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# Shared genetic architecture between schizophrenia and gastrointestinal diseases: insights from large-scale genome-wide cross-trait analysis

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**Background:** Patients with schizophrenia (SCZ) frequently present with comorbid gastrointestinal diseases. However, the cross-disorder genetic correlations and shared mechanisms remain largely unknown. This study aims to elucidate the shared genetic architecture between SCZ and five types of gastrointestinal diseases: inflammatory bowel disease, Crohn's disease, ulcerative colitis, constipation, and irritable bowel syndrome. Furthermore, we seek to identify shared genetic risk loci, pinpoint potentially implicated tissues, and conduct in-depth analyses of the genetic mechanisms.

**Methods:** Using summary statistics from large-scale genome-wide association studies (GWAS), we conducted an in-depth analysis of the genetic correlations between schizophrenia (SCZ) and gastrointestinal diseases via linkage disequilibrium score regression (LDSC) and high-definition likelihood

(HDL) methods. Significant genetic correlations were observed between SCZ and gastrointestinal diseases. To further investigate the shared genetic basis, we performed cross-trait pleiotropy analyses to identify common pleiotropic loci and genes. Additionally, to uncover potential links between these complex traits, we conducted comprehensive functional annotation and tissue-specific enrichment analyses. Heritability enrichment analysis was employed to assess the contributions of key tissues. Finally, immune colocalization approaches were utilized to explore immune-mediated relationships between SCZ and gastrointestinal diseases.

**Results:** Our research highlighted shared genetic mechanisms between SCZ and five gastrointestinal diseases. A total of 2,367 novel SNPs were identified at a genome-wide significance level ( $P < 5 \times 10^{-8}$ ), and annotation revealed 96 pleiotropic genome-wide risk loci, among which 32 passed causal colocalization analysis. Shared loci were identified at regions 1q32.1, 2q33.1, 3p21.31, 10q21.2, 16p11.2, and 18q21.2. Further gene-level analyses identified pleiotropic genes including C1orf106, SLC26A6, FES, BSN, C3orf62 and CELSR3. Pathway analyses revealed critical roles of FOXP3 target genes, lymphocyte activation, T cell activation, and PDZ domain-related pathways in these diseases. Finally, phenotype-level immune colocalization analysis uncovered immunological mediators including PD-L1, CD3, T cells, and CD28 that bridge SCZ and gastrointestinal diseases.

**Conclusion:** Our findings support a shared genetic architecture between SCZ and gastrointestinal diseases and shed light on the potential mechanism that might involve in. These findings hold important implications for coordinated interventions targeting SCZ and its comorbid conditions.

**Keywords:** schizophrenia, GWAS, genetic correlation, gastrointestinal diseases, immune colocalization1.

## 1. Introduction

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Schizophrenia (SCZ) is a severe psychiatric disorder, typically characterized by hallucinations, delusions, and marked deficits in cognitive and behavioral functioning (1). Its pathogenesis is considered to involve intricate interactions among genetic predisposition, immune dysregulation, and neurotransmitter imbalance (2,3). In addition, SCZ is frequently comorbid with other psychiatric conditions (such as depression and anxiety) (4), cardiovascular diseases (5), dermatological disorders (6), and gastrointestinal diseases (7). **Among these, the incidence of gastrointestinal diseases remains consistently high in SCZ patients.** Epidemiological investigations have revealed a mechanistic link between SCZ and gastrointestinal diseases. Multiple reports demonstrate that patients with SCZ have a 1.64 times increased risk of developing inflammatory bowel disease (IBD) compared to the general population (8). Further analyses show that the risk of SCZ is elevated by 1.47 times in individuals with ulcerative colitis (UC) (9), and up to three times in those with Crohn's disease (CD) (10). Notably, this association has been corroborated in reverse-direction analyses. A multinational meta-analysis reported a constipation comorbidity rate of 21% among individuals with SCZ (11).

In recent years, the rapid advancement of genome-wide association study (GWAS) technology has led to the identification of an increasing number of genetic variants associated with SCZ and its related comorbidities. **However, existing studies have mainly focused on the pathological mechanisms of the brain-gut axis between SCZ and gastrointestinal diseases.** This axis interacts through neural, immune, and microecological pathways, forming an "gut-immune-brain" network (12). Inflammatory factors, intestinal barrier dysfunction, and abnormal gut microbiota metabolism collectively promote neuroinflammation and neurotransmitter disorders, thereby establishing a bidirectional pathogenic loop between psychiatric symptoms and gastrointestinal inflammation (13). For instance, SCFAs

affect the synthesis of dopamine (DA) by regulating tyrosine hydroxylase. In particular, acetate and propionate can cross the blood-brain barrier, act on the nigrostriatal pathway, influence DA synthesis, and exacerbate SCZ symptoms (14). These metabolites may modulate dopaminergic signaling and inflammatory processes through genetically related regulatory mechanisms, including G protein-coupled receptor signaling, epigenetic modifications, and FOXP3-mediated transcriptional activation (15,16). Nevertheless, these studies primarily emphasize mechanisms at the physiological and microbial levels, while the genetic basis underlying the shared susceptibility to SCZ and gastrointestinal diseases remains poorly understood.

To date, only Gong et al. have reported the shared genetic mechanisms between SCZ and gastrointestinal diseases. By integrating multiple complementary statistical genetic approaches, including LDSC, TWAS, H-MAGMA, and bidirectional Mendelian randomization, their study systematically explored the shared genetic etiology of the two disorders across variant, gene, and pathway levels (17). This highlights a clear gap in our understanding of the pleiotropic genetic mechanisms and potential associations between SCZ and gastrointestinal diseases. Therefore, it is crucial to investigate the shared genetic architecture of SCZ and gastrointestinal disorders, it not only helps uncover their complex pathogenic mechanisms but also may provide important genetic evidence for the development of novel therapeutic strategies.

This study adopted a multi-stage analytical strategy. Compared with recent related research in this field (18), we integrated large-scale GWAS datasets from European populations, and applied multiple advanced genetic approaches to systematically investigate the shared genetic architecture between SCZ and five common gastrointestinal diseases, including IBD and its subtypes UC and CD, as well as irritable bowel syndrome (IBS) and

constipation. First, linkage disequilibrium score regression (LDSC) (19) and high-definition likelihood (HDL) (20) were used to quantify the genetic correlations between SCZ and the five gastrointestinal traits. To further explore the biological mechanisms underlying these shared genetic signals, we applied methods including stratified LDSC (S-LDSC) (21), multi-marker analysis of genomic annotation (MAGMA) (22), and pleiotropy analysis under the composite null hypothesis (PLACO) (23) to dissect potential shared mechanisms at the levels of tissue enrichment, pathway enrichment, pleiotropic loci, and pleiotropic genes. In addition, by integrating immune-related multi-trait colocalization analysis, we identified possible immune regulatory mechanisms that may underlie the observed comorbidities. Collectively, these analyses are expected to complement and extend previous findings, offering novel insights into the genetic basis of SCZ and gastrointestinal diseases, and establishing a foundation for future studies in precision medicine. Our study workflow is illustrated in Figure 1.

## 2. Methods

### 2.1. GWAS Data

The summary statistics of genome-wide association studies (GWAS) utilized in this research were derived from large-scale GWAS or GWAS meta-analyses, with all datasets based on populations of European ancestry. IBD and its subtypes (UC, CD), as well as IBS, were mainly obtained from the publicly accessible IEU Open GWAS project (<https://gwas.mrcieu.ac.uk/>). For IBD, the dataset comprised 25,042 cases and 34,915 controls. Among its subtypes, the UC dataset included 12,366 cases and 33,609 controls, while the CD dataset contained 12,194 cases and 28,072 controls (24). Similarly, the IBS dataset consisted of 53,400 cases and 433,201 controls (25). The GWAS data related to constipation were retrieved from the FinnGen database (<https://www.finngen.fi/en>), which incorporated a total of 44,590 cases and 409,143 controls (26). For SCZ, the GWAS summary data

were sourced from the Psychiatric Genomics Consortium (PGC), encompassing 52,017 cases and 75,889 controls of European ancestry in total (27).

All studies adhered to a unified quality control protocol and used logistic regression to evaluate the association between SCZ and SNP genotypes, with genetic principal components included as covariates. The resulting risk estimates were combined using a fixed-effect inverse-variance weighted (IVW) meta-analysis. The sources and detailed descriptions of these datasets are provided in Supplementary File 1: Table S1.

## 2.2. Quality Control Standards

To ensure the accuracy and reliability of the genome-wide association study (GWAS) data, this study implemented strict quality control measures. First, single nucleotide polymorphisms (SNPs) located within the major histocompatibility complex (MHC) region (chromosome 6: 25–35 Mb) were excluded to avoid potential false-positive associations arising from the region's complex gene structure and extensive linkage disequilibrium. Second, only common variants with a minor allele frequency (MAF) greater than 0.01 were retained to enhance statistical power and reduce the likelihood of spurious associations. Furthermore, we removed all non-biallelic SNPs, SNPs with strand-ambiguous alleles (A/T or C/G), duplicate SNPs, indels and poorly imputed variants (INFO < 0.8), as well as those whose alleles did not match the Phase 3 reference panel of the 1000 Genomes Project. To minimize bias caused by missing genotype data, SNPs with a call rate below 95% were excluded. In addition, variants showing significant deviation from Hardy-Weinberg equilibrium (HWE,  $P < 1 \times 10^{-6}$ ) in control samples were also removed, as such deviations may indicate genotyping errors or population substructure.

## 2.3. Genetic correlation

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To evaluate the shared genetic architecture between SCZ and gastrointestinal diseases, we applied the LDSC method (19). The LD scores used in LDSC analysis were calculated based on common SNP genotypes from European-ancestry samples in the 1000 Genomes Project (28). Standard errors (SE) were estimated via leave-one-out validation in LDSC and further used to correct attenuation bias. Additionally, the LDSC intercept was utilized to assess potential population overlap across studies. Notably, the analyzed trait combinations did not exhibit significant population overlap, which enhanced the reliability of our findings. To further validate the results of LDSC analysis, we introduced the HDL method, which is a recent methodological extension of LDSC and is used to estimate genetic correlations after stratifying variants by MAF (29). Compared with the LDSC method, HDL has a stronger ability to process multi-dimensional phenotypic data and can integrate multiple data sources, such as genomic, transcriptomic, and epigenomic data, to provide more accurate results of genetic association analysis. Through validation by HDL, we ensured the credibility of the genome-wide analysis of genetic overlap. Finally, we employed the Bonferroni correction (significance threshold:  $P < 0.05/5 = 0.01$ ) to control for false positives. Only the correlations that remained significant after this correction were interpreted as robust evidence for shared genetic structures.

