, these findings underscore the importance of TNFRSF14 in RA and provide valuable insights into the immunological underpinnings of the disease.

TNFRSF14 plays a significant role in the pathological processes associated with MS. It may influence disease progression by modulating the interactions between immune cells and central nervous system (CNS) cells. Abnormal functioning of TNFRSF14 can lead to excessive activation of immune cells, which may trigger the immune system's erroneous attack on the myelin sheath of the CNS, resulting in an inflammatory response—a hallmark pathological feature of MS. Furthermore, TNFRSF14 may also be involved in regulating the immune microenvironment within the CNS; its abnormalities could disrupt immune tolerance mechanisms and

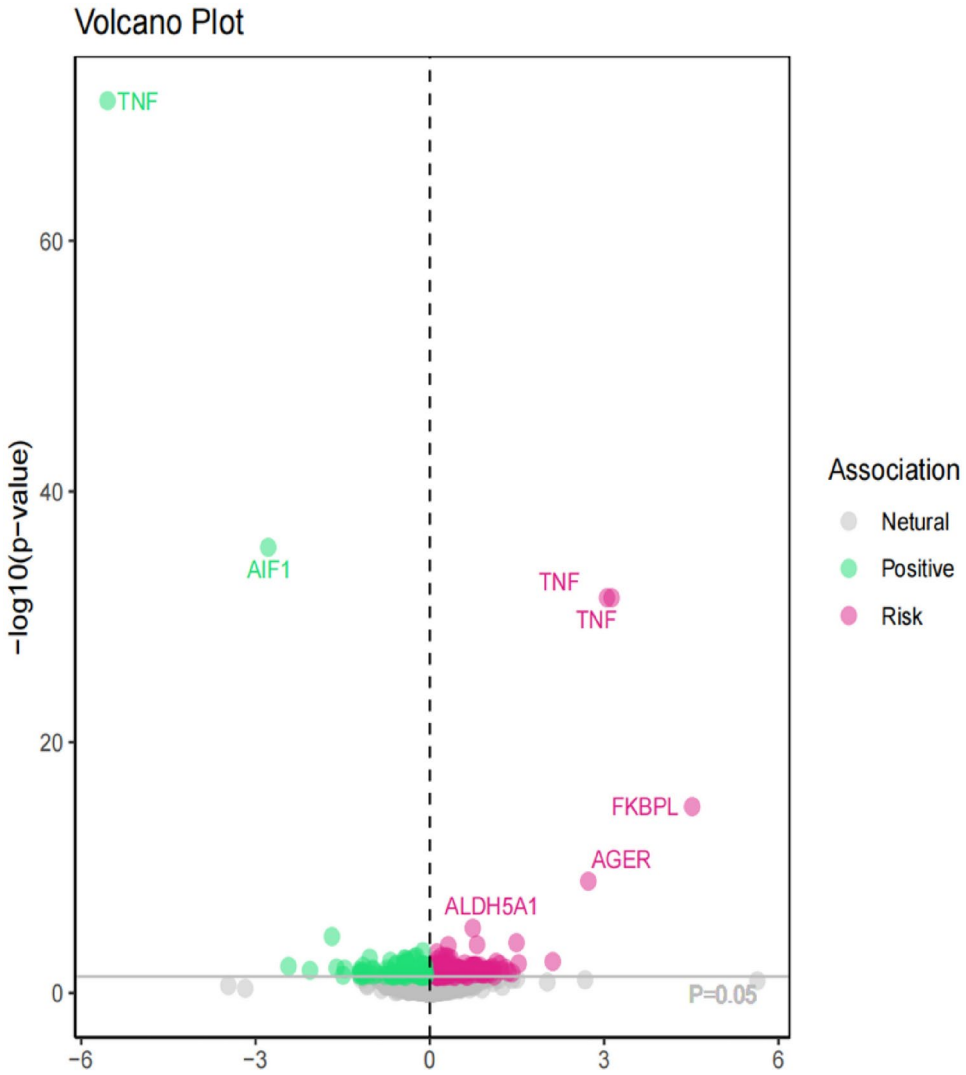

Fig. 10. Volcanic diagram of MR analysis results of ankylosing spondylitis.

exacerbate the development of MS. Studies have indicated that polymorphisms in the TNFRSF14 gene are linked to susceptibility to MS[39]. In these studies, the frequency of this gene variant in MS patients was significantly higher than in healthy controls, with patients carrying this allele exhibiting an increased risk of developing the disease. Consequently, the relationship between TNFRSF14 and MS is primarily reflected in its role in immune regulation, particularly in the activation of T cells and B cells, as well as in the immune response. Nevertheless, the specific mechanisms of action and therapeutic potential of TNFRSF14 warrant further investigation to elucidate.

Previous studies have demonstrated that the protein encoded by the TNFRSF14 gene plays a crucial role in cellular signaling, immune response, and tumor suppression. Abnormal expression of this protein is associated with immune bone diseases[40], and TNFRSF14 is recognized as one of the susceptible loci for RA. Mutations in TNFRSF14 influence individual susceptibility to RA, and its activation is closely linked to the inflammatory response, contributing to the pathological processes of arthritis. This activation results in joint damage and dysfunction, and the expression level of TNFRSF14 can serve as a biomarker for RA, aiding in the monitoring of disease activity and therapeutic response[41].In addition, there is an overexpression of genes involved in the TNF signaling pathway and the NFκB pathway in RA. Variations in these genes may increase the risk of developing RA[42].Concurrently, TNFRSF14 can enhance the survival and activity of CD4 + memory T cells, which aids in maintaining effective immune surveillance. This function not only helps resist pathogen attacks but also mitigates autoimmunity, thereby alleviating symptoms of MS[43]. Furthermore, TNFRSF14 plays a crucial role in the costimulatory signaling of T cells. It enhances T cell activation, promotes T cell proliferation and functionality, and thereby bolsters the immune response. Conversely, it can also inhibit excessive immune responses through costimulation, maintaining immune system balance. This bidirectional regulatory function is significant for preserving immune tolerance and preventing unnecessary immune reactions against self-antigens[44]. In terms of therapeutic implications, the pivotal role of TNFRSF14 in regulating apoptosis, promoting immune responses, and inhibiting inflammation suggests that inhibitors or agonists targeting TNFRSF14 may represent

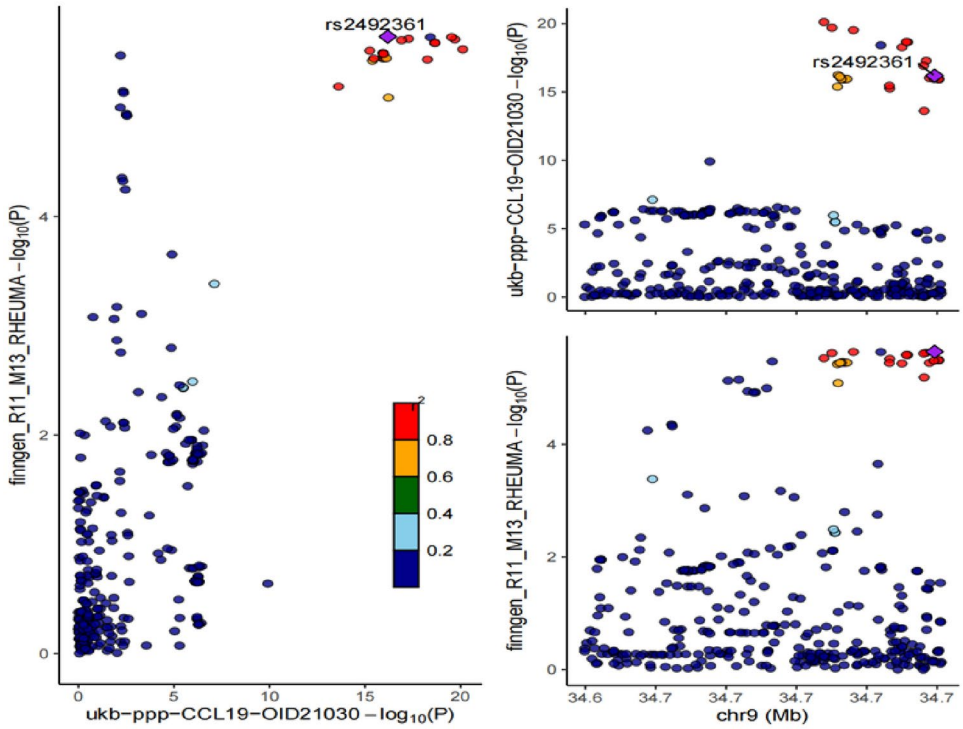

Fig. 11. Bayesian colocalization of CCL19 and rheumatoid arthritis.

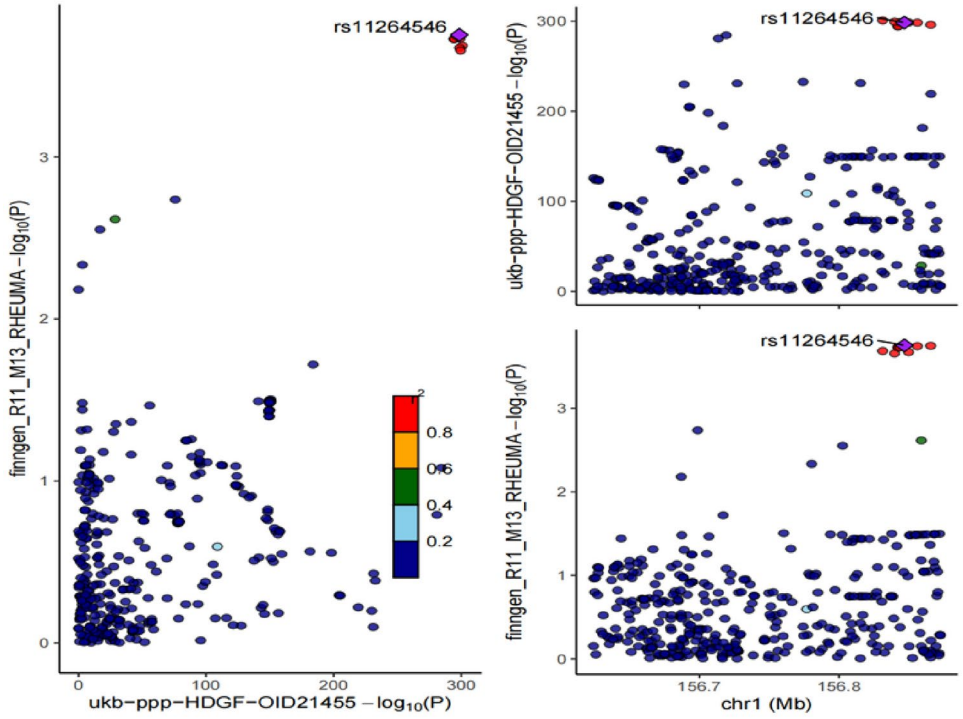

Fig. 12. Bayesian colocalization of HDGF and rheumatoid arthritis.

a novel strategy for treating immune-mediated bone diseases. By modulating its activity, such treatments could effectively reduce inflammatory responses and improve clinical symptoms in patients[33]. Additionally, TNFRSF14-targeted therapy can selectively target specific immune pathways without broadly suppressing the overall immune response, thus alleviating disease symptoms while preserving the body's immune function[45].

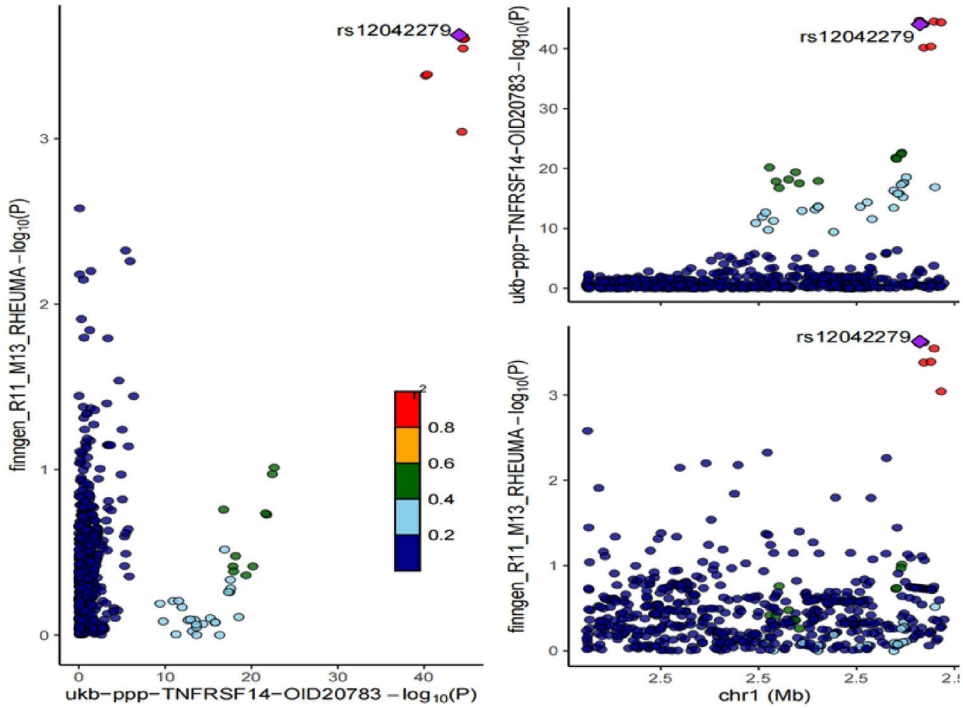

Fig. 13. Bayesian colocalization of TNFRSF14 and rheumatoid arthritis.

