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Genetic overlap between inflammatory bowel disease and iridocyclitis: insights from a genome-wide association study in a European population

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Abstract

Background Inflammatory bowel disease (IBD) is occasionally associated with ophthalmic diseases, including iridocyclitis (IC). The co-occurrence of IBD and IC has been increasingly observed, possibly due to shared genetic structures.

Methods A three-part analysis was executed utilizing genome-wide association study (GWAS) data on IBD and IC. First, the overall genetic correlation between the two traits was observed using linkage disequilibrium score regression (LDSC). Subsequent to this, a local genetic correlation analysis was conducted utilizing the heritability estimation from summary statistics (HESS) methodology. Finally, the conditional/conjunctional false discovery rate (cond/conjFDR) statistical framework was utilized to ascertain the degree of genetic overlap between the two traits.

Results Positive overall correlations were observed among IBD, ulcerative colitis (UC), and IC, encompassing both acute/subacute and chronic IC presentations. While a significant correlation was identified between Crohn's disease (CD) and IC, it was not evident for acute/subacute or chronic IC ($P > 0.05$). Notably, IBD (encompassing CD and UC) demonstrated local genetic correlations with IC and acute/subacute IC, with pronounced enrichment notably on chromosomes 1 and 6, though such correlations were not observed with chronic IC. The conjFDR analysis confirmed the genetic overlap between the two diseases. The shared genes overlapping between IBD (encompassing CD and UC) and IC were IL23R, GPR35, and ERAP1. For acute/subacute IC and chronic IC, there were six overlapping genes (GPR35, RPL23AP12, IL23R, SNAPC4, ERAP1, and INAVA) and one overlapping gene (INAVA), respectively.

Conclusion This study confirms the existence of a shared genetic structure between IBD and IC, providing a biological basis for their comorbidity. Additionally, this finding has significant implications for preventing and treating these two diseases.

Keywords Genetic association, Genetic risk loci, Genetic structure, Iridocyclitis, Inflammatory Bowel Disease

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Introduction

Inflammatory bowel disease (IBD) represents an immune-mediated inflammatory disease primarily impacting the gastrointestinal tract. Clinically, it manifests in two primary forms: Crohn's disease (CD) and ulcerative colitis (UC) [1, 2]. A recent survey underscores a persistent escalation in the global prevalence of IBD, inevitably imposing substantial economic strains on both society and public healthcare systems [3]. Throughout the diagnostic and therapeutic phases, numerous clinicians have noted that IBD often presents with ophthalmic conditions alongside typical intestinal symptoms [4]. Among them, iridocyclitis (IC) (also known as anterior uveitis) warrants particular attention [5]. As the prevailing form of uveitis, IC exhibits a prevalence of 17% among individuals with IBD [6]. Common clinical manifestations of IC include eye pain, photophobia, redness, swelling, and blurred vision [6]. Although IC does not pose a significant threat to human life in most cases, it can precipitate serious complications, including cataracts and secondary glaucoma, and even carries the risk of blindness [4]. As an extraintestinal manifestation of IBD, IC may exhibit a correlation with the activity of the intestinal disease, potentially increasing in frequency as the disease advances, thereby exerting a notable impact on the quality of life for individuals with IBD [7].

Two recent epidemiological studies have suggested a potential association between IBD and IC [8, 9]. However, these observational studies may be influenced by unmeasured confounding factors, reporting bias from participants, and reverse causality, which could lead to biased results. This has prompted researchers to explore the relationship between the two from a genetic perspective, gradually recognizing that genetic factors play an important role in the development of both IBD and IC. A population-based familial study showed that the risk of first-degree relatives of CD patients developing the disease was 10 times higher than that of first-degree relatives of healthy controls, while the risk for UC was 8 times higher [10]. In addition, twin studies also demonstrated a high heritability for IBD, with 17 out of 20 pairs of twins concordant for CD, and similar findings observed for UC [11]. Similarly, in genetic studies of IC, the incidence rate among first-degree relatives of patients was 13%, compared to only 1% among healthy controls [12]. These studies indicate that both IBD and IC are highly heritable diseases. However, no study has systematically explored the genetic relationship between IBD and IC from a genetic perspective. Therefore, identifying whether there is a shared genetic basis between the two diseases could provide important insights into the underlying pathological mechanisms. If we can identify their genetic overlap at the single-locus level and further determine the significant genetic risk loci, it may lead to the discovery of new therapeutic targets and promote the development of precision medicine.

Based on this, our study conducted a three-part analysis of the genome-wide association study (GWAS) datasets for IBD (including CD and UC) and IC (acute/subacute and chronic IC) to progressively elucidate the genetic basis of these two diseases. First, we quantified the overall genetic correlation between IBD and IC using linkage disequilibrium score regression (LDSC) [13]. Second, utilizing the heritability estimation method from summary statistics (HESS), we further analyzed their local genetic correlation [14]. Finally, using the conditional/conjunction false discovery rate (cond/conjFDR) method, we identified shared genetic variants between the two diseases and conducted an in-depth analysis of the polygenic overlap [15]. Through these approaches, we aim to reveal the potential genetic links between IBD and IC, providing new insights into the pathological mechanisms of these two complex diseases.

Table 1 Date sources

Phenotypes	Phenotypic code	Cases/Controls	Ancestry
IBD	ebi-a-GCST004131	25,042/34,915	European
CD	ebi-a-GCST004132	12,194/28,072	European
UC	ebi-a-GCST004133	12,366/33,609	European
IC	H7_IRIDOCYCLITIS	8,016/376,237	European
Acute and subacute IC	H7_IRIDOACUTE	6,755/376,237	European
Chronic IC	H7_IRIDOCHRONIC	1,551/376,237	European

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IC: iridocyclitis; Acute and subacute IC: Acute and subacute iridocyclitis; Chronic IC: Chronic iridocyclitis

Methodology

GWAS data

The GWAS datasets for IBD and its subtypes (CD, UC) were retrieved from the IEU GWAS database (https://gwas.mrcieu.ac.uk/), with corresponding ID numbers ebi-a-GCST004131, ebi-a-GCST004132, and ebi-a-GCST004133. The data for IC and its subtypes (acute/subacute and chronic IC) were selected from the FinnGen database (https://r10.finngen.fi/) [16]. Detailed information about the above GWAS data can be found in Table 1. The flow chart of this study is shown in Fig. 1.

Genetic correlation analysis

The LDSC analysis provides an estimated value of the genetic correlation (R_g) between these two traits [17]. R_g reflects their true overall genetic effect, ranging from −1 to +1. A genetic correlation score of +1 signifies a completely positive genetic association between the two traits, denoting that shared genetic variations exert influence on both traits in the same direction. Conversely, a score of -1 indicates a completely negative genetic correlation, suggesting that shared genetic variations manifest opposite effects on the two traits [17]. The analysis

