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Investigating the shared genetic basis of inflammatory bowel disease and systemic lupus erythematosus using genetic overlap analysis

Weichao Yuan[1], Qinghua Luo[2] and Na Wu[2,3*]

Abstract

Background Inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE) are autoimmune diseases that often coexist clinically. This phenomenon might be due to shared genetic components.

Methods Genome-wide association study (GWAS) data for IBD and SLE were analyzed to determine both global and local genetic correlations using three methodologies: linkage disequilibrium score regression (LDSC), genetic covariance analyzer (GNOVA), and SUPERGNOVA. The genetic overlap and risk loci were subsequently examined using the conditional/conjunctional false discovery rate (cond/conjFDR) statistical framework. Furthermore, a multi-trait analysis of MTAG was employed to validate the loci, followed by an LDSC analysis focusing on tissue-specific gene expression.

Results GWAS findings demonstrated a marked global genetic correlation between IBD (including Crohn's disease and ulcerative colitis) and SLE. Locally, SLE showed a strong association with IBD and Crohn's disease on chromosomes 10, 19, and 22. ConjFDR analysis confirmed the genetic overlap and identified relevant genetic risk loci. MTAG further validated several shared susceptibility genes. Additionally, the LDSC-SEG analysis results indicate that IBD (including CD and UC) and SLE are jointly enriched in the tissues of Spleen and Whole Blood.

Conclusion This study confirms a genetic overlap between IBD and SLE, identifying marked comorbid genes and offering new insights for treating these diseases.

Keywords Genetic overlap, Genetic structure, Genetic risk loci, Systemic lupus erythematosus, Inflammatory bowel disease

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Introduction

Inflammatory bowel disease (IBD) is an immune-mediated disorder characterized by inflammatory alterations in the intestinal tract, primarily classified into Crohn's disease (CD) and ulcerative colitis (UC) [1]. The global incidence and prevalence of IBD are significant, with current rates exceeding 0.3%. Projections suggest that the global incidence could reach 1% by 2030 [2]. Although the precise etiology of IBD remains undetermined, it is widely accepted to result from the interplay of genetic, immune, and environmental factors [3]. Common symptoms of IBD include persistent diarrhea, abdominal pain, weight loss, and fever [4]. Clinically, IBD has been found to be closely associated with other autoimmune diseases, particularly systemic lupus erythematosus (SLE), warranting considerable attention [5]. SLE, a prototypical autoimmune disease, often presents with dermatological manifestations such as polymorphous light eruption, rosacea, and hair loss, and in severe cases, it can impact the musculoskeletal system, kidneys, and central nervous system, necessitating prompt diagnosis and treatment [6]. Current clinical research on the comorbidity of IBD and SLE remains limited, and existing treatment approaches have yet to fully address the complex relationship between these two conditions. Conducting genome-wide genetic correlation analyses to identify shared genes between IBD and SLE could enhance diagnostic methods and provide a critical foundation for developing more effective, personalized treatment strategies.

Numerous studies have investigated the genetic correlation analysis of different traits, employing novel statistical methods to determine genetic overlap between two diseases and identify high-confidence genetic risk loci [7–9]. To fulfill the objectives of this study, these methods were utilized to comprehend the shared genetic architecture and comorbid genes between IBD and SLE.

This study investigates the fundamental genetic basis between IBD and SLE through a longitudinal, progressive approach. The specific steps include: ① Assessing the genetic correlation between IBD and SLE using linkage disequilibrium score regression (LDSC) [10] and genetic covariance analyzer (GNOVA) [11] for global aspects, and SUPERGNOVA [12] for local aspects; ② Conducting conditional/conjunctional false discovery rate (cond/conjFDR) analysis to examine genetic overlap and loci between different traits [13]; ③ Performing genome-wide association study (GWAS) multi-trait analysis (MTAG) [14] for the two diseases to identify shared risk loci; and ④ Applying LDSC specifically expressed gene (LDSC-SEG) analysis in determining tissues markedly associated with both diseases [15].

Methodologies and materials

GWAS data selection and characteristics

In order to ensure greater accuracy in our research, we should select GWAS data with the largest sample size and the highest number of SNPs, as well as those with a publication date that is relatively recent. Following these criteria, we have chosen the IBD and subtype (CD and UC) GWAS data provided by de Lange KM et al. [16], which correspond to patient numbers of 25,042, 12,366, and 12,194 respectively.For SLE, the GWAS by Bentham J et al. [17] was utilized, and it included 5,201 patients. All participants in these studies were of European descent.

Global and local genetic correlation analyses

Pairwise genetic correlation analysis was performed using linkage disequilibrium score regression (LDSC) and genetic covariance analyzer (GNOVA). For the former, pre-computed linkage disequilibrium (LD) scores were used, derived from approximately 1.2 million common SNPs (excluding the human leukocyte antigen region) from the HapMap3 reference panel of European ancestry [18]. GNOVA served as a complementary analysis. Quality control for both analyses was ensured using the munge_sumstats.py script. The genetic correlation estimate (rg) ranges from −1 to +1, where −1 indicates a complete negative correlation and +1 indicates a complete positive correlation. Bonferroni-corrected P-values were employed to determine statistical significance in both analyses.

SUPERGNOVA was utilized to estimate pairwise local genetic correlations. This method divides the entire genome into approximately 2,353 blocks, calculates the similarity between pairs of traits driven by genetic variation in each region, and identifies loci with local genetic correlations [12]. Throughout this process, Bonferroni correction was applied to the *P*-values ($P<0.05/2{,}353$).

Genetic overlap analysis

Conditional quantile-quantile (QQ) plots are instrumental in visualizing the enrichment of polygenic signals across different phenotypes. A leftward shift in the proportion of SNPs associated with one phenotype (e.g., IBD) in the QQ plot, as the *P*-value of another phenotype (e.g., SLE) decreases, indicates a marked enrichment phenomenon and substantial genetic overlap between the two phenotypes [19]. The *P*-values in all QQ plots are categorized into three intervals: "$P<0.10$", "$P<0.01$", and "$P<0.001$". The precimed/mixer package in Python 3.11 (https://github.com/precimed/mixer) was employed to generate these QQ plots.

