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ORIGINAL RESEARCH

# The Role of Programmed Cell Death–Related Genes in Asthma, Chronic Obstructive Pulmonary Disease, and Lung Function: A Multi-Omics Mendelian Randomization Study

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**Purpose:** Programmed cell death (PCD) has been linked to asthma, chronic obstructive pulmonary disease (COPD) and lung function, but the underlying genetic determinants remain unclear.

**Patients and Methods:** A comprehensive multi-omics analysis was conducted by integrating genome-wide association studies (GWAS) with methylation quantitative trait loci (mQTL), expression quantitative trait loci (eQTL), and protein quantitative trait loci (pQTL) data. To determine the causality between exposures and respiratory traits, Summary Data-Based Mendelian Randomization (SMR) and colocalization analyses were applied. External validation was performed using replication cohorts, along with transcriptome-wide association studies (TWAS), gene-based analysis, and tissue-specific analysis. Additionally, enrichment analysis was carried out to identify biological pathways linked to respiratory traits. To explore potential therapeutic targets, drug prediction and molecular docking analyses were employed to assess the pharmacological feasibility of candidate compounds.

**Results:** Through the integration of multi-omics analysis, we identified six PCD-related genes associated with respiratory traits. ERBB3, SFRP1, and FGFR1 demonstrated tier 1 evidence, linking them to COPD in never-smokers, forced expiratory volume in 1 second (FEV1), and FEV1/forced vital capacity (FVC), respectively. Additionally, HSPA1B and MAPK3 were classified as tier 2 genes, associated with non-allergic asthma risk and overall COPD risk, respectively. IDUA, categorized as a tier 3 gene, was related to overall asthma. These genes play critical roles in apoptotic signaling, mesenchymal development, and molecular binding processes, emphasizing their biological significance. Additionally, molecular docking demonstrated stable binding for candidate drugs and proteins encoded by identified genes.

**Conclusion:** Our study offers critical insights into the genetic basis of asthma, COPD, and lung function by identifying six genes as potential biomarkers and therapeutic targets, contributing to the development of more effective interventions for these respiratory traits.

**Keywords:** respiratory diseases, multi-omics, genetics, quantitative trait loci

## Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the two most common diseases within the spectrum of chronic respiratory diseases (CRDs), which represent the third leading cause of mortality worldwide. In 2019, an estimated 262.4 million people were affected by asthma, and 212.3 million suffered from COPD.[1] Asthma is characterized by chronic airway inflammation and bronchial hyperresponsiveness, accompanied by varying degrees of expiratory airflow limitation.[2] COPD is defined by ongoing airway inflammation and dysfunctional tissue repair mechanisms, resulting in progressive and irreversible airflow obstruction.[3] In these two conditions, impaired lung function is a main clinical feature and plays a crucial role in their diagnosis.[2,3] The pathogenesis of asthma and COPD, while not fully

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elucidated, is thought to arise from a multifaceted interaction among genetic predisposition, immune dysregulation, and environmental exposures, including smoking, air pollution, and occupational hazards.[3–5] Further elucidation of the intricate mechanisms underlying this interplay could offer pivotal insights into the pathogenesis of these conditions, potentially revealing novel therapeutic targets and enabling the development of innovative treatment strategies and preventive measures.

Programmed cell death (PCD) plays a critical role in developmental processes, ensuring proper tissue homeostasis, and facilitating the elimination of damaged or abnormal cells.[6] Several forms of PCD have been identified in recent years, such as apoptosis, pyroptosis, autophagy, necroptosis, ferroptosis, cuproptosis, disulfidptosis, parthanatos, entotic cell death, netotic cell death, lysosome-dependent cell death, alkaliptosis, oxeiptosis, and zinc-dependent cell death.[7–10] Dysregulation of PCD has been implicated in multiple diseases, including asthma and COPD.[6,11] In asthma, epithelial apoptosis is mediated by several mechanisms, such as oxidative stress and viral infection.[12] Meanwhile, it has been revealed that the autophagy pathway activity is heightened in the lungs of COPD patients, with this activation particularly in epithelial cells and macrophages.[13]

Despite growing research, a thorough understanding of the association between PCD and asthma, COPD, and lung function remains elusive, particularly in relation to the critical PCD pathways driving disease progression and their prospective synergistic mechanisms. Mendelian randomization (MR) analysis, which uses genetic variants naturally randomized at conception as instrumental variables (IVs) to minimize the risk of reverse causation and confounding bias, has gained widespread adoption in research for uncovering causal links between exposures and outcomes. Moreover, it has been extensively utilized in identifying novel therapeutic targets.[14,15] As an extension of traditional MR, the summary data-based MR (SMR) method was devised to strengthen the ability to investigate genetic associations between molecular phenotypes and various diseases.[16] Accordingly, this research sought to explore the genetic association between PCD, as represented by PCD-related genes, and asthma, COPD, and lung function through the integration of multi-omics data, including protein abundance, gene expression, and DNA methylation.

## Materials and Methods

The study design is summarized as follows. The role of PCD-related genes at three biological levels was examined in this study using publicly available datasets (Table S1): protein abundance, gene expression, and gene methylation. For each biological level, MR analyses were performed for asthma and its two subtypes (allergic and non-allergic asthma), COPD and its two subtypes (COPD in ever-smokers and COPD in never-smokers), as well as lung function metrics, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and peak expiratory flow (PEF). Afterward, colocalization analyses were applied to enhance causal inference robustness. Potential causal genes were identified by integrating the results from MR analyses across these three distinct biological levels. Figure 1 presents an overview of the workflow based on the three key assumptions of Mendelian randomization.[17] This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Table S2).

### Data Sources and Gene Sets Associated with PCD

We explored the underlying molecular networks of PCD by integrating multi-omic data. Quantitative trait loci (QTL) was used to reveal relationships between single nucleotide polymorphisms (SNPs) and variation in protein abundance, gene expression levels, and DNA methylation. For the discovery cohorts, SNP-CpG associations in blood were obtained from the methylation quantitative trait loci (mQTL) dataset by Hatton et al, which included 3701 individuals of European ancestry.[18] Blood expression quantitative trait loci (eQTL) data were acquired from the eQTLGen consortium, comprising 31,684 mostly European individuals.[19] Additionally, blood protein quantitative trait loci (pQTL) data were sourced from Ferkingstad et al, involving 35,559 Icelanders.[20] For the replication cohorts, blood mQTL data from Hannon et al, involving 1175 European individuals[21] and blood eQTL data from the Genotype-Tissue Expression (GTEx) project, encompassing 755 mostly European individuals, were utilized. Additionally, pQTL data were drawn from Pietzner et al[22] and Sun_BB et al,[23] involving 10,708 and 3301 European individuals, respectively. Moreover, lung tissue eQTL data was sourced from the GTEx project, including 578 mostly European individuals.