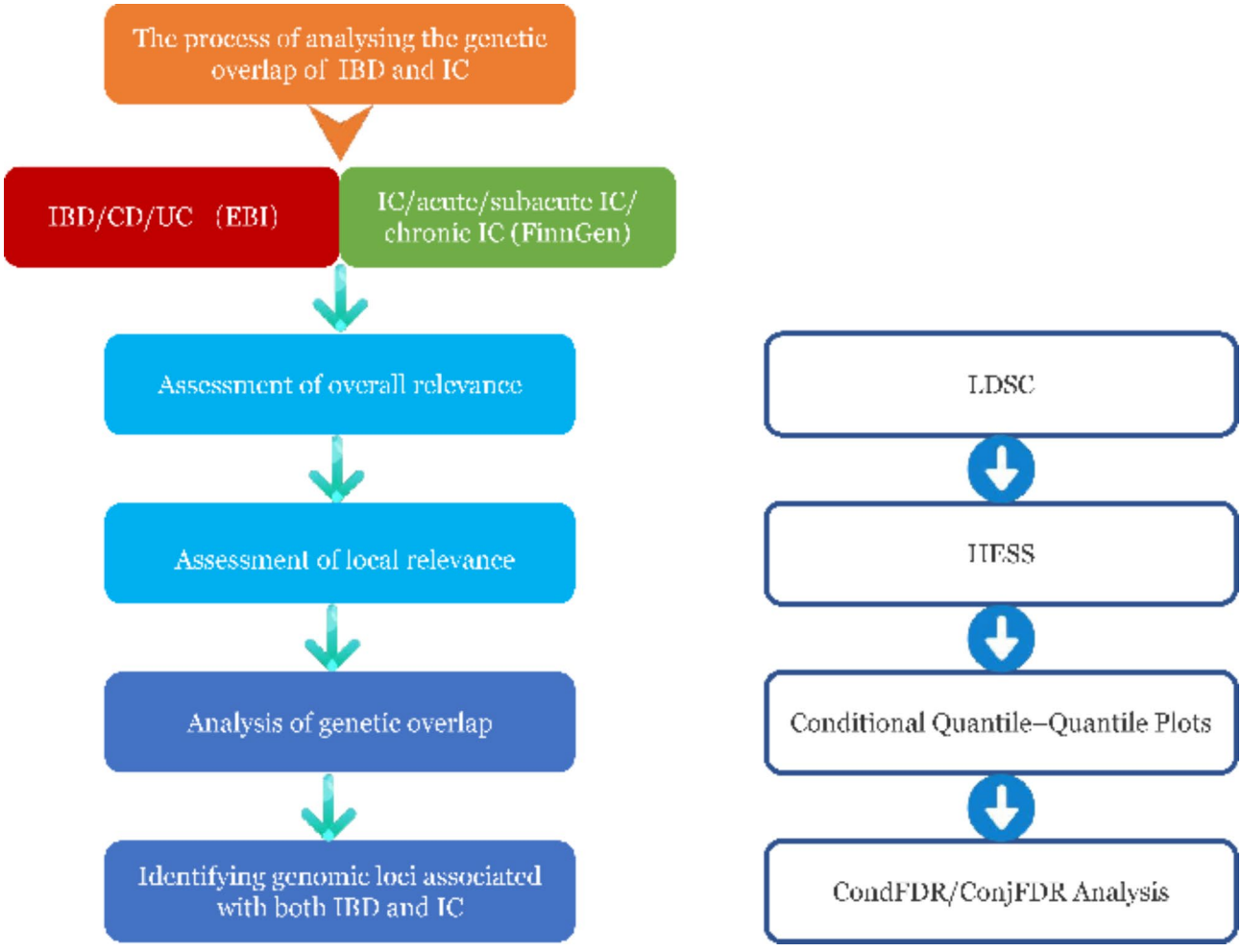

Fig. 1 Flowchart of the study. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IC: iridocyclitis; Acute and subacute IC: Acute and subacute iridocyclitis; Chronic IC: Chronic iridocyclitis.; LDSC: linkage disequilibrium score regression

process utilized default parameters related to munge_sumstats.py, -rg, -ref-ld-chr, and -w-ld-chr, which are accessible for download from the website (https://alkesgroup.broadinstitute.org/LDSCORE/). Participants of European ancestry were selected for the LDSC analysis to reduce potential biases caused by changes in population genetic structure.

Local genetic correlation analysis

We employed the HESS to estimate the local genetic correlation in order to examine whether IBD has genetic correlations shared with IC in the local independent regions of the genome.

ρ-HESS calculates local genetic correlation through the following steps [14]:

1. **Partitioning the genome**: HESS begins by dividing the genome into 1703 independent linkage disequilibrium (LD) regions, each around 1.6 Mb in size. This ensures that SNPs within each region are in LD with one another.
2. **Using GWAS summary statistics**: HESS relies on summary statistics from genome-wide association studies (GWAS), including the effect sizes and standard errors for each SNP. These data are used to estimate the correlation between traits in specific genomic regions.
3. **Calculating local genetic covariance**: ρ-HESS computes local genetic covariance using the following formula:

$$\text{Local genetic covariance} = \widehat{\beta}_f^T V^{-1} \widehat{\beta}_g \quad (1)$$

where $\widehat{\beta}_f$ and $\widehat{\beta}_g$ represent the effect sizes for two traits, and V is the LD matrix. This computation accounts for sample overlap and LD structure within each region.

4. **Regularization**: To mitigate noise in the LD matrix, which may arise due to small sample sizes, HESS applies truncated singular value decomposition (truncated-SVD) to regularize the LD matrix, enhancing the accuracy of estimates and reducing standard errors.
5. **Standardizing genetic covariance**: To make results comparable across different traits and regions, HESS standardizes the local genetic covariance to local genetic correlation using the formula:

$$\text{Local genetic correlation} = \frac{\text{Local genetic covariance}}{\sqrt{-1}\sqrt{h^2_{f,\text{local}}}\sqrt{h^2_{g,\text{local}}}}$$

where $h^2_{f,\text{local}}$ and h_g, local^2 represent the local SNP heritability for each trait in that region.

By following these steps, HESS identifies genomic regions with significant local genetic correlations, even when no significant correlation is observed at the genome-wide level. The results require Bonferroni correction($p<0.05/1703=2.94\text{E-}05$).

Conditional quantile–quantile plots

The enrichment of multi-epitope genes can be elucidated through the development of conditional quantile-quantile (Q-Q) plots. This visualization method illustrates enrichment when the proportion of SNPs linked with the primary phenotype (e.g., IBD) rises in correspondence with the strength of association with the secondary phenotype (e.g., IC) [18]. All Q-Q plots were generated using the precimed/mixer software package in Python 3.11 (https://github.com/precimed/mixer).

CondFDR/ConjFDR analysis

The condFDR/conjFDR methodology offers significant advantages in mining comorbid genes by precisely pinpointing specific shared loci that surpass the significance threshold, which is impossible in traditional GWAS analysis [19]. The steps for performing a conditional false discovery rate (condFDR) analysis are as follows:

1. **Compute FDR**: The false discovery rate (FDR) is computed using empirical cumulative distribution functions (cdfs). SNP enrichment between the two traits is analyzed to adjust the test statistics for SNPs in the primary phenotype.
2. **Build a 2D Look-Up Table**: The condFDR value for each SNP, conditional on the secondary phenotype, is calculated and organized into a two-dimensional look-up table. This table helps identify SNPs that are significant in both traits.
3. **Control for Multiple Testing**: The FDR framework inherently controls for multiple testing, avoiding the loss of power associated with traditional methods such as Bonferroni correction.
4. **Conjunctional FDR**: By repeating the above steps and switching the roles of the primary and secondary phenotypes, conjunctional FDR (conjFDR) is calculated to identify SNPs that are significantly associated with both traits simultaneously.

This procedure enhances the discovery power of genome-wide association studies (GWAS) and identifies shared genomic loci between traits. We assess the effect size of the shared genetic loci through z score. A z score of "–" indicates that the gene exhibits a protective role in the disease. A z score of "+" indicates that the gene presents a risky role in the disease. The magnitude of the value suggests the intensity of the effect.

