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ORIGINAL RESEARCH

Cross-Trait Genome-Wide Association Study Identifies Shared Genetic Risk Loci Between COPD and Five Autoimmune Diseases

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Background: Chronic obstructive pulmonary disease (COPD) frequently co-occurs with autoimmune diseases (ADs), yet their shared genetic basis remains incompletely understood. This study aimed to evaluate genetic correlations between COPD and seven ADs and identify shared genetic risk loci underlying this comorbidity.

Methods: We integrated summary statistics from large-scale genome-wide association studies (GWAS) of COPD and seven ADs in European populations. Genetic correlations were assessed using linkage disequilibrium score regression (LDSC) and high-definition likelihood (HDL). Pleiotropic loci were identified via the Pleiotropic Analysis under Composite Null Hypothesis (PLACO) and annotated through the FUMA platform. Multidimensional enrichment analyses were conducted using MAGMA and Metascape, and complementary evidence for the identification of pleiotropic genes was provided by summary-based Mendelian randomization (SMR) and transcriptome-wide association studies (TWAS).

Results: Significant genetic correlations were observed between COPD and five of the seven ADs analyzed. Joint analyses identified 57 shared risk loci, including 17q12 and 16p11.2, with 22 loci supported by colocalization evidence. MAGMA identified 162 pleiotropic genes, such as ORMDL3, GSDMB, and MAPK3. Pathway analyses demonstrated enrichment in immune-related processes, particularly T cell activation and regulation of immune responses. SMR and TWAS further implicated ORMDL3, PGAP3, MAPK3, and GMPPB as putative contributors to shared disease susceptibility. However, additional experimental validation is warranted to substantiate these associations.

Conclusion: This study highlights shared genetic loci and immune pathways linking COPD and ADs in European ancestry populations. Findings lay the groundwork for future research but require functional validation and replication in diverse cohorts to establish causality.

Keywords: chronic obstructive pulmonary disease, autoimmune diseases, PLACO, FUMA, MAGMA

Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of global disease burden, is characterized by persistent airflow limitation and chronic airway inflammation.[1–3] Although traditionally attributed to environmental exposures such as cigarette smoking, mounting evidence implicates immune dysregulation in COPD pathogenesis.[4] In particular, hyperactivated neutrophils and macrophages disrupt the protease–antiprotease balance and increase oxidative stress, creating a sustained inflammatory microenvironment that exacerbates local tissue damage and may trigger systemic immune abnormalities.[4] Moreover, transcriptomic analyses reveal upregulated B-cell–related gene expression and elevated autoantibody levels in COPD patients, indicating immunopathological overlap with autoimmune diseases (ADs).[5–7]

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Furthermore, epidemiological studies show that individuals with ADs—such as rheumatoid arthritis (RA),[8] systemic lupus erythematosus (SLE),[9] multiple sclerosis (MS),[10] and Crohn's disease (CD)—have a 1.3–1.7-fold higher risk of developing COPD.[11] Conversely, COPD patients exhibit increased rates of CD and ulcerative colitis (UC), suggesting a bidirectional association.[12] These findings underscore the need to investigate the underlying genetic and immunological mechanisms.Building on these observations, numerous studies have demonstrated convergence between COPD and ADs at genetic, immunological, and inflammatory levels (Figure 1). Notably, key immune-regulatory genes—including HLA-DRB1, PTPN22, and IL6 promoter polymorphisms—confer susceptibility to both conditions, implying a shared genetic basis.[13–17] These variants impair T and B-cell tolerance to self-antigens, precipitating immune imbalance.[18,19] In COPD, chronic inflammation persistently activates dendritic cells and Th1/Th17 subsets, which release proinflammatory mediators such as IL-1β, IL-6, and IL-17.[20,21] This "inflammatory spillover" further aggravates systemic immune dysregulation.[22] Additionally, the formation of inducible bronchus-associated lymphoid tissue (iBALT) sustains local autoantibody production against pulmonary matrix components, amplifying both local and systemic immune responses.[23] Epithelial barrier dysfunction, chronic smoking, and recurrent infections serve as additional insults that, together with genetic predisposition, constitute a two-hit model of disease pathogenesis.[24] Consequently, COPD exhibits features of autoimmunity alongside chronic airway pathology, and individuals with ADs—due to shared genetic and immune predispositions—are prone to chronic pulmonary inflammation.[23] However, most current evidence remains observational or limited to regional genomic analyses, highlighting the need for comprehensive, genome-wide pleiotropy studies.To date, no large-scale genome-wide studies have comprehensively evaluated the extent of pleiotropy between COPD and multiple ADs or applied advanced cross-trait approaches.This knowledge gap limits understanding of the molecular architecture underpinning COPD–autoimmunity comorbidity and constrains opportunities for therapeutic innovation.

Therefore, the primary aim of this study was to systematically characterize shared genetic risk factors between COPD and ADs by employing methods such as linkage disequilibrium score regression (LDSC),[25] high-definition likelihood