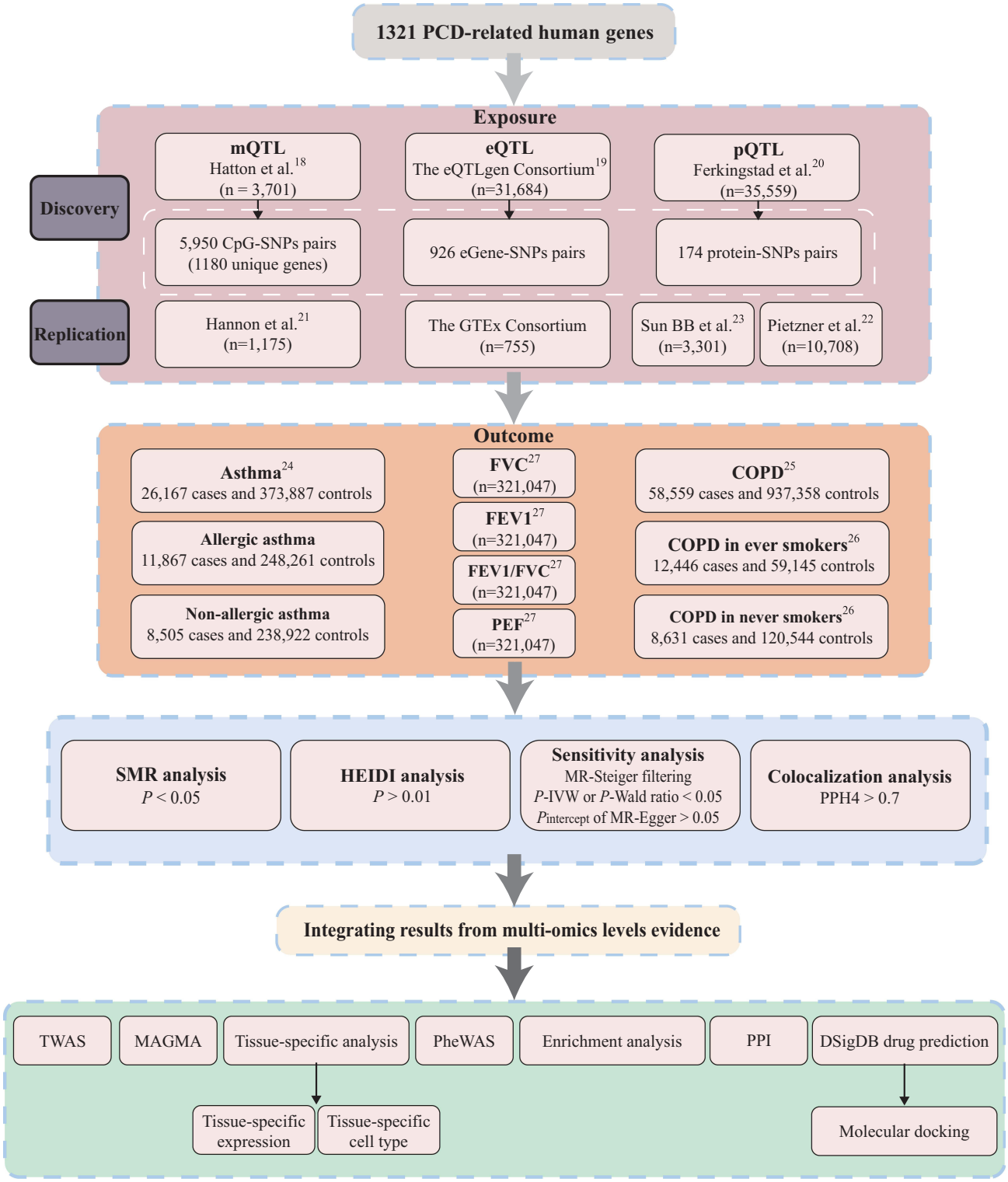


**Figure 1** Study design.

**Abbreviations**: PCD, programmed cell death; QTL, quantitative trait loci; SNP, single nucleotide polymorphism; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease; SMR, Summary data-level Mendelian randomization; HEIDI, heterogeneity in dependent instruments; MR, Mendelian randomization; PPH4, posterior probability of H4; TWAS, transcriptome-wide association studies; MAGMA, multi-marker analysis of genomic annotation; PheWAS, phenome-wide association study; PPI, protein-protein interaction; DSigDB, Drug Signatures Database.


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In this study, the genome-wide association study (GWAS) summary statistics for outcomes were exclusively derived from individuals of European descent. For overall asthma, we utilized the complete European subset of the asthma GWAS from the United Kingdom Biobank (UKB), provided by the Lee Lab (Phecode 495), which included 26,167 cases and 373,887 controls.[24] The GWAS for asthma subtypes, including allergic asthma (11,867 cases and 248,261 controls) and non-allergic asthma (8505 cases and 238,922 controls), was obtained from the R11 data release of the FinnGen study, with the diagnoses determined based on the International Classification of Diseases, 10th Revision (ICD-10). There were 58,559 cases and 937,358 controls in the COPD GWAS sourced from the Global Biobank Meta-analysis Initiative (GBMI),[25] with diagnoses determined according to ICD-9 and ICD-10. Subtypes for COPD included 12,446 cases and 59,145 controls for ever-smokers, and 8631 cases and 120,544 controls for never-smokers. Ever-smokers were defined as individuals who smoked regularly or occasionally, both in the past and currently, while never-smokers were those who had never smoked or had smoked less than 100 cigarettes in their lifetime.[26] As for lung function parameters (N = 321,047), FEV1, FVC, FEV1/FVC, and PEF were included, with genome-wide association testing conducted using a genetic model implemented through BOLT-LMM v2.3.[27,28] It is noteworthy that exposure and outcome samples did not overlap. An exhaustive set of 1321 unique genes associated with 14 different PCD pathways has been identified. Detailed gene lists are provided in Table S3 and Supplementary Material 1.