Results

Overall genetic correlation

In the LDSC analysis of IBD (encompassing CD and UC) and IC (Table 2), IC was found to be positively correlated with IBD ($R_g = 0.4344$, $P=0.0012$), CD ($R_g = 0.3088$, $P=0.0132$), and UC ($R_g = 0.419$, $P=0.005$). Additionally, significant positive overall correlations were observed between acute/subacute IC and IBD ($R_g = 0.523$,

Table 2 Genetic correlation of IBD(encompassing CD and UC) and IC (acute/subacute and chronic IC)

Trait1	Trait2	H2(trait1)	H2(trait2)	Rg	Se	*P*
IBD	IC	0.3127	0.003	0.4344	0.1337	0.0012
CD	IC	0.4457	0.003	0.3088	0.1246	0.0132
UC	IC	0.2387	0.003	0.419	0.1492	0.005
IBD	Acute and subacute IC	0.3127	0.0018	0.523	0.2224	0.0187
CD	Acute and subacute IC	0.4457	0.0018	0.3617	0.1925	0.0603
UC	Acute and subacute IC	0.2387	0.0018	0.5073	0.235	0.0309
IBD	Chronic IC	0.3127	0.002	0.377	0.1556	0.0154
CD	Chronic IC	0.4457	0.002	0.1607	0.1385	0.246
UC	Chronic IC	0.2387	0.002	0.5277	0.1845	0.0042

H2: Represents the observed genetic contribution, the larger the better. Rg: Correlation between two traits, rg ranges from – 1 to 1, and the closer the value is to 1 or -1, the stronger the correlation is (plus or minus represents positive and negative correlation). Se: standard error of genetic correlation. P: the statistically significant association is defined to be p. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

P=0.0187) as well as UC (R_g = 0.523, P=0.0309). In contrast, the correlation with CD (R_g = 0.3617, P=0.0603) was not significant (Table 2). Similar results were found between IBD (encompassing CD and UC) and chronic IC (Table 2). IBD (R_g = 0.377, P=0.0154) and UC (R_g = 0.5277, P=0.0042) showed positive associations with chronic IC, while the correlation with CD (R_g = 0.246, P=0.1607) did not reach statistical significance.

Regarding genetic susceptibility (Table 2), the genetic susceptibilities of IBD, CD, and UC are 0.3127, 0.4457, and 0.2387, respectively. The genetic susceptibilities of IC, Acute and subacute IC, and Chronic IC in this instance are 0.003, 0.0018, and 0.002, respectively.

Localized genetic correlations

In the local genetic correlation analysis plot, chromosome 1 exhibited enrichment for both IC and IBD, while chromosomes 1 and 6 showed enrichment for CD and UC, respectively (Fig. 2). Visually, it was observed that IBD (encompassing CD and UC) and acute/subacute IC shared local genetic overlap, primarily concentrated on chromosomes 1 and 6, with chromosome 1 being

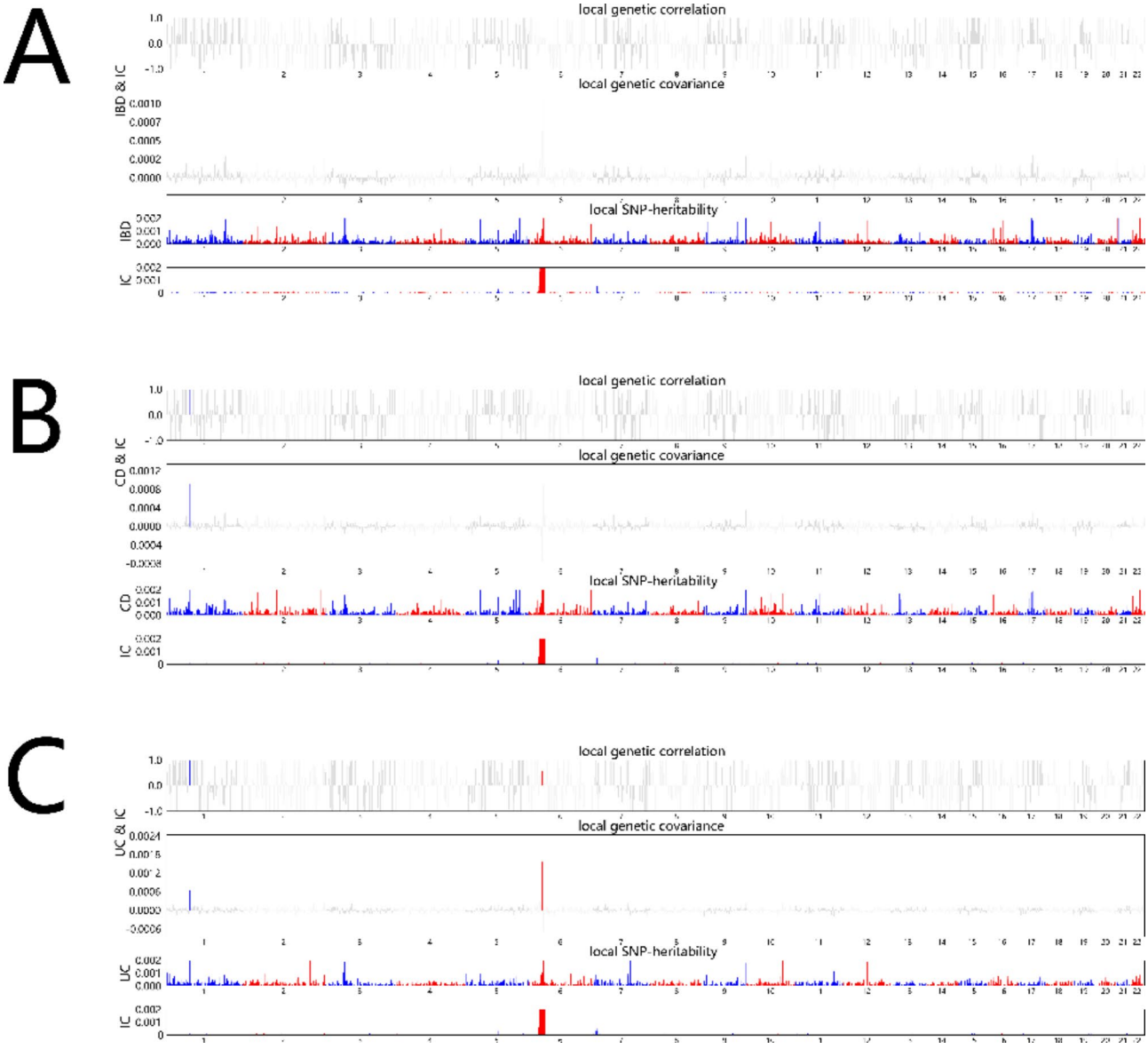

Fig. 2 HESS analysis of IC and IBD, CD and UC. The top and middle sections of each subgraph represent local genetic correlations and covariances, respectively, and the colored bars represent loci with significant local genetic correlations and covariances. The bottom portion represents the local snp heritability of an individual trait, and the colored bars represent loci with significant local snp heritability. (**A**) Local genetic correlation between IBD and IC. (**B**) Local genetic correlation between CD and IC. (**C**) Local genetic correlation between UC and IC. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

