Journal of Inflammation Research

Dovepress
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ORIGINAL RESEARCH

Druggable Targets for Pelvic Inflammatory Disease: Mendelian Randomization and Experimental Validation

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Background: Pelvic inflammatory disease (PID) is a common gynecological disorder that seriously affects women's physical and mental health, yet there are few effective therapeutic options.

Objective: Mendelian randomization (MR) has been used to repurpose existing drugs and identify new therapeutic targets. Therefore, we performed a systematic drugable genome-wide MR analysis to explore potential therapeutic targets for PID.

Methods: We utilized cis-expressed quantitative trait loci (cis-eQTL) of druggable genes and PID Genome-Wide Association Study (GWAS) data to perform MR analysis and colocalization analysis, screened candidate drugs through drug prediction, identified the most stable druggable genes with the highest binding affinity through molecular docking, and finally constructed a PID rat model to validate gene expression.

Results: MR analysis, colocalization analysis, and protein interaction analysis identified six key genes. Drug enrichment analysis and molecular docking revealed two potential drugs (Sunitinib and Everolimus) targeting Albumin (ALB), Interleukin 6 (IL6), and Cluster of Differentiation 4 (CD4). In the PID rat model, ALB and IL6 expression decreased, while CD4 expression increased.

Conclusion: Our MR analysis provides genetic evidence supporting ALB, IL6, and CD4 as druggable genes for PID treatment. Among the drug candidates with repurposing opportunities targeting the above genes, Sunitinib and Everolimus were effective. Subsequent in vivo experiments validated the differential expression of ALB, IL6, and CD4 in PID rats.

Keywords: pelvic inflammatory disease, druggable gene, molecular docking, co-localization analysis, mendelian randomization

Introduction

Pelvic inflammatory disease (PID) is an inflammatory disease involving the female genital tract, uterus, and fallopian tubes, which is usually caused by pathogenic microorganisms such as Staphylococcus aureus and Escherichia coli.[1–3] If left untreated, it may lead to destruction, extensive adhesions, hyperplasia, and scarring of the upper genital tract and its surrounding tissues in women, with clinical manifestations such as infertility, chronic pelvic pain, and tubal pregnancy.[4,5] In the United States, approximately 4.4% of sexually active women and 10% of women diagnosed with sexually transmitted infections have been diagnosed with PID at some point in their lives.[6] Given its long course and tendency to recur, PID significantly impacts women's reproductive health and increases both direct and indirect medical costs.[5,7]

Physiotherapy, antimicrobial drugs, or surgery are mostly used for PID to relieve pain and loosen tissue adhesions, but their long-term efficacy is unsatisfactory. Prolonged use of antibiotics can lead to pathogen resistance and has the risk of inducing diseases such as endometritis, ovarian inflammation, and ovarian cysts.[8] Over the past decade or so, continuous attempts have been made to explore effective treatments for PID. However, the unclear pathogenesis of PID, including aspects such as

Received: 13 May 2025
Accepted: 23 August 2025
Published: 19 September 2025

immune dysregulation (eg, imbalance in CD4+ T cell function),[9] inflammatory responses (eg, elevated levels of pro-inflammatory factor Interleukin 6 (IL6)),[10] and systemic effects (eg, reduced serum albumin (ALB) levels reflecting nutritional depletion and inflammatory status),[11,12] has hindered progress in this field. Integrating genetics into drug development may provide a novel approach. Large-scale human genetics studies offer opportunities for new drug development in many complex diseases, as drug targets supported by genetic evidence have a greater chance of success in drug discovery.[13,14]

Mendelian randomization (MR) is an epidemiological method to investigate potential causal relationships by reducing confounding factors,[15] while protein or gene expression profiles of druggable genes provide important clues about pharmacological targets.[15] In MR analysis of druggable targets, expression quantitative trait loci (eQTL) are used as instrumental variables (IVs) to examine the impact of druggable genes. Specifically, cis-eQTLs in the proximal genomic region of a target gene are usually selected because the target gene is closely associated with gene expression. Several studies have used cis-eQTL located within genes as IVs to reveal potential druggable targets for a variety of disorders by analyzing the causal relationship between the investigated genes and the disease.[16–18] However, no studies have yet used drug target MR to identify potential druggable targets in the context of PID.

Materials and Methods

Research Design of Study

A flow chart visually describing the study as a whole is shown in Figure 1. Firstly, we obtained data on druggable genes and screened for genes within uterine eQTL and blood eQTL, and then performed a two-sample MR analysis using PID GWAS data to identify genes highly associated with PID. Second, we performed a co-localization analysis to validate the robustness of our results. Third, we constructed protein-protein interaction (PPI) networks and performed functional enrichment analyses on the identified proteins. Fourth, molecular docking and drug enrichment analysis were performed to investigate the relationship between drugs and key genes. Finally, the relevant genes were validated by establishing a PID rat model.

Druggable Genes

Druggable genes are defined as a set of genes encoding proteins that have the potential to be regulated by drug-like small molecules based on sequence and structural similarity to existing drug targets.[19] The druggable genes used in the study