## SMR Analysis

We used SMR analysis to examine the relationships between PCD-related protein abundance, gene expression, and gene methylation with the risk of asthma and COPD, including their subtypes, as well as lung function. With SMR, the top cis-QTL can be used to obtain greater statistical power than traditional MR analysis.[16] The top cis-QTL were identified by delineating a chromosomal region of ±1000 kb around the target gene and selecting those variants that met a *P*-value threshold of $5.0\times10^{-8}$. Heterogeneity in Dependent Instrument (HEIDI) analysis was used to determine whether gene phenotypes resulting from SNPs were due to linkage disequilibrium (LD). The *P*-value of the HEIDI test >0.01 suggested that the relationship between cis-QTL and outcome was unlikely caused by pleiotropy. We performed the SMR and HEIDI tests using SMR software (SMR v1.3.1). *P*-values were adjusted using the false discovery rate (FDR) with the Benjamini–Hochberg method, and associations with FDR < 0.05 were considered statistically significant. Associations with *P*-SMR <0.05 were identified as potentially causal links, and sensitivity analysis was subsequently conducted.

## Sensitivity Analysis

The R TwoSampleMR package was utilized to perform two sample MR (TSMR) to assess the robustness of our results and evaluate the causal relationships between mQTL and eQTL, as well as between eQTL and pQTL. Associations that failed the sensitivity analysis were excluded from further investigation. Additional methodological details are provided in Supplementary Material 1.

## Colocalization Analysis

To determine whether the cis-QTL and outcome share a causal variant and to separate this from confounding due to LD, we conducted colocalization analysis on associations with FDR < 0.05 identified in the SMR analysis. The coloc R package was used to estimate the posterior probability of shared variants.[29] Genomic region windows were set at ±1000 kb for both pQTL-GWAS and eQTL-GWAS and at ±500 kb for mQTL-GWAS. A posterior probability for H4 (PPH4) > 0.7 across various priors and window settings was regarded as strong evidence for colocalization, whereas PPH4 > 0.5 was interpreted as moderate evidence for colocalization.

## Evidence Integration at the Multi-Omics Level

We integrated findings from three distinct tiers of gene regulation to explore the underlying epigenetic mechanisms in the blood, aiming to investigate the relationships between the regulation of PCD-related genes and asthma, COPD, and lung function. As proteins represent the final expression products of genes, it is crucial to identify causality at the protein level. Therefore, evidence from multi-omics must demonstrate a causal link between pQTL and outcome. In accordance with this principle, we classified the causal candidate genes into three distinct tiers as follows: 1) Tier 1 genes exhibited

robust associations between pQTLs and outcomes (FDR < 0.05) with strong colocalization evidence (PPH4 > 0.7). Additionally, both mQTLs and eQTLs showed significant associations with outcomes (FDR < 0.05). 2) Tier 2 genes were characterized by significant associations between pQTLs and outcomes (FDR< 0.05) and strong colocalization PPH4 > 0.7. At the eQTL and mQTL levels, one type demonstrated significant associations with the outcomes (FDR < 0.05), while the other indicated potential relationships (*P*-value < 0.05). 3) Tier 3 genes were defined by significant associations between pQTLs (FDR < 0.05) and outcomes, with moderate colocalization strength (0.5 ≤ PPH4 < 0.7). These genes also exhibited potential associations with outcomes at both the eQTL and mQTL levels (*P*-values < 0.05).

## Transcriptome-Wide Association Studies Analysis and Gene Analysis

To validate the target genes, we applied Functional Summary-based Imputation (FUSION) for transcriptome-wide association studies (TWAS), enabling the prediction of gene expression levels and their potential associations with the outcomes.[30] Cross-tissue gene expression weights constructed using sparse canonical correlation analysis (sCCA) from the GTEx were utilized, enhancing statistical power by integrating signals across multiple tissues and offering an advantage over single-tissue TWAS.[31] Subsequently, the sCCA-TWAS test results were combined using the aggregate Cauchy association test (ACAT). In addition, multi-marker analysis of genomic annotation (MAGMA, version 1.08) was applied to perform gene analysis of GWAS data, uncovering relationships between genetic variants and phenotypic traits.[32] Default parameters were used to aggregate SNP-level association statistics into gene scores, which quantified the degree of association between each gene and the phenotype.

## Tissue-Specific Analysis

As potential drug targets, the identified PCD-related genes were further examined for their potential causality with outcomes using lung tissue eQTL data derived from GTEx. Besides, the Human Protein Atlas (HPA, https://www.proteinatlas.org/) was employed to investigate the transcriptome of these targets in normal human lung tissues, including their expression levels across various cell types.

## Phenome-Wide Association Analysis

To further evaluate the horizontal pleiotropy and potential side effects of the identified targets, a phenome-wide association study (PheWAS) was conducted using the AstraZeneca PheWAS Portal (https://azphewas.com/), which included data from the UKB.[33] To mitigate the risk of false positives, we applied multiple corrections and established a stringent threshold of 2E−9, as set by default in the AstraZeneca PheWAS Portal.

## Enrichment Analysis

The R ClusterProfiler package[34] was employed to examine the functional attributes and biological importance of the identified PCD-related genes in relation to respiratory traits through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. The GO analysis covered biological process (BP), molecular function (MF), and cellular component (CC). Additionally, the KEGG pathway analysis provided detailed insights into relevant metabolic pathways. It was considered significant for GO terms and KEGG pathways with FDR < 0.1.

## Protein-Protein Interaction (PPI) and Candidate Drug Prediction

PPI networks were developed through STRING (https://string-db.org/)[35] and GeneMANIA (https://genemania.org/)[36] to explore the potential interactions among the identified targets associated with respiratory traits. Visualization of PPI results was further enhanced by Cytoscape (version 3.10.1).[37] To evaluate the potential of the identified genes as therapeutic targets, we investigated their interactions with various drugs by querying the Drug Signatures Database (DSigDB).[38] Through DSigDB, medicines and chemicals can be correlated with the target genes, allowing for the prediction of drug candidates and the assessment of therapeutic potential.