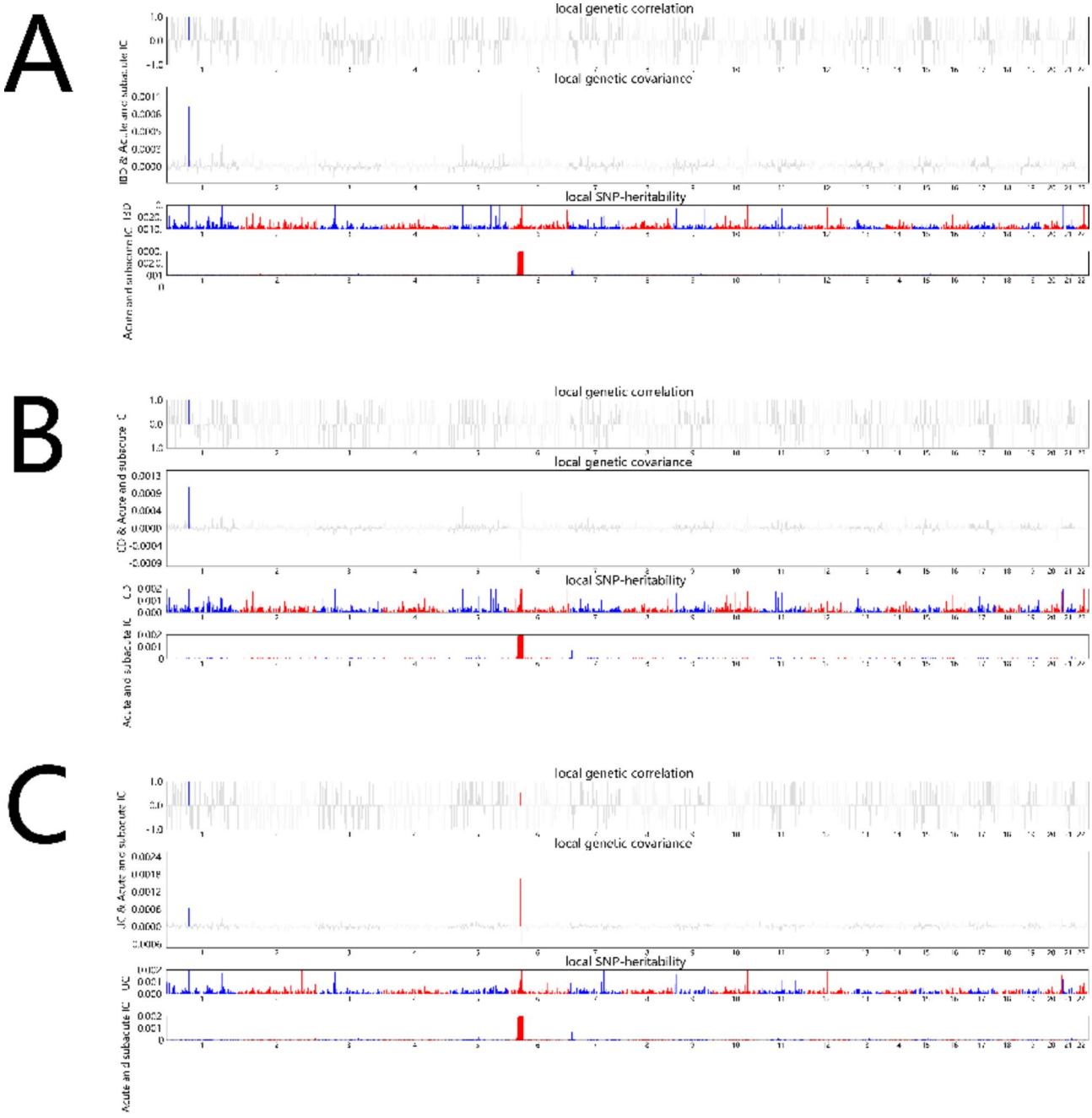

Fig. 3 HESS analysis of acute/subacute IC and IBD, CD and UC. The top and middle sections of each subgraph represent local genetic correlations and covariances, respectively, and the colored bars represent loci with significant local genetic correlations and covariances. The bottom portion represents the local snp heritability of an individual trait, and the colored bars represent loci with significant local snp heritability. (**A**) Local genetic correlation between IBD and acute/subacute IC. (**B**) Local genetic correlation between CD and acute/subacute IC. (**C**) Local genetic correlation between UC and acute/subacute IC. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

common and particularly noteworthy (Fig. 3). However, the local genetic correlation between IBD (encompassing CD and UC) and chronic IC did not reach statistical significance (Supplementary Fig. 1A-1 C).

ConjFDR analysis identifies shared genomic loci between two traits

From the Q-Q plot (Figs. 4, 5 and 6), it was observed that as the *P*-value of one disease decreases, the curve of the other disease consistently shifts to the left. This suggested a strong correlation between IBD (encompassing CD and UC) and IC (encompassing acute/subacute and chronic IC), indicating shared overlapping genetic risk loci and a common genetic background, indicative of a relationship of genetic enrichment.

Upon setting the screening condition to "conjFDR < 0.05", high-confidence shared loci between the two traits were obtained. Twelve shared genetic loci and eight genes (IL23R, USP34, GPR35, ERAP1, IKZF1, EPPK1, LSP1, and GVQW3) were identified between IBD and IC (Fig. 7A, Supplementary Table 1). For CD and UC, 17 and 10 genetic risk loci corresponding to IC were identified, involving 12 and 6 genes, respectively (Fig. 7B-C, Supplementary Tables 2–3). Across all three analyses, two SNPs (rs4676410 and rs2014857) and three common genes (IL23R, GPR35, and ERAP1) were consistently identified. To further investigate the overall biological functions and mechanisms shared between IBD and IC, we conducted a functional enrichment analysis of the eight genes using GeneMania [20]. The results revealed significant enrichment in several processes, including positive T cell selection, T cell selection, positive regulation of T cell proliferation, positive regulation of T cell activation, T-helper cell lineage commitment, positive regulation of leukocyte proliferation, and positive regulation of leukocyte activation (Fig. 8).

Regarding acute/subacute IC, it was found to share 15, 19, and 9 genetic risk loci with IBD, CD, and UC, respectively (Fig. 9, Supplementary Tables 4–6). Among them, the overlapping loci included four SNPs (rs4676410, rs3124994, rs2014857, and rs9977672) and six genes (GPR35, RPL23AP12, IL23R, SNAPC4, ERAP1, and INAVA). For chronic IC, the numbers of shared genetic risk loci with IBD, CD, and UC were 5, 3, and 4, respectively (Fig. 10, Supplementary Tables 7–9). The intersecting SNPs were rs374827 and rs34920518, and the common gene was INAVA.

Discussion

In this study, the overall genetic correlation analysis revealed significant positive correlations in all cases except for CD and acute/subacute and chronic IC. The

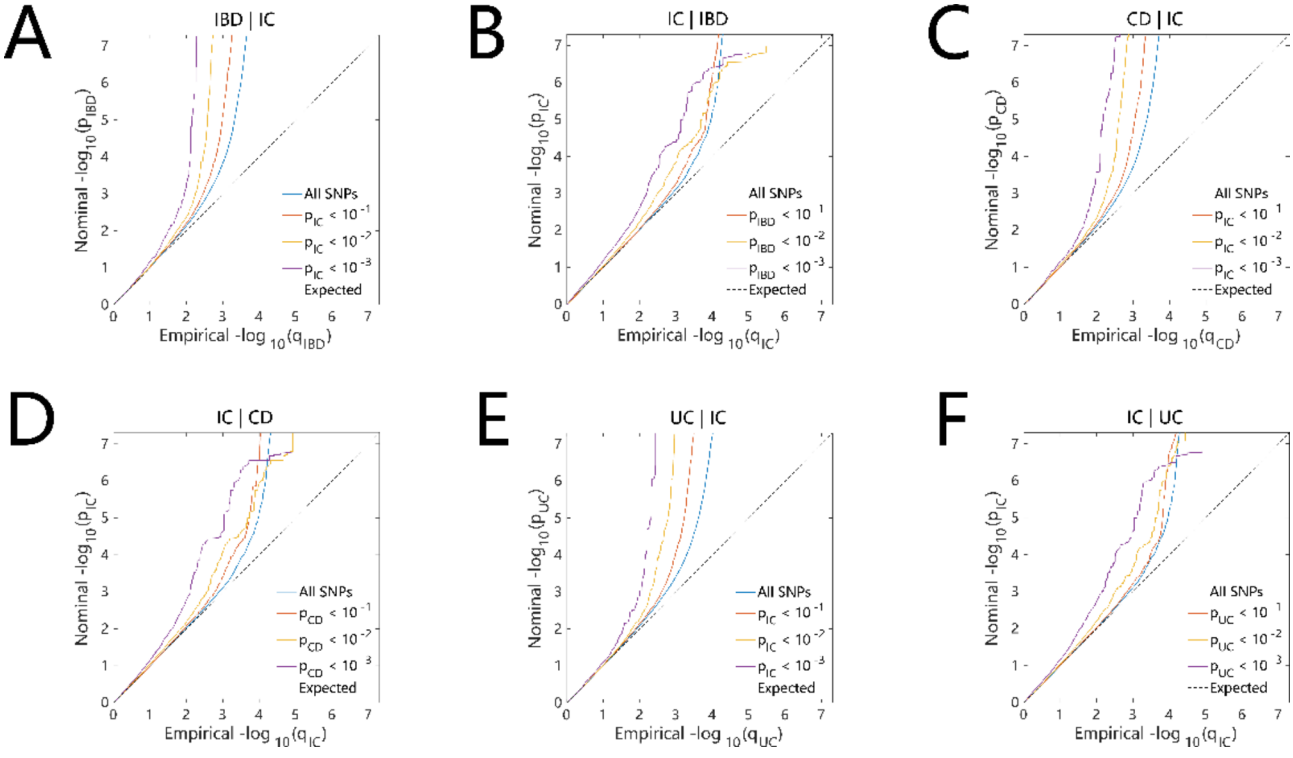

Fig. 4 Conditional quantile-quantile plot. The dashed line indicates the expected line under the null hypothesis, and the deflection to the left indicates the degree of pleiotropic enrichment. (**A**) IBD-IC. (**B**) IC-IBD. (**C**) CD-IC. (**D**) IC-CD. (**E**) UC-IC. (**F**) IC-UC. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