#### 2.4. Organ-level association analysis

To reveal the associations between SCZ and gastrointestinal diseases across different tissues and organs, we further analyzed the SNP heritability enrichment in tissues. We used the Stratified LD Score regression (S-LDSC) method to evaluate genetic enrichment in specific tissue (30). For this purpose, we downloaded datasets from the GTEx database for 54 human tissues (31), and evaluated the significance of SNP heritability enrichment in each tissue. We adopted the P-value corrected by FDR ( $PFDR < 0.05$ ) as the

criterion for determining the statistical significance of enrichment results. Meanwhile, for the purpose of exploratory analysis, we also reported the organizational results at the nominal significance level ( $P < 0.05$ ).

## 2.5. Gene-level Exploration and Analysis

To explore the shared mechanisms of the identified loci, we mapped nearby genes based on the lead SNPs at each locus. Furthermore, we utilized the MAGMA approach to perform gene-level association analysis on the GWAS data, aiming to characterize the biological functions of pleiotropic loci. Specifically, we performed MAGMA gene analysis, incorporating linkage disequilibrium (LD) between markers to identify pleiotropic genes and detect multi-marker effects ( $P_{fdr} < 0.05$ ) (32). We further conducted MAGMA gene-set analysis to investigate the potential biological functions of lead SNPs. In total, 10,678 gene sets from the Molecular Signatures Database (MSigDB) were tested, including curated gene sets (c2.all) and GO terms (c5.bp, c5.cc, and c5.mf) (33). To minimize the likelihood of false positives, all tested gene sets were evaluated using Bonferroni correction ( $P < 0.05 / 10,678 = 4.68 \times 10^{-6}$ ). We performed pathway enrichment analysis using the Metascape web platform (metascape.org) to annotate the functions of the mapped genes based on the MSigDB (34). Leveraging data from 54 human tissues provided by the GTEx project, we conducted genome-wide tissue-specific enrichment analysis for the pleiotropic loci identified through PLACO. Furthermore, we calculated the average expression levels (log<sub>2</sub>-transformed) of all identified pleiotropic genes across the 54 GTEx tissues, and tested tissue specificity by differentially expressed genes (DEGs) in each tissue (up- and down-regulated DEGs were precomputed by the signs of the t-statistics).

## 2.6. SNP-level Exploration and Analysis

In this study, we utilized GWAS summary statistics and applied the

pleiotropy analysis under the composite null hypothesis (PLACO) to systematically identify SNP-level genetic overlaps between SCZ and multiple gastrointestinal diseases. PLACO is a statistical framework specifically designed to detect genetic pleiotropy. Variants were ranked based on their squared Z statistics, and those with  $Z^2 > 80$  were excluded as potential outliers. To account for trait correlations, a Z-score correlation matrix was computed and combined across traits. The null hypothesis of no pleiotropy was tested using a level- $\alpha$  intersection-union test (IUT) framework, yielding the final pleiotropy P values. Genome-wide significant pleiotropic variants were defined as SNPs with  $P < 5 \times 10^{-8}$ . To avoid counting correlated variants within the same linkage disequilibrium (LD) block, LD pruning was performed using the European reference panel from the 1000 Genomes Project, with independent variants defined at  $r^2 < 0.1$  (23).

In addition, to further validate the biological significance of the pleiotropic SNPs, we employed the Functional Mapping and Annotation (FUMA) platform to localize these risk variants within the genome. We performed functional mapping using the FUMA-v1.6.5-web platform. SNPs in strong linkage disequilibrium ( $r^2 \geq 0.6$ ) within a 250 kb window were clustered to define genomic risk loci, and approximately independent lead SNPs were defined at  $r^2 < 0.1$ . Independent significant SNPs and their LD proxies were then annotated for functional consequences using ANNOVAR, CADD, RegulomeDB, and ChromHMM (35). Subsequently, to evaluate whether associated signals across phenotypes shared a causal variant, we conducted a Bayesian colocalization analysis. This analysis evaluated posterior probabilities for five hypotheses: H0, no association with either trait; H1, association with trait 1 only; H2, association with trait 2 only; H3, independent associations with each trait; and H4, a shared association signal for both traits. Colocalization was determined if the posterior probability for H4 (PP.H4) exceeded 0.70 (36).

## 2.7. Potential Exploration of Drug Targets in European Populations

This study employed summary data-based Mendelian randomization (SMR) analysis to identify potential drug targets for SCZ and related gastrointestinal diseases (37). The SMR method integrates GWAS summary statistics with eQTL data, leveraging pleiotropic mechanisms to detect causal relationships between gene expression and traits. When a SNP is significantly associated with both gene expression and the trait ( $P_{SMR} < 0.01$ ), it suggests a causal pleiotropic effect between the gene expression level and the target trait. To eliminate spurious signals caused by linkage disequilibrium (LD), we further applied the heterogeneity in dependent instruments (HEIDI) test. If  $P_{HEIDI} < 0.05$ , the association is considered potentially attributable to linkage effects and thus excluded from subsequent analyses. Finally, we combined the results of PLACO, FUMA, and MAGMA to screen for genes significantly associated with multiple traits. In summary, the combined analysis of SMR and HEIDI not only helps identify key pathogenic genes for SCZ and gastrointestinal diseases but also provides important clues for subsequent targeted therapy and precision medicine research.

## 2.8. Phenotypic-level Immune colocalization Analysis

Building upon a previously established hypothesis-prioritized multi-trait colocalization (HyPrColoc) framework (38), we incorporated an extensive collection of immune-related GWAS datasets covering 731 immune cell types to perform an integrated immune-trait colocalization analysis. This method accurately approximates the posterior probability of colocalization for a single variant by enumerating only a small number of putative causal associations (assuming that there is at most one causal variant per trait), avoiding repeated pairwise colocalization analyses, and identify co-localization signals between multiple traits efficiently and quickly. A regional posterior probability greater than 0.6 was considered indicative of

significant colocalization, suggesting that specific immune cell types may act as mediators in this process. These immune cell datasets are publicly accessible from the GWAS Catalog (GCST0001391 to GCST0002121, Supplementary File 1: Table S2)(39).

### 3. Results

#### 3.1. Genetic Correlations between SCZ and gastrointestinal diseases

First, we evaluated the genetic correlations between SCZ and five gastrointestinal diseases. The results obtained from LDSC and HDL were highly consistent (Table 1). Specifically, both LDSC and HDL analyses revealed significant genetic correlations ( $P < 0.05$ ) between SCZ and all five gastrointestinal diseases, including IBD, UC, CD, IBS, and constipation. Notably, even after applying the Bonferroni correction ( $P < 0.05/5$ ), the genetic correlations between SCZ and each of the five gastrointestinal diseases remained significant, further supporting the robustness of these associations (Supplementary File 1: Table S3).

#### 3.2. Organ association results

Based on the results of S-LDSC analysis, the SNP heritability of SCZ was significantly enriched in multiple brain tissues, including the Frontal Cortex, Cortex, Hippocampus, Cerebellum, and Cerebellar Hemisphere ( $PFDR < 0.05$ ). For the five types of gastrointestinal diseases, S-LDSC results showed that each disease exhibited nominally significant heritability enrichment in multiple tissues ( $P < 0.05$ ). Among them, IBD and its subtypes UC and CD were mainly enriched in immune-related tissues such as Whole Blood, Lung, and Spleen; IBS and Constipation were enriched in brain regions including the Cortex, Anterior Cingulate Cortex, Hippocampus, and Frontal Cortex (Figure 2). However, after FDR correction, none of the enrichment signals in these brain regions reached statistical significance (all  $PFDR > 0.05$ ) (Supplementary File 1: Table S4). After multiple comparison correction, no

tissue in the GTEx tissue dataset showed significant heritability enrichment in both SCZ and the five gastrointestinal diseases.

### 3.3. MAGMA Gene-Level Enrichment Analysis

MAGMA gene enrichment analysis performed using the FUMA tool identified 843 significantly enriched genes ( $P_{fdr} < 0.05$ ) that are associated with multiple gastrointestinal diseases and SCZ (Figure 3). Further analysis of these genes revealed their involvement in several critical biological pathways in SCZ and IBS, IBD, CD. These pathways include FOXP3 target genes, lymphocyte activation, T cell activation, and PDZ domain signaling (Figure 4A; Supplementary File 2). In addition, gene set analysis indicated that these genes are critically involved in the immune system, striatum/subpallium development, and the regulation of gene expression and metabolism. Further tissue-specific analysis showed that after Bonferroni correction ( $P_{bon} < 0.05$ ), these genes exhibited significant enrichment in brain tissues, which were mainly distributed in regions such as the Cerebellum, Frontal Cortex, and Cerebellar Hemisphere (Figure 4B; Supplementary File 2).

### 3.4. Results of SNP-level Pleiotropy Evaluation and Risk Loci Analysis

Given the shared genetic architecture between SCZ and gastrointestinal diseases identified through LDSC and HDL analyses, we applied a novel pleiotropy analysis method—PLACO—to identify potential pleiotropic loci associated with these six diseases. We identified 2,367 novel SNPs ( $P < 5 \times 10^{-8}$ ) related to SCZ and gastrointestinal diseases (Supplementary File 3). Based on the PLACO results, we annotated 96 pleiotropic genome-wide risk loci using the FUMA platform (Supplementary File 4: Table S1). Colocalization analysis ultimately revealed that among 96 loci, 32 exhibited strong evidence of colocalization ( $PP.H4 > 0.7$ ) (Supplementary File 4: Table S2). Specifically, the SCZ-IBD and SCZ-CD share the most pleiotropic loci, with 10 loci each; SCZ-IBS shares 8 loci, while SCZ-UC and

SCZ-Constipation share only 2 loci each. Notably, several pleiotropic regions were found to be shared across different trait pairs. For instance, pleiotropic regions 1q32.1, 2q33.1, 3p21.31, 10q21.2, 16p11.2, and 18q21.2 were identified in three trait pairs (Figure 5; Supplementary File 4: Table S3).