## Molecular Docking

To gain a comprehensive understanding of the effects of drug candidates on targets associated with respiratory traits and assess their druggability, molecular docking simulations were conducted at the atomic level. A binding energy score below −5.0 kcal/

mol was considered indicative of potentially stable binding affinity. Additional methodological details are provided in Supplementary Material 1.

# Results

## Causal Effect Estimation from Multi-Omics Levels

A comprehensive multi-omics analysis revealed a hierarchical classification of PCD-related genes associated with asthma, COPD, including their subtypes, as well as lung function parameters. Our investigation identified ERBB3, SFRP1, and FGFR1 as tier 1 genes linked to COPD in never-smokers, FEV1, and FEV1/FVC, respectively, all of which are involved in apoptosis. Additionally, HSPA1B and MAPK3 were categorized as tier 2 genes, with HSPA1B linked to non-allergic asthma and MAPK3 to overall COPD, where HSPA1B is associated with apoptosis and MAPK3 with autophagy. Furthermore, IDUA was classified as a tier 3 gene for overall asthma, functioning in lysosome-dependent cell death.

### Asthma

A total of 960 CpG sites near 377 distinct genes, 163 gene expressions, and 27 proteins passed the HEIDI test and sensitivity analysis across asthma and its subtypes (Figure 2 and Tables S4–S12). Following FDR correction, 75 CpG sites near 38 unique genes, 25 gene expressions, and 4 proteins were retained (Tables S4–S12). Among these, 72 associations exhibited

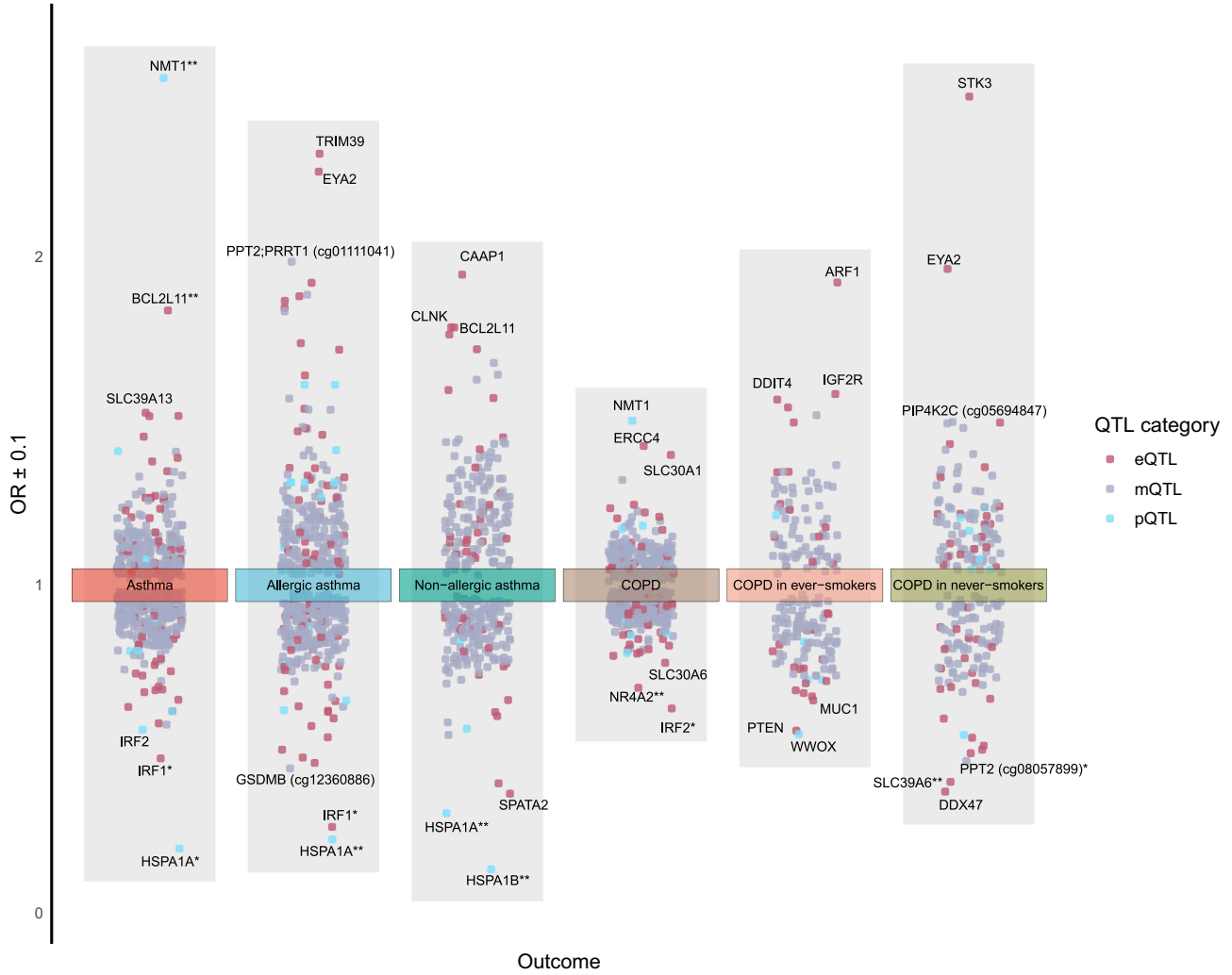


**Figure 2** Volcano plot for associations between genetically predicted gene methylation, gene expression and protein abundance of programmed cell death-related genes with asthma and chronic obstructive pulmonary disease. *FDR < 0.05; **FDR < 0.05 and PPH4 > 0.5.
**Abbreviations**: COPD, chronic obstructive pulmonary disease; QTL, quantitative trait loci; OR, odds ratio.

colocalization evidence (Tables S13–S15). For overall asthma, genetically predicted methylation level of cg14652403 (OR = 1.113), IDUA expression level (OR = 1.121), and IDUA protein abundance (OR = 1.079) showed positive associations with disease risk (Figures 3 and 4). In the context of non-allergic asthma, genetically predicted methylation level of cg12614213 (OR = 0.758) and HSPA1B protein abundance (OR = 0.136) were inversely associated with disease risk, whereas HSPA1B expression level (OR = 1.246) showed a positive association (Figures 3 and 4). Detailed links between methylation, gene expression, and protein abundance for these genes are presented in Supplementary Material 2 and Tables S16 and S17.