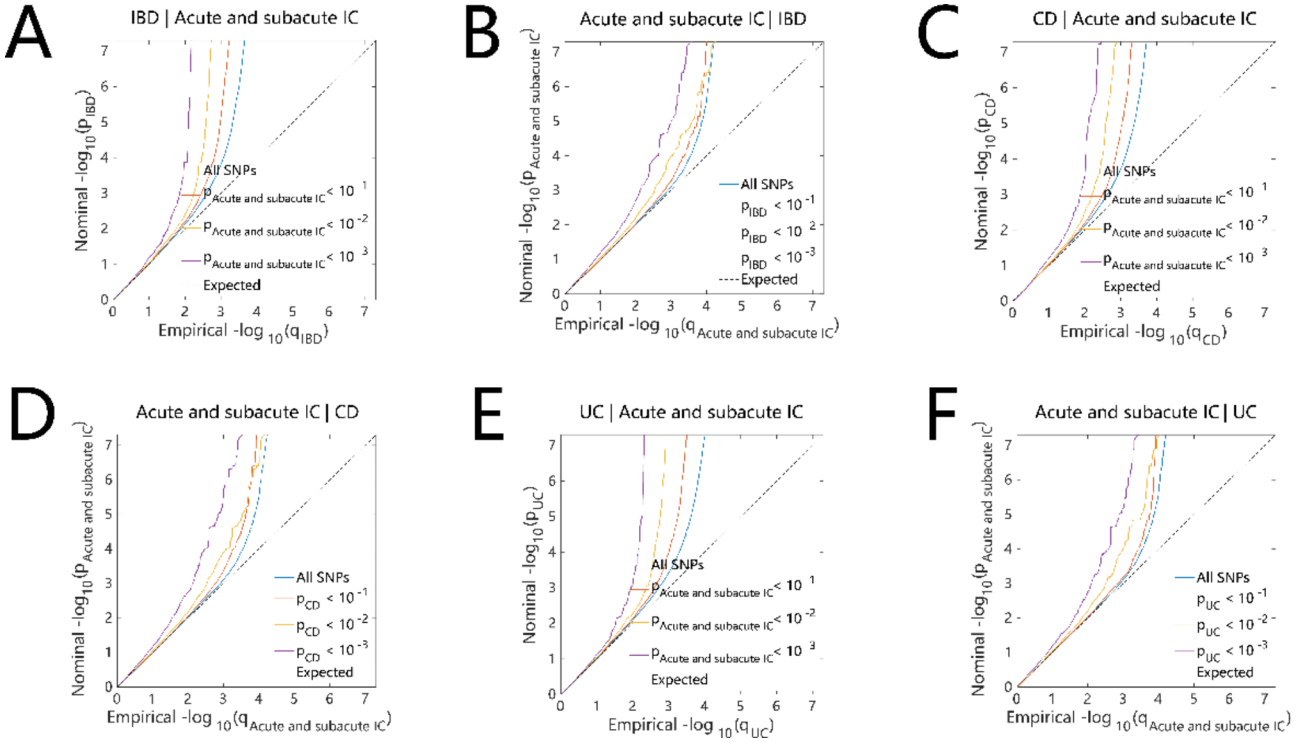

Fig. 5 Conditional quantile-quantile plot. The dashed line indicates the expected line under the null hypothesis, and the deflection to the left indicates the degree of pleiotropic enrichment. (**A**) IBD-acute/subacute IC. (**B**) acute/subacute IC-IBD. (**C**) CD-acute/subacute IC. (**D**) acute/subacute IC-CD. (**E**) UC-acute/subacute IC. (**F**) acute/subacute IC-UC. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

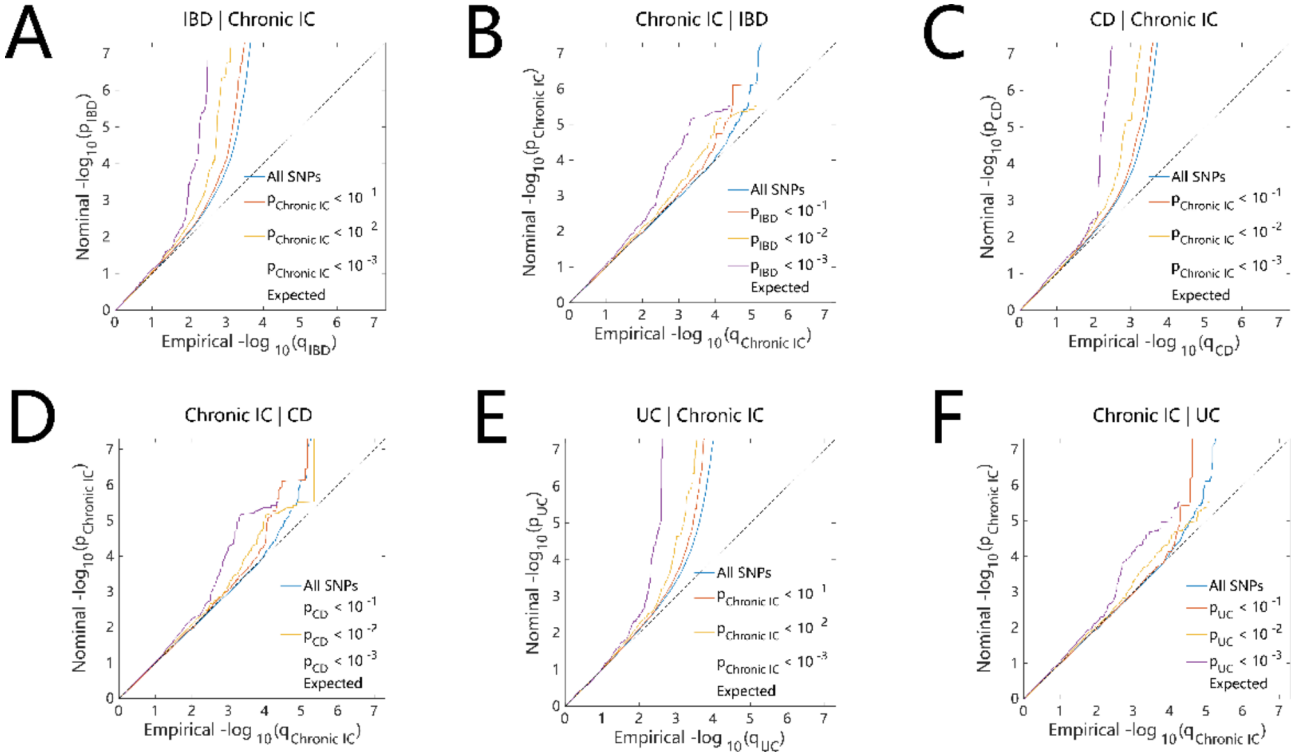

Fig. 6 Conditional quantile-quantile plot. The dashed line indicates the expected line under the null hypothesis, and the deflection to the left indicates the degree of pleiotropic enrichment. (**A**) IBD-acute/subacute IC. (**B**) chronic IC-IBD. (**C**) CD-chronic IC. (**D**) chronic IC-CD. (**E**) UC-chronic IC. (**F**) chronic IC-UC. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