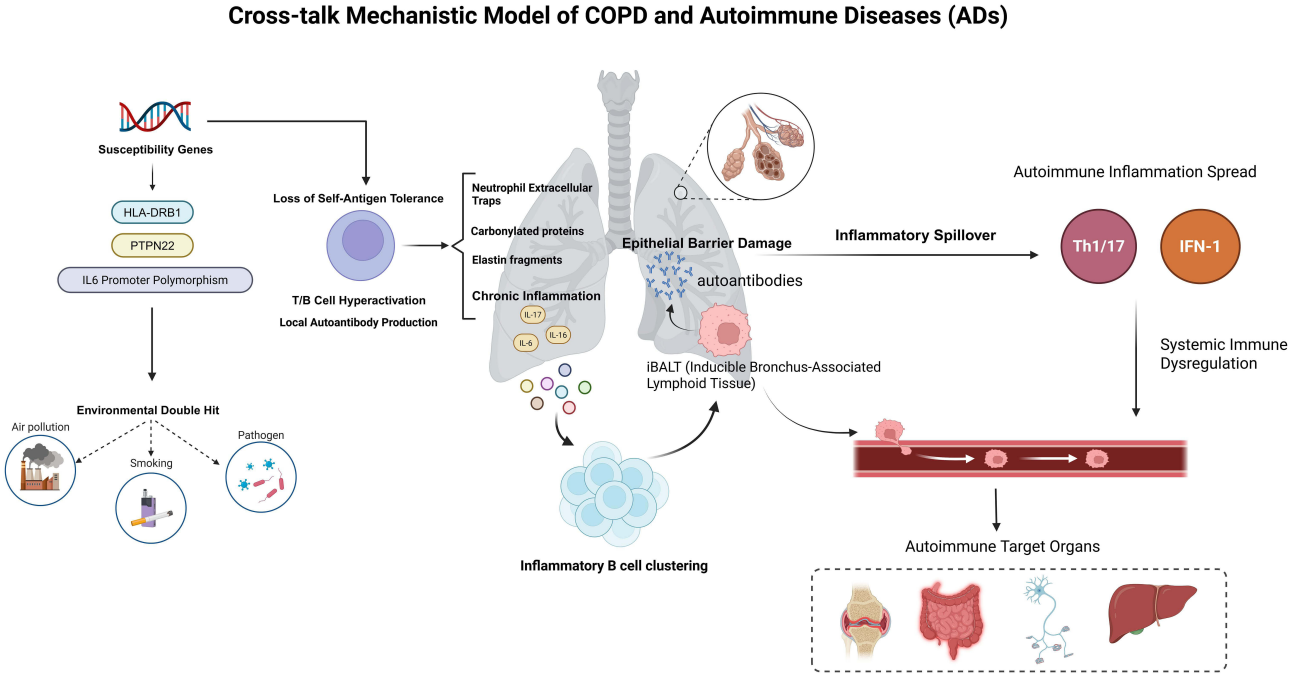

Figure 1 Shared Genetic and Immunological Mechanisms Linking COPD and ADs. This schematic illustrates the interplay between genetic susceptibility, environmental triggers, and immune dysregulation contributing to COPD and its comorbidity with autoimmune diseases. Key immune-regulatory gene polymorphisms (HLA-DRB1, PTPN22, IL6 promoter variants) confer a predisposition to immune imbalance. Environmental exposures—including air pollution, smoking, and pathogens—synergistically trigger chronic airway inflammation characterized by epithelial barrier dysfunction, the release of autoantigens, and persistent production of proinflammatory cytokines (IL-6, IL-16, IL-17). Activated dendritic cells and macrophages promote Th1/Th17 polarization and type I interferon (IFN-1) responses, which facilitate systemic dissemination of autoreactive immune cells and inflammatory mediators. This "inflammatory spillover" exacerbates extra-pulmonary immune activation, ultimately driving autoimmunity in distal organs such as joints, intestines, the central nervous system, and the liver. Created with BioRender.com (2025) https://BioRender.com/qo6mhea.

(HDL),[26] and Pleiotropic Analysis under the Composite Null Hypothesis (PLACO).[27–29] We hypothesized that COPD and ADs share common genetic architectures involving pleiotropic loci and convergent immune-mediated pathways.

In this study, we focused on seven ADs—SLE, MS, primary sclerosing cholangitis (PSC), RA, IBD, CD, and UC—selected based on robust epidemiological evidence of COPD comorbidity, the availability of high-quality genome-wide association study (GWAS) summary statistics, and their relevance to immune dysregulation. All analyses were conducted in European-ancestry populations to reduce population heterogeneity and maximize statistical power.

In summary, this study integrates GWAS summary statistics from large European-ancestry cohorts to systematically characterize genetic correlations, pleiotropic loci, and pleiotropic genes between COPD and seven ADs (Figure 2). By explicitly identifying shared genetic signals and quantifying their contribution to comorbidity, our findings aim to clarify disease mechanisms and inform future therapeutic strategies. While this study emphasizes genetic contributions, it is important to acknowledge that environmental exposures and microbial factors—including smoking, air pollution, and microbiome composition—also play critical roles in shaping disease susceptibility and progression.[24]

Material and Methods

GWAS Summary Data Sources for ADs and COPD

The GWAS data for COPD were obtained from the most recent and largest meta-analysis to date. This analysis integrated genetic information from 58,550 individuals of European ancestry diagnosed with COPD and 937,358 European ancestry controls, forming the most comprehensive COPD GWAS dataset currently available.[30] In parallel, summary-level GWAS data for the seven ADs included in this study were retrieved from publicly available databases. For IBD, the dataset included 12,882 cases and 21,770 controls, provided by the International Inflammatory Bowel Disease Genetics Consortium(IIBDGC).[31] This dataset also encompassed UC (6,968 cases and 20,464 controls) and CD (5956 cases and 14,927 controls). Similarly, data for PSC were obtained from the International Primary Sclerosing Cholangitis Study Group (IPSCSG), consisting of 2,871 cases and 12,019 controls.[32] The dataset for MS, comprising 47,429 cases and 68,374 controls, was made available by the International Multiple Sclerosis Genetics Consortium (IMSGC).[33] Summary statistics for SLE and RA were obtained from publicly accessible GWAS meta-analyses (Table S1).[34,35] To minimize potential confounding effects due to differences in allele frequencies and linkage disequilibrium (LD) structure across populations, all analyses were limited to individuals of European ancestry. In addition, comprehensive quality control procedures were applied to the GWAS summary statistics. A full description of these procedures is available in Supplementary Material 1.

Global Genetic Correlation Analysis Between COPD and ADs

To explore the shared genetic architecture between COPD and the seven ADs, we employed LDSC. This regression-based method estimates trait heritability, accounts for population stratification, and assesses genetic correlations using GWAS summary statistics and LD structure.[25] To ensure the accuracy of parameter estimates, we used a reference LD panel derived from the European population subset of the 1000 Genomes Project Phase 3 (GRCh37, baselineLD v2.2).[36] We also implemented the block jackknife method to calculate standard errors (SE) and correct for potential attenuation bias. In addition, we examined the LDSC intercept to assess the presence of residual population stratification, thereby enhancing the robustness and reliability of the genetic correlation estimates. To confirm the observed correlations, we further HDL analysis. Compared to LDSC, HDL utilizes a more sophisticated likelihood model and a full LD correlation matrix. This reduces attenuation bias and improves the accuracy and reliability of the estimated genetic correlations between COPD and ADs.[26]

Pleiotropic Risk Locus Identification and Colocalization Analysis

In addition to estimating genetic correlations, we aimed to identify shared genetic loci that contribute to both COPD and ADs. For this purpose, we applied the PLACO method—an advanced statistical framework that enhances detection power through a dual-hypothesis testing approach. PLACO evaluates a composite null hypothesis (H0: the locus is associated with neither phenotype or only one phenotype) against an alternative hypothesis (H1: the locus is associated