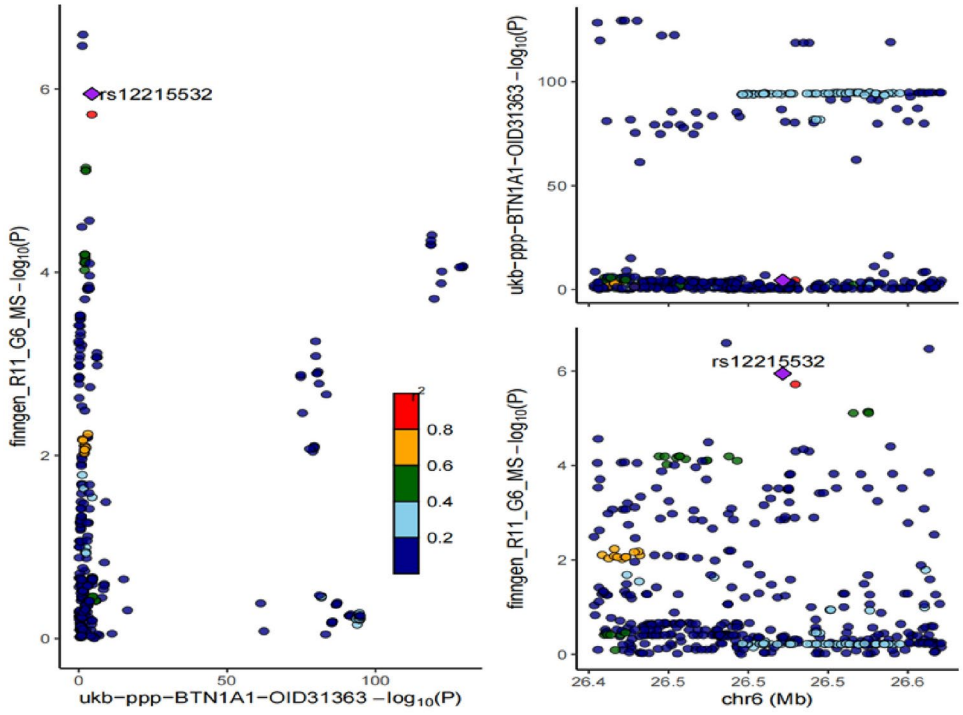

Fig. 14. Bayesian co localization results of BTN1A1 and multiple sclerosis.

As research progresses, the therapeutic significance of TNFRSF14 in immune diseases is underscored by its function as a tumor suppressor, its ability to regulate T-cell immune responses, and its role in susceptibility loci associated with autoimmune diseases. Future research will further reveal potential therapeutic strategies for this gene, which may open up new directions to improve the therapeutic effect of patients with autoimmune diseases.

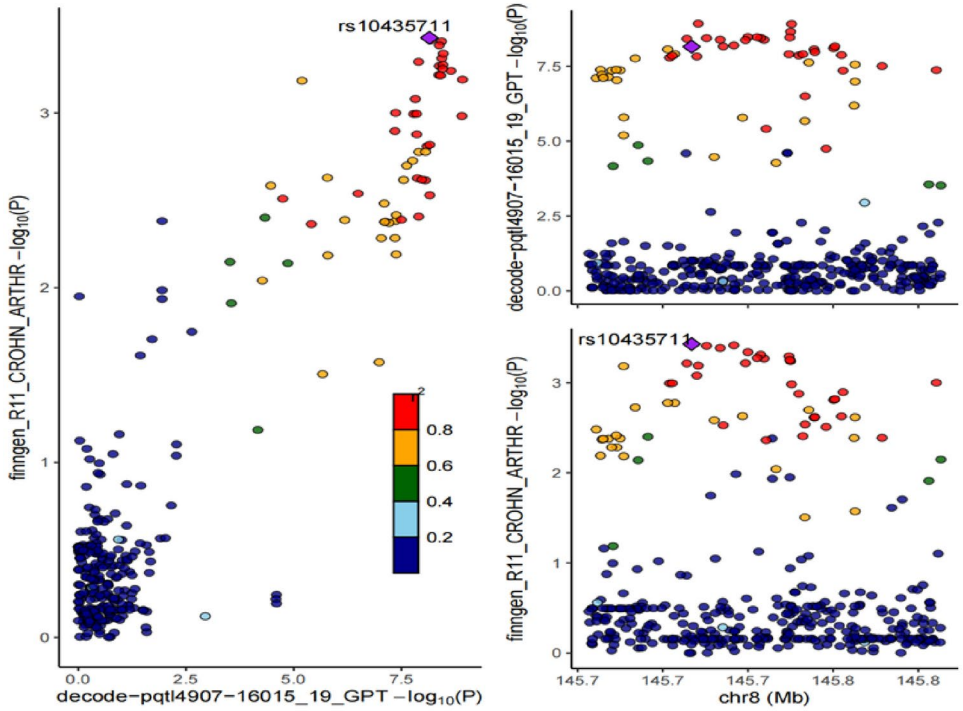

Fig. 15. Bayesian colocalization of GPT and Crohn's disease-related arthropathy.

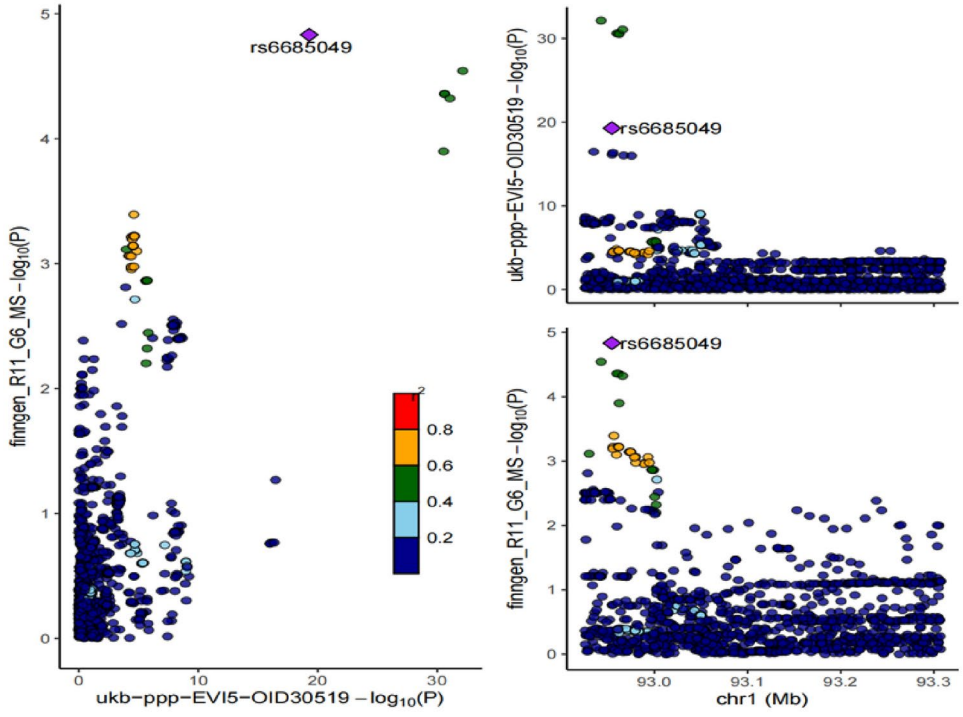

Fig. 16. Bayesian co localization results of EVI5 and multiple sclerosis.

In this study, we observed that 7,12-dimethylbenzo[a]anthracene (DMBA) binds significantly to TNFRSF14. As a carcinogen, DMBA's role extends beyond direct DNA damage; it also promotes tumor development by influencing cell proliferation. This process is accompanied by complex immune regulation, including an increase in regulatory T cells and modulation of both humoral and cellular immune responses. Studies have demonstrated that DMBA can elevate the number of regulatory T cells[46]. As the dosage of DMBA increases, the immune

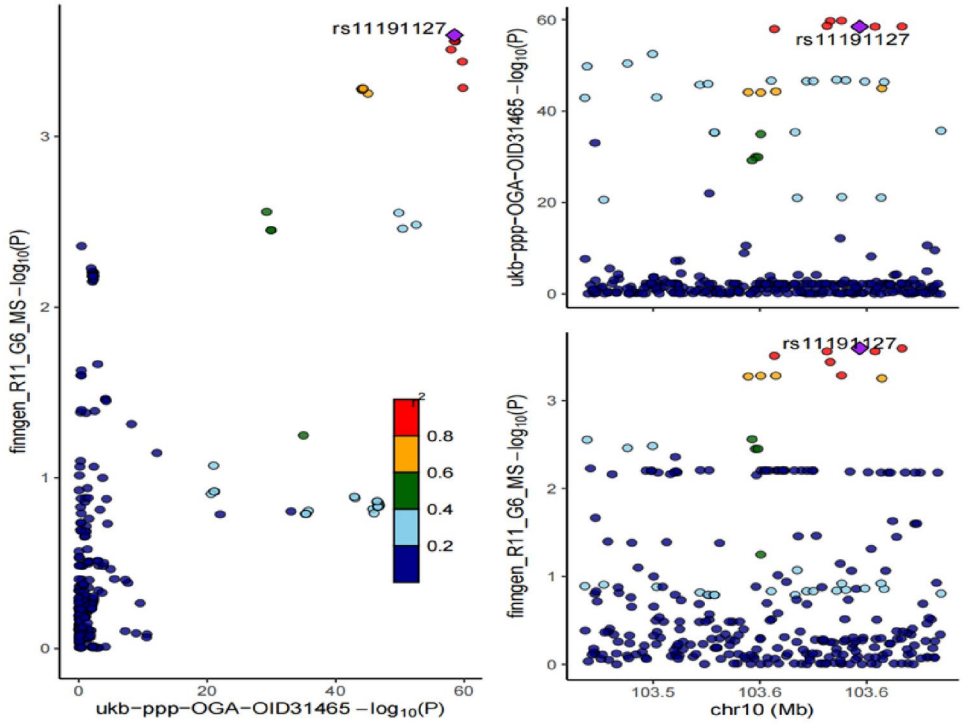

Fig. 17. Bayesian co localization results of OGA and multiple sclerosis.

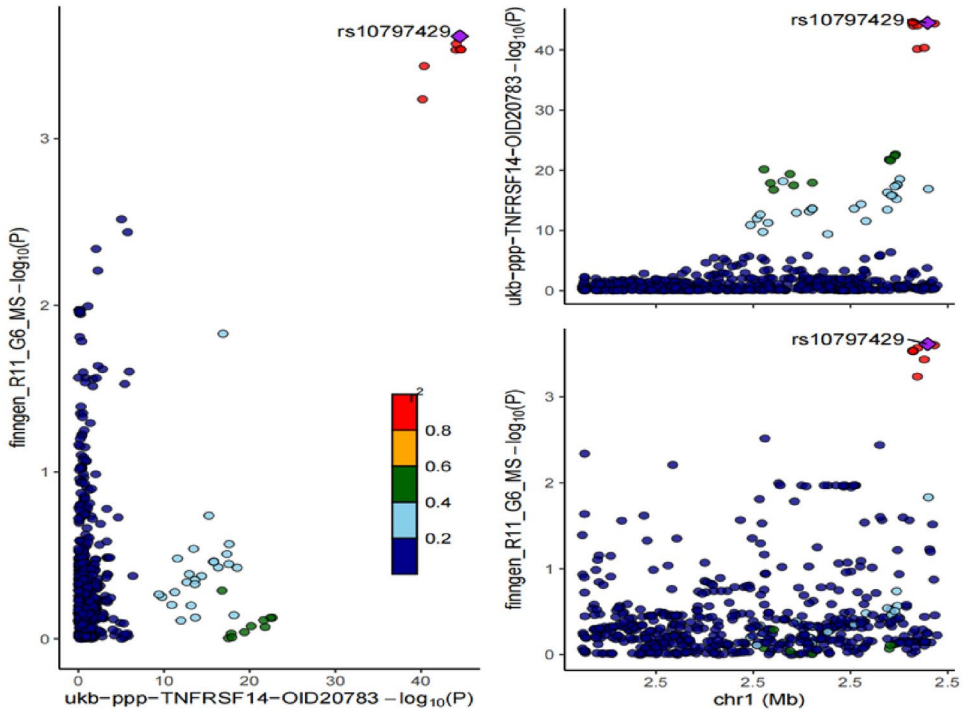

Fig. 18. Bayesian co localization results of TNFRSF14 and multiple sclerosis.

response diminishes, leading to Treg cell proliferation and an immunosuppressive state. Additional research has indicated that DMBA exerts inhibitory effects on both cellular and humoral immunity in mice[47,48]. Regarding humoral immunity, DMBA significantly reduces antibody production. In our experiments, the quantity of antibodies produced by DMBA-treated mice post-vaccination was markedly lower than that of control mice. In terms of cellular immunity, DMBA treatment resulted in diminished cytotoxic T cell function, abnormal

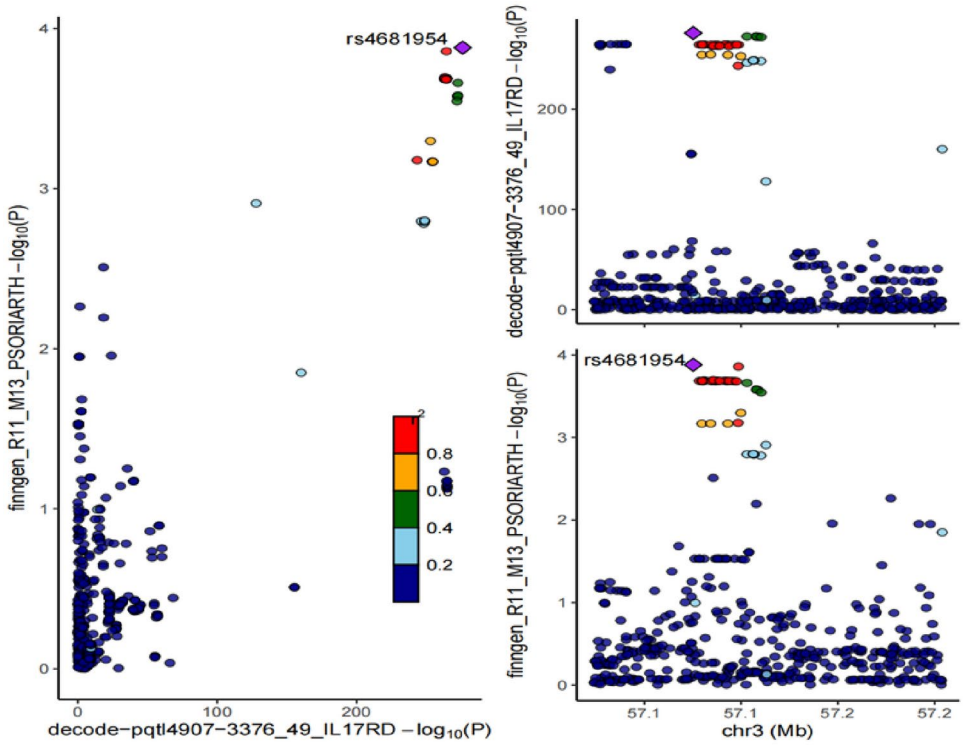

Figure 19. Bayesian co localization results of IL17RD and psoriatic arthritis.