Conducting conditional/conjunctional false discovery rate (cond/conjFDR) analysis

The conditional false discovery rate (condFDR) and conjunctional false discovery rate (conjFDR) methods within the empirical Bayesian statistical framework have recently gained popularity for identifying genetic risk variants associated with comorbidities across different traits [20]. These methods ensure high confidence in the results and identify loci that may not exceed traditional significance thresholds [20]. The FDR value serves as a reference for evaluating pleiotropy. The condFDR method identifies gene loci associated with one trait (e.g., IBD) by referencing the gene loci of another trait (e.g., SLE) [21]. This approach re-ranks the test statistics using the association between variants and one trait (e.g., SLE) and then recalculates the association with another trait (IBD). A reverse study is also conducted to obtain the reverse condFDR value. The maximum condFDR value from the bidirectional analysis is used as conjFDR, which then determines the genetic loci shared by the two traits, with the significance level set at "condFDR ≤ 0.05". Detailed conjFDR analysis procedures are available on the website (https://github.com/precimed/pleiofdr). The SNPs associated with the identified loci were uploaded to the SNP2Gene module of FUMA (https://fuma.ctglab.nl/) [22] for gene annotation.

Cross-trait meta-analysis

A cross-trait meta-analysis was conducted using multi-trait analysis (MTAG) [14] through Python 3.11.5, focusing on IBD (including Crohn's disease and ulcerative colitis) and SLE. MTAG enhances the power of statistical analysis and offers broader applications compared to other meta-analysis methods. It can further identify SNPs markedly associated with the comorbidity risk of both traits [14]. Additionally, MTAG mitigates potential sample overlap between GWAS by leveraging the shared variance-covariance matrix of effect sizes across different traits [14]. The GWAS results from the MTAG analysis between the two traits were submitted to FUMA [22] to obtain common genetic risk loci and tissue enrichment results.

Table 1 Genetic correlation of SLE and IBD(including CD and UC).SLE, systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

Trait1	Trait2	LSDC-Genetic correlation	LSDC-*P*	GNOVA-Genetic correlation	GNOVA-*P*
IBD	SLE	0.1878	0.0004	0.1029	0.0018
CD	SLE	0.1319	0.0141	0.0724	0.1189
UC	SLE	0.2199	0.0010	0.1162	1.5347e-06

Tissue enrichment analysis

To identify tissues with marked trait enrichment, LDSC specifically expressed gene (LDSC-SEG) analysis was conducted [15, 23]. The principle of LDSC-SEG involves several steps: first, the t-statistic of each gene's expression in 53 human tissues is calculated for the trait; second, genes are ranked from high to low based on their t-statistic scores. The top 10% of genes, considered markedly associated with the trait, are identified. To ensure linkage disequilibrium (LD), a 100 kb window position is set on both sides of the transcription region. The final step involves evaluating the role of key genomic annotations in the genetic heritability of the trait by combining GWAS summary statistics. Genome annotation references the gene expression data of 53 tissue types provided by Finucane et al. [23]. Detailed LDSC-SEG analysis procedures are available on the website (https://github.com/bulik/ldsc/wiki/Cell-type-specific-analyses).

Results

Global and local genetic correlation

LDSC analysis demonstrated marked positive correlations between SLE and IBD (rg=0.1878, P=0.0004), CD (rg=0.1319, P=0.0141), and UC (rg=0.2199, P=0.0010) (Table 1), with the correlation between SLE and UC being higher than that with CD. GNOVA results, excluding CD, also showed marked positive correlations for IBD and UC (Table 1).

In local genetic correlation analysis, marked negative correlations were identified between SLE and both IBD and CD on chromosome 19 ($P_{SLE-IBD-19}$=1.99E-06,$P_{SLE-CD-19}$=4.88E-06), while positive correlations were observed on chromosomes 10 ($P_{SLE-IBD-10}$=1.30E-05,$P_{SLE-CD-10}$=5.04E-08) and 22 ($P_{SLE-IBD-22}$=8.69E-06,$P_{SLE-CD-22}$=1.22E-05)(Table 2). No local correlations were detected between UC and SLE. Detailed analysis results are provided in Supplementary Tables S1-3.

Based on the genetic correlation analysis above, we have reached the following conclusions: ① IBD (including CD and UC) is positively correlated with SLE overall; ② IBD and CD also exhibit local correlations with SLE.

ConjFDR analysis identifies shared genomic loci between IBD (including CD and UC) and SLE

According to the Q-Q plots (Fig. 1A-F), as the P-value for one trait (e.g., SLE) increases from 0.001 to 0.1, the curve for another trait (e.g., IBD) shifts rightward. This pattern indicates a strong correlation between the two traits, suggesting genetic overlap and shared genetic risk loci.

ConjFDR analysis identifies overlapping genes between two traits, ultimately yielding high-quality shared risk loci. When conjFDR<0.05, 41 shared risk loci were identified between IBD GWAS and SLE GWAS, with 18 genes exhibiting consistent effects in both diseases

Table 2 The results of local genetic correlation between SLE and IBD and CD.h2: represents the observed genetic contribution, the larger the better .P: the statistically significant association is defined to be $p < 0.05/2353 = 2.12495E\text{-}05$.SLE, systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease

Trait1	Trait2	chr	start	end	Genetic correlation	h2_1	h2_2	*p*
IBD	**SLE**	19	759,261	1,089,241	-0.968336359	0.000760744	0.003248501	1.99E-06
		22	21,866,569	23,015,302	1.011759486	0.001401821	0.005635341	8.69E-06
		10	33,656,119	36,017,592	0.814827581	0.002406945	0.003465586	1.30E-05
CD	**SLE**	10	33,656,119	36,017,592	0.778488833	0.004467251	0.003458251	5.04E-08
		19	759,261	1,089,241	-1.068656772	0.000989874	0.003247391	4.88E-06
		22	21,866,569	23,015,302	0.980541931	0.002186972	0.005636462	1.22E-05