### COPD

Our results revealed 586 CpG sites near 263 unique genes, 121 gene expressions, and 18 proteins passed the HEIDI test and sensitivity analyses across COPD and its subtypes (Figure 2 and Tables S18–S26). After FDR correction, significant associations were identified for 40 CpG sites in proximity to 19 distinct genes, 14 gene expressions, and 3 proteins (Tables S18–S26). Among these, 35 associations demonstrated colocalization evidence (Tables S27–S29). For overall COPD, genetically predicted MAPK3 expression level (OR = 0.924) and MAPK3 protein abundance (OR = 0.848) were inversely correlated with disease risk, whereas the methylation level of cg00192773 (OR = 1.081) showed positive associations with disease risk (Figures 3 and 4). With regard to COPD in never-smokers, genetically predicted methylation levels of cg10869879 (OR = 0.765), cg23731805 (OR = 0.785), cg00907267 (OR = 0.648), ERBB3 expression levels (OR = 0.654) and ERBB3 protein abundance (OR = 0.544) were inversely associated with disease risk. Conversely, methylation of cg17843101 (OR = 1.398) showed positive associations with disease risk (Figures 3 and 4). A detailed description of the relationships among methylation, gene expression, and protein abundance for these genes is available in Supplementary Material 2 and Tables S16 and S17.

### Lung Function Parameters

Our analysis identified 1763 CpG sites near 569 unique genes, 295 gene expressions, and 43 proteins passed the HEIDI test and sensitivity analyses across 4 lung function parameters (Figure 5 and Tables S30–S38). After FDR correction, 722 CpG sites near 292 unique genes, 131 gene expressions, and 24 proteins were retained (Tables S30–S38). Among these, 337 associations exhibited colocalization evidence (Tables S39–S41). In the context of FEV1, genetically predicted methylation levels of cg14904908 (Beta = −0.047), cg07935886 (Beta = −0.065), cg01074584 (Beta = −0.072), cg03133371 (Beta = −0.069), cg00000321 (Beta = −0.078), cg10406295 (Beta = −0.081), cg14824386 (Beta = −0.050), SFRP1 expression level (Beta = −0.117), and SFRP1 protein abundance (Beta = −0.074) were inversely associated with FEV1 (Figures 4 and 6). For FEV1/FVC, genetically predicted methylation level of cg12614213 (Beta = −0.065) was negatively correlated with FEV1/FVC, whereas methylation levels of cg15321288 (Beta = 0.021) and cg24828864 (Beta = 0.057), along with FGFR1 expression level (Beta = 0.043) and FGFR1 protein abundance (Beta = 0.127), exhibited positive associations with FEV1/FVC (Figures 4 and 6). Further details on the relationships between methylation, gene expression, and protein abundance for these genes are presented in Supplementary Material 2 and Tables S16 and S17.

Among the target genes, the associations between mQTL-eQTL and eQTL-pQTL for these target genes were further supported by colocalization analysis with PPH3+PPH4 > 0.8 except the colocalization between cg00000321 and cg01074584 and SFRP1 expression level[39] (Tables S16 and S17). Although not all correlations found in the validation cohorts achieved statistical significance, a substantial proportion of the investigated genetic relationships demonstrated directional consistency with the discovery cohort (Table S42). Interestingly, for asthma, COPD, and lung function, we observed genetic overlaps in QTLs that passed FDR correction and colocalization analysis across three molecular levels (Figure 7).

## TWAS and Gene Analysis

Through cross-tissue TWAS analysis, IDUA, MAPK3, SFRP1, and FGFR1 were identified as susceptibility genes associated with their respective phenotypes, while the analysis of HSPA1B and ERBB3 was excluded due to the unavailability of weight data (Table S43). Furthermore, MAGMA gene-based analysis confirmed five out of the six target genes, excluding IDUA, as pathogenic genes linked to their corresponding phenotypes (Table S44).

| Outcome | Tier | PCD pattern | Gene | probe ID | OR (95%CI) | P_SMR | FDR | P_HEIDI | P_MR | P_Intercept |
|---|---|---|---|---|---|---|---|---|---|---|
| COPD in never−smokers | Tier 1 | Apoptosis | ERBB3 | | 0.544 (0.395, 0.749) | 1.89e−04 | 0.013 | 0.022 | 2.04e−05 | / |
| | | | ERBB3 | | 0.654 (0.537, 0.797) | 2.4e−05 | 0.007 | 0.059 | 2.27e−04 | 0.259 |
| | | | ERBB3 | cg23731805 | 0.785 (0.705, 0.874) | 1.01e−05 | 0.009 | 0.547 | 3.01e−06 | / |
| | | | ERBB3 | cg17843101 | 1.398 (1.174, 1.665) | 1.67e−04 | 0.049 | 0.105 | 2.95e−05 | / |
| Overall COPD | Tier 2 | Autophagy | MAPK3 | | 0.848 (0.797, 0.902) | 1.9e−07 | 3.28e−05 | 0.298 | 2.77e−13 | 0.847 |
| | | | MAPK3 | | 0.924 (0.898, 0.951) | 9.8e−08 | 4.53e−05 | 0.395 | 8.24e−17 | 0.190 |
| | | | MAPK3 | cg00192773 | 1.081 (1.004, 1.164) | 0.040 | 0.433 | 0.010 | 0.035 | / |
| Non−allergic asthma | Tier 2 | Apoptosis | HSPA1B | | 0.136 (0.062, 0.298) | 6.21e−07 | 5.4e−05 | 0.011 | 0.016 | 0.157 |
| | | | HSPA1B | | 1.246 (1.078, 1.441) | 0.003 | 0.333 | 0.010 | 1.63e−04 | 0.963 |
| | | | HSPA1B | cg21080034 | 0.758 (0.664, 0.866) | 4.26e−05 | 0.036 | 0.198 | 0.002 | 0.544 |
| Overall asthma | Tier 3 | Lysosome−dependent cell death | IDUA | | 1.079 (1.035, 1.124) | 3.5e−04 | 0.020 | 0.017 | 0.002 | 0.913 |
| | | | IDUA | | 1.121 (1.050, 1.197) | 6.65e−04 | 0.031 | 0.240 | 0.007 | 0.664 |
| | | | IDUA | cg14652403 | 1.113 (1.047, 1.182) | 5.28e−04 | 0.028 | 0.252 | 2.56e−04 | 0.275 |


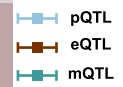


**Figure 3** Associations of genetically predicted molecular features of identified PCD-related genes with asthma and COPD.
**Abbreviations**: PCD, programmed cell death; OR, odds ratio; CI, confidence interval; SMR, Summary data-level Mendelian randomization; HEIDI, heterogeneity in dependent instruments; MR, Mendelian randomization; QTL, quantitative trait loci; COPD, chronic obstructive pulmonary disease.