### 3.5. Drug Targets in European Populations

Using the SMR method, we initially identified 3,054 potential preliminary drug targets within complex genomic signals ( $p_{SMR} < 0.01$ ,  $p_{HEIDI} > 0.05$ ). To further refine these candidate targets, we integrated results from PLACO with those obtained from FUMA, MAGMA, and SMR analyses. We identified a set of genes significantly associated with multiple traits, genes such as BSN, C3orf62, CELSR3, IP6K2, NCKIPSD, NICN1, QARS, and SLC26A6 were shared across three trait pairs in different analyses. Notably, in the SCZ-IBD and SCZ-CD phenotypes, we identified C1orf106, FES and SLC26A6 as genes with significant potential as drug targets in this integrated analysis framework. (Figure 6; Supplementary File 4: Table S4). These genes exhibit significant genetic signals across multiple tissues. Additionally, eQTL and SMR analyses further support their pleiotropic roles and provide precise annotations for their chromosomal positions.

### 3.6. Results of Immuno-Colocalization

To clarify the role of the immune system in mediating the observed comorbidities, we employed the HyPrColoc method to identify immune cell types showing colocalization signals at pleiotropic loci. Multi-trait colocalization analysis via the HyPrColoc approach identified a total of 4 immune cell types with shared causal variants between SCZ and gastrointestinal diseases (posterior probability  $> 0.6$ ). These colocalization signals primarily involved immune regulatory traits such as PD-L1, CD3, T cells, and CD28. Among them, PD-L1, CD3, and T cells exhibited significant colocalization in both SCZ-CD and SCZ-IBD, suggesting that these immune

traits may jointly participate in the cross-disease regulation of neuroinflammation and intestinal inflammation. Additionally, CD28 showed a distinct colocalization signal in SCZ-IBD, further supporting the important role of the T cell activation and costimulatory pathways in the common mechanisms underlying the two types of diseases. Detailed results are available in Supplementary File 4: Table S5.

#### 4. Discussion

Given the complex relationship between SCZ and gastrointestinal diseases, this study employed comprehensive genetic approaches to investigate their underlying genetic correlation.

Through genetic correlation analysis, we observed significant genetic associations between SCZ and five gastrointestinal diseases: IBD, UC, CD, IBS, and constipation. We provided robust evidence supporting shared genetic mechanisms between SCZ and the gastrointestinal diseases included in this study. Additionally, results from HDL analysis suggest that individuals with SCZ may carry an elevated risk for developing gastrointestinal diseases, consistent with previous findings (40,41). Moreover, among 256 diagnosed and followed-up SCZ patients, 21 had received treatment for constipation or constipation-related therapeutic interventions (42). We believe that, aside from the effects of antipsychotic medications such as clozapine, olanzapine, and chlorpromazine, there is a genetic association between constipation and SCZ, which may be related to the comorbidity of these two conditions. We also observed a notable genetic predisposition from IBD toward SCZ, which was ambiguous in previous studies: a two-sample Mendelian randomization study supported a genetic predisposition linking SCZ and IBD; however, bidirectional MR analysis revealed no increased SCZ risk among IBD patients (43).

We identified a set of genetic risk loci associated with both

gastrointestinal diseases and SCZ, several of which were observed across multiple phenotype pairs, including 1q32.1, 2q33.1, 3p21.31, 10q21.2, 16p11.2, and 18q21.2. Prior studies have provided evidence supporting the pivotal roles of these loci in the pathogenesis of both gastrointestinal diseases and SCZ. For example, the 16p11.2 locus (MAPK3) has been demonstrated to be associated with the risk of SCZ (44), and this gene has also been identified as a susceptibility locus for UC (45). Additionally, the 16p11.2 locus has been implicated in developmental abnormalities of both the kidney and the intestine, with deletions at this locus potentially leading to intestinal dysfunction and contributing to constipation (46). EGR2 (10q21.2) is considered a key biomarker for SCZ (47), and functions as a crucial enzyme in the sterol biosynthesis pathway. Loss or inhibition of EGR2 results in the accumulation of sterol metabolic intermediates, triggering cellular stress responses that may subsequently influence inflammatory signaling by altering lipid raft structures or membrane fluidity (48). Furthermore, EGR2 may suppress inflammation by directly or indirectly downregulating IL-1 $\beta$  expression at the transcriptional level. Prior studies have shown that EGR2 is implicated in the development and progression of various gastrointestinal diseases, including IBD (49), UC (50), and CD (51). Recent studies have also emphasized the role of non-coding genetic variation □ rs796364 □ in SCZ risk. Research indicates that rs796364 disrupts the binding of transcription factors CTCF and RAD21, thereby modulating the expression of the distal gene TYW5. This regulatory mechanism affects neurodevelopment and dendritic spine- formation, ultimately contributing to increased susceptibility to SCZ (52). We recently searched the GWAS catalog for previously identified risk loci (53), and found that several reported loci are associated with both SCZ and gastrointestinal diseases, the finding that was also validated in our study. For instance, the 22q13.2 locus has been linked to IBS (54) and constipation (55). This locus, which contains the EP300 and CYP2D6 genes, is potentially involved in neural development,

neurotransmission, and immune function regulation (56).

To investigate whether shared susceptibility at the organ level drives the comorbidity SCZ and gastrointestinal diseases, we performed S-LDSC analysis. We found that SCZ was significantly enriched in multiple brain tissues, including the Frontal Cortex, Cortex, Hippocampus, Cerebellum, and Cerebellar Hemisphere ( $PFDR < 0.05$ ), while IBS and constipation showed nominally significant enrichment in some brain regions such as the Cortex and Hippocampus ( $P < 0.05$ ). However, results after multiple comparison correction indicated that no significant shared genetic enrichment was observed between SCZ and the five gastrointestinal diseases in any organ. Notably, further gene-level tissue enrichment analysis indicated that SCZ and the five studied gastrointestinal diseases were enriched in regions such as the Cerebellum, Frontal Cortex, and Cerebellar Hemisphere ( $P_{bon} < 0.05$ ). This may be attributed to the fact that the cerebellum, through its neural circuit connections with the prefrontal lobe and limbic system, is involved in higher cognitive functions and emotional regulation. Structural or functional abnormalities of the cerebellum are considered an important pathological basis for executive dysfunction, flattened affect, and thought disorders in SCZ patients (57). In addition, the cerebellum can indirectly affect gastrointestinal motility and the integrity of the intestinal barrier by regulating the activity of vagal nuclei and the function of the hypothalamic-pituitary-adrenal (HPA) axis (58). Neuroimaging studies have demonstrated a significant reduction in cerebellar hemisphere gray matter volume in patients with SCZ. The cerebellar hemisphere maintains bidirectional communication with the brainstem and vagal nuclei, allowing it to perceive visceral sensory signals originating from the gut (59,60). However, given the discrepancies between the results of S-LDSC analysis and gene-level tissue enrichment analysis, we speculate that these two approaches may reflect genetic regulatory characteristics at different levels.

Therefore, current evidence remains insufficient to support a definitive organ or tissue level genetic association between SCZ and gastrointestinal diseases, and further research is required to validate this.

FOXP3 target gene pathway, previously reported to be associated with SCZ, were also observed in our study to be linked to CD (61,62). FOXP3, as a key transcription factor for the differentiation and suppressive function of regulatory T cells (Treg), plays a core role in maintaining immune tolerance and inhibiting excessive inflammation (63). In CD, the reduced number and functional impairment of FOXP3<sup>+</sup>Treg cells lead to the disruption of mucosal immune homeostasis and the persistence of chronic inflammation (64). Similarly, decreased FOXP3 expression and impaired Treg function have also been observed in the peripheral blood of patients with SCZ. This finding suggests that the defect in their immunosuppressive function may result in the activation of systemic inflammation and the persistence of neuroinflammation (65). In addition, the enrichment of the T cell activation pathway further supports the existence of a common immune-mediated pathological basis between these two diseases. Aberrant activation of T cell receptor signaling and its downstream NF-κB and JAK-STAT pathways is considered to be involved in intestinal mucosal barrier damage and neuroinflammatory responses (66-68). Overactivated T cells can secrete large amounts of proinflammatory cytokines (e.g., IL-6, IL-17, IFN-γ), and these cytokines can promote the production of kynurenone, a tryptophan metabolite. As an endogenous N-methyl-D-aspartate (NMDA) receptor antagonist, kynurenone can inhibit glutamatergic neurotransmission, and this process may be involved in the occurrence and development of SCZ (69).

In addition, previous studies have linked PDZ domain protein signaling pathways to gastrointestinal diseases (70), and our research suggests a potential association with SCZ. This finding indicates that this pathway may be involved in immune imbalance mechanisms related to the gut-brain axis.

Meanwhile, through a rigorous triple-screening strategy incorporating FUMA, MAGMA, and SMR analyses, we identified several potential drug targets, including C1orf106, FES, and SLC26A6, which exhibit significant therapeutic potential in the SCZ-IBD and SCZ-CD phenotypes. Previous studies have associated C1orf106 with IBD (71), and our research confirms this association. C1orf106 maintains the barrier function by promoting the stability of adherens junctions via regulation of the ubiquitination and degradation of cytohesin-1, a regulator of protein trafficking. Previous studies have attempted to identify compounds through small molecule screening that can stabilize C1ORF106 protein, with the aim of restoring intestinal barrier function in IBD patients (72). In addition, due to the critical role of SLC26A6 in intestinal fluid absorption and oxalate clearance, selective isoxazolopyrimidine inhibitors targeting the intestinal anion exchanger SLC26A6 (PAT1) are considered novel candidate drugs for the treatment of intestinal disorders (73). In addition, KIF21B exhibits a correlation in SCZ-UC, KIF21B has been reported to be associated with multiple sclerosis (74), hepatocellular carcinoma (75), and IBD (76). Although direct evidence linking KIF21B to SCZ is currently lacking, functional abnormalities of KIF21B have been observed to interfere with intracellular transport mechanisms in neurons, potentially contributing to neurodevelopmental impairments (77).

Immunological colocalization analysis revealed significant enrichment of PD-L1, CD3, CD28, and T cells in SCZ-UC and SCZ-IBD. In patients with SCZ, the central nervous system exhibits microglial activation accompanied by increased levels of proinflammatory cytokines. PD-L1 can bind to PD-1 receptors on T cells, activating SHP-1/2 phosphatases to inhibit TCR signaling, thereby reducing pro-inflammatory cytokine release and alleviating neuroinflammation (78). In IBD patients, reduced PD-L1 expression in gut mucosal tissues impairs the PD-1/PD-L1 pathway, disabling

the negative regulatory mechanism that restrains effector T cell overactivation and increasing pro-inflammatory cytokine release, leading to chronic intestinal inflammation (79). These findings collectively suggest that PD-L1 plays a pivotal role in the pathogenesis of both SCZ and gastrointestinal diseases. Moreover, abnormal activation of CD3 in SCZ patients with comorbid UC points to a critical mechanism of neuro-gut immune interaction. This may involve amplification of inflammatory cytokine cascades via the JAK-STAT signaling pathway, which in turn promotes the migration of peripheral immune cells into the central nervous system and aggravates intestinal barrier dysfunction (80).