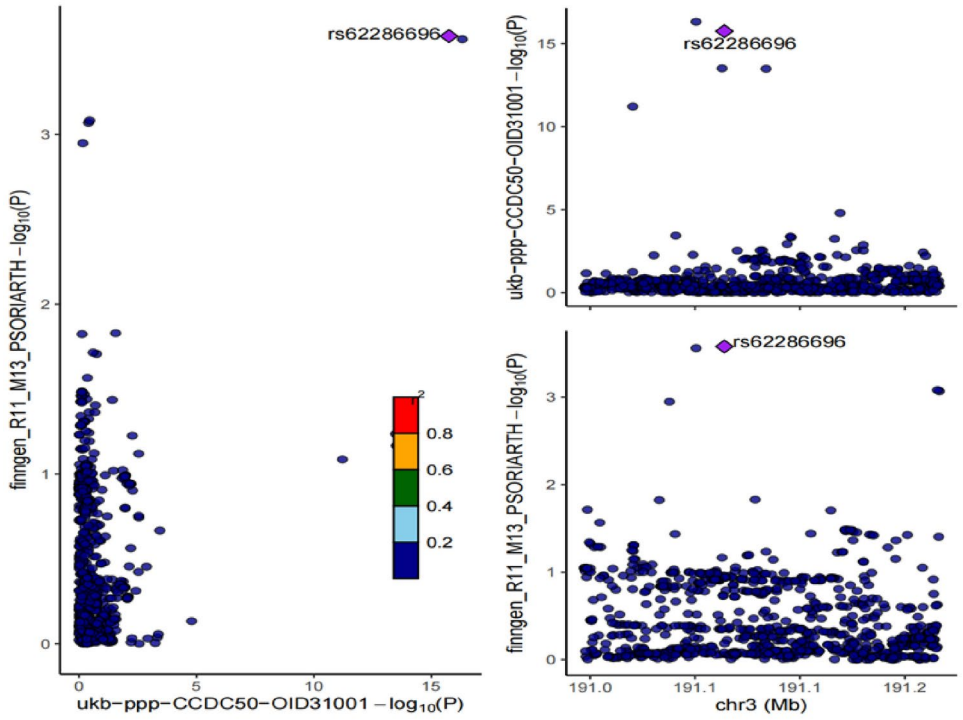

Fig. 20. Bayesian co localization results of CCDC50 and psoriatic arthritis.

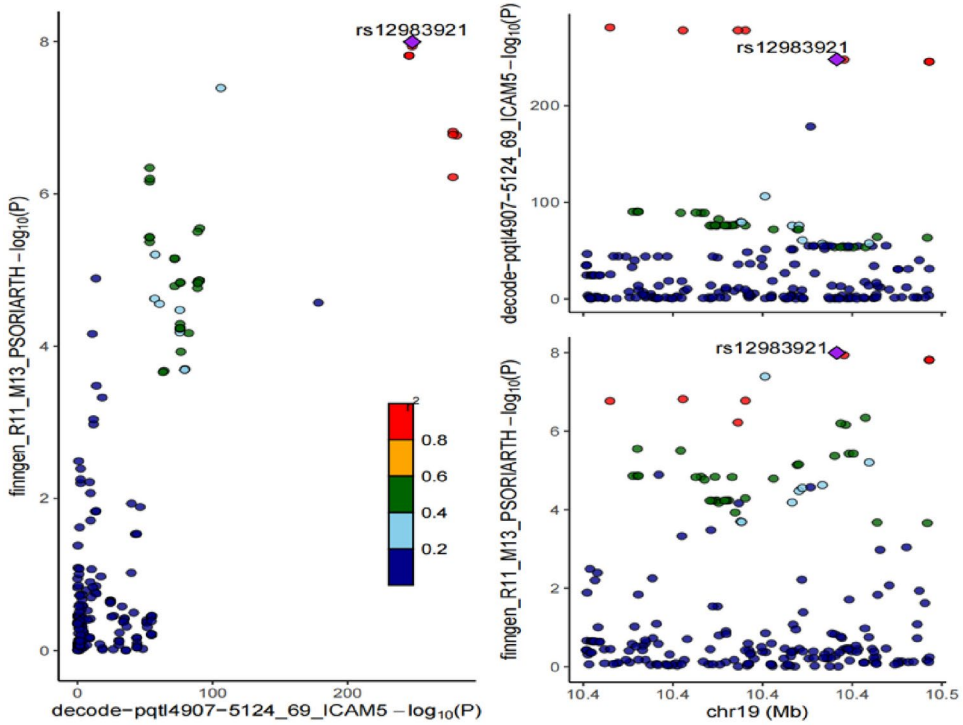

Fig. 21. Bayesian co localization results of ICAM5 and psoriatic arthritis.

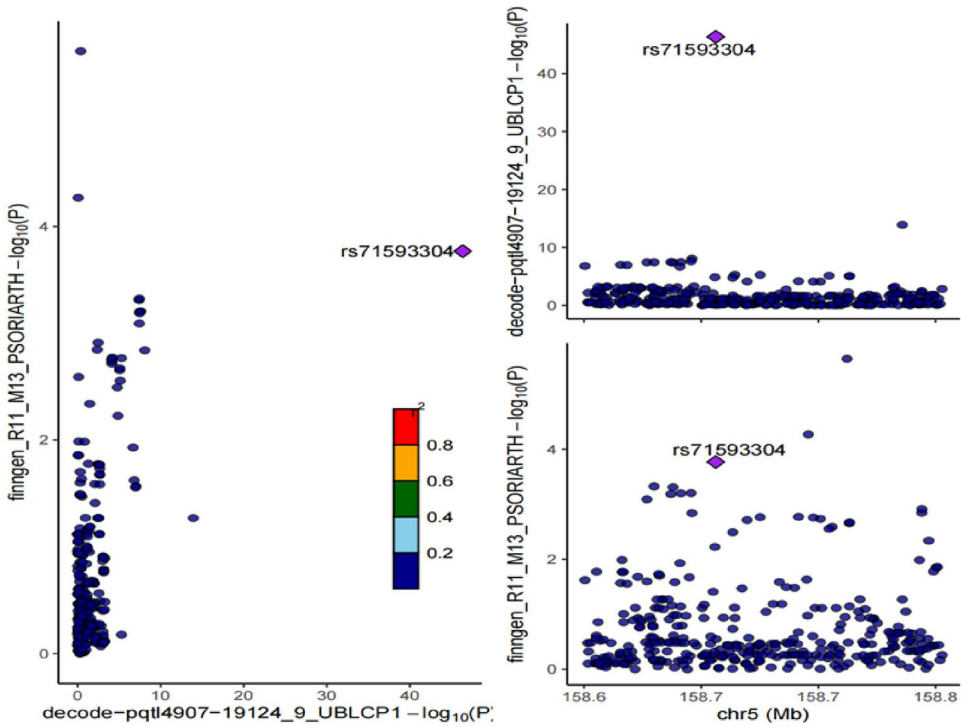

Fig. 22. Bayesian co localization results of UBLCP1 and psoriatic arthritis.

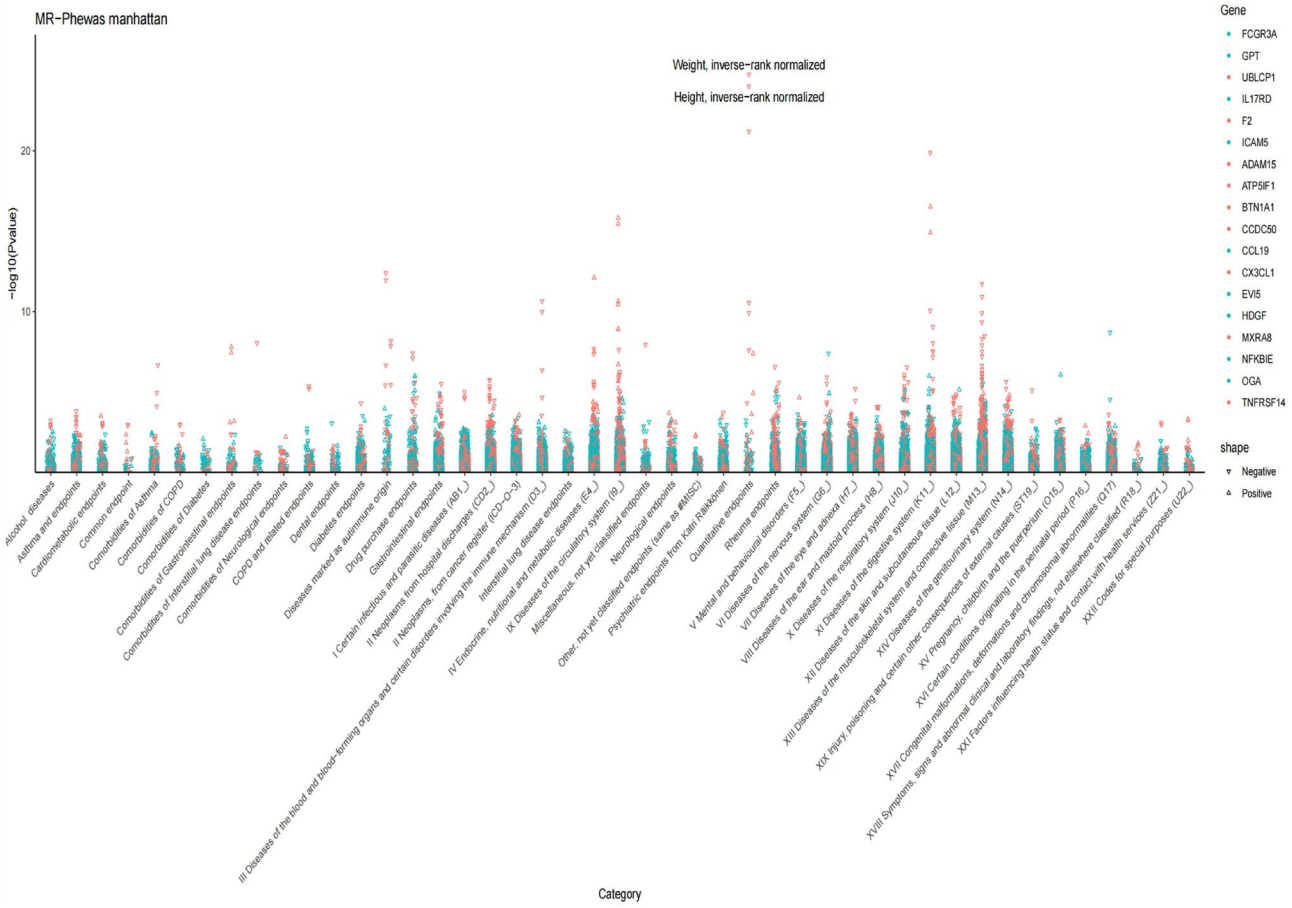

Fig. 23. Manhattan plot of Phewas, a significantly positive gene for immune related bone diseases.

immune cell activation, and reduced cytokine secretion, suggesting that DMBA has a direct toxic effect on immune cells. The immunosuppressive effects of DMBA intensify with increasing doses, and the observed increases in T cells, antibody production, and cytotoxic T cell function are all dose-dependent. As research deepens and the immune mechanisms affected by DMBA are further explored, novel strategies may emerge for the prevention and treatment of related diseases.

The relationship between CCL19 and RA

CCL19, also known as macrophage inflammatory protein-3β (MIP-3β), is a member of the CC chemokine family, which plays a pivotal role in immune regulation and various biological processes. In particular, CCL19 is crucial for the maintenance and function of lymphoid tissue, as it regulates the positioning of immune cells by directing them to specific areas. Research has demonstrated that lymph node stromal cells influence the lymph node microenvironment through the concentration gradients of CCL19 and CCL21[49]. Moreover, the expression of CCL19 is closely associated with the activity of specific CD4 + T cell subsets, particularly during immune responses[50]. Variations in CCL19 levels can serve not only as indicators of immune-related diseases, such as autoimmune disorders and lymphoid tumors, but also as biomarkers for evaluating treatment responses and monitoring disease progression.

In RA, the role of CCL19 is supported by extensive research. As a B-cell chemokine, CCL19 is associated with a decrease in memory B cells in the blood of RA patients and correlates with clinical responses to rituximab treatment[51]. CCL19 significantly increases the expression of IL-1β and TNF-αin synovial cells, while also promoting IL-1βexpression in peripheral blood mononuclear cells[52]. These pro-inflammatory cytokines activate various immune cells, triggering joint and tissue inflammation, which can exacerbate the onset and progression of RA. The interaction of CCL19 with its receptor CCR7 enhances its biological effects, potentially by promoting IL-1β expression, thus upregulating CCR7 function through IL-1β. Additionally, the study found that CCL19 regulates B cell recruitment in the RA synovium and is closely related to joint and synovial destruction[53]. In the early stages of RA, CCL19 expression is stimulated by TNF-α and LTα1β2, leading to significant changes in the lymph node microenvironment[54]Clinical studies have shown that CCL19 levels serve as disease markers and prognostic indicators of RA. ELISA testing reveals that CCL19 is highly expressed in RA patients, and treatment with disease-modifying antirheumatic drugs (DMARDs) results in a significant decrease in CCL19 levels[55]. Therefore, the expression level of CCL19 in RA, its interaction with inflammatory factors, and its correlation with clinical indicators all underscore its critical role in the pathogenesis of RA.