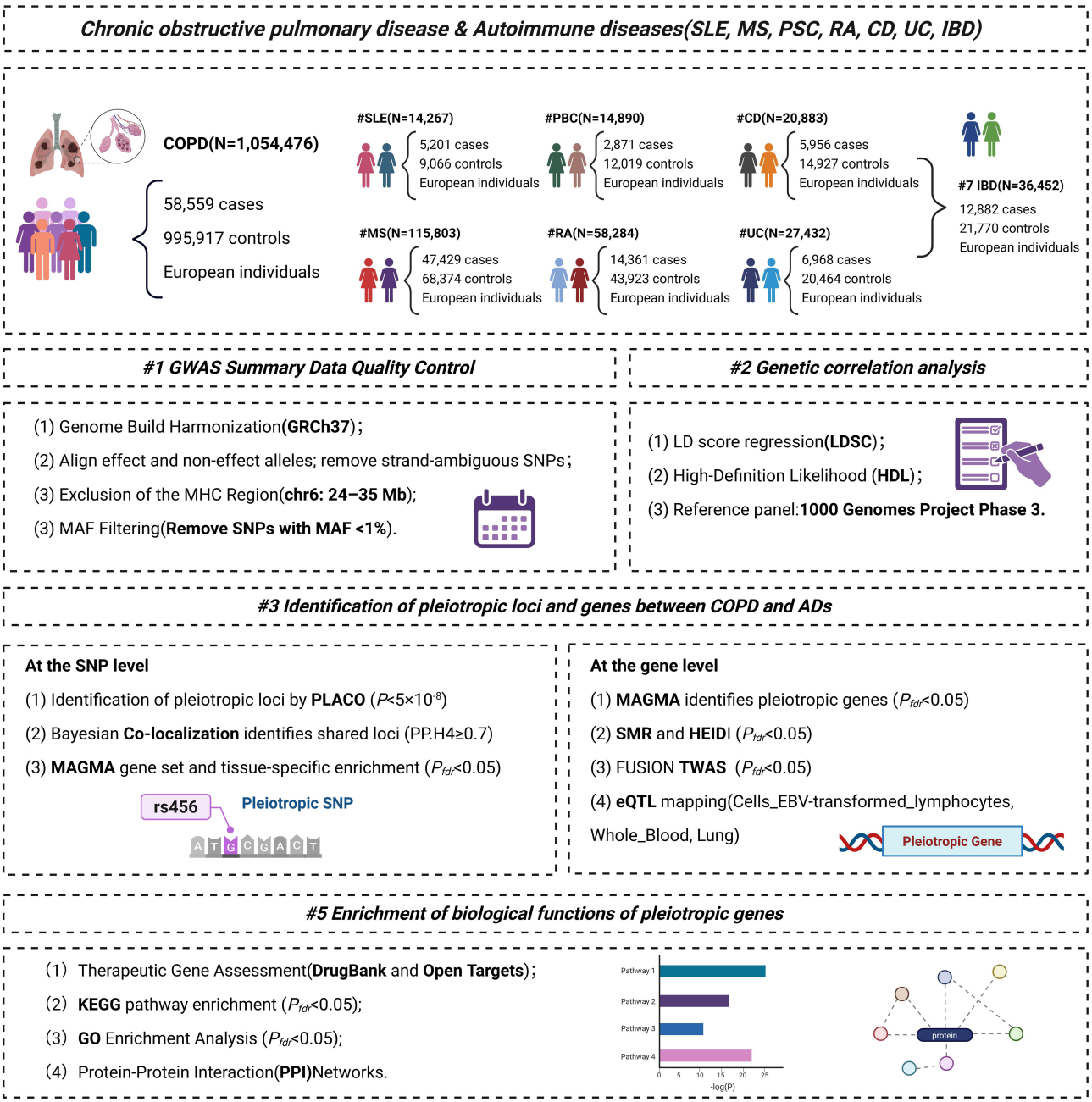

Figure 2 Overview of the Study Design.

Notes: This study commenced with an evaluation of the global genetic correlations between COPD and seven ADs using LDSC and HDL. Following this, pleiotropic SNPs and associated risk loci were identified through PLACO and CPASSOC, in conjunction with FUMA.To further characterize shared genetic determinants, MAGMA, SMR and TWAS were applied to identify pleiotropic genes and potential therapeutic targets. Functional enrichment of these genes was conducted using Metascape to elucidate involved biological pathways. Created with BioRender.com (2025) https://BioRender.com/alb0iey.

Abbreviations: LDSC, Linkage Disequilibrium Score Regression; HDL, High-Definition Likelihood; COPD, Chronic Obstructive Pulmonary Disease; Ads, Autoimmune Diseases; PLACO, Pleiotropic Analysis under Composite Null Hypothesis; CPASSOC, Cross-Phenotype Association analysis using Summary-level data from GWAS; FUMA, Functional Mapping and Annotation; MAGMA, Multi-marker Analysis of Genomic Annotation; SMR, Summary-data-based Mendelian Randomization; SNPs, Single Nucleotide Polymorphisms.

with both phenotypes). It generates standardized test statistics to build a probabilistic inference model, enabling accurate signal identification under multiple testing correction.[27] Moreover, to validate the robustness of the pleiotropic loci identified through PLACO, we conducted additional analyses using the Cross-Phenotype Association analysis using Summary-level data from GWAS (CPASSOC) method.[36] A stringent genome-wide significance threshold ($P < 5\times10^{-8}$) was applied.Subsequently, we mapped and functionally annotated pleiotropic loci using the Functional Mapping and

Annotation of Genome-Wide Association Studies (FUMA) platform.[37] Specifically, These SNPs were clustered into genomic loci based on strong LD ($R^2 \geq 0.6$) within a 250 kb window, with lead SNPs defined as approximately independent ($R^2 < 0.1$). We then conducted Bayesian colocalization analysis (COLOC) to evaluate whether associated signals across phenotypes shared a causal variant. A posterior probability threshold (PP.H4 ≥ 0.70) was set to indicate strong evidence for colocalization.[38] Finally, comprehensive descriptions of the fundamental principles, parameter settings, and implementation details for the PLACO, CPASSOC, FUMA and COLOC methods are provided in Supplementary Material 1 and Supplementary Figure 1.

Identification and Functional Enrichment of Pleiotropic Genes

This study employed the Multi-marker Analysis of GenoMic Annotation (MAGMA) to identify pleiotropic genes based on PLACO results.[39] Gene boundaries were defined using the ENSEMBL genomic coordinate system. GWAS summary statistics for SNPs within each gene region (typically P-values) were aggregated to compute gene-level statistics, allowing the translation of SNP-level signals into gene-level associations. A Bonferroni-adjusted significance threshold was applied to account for multiple testing ($P_{fdr}<0.05$).[40] After identifying candidate pleiotropic genes, we investigated their potential biological functions. To assess the functional relevance of lead SNPs, MAGMA gene-set enrichment analysis was performed. A cross-omics strategy was used to integrate 10,678 functional gene sets from the Molecular Signatures Database (MSigDB), applying a FDR-corrected threshold of $P_{fdr}<0.05$. To further interpret the biological relevance of the identified pleiotropic genes, we conducted functional annotation and pathway enrichment analyses using the Metascape platform. This analysis integrated three major biological knowledge bases: Gene Ontology (GO), the Kyoto Encyclopedia of Genes and Genomes (KEGG), and the STRING protein–protein interaction (PPI) network. Enrichment was assessed using the hypergeometric test, with statistical significance defined as a FDR-adjusted P value <0.05. We conducted tissue-specific gene expression enrichment analysis using MAGMA the FUMA platform. MAGMA applies a gene-property analysis using a multiple regression framework. This evaluates the association between gene-level GWAS statistics and tissue-specific expression levels from GTEx v8 across 54 tissues. The model tests whether the average expression of each gene in a tissue predicts its GWAS signal while adjusting for confounders such as gene size, gene density, and local linkage disequilibrium. To account for correlations among tissues, we used FUMA's conditional analysis, which adjusts for the expression of all other tissues. Multiple testing correction was performed using FDR adjustment, and tissues with adjusted P values <0.05 were considered significantly enriched.[37,41]