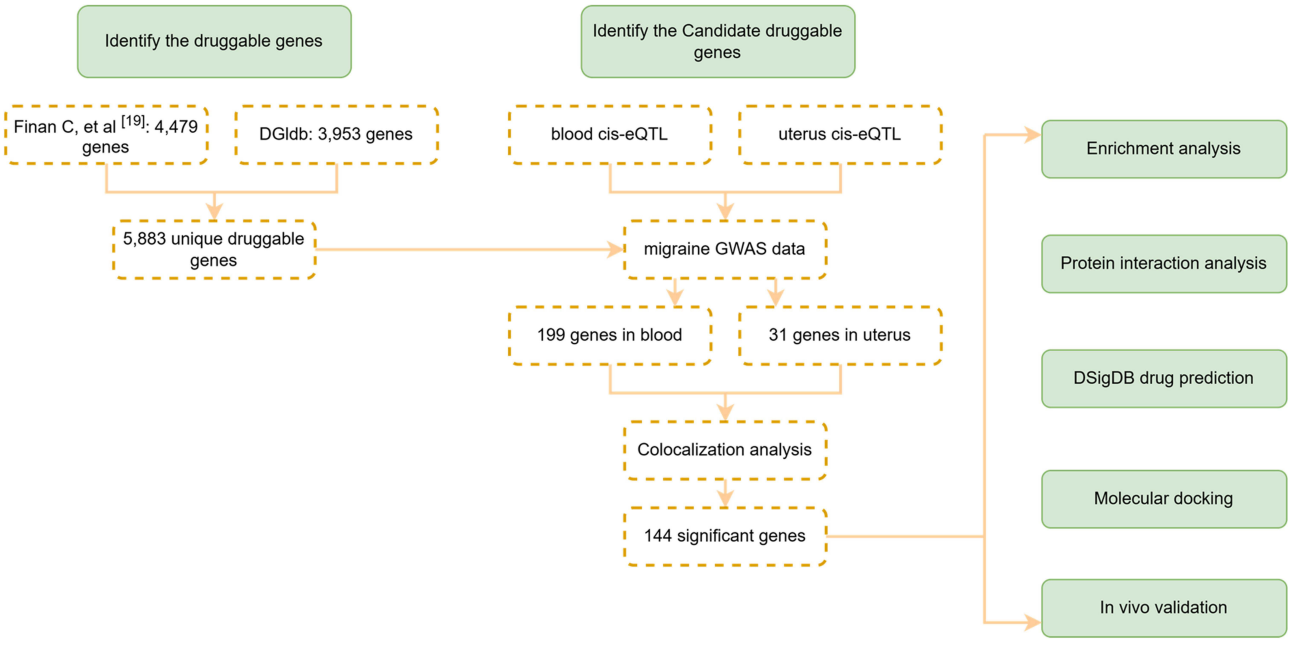

Figure 1 Overview of the study design.
Abbreviations: DGIdb, Drug-Gene Interaction Database; eQTL, expression quantitative trait loci; GWAS, genome-wide association studies; DSigDB, Drug Signatures Database.

were obtained from the Drug-Gene Interaction Database (DGIdb, https://www.dgidb.org/)[20] and from a review of gene "druggability".[19] To achieve a high degree of accuracy, we took the intersection of drug genes from both sources for subsequent studies.

eQTL Datasets

The blood eQTL dataset was obtained from eQTLGen (https://eqtlgen.org/),[21] which provides cis-eQTLs for 16,987 genes from 31,684 blood samples of healthy individuals of European ancestry. We obtained fully significant cis-eQTLs based on a false discovery rate (FDR) of less than 0.05 and a minor allele frequency (MAF) of greater than 0.01. In addition, cis-eQTLs for PID-associated tissues (uterus)[22] were obtained from the Genotype-Tissue Expression Project (GTEx) V.8 database (https://gtexportal.org/home/datasets).

Outcome Data

The FinnGen study is a large biomedical database and research resource containing in-depth genetic and health information from more than 370,000 participants. The GWAS summary statistics for the PID are derived from the FinnGen Consortium version R11 data. This GWAS dataset contains 28,179 cases and 226,439 controls, with GWAS analyses adjusted for covariates such as age, top 10 principal components, and genotyping batch.[23]

Mendelian Randomization Analysis

Using eQTL as a tool, the association between gene expression levels and the outcome of interest was investigated using pooled data from GWAS and eQTL studies, and SMR analysis was performed by SMR software (version 1.03).[24] The presence of chain disequilibrium in the association between the observed gene expression and the outcome was assessed by the Heterogeneity of Instruments of Dependence (HEIDI) test,[25] with a p-value of less than 0.05 indicating that there may be a chain disequilibrium in this association. Pharmacokinetic genes were taken as intersections with genes showing significant MR results in blood and uterus, respectively, and combined for subsequent analysis.

Co-Localization Analysis

Co-localization analysis was performed using the R package "coloc".[26] The posterior probabilities of the following five hypotheses were derived from the co-localization analysis: PPH0, not associated with the expression of druggable genes or the outcome; PPH1, associated with the expression of druggable genes but not with the outcome; PPH2, associated with the outcome but not with the expression of druggable genes; PPH3, associated with the expression of druggable genes and the outcome, with different causal variants; PPH4, associated with the expression of druggable genes and the outcome, with common causal variants. Due to the limited efficacy of co-localization analyses, we restricted our analyses to genes that achieved PPH4/PPH3+PPH4 $\geq$ 0.8.[26]

Functional Enrichment and Protein Interaction Analyses

To explore the functional characteristics and biological relevance of druggable genes, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the "clusterProfiler" and "enrichplot" software packages.[27] GO includes three terms: biological process (BP), molecular function (MF), and cellular component (CC). KEGG pathway can provide information about metabolic pathways. Finally, enrichment analyses were filtered by significance thresholds $p \leq 0.05$ and $Q \leq 0.05$. In addition, we examined the relationship between protein interactions of important druggable genes by protein interaction analysis.[28]

Candidate Drug Prediction

The Drug Signature Database (DSigDB, http://dsigdb.tanlab.org/DSigDBv1.0/)[29] is a large database with 22,527 gene sets and 17,389 unique compounds spanning 19,531 genes. This database is used to predict candidate drugs based on previously identified important druggable genes.