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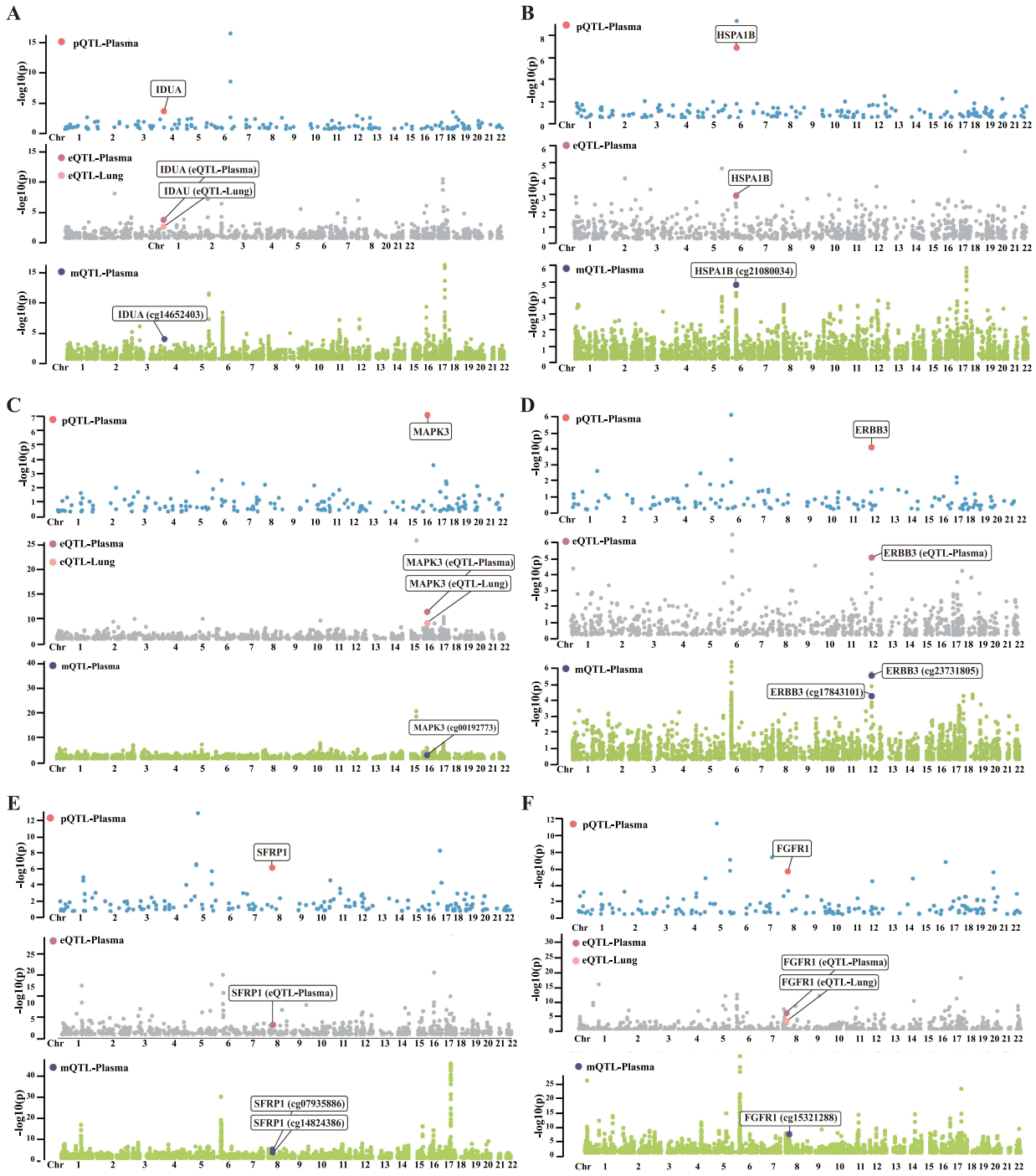


**Figure 4** Manhattan plot for associations between molecular features of identified PCD-related genes and asthma, COPD, and lung function. (**A**) Manhattan plot for associations between molecular features of IDUA and overall asthma. (**B**) Manhattan plot for associations between molecular features of HSPA1B and non-allergic asthma. (**C**) Manhattan plot for associations between molecular features of MAPK3 and overall COPD. (**D**) Manhattan plot for associations between molecular features of ERBB3 and COPD in never-smokers. (**E**) Manhattan plot for associations between molecular features of SFRP1 and FEV1. (**F**) Manhattan plot for associations between molecular features of FGFR1 and FEV1/FVC.

**Abbreviations**: PCD, programmed cell death; QTL, quantitative trait loci; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.