This study has several limitations. First, similar to many previous studies, our analyses were based on summary-level rather than individual-level genetic data. This limits our ability to conduct more detailed population stratification analyses (e.g., by sex, age, or other demographic factors). Although all samples were derived from a relatively homogeneous population, subtle cryptic relatedness or ancestry differences cannot be entirely excluded and may have introduced minor confounding effects in the association estimates. Future studies should use stratified data to explore genetic heterogeneity among population subgroups. Second, although the combined use of LDSC and HDL provides a robust framework for assessing genome-wide genetic correlations, certain limitations remain when applied to highly polygenic and complex traits. Both methods rely on the assumption of a linear relationship between linkage disequilibrium (LD) and association statistics, which may not fully capture nonlinear or environment-dependent effects. Moreover, the genetic correlations estimated by LDSC and HDL reflect genome-wide averages of shared variation rather than localized or pathway-specific effects. Third, the sample size for immune cell GWAS was relatively small, which may affect the robustness of immune cell-related findings; thus, these results should be interpreted with caution. Lastly, the

study population consisted exclusively of individuals of European ancestry, and therefore, the conclusions may not be directly generalizable to other populations with different ethnic or genetic backgrounds.

## 5. Conclusion

This study provides systematic genetic evidence supporting a shared etiological basis between SCZ and gastrointestinal disorders. Through integrated cross-trait GWAS analyses, we identified significant genetic correlations, common pleiotropic loci, and immune-related pathways that underpin this comorbidity. Immune colocalization further suggested that PD-L1, CD3, CD28, and T cells may serve as key mediators linking neuroinflammatory and intestinal inflammatory processes. These findings deepen current understanding of the “gut-immune-brain” connection and offer a foundation for future mechanistic and therapeutic research.

## 6. Ethics statement.

Not applicable.

## 7. Author contributions

Y.D, Q.L: designed the study and wrote the paper; P.S, Z.X, C.D: conducted data analysis. L.Z, J. W provided necessary manuscript review and language correction. All authors have read and approved the final manuscript.

## 8. Acknowledgments

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## 9. Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a

potential conflict of interest.

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### Figure legend

Figure 1. The Flowchart of Our Study. In this study, we assessed genetic correlations using LDSC and HDL methods. Additionally, we employed S-LDSC to evaluate the heritability enrichment across tissues. Then used PLACO to identify significant pleiotropic SNPs, which were subsequently

annotated using the FUMA platform. MAGMA was applied for comprehensive genome-wide tissue-specific enrichment and pathway analyses, while SMR was utilized to explore potential gene loci and drug targets. Finally, we conducted immune colocalization using HyPrColoc to investigate immune cell types involved in shared disease risks. SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; IBS, Irritable bowel syndrome. LDSC, linkage disequilibrium score regression; HDL, High-Definition Likelihood; S-LDSC, stratified LDSC; PLACO, pleiotropy analysis under composite null hypothesis; FUMA, functional mapping and annotation; MAGMA, Multi-marker Analysis of Genomic Annotation; SMR, summary-data-based Mendelian randomization; HyPrColoc, Hypothesis Prioritisation in multi-trait Colocalization

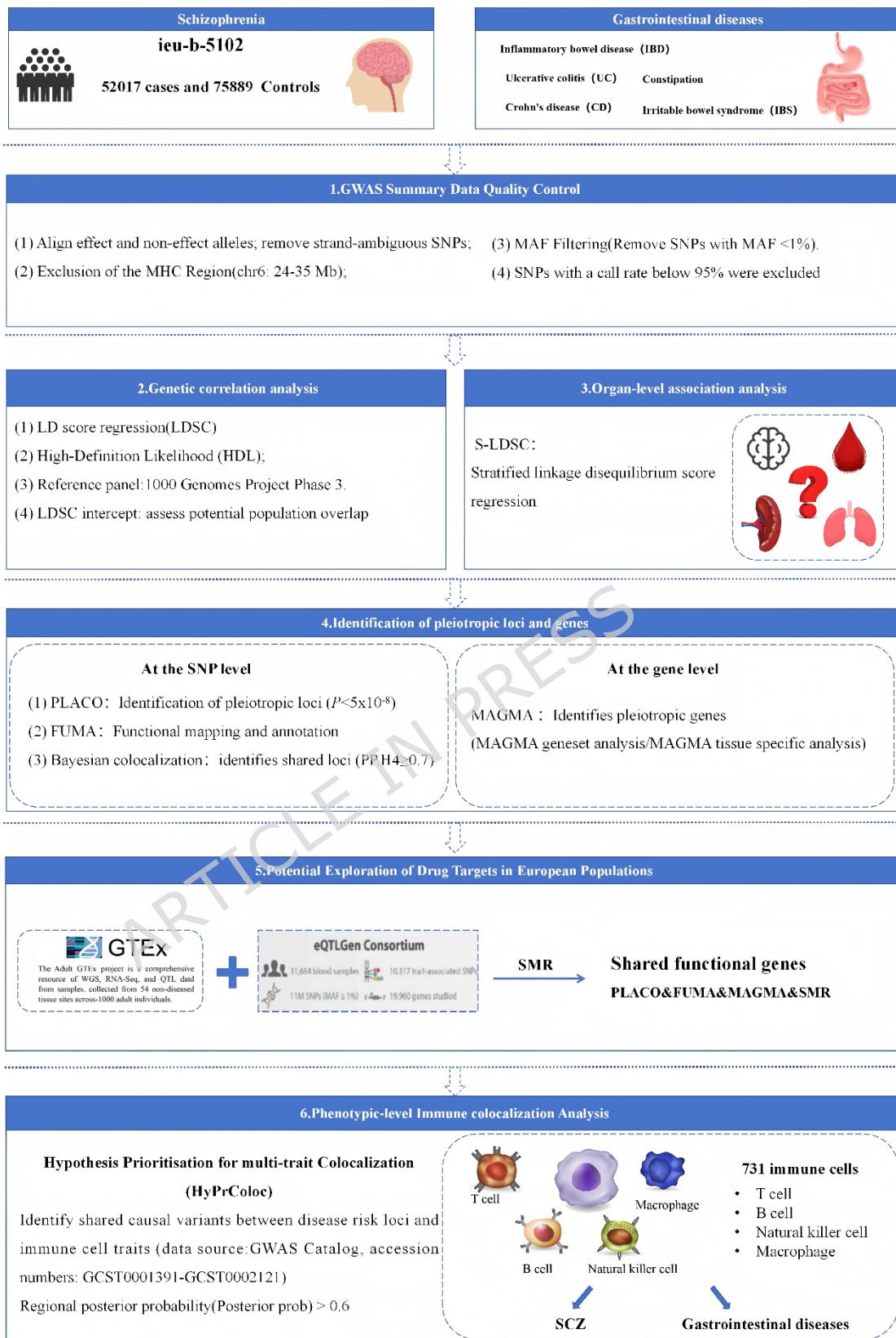


Figure 2. Results of genetic enrichment of traits in different tissues based on S-LDSC. Darker colors correspond to smaller P-values, which are sequentially categorized into five intervals:  $\leq 0.001$ ,  $(0.001, 0.01]$ ,  $(0.01,$

0.05], (0.05, 0.1], and >0.1. Blank and gray regions indicate no significant heritability enrichment was detected. SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; IBS, Irritable bowel syndrome.

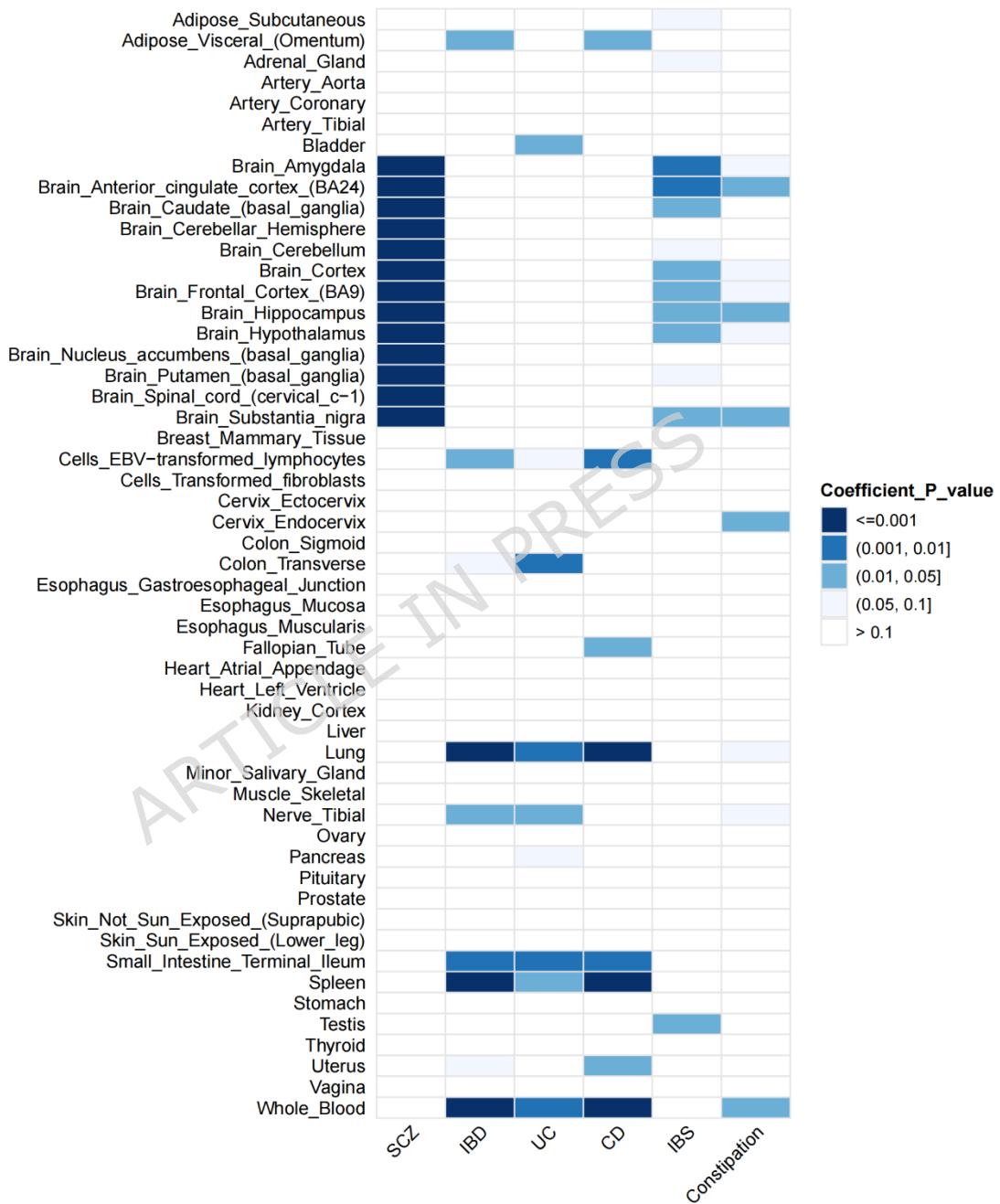


Figure 3. Analysis results of magma gene enrichment. SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease;

IBS, Irritable bowel syndrome. The red line indicates the correction threshold.