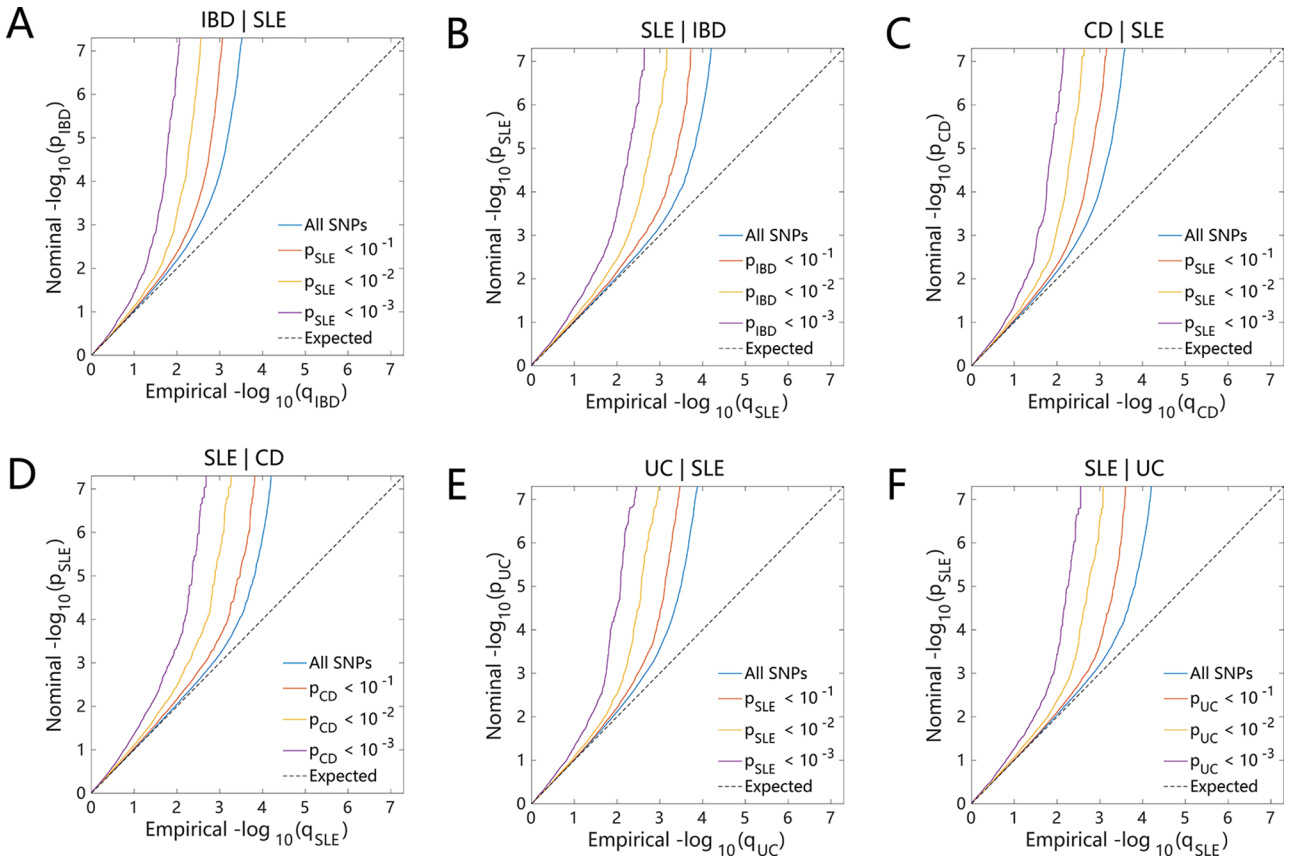

Fig. 1 Conditional quantile-quantile plot. The dashed line indicates the expected line under the null hypothesis, and the deflection to the left indicates the degree of pleiotropic enrichment. (**A**) IBD-SLE. (**B**) SLE-IBD. (**C**) CD-SLE. (**D**) SLE-CD. (**E**) UC-SLE. (**F**) SLE-UC.SLE, Systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

(Fig. 2A, Supplementary Table S4). For CD and UC, there are 40 and 20 genetic risk loci corresponding to SLE, respectively. Of these, CD shares 18 loci with consistent effects, while UC shares 7 (Fig. 2B-C, Supplementary Table S5-S6).

The conclusions of the ConjFDR analysis indicate that: ① IBD (including CD and UC) and SLE have a genetic overlap; ② IBD, CD, and UC share 41, 40, and 20 risk loci with SLE, respectively.

MTAG

MTAG analysis on the GWAS data for IBD and SLE produced a new two-trait-related GWAS dataset, which was annotated using Fuma. The analysis identified 93 shared risk loci between IBD and SLE (Fig. 3A, Supplementary Table S7), with five genes (Fc Gamma Receptor IIa(FCGR2A), RP11-95M15.1, Janus Kinase 2(JAK2), IFNG Antisense RNA 1(IFNG-AS1), and Ubiquitin Conjugating Enzyme E2 L3(UBE2L3)) emerging as common intersections between conjFDR and MTAG analyses (Fig. 3B). Subsequently, GeneMania [24] was utilized to construct a detailed gene-gene interaction network based on these genetic risk genes and their neighboring