Summary-Data-Based Mendelian Randomization (SMR)

Building on the functional characterization of pleiotropic genes, we next evaluated their potential regulatory roles in disease susceptibility. To prioritize candidate genes with putative causal effects, we applied a causal inference framework leveraging SMR. In this approach, GWAS data and expression quantitative trait loci (eQTL) datasets were harmonized within a unified genomic coordinate system to construct networks linking gene expression to disease phenotypes. To mitigate false-positive associations driven by linkage disequilibrium, we employed the heterogeneity in dependent instruments (HEIDI) test to exclude non-causal signals.[42] Multiple testing correction was conducted using a FDR, with an FDR threshold of <0.05 considered statistically significant. Subsequently, a dual-validation strategy was implemented to robustly identify core genes with potential regulatory associations. Collectively, these analyses yielded a prioritized list of candidate regulatory genes, establishing a molecular framework to inform future functional validation and therapeutic development.

Transcriptome-Wide Association Analysis (TWAS)

To validate the robustness of putative pleiotropic genes identified by SMR, we conducted TWAS using the FUSION framework. FUSION assesses associations between the cis-genetic component of gene expression and the phenotype of interest based on GWAS summary statistics, thereby providing independent supporting evidence.[43,44] Specifically, we obtained precomputed gene expression weights from GTEx v8 across relevant tissues, including whole blood, EBV-transformed lymphocytes, and lung. For each gene, FUSION selected cis-SNPs within ±500 kb of gene boundaries and built prediction models using BLUP, BSLMM, LASSO, and elastic net regression. The optimal model for each gene was

determined by cross-validation R^2 to maximize predictive accuracy. Using GWAS summary statistics for the target phenotype, we integrated SNP–trait effect sizes with SNP–expression weights, while adjusting for local LD patterns derived from the 1000 Genomes Project Phase 3 European reference panel. We then calculated association statistics and applied FDR correction to account for multiple testing, with an FDR threshold of <0.05 considered statistically significant. To further mitigate potential confounding from LD and primary GWAS signals, we performed permutation tests implemented in FUSION to evaluate whether the observed expression–trait associations exceeded the level expected under the locus-specific GWAS architecture.

Therapeutic Gene Assessment

To assess the therapeutic potential of the candidate genes identified by SMR and TWAS analyses in COPD and ADs, we conducted an extensive drug target evaluation using publicly available databases, including DrugBank and Open Targets.[45,46] We systematically searched these resources for each gene to identify approved, investigational, or experimental compounds that target the corresponding proteins. In addition, we assessed the established or predicted druggability of these targets and compiled evidence supporting their associations with COPD and ADs. Specifically, DrugBank was used to catalogue compounds known to interact directly with the encoded proteins. Open Targets provided integrated data on disease-gene associations, genetic evidence scores, and information derived from clinical trials, literature mining, and pathway analyses.Based on this evidence, we prioritized genes with strong drug-target interaction data or promising drug repurposing potential for further experimental validation and therapeutic development.

Statistical Analysis and Software Resources

The main statistical analyses were performed in R (version 4.4.3). Linkage disequilibrium score regression (LDSC) analyses were conducted using the LDSC software (version 1.0.1; https://github.com/bulik/ldsc).[25] HDL analyses were performed with the HDL software (https://github.com/zhenin/HDL).[26] Pleiotropy analysis was conducted using the PLACO R package (https://github.com/RayDebashree/PLACO).[27] Cross-phenotype association analyses were performed using CPASSOC software (https://github.com/ZhiGroup/CPASSOC).[36] Functional annotation and enrichment analyses were conducted via the FUMA web platform (version 1.6; https://fuma.ctglab.nl/snp2gene). MAGMA gene and gene-set analyses were performed using MAGMA software (version 1.08; https://ctg.cncr.nl/software/magma).[37] Bayesian colocalization analyses were conducted with the coloc R package (version 5.2.1).[38] TWAS were performed using the FUSION software (http://gusevlab.org/projects/fusion/).[44] SMR analyses were conducted with the SMR software (version 1.3.1; https://yanglab.westlake.edu.cn/software/smr).[42] In addition, parts of the analysis workflow and code structure were adapted from publicly available resources available at https://github.com/biostatYu/MRcode-/tree/main/AD_BALL.[29]

Results

Genetic Correlations Between COPD and ADs

To investigate the global genetic correlations between COPD and seven ADs, we first applied LDSC (Table 1). Statistically significant genetic correlations were identified between COPD and MS (rg = 0.125, P = 1.22×10^{-4}), RA (rg = 0.205, P = 5.74×10^{-8}), and PSC (rg = –0.205, P = 8.86×10^{-4}). In contrast, no significant correlations were observed between COPD and IBD, CD, UC, or SLE.

To further assess the robustness of these associations, we conducted HDL analyses. The HDL results were largely consistent with the LDSC findings, identifying significant genetic correlations between COPD and MS (rg = 0.149, P = 1.23×10^{-5}) and RA (rg = 0.266, P = 2.13×10^{-6}). Additionally, HDL suggested nominal evidence of genetic correlation between COPD and CD (rg = 0.114, P = 0.025) and between COPD and SLE (rg = 0.113, P = 0.042). However, due to data availability constraints, HDL analysis for PSC was not feasible.

Overall, while the LDSC and HDL approaches identified several statistically significant genetic correlations between COPD and selected ADs, the estimated effect sizes were modest.

Table 1 Global Genetic Correlation Analysis of COPD and ADs

Trait Pair	LDSC		HDL	
	r_g (SE)	P-Value	r_g (SE)	P-Value
COPD-CD	0.056(0.037)	0.137	0.114 (0.05)	**0.024**
COPD-IBD	0.066(0.037)	0.075	0.075 (0.04)	0.062
COPD-MS	0.125(0.033)	**1.22×10^{-4}**	0.149 (0.034)	**1.23×10^{-4}**
COPD-PSC	−0.205(0.062)	**8.86×10^{-4}**	/	/
COPD-RA	0.206(0.038)	**8.73×10^{-8}**	0.266 (0.056)	**2.13×10^{-6}**
COPD-SLE	0.099(0.055)	0.072	0.113 (0.056)	**0.042**
COPD-UC	0.039(0.047)	0.405	0.006 (0.047)	0.895

Notes: Bold values indicate statistically significant results (eg, $P < 0.05$).
Abbreviations: LDSC, Linkage Disequilibrium Score Regression; HDL, High-Definition Likelihood; IBD, Inflammatory Bowel Disease; UC, Ulcerative Colitis; CD, Crohn's Disease; MS, Multiple Sclerosis; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; PSC, Primary Sclerosing Cholangitis.