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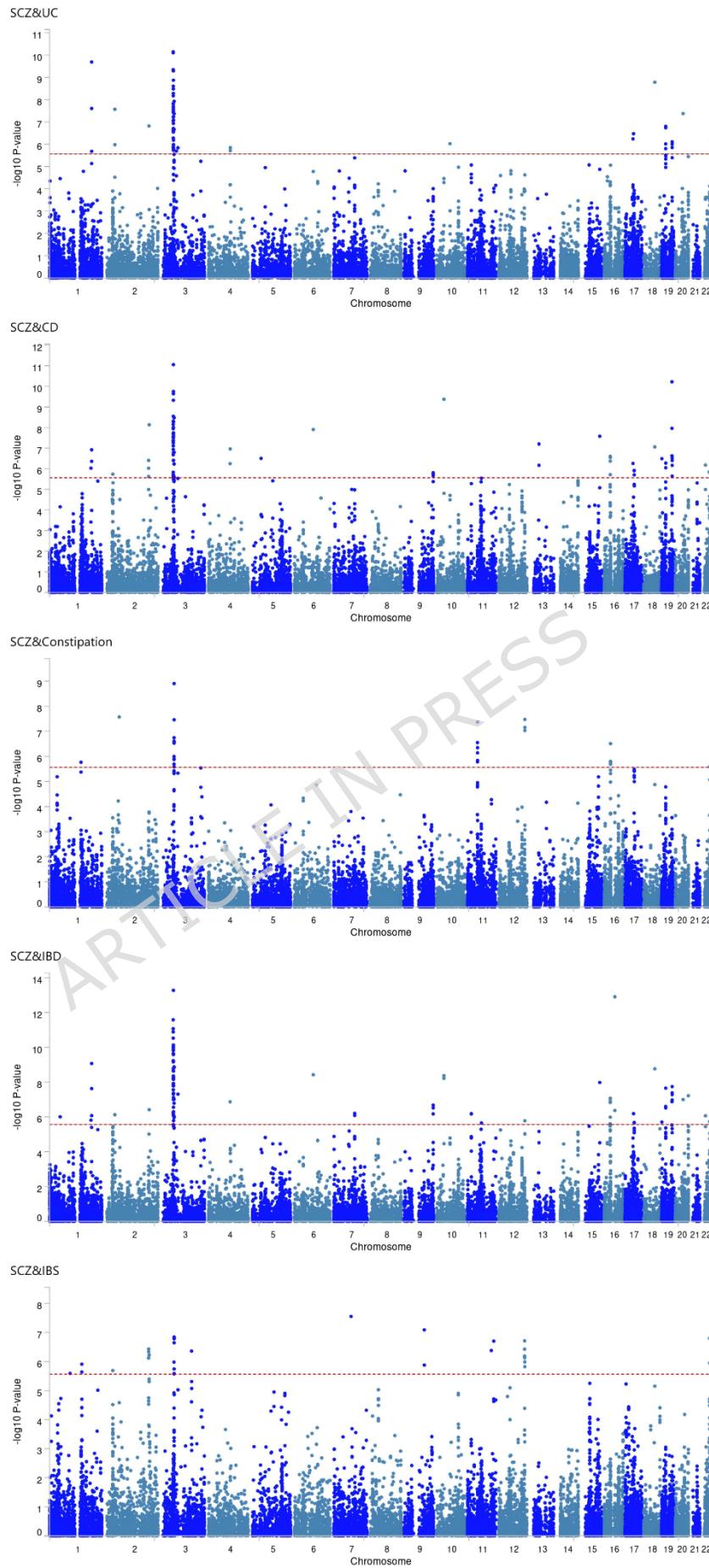


Figure 4. Bar plot of MAGMA gene-set (A) and tissue-specific (B) analysis for genome-wide pleiotropic results. **The red dotted line indicates a significance threshold of 0.05 after multiple corrections, while the blue line represents a threshold of 0.05.** SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; IBS, Irritable bowel syndrome.

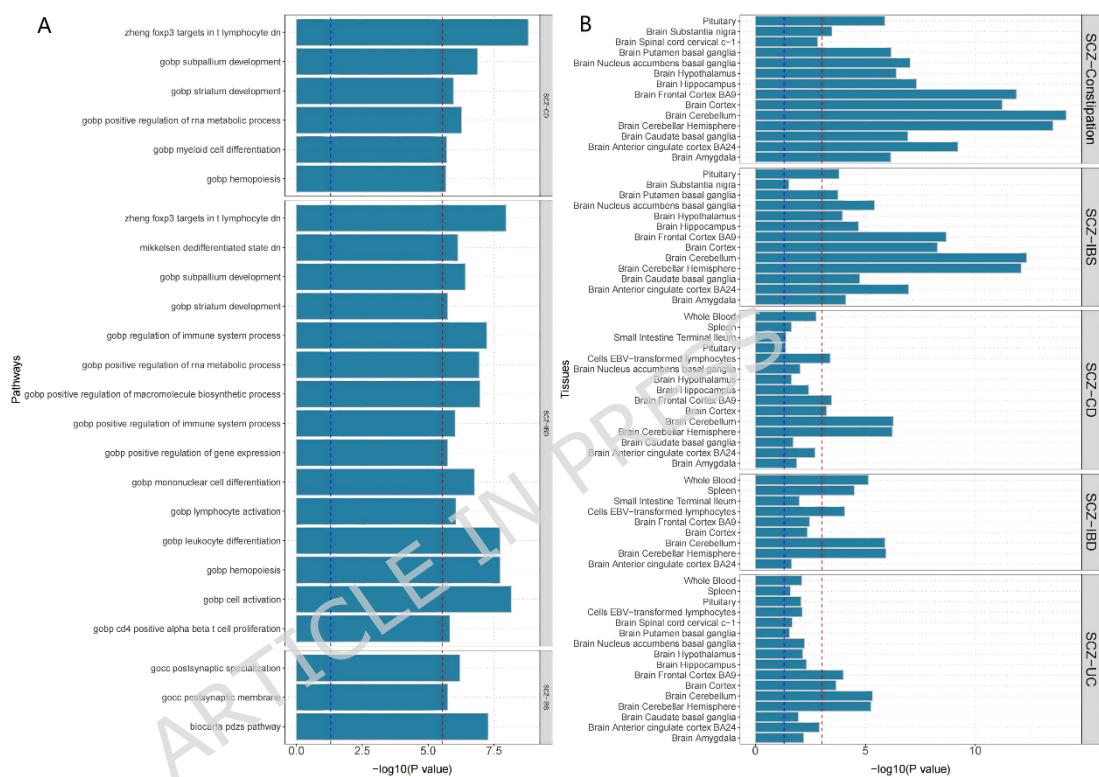


Figure 5: The circular diagram presents pleiotropic loci among different trait pairs. **Red represents association with at least three trait pairs.** SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; IBS, Irritable bowel syndrome.