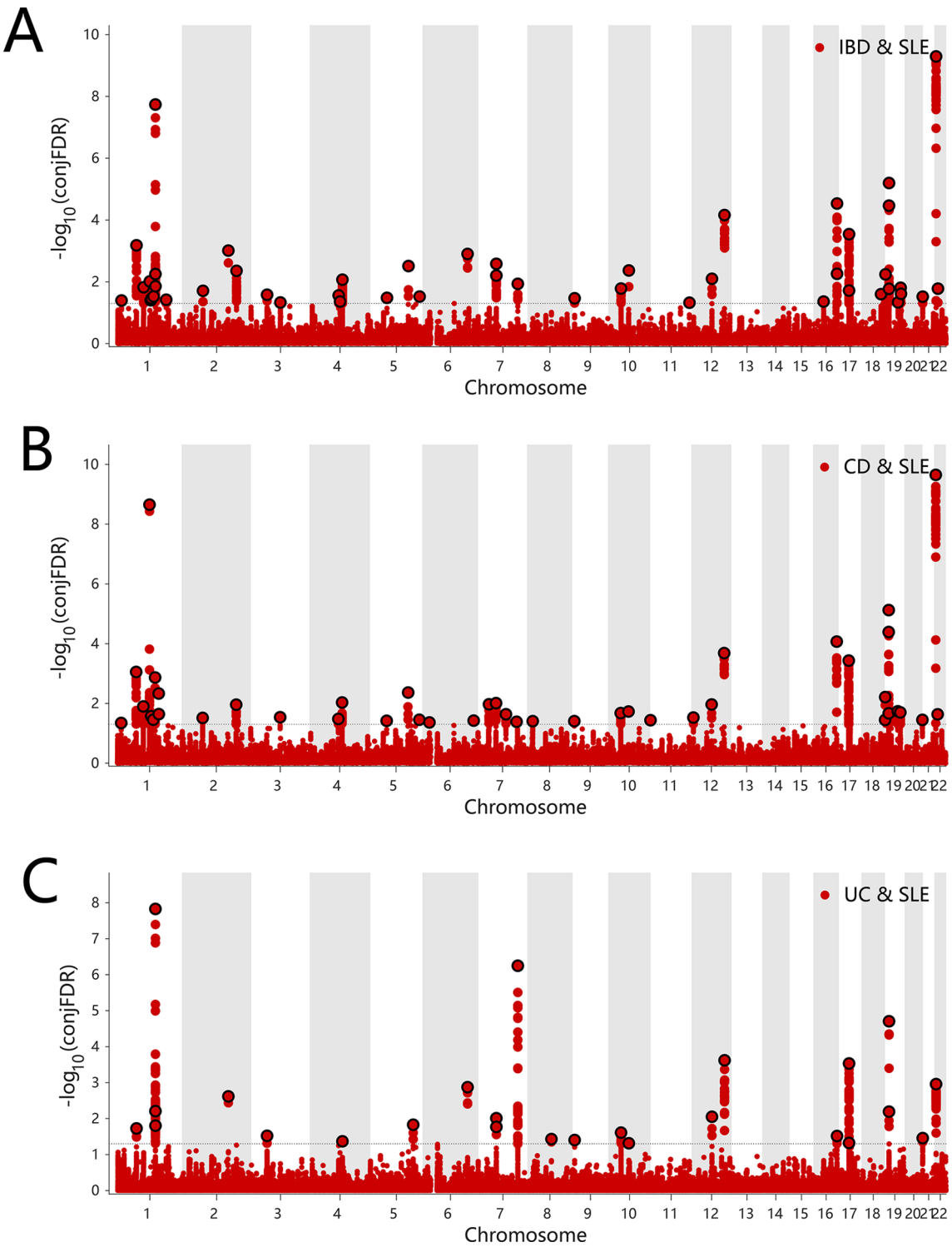

Fig. 2 (**A**) ConjFDR Manhattan plot of IBD and SLE. (**B**) ConjFDR Manhattan plot of CD and SLE. (**C**) ConjFDR Manhattan plot of UC and SLE.The shared risk loci between SLE and IBD, CD and UC were marked. The statistically significant causality is defined to be conjFDR < 0.05. SLE, Systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

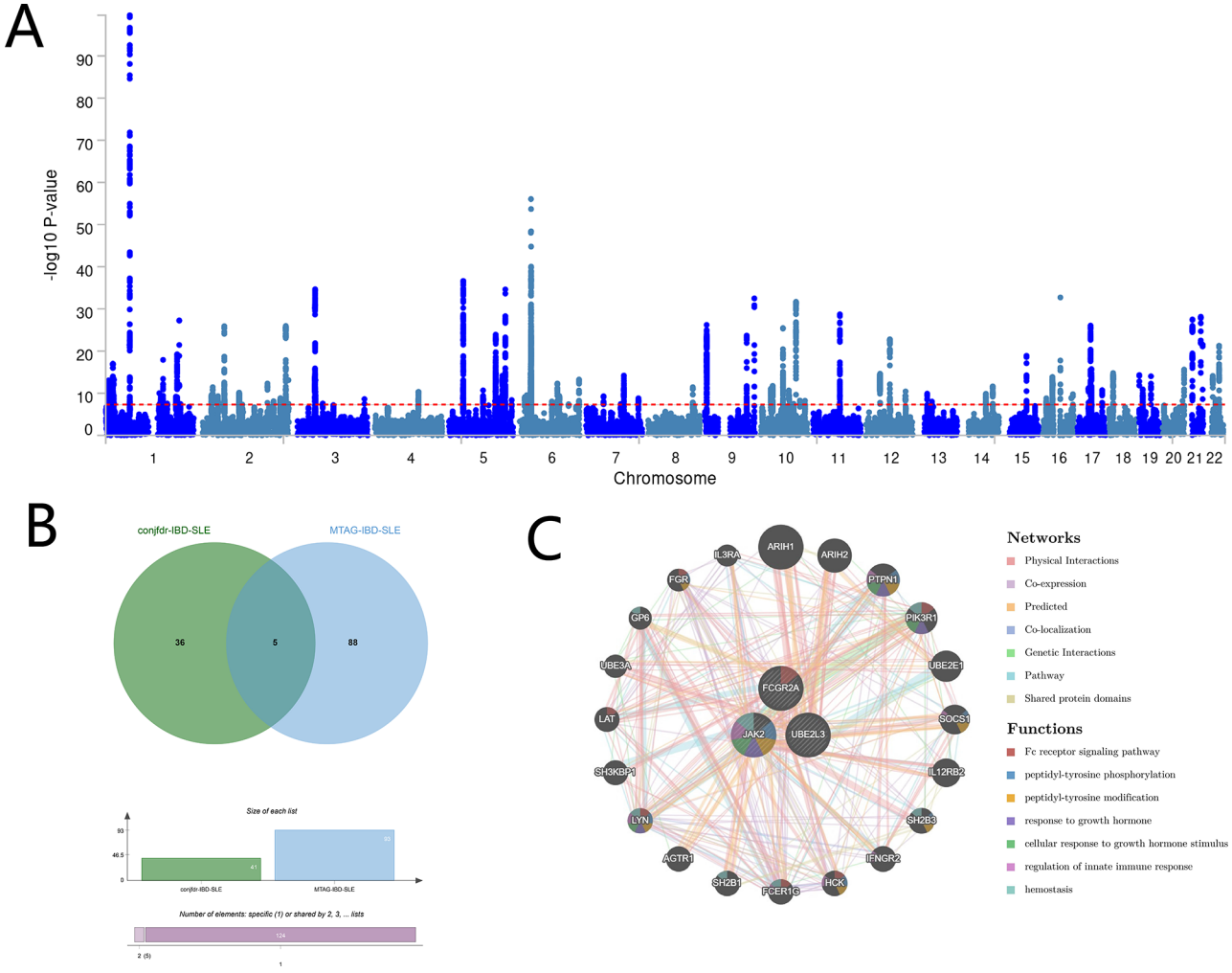

Fig. 3 (**A**) Manhattan map of genetic risk loci for IBD and SLE by MTAG. (**B**) Intersection gene map of IBD and SLE after conjfdr and MTAG analysis. (**C**) Gene-gene interaction network of comorbidity genes between IBD and SLE.SLE, Systemic Lupus Erythematosus; IBD, inflammatory bowel disease

genes (Fig. 3C). This network analysis identified 20 frequently mutated genes closely associated with the target genes, revealing several key biological pathways shared by both diseases. These pathways include Fc receptor signaling, peptidyl-tyrosine phosphorylation, peptidyl-tyrosine modification, response to growth hormone, cellular response to growth hormone stimulus, regulation of innate immune response, and hemostasis. The comprehensive network analysis offers valuable insights into the roles these mapped genes play in the progression of comorbidities.