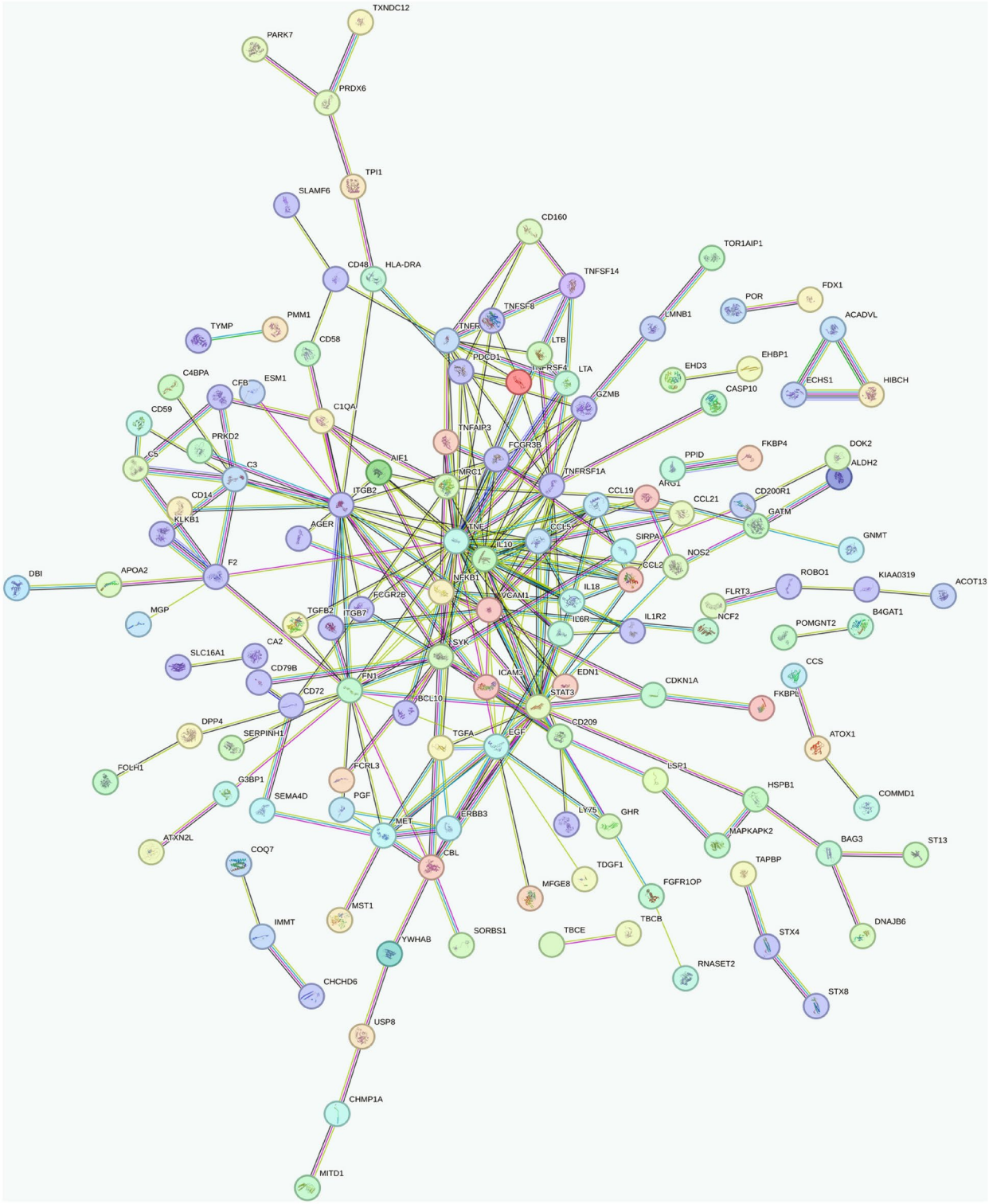

Fig. 24. STRING database protein interaction network diagram.

Previous studies have demonstrated that CCL19, a chemokine crucial to the immune system, is regulated by a variety of cytokines and transcription factors. Inflammatory factors, such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), can upregulate its expression[56]. Upon binding to CCR7, CCL19 induces immune cell migration, activates intracellular signaling pathways, promotes cell migration and aggregation to lymph nodes, enhances antigen presentation and immune response, and initiates a series of intracellular signaling events that facilitate cytoskeletal reorganization and cellular recombination. CCL19 is predominantly expressed in lymphoid tissues and certain immune cells, and it regulates cell migration, thereby influencing the

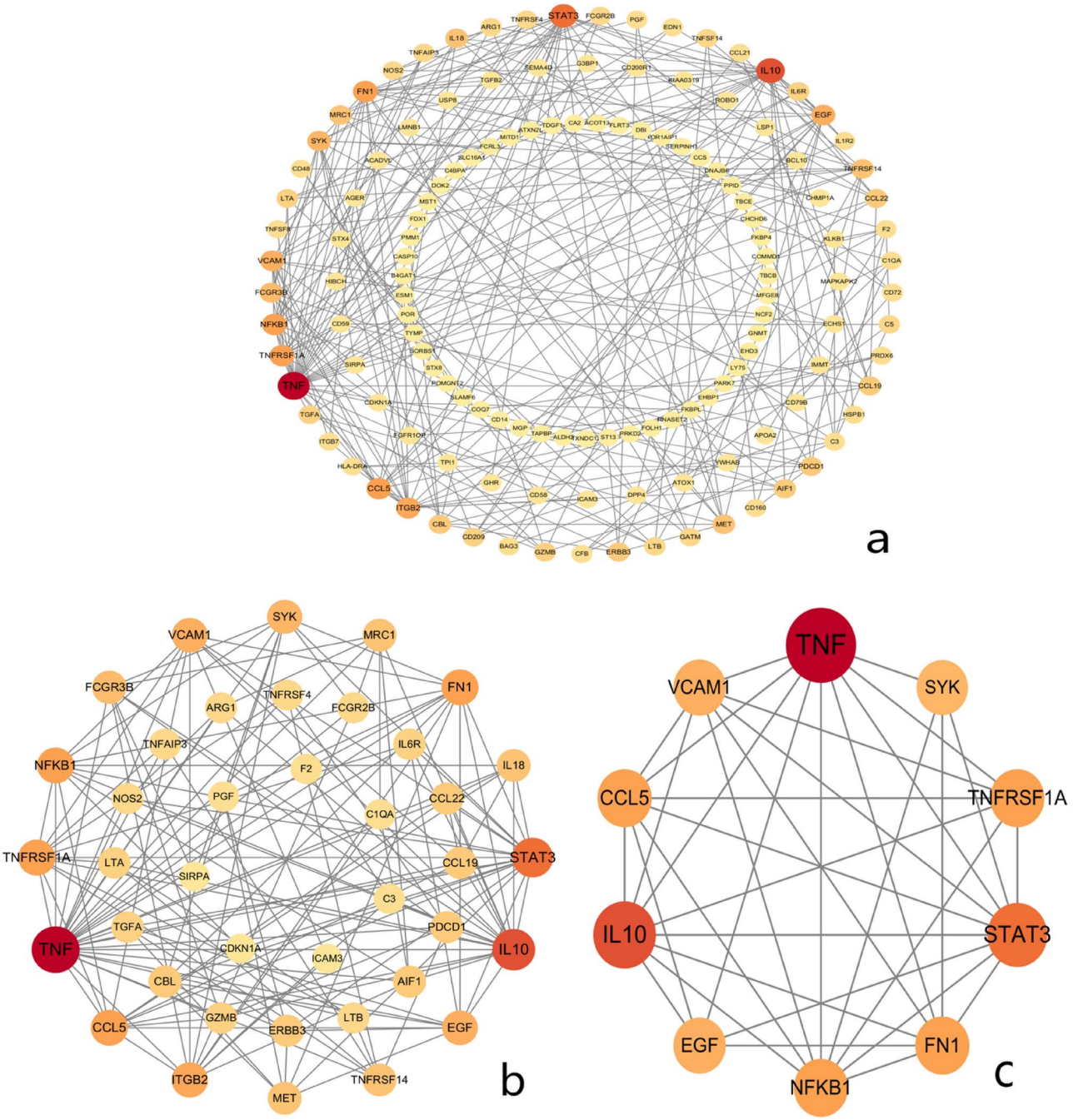

Fig. 25. Results of core genes based on CytoNCA analysis.Figure a represents the network construction diagram of all significantly positive genes, and Figure b and Figure c represent the result diagrams of core genes based on the CytoNCA analysis.

immune response[57]. Given this context, CCL19 holds significant potential for application in the treatment of RA. As a key chemokine, CCL19 modulates the migration and activation of immune cells via its interaction with the CCR7 receptor, thereby playing a pivotal role in the inflammatory response associated with RA[58]. Consequently, targeting CCL19 and its receptor, CCR7, may represent a novel therapeutic strategy to mitigate inflammation and joint destruction by obstructing their interactions and reducing the recruitment of immune cells to the inflammatory site. Additionally, fluctuations in CCL19 levels may serve as a biomarker for monitoring disease progression in RA patients, aiding in the assessment of treatment efficacy and disease activity[59] .Future studies will further investigate the interaction of CCL19 with other cytokines and chemokines, examine the regulation of their expression by various cytokines, and explore the feasibility of gene therapy. Additionally, more clinical trials will be conducted to evaluate CCL19-based treatment methods. Assessing the effectiveness and safety of these approaches will enhance our understanding of the comprehensive mechanisms of action in the immune

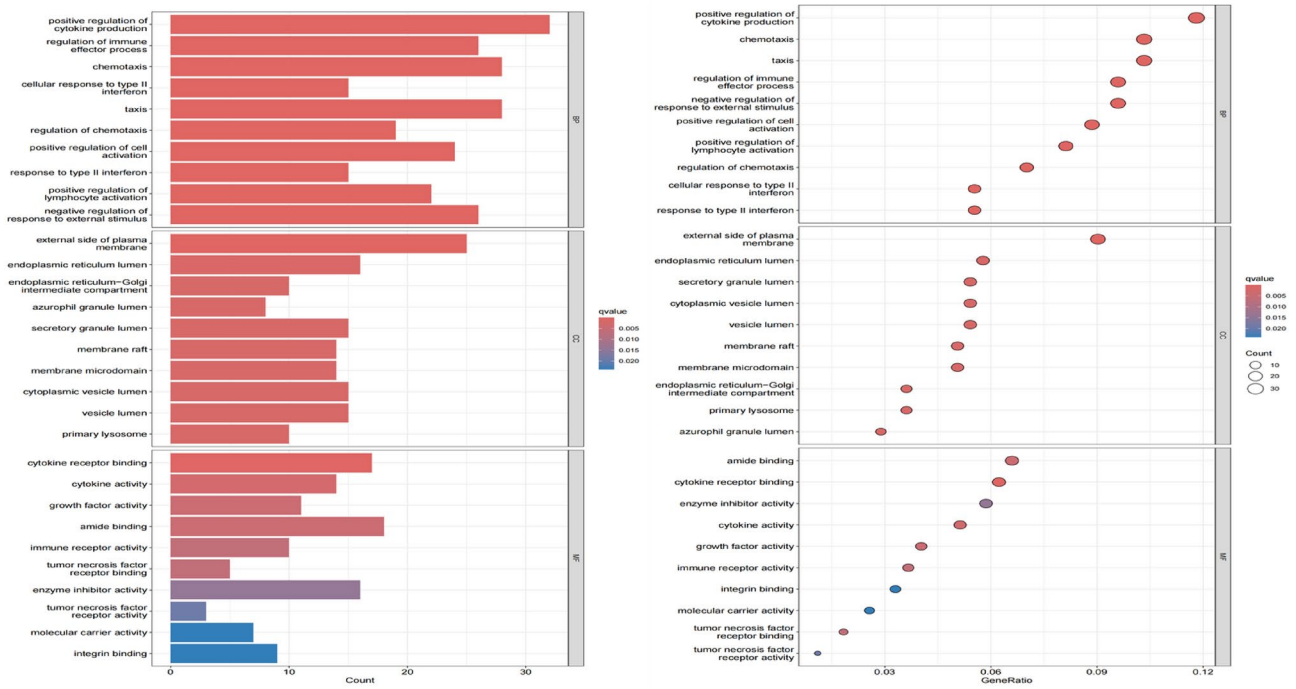

Fig. 26. GO enrichment analysis of immune related bone disease positive genes(Bar chart and bubble chart).

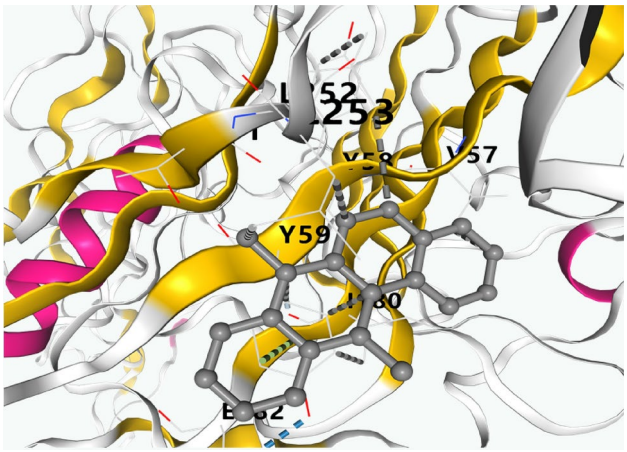

Fig. 27. Molecular Docking of TNFRSF14 with DMBA.

response, facilitate the development of new immunotherapy strategies, and provide additional options for treating immune diseases. This research holds significant value and is expected to improve the quality of life for patients with immune disorders.

1-Nitropyrene is a polycyclic aromatic hydrocarbon that has been shown to possess significant carcinogenic and mutagenic properties. Our research indicates that CCL19 exhibits a high binding affinity for 1-nitropyrene[60]. Furthermore, studies suggest that 1-nitropyrene may play a role in immune regulation by activating intracellular signaling pathways. Notably, 1-nitropyrene significantly enhances the expression of the Cyp1a1 protein, which is crucial for metabolic processes and may substantially influence the activity of immune cells and inflammatory responses. This compound may be integral to the mechanisms underlying inflammation, infection, and tissue damage responses. It has the potential to trigger chronic inflammation, which can adversely affect immune function. Chronic inflammation is closely linked to the development of various diseases, including autoimmune disorders and cancer, potentially exacerbating disease progression by promoting the release of inflammatory factors and intensifying the immune system's excessive responses[61]. Additionally, studies have shown that 1-nitropyrene is associated with cellular senescence; mice exposed to this compound exhibit increased susceptibility to telomere damage and cellular senescence in lung and alveolar epithelial cells[62]. In summary, the interaction between 1-nitropyrene and the immune system is highly complex, encompassing multiple levels of

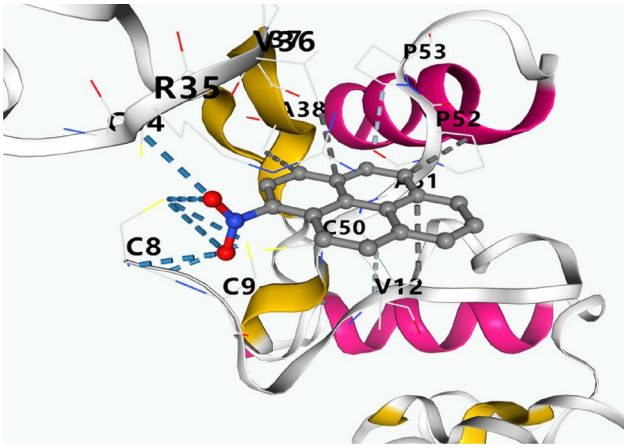

Fig. 28. Molecular Docking of CCL19 with 1-Nitropyrene.