Molecular Docking

Molecular docking was performed to assess the binding energy and mode of interaction between the drug candidates and their corresponding target genes. The PubChem Compound Database (https://pubchem.ncbi.nlm.nih.gov/) provides structural information on the drugs and the Protein Database (http://www.rcsb.org/) provides structural information about proteins. Molecular docking of proteins encoded by important druggable genes with corresponding drugs was performed using the computerized protein-ligand docking software AutoDock 4.2.6 (http://autodock.scripps.edu/)[30] and CB-Dock2 (https://cadd.labshare.cn/cb-dock2/php/index.php) to visualize the results. Vina Score represents binding energy (kcal/mol), with more negative values indicating stronger predicted binding affinity.

Animal Management

In this study, we used fertile female Wistar rats born in the same batch and bred together, purchased from Shandong Pengyue Laboratory Animal Breeding Co. Ltd. ([SCXK(Lu)2014–0007]). After 1 week of adaptive feeding, 20 female rats with at least two consecutive 4–5 days of estrous cycles (with a large number of non-nucleated keratinized cells in the vaginal smear) weighing 220±20g were randomly divided into a blank group (Group A) and a model group (Group B), with 10 rats in each group. The blank control group was fed normally, and the disease model group was constructed with PID rat model using exercise fatigue and starvation-assisted E. coli upstream infection method.[31] After the end of modeling, the model was normally kept for 14 days, and the material was taken under anesthesia after 12 hours of fasting to observe the thickening, obstruction, or accumulation of water in the oviducts, adhesions, masses, or cysts in the oviducts and ovaries, and hyperplasia or adhesion of pelvic connective tissues in the rats,[31] and the adhered parts of the tissues were taken and placed in centrifuge tubes containing 4% paraformaldehyde fixative (G1101, Servicebio, China), and fixed at room temperature for 48 hours, and then histopathological testing was performed. On 14 November 2024, the Ethical Review Committee of Experimental Animal Welfare of Shandong University of Traditional Chinese Medicine approved the experiment (No. SDUTCM20241114223). This experiment was conducted in accordance with the Laboratory Animal-Guideline for ethical review of animal welfare (GB/T 35892–2018).

Morphological and Histological Assessment

After paraffin embedding and sectioning of the fixed connective tissue adhesion sites of the rat fallopian tubes in each group, hematoxylin eosin (HE) and Masson staining were performed, and the modeling was judged according to the pathological morphology of the adherent tissues and the degree of fibrosis.

Western Blotting (WB)

RIPA lysis buffer (R0010, Solarbio, China) was used in lysing the tissue samples. Protein concentration was determined using BCA Protein Assay Kit (PC0020, Solarbio, China). Proteins were separated by SDS-PAGE and transferred to a polyvinylidene difluoride membrane (PVDF; IPVH00010, Merck, Germany). The membranes were then incubated with primary antibodies (ALB, dilution 1:1500, A24161, ABclonal; IL6, dilution 1:1000, A26791, ABclonal; Cluster of Differentiation 4 (CD4), dilution 1:1000, ab133616, Abcam) and secondary antibodies. Protein blot images were captured using a chemical illumination image analysis system (Tanon 5200, Tanon, China). The intensity of the bands was quantified using Image J software.

Results

Druggable Genome

We identified 3953 druggable genes from DGIdb and extracted 4463 druggable genes from the review. Finally, 5883 unique druggable genes with Human Genome Organisation Gene Nomenclature Committee names were pooled from these two sources for subsequent analysis (Supplemental Table 1).

Candidate Druggable Genes for PID

We performed MR analysis of cis-eQTLs from uterine tissue and blood with PID and identified a total of 831 genes after excluding genes with possible linkage disequilibrium. After taking the intersection with the druggable genes, 31 genes were found to be significant in uterine tissues and 199 genes were found to be significant in blood, and after combining

and de-emphasizing them, a total of 205 relevant genes were used in the subsequent analysis (Supplemental Table 2). Among them, ALOX15, BTN3A1, CNGA1, CTSW, and XPNPEP3 reached significance in both blood and uterine tissues (Figure 2A and B).

Colocalization Analysis

Co-localization analysis was performed on 205 genes to further determine the probability of sharing a causal genetic basis between PID and target gene-associated SNPs. The results of the co-localization analysis showed that only one gene had a PPH4 > 0.8, and five genes had a PPH4 > 0.5. Notably, the probability of [PPH4/(PPH3 + PPH4)] indicates the probability of co-localization provided that there is a causal variant in the outcome, which provides some evidence for co-localization.[32] Thus, out of 205 genes, a total of 144 genes had the possibility of co-causal variability between the genes and the risk of pelvic inflammatory disease in women [PPH4/(PPH 3 + PPH 4) > 0.8] (Figure 2C and D, Supplemental Tables 3 and 4). Therefore, based on MR and co-localization analysis, these 144 genes were identified as potential drug targets for PID.

Enrichment Analysis

GO enrichment analysis showed that genes were mainly enriched in BP of activation of immune response (GO:0002253), positive regulation of MAPK cascade (GO:0043410), and leukocyte proliferation (GO:0070661). Major CC include cytoplasmic vesicle lumen (GO:0060205) and vesicle lumen (GO:0031983). Major MF included scaffold protein binding (GO:0097110), phosphatase binding (GO:0019902), and mitogen-activated protein kinase binding (GO:0051019). KEGG analysis showed that the target genes were mainly enriched in the VEGF signaling pathway, cGMP-PKG signaling pathway, and other pathways (Figure 3).

Protein-Protein Interaction Network Construction

One protein-protein interaction analysis was performed on 144 target genes to further mine the key genes among them. As shown in Figure 4A, key genes with more than 15 interacting proteins included ALB, IL6, CD4, Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1), Heat Shock Protein A4 (HSPA4), and Cell Division Cycle 42 (CDC42). Figure 4B–G shows the relationship between cis-eQTLs contained in single genes and disease risk.