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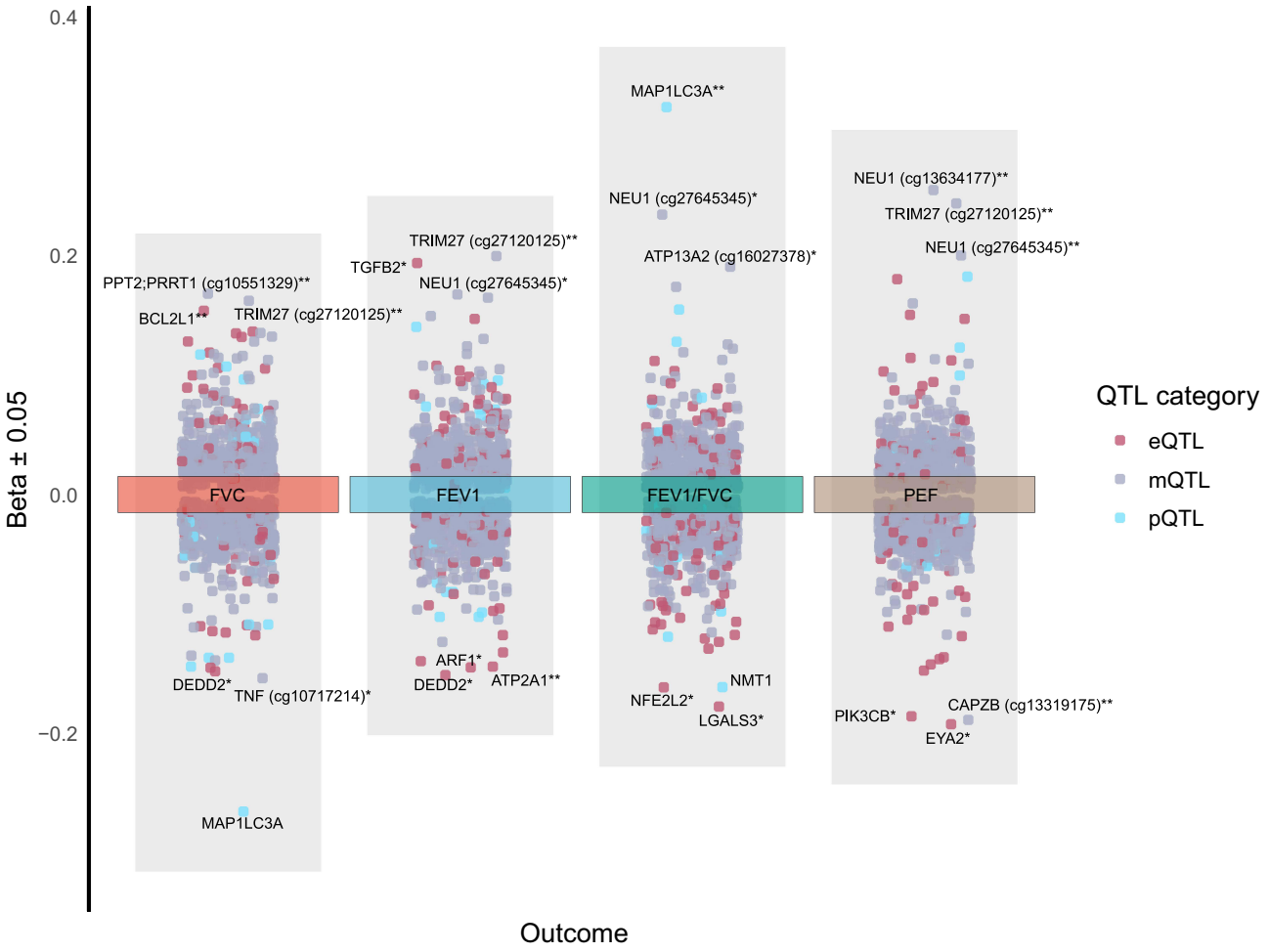


**Figure 5** Volcano plot for associations between genetically predicted gene methylation, gene expression, and protein abundance of PCD-related genes with lung function. *FDR < 0.05; **FDR < 0.05 and PPH4 > 0.5.
**Abbreviations**: PCD, programmed cell death; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; QTL, quantitative trait loci.

## Tissue-Specific Analysis

Among the target genes, HSPA1B, ERBB3, and SFRP1 were excluded from the tissue-specific SMR analysis due to the unavailability of lung tissue data. As shown in Table S45, in lung tissue, genetically predicted expression of IDUA (OR = 1.092) and FGFR1 (Beta = 0.066) were positively associated with overall asthma risk and FEV1/FVC, respectively. Conversely, genetically predicted expression of MAPK3 (OR = 0.767) exhibited a positive association with overall COPD risk. Notably, the direction of these causal relationships was consistent with the findings from the discovery cohort.

Further tissue-specific cell type analysis (Figure 7), based on data from the HPA, revealed that ERBB3 was enriched in alveolar type 1 and alveolar type 2 cells, as well as macrophages, while SFRP1 was enriched in Fibroblast_2 and mast cells within lung tissue. Additionally, HSPA1B, MAPK3, and FGFR1 were all enriched in smooth muscle, NK, Fibroblast_1, and endothelial cells in lung tissue. These findings underscore the potential roles of these target genes in regulating pulmonary immune responses, alveolar and airway function, tissue and vascular repair, and inflammation. However, IDUA was not enriched in any specific cell type within lung tissue.

## PheWAS

As shown in Table S46, the PheWAS analysis suggested that elevated levels of IDUA may contribute to oncology suppression while simultaneously increasing the risk of asthma. In contrast, higher ERBB3 levels were associated with

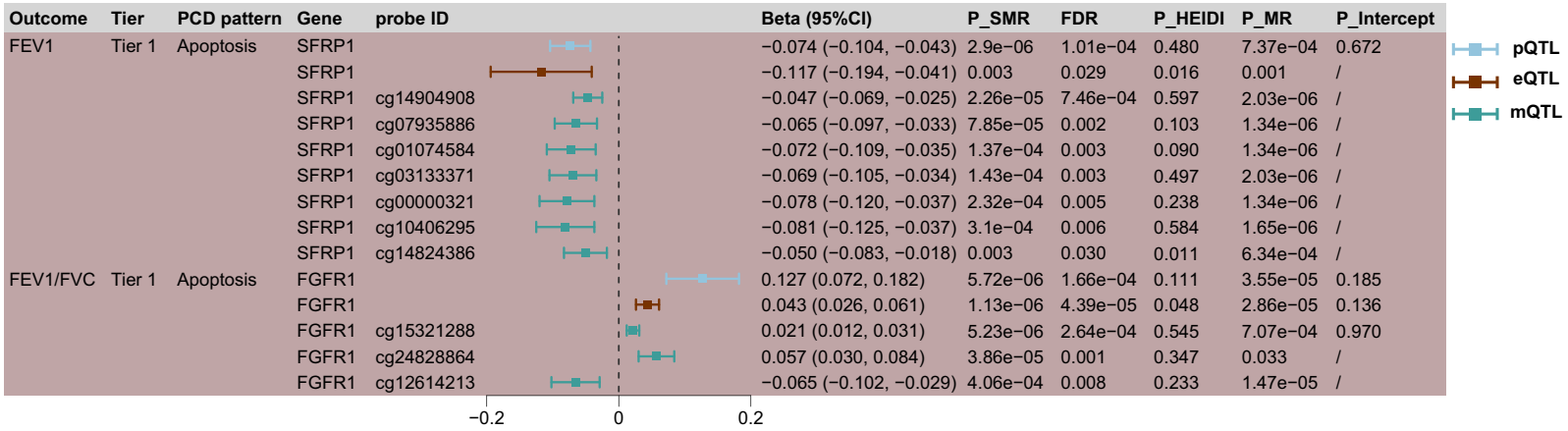


**Figure 6** Associations of genetically predicted molecular features of identified PCD-related genes with lung function.