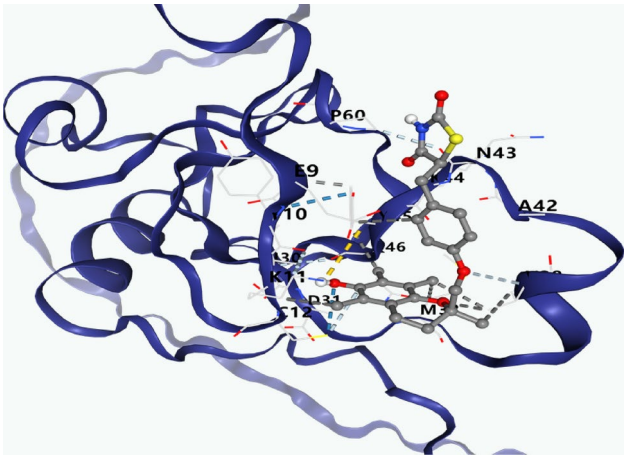

Fig. 29. Molecular Docking of HDGF with Troglitazone.

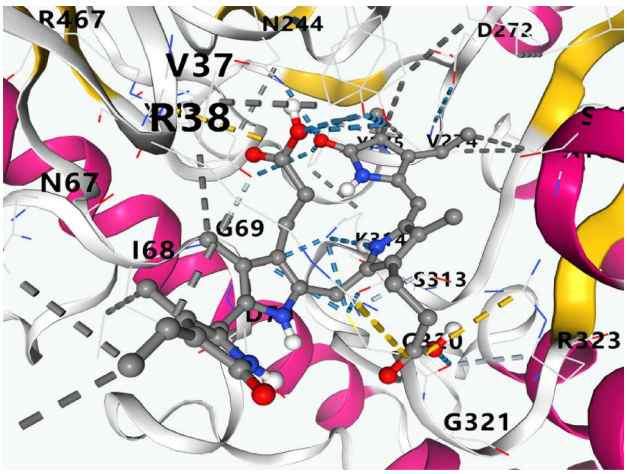

Fig. 30. Molecular Docking between GPT and Bilirubin.

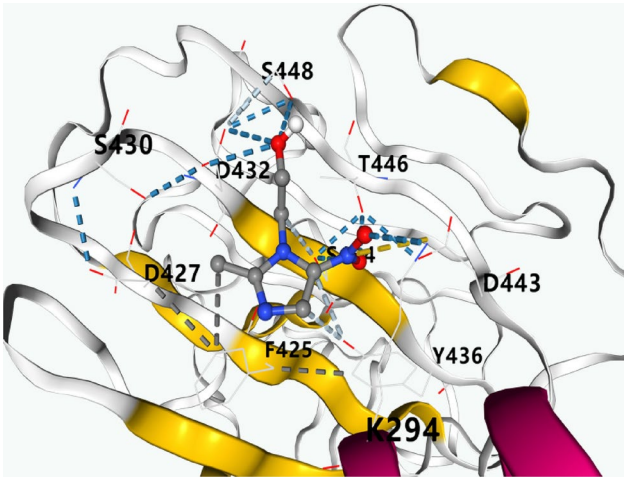

Fig. 31. Molecular Docking between BTNA1 and metronidazole.

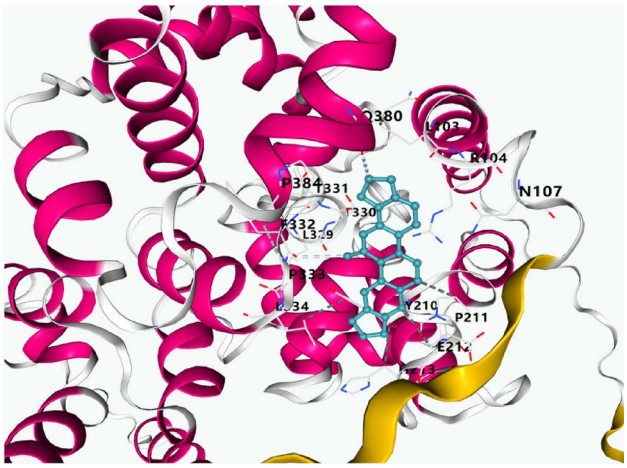

Fig. 32. Molecular Docking of EVI5 with Sanguinarine.

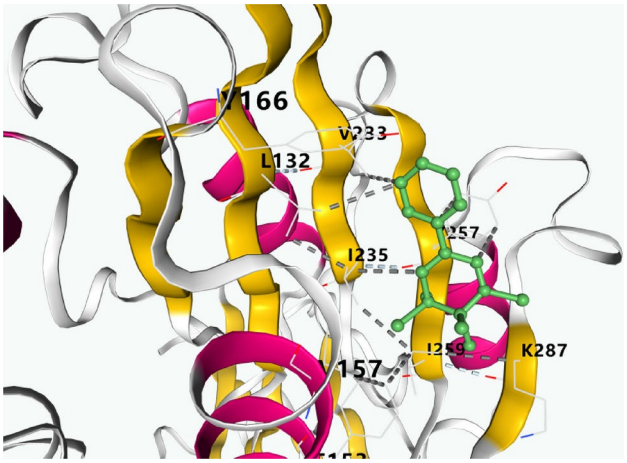

Fig. 33. Molecular Docking between ICAM5 and PCB118.

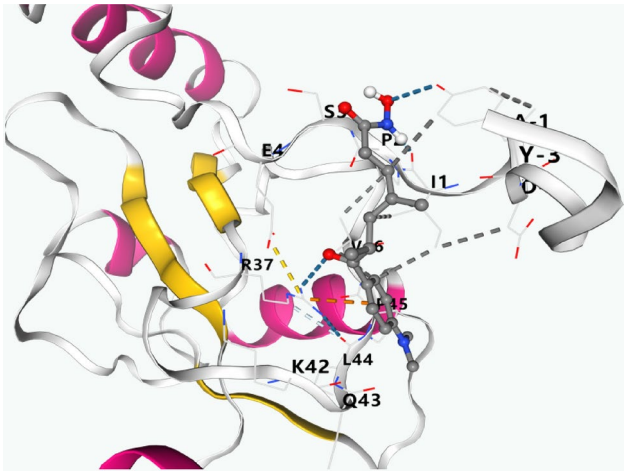

Fig. 34. Molecular Docking between CCDC50 and MMS.

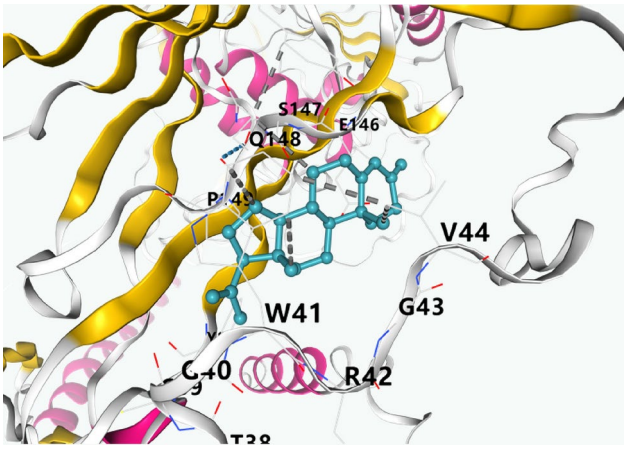

Fig. 35. Molecular docking of IL17RD with progesterone.

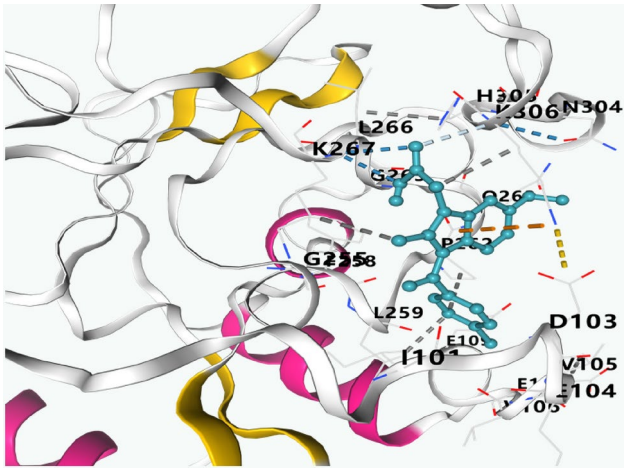

Fig. 36. UBLCP1 molecular docking with indomethacin.

Gene	Disease	P_IVW	OR	95%CI	P_SMR	P_HEIDI	PP.H4	LDSC_P
HDGF	Rheumatoid arthritis	0.0338	1.0373	1.0028–1.073	0.0338	0.0628	0.8426	0.9094
CCL19	Rheumatoid arthritis	0.0000	0.4644	0.3366–0.6406	NA	NA	0.9762	0.0000
TNFRSF14	Rheumatoid arthritis	0.0007	0.6947	0.5634–0.8566	0.0001	0.0001	0.8016	0.0258
GPT	Crohn's related joint disease	0.0006	0.0057	0.0003–0.1111	NA	NA	0.8126	NA
BTN1A1	Multiple sclerosis	0.0000	0.6101	0.4813–0.7733	NA	NA	0.7660	0.2640
EVI5	Multiple sclerosis	0.0000	0.3032	0.1981–0.4642	0.1095	0.0575	0.9800	0.5764
OGA	Multiple sclerosis	0.0005	0.4599	0.2966–0.7131	NA	NA	0.8569	0.2745
TNFRSF14	Multiple sclerosis	0.0002	0.4026	0.2505–0.6471	0.0004	0.0016	0.8904	0.4049
ICAM5	Psoriatic arthritis	0.0281	1.1742	1.0174–1.3552	0.0682	0.0006	0.9476	0.4539
CCDC50	Psoriatic arthritis	0.0092	0.7359	0.5843–0.9269	0.5621	0.3590	0.9091	0.2432
IL17RD	Psoriatic arthritis	0.0006	0.7887	0.6886–0.9034	NA	NA	0.9301	0.1982
UBLCP1	Psoriatic arthritis	0.0021	0.6901	0.5448–0.8741	0.2599	0.0000	0.8862	0.4038

Table 1. Positive genes obtained through the comprehensive analysis strategy of MR, SMR, Bayesian colocalization, and LDSC.

both innate and adaptive immunity. By influencing macrophage function, inducing specific immune responses, and modulating cell signaling pathways, 1-nitropyrene has profound effects on the immune system.

The relationship between HDGF and RA

Liver cancer-derived growth factor (HDGF) is a multifunctional protein that plays a critical role in liver cancer and various other diseases. As a cell growth factor, it exhibits essential functions in biological processes such as cell proliferation, angiogenesis, and neuroprotection. Studies have demonstrated that HDGF is integral to cell signal transduction and the regulation of gene expression. It is expressed in multiple cell types, particularly in the liver and certain cancer cells, with its expression level significantly elevated in association with the occurrence and progression of liver cancer[63,64]. HDGF enhances the survival of liver cancer cells by promoting tumor cell proliferation and inhibiting apoptosis[65]. Furthermore, HDGF is implicated in the progression of various diseases, including cardiovascular and neurodegenerative diseases, with its role in regulating redox homeostasis and mitochondrial bioenergetics being crucial for cellular energy metabolism[66]. Recent research has elucidated the mechanisms by which HDGF participates in multiple cell signaling pathways, such as the regulation of the Wnt signaling pathway, and has explored its potential application as a biomarker for the early diagnosis of liver cancer[63]. Additionally, HDGF is considered a therapeutic target, with the inhibition of its function potentially aiding in the reduction of tumor growth and enhancement of therapeutic outcomes[64,65]. In summary, HDGF is significantly associated with a range of diseases and various biological mechanisms. Comprehensive research on HDGF may provide new insights for the early diagnosis and targeted treatment of diverse diseases.

Previous studies have demonstrated that HDGF is involved in the regulation of multiple signaling pathways, notably promoting cell proliferation through the activation of the Akt and ERK signaling pathways. The MEK/ERK and PI3K/AKT pathways are crucial for regulating cell survival, proliferation, and metabolism. HDGF enhances Akt activity, which subsequently amplifies downstream effects, thereby facilitating cell growth[67]. Additionally, HDGF can augment Wnt signaling transmission, contributing to tumor growth and metastasis. In the context of RA onset, the MEK/ERK, Wnt/β-catenin, and PI3K/AKT pathways emerge as three key players[68]. Notably, the MEK/ERK pathway is abnormally activated during the onset of RA, promoting synovial cell proliferation by regulating the expression of cyclin-related and apoptosis-related genes. Following activation, this pathway can also stimulate the release of pro-inflammatory cytokines such as IL-6 and TNF-α. Currently, inhibitors targeting the MEK/ERK pathway are under investigation and hold promise for RA treatment[69]. The Wnt/β-catenin pathway also exhibits dysfunction in RA, promoting the proliferation and migration of synovial cells through the regulation of β-catenin expression. Furthermore, activation of this pathway can inhibit cell apoptosis, enhancing the survival of synovial cells and interacting with the MEK/ERK and PI3K/AKT pathways[70]. During the RA process, the PI3K/AKT pathway increases synovial cell survival by inhibiting the expression of apoptosis-related proteins, while also promoting the generation of pro-inflammatory cytokines. Research has indicated potential for inhibitors targeting this pathway in anti-RA therapy[69]. Collectively, the MEK/ERK, Wnt/β-catenin, and PI3K/AKT pathways coordinate with each other and exhibit feedback regulation mechanisms, collectively influencing the pathological processes of RA.Therapeutic strategies targeting these three pathways are anticipated to generate new insights for the clinical management of RA. A thorough investigation of their interactions and their roles in the pathogenesis of RA will be crucial for developing treatment methods that enhance the quality of life and prognosis for RA patients.

Research on the relationship and mechanisms involving HDGF, RA and immune arthritis has garnered increasing attention. Studies indicate that serum HDGF levels in RA patients correlate closely with disease activity, suggesting that HDGF may play a pivotal role in the pathogenesis of RA[71]. HDGF influences the pathological processes of RA through multiple pathways: firstly, it may exacerbate the inflammatory response in joints by regulating the activation of inflammatory cells and the secretion of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin (IL)[72]. Secondly, HDGF can promote the proliferation and migration of fibroblasts and immune cells, which are critical in the pathological progression of RA, as the hyperactivity

of these cells can lead to the destruction of articular cartilage and bone[73,74]. Additionally, HDGF may impact the functionality of immune cells by enhancing the activation and proliferation of T cells and B cells, thereby intensifying the autoimmune response and worsening the condition of RA[71,75]. Beyond RA, HDGF exhibits similar mechanisms in other immune arthritides, such as Sjögren's syndrome and inclusion body myositis. In summary, the mechanisms through which HDGF operates in various immune diseases demonstrate complex and diverse characteristics[76]. At this stage, an in-depth exploration of the functions and specific mechanisms of HDGF can not only provide new perspectives for the diagnosis and treatment of related diseases but also assist in exploring its potential as a therapeutic target in clinical practice, thereby laying a solid foundation for the future optimization of diagnostic and treatment strategies for immune diseases.