For CD, MTAG analysis identified 73 risk loci (Fig. 4A, Supplementary Table S8). The overlapping genes between conjFDR and MTAG analyses were UBE2L3, RP1-15D23.2, AC020743.4, Fucosyltransferase 2(FUT2), and JAK2 (Fig. 4B), with their corresponding functional enrichment results depicted in Fig. 4C. In the case of UC, MTAG analysis revealed 52 risk loci (Fig. 5A, Supplementary Table S9). FCGR2A, RP11-95M15.1,Interferon Regulatory Factor 5(IRF5), JAK2, and IFNG-AS1 were the overlapping genes identified between conjFDR and MTAG analyses (Fig. 5B), and their enrichment status is presented in Fig. 5C.

In conclusion, the analysis using MTAG has provided valuable insights: ① Genes associated with risk loci such as FCGR2A, UBE2L3, FUT2, JAK2, and IRF5 have been validated and warrant attention; ② These genes are enriched in multiple pathways, including the Fc receptor signaling pathway.

Trait-related tissue

To identify tissues markedly associated with the traits, LDSC-SEG analysis was conducted, referencing tissue expression data from GTEx. At a coefficient of $P<0.05$, ten tissues were found to be associated with IBD (Fig. 6A). The tissues showing marked associations with SLE included Epstein-Barr virus (EBV)-transformed lymphocytes, spleen, pituitary, and whole blood (Fig. 6B).

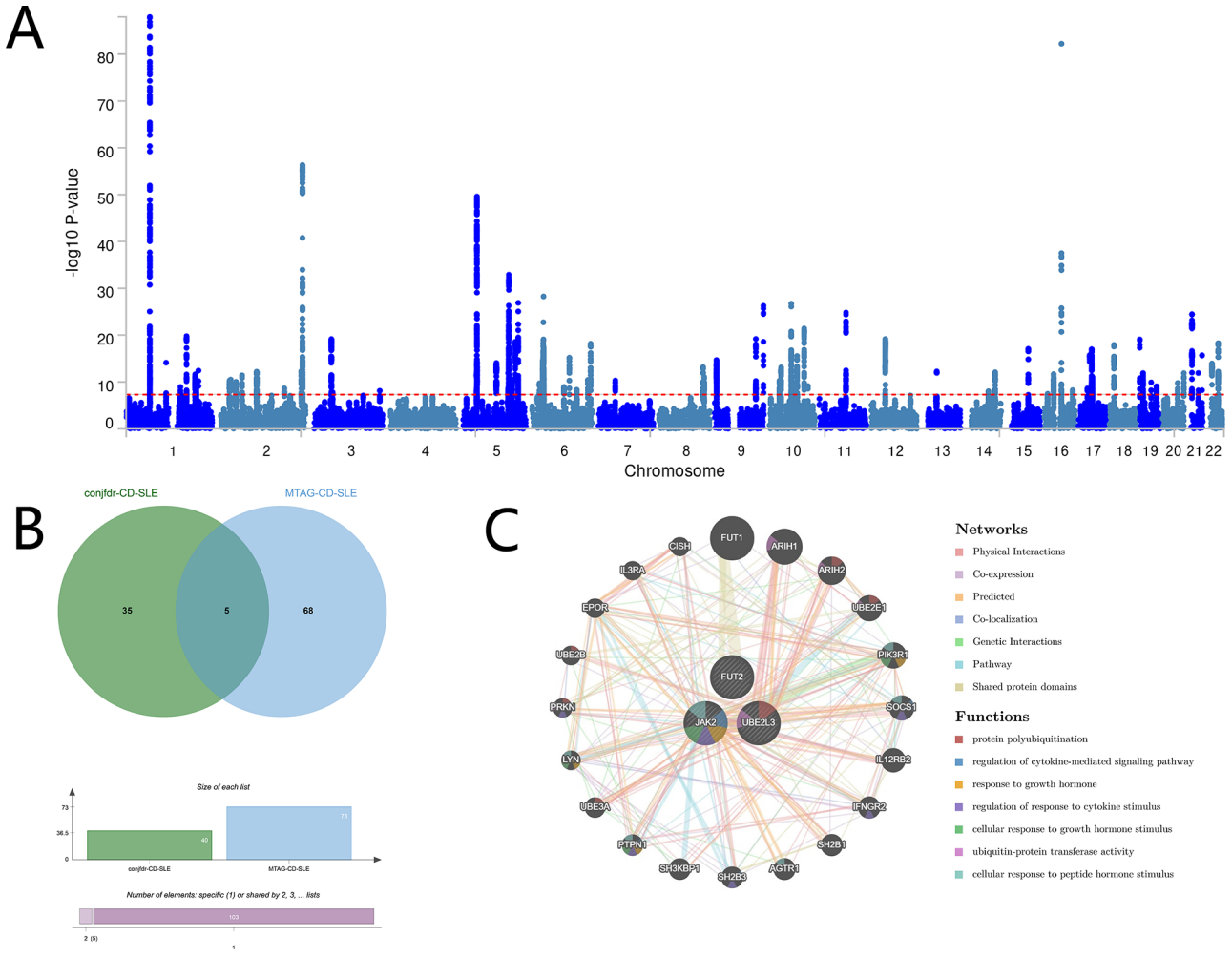

Fig. 4 (**A**) Manhattan map of genetic risk loci for CD and SLE by MTAG. (**B**) Intersection gene map of CD and SLE after conjfdr and MTAG analysis. (**C**) Gene-gene interaction network of comorbidity genes between CD and SLE.SLE, Systemic Lupus Erythematosus; CD, Crohn's disease

Eight tissues were markedly associated with CD, while seven tissues were associated with UC (Fig. 6C-D). Notably, the spleen and whole blood were common to both IBD and its subtypes, as well as SLE, suggesting shared tissue origins. Detailed analysis results are provided in Supplementary Tables S10-S13. Additionally, MAGMA tissue expression analysis was performed using Fuma to annotate the MTAG results (Fig. 7A-C). The enriched tissues included the spleen and whole blood, as well as the small intestine terminal ileum, colon transverse, adipose visceral omentum, lung, and EBV-transformed lymphocytes.

The results of the LDSC-SEG analysis demonstrate enrichment of IBD (including CD and UC) and SLE in both Spleen and Whole Blood tissues. This finding is further validated by MAGMA results.