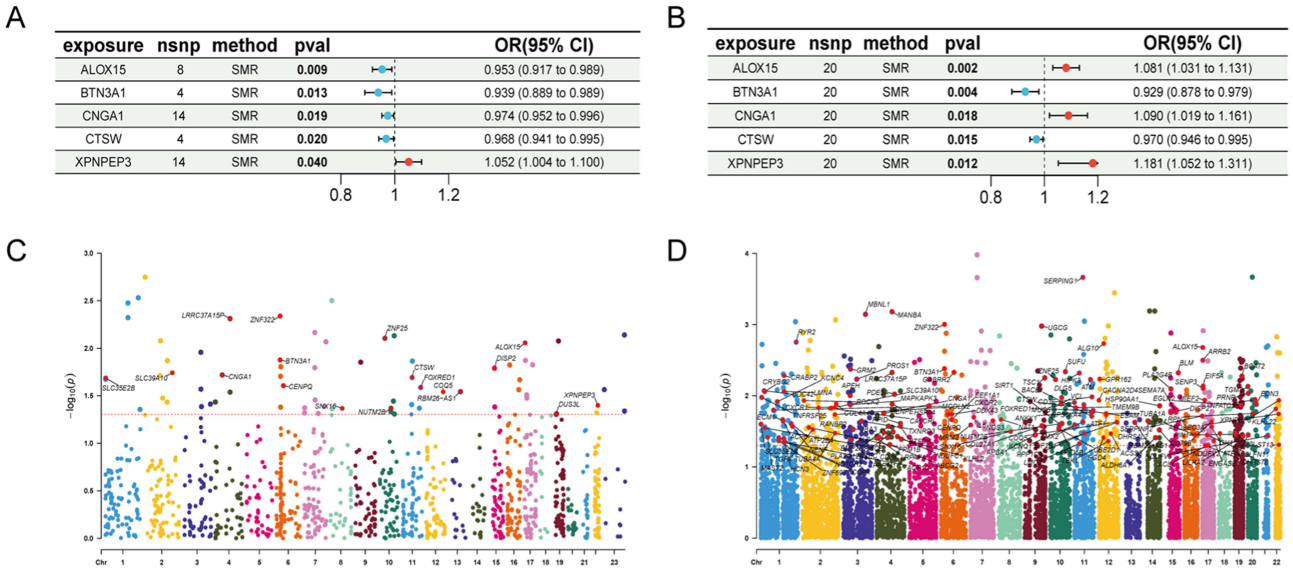

Figure 2 Genes with causal association with PID. (**A**) Forest plot of 5 genes associated with commonly used medications for migraine from blood. (**B**) Forest plot of 5 genes associated with commonly used medications for migraine from uterus. (**C**) Manhattan map of phenome-wide MR results from blood available genotypes. (**D**) Manhattan map of phenome-wide MR Results from the uterus. Notes: The bold data format represents the P-value of causal significance.