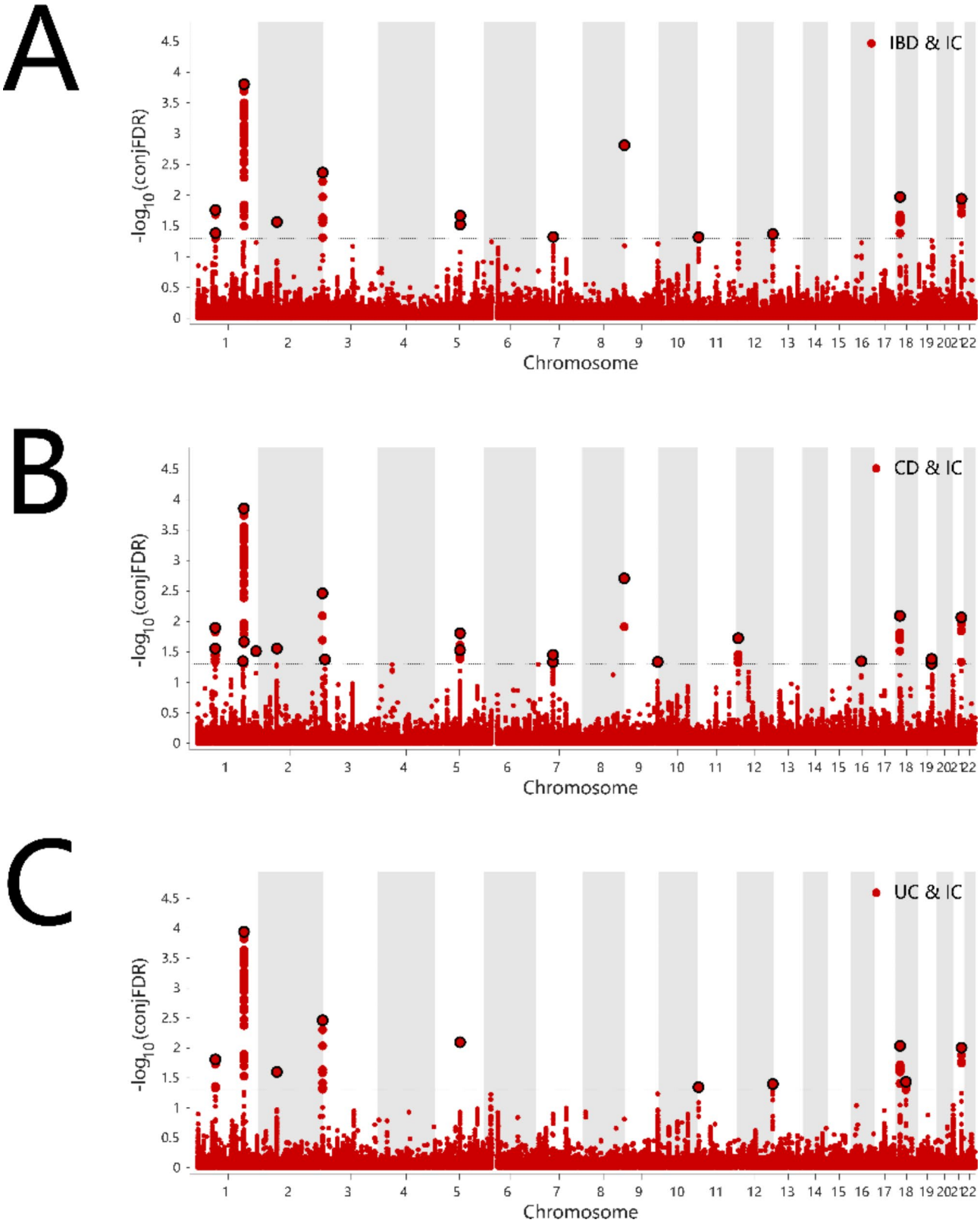

Fig. 7 (**A**) ConjFDR Manhattan plot of IBD and IC. (**B**) ConjFDR Manhattan plot of CD and IC. (**C**) ConjFDR Manhattan plot of UC and IC. The shared risk loci between IC and IBD, CD and UC were marked. The statistically significant causality is defined to be conjFDR < 0.05. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

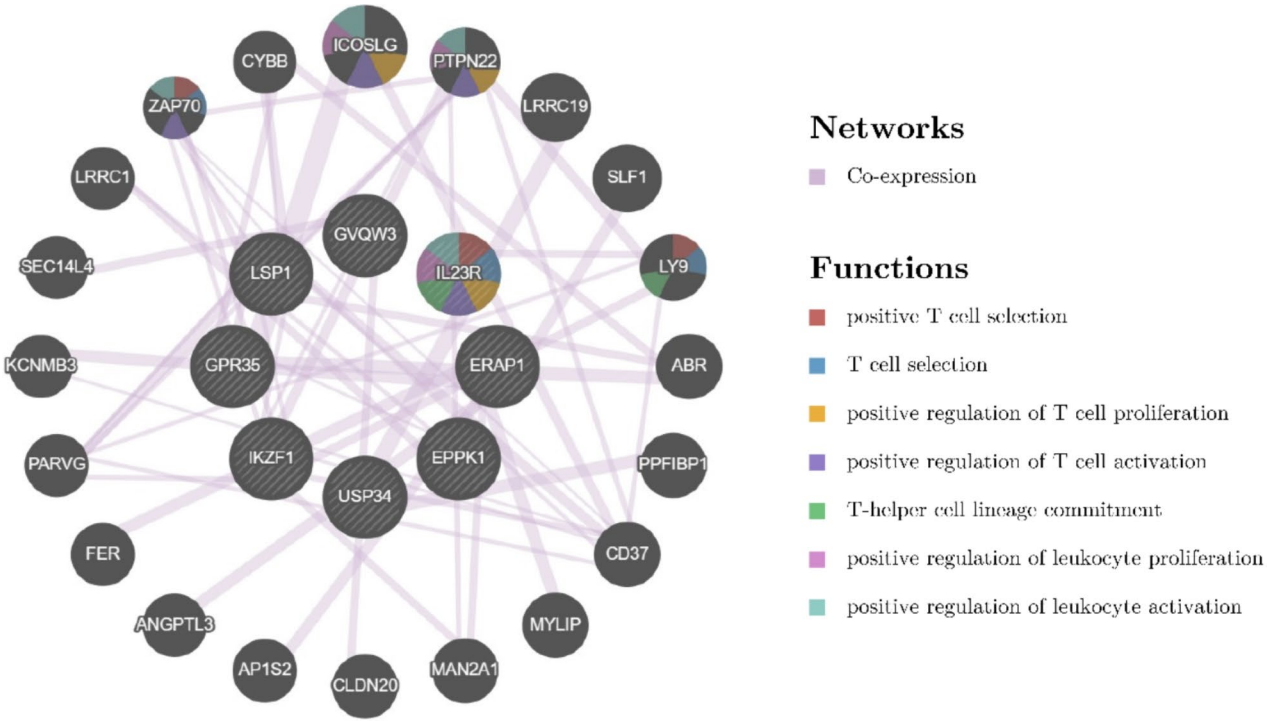

Fig. 8 Gene-gene interaction network of comorbidity genes between IBD and IC. IC, iridocyclitis; IBD, inflammatory bowel disease

local genetic correlation analysis demonstrated that IC and acute/subacute IC were predominantly associated with IBD, clustering on chromosome 1, while the findings for chronic IC were less pronounced. Moreover, both aspects of the results confirmed that UC has a closer relationship with IC than CD, and acute/subacute IC displays a more intimate association with IBD compared to chronic IC. Q-Q plots were constructed at the SNP level, and the conjFDR statistical method was employed, further verifying the strong correlation between IBD and IC and identifying corresponding genetic risk loci. Consequently, our research findings deepen the understanding of the genetic structure between these two diseases and reveal their overlapping mechanisms.