Molecular docking results indicate that Troglitazone exhibits strong binding affinity with HDGF. Troglitazone is a thiazolidinedione drug primarily utilized for the treatment of type 2 diabetes by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby enhancing insulin sensitivity. Recent studies have revealed that PPAR-γ not only plays a crucial role in metabolic regulation but is also implicated in inflammatory responses and the immune system. Patients with RA often experience insulin resistance and an increased risk of diabetes, providing a theoretical foundation for the potential application of Troglitazone in RA treatment[77]. Experimental research has demonstrated that Troglitazone can induce apoptosis in RA synovial cells and significantly inhibit the production of matrix metalloproteinase-3 (MMP-3) in synoviocytes[78]. MMP-3 is a key player in the inflammatory process and joint destruction associated with RA[79]. Furthermore, clinical trials suggest that the combination of Troglitazone and methotrexate may yield a synergistic effect in RA patients, alleviating symptoms by improving metabolic status[80]. The mechanism of action may involve the promotion of anti-inflammatory gene expression through PPAR-γ activation while concurrently inhibiting pro-inflammatory gene expression, thus regulating the inflammatory response. Another study has indicated that the activation of mTORC1 serves as a common link between RA and diabetes, potentially elucidating an important mechanism by which Troglitazone exerts its effects[81]. Consequently, Troglitazone holds significant potential for application in RA treatment, particularly in patients with insulin resistance, and may offer novel strategies for the management of RA.

The relationship between GPT and IBD-related arthritis

Alanine aminotransferase (GPT), also known as alanine aminotransferase (ALT), plays a crucial role in human metabolism, particularly in the alanine cycle. This cycle primarily occurs between the liver and skeletal muscles, facilitating the conversion of ammonia in the muscles into harmless alanine, which is then transported to the liver via the bloodstream[82,83]. In the muscle, GPT catalyzes the transamination reaction between pyruvate and amino acids to produce alanine. In the liver, alanine undergoes deamination to yield pyruvate and ammonia. The ammonia subsequently enters the urea cycle, while pyruvate is converted to glucose through gluconeogenesis before being transported back to the muscle. This process not only detoxifies ammonia but also supplies energy to the muscles. Notably, under hypoxic conditions, lactic acid and alanine produced by the muscles are converted into glucose in the liver, thereby maintaining the balance of energy metabolism. The alanine cycle enhances the metabolic connection between the muscles and the liver, which is vital for sustaining overall metabolic health and preventing related diseases.

GPT is significantly associated with various inflammatory factors. Elevated GPT levels, often resulting from liver disease and abnormal liver metabolic function, frequently coincide with changes in inflammation levels[84–86]. The relationship between GPT and IBD is noteworthy. Patients with IBD often experience systemic inflammation, characterized by increased levels of inflammatory factors such as IL-6 and TNF-α, which not only exacerbate intestinal inflammation but may also impair muscle tissue anabolism and negatively affect bone structure and function[87,88]. A clinical study indicated that low ALT levels are more prevalent among patients with IBD, In a study involving children with IBD, nearly half exhibited low ALT levels[89]. Furthermore, another investigation demonstrated that the loss of muscle mass and strength in IBD patients is directly correlated with elevated levels of the aforementioned inflammatory factors[89]. These factors disrupt the response of muscle tissue to growth hormone, leading to decreased muscle protein synthesis and potentially resulting in muscle atrophy. Changes in ALT levels are more frequently observed in Crohn's disease compared to ulcerative colitis, which indirectly supports our findings[89,90]. Additionally, a prospective survey tracking 127 adult patients with IBD in Denmark over a 10-year period revealed that nearly all patients with Crohn's disease experienced at least one episode of subnormal ALT levels[90]. Beyond its metabolic functions in the liver and muscles, GPT is also closely linked to bone health. The intestinal microbiota influences bone metabolism via the gut-bone axis, and its metabolites, such as short-chain fatty acids, can inhibit inflammatory responses and directly affect osteoclast precursors, thereby reducing bone resorption and enhancing bone density[91].These findings reveal complex interactions among gut microbiota, skeletal muscle, and bone. GPT acts as a bridge in this process, linking muscle metabolism with bone health and underscoring its critical role in overall metabolic health. In summary, the relationship between GPT and IBD-related arthritis is multifaceted, involving inflammatory factors, imbalances in intestinal microbiota, and interactions between muscle and skeletal systems. Collectively, these elements may influence bone health in individuals with IBD, including the development of arthritis.

Previous studies have confirmed that GPT is involved in several important signaling pathways, including AGEs/RAGE, p38 MAPK/NF-kappa B[92], and PI3K/AKT[93]. These pathways are crucial in the pathogenesis of IBD and its articular manifestations. Specifically, regarding glycosylation end products (AGEs) and their receptor RAGE, AGEs are complexes formed through non-enzymatic reactions between sugars and proteins or lipids, which are prevalent in organisms, particularly in pathological states such as inflammation and diabetes. In the context of IBD, the accumulation of AGEs is closely associated with intestinal inflammation and injury, activating a series of intracellular signaling pathways upon binding to the specific receptor RAGE. When AGEs bind to RAGE, they induce the activation of downstream p38 MAPK and NF-kappa B signaling pathways,

which subsequently promote the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8, thereby exacerbating intestinal inflammatory responses[94]. The p38 MAPK/NF-kappa B signaling pathway holds significant importance in the pathogenesis of IBD. As a key stress kinase, p38 MAPK regulates cellular inflammation and apoptosis, and is considered one of the crucial downstream effects of AGEs/RAGE signaling in IBD[95]. The activation of the p38 MAPK pathway ultimately triggers the activation of NF-kappa B, which is responsible for regulating the expression of various pro-inflammatory factors. Through this mechanism, the p38 MAPK pathway plays a vital role in the inflammatory process of IBD, with its activation leading to the promotion of various pro-inflammatory cytokines and chemokines by NF-kappa B, thus further exacerbating intestinal inflammation and creating a vicious cycle[96].The PI3K/AKT signaling pathway is crucial for cell proliferation, survival, and metabolism. In inflammatory bowel disease (IBD), abnormal activation of this pathway is associated with the development of intestinal inflammation and its related joint manifestations. On one hand, activation of the PI3K/AKT signaling pathway can enhance the survival and proliferation of intestinal epithelial cells, thereby providing some resistance to intestinal damage. However, excessive activation of this pathway may lead to abnormal cell proliferation and inflammation[95,97]. On the other hand, the PI3K/AKT pathway exhibits a reciprocal regulatory relationship with the NF-kappa B pathway, as AKT can enhance the transcriptional activity of NF-kappa B, further exacerbating the inflammatory response[94]. In the context of IBD, joint symptoms such as arthritis frequently accompany intestinal manifestations, which are closely linked to a systemic inflammatory response. The AGEs/RAGE, p38 MAPK/NF-kappa B, and PI3K/AKT pathways also significantly contribute to this process. Intestinal inflammation can instigate systemic inflammation through the bloodstream, impacting the joints. The accumulation of advanced glycation end-products (AGEs) and the activation of the receptor for AGEs (RAGE) may play a pivotal role in the pathogenesis of arthritis. Additionally, the release of pro-inflammatory cytokines in patients with IBD not only affects the intestines but may also lead to arthritis and joint injury, thereby creating an interaction between IBD and arthritis. Overall, the GPT may play a key role in inflammatory bowel disease and its articular manifestations by mediating the AGEs/RAGE, p38 MAPK/NF-kappa B, and PI3K/AKT signaling pathways.

Bilirubin is the primary product of hemoglobin breakdown and its associated heme proteins. It is predominantly produced within the mononuclear-phagocytic cell system, including the spleen, liver, and bone marrow, and is closely linked to the human immune system. We observed a high binding affinity between GPT and bilirubin, suggesting that bilirubin may play a significant role in immune regulation. Research indicates that bilirubin enhances the antioxidant capacity of immune cells by activating the Nrf2 signaling pathway, thereby mitigating inflammatory responses[98]. Furthermore, bilirubin influences the intensity and direction of immune responses by modulating interactions among immune cells[99]. It can also directly impact the transcription of genes associated with inflammation and immune responses, altering the behavior of immune cells through the regulation of immune gene expression[100]. In clinical contexts, the immunosuppressive properties of bilirubin offer novel strategies for treating autoimmune diseases by regulating bilirubin levels or utilizing its derivatives to alleviate autoimmune reactions[101]. Regarding anti-inflammatory treatment, the anti-inflammatory properties of bilirubin present opportunities for developing drugs that target specific inflammatory pathways[102]. Notably, in inflammatory bowel disease, bilirubin is associated with alterations in various immune cells, including T cells and CD39[103]. Clinical studies have demonstrated that bilirubin-linked low-molecular-weight nanoparticles can repair the intestinal mucosal barrier, modulate immunity, and restore intestinal microflora, providing a new approach for treating related diseases[104]. The role of bilirubin in the immune system is multifaceted, encompassing immune tolerance, antioxidant activity, anti-inflammatory effects, and other mechanisms. Its potential applications in immune regulation warrant further investigation.

The relationship between BTN1A1 and MS

The protein encoded by the Butyrophilin Subfamily 1 Member A1 (BTN1A1) gene belongs to the butyrylcholine receptor (butyrophilin) family. Under normal physiological conditions, BTN1A1 may play a role in processes such as immune regulation. One study demonstrated that BTN1A1 can bind to activated T cells and inhibit the proliferation of CD4 + T cells, suggesting the presence of BTN1A1 receptors on T cells[105]. BTN1A1 may function in trans as an immune checkpoint protein through a mechanism analogous to that of programmed death ligand 1. An animal study indicated that when BTN1A1 is highly expressed on the surface of tumor cells, it can inhibit T cell responses in both in vitro and in vivo environments, highlighting its close association with immune-related pathways and its participation in the regulation of the JAK/STAT pathway in immune mechanisms[106]. Additionally, another study revealed that tumors harboring murine sarcoma toxin oncogenic homolog B1 (BRAF) mutations exhibited elevated expression levels of immune checkpoint molecules in the novel butyrophilin subfamily, including BTN1A1 and BTNL9[107]. This increase suggests a potential role in enhancing immunological responses. Other research has indicated that BTN1A1 may be involved in ligand-dependent Wnt activation and alterations in drug transport and metabolism. Furthermore, studies have shown that BTN1A1 expression is significantly altered in certain immune and inflammatory diseases, such as ulcerative colitis[108].

Previous studies have demonstrated that BTN1A1, a gene closely associated with immune regulation, is linked to multiple biological pathways, primarily involving the innate immune system and MHC class I-mediated antigen processing, among other significant pathways[109,110]. BTN1A1 is recognized as a novel immune checkpoint that operates independently of PD-L1, making it a vital target for cancer immunotherapy research[106]. Its dysfunction in the immune system is associated with various diseases, including tibial neuropathy. Understanding the function and role of BTN1A1 in diseases can aid in the development of new therapeutic strategies. Within the immune system, BTN1A1 serves multiple roles, interacting with T cell surface proteins to influence T cell activation status and function. It also plays a critical role in the processing and presentation of MHC class I antigens, which is essential for cellular immune responses. In the innate immune system, BTN1A1

binds to other immune molecules, such as xanthine oxidoreductase, to help regulate immune responses, thereby affecting the activation of innate immune cells like macrophages and dendritic cells[109]. Regarding MHC class I-mediated antigen processing, BTN1A1 may enhance the immune response of cells to pathogens by improving the efficiency of antigen presentation, and it may also contribute to maintaining immune tolerance by regulating T cell activity and preventing autoimmune reactions. Abnormal function of BTN1A1 can trigger a range of immune-related diseases, and its expression levels are closely linked to certain autoimmune disorders. Therefore, exploring potential therapeutic targets, examining the interaction between BTN1A1 and other immune checkpoints such as PD-L1, investigating the feasibility of combination therapies, and further clarifying the role of BTN1A1 in specific conditions such as autoimmune diseases will provide new insights and strategies for immunotherapy.

Abnormalities in the immune system play a critical role in the pathogenesis of MS. BTN1A1 may indirectly influence the onset and progression of MS by participating in the regulation of immune cells. Research indicates that the BTN1A1 molecule is significant in the study of autoimmune diseases, particularly MS[111]. Experimental studies on milk have demonstrated that BTN1A1 is important in increasing the incidence of MS[112]. A deeper exploration into the pathogenesis of MS reveals that the extracellular domain of myelin oligodendrocyte glycoprotein (MOG) is essential. As a key protein component of the BTN family, MOG is widely distributed on the surface of oligodendrocytes and myelin sheaths within the central nervous system. Due to its remarkable immunogenicity, it is readily recognized and targeted by the immune system, making it a core target of autoimmune attacks. From this perspective, BTN1A1 is not only closely related to MS but also one of the key factors promoting the continuous progression of the disease. The potential therapeutic application of BTN1A1 in MS is garnering increasing attention. As an immune checkpoint, BTN1A1 can regulate T cell activity and inhibit their overactivity, thereby potentially slowing the progression of MS. Studies have shown that the expression of BTN1A1 is mutually exclusive with PD-L1, a characteristic that imparts a unique role in immune regulation[106]. With ongoing research, BTN1A1 is poised to become an important target in the field of MS treatment, offering patients new therapeutic options and enhancing their quality of life.

Metronidazole (MTZ) is a widely utilized antibacterial agent primarily employed in the treatment of anaerobic bacterial infections, trichomoniasis, and amoebiasis. Our findings indicate that metronidazole exhibits a high binding affinity for BTN1A1. Research has established a significant association between MTZ and both inflammation and the immune system. One study highlighted that MTZ can markedly reduce the ratio of circulating neutrophils to monocytes in the peripheral blood lymphocytes of both Balb/c mice and humans, while simultaneously increasing the ratio of circulating lymphocytes, suggesting its potential to induce immunosuppression[113]. Furthermore, MTZ may elevate the risk of drug-induced immune thrombocytopenia (DITP) by disrupting immune system functionality[114]. Another investigation noted that the side effects of certain medications, including MTZ, could contribute to a higher incidence of immune-related diseases such as IBD and MS[115]. Consequently, while preliminary evidence indicates that MTZ may influence immune function and trigger drug-induced immune responses in specific instances, these findings are not definitive, and further research is warranted to elucidate its effects on the immune system and its relationship with immune-related diseases.