Shared Pleiotropic Genetic Loci of COPD and ADs

Building on the identified cross-trait genetic correlations, we next sought to uncover specific shared genetic variants between COPD and ADs. To this end, we employed the PLACO method to identify pleiotropic SNPs across the five identified trait pairs, resulting in 2,020 genome-wide significant loci ($P < 5\times10^{-8}$; Table S2). Notably, 1,100 pleiotropic SNPs were independently replicated using the CPASSOC method (Table S3). Integration of PLACO results with FUMA annotations revealed 57 pleiotropic loci shared between COPD and five ADs, as illustrated in Figure 2. Specifically, COPD shared 18 loci with CD, 17 with MS, 10 with RA, 9 with SLE, and 3 with PSC (Figure 3 and Table S4). Notably, 22 of these 57 loci (38.6%) demonstrated strong evidence of colocalization (PP.H4 ≥ 0.70; Table S4). Importantly, 43 out of the 57 pleiotropic loci were independently corroborated through CPASSOC analyses, supporting the robustness and cross-method reproducibility of these results (Tables S5 and S6). Additionally, loci on chromosomes 16p11.2 and 17q12 were associated with at least 4 trait pairs, suggesting that these regions may serve as genetic convergence points in the shared pathogenesis of COPD and ADs (Table S6).

To investigate the biological relevance of these loci, we conducted MAGMA gene set enrichment analysis. The results showed that these pleiotropic genes were significantly enriched in biological processes related to T cell and leukocyte activation and differentiation, such as alpha-beta T cell activation, CD4-positive T cell differentiation, hematopoiesis, and cytokine production. These findings highlight their central role in immune regulation.Furthermore, pathways involved in transcriptional regulation, including RNA metabolism and transcription factor activity, and metabolic processes such as NADH metabolism, were also significantly enriched (Figure 4 and Table S7).Tissue-specific analysis revealed pronounced enrichment in immune-related tissues, including whole blood, spleen, and EBV-transformed lymphocytes (Figure 4 and Table S8). Together, these results suggest that immune, transcriptional, and metabolic mechanisms may contribute to the comorbidity between COPD and ADs.

Identification and Functional Characterization of Pleiotropic Genes with Drug Target Evaluation

To identify candidate genes underlying the pleiotropic SNPs, we conducted gene mapping via FUMA and gene-based analysis using MAGMA. Across the five trait pairs, we identified 162 pleiotropic genes, of which 125 were unique (Table S9). Notably, 88.6% (140/158) of these genes were located within pleiotropic loci shared between COPD and ADs. In addition, 23.2% (29/125) of the genes were observed in more than one trait pair. Among the most notable pleiotropic genes, ORMDL3, ZPBP2, and GSDMB were associated with four trait pairs, while BACH2, ERBB2, and PGAP3 were

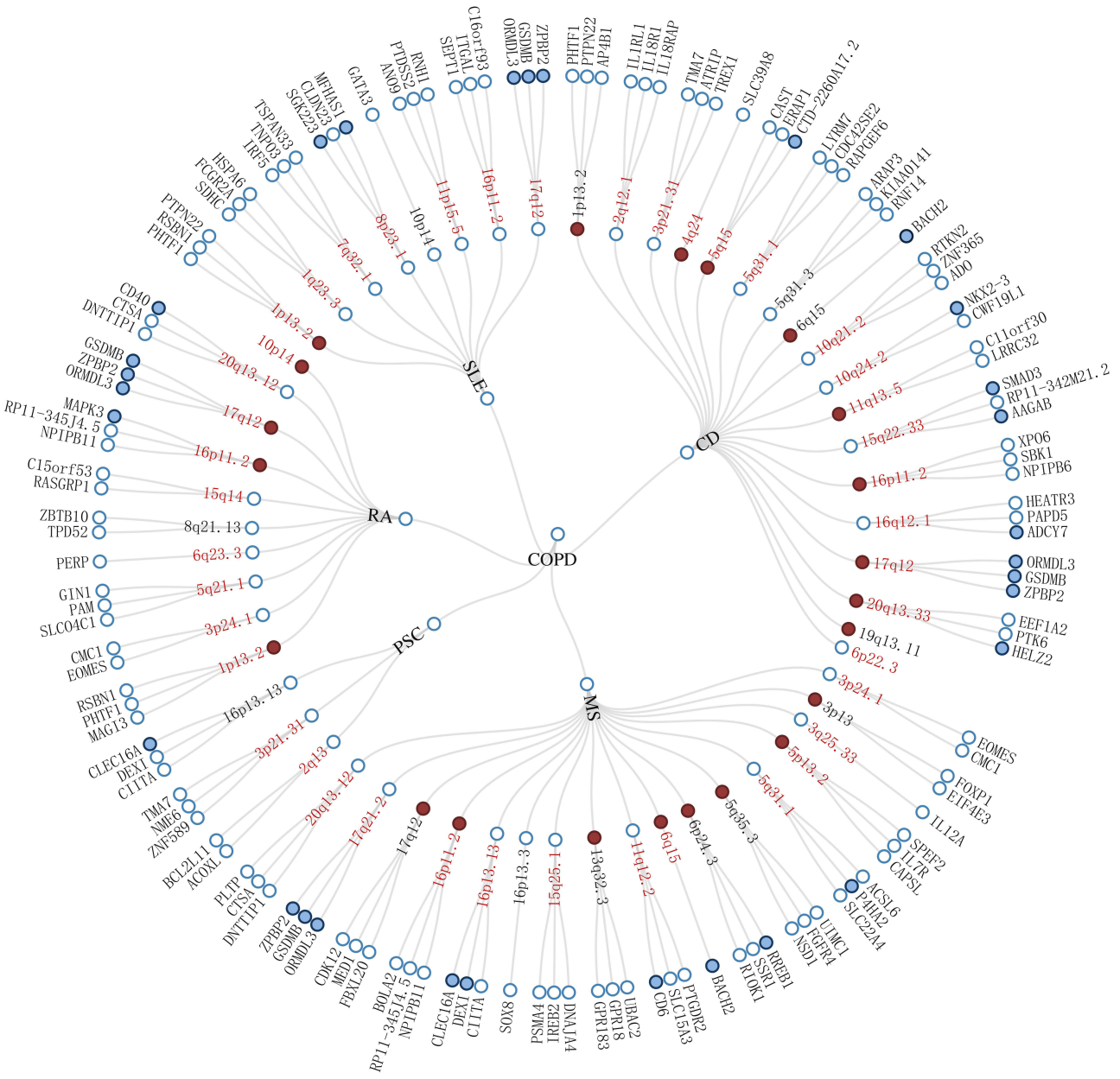

Figure 3 The circular diagram illustrates the shared genetic architecture among five complex traits.