Previous research has also demonstrated a certain degree of correlation between IBD and IC. A two-sample Mendelian randomization study on the two diseases mentioned that IBD (encompassing CD and UC) has a positive causal link with IC (encompassing acute/subacute and chronic IC) [21]. A nationwide cohort study in Denmark found that the incidence rate ratio of IC in individuals with CD was 8.24 (95% CI: 3.42 to 19.89), while for UC, it was 3.29 (95% CI: 1.71 to 6.29) [8]. In another cross-sectional study involving 47,325 individuals with IBD, the odds ratio for IC in CD patients was 3.6 (95% CI: 2.7 to 4.7), and the incidence rate in UC patients was 2.4 (95% CI: 2.0 to 2.9) [9]. According to a previous analysis involving more than 75,000 patients and controls, the overall genetic susceptibility of IBD was estimated to range from 0.3 to 0.5 [22]. The genetic susceptibility of CD was estimated to be approximately 0.5–0.6 [22]. The genetic susceptibility of UC was estimated to be roughly 0.2–0.3 [22]. A study in Sweden was also approximately at this level [11]. At present, there are relatively few studies conducted on the genetic susceptibility of IC. In patients with positive HLA-B27, the genetic susceptibility of IC is higher (0.4–0.7). Nevertheless, for patients with HLA-B27 negativity, the genetic susceptibility of IC is relatively low [23]. On the whole, our research is largely consistent with the previous data and possesses certain reference value. Moreover, the findings of this research, conducted at the genetic level, offer novel insights into the similarity of pathogenic mechanisms between the two diseases and confirm the existence of genetic overlap between them.

This study focused on the identified risk genes. IL23R, a protein comprising IL-12β1 and IL-23R chains, is a pro-inflammatory cytokine member. Previous GWAS studies have recognized it as an IBD gene. Additionally, a cohort study validated the role of the IL23R gene in increasing susceptibility to CD in North American and European populations [24]. IL23R has been identified as a gene that can influence the genetic progression of IC [25]. INAVA has the capability to induce MAPK and NF-κB pathways, clear cytokines, and intracellular bacteria, potentially contributing to intestinal immune homeostasis and reducing the risk of IBD [26]. Our discovered loci vary to some extent from certain previous studies. For instance, the research on GPR35 in the context of IC

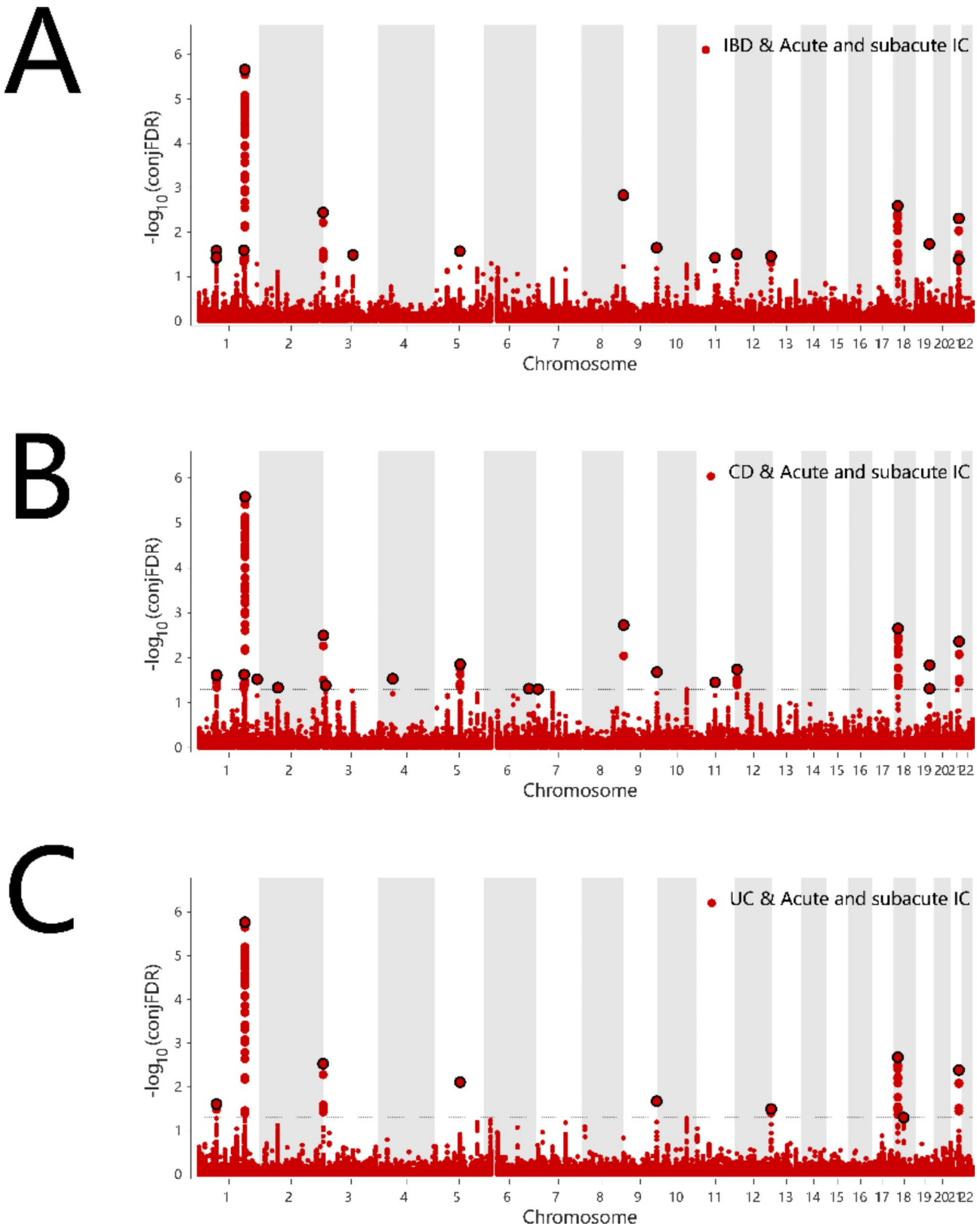

Fig. 9 (**A**) ConjFDR Manhattan plot of IBD and acute/subacute IC. (**B**) ConjFDR Manhattan plot of CD and acute/subacute IC. (**C**) ConjFDR Manhattan plot of UC and acute/subacute IC. The shared risk loci between acute/subacute IC and IBD, CD and UC were marked. The statistically significant causality is defined to be conjFDR < 0.05. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