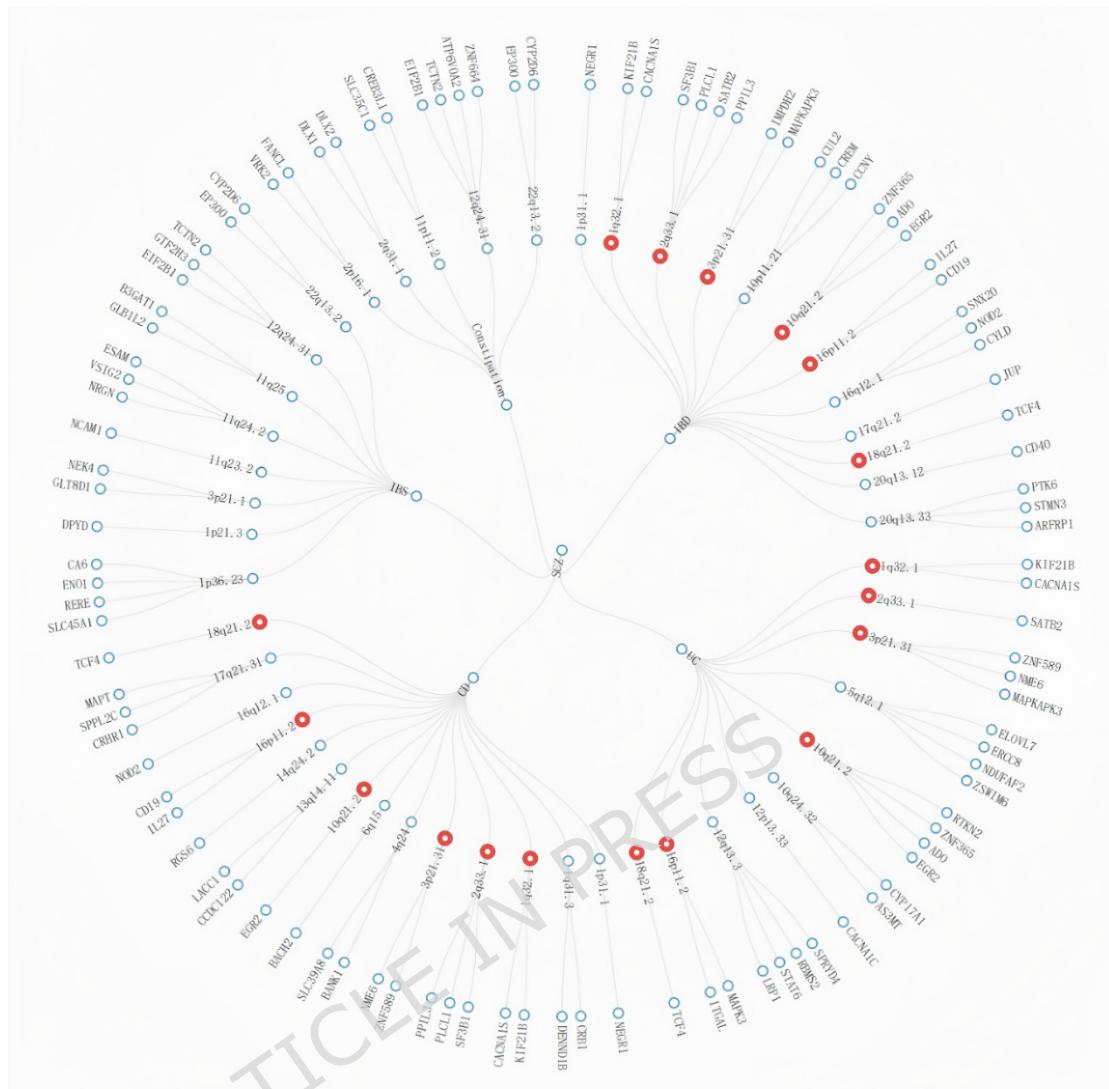


Figure 6: Heatmap of pleiotropic genes as potential drug targets across multiple analytical methods. The columns represent the genes that were selected, and the rows represent the different analytical methods used. The color intensity of each gene reflects the number of trait pairs in which the gene was repeatedly identified by the respective method: darker colors indicate that the gene was detected in more trait pairs, suggesting its potential association with multiple traits.

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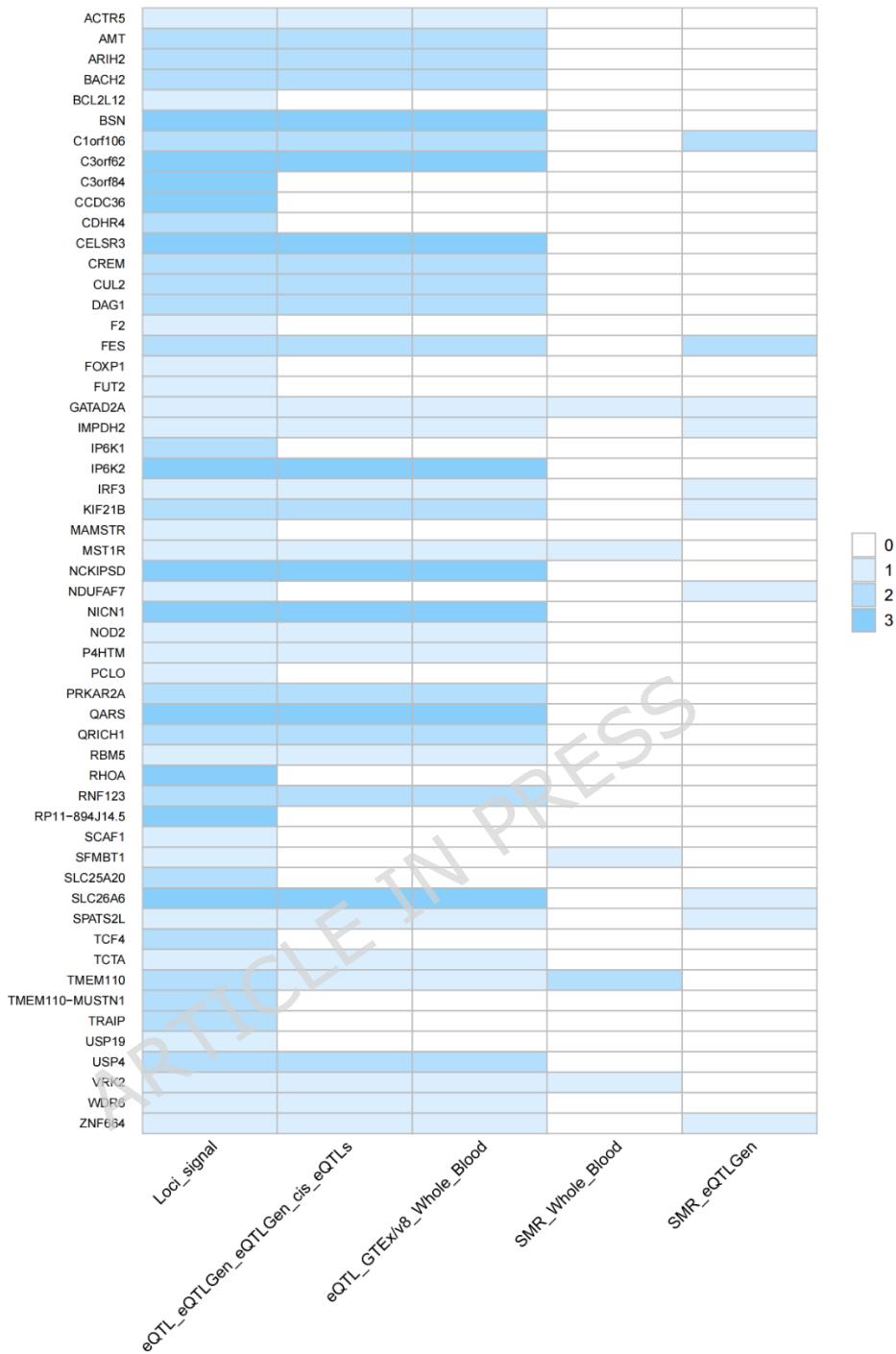
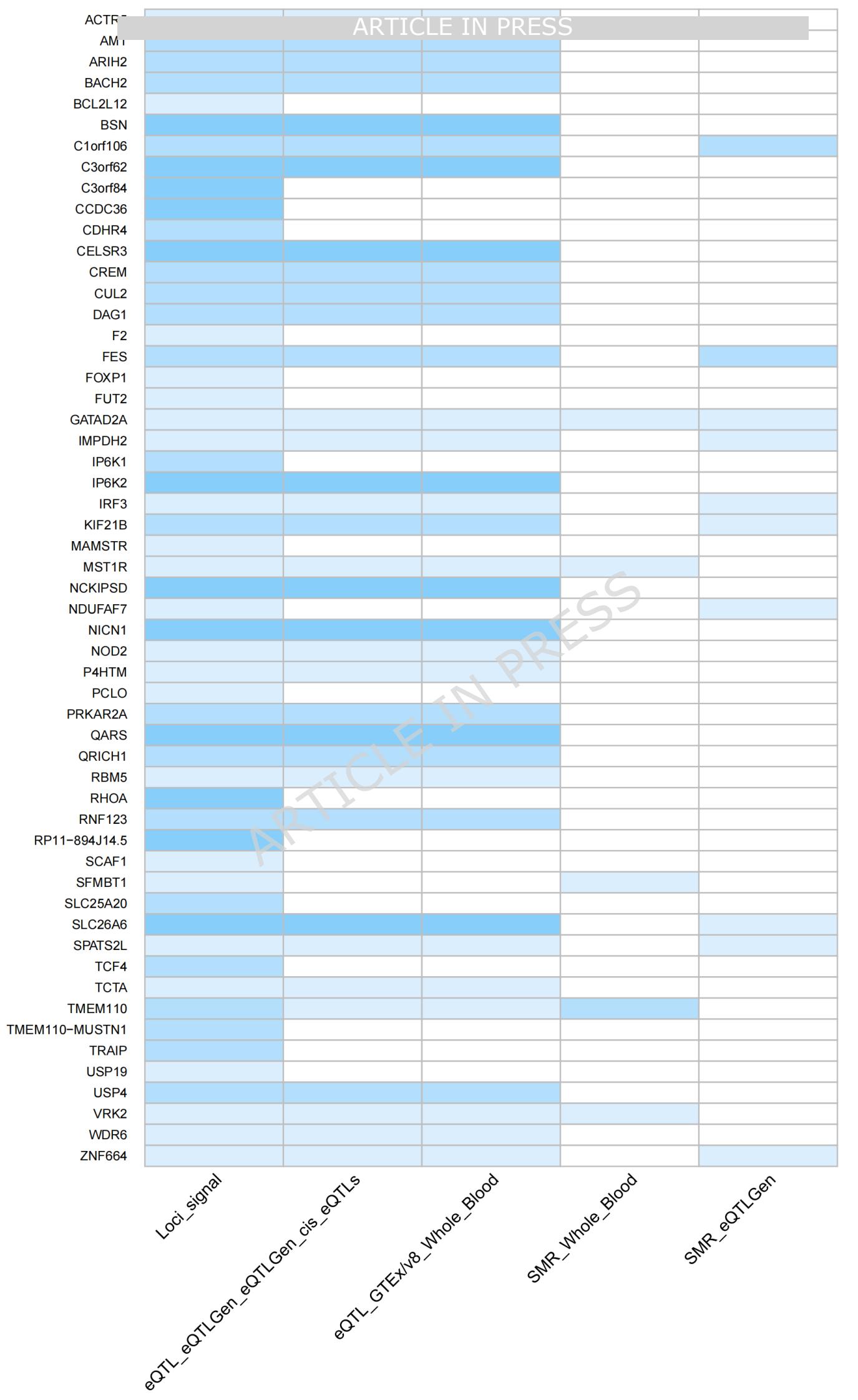