Notes: Risk loci with strong evidence of colocalization (PP.H4 ≥ 0.7) are highlighted in orange, indicating regions likely driven by shared genetic factors. Pleiotropic genes identified through MAGMA analysis are shown in sky blue. Loci highlighted in red were repeatedly identified by the CPASSOC method, marking pleiotropic regions independently confirmed by an alternative approach. For trait pairs with more than three pleiotropic genes, only the top three candidates—ranked by statistical significance—are displayed for clarity. Comprehensive details on all identified genes and their associations are provided in the Supplementary Materials.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CD, Crohn's Disease; MS, Multiple Sclerosis; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; PSC, Primary Sclerosing Cholangitis.

shared across three. eQTL analyses revealed that ORMDL3, GSDMB, BACH2, ERBB2, and PGAP3 are significantly expressed in EBV-transformed lymphocytes, whole blood, and lung (Figure 5 and Table S10). Supporting these findings, SMR, HEIDI, and TWAS analyses further suggested that ORMDL3, PGAP3, GMPPB, and MAPK3 may act as key genetic contributors to shared disease susceptibility between COPD and ADs, laying the groundwork for elucidating the common pathological mechanisms underlying these conditions (Figure 5 and Table S11).

The drug target assessment demonstrated considerable variability in druggability among the four candidate genes. ORMDL3 and PGAP3 showed low druggability, with no approved therapies, though mechanistic studies and exploratory

Figure 4 Heatmap of functional enrichment for genes shared between COPD and five autoimmune diseases. Columns represent COPD paired with CD, MS, PSC, RA, SLE. Rows correspond to annotation categories: Gene Ontology – Biological Process, Cellular Component, Molecular Function, Tissue-Specific Expression Analysis, Gene Set Enrichment Analysis, and KEGG pathways. Each cell shows the number of trait pairs with significant enrichment (*Pfdr* < 0.05) in that category; higher values indicate more enriched trait pairs.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CD, Crohn's Disease; MS, Multiple Sclerosis; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; PSC, Primary Sclerosing Cholangitis.

strategies such as antibody development or gene therapy are ongoing. MAPK3 exhibited high druggability, supported by several approved MAPK/ERK inhibitors (eg, trametinib, cobimetinib). GMPPB had moderate to low druggability, with no established treatments. These results outline a range of translational potential and provide a foundation for future functional and therapeutic studies. Detailed information is summarized in Table S12.

Functional Characterization and Therapeutic Target Assessment of Pleiotropic Genes

To further elucidate the functional roles of the identified genes, we performed comprehensive GO enrichment analysis using a stringent significance threshold ($P_{fdr} < 0.05$). The results showed that these genes were significantly enriched in immune regulatory processes, including the proliferation and activation of leukocytes and T cells, highlighting their essential roles in maintaining immune homeostasis. In addition, pathways related to lipid and amine metabolism, such as glycerolipid and triglyceride metabolism, as well as synaptic organization, were also overrepresented. Together, these findings suggest that metabolic and neuro-immune regulatory mechanisms may contribute to disease susceptibility. Overall, the data underscore the potential involvement of immune regulation, metabolic processes, and synaptic pathways in the comorbidity between COPD and ADs (Figure 6 and Table S13). Although several pathways demonstrated nominal significance in the KEGG enrichment analysis, no pathways remained statistically significant after FDR correction (Table S14). Additionally, protein-protein interaction (PPI) network analysis identified several hub genes—including MAPK3, SMAD3, ERBB2, RHOA, and MTMR9—linked to leukocyte proliferation and neutrophil function (Figure 6), underscoring the central role of immune signaling in COPD-AD comorbidity.

Discussion

This study employed comprehensive genetic analyses to uncover significant genetic correlations and shared pleiotropic loci between COPD and several ADs. These findings provide new insights into the shared genetic architecture of these conditions. Unlike previous research that primarily focused on clinical and epidemiological associations, our study offers the first systematic genetic evidence supporting a common heritable basis. This overlap may help explain the high comorbidity observed in clinical practice and provide a foundation for identifying potential therapeutic targets. To further investigate this comorbidity, we conducted quantitative genetic correlation analyses.

Analyses using LDSC and HDL methods revealed strong genetic correlations between COPD and ADs such as MS, RA, and CD. These findings suggest the existence of shared pathogenic mechanisms. Supporting clinical evidence includes a higher prevalence of COPD among MS patients across all age groups,[47] and a national cross-sectional study