The relationship between EVI5 and MS

Ecotropic Viral Integration Site 5 (EVI5) is a critical checkpoint in the retroviral integration process and is closely associated with various physiological processes, including the cell cycle. It plays a significant role in essential biological activities such as cell growth, division, and differentiation. In the context of MS, the proliferation and differentiation of neural stem cells and neural precursor cells may be disrupted. Mutations in the EVI5 gene can impair the normal cell cycle processes of these cells, potentially influencing the pathogenesis of MS. By regulating the expression of lymphocyte-specific factors, EVI5 has been shown to be crucial in T cell differentiation, particularly in the high expression of TH1 and TH2 cells[116]. The deletion of EVI5 adversely affects the differentiation of helper T cells, especially TH17 cells, leading to a significant decrease in IL-17A production. Moreover, EVI5 also impacts genes such as HLA-DRB, CLEC16A, CD58, and IL7R, which may be linked to the immunomodulatory effects in MS[117]. Therefore, EVI5 may influence the pathogenesis of MS by modulating T cell differentiation and function. As a GTPase-activating protein (GAP) of Rab11, EVI5 activates the GTPase activity of Rab11, potentially participating in the regulation of the downstream RAB11 pathway[118]. This pathway is vital for the formation of immune synapses and T cell function. EVI5 interacts with GTP-Rab11 through its TBC domain, promoting the conversion of GTP to GDP, thereby inactivating Rab11. This regulatory mechanism may affect immune synapse formation and T cell functionality, subsequently influencing the immune response in MS. Additionally, EVI5 is involved in lipid metabolism-related pathways, which may further impact the pathological processes associated with MS[119]. As a member of the protein family containing the Tre-2/Bub2/Cdc16 (TBC) domain, EVI5 plays a regulatory role in the cell cycle, cell division, and cell membrane transport. The function of EVI5 may be linked to its regulatory role in cell membrane transport, which could indirectly influence lipid metabolism and inflammatory responses in MS. Additionally, EVI5 protein is closely associated with endocytosis and cell signaling. Research indicates that EVI5 may impact myelin repair by modulating the function of oligodendrocytes, the cells responsible for the formation and maintenance of myelin sheaths[118]. Variations in EVI5 activity can affect the survival, proliferation, and differentiation of these cells, thereby facilitating myelin regeneration. Furthermore, EVI5 may regulate immune responses by influencing cell signaling pathways. In MS, the immune system's attack on the myelin sheath is a critical factor in initiating pathological changes. The regulatory effects of EVI5 help control immune cell activity, mitigate damage to the myelin sheath, and create favorable conditions for myelin repair[120]. Moreover, EVI5 may participate in the neuroinflammatory process by regulating the function of nerve cells. Neuroinflammation is a significant characteristic of MS, which can lead to myelin damage and neurodegeneration. EVI5 contributes to this process by affecting the recycling

of endosomes and signaling pathways[121]. In summary, EVI5 is intricately linked to the onset and progression of MS and represents a crucial gene in the pathogenesis of the disease.

The potential therapeutic application of the EVI5 gene in MS shows considerable promise. Research has demonstrated that variations in the EVI5 gene are significantly associated with the risk of developing MS[122]. These variations may influence the function of the EVI5 protein and, consequently, play a role in the pathophysiological processes underlying MS[123]. Furthermore, variations in EVI5 may not only act as risk factors for MS but also serve as potential biomarkers for early diagnosis and prognostic assessment of the disease. By regulating the expression of EVI5, the activation of T cells and B cells, as well as their roles in MS, can be modulated, potentially improving patient symptoms[123]. These characteristics position EVI5 as a promising target for MS treatment, providing both a theoretical foundation and the possibility for the development of novel therapeutic strategies.

Sanguinarine is an alkaloid extracted from the bloodroot plant, which belongs to the poppy family. It exhibits a high binding energy with EVI5. Recent research has revealed its multifaceted effects on the immune system, demonstrating its ability to modulate the host's immune response through various mechanisms. Sanguinarine shows potential in enhancing immune function and combating certain immune-related diseases. It can bolster the body's defense against pathogens by adjusting the composition and diversity of intestinal flora, which may enhance the host's immune response through the regulation of the intestinal microbiome[124]. Furthermore, sanguinarine plays a significant role in strengthening the body's innate immune response by regulating reactive oxygen species (ROS) and activating the PMK-1/SKN-1 signaling pathway[124]. This mechanism has shown promising effects across different organisms, including improvements in the body's resistance to oxidative stress. At the level of immune cells, sanguinarine influences the production of inflammatory cytokines by modulating multiple signaling pathways, such as MAPK, Wnt/β-catenin, NF-κB, JAK/STAT, TGF-β, and PI3K/Akt/mTOR pathways[125]. These interactions indicate that sanguinarine has dual effects on inflammatory and immune responses. Given its complex effects on the immune system and chronic inflammation, sanguinarine holds promise for applications in the treatment of immune-related diseases, chronic inflammation, and allergic reactions.

The relationship between OGA and MS

O-GlcNAcase (OGA) plays a critical role in regulating protein glycosylation modifications, primarily by catalyzing the hydrolysis of O-GlcNAc on proteins[126]. In the dynamic process of O-GlcNAcylation, O-GlcNAc transferase (OGT) and OGA function in concert. OGT is responsible for adding monosaccharides to proteins, while OGA removes these monosaccharides, thereby maintaining a dynamic balance of protein O-GlcNAcylation levels. This precise regulation is essential for the structural integrity, functional performance, and stability of proteins, and it plays a central role in key biological processes, including cell signal transduction, metabolic regulation, immune response, and tumor initiation and progression. Consequently, the balance of OGA and OGT activities is vital for sustaining the stability of the intracellular environment.

MS is a chronic inflammatory disease of the central nervous system that is mediated by the immune system. It is characterized by the destruction of the myelin sheath, which exposes nerve fibers and adversely affects the transmission of nerve signals, leading to a range of neurological dysfunctions. Previous studies have indicated that OGA plays a crucial role in various signaling pathways, primarily by removing glycosylation modifications that regulate numerous cellular processes. In particular, the MAPK/ERK signaling pathway is significant for cell proliferation, differentiation, and survival. OGA influences cell proliferation and differentiation through the regulation of key genes. Some research has demonstrated that differentially expressed genes targeted by OGA are associated with the MAPK/ERK signaling pathway, where gene upregulation can enhance cell proliferation and alter differentiation[127].In the G-protein coupled receptor (GPCR) signaling pathway, GPCRs play a crucial role in various physiological processes as a significant mechanism for signal transduction. The activity of OGA influences the function of GPCRs by modulating their glycosylation state, which can alter the affinity and signaling capacity of these receptors. Consequently, this modulation may impact cellular responses to external stimuli[128]. OGA is associated with various growth factor signaling pathways, including insulin and epidermal growth factor. These pathways are crucial for cell growth and metabolism. OGA modulates the efficiency of growth factor signaling by removing O-GlcNAc modifications, thereby influencing cellular responses to growth factors. In pathways related to the extracellular matrix (ECM), the ECM serves a vital role in providing cell support and facilitating signaling. OGA regulates the interaction between cells and their microenvironment by modulating the expression of ECM-related genes. Notably, multiple ECM-related genes are identified among the differentially expressed genes targeted by OGA, which may enhance cell migration and tissue reconstruction[127].OGA activity is closely linked to mitochondrial function, as mitochondria serve as the energy production factories of the cell and play a crucial role in cell signaling. Research has demonstrated that the copy number of mitochondrial DNA and the activity of mitochondrial enzymes are associated with OGA activity and the levels of OGT protein. This suggests that OGA may influence the cellular metabolic state by modulating mitochondrial function[129].OGA may play a crucial role in the regulation of the cell cycle. Glycosylation modifications impact the stability and activity of cyclins. OGA functions by removing these modifications, thereby regulating cell cycle progression and influencing cell proliferation and growth[127].In addition, OGA is also associated with the immune response. It may influence the secretion of cytokines and the transmission of immune signals by regulating the glycosylation status of immune cells, and thus play a role in inflammatory responses and autoimmune diseases.Studies have indicated that OGA may influence the function and signaling of nerve cells by regulating the glycosylation state of specific neural proteins[130]. Abnormal glycosylation can lead to structural instability of myelin-related proteins, thereby increasing the susceptibility of myelin to immune attack or dysfunction, and contributing to the pathological processes associated with MS[131].OGA may influence nerve cell function and disease progression in MS by regulating the glycosylation state of neuroproteins. The potential application of OGA inhibitors in the treatment of MS has garnered significant attention. OGA is crucial for the regulation of O-GlcNAcylation; by

inhibiting OGA, the levels of O-GlcNAc can be elevated, thereby modulating signaling pathways associated with inflammation and neuroprotection[132,133].The inhibition of OGA can also improve the metabolic state of cells, such as increasing glucose metabolism, which is crucial for the neuroprotection and functional recovery of patients with MS[134].Clinical studies have shown that OGA inhibitors perform well in terms of tolerability and safety, demonstrating their potential in the treatment of MS[135].In conclusion, OGA plays a regulatory role in various signaling pathways and has significant implications for the immune system, inflammatory response, myelin regeneration, and receptor alterations. These factors not only influence the physiological state of cells but also contribute to the onset and progression of diseases. Future inhibitors targeting OGA have demonstrated considerable potential in the treatment of MS. By modulating O-GlcNAcylation, enhancing metabolic function, and exhibiting anti-inflammatory effects, these compounds may pave the way for new treatment options for MS patients.

The relationship between ICAM5 and PsA

Intercellular adhesion molecule 5 (ICAM5), also known as telencephalin or TLN, is a gene that encodes proteins in humans and is a member of the immunoglobulin (Ig) superfamily. ICAM-5 is the largest member of this family, and its extracellular domain comprises multiple Ig-like domains, which facilitate strong binding to other cells or molecules. This structural feature is crucial for the development of the nervous system and serves as an intercellular mediator in the immune system. ICAM-5 is associated with various diseases, particularly in the regulation of T cell activation under pathological conditions such as cerebral ischemia, epilepsy, and encephalitis[136,137]. Furthermore, soluble ICAM-5 can be detected in human physiological fluids, indicating its significant role in immune regulatory responses and the leukocyte adhesion process. In pathological conditions, ICAM-5 can be cleaved from the central nervous system and released into the cerebrospinal fluid and blood, suggesting its involvement in the regulation of immune responses and leukocyte adhesion[138].

Previous studies have demonstrated that ICAM-5 can regulate the PI3K/Akt signaling pathway. The activation of ICAM-5 may promote the activation of PI3K, which subsequently activates Akt, resulting in enhanced cell proliferation and survival signaling. This indicates that ICAM-5 plays a crucial role in cell proliferation, survival, and metabolic regulation. Furthermore, its overactivation is significant in the context of autoimmune diseases[139].In PsA, an inflammatory joint disease associated with psoriasis, the PI3K/Akt signaling pathway has garnered significant attention. In psoriasis, the overexpression of the PI3K/Akt/mTOR pathway is closely linked to its pathogenesis, with abnormal activation resulting in hyperproliferation of keratinocytes and inhibition of apoptosis, which ultimately contributes to skin damage. Specifically, PI3K activates mTOR upon binding to Akt, thereby promoting keratinocyte proliferation[140].In PsA, this signaling pathway is in an activated state in the joint tissues of patients and serves as a key regulatory factor.

The pathogenesis of psoriasis is a complex, multifactorial process involving numerous signaling pathways and interactions among immune cells. Among these, the IL-23 pathway is crucial, as it exacerbates skin inflammation by activating Th17 cells and promoting the production of IL-17[141]. ICAM5 may contribute to psoriasis through several mechanisms[142]: First, it is closely linked to the regulation of inflammatory immune responses. During episodes of psoriatic skin inflammation, ICAM5 may enhance the local immune response by facilitating the adhesion of T cells and other inflammatory immune cells, thereby worsening psoriasis symptoms. Second, ICAM5 plays a significant role in cell–cell adhesion and signal transduction, potentially influencing the function and activity of immune cells within psoriasis lesions and regulating cell–cell interactions, which may further contribute to the pathogenesis of the disease. Finally, ICAM5 may be involved in psoriasis-related gene regulatory systems; it is associated with the IL-23 pathway, and its expression levels are elevated in patients with psoriasis, indicating its potential role in gene expression regulation. Considering these mechanisms, ICAM5 may be central to the onset and progression of psoriasis. Additionally, ICAM5 is also expressed in certain immune-mediated joint diseases. Studies have demonstrated that ICAM-5 levels are significantly increased in active systemic juvenile idiopathic arthritis (JIA), and this elevation is important for distinguishing localized JIA from systemic JIA[143].Although research on ICAM-5 in relation to psoriasis and associated arthritis remains limited, its significant role in inflammatory cell function and immune response necessitates further investigation into the regulation of immune cell attachment, movement, and participation. Understanding the modulation of the inflammatory response and the interaction with keratinocytes is crucial for elucidating their roles in the pathogenesis of psoriasis and its sequelae, including arthritis. Future studies are anticipated to clarify the specific role of ICAM-5 in psoriasis and explore its potential therapeutic applications.

As a member of the polychlorinated biphenyl (PCBs) family, 3,3′,4,4′,5-pentachlorobiphenyl (PCB118) is a widely distributed environmental pollutant that was historically utilized in various industrial products. PCB118 exhibits a high binding affinity to ICAM5. Scientific research has increasingly elucidated the effects of PCB118 on inflammatory responses, immune system function, and associated diseases. PCB118 influences the inflammatory process through multiple mechanisms, including the promotion of pro-inflammatory cytokines such as TNF-α and IL-6, which are pivotal in activating immune responses during inflammation and in propagating the spread of inflammation[144]. Additionally, exposure to PCB118 is linked to elevated levels of oxidative stress, which can result in cellular damage and further stimulate inflammatory responses, contributing significantly to the onset of various chronic inflammatory and immune diseases[145]. Furthermore, PCB118 can alter the functionality of specific immune cells, including T cells and B cells. This inhibitory effect may reduce the body's resistance to infections and certain diseases, thereby increasing susceptibility to infections. Concurrently, PCB118 exposure has also been associated with the development of specific autoimmune diseases[146]. Consequently, environmental monitoring and health risk assessment of PCB118 are essential to mitigate its potential impact on human health.

The relationship between CCDC50 and PsA

Coiled-coil domain protein 50 (CCDC50), also known as C3orf6, DFNA44, and YMER, is a multifaceted protein with various functions. It contains multiple domains that bind to ubiquitin, acts as a negative regulator of the NF-κB signaling pathway, and plays a crucial role in epidermal growth factor (EGF)-mediated cell signaling[147]. As a novel receptor for autophagy activity, CCDC50 is integral in regulating NLRP3 inflammasome activation and autoimmune diseases. Additionally, CCDC50 influences viral infections and certain autoimmune conditions through its autophagy activity[148,149]. It regulates type I interferon (IFN) signaling by delivering K63 polyubiquitinated STING to autophagic lysosomes for degradation, indicating its role in viral defense and immunomodulation in autoimmune diseases. Furthermore, CCDC50 is essential for maintaining skin barrier function and participating in immune responses. Studies have demonstrated a relationship between peroxisome proliferator-activated receptor β/δ (PPARβ/δ) and CCDC50 in keratinocytes, suggesting that abnormalities in CCDC50 may contribute to significant skin disease processes[150].