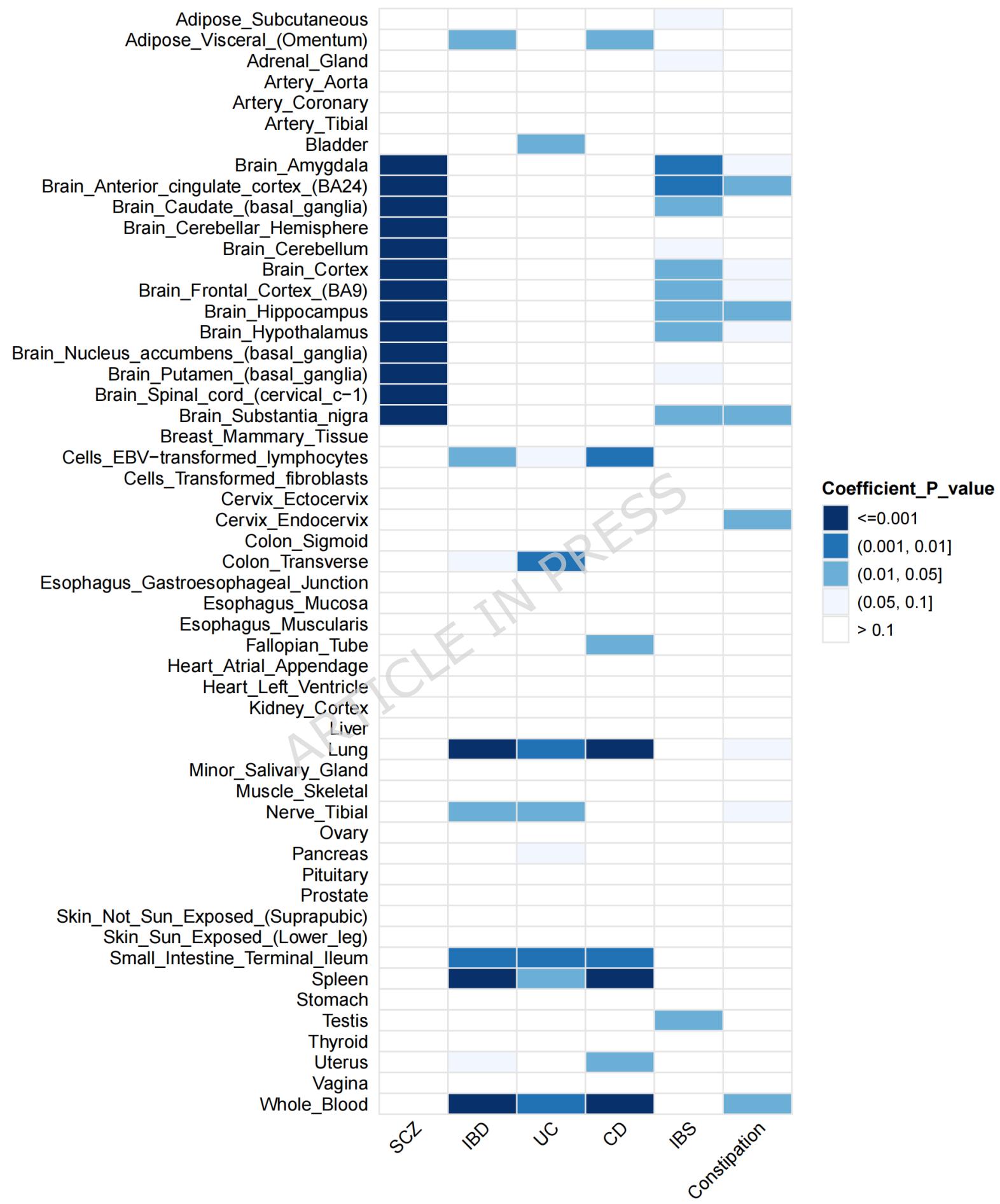
Table 1: Genetic Correlation Results for Trait Pairs Based on LDSC and GNOVA. SCZ, Schizophrenia; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; IBS, Irritable bowel syndrome.

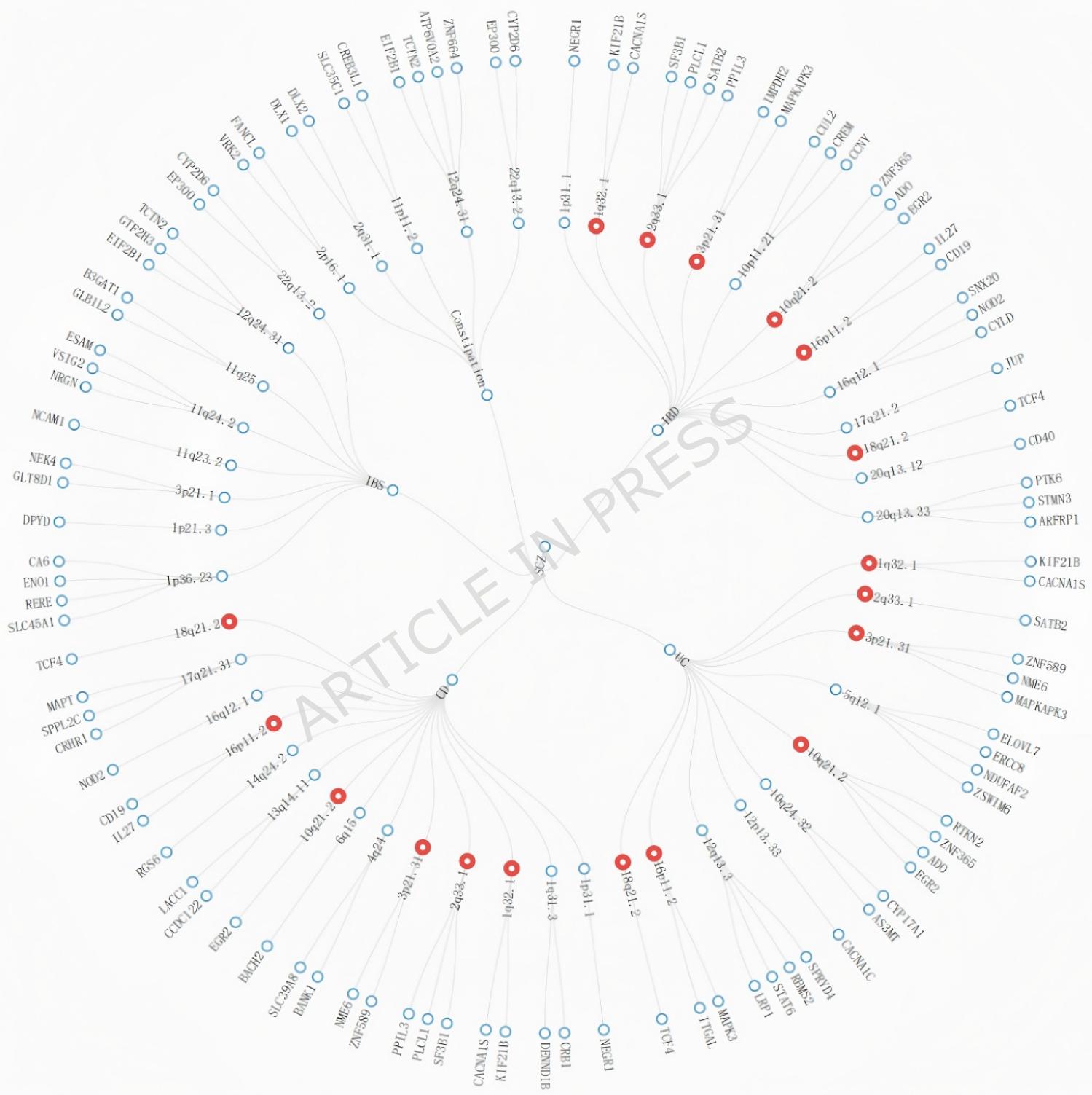
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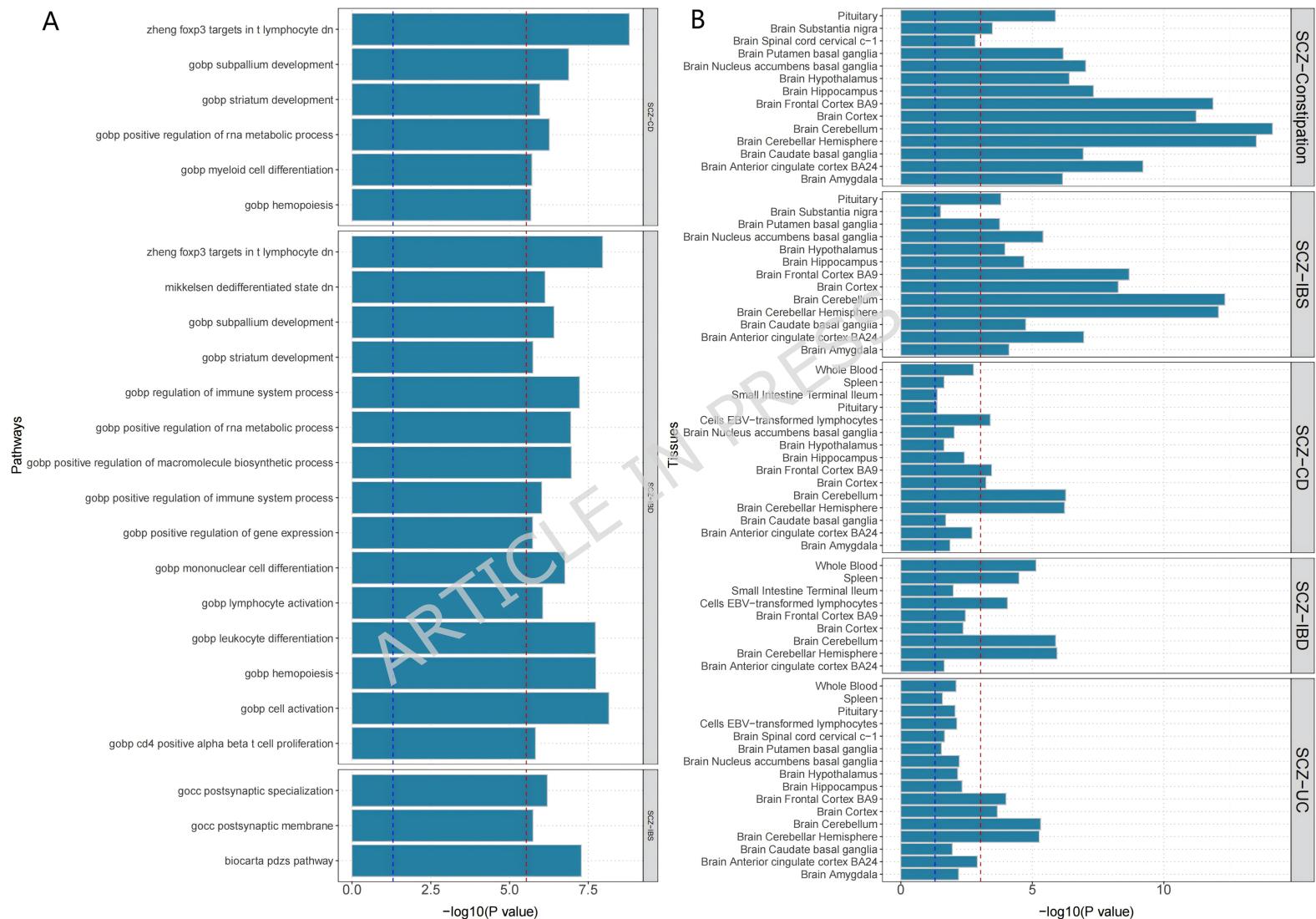
	<b>LDSC</b>		<b>HDL</b>	
<b>Trait pairs</b>	<b>r<sub>g</sub>(SE)</b>	<b>P</b>	<b>r<sub>g</sub>(SE)</b>	<b>P</b>
SCZ & IBD	0.1477 ±0.0250	3.6054e-09	0.1217(0.022)	4.22e-08
SCZ & UC	0.1545 ±0.0273	1.4359e-08	0.1321(0.0208)	2.05e-10
SCZ & CD	0.1227 ±0.0258	2.0678e-06	0.1067(0.0249)	1.89e-05
SCZ & IBS	0.1793 ±0.0286	3.679e-10	0.1891(0.0253)	8.01e-14
SCZ & Constipation	0.2405 ±0.0356	1.4284e-11	0.2879(0.0397)	4.18e-13