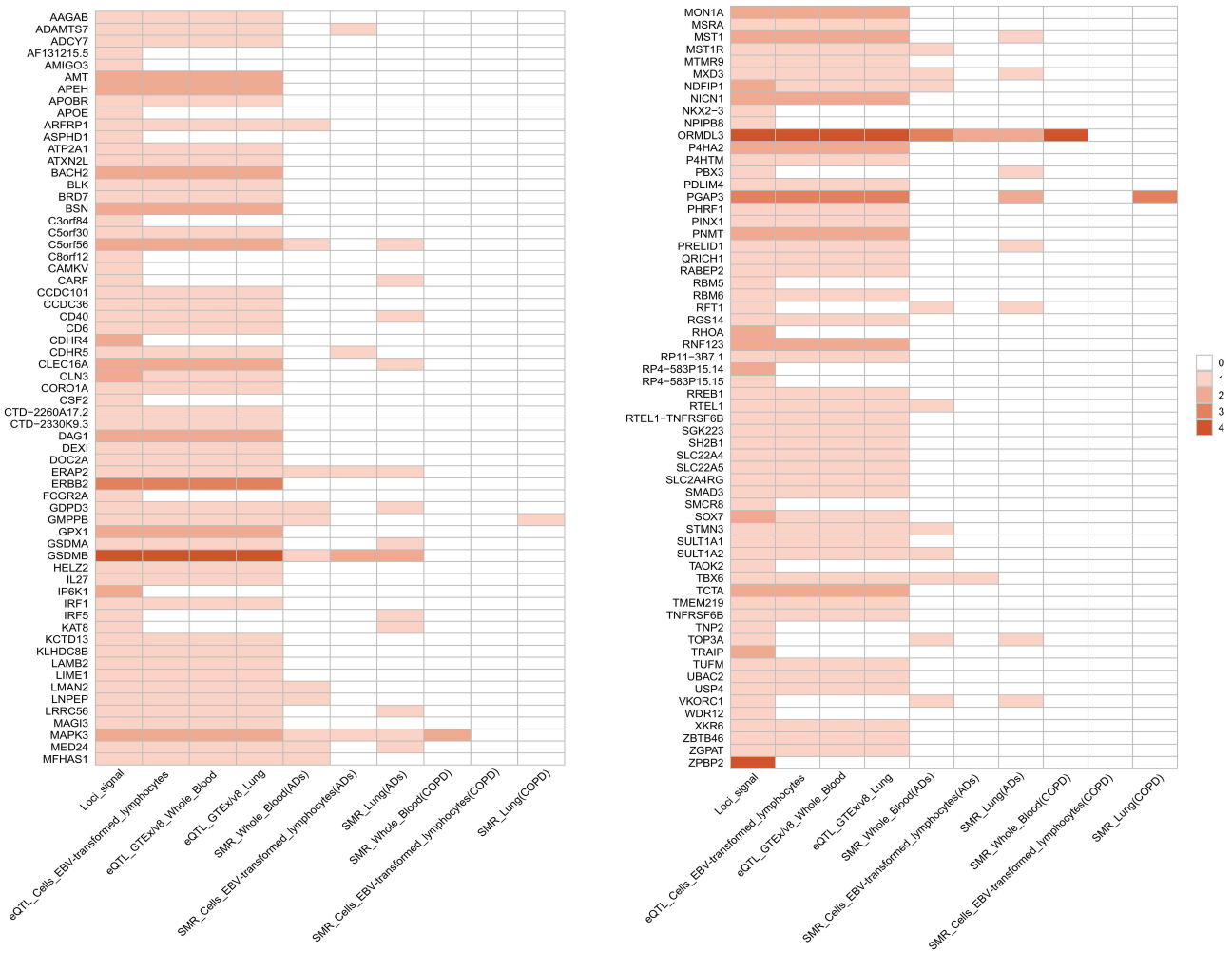

Figure 5 Summary of eQTL and SMR analysis results across multiple tissues for pleiotropic genes identified by MAGMA.
Notes: The intensity of the color indicates the number of trait associations per pleiotropic gene.
Abbreviations: Ads, autoimmune diseases (CD, Crohn's disease; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PSC, Primary Sclerosing Cholangitis). eQTL, expression quantitative trait locus; SMR, summary data-based Mendelian randomization; COPD, Chronic Obstructive Pulmonary Disease.

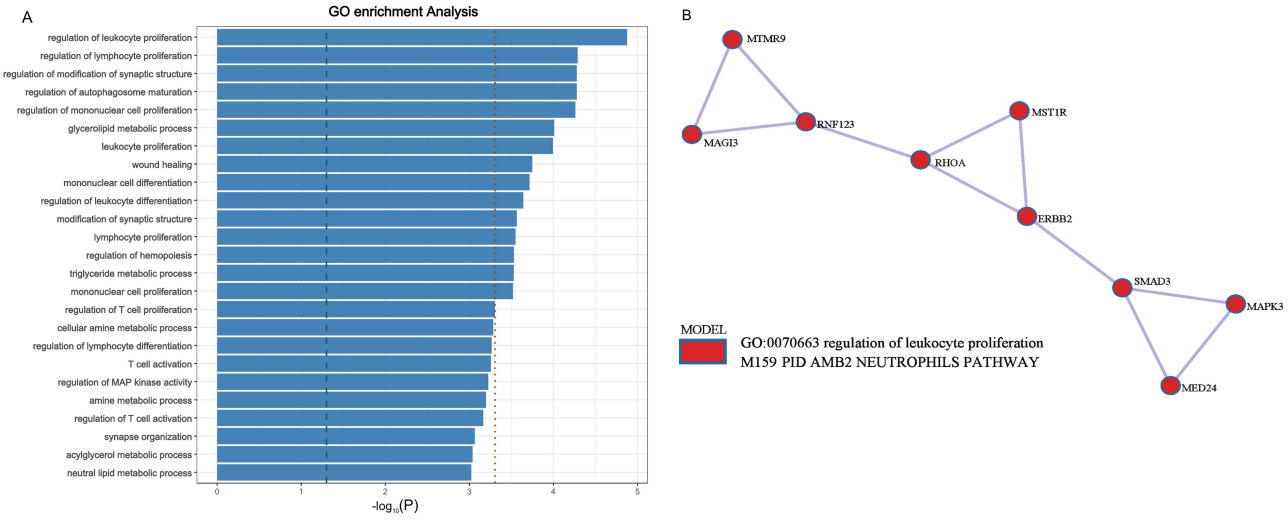

Figure 6 Enrichment analysis of pleiotropic genes.
Notes: (**A**) Displays the associated GO biological processes. (**B**) Presents the protein-protein interaction network constructed from the identified pleiotropic genes.

reporting increased COPD risk in RA patients. Additionally, a cohort analysis from the UK Biobank found that 3.2% of COPD patients were later diagnosed with RA, compared to 1.1% in the control group.[48] Large-scale population studies have also indicated a bidirectional relationship between COPD and CD.[49] In contrast, we observed a negative genetic correlation between COPD and PSC, which diverges from previous clinical observations.[50] This discrepancy underscores the need for further investigation using larger and more diverse cohorts.

We further identified specific pleiotropic loci shared between COPD and ADs through PLACO and colocalization analyses. Interestingly, the 17q12 and 16p11.2 regions were recurrently implicated across multiple disease pairs. The 17q12 locus, which includes ORMDL3, has been linked to childhood asthma and is strongly associated with COPD.[51,52] This region also contains risk variants for MS,[53] RA,[54] CD,[19] and SLE,[55] and harbors several key pleiotropic genes, including ORMDL3, GSDMB, ZPBP2, and PGAP3.

Focusing on the 17q12 region, ORMDL3 encodes an endoplasmic reticulum-resident protein that participates in inflammatory responses by regulating ER calcium homeostasis and activating the unfolded protein response (UPR). It also plays a central role in the pathogenesis of COPD, primarily by negatively regulating serine palmitoyltransferase (SPT) in a feedback loop to control sphingolipid metabolism. Aberrant expression of ORMDL3 has been closely associated with various ADs.[56,57] Animal studies have shown that ORMDL3 deficiency increases sphingolipid synthesis, disrupts B cell maturation, and impairs immune homeostasis through lymphocyte-intrinsic mechanisms. Sphingolipid imbalance not only affects lipid raft formation and B cell receptor (BCR) signaling but also promotes the survival of autoreactive B cells.[58,59]

In addition, variants within the 17q12 locus can regulate the expression of neighboring genes, such as GSDMB and ZPBP2, which share regulatory elements with ORMDL3 and exhibit tissue-specific circadian rhythms. Deletion of ZPBP2 increases ORMDL3 expression and disrupts the circadian rhythm of the clock gene NR1D1, thereby influencing lipid metabolism and immune signaling pathways. These findings suggest that ORMDL3 and ZPBP2 may cooperatively regulate inflammation and immune balance in a time-dependent manner.[60] PGAP3, another critical gene within 17q12, is responsible for fatty acid remodeling. Its deletion disrupts the anchoring of GPI-anchored proteins within lipid rafts, thereby impairing immune signaling. In PGAP3–/– mice, GPI-anchored proteins such as CD14 are mislocalized, resulting in autoimmune-like phenotypes, including elevated autoantibody production, spontaneous germinal center formation, and immune complex deposition. Moreover, PGAP3 contributes to airway inflammation and remodeling by reorganizing lipid raft-associated signaling networks.[61,62]