Discussion

This study demonstrated a marked global genetic correlation between IBD (including CD and UC) and SLE at the genome-wide level. Local genetic analysis highlighted marked associations between SLE and IBD, as well as CD, particularly on chromosomes 10, 19, and 22. Quantile-quantile (QQ) plots at the SNP level suggested genetic overlap between these disorders. ConjFDR and MTAG analyses identified shared genetic risk loci and overlapping genes between the corresponding traits. Furthermore, LDSC-SEG analysis revealed that IBD and its subtypes (CD and UC) share common tissue origins with SLE, specifically in the spleen and whole blood, providing evidence for a tissue-level connection. The MTAG-based MAGMA tissue expression analysis confirmed these findings. Overall, the study enhances understanding of the genetic architecture of IBD (including CD and UC) and SLE, revealing gene overlap, shared susceptibility genes, and enriched pathways.

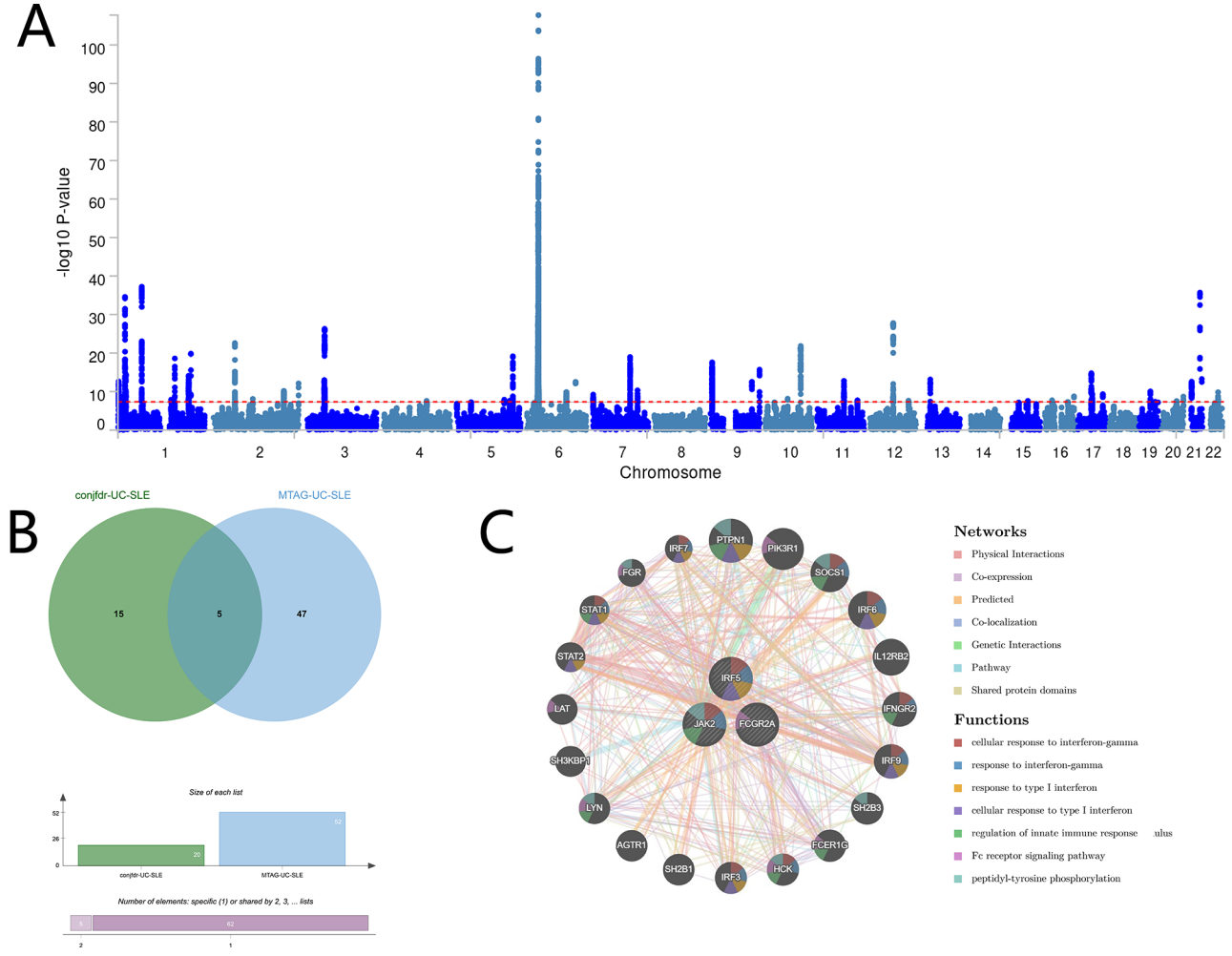

Fig. 5 (**A**) Manhattan map of genetic risk loci for UC and SLE by MTAG. (**B**) Intersection gene map of UC and SLE after conjfdr and MTAG analysis. (**C**) Gene-gene interaction network of comorbidity genes between UC and SLE.SLE, Systemic Lupus Erythematosus; UC, ulcerative colitis

The close genetic association between IBD and SLE has been suggested in previous studies, confirming their shared genetic susceptibility [25, 26]. The beneficial effects of overlapping therapies further support this correlation [27]. Historically, literature on the association between SLE and IBD has primarily been based on case reports and series. Brown et al. reported the first case of SLE combined with UC in 1956 [28]. Previous studies indicated that the prevalence of UC in the SLE population is 0.4%, higher than in the general population [29]. A multicenter study in Israel involving 5,018 SLE patients and 25,090 controls found that the prevalence of CD in the SLE population was twice that of the control group [5]. A meta-analysis reported prevalence rates for IBD, CD, and UC in SLE populations as 1.19%, 0.85%, and 0.69%, respectively [30]. While these studies avoided confounding factors such as environmental exposure, their results were not entirely convincing. The genetic perspective of this study avoids such confounding factors, providing new insights into the shared pathogenesis of the two diseases and confirming their genetic overlap.