Previous studies have demonstrated that CCDC50 is involved in multiple signaling pathways, including the growth factor signaling pathway, the PI3K/AKT pathway, the MAPK pathway, the NF-κB pathway, the autophagy pathway, and the cell cycle. The interplay among these signaling pathways positions CCDC50 as a crucial regulator of cell proliferation, inflammatory responses, and tumorigenesis. Research has indicated that CCDC50 can modulate the activity of NF-κB, thereby influencing the expression of genes associated with inflammation. The NF-κB signaling pathway plays a significant role in psoriatic skin lesions and joint lesions[151].Abnormal activation of the NF-κB signaling pathway is closely associated with the development of psoriatic arthritis. This activation not only exacerbates the symptoms of arthritis but may also contribute to joint damage[152].In addition, CCDC50 is closely associated with autophagy and plays a significant role in the regulation of immune and inflammatory signaling pathways, including RLR (RIG-I-like receptor), CGAS-STING1, and NLRP3. Through its regulation of autophagy, CCDC50 is instrumental in the context of viral infections and autoimmune diseases[151].

Psoriasis and PsA are complex diseases influenced by a multitude of factors, including genetic and environmental components. Psoriasis is closely associated with inflammation and immune responses, and CCDC50 may play a role in the pathogenesis of psoriasis by modulating these processes. Specifically, CCDC50 might be involved in regulating the migration and adhesion of immune cells, as well as influencing the expression of cytokines and inflammatory mediators. Additionally, similar to other members of the immunoglobulin superfamily, CCDC50 may interact with integrin family members through heterophilic interactions, thereby impacting immune responses and cellular behavior in psoriasis[153]. Studies that integrate whole blood transcriptomics and bioinformatics support this perspective. In transcriptomic analyses comparing patients with PsA in remission to healthy controls, findings were validated through real-time quantitative polymerase chain reaction (RT-qPCR), confirming that the CCDC50 gene is differentially expressed in PsA[147]. This suggests that CCDC50 plays a significant role in coordinating inflammation and bone metabolism, indicating a potential link to the pathophysiology of PsA. In summary, while the relationship between CCDC50 and both psoriasis and PsA remains incompletely understood, its characteristics as a member of the Ig superfamily imply that it may influence immune and cellular biological processes in these conditions. Elucidating the specific mechanisms through which CCDC50 operates in psoriasis could unveil new therapeutic targets.

Methyl methanesulfonate (MMS), an alkylating agent, is extensively utilized in biomedical research to investigate cell death and inflammatory responses. MMS influences cellular physiological functions by inducing both apoptosis and necrotic cell death, thereby affecting the immune system and related diseases. The high binding energy of MMS to CCDC50 indicates its potential significance in cell signaling. As a highly reactive compound, MMS can interact with DNA nucleotides, resulting in DNA damage that may lead to cell death or mutation. MMS initiates apoptosis by activating external signaling pathways, while it may also induce necrosis through internal signaling pathways, both of which are critical for cell survival and function[154]. Regarding inflammatory responses, MMS can activate cell signaling pathways and stimulate the release of pro-inflammatory cytokines such as TNF-α and IL-1, thereby playing a pivotal role in inflammation-related diseases,The pro-inflammatory characteristics of MMS may be linked to both acute and chronic inflammatory conditions, including systemic lupus erythematosus and RA[155]. These diseases are often characterized by prolonged immune responses and tissue damage, and the cytotoxicity of MMS may exacerbate these processes, leading to increased cell death and apoptosis. Consequently, the role of MMS in inflammation and the immune system is intricate and multifaceted. The cell death and release of inflammatory factors induced by alkylation not only affect the individual cells but may also significantly impact the overall function of the immune system.

The relationship between IL17RD and PsA

IL-17RD is a member of the IL-17 receptor family and contains multiple transmembrane domains, which facilitate its integration into cell membranes and enable interactions with intracellular signal transduction pathways. This structural characteristic grants IL-17RD a crucial role in cellular physiological activities, particularly in the regulation of signaling. Within the immune system, IL-17RD exhibits dual functions: first, it negatively regulates the immune response initiated by Toll-like receptors (TLR), thereby protecting the body from autoimmune diseases and maintaining immune homeostasis[156]; second, IL-17RD acts as a negative regulator of fibroblast growth factor receptor (FGFR) signaling, inhibiting the activation of the FGF signaling pathway, which adversely affects cell proliferation and differentiation, and is essential for tissue development and repair[157]. IL-17RD plays an important role in both inflammatory and autoimmune diseases[158]. By regulating the activity of the IL-17 signalling pathway, such as the MAPK pathway[159], it helps to alleviate the progression of inflammatory diseases.

In the onset and progression of psoriasis, IL-17A plays a crucial pro-inflammatory role by interacting with keratinocytes in the skin, promoting cell proliferation and triggering an inflammatory response. This process is regulated by the IL-17 receptor and mediated by downstream signaling pathways[160]. As a significant regulatory

factor in this signaling system, IL-17RD may modulate the activation and chemotaxis of inflammatory cells by influencing IL-17 signaling, thereby impacting the severity of the disease. Regarding treatment, due to the central role of IL-17 in psoriasis, inhibitors targeting IL-17 have become a key component of treatment strategies, with their efficacy dependent on comprehensive research into regulatory factors such as IL-17 to optimize treatment options. Additionally, IL-17 plays a central role in PsA, a common complication of psoriasis[161]. Clinical studies have demonstrated that PsA is associated with single nucleotide polymorphisms in IL23R and the downstream molecule TRAF3IP2 (Act1), indicating a close relationship between the IL-23/IL-17 axis and the onset and progression of PsA[162]. Further research has shown that IL-17-producing T cells are integral to the pathogenesis of PsA. The expression level of IL-17 in the synovial fluid of patients was significantly upregulated, underscoring its pivotal role in joint inflammation and injury[163]. These findings suggest that the expression level of IL-17RD may be closely associated with the severity of PsA. Studies have also indicated that the upregulation of IL-17RD correlates with the activity and severity of arthritis, suggesting that regulating IL-17RD expression may aid in alleviating joint symptoms[164,165]. In summary, IL-17RD plays an important role in the onset and treatment of psoriasis skin lesions and arthritis, providing a potential new direction for the development of future treatment strategies.

As a key sex hormone, progesterone plays a vital role in the female reproductive system. It not only maintains pregnancy and regulates the menstrual cycle but also significantly impacts the immune system and inflammatory response. The high binding energy of progesterone to IL17RD suggests that it may play an important role in immune cell signaling. Studies have demonstrated that progesterone can inhibit the infiltration and activity of inflammatory immune cells, thereby reducing inflammatory responses[166]. This effect is critical for modulating immune tolerance and preventing excessive immune reactions. Additionally, progesterone influences the nature of the body's immune response by regulating T cell activation and cytokine production. This regulatory role may explain the changes in immune status observed in women during pregnancy and the lower incidence of autoimmune diseases during this period[167]. Furthermore, progesterone exhibits anti-inflammatory effects, which can be attributed to its ability to inhibit macrophage activation[168].In inflammatory conditions, progesterone can mitigate inflammation by suppressing the activity of inflammatory cells. These properties position progesterone as a potential treatment for various inflammatory and immune diseases, such as inflammatory bowel disease and chronic bronchitis[169]. In summary, progesterone plays a crucial regulatory role in human immune and inflammatory responses. By inhibiting the activity of inflammatory cells, regulating T cell and macrophage function, and promoting the production of specific cytokines, progesterone influences the nature and intensity of the body's inflammatory and immune responses. These properties not only benefit the mother during pregnancy but also offer new perspectives for the treatment of autoimmune diseases and related conditions.

The relationship between UBLCP1 and PsA

Ubiquitin-like domain-containing C-terminal phosphatase 1 (UBLCP1) is a protein characterized by the presence of a UBL domain, which enables it to interact directly with the proteasome and is essential for its function within cells. Predominantly localized in the nucleus, UBLCP1 regulates specific proteins, including transcription factors and other nuclear proteins, thereby influencing their stability[170]. As an inhibitory regulator, UBLCP1 modulates proteasome activity through multiple pathways. Under normal physiological conditions, it inhibits proteasome activity via dephosphorylation, particularly targeting nuclear proteasome activity[171]. UBLCP1 specifically removes the phosphate group from the proteasome-related protein Rpt1, thereby regulating proteasome function and the degradation rate of intracellular proteins[172]. The interaction between UBLCP1 and Rpn1, a component of the proteasome, is also crucial for proteasome regulation. The phosphatase activity of UBLCP1 is intricately linked to the dephosphorylation of Rpn1, which influences the stability, substrate recognition, and selection of the proteasome. UBLCP1 plays a crucial role in cellular stress responses. Under stress conditions, cells can maintain intracellular homeostasis by rapidly regulating protein degradation. The dephosphorylation of UBLCP1 facilitates cellular adaptation to environmental changes[173]These physiological properties render UBLCP1 relevant to various immune and infectious diseases[174].

UBLCP1 plays a crucial role in various immune-related signaling pathways. It influences both the strength and duration of the immune response by regulating the cell cycle, T cell signaling, cytokine signaling pathways, and the functionality of antigen-presenting cells. These regulatory effects subsequently impact psoriasis and its extra-articular manifestations. Numerous prior studies have identified UBLCP1 as a genetic risk checkpoint for psoriasis[175].Psoriasis is a chronic autoimmune skin disease characterized by an imbalance of multiple cytokines and abnormal intracellular signal transduction pathways, which is accompanied by excessive keratinocyte proliferation and immune cell dysfunction. Research has established an association between UBLCP1 and psoriasis, suggesting that UBLCP1 may contribute to the disease's pathogenesis[176]. A transcriptome-wide association study (TWAS) identified UBLCP1 as one of the conditionally independent genes linked to psoriasis, indicating its significant role in the genetic mechanisms underlying the condition and its involvement in physiological and pathological processes, including psoriasis-related skin development[175]. Furthermore, a study utilizing a priority index (Pi) demonstrated that UBLCP1 is a potential therapeutic target for PsA, highlighting its importance in the pathogenesis of PsA and suggesting that modulation of UBLCP1 may represent a promising avenue for future PsA treatment research[177]. Consequently, the structure and function of UBLCP1 are critical within cellular contexts. Although the specific relationship between UBLCP1 and both psoriasis and PsA necessitates further investigation, its potential involvement in the pathogenesis of psoriasis and related arthritic conditions warrants in-depth exploration.

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) that exerts its anti-inflammatory effects by inhibiting the activity of cyclooxygenase (COX) and reducing prostaglandin synthesis. It is widely utilized in the treatment of inflammatory diseases such as osteoarthritis, RA, and AS. The high binding energy of indomethacin to UBLCP1 suggests that it may play a significant role in cell signaling. During the inflammatory

response, indomethacin exhibits its anti-inflammatory properties by inhibiting both COX-1 and COX-2, thereby decreasing the production of prostaglandins[178]. Furthermore, indomethacin has a notable impact on the immune system, as it inhibits nucleic acid-induced interferon (IFN) expression and influences immune cell responses[179]. This regulatory effect aids in controlling the development of autoimmune diseases. Additionally, indomethacin has been associated with viral infections, with studies demonstrating its capacity to inhibit viral replication and mitigate inflammatory responses. In a co-culture system of lung epithelial cells and macrophages, indomethacin has been shown to impede viral spread and diminish inflammatory responses[180]. Thus, indomethacin not only exerts anti-inflammatory effects through the inhibition of prostaglandin synthesis but also plays a regulatory role in the immune system, proving to be significantly effective in the treatment of inflammatory and immune-related diseases.

This study, while implementing rigorous data analysis and comprehensively examining a series of new GWAS data, inevitably has limitations. First, it primarily focuses on individuals of European ancestry, necessitating further exploration of the applicability of its conclusions to other ethnic groups. Secondly, the collection and integration of raw data may involve different data resources, such as microarrays and batch RNA sequencing with varying sample sizes, when conducting meta-analyses of differentially expressed genes in plasma proteins. This variability can lead to discrepancies in results. Additionally, the limited sample size and unbalanced grouping may introduce bias. Although the use of high thresholds and multiple corrections enhances the rigor of the analysis, there is a possibility of overlooking true associations that lack statistical significance in smaller samples. Furthermore, small effects of genetic variation may diminish statistical power and increase the risk of false positives. The pathogenesis of the disease is complex, involving genetics, environmental factors, and numerous unknown variables. Therefore, large-scale, multi-center, and well-designed studies are essential to address these gaps.

Conclusion

This study comprehensively employed MR, SMR, Bayesian co-localization analysis, and LDSC analysis methods to draw the following conclusions regarding immune-related bone diseases: the HDGF, CCL19, and TNFRSF14 genes may play a role in the onset and progression of RA. The GPT gene may be implicated in the onset and progression of Crohn's disease-related arthropathy. Additionally, the BTN1A1, EVI5, OGA, and TNFRSF14 genes may influence the onset and progression of MS. Finally, the ICAM5, CCDC50, IL17RD, and UBLCP1 genes may be involved in the onset and progression of PsA.

Data availability

All types of data involved in this study have clear source channels for easy query and acquisition. Among these, the complete GWAS information of UK Biobank plasma pQTLs can be downloaded directly from s3://ukbiobank.opendata.sagebase.org/. The GWAS data for Icelandic plasma proteins is available in the literature titled 'Large-scale integration of the plasma proteome with genetics and disease' and can be accessed at https://www.decode.com/summarydata/. Additionally, the complete GWAS data for RA, SP-RA, SN-RA, Crohn's arthritis, ulcerative colitis arthritis, AS, MS, and PsA can be downloaded from https://www.finngen.fi/en, while the com plete GWAS data for JRA can be obtained from https://www.nature.com/articles/s41588-021-00931-x. Other relevant data can be sourced from original documents and websites.

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Author contributions
Author W.Y. contributed to the conception and design of this study. Z.H.L. and M.C. supervised the research process. W.Y., and C.L.L. conducted the data analysis. The manuscript was written by W.Y., M.C., and C.L.L., while W.Y. undertook its revision and polishing. W.Y.,and C.L.L. were responsible for visualizing the results, and all authors revised and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval and consent to participate
For this study, all of our GWAS data were sourced from already published statistical data, so there was no need for us to seek additional ethical approval.

Additional information
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