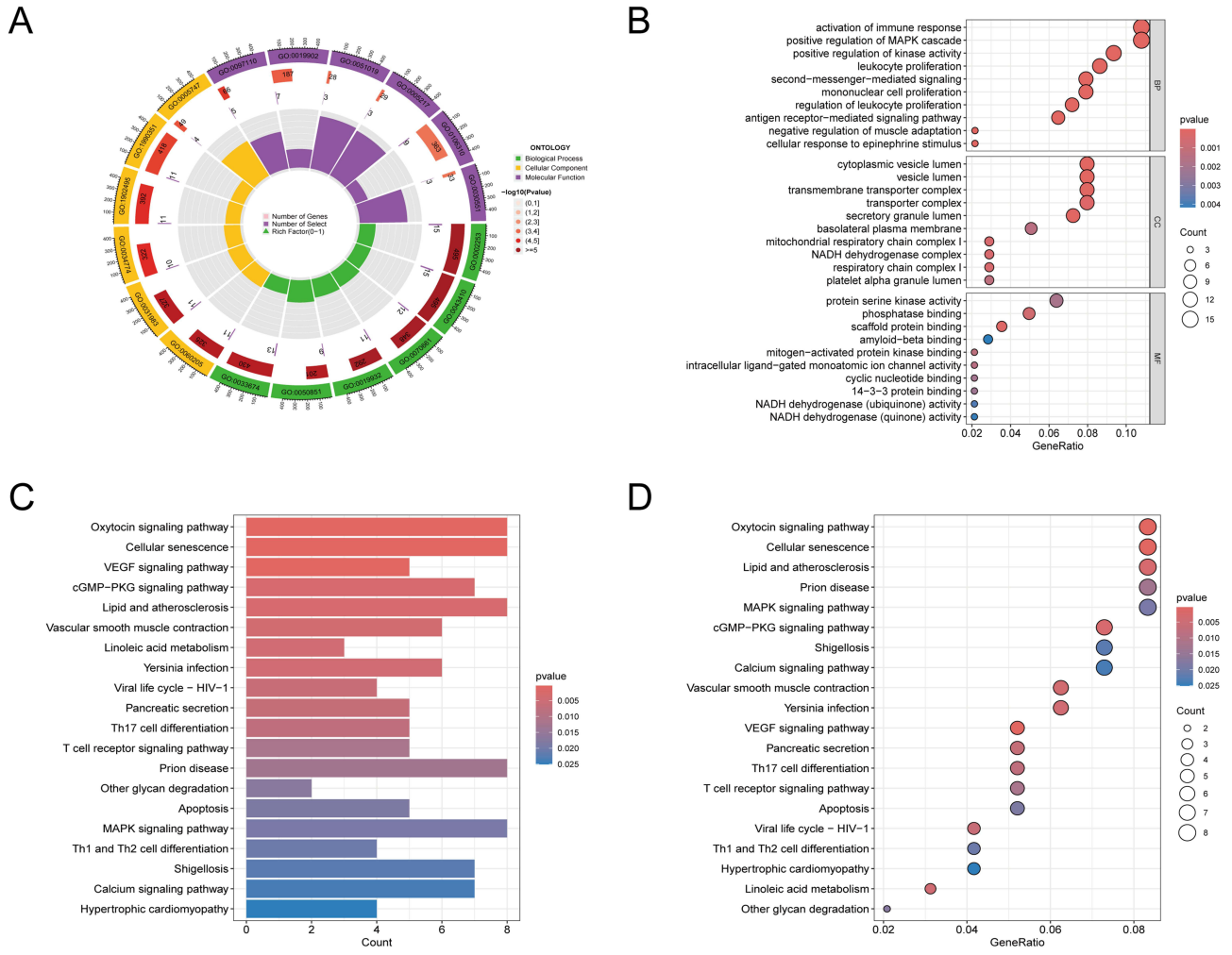

Figure 3 Results of enrichment analysis. (**A**) Circlize chart and (**B**) Bubble chart of GO enrichment results. (**C**) Cnetplot chart and (**D**) Bubble chart of KEGG enrichment results.

Candidate Drug Prediction

We used the enricher function to identify potentially effective intervention drugs from the DSigDB database and listed the top 10 potential intervention drugs with lower p-values based on adjusted p-values: ivomectin, sunitinib, PLATINUM, sulforaphane, Everolimus, phenylpropanolamine, sapropterin, oseltamivir, vincristine sulfate, and PD 98059 (Figure 5). Among them, Sunitinib, sulforaphane, and Everolimus have been used for anti-inflammatory and anti-infective diseases,[33–36] but not for the treatment of PID.

Molecular Docking

We used CB-Dock2 to analyze the binding sites and interactions of three drug candidates with the proteins encoded by their respective key target genes. The key target genes of these drug candidates are ALB, IL6, CD4, HSP90AA1, and HSPA4. Based on previous research,[37–40] we set Vina Score < −5 kcal/mol as the minimum standard for binding ability and obtained six effective protein-drug pair docking results, all with Vina Scores < −7 kcal/mol. All docking results are shown in Supplemental Table 5. Among them, the binding between IL6 and Everolimus was the most stable The docked amino acid residues and hydrogen bond lengths are shown in Figure 6.

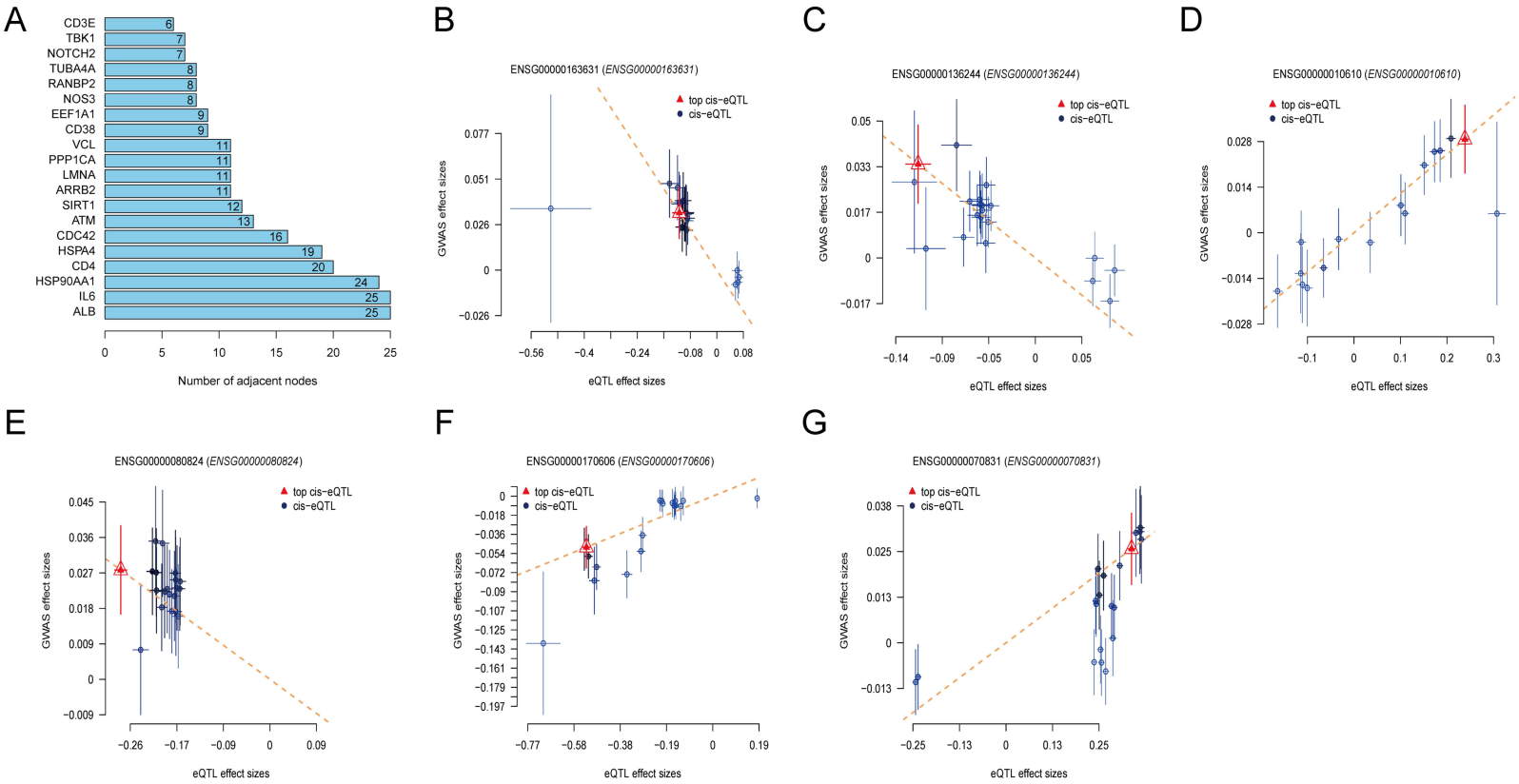

Figure 4 Relationship between key genes and risk of PID. (**A**) The top 20 key genes. (**B**–**G**) Scatter plot of cis-eQTLs contained in ALB, IL6, CD4, HSP90AA1, HSPA4, CDC42, and risk of PID.