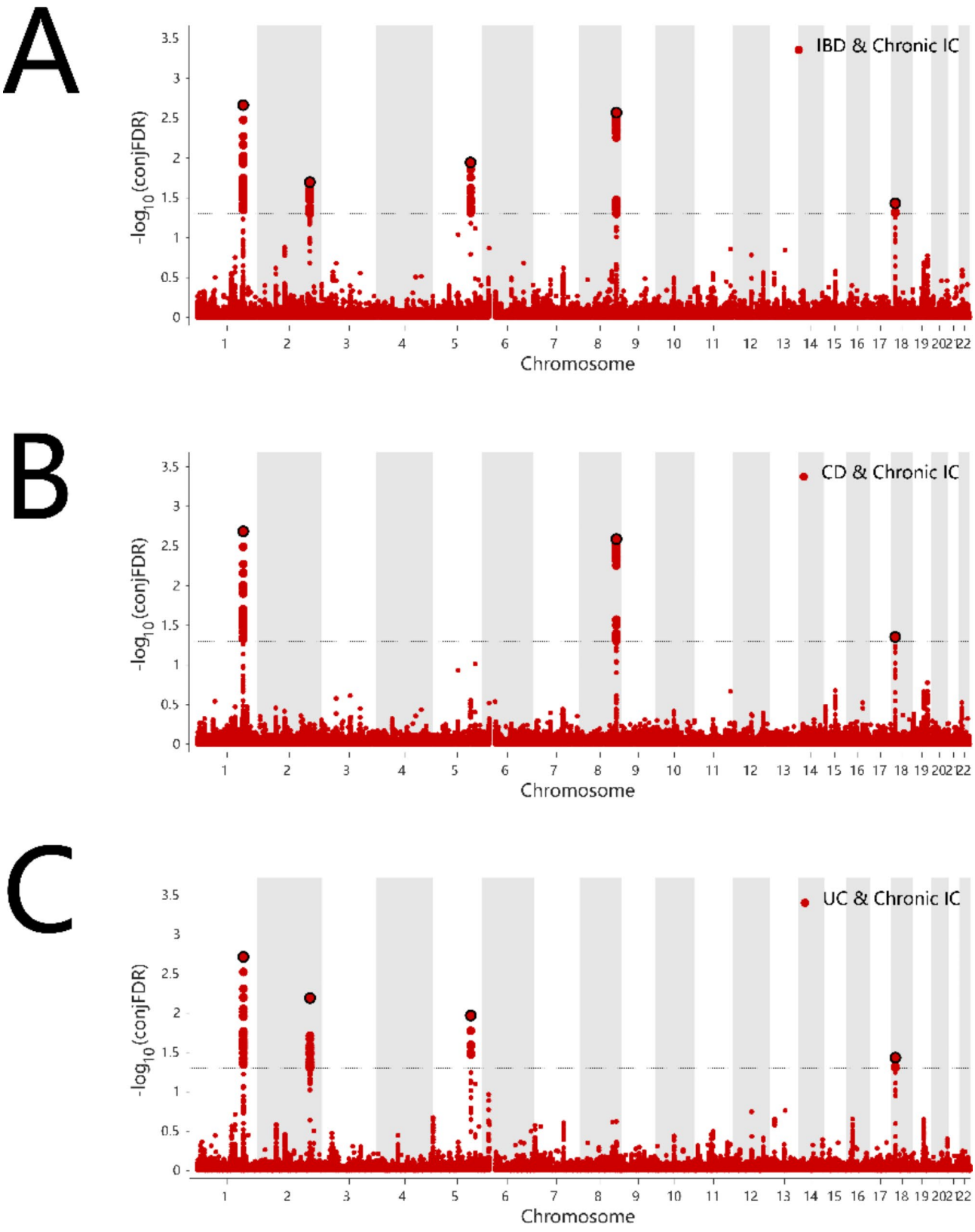

Fig. 10 (**A**) ConjFDR Manhattan plot of IBD and chronic IC. (**B**) ConjFDR Manhattan plot of CD and chronic IC. (**C**) ConjFDR Manhattan plot of UC and chronic IC. The shared risk loci between acute/subacute chronic IC and IBD, CD and UC were marked. The statistically significant causality is defined to be conjFDR < 0.05. IC, iridocyclitis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

was not significant, but corresponding studies have been conducted in IBD. It is a susceptibility gene for the intestine and has been utilized as a target for ameliorating intestinal inflammation and restoring intestinal mucosa [27–29]. ERAP1 is a set of enzyme proteins that are of crucial significance for protein digestion and plays a role in autoimmune and autoinflammatory diseases [30]. It is a high-risk gene in both diseases ($z>0$). Although ERAP1 was identified as a novel locus gene in a GWAS study on acute IC [31], and another extraction analysis confirmed it as an IC-related gene, it demonstrated a protective effect [32], contrary to our results. ERAP1 can serve as a risk gene for inflammation in the occurrence and development of IBD [33, 34], which is in accordance with our findings. However, research on RPL23AP12 and SNAPC4 in IBD and IC has not yet been conducted and requires further investigation.

The overall biological functions between IBD and IC are enriched in pathways such as T cell activation and leukocyte proliferation, which is an intriguing finding. T cell activation plays a vital role in the pathogenesis of IBD, promoting the occurrence and continuous development of inflammation [35]. Current studies demonstrate that antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, present microbial or environmental antigens in the intestine to T cells, resulting in their excessive activation and thereby driving intestinal inflammation [36]. T cell activation typically involves effector T cell subsets like Th1 and Th17, which, respectively, secrete pro-inflammatory cytokines such as IFN-γ and IL-17 to further recruit and activate neutrophils and macrophages, intensifying the local inflammatory response [37]. FN-γ and IL-17 can also stimulate the proliferation and recruitment of white blood cells (including neutrophils, monocytes, and lymphocytes), which are recruited to the intestinal inflammatory site. They further release reactive oxygen species, enzymes, and pro-inflammatory cytokines, resulting in damage to the intestinal epithelial barrier and the perpetuation of chronic inflammatory responses, aggravating the disease condition of IBD [35]. T cells, particularly CD4+T helper cells, play a crucial role in the development and progression of IC [38]. In patients with chronic IC, the persistent activation of T cells triggers sustained inflammation, preventing the ocular tissues from returning to normal immune homeostasis [39]. Activated T cells promote the proliferation of leukocytes and their infiltration into the anterior chamber, further exacerbating local inflammation and tissue damage [39]. Additionally, this process is accompanied by the release of large amounts of reactive oxygen species (ROS) and enzymes, which intensify the damage to uveal tissues, ultimately aggravating the severity of IC [40].

The "gut-retina" axis is currently a highly popular research topic concerning the relationship between intestinal diseases and ophthalmic diseases [41]. This axis is influenced by both the ocular and intestinal immune systems, playing a crucial role in the onset and progression of various eye diseases, such as uveitis (encompassing IC), conjunctivitis, and diabetic retinopathy [42]. Moreover, the "gut-retina" axis is recognized as a new frontier in ophthalmic basic and clinical research. Some studies have proposed hypothetical pathways contributing to the disruption of the gut microbiota-ocular surface-lacrimal gland axis [43]. Both IBD and IC, being immune-mediated diseases, interact with each other, thus contributing to the formation of this "gut-retina" axis. The genetic structural overlap between these conditions may serve as a potential basis for elucidating the underlying mechanisms of action.

This study faces several unavoidable limitations. Firstly, it is challenging to rule out the possibility of LD entirely. Despite employing methods such as LDSC, HESS, and conjFDR, which mitigate sample overlap, there remains a risk of exaggerated enrichment results due to potential overlap. Additionally, uncontrollable factors such as behavioral, social, and environmental influences may impact the findings. Moreover, the GWAS conducted in this study focused solely on individuals of European ancestry, potentially limiting the generalizability of our findings to other populations. The incidence of IC does indeed present gender differences. However, the GWAS data involved in this study did not distinguish between males and females, thus preventing the conduct of gender-specific analyses. We anticipate the availability of appropriate GWAS data in the future to enable corresponding research. Lastly, since this study is based on computational simulation methods utilizing publicly available GWAS data, it lacks validation from an independent cohort.

Conclusion

In conclusion, this study demonstrates an overlap in the genetic structure between IBD and IC. SNPs and genes linked to shared risk for both conditions across different scenarios have been identified, potentially offering targets for novel immunotherapies. Future research utilizing larger and more ethnically diverse GWAS samples is expected to further clarify the underlying genetic mechanism, ultimately benefiting the treatment of comorbidities associated with these two diseases.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
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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. IEU database: https://gwas.mrcieu.ac.ukFinnGen FinnGen database (https://r10.finngen.fi/) LDSC: https://github.com/bulik/ldsc conjFDR: https://github.com/precimed/pleiofdr FUMA: https://fuma.ctglab.nl.

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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