The comorbid genes identified in this study are marked. UBE2L3, also known as UBcH7, is a component of the ubiquitin-conjugating enzyme E2. UBE2L3 is involved in the ubiquitination of numerous substrate proteins and regulates various signaling pathways, such as NF-κB, GSK3β/p65, and DNA double-strand break repair pathways. It exhibits abnormal expression in immune diseases, tumors, Parkinson's disease, and other conditions, promoting their occurrence and progression [31]. The conjFDR analysis results also indicate that UBE2L3 has a positive regulatory effect on IBD and SLE ($Z>0$), with the smallest corresponding conjFDR value. The pathophysiology of IBD, including its subtypes, is complex, and ubiquitination and post-translational modifications are crucial in its pathogenesis and development. As a representative of ubiquitin-modifying enzymes, UBE2L3 can influence intestinal inflammation, function, and immune responses by regulating various aspects, such as

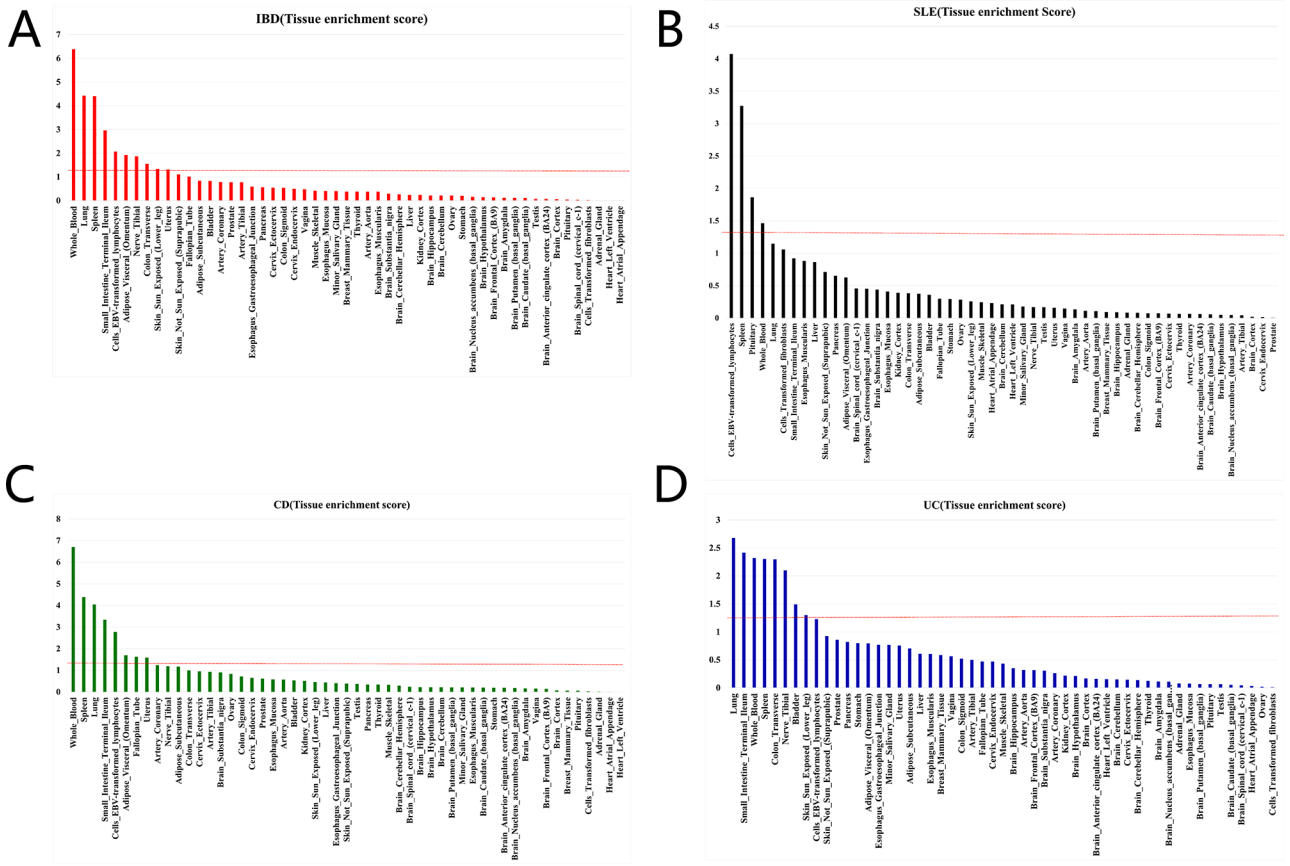

Fig. 6 Tissues enrichment results of IBD (**A**), SLE (**B**), CD (**C**), and UC (**D**) using gene expression data of 53 tissues from GTEx.SLE, Systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

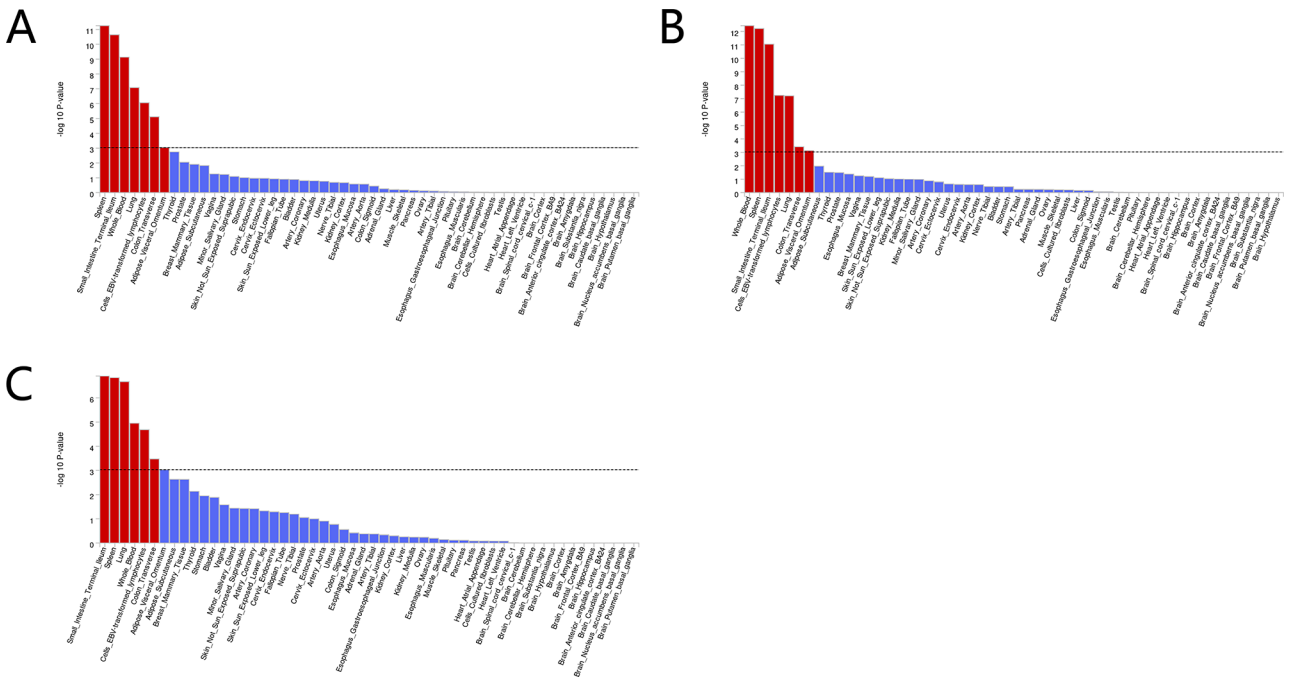

Fig. 7 The tissue expression analysis of MAGMA was obtained by MTAG. (**A**) SLE-IBD. (**B**) SLE-CD. (**C**) SLE-UC.SLE, Systemic Lupus Erythematosus; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