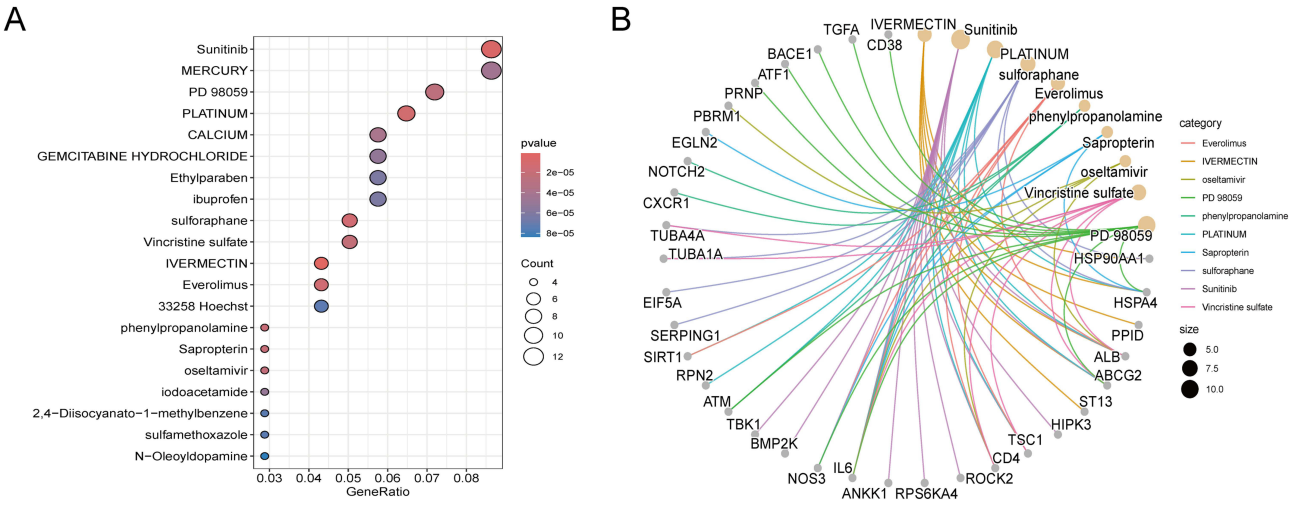

Figure 5 Candidate drug predicted by DSigDB. (**A**) Top 20 enriched drugs based on DSigDB predictions. (**B**) Candidate drugs and their corresponding druggable genes.

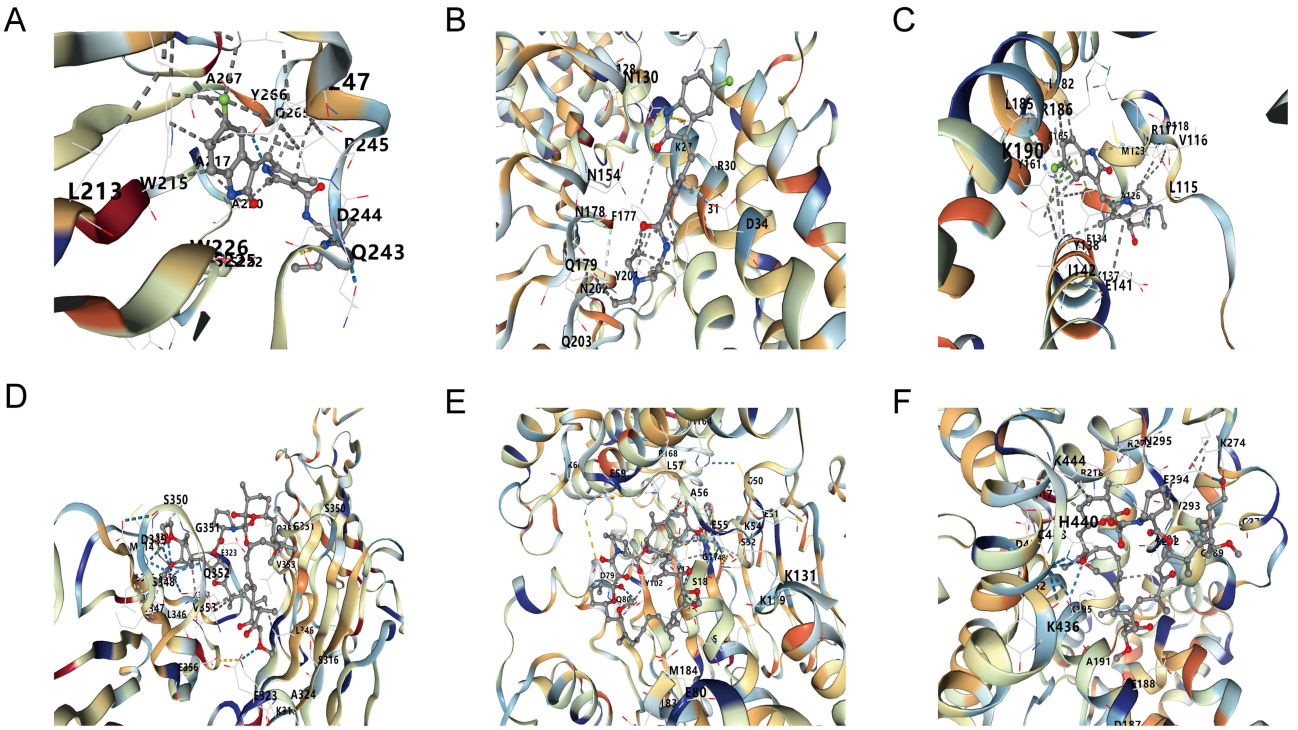

Figure 6 Molecular docking results of available proteins and drugs. (**A**) CD4 docking Sunitinib, (**B**) IL6 docking Sunitinib, (**C**) ALB docking Sunitinib, (**D**) CD4 docking Everolimus, (**E**) IL6 docking Everolimus, (**F**) ALB docking Everolimus.