A search of the GWAS Catalog confirmed that the 16p11.2 region is associated with COPD and multiple ADs.[63–67] This locus contains pleiotropic genes including MAPK3. In COPD, MAPK3 expression is elevated due to pulmonary inflammation.[68] In dendritic cells (DCs), MAPK3 suppresses T cell activation by limiting antigen presentation and the expression of costimulatory molecules.[55] Bone marrow chimera models have shown that MAPK3 plays a regulatory role in the immune system, and its deficiency exacerbates autoimmune encephalomyelitis. By maintaining DCs in an immature state, MAPK3 mitigates excessive inflammatory responses, and its dysfunction may contribute to ADs such as MS.[69] Another key immune regulator is BACH2 (6q15). Its downregulation reduces the expression of stemness-related genes (eg, Lef1, Myb, Elf4) in naive $CD8^{+}$T cells and increases the expression of genes related to activation and effector differentiation.[70] Mouse models confirm that BACH2 deficiency shifts T cell fate toward effector phenotypes, a mechanism thought to promote autoimmunity.[70] Moreover, BACH2 inhibits Gata3 and promotes Foxp3, enabling the differentiation of induced regulatory T cells (iTregs) and suppressing Th2-driven immune responses. These functions are crucial for preventing chronic pulmonary inflammation and immune-mediated lung diseases.[71]

Based on our enrichment analyses and pleiotropic gene findings, we propose that COPD and ADs share a convergent genetic framework characterized by disrupted immune homeostasis, dysregulated inflammatory responses, and metabolic imbalance. Multi-layered analyses using MAGMA, GO, and KEGG revealed that the associated genes are significantly enriched in pathways related to T cell activation and differentiation, immune tolerance, cellular metabolism, and protein modification, with particularly strong enrichment observed in Th17 cell differentiation and T cell receptor signaling. These genes also exhibit high expression levels in the lung, peripheral blood, and EBV-transformed lymphocytes, suggesting that COPD and ADs may share common immune microenvironments and tissue-specific regulatory mechanisms. Interestingly, although key genes such as ORMDL3 and MAPK3 have long been recognized as involved in disease

pathogenesis, this study advances existing knowledge by providing deeper mechanistic and integrative insights. Among these genes, pleiotropic loci within the 17q12 region—including ORMDL3, GSDMB, ZPBP2, and PGAP3—appear to constitute a genetic "hotspot" underlying COPD–AD comorbidity. These genes form an interconnected network encompassing lipid metabolism, signal transduction, and circadian regulation, collectively contributing to shared disease susceptibility. Altogether, these findings substantially deepen our understanding of the molecular mechanisms linking COPD and ADs and offer promising therapeutic targets for future intervention strategies.

Interestingly, while this study revealed an overarching convergent genetic framework shared between COPD and multiple autoimmune diseases, the enrichment and pleiotropy analyses also demonstrated marked heterogeneity across individual conditions. For example, the pleiotropic loci shared between COPD and CD were significantly enriched in mucosal immune regulation pathways, including T cell activation, differentiation, and type II interferon responses, consistent with the central role of intestinal barrier dysfunction and Th1-mediated inflammation in CD.[72] In contrast, the loci shared by COPD and multiple sclerosis were primarily involved in transcriptional regulation and systemic immune activation, reflecting the distinct neuroinflammatory processes characteristic of MS. The shared loci between COPD and PSC were enriched in pathways related to hematopoiesis and bone marrow cell proliferation, suggesting that disruptions in immune cell production may contribute to their comorbidity. Meanwhile, the pleiotropy observed between COPD and RA, as well as SLE, predominantly involved T cell differentiation and mononuclear cell activation, highlighting the central role of adaptive immune dysregulation in these disease pairs.[73,74] This heterogeneity underscores that, despite shared genetic underpinnings, disease-specific immune and metabolic pathways likely shape the patterns of comorbidity. Thoroughly identifying and disentangling these mechanistic differences will be crucial for developing precise, targeted intervention strategies in the future.

Nevertheless, this study has several limitations. First, all GWAS data analyzed were derived from individuals of European ancestry, which limits the generalizability of the results to other populations. Replication in multi-ethnic cohorts is needed to assess the broader relevance of these findings.Second, although we applied rigorous multiple testing correction and multiple approaches (PLACO, CPASSOC) to detect pleiotropy, marginally significant loci may still be influenced by population-specific LD structure, weak cross-trait effects, or LD contamination.Third, the reliance on publicly available summary statistics may introduce heterogeneity due to differences in data quality, study designs, and analysis pipelines. Future studies combining individual-level data and consistent processing would improve robustness.Fourth, genes such as ORMDL3 and PGAP3 were prioritized as potential shared susceptibility factors, but the current evidence is mainly based on statistical inference and functional annotations. Fifth, due to data limitations, we did not conduct sex- or age-stratified analyses, even though these factors may influence genetic effects. Future research should explore genetic heterogeneity across demographic subgroups using stratified data.Sixth, although colocalization analyses were performed using COLOC to assess whether GWAS and eQTL signals share a common causal variant, the lack of individual-level genotype data and variability in LD structure across datasets limited our ability to conduct independent validation using alternative approaches such as eCAVIAR or JLIM. As a result, the interpretation of colocalization results should remain cautious, and future studies leveraging large-scale molecular QTL resources and harmonized LD reference panels will be needed to confirm these findings. Seventh, although this study used the largest available COPD GWAS data, including UK Biobank, the absence of similarly large independent datasets prevented formal replication. This limits assessment of robustness, and findings should be interpreted cautiously until confirmed by future studies.Finally, we acknowledge that pleiotropy detection may be influenced by confounding and LD structure, and some associations could reflect linkage rather than true pleiotropy. eQTL results are also limited by tissue specificity; blood-derived signals may not fully represent gene regulation in lung or immune cells. Future studies using single-cell and disease-specific data will help improve interpretation.

Overall, these limitations underscore the need for cautious interpretation and emphasize the importance of further validation through more diverse and detailed investigations. Future research should include large, multi-ethnic cohorts to replicate these findings and assess their generalizability across populations. Additionally, integrating functional genomics and molecular biology approaches will be essential to elucidate the causal roles of pleiotropic genes. Studies investigating gene–environment interactions, as well as risk locus effects in disease-relevant immune cell subsets and lung tissues, may further reveal therapeutic targets and advance precision interventions for COPD and associated autoimmune conditions.

Conclusion

This study provides systematic genetic evidence supporting a shared etiological basis between COPD and ADs. Through integrated cross-trait GWAS analyses, we identified significant genetic correlations, convergent pleiotropic loci, and immune-related pathways that underpin this comorbidity. Notably, loci such as 17q12 and genes including ORMDL3 and PGAP3 emerge as central nodes within a common immunogenetic network. These findings not only deepen our understanding of COPD pathogenesis beyond the respiratory domain but also highlight novel molecular targets for precision interventions. Future research integrating multi-omics and experimental validation across diverse populations will be essential to translate these insights into therapeutic strategies.

Data Sharing Statement

The original data used in the study are included in the article and its Supplementary Materials. For further inquiries, please contact the corresponding author directly.

Ethics Approval and Consent to Participate

This study complies with the conditions for exemption from review as stated in the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans." Since the data do not involve identifiable personal information, the study avoids direct human subject research and meets the requirements for ethical exemption.

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Disclosure

The authors report no conflicts of interest in this work.

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