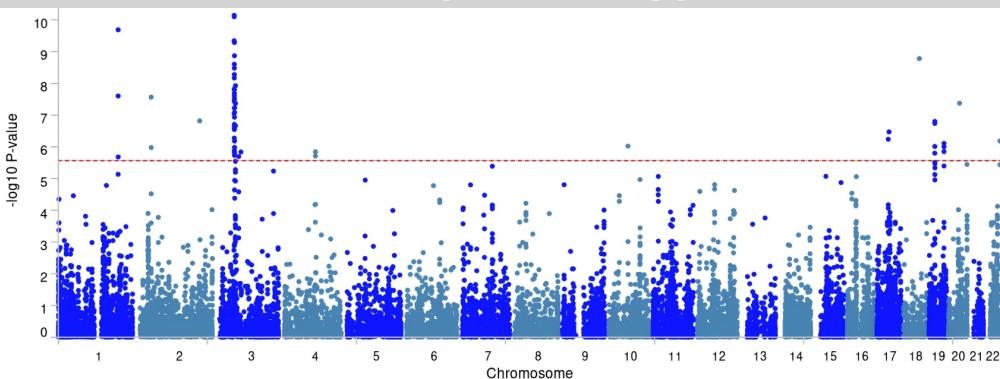
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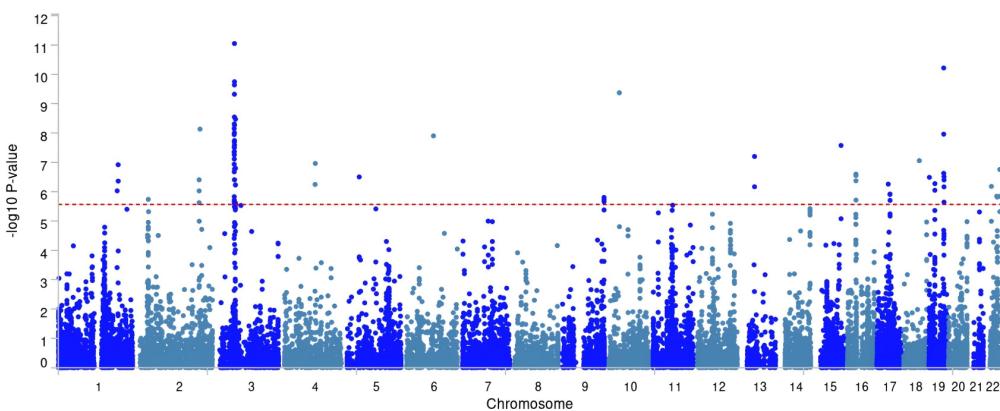




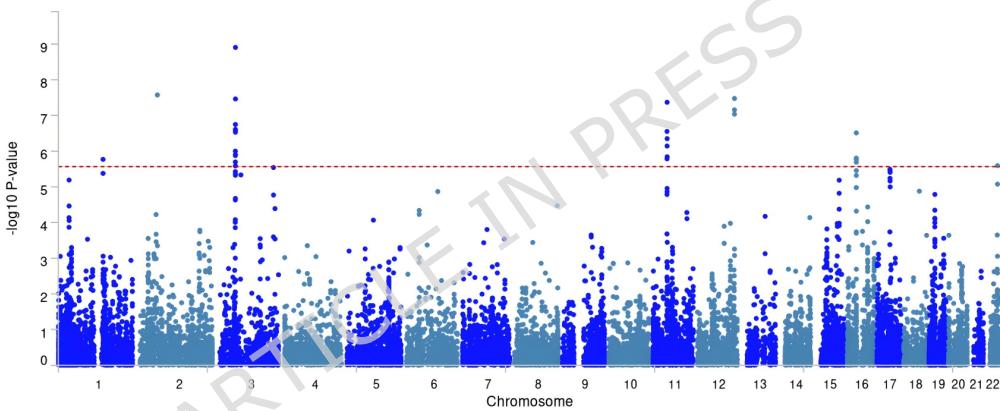




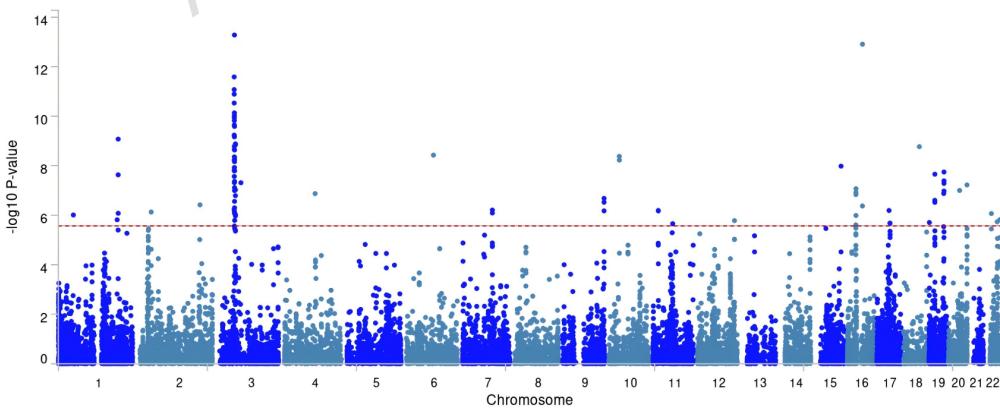
SCZ&amp;CD



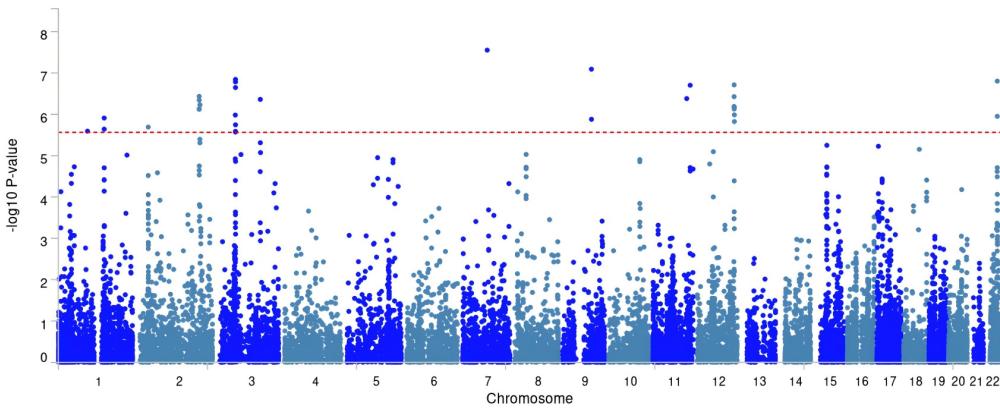
SCZ&amp;Constipation



SCZ&amp;IBD



SCZ&amp;IBS





ieu-b-5102

52017 cases and 75889 Controls



Inflammatory bowel disease (IBD)

Ulcerative colitis (UC) Constipation

Crohn's disease (CD) Irritable bowel syndrome (IBS)



### 1.GWAS Summary Data Quality Control

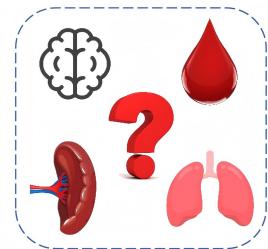
- (1) Align effect and non-effect alleles; remove strand-ambiguous SNPs;  
 (3) MAF Filtering(Remove SNPs with MAF <1%).  
 (2) Exclusion of the MHC Region(chr6: 24-35 Mb);  
 (4) SNPs with a call rate below 95% were excluded

### 2.Genetic correlation analysis

- (1) LD score regression(LDSC)  
 (2) High-Definition Likelihood (HDL);  
 (3) Reference panel:1000 Genomes Project Phase 3.  
 (4) LDSC intercept: assess potential population overlap

### 3.Organ-level association analysis

S-LDSC:  
 Stratified linkage disequilibrium score regression



### 4.Identification of pleiotropic loci and genes

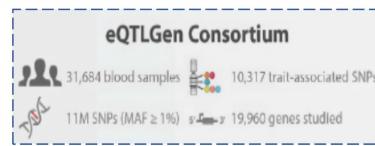
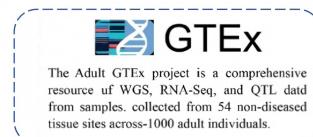
#### At the SNP level

- (1) PLACO: Identification of pleiotropic loci ( $P < 5 \times 10^{-8}$ )  
 (2) FUMA: Functional mapping and annotation  
 (3) Bayesian colocalization: identifies shared loci ( $PP.H4 \geq 0.7$ )

#### At the gene level

MAGMA : Identifies pleiotropic genes  
 (MAGMA geneset analysis/MAGMA tissue specific analysis)

### 5.Potential Exploration of Drug Targets in European Populations



SMR

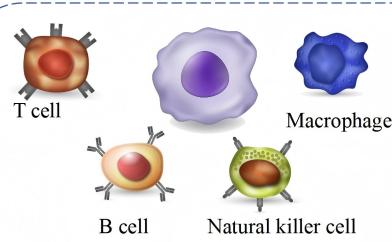
**Shared functional genes**  
**PLACO&FUMA&MAGMA&SMR**

### 6.Phenotypic-level Immune colocalization Analysis

#### Hypothesis Prioritisation for multi-trait Colocalization (HyPrColoc)

Identify shared causal variants between disease risk loci and immune cell traits (data source: GWAS Catalog, accession numbers: GCST0001391-GCST0002121)

Regional posterior probability(Posterior prob) > 0.6



**731 immune cells**

- T cell
- B cell
- Natural killer cell
- Macrophage

SCZ

Gastrointestinal diseases