Protein–Protein Interaction Network Construction

HE staining showed that the tubal structure of the blank group was clear and no obvious inflammatory cell infiltration was observed, while the tubal structure of the model group was unclear, with disorganised and coarsened cilia, the proliferation of fibrous connective tissues, and obvious inflammatory cell infiltration. Masson staining showed that compared with that of the blank group, the collagen fiber volume ratio of the model group was significantly increased. It indicated that the pelvic inflammatory rat model was successfully constructed (Figure 7A).

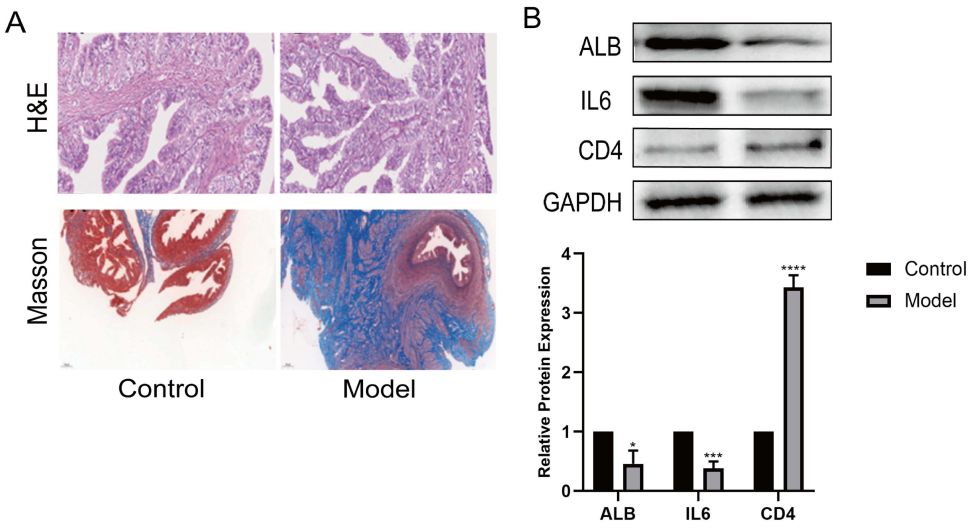

Figure 7 In vivo experiment to investigate the expression of related genes. (**A**) HE staining and Masson staining of tubal adhesion tissue in rats. (**B**) ALB, IL6, and CD4 protein expression bands in pelvic adhesion tissue of rats. *p < 0.05, ***p < 0.001 and ****p < 0.0001 vs Control.

Validation in vivo Experiment

To further determine whether druggable genes differed in normal rats and pelvic inflammatory model rats, we evaluated them by Western blotting. The results showed that the expression of ALB and IL6 was significantly higher in the blank group than in the model group, while the expression of CD4 was significantly higher in the model group than in the blank group (Figure 7B and Supplemental Figure 1). These findings suggest that regulating the expression of ALB, IL6, and CD4 can influence the progression of the disease.

Discussion

The development of new therapeutic agents for PID is a great challenge because the pathogenesis of PID is still unclear. In this study, based on drugable eQTLs in blood and uterus, we identified 144 drugable genes that may affect the outcome of PID, and further molecular docking yielded three drugable genes and corresponding two possible drugs, which were finally validated by in vivo experiments. It provides a promising reference for further research and potential therapeutic development of PID.

Albumin (ALB) is the gene encoding albumin, which is often used clinically to assess liver function, nutritional status, and renal disease, as well as an important protein involved in antioxidant and anti-inflammatory functions.[41] Albumin binds pathogen-associated molecular patterns, such as lipopolysaccharides, and reduces the release of pro-inflammatory factors, as well as scavenging oxygen free radicals and attenuating tissue damage from oxidative stress.[41,42] In contrast, persistent chronic inflammation and catabolic alterations in the body affect albumin metabolism and synthesis (eg, preferential synthesis of C-reactive protein), as well as increased vascular permeability and leakage of albumin into the tissue interstitial space, which leads to decreased albumin levels and exacerbates the inflammatory response.[43] In addition, it can bind and transport antibiotics, hormones, and immunomodulatory factors with the potential to enhance the physicochemical properties of therapeutic drugs, which may improve the pharmacological effects of the drugs, and is considered a promising scaffold for the delivery of targeted drugs.[11] Therefore, drug development against ALB is promising in the treatment of PID, and further pharmacological studies are needed to elucidate the potential mechanisms of ALB in the treatment of PID.