the intestinal barrier [32]. In a study on the gene expression profile of inflammatory pathway-related mediators in intestinal tissues of patients with UC, UBE2L3 expression in the colonic mucosa (both quiescent and active) of patients was markedly higher than that in the control group ($P<0.05$) [33]. Several GWAS analyses have reported UBE2L3 as a susceptibility gene for IBD [34–36]. UBE2L3 is also closely related to SLE, as it can regulate TLR7-induced B cell autoreactivity in SLE [37]. The UBE2L3 risk haplotype and variations can increase the risk of developing SLE [38, 39]. Fucosyltransferase 2 (FUT2) gene polymorphism affects the composition of the gut microbiota, which plays a crucial role in the pathogenesis of IBD [40]. FUT2 may influence the secretory status of ABO blood group antigens in the coagulation cascade, thereby increasing the probability of developing SLE in the population [41, 42]. JAK2 polymorphism and its interaction with other genes can increase susceptibility to IBD and its subtypes [43]. JAK2 can stimulate the expression of pro-inflammatory and anti-inflammatory cytokines in monocyte-derived macrophages, thereby affecting the pathogenesis of IBD [44]. In a mouse model, targeted inhibition of JAK2 was found to affect the IL-6 signal transduction pathway, ultimately improving SLE [45]. In cohort studies of Caucasian and Korean populations, FCGR2A was identified as a susceptibility locus for IBD [46, 47]. Platelet transcriptome studies also found that FCGR2A polymorphism affects SLE disease activity [48]. Interferon regulatory factor 5 (IRF5) is a key transcription factor in the toll-like receptor signaling pathway and is associated with autoimmune diseases [49]. The insertion-deletion polymorphism of IRF5 confers a risk of IBD [50]. IRF5 can influence IBD disease activity by regulating Th1 and Th17 immune responses and cytokines, making it a potential therapeutic marker for IBD [51]. The loss of negative regulation by IRF5 can lead to excessive production of type I interferon and other cytokines, ultimately leading to the development of SLE. To date, all studied SLE mouse models have shown that IRF5 can affect the progression of SLE by influencing dendritic cells and B cells [52]. To the best of our knowledge, these genes are being identified for the first time as playing pleiotropic roles in both IBD and SLE. This discovery not only aids in understanding the shared pathological mechanisms of these two conditions but may also contribute to the development of new biomarkers, improving early detection and disease prediction for these complex diseases.

The Fc receptor signaling pathway is notably enriched among the intersection genes of IBD and SLE, warranting significant attention. As part of the immunoreceptor tyrosine-based activation motif-associated receptor family, Fc receptors play a crucial role in regulating humoral and innate immunity, which is crucial for effectively responding to infections and preventing chronic inflammation or autoimmune diseases [53]. Targeting FcγR signaling can enhance colonic immunoglobulin G levels and activate the FcγR receptor transcript pathway to treat IBD. Additionally, manipulation of FcγR signaling and the use of inhibitors have proven effective in treating IBD [54]. The Fc receptor signaling pathway controls the immune functions of monocytes and B cells, influencing inflammatory factors such as tumor necrosis factor α, interleukin-10, and interleukin-13, which increases susceptibility to SLE [55]. Given the involvement of the Fc receptor signaling pathway in the long-term progression of chronic inflammation and autoimmune diseases, we recommend designing longitudinal cohort studies in the future to observe the dynamic changes of this pathway during disease onset and progression. This approach will help identify critical time points and propose optimal intervention windows.

The LDSC-SEG enrichment in the spleen is a valuable finding. As the largest lymphoid organ, the spleen regulates the immune system throughout the body. The size of the spleen and the severity of IBD show a high degree of correlation, and spleen function is markedly impaired in patients with IBD [56, 57]. Celastrol, a bioactive compound extracted from Tripterygium wilfordii, can improve SLE by preventing spleen and lymph node enlargement and reducing antinuclear antibodies and anti-double-stranded DNA antibody levels [58]. The inclusion of the small intestine terminal ileum and colon transverse in the MAGMA tissue expression analysis results of MTAG also indirectly confirms the existence of the gut-skin axis. Targeted therapies focusing on the spleen and the gut-skin axis may offer patients more precise and effective treatment options.

This study conducted research using four aspects, employing methods such as LDSC, GNOVA, SUPER-GNOVA, conjFDR, LDSC-SEG, and MTAG. IBD and SLE were analyzed from three levels (genome, SNP, and tissue), making the process comprehensive and thorough. However, certain limitations exist. First, it is impossible to achieve a complete absence of LD. Second, there is a possibility of sample overlap. Additionally, the influence of behavioral, social, and environmental factors cannot be entirely avoided. The GWAS data involved in this study were all from European populations, which may limit the generalizability of the research results to other populations. Finally, the entire analysis is essentially a computer simulation process, and corresponding validations at the population level have not been conducted.

Conclusion

Our study demonstrates significant genetic overlap between IBD (including CD and UC) and SLE, highlighting their close genetic relationship and providing new

evidence of shared genetic associations. However, these genetic insights require further validation across diverse populations to assess their generalizability and applicability. Additionally, our multi-level evaluation of pleiotropy across loci, genes, and tissues may offer a crucial foundation for developing novel precision therapies. Future research should focus on translating these findings into actionable therapeutic interventions to improve clinical outcomes for patients with IBD and SLE.

In summary, these discoveries not only offer new perspectives on the shared pathophysiological mechanisms of IBD and SLE but also point toward potential directions for future clinical interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12864-024-10787-0.

Supplementary Material 1

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Author contributions
WY: Conceptualization, methodology, formal analysis, data curation, writing-original draft preparation; QL: writing-original draft preparation, visualization; NW: Supervision, writing-review and editing. All authors contributed to the article and approved the final version of the manuscript.

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Data availability
All the GWAS data and statistical software used in this study were publicly available (which can be accessed through the following URLs), and all the generated results in this study were provided in the main text and supplemental data.

Declarations

Ethics approval and consent to participate
Not applicable. The data used for analysis were obtained from published studies and public databases. The GWAS database is a database of publicly available datasets, where each study has been approved by local institutional review boards and ethics committees.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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