Interleukin 6 (IL6) is a key pro-inflammatory cytokine gene, and the glycoprotein IL6 it encodes is a central regulator of the inflammatory response. Appropriate amounts of IL6 can promote pathogen clearance and tissue repair, whereas in the course of PID, sustained high expression of inflammation-induced IL6 induces immune regulatory disorders, drives B cells to produce anti-endometrial antibodies, and also promotes fibroblast proliferation and collagen deposition, exacerbating tissue adhesion and injury, thus facilitating the localized inflammatory response and fibrosis in the pelvic region.[10,44,45] These studies support IL6 as a promoter of the pathological process of PID, with its role being more to exacerbate the inflammatory response

rather than "initiate the disease". Clinical data also show that elevated IL6 levels in patients with inflammation are typically positively correlated with disease activity (such as pain severity and white blood cell count) and decrease as inflammation resolves following antimicrobial therapy.[46–48] However, our study found that IL6 is negatively correlated with the risk of developing PID. This may suggest that genetically determined higher baseline IL6 levels may reflect a stronger innate immune state, which could reduce the risk of infection progressing to PID by enhancing genital tract mucosal barrier function or accelerating early pathogen clearance, thereby highlighting the potential importance of baseline immune status in PID pathogenesis. However, given that SNPs in the IL6 gene promoter region (eg, −174G/C) may influence IL6 expression levels,[49] whether individuals with high IL6 expression genotypes are more prone to developing severe PID after infection remains to be clarified through further research. If our findings can be sufficiently validated, they may provide insights for risk stratification or preventive strategies.

CD4 molecule (CD4) is the gene encoding the CD4 protein, and the association of CD4 with inflammation is mainly reflected in the CD4+ T cell-mediated immune response. Activated CD4+ T cells secrete TNF-α, IFN-γ, and activate macrophages to release matrix metalloproteinases, causing tissue damage.[50,51] Meanwhile, activated CD4+ T cells can differentiate into different subpopulations (eg, Th1, Th2) and secrete cytokines such as IL4 and IL13, which promote the proliferation of fibroblasts and collagen deposition, and aggravate tissue adhesions.[9] However, current studies have focused on liver diseases and autoimmune diseases, etc., and there have been no specific studies on PID. Consistent with these results, for the effect of cis-qQTLs in blood or uterine tissues on the outcome of PID, we provide genetic evidence for CD4 to be druggable. However, its exact role is unknown.

In this study, DSigDB predicted 10 potential PID drugs, and our molecular docking results focused on sunitinib and everolimus. Sunitinib is an oral small molecule multi-targeted tyrosine kinase inhibitor currently used in the treatment of anti-tumors such as gastrointestinal tumors and renal cell carcinoma.[52,53] Recent findings have revealed that oral sunitinib in mice can reduce TNF-α production, inhibit inflammatory gene expression, and attenuate organ damage by inhibiting NF-κB, and may act as a potent inhibitor of inflammatory responses.[34] Everolimus is a rapamycin (mTOR) inhibitor that is commonly used to inhibit the PI3K signaling pathway to stop tumor growth.[54] Previous studies[55–57] have shown that activated mTOR promotes the activation of the NF-κB signaling pathway in neuroinflammatory and in vivo obstructive sleep apnoea models of Parkinson's disease and that rapamycin exerts its anti-inflammatory effects through the mTOR/NF-κB signaling pathway. In addition, everolimus can ameliorate H. pylori-induced oxidative stress by reducing reactive oxygen species and malondialdehyde, while decreasing the expression of pro-inflammatory cytokines IL6 and TNF-α.[58] In line with previous studies, we similarly highlight the possibility of sunitinib and everolimus as potential drug candidates for inflammatory diseases.

Our study also has some non-negligible drawbacks: firstly, drugs have a wide range of effects on their targets, and many off-target effects cannot be explored by MR, which may therefore not accurately reflect the magnitude of the effects observed in the actual clinical setting, nor can it fully predict the effects of drugs. Second, MR only simulates lifetime low-dose exposure of a drug under ideal conditions; the actual situation will be more complex due to the interference of other factors, and we only performed simple animal experiments, so it is not a complete substitute for clinical trials, which are still necessary as the actual efficacy of the drug is uncertain. Third, although we identified potential drugs and target genes with supporting evidence for the treatment of PID, it is crucial to assess their side effects and safety, especially in the elderly population. Fourth, molecular docking simulations reflect binding under ideal conditions, ignoring protein flexibility and in vivo solvent dynamics. Due to experimental limitations, this study was relatively simple with a small sample size. Further clarification is needed through combined molecular, cellular, and animal-level experiments, such as observing inflammatory cell infiltration, pathological damage severity, and changes in inflammatory markers after LMNA expression recovery in PID rat uterine tissue following intraperitoneal injection of the LMNA adenovirus vector. Finally, our MR results cannot be generalized to non-Europeans living in different geographic regions because genetic heterogeneity varies by population, environment varies by region, and different living environments and genetic backgrounds lead to differences in the appearance of specific traits in different racial and ethnic groups. We urge future studies to include more data from diverse populations in genetic resource databases, particularly in regions such as Africa and parts of Asia where the burden of PID is particularly high.

Conclusions

In this study, we identified three robust druggable genes (EPHX2, SERPINB1, and SIGLEC11) and 144 candidate PID druggable genes using MR and co-localization analyses, and performed a simple validation of the three druggable genes. We provide genetic evidence supporting the potential therapeutic benefit of the three druggable genes for PID, which will help prioritize drug development for PID.

Abbreviations

PID, pelvic inflammatory disease; MR, mendelian randomization; SMR, summary-data-based MR; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; GWAS, genome-wide association study; eQTLs, expression quantitative trait loci; FDR, false discovery rate; MAF, minor allele frequency; LD, linkage disequilibrium; HEIDI, heterogeneity in dependent instruments; GO, Gene Ontology; BP, biological process; MF, molecular function; CC, cellular component; PPI, Protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Data Sharing Statement

Data supporting the findings of this study are available from the paper and its supplementary Information document.

Ethics Statement

The Ethical Review Committee of Experimental Animal Welfare of Shandong University of Traditional Chinese Medicine approved this study (No. SDUTCM20241114223). According to item 1 and 2 of Article 32 of "the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects", this study is exempt from ethical review and approval.

Acknowledgments

We thank the GWAS database and the experimental animals.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Natural Science Foundation of Shandong Province (No.ZR2021MH079).

Disclosure

The authors declare no conflicts of interest in this work.

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