**Abbreviations**: PCD, programmed cell death; CI, confidence interval; SMR, Summary data-level Mendelian randomization; HEIDI, heterogeneity in dependent instruments; MR, Mendelian randomization; QTL, quantitative trait loci; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

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a reduced risk of COPD in never-smokers and demonstrated a potential role in suppressing inflammation. Additionally, no significant associations were observed between the other target genes and any phenotypes at the gene level.

## Enrichment Analysis and PPI Networks

As illustrated in Figure 7, within the BP category of the GO term, six target genes in relation to respiratory traits were primarily enriched in pathways related to apoptotic signaling (including the extrinsic apoptotic signaling pathway and extrinsic apoptotic signaling pathway in the absence of ligand), mesenchymal development, and signal transduction under ligand-absent conditions.

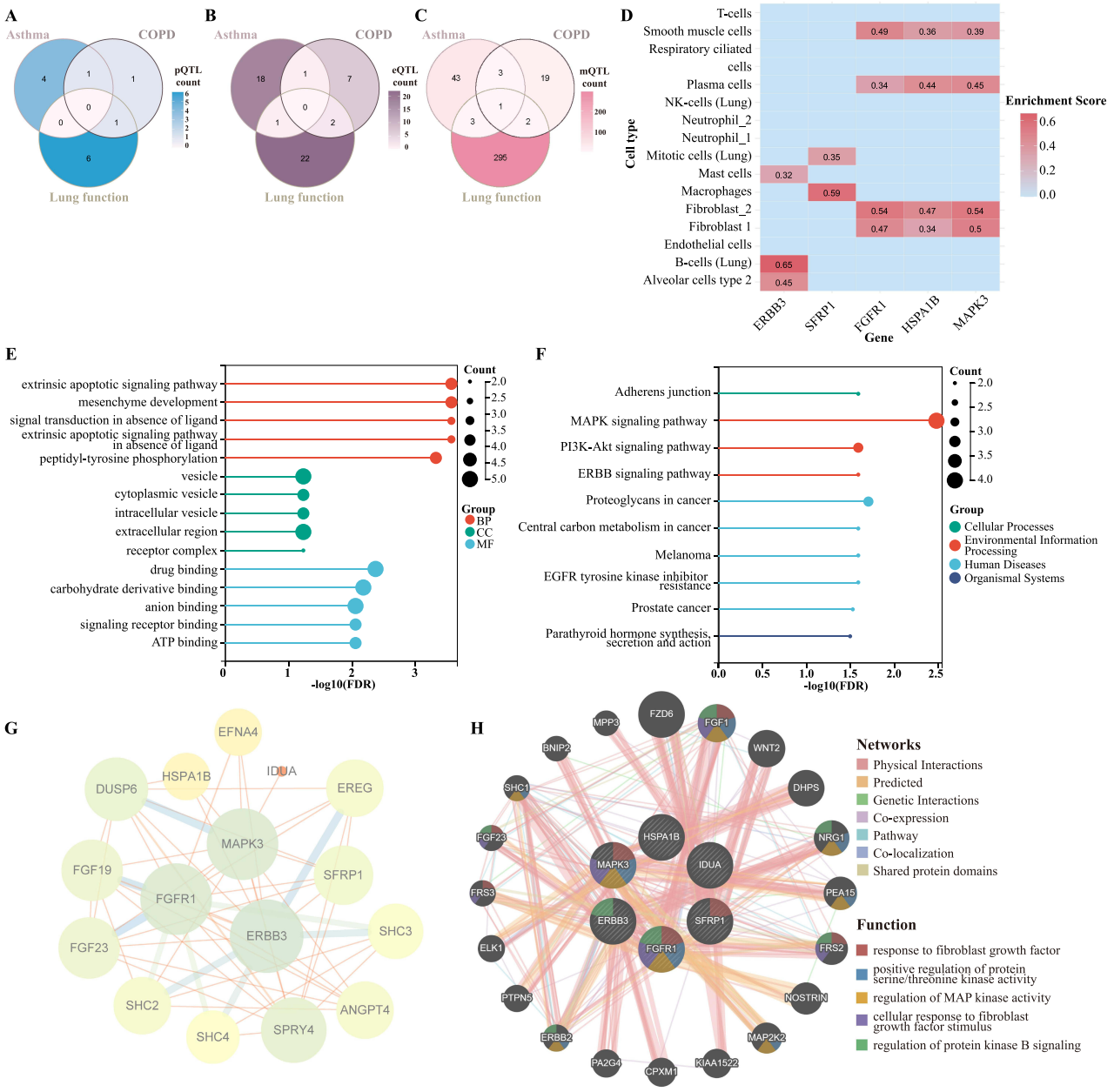


**Figure 7** Multi-omics integration reveals cross-trait QTL overlaps, tissue/cell-type specificity, functional enrichment, and interaction networks of identified PCD-related genes. (**A**) Venn diagram quantifying the overlapping pQTLs that passed FDR correction and colocalization analysis. (**B**) Venn diagram quantifying the overlapping eQTLs that passed FDR correction and colocalization analysis. (**C**) Venn diagram quantifying the overlapping mQTLs that passed FDR correction and colocalization analysis. Encircled numbers represent the number of genes shared between two or more phenotypes. (**D**) Heatmap of enrichment scores for cell types of identified PCD-related genes in lung tissue. (**E**) GO enrichment results for identified PCD-related genes. (**F**) KEGG enrichment results for identified PCD-related genes. (**G**) PPI network of proteins encoded by identified PCD-related genes constructed by STRING. (**H**) PPI network of proteins encoded by identified PCD-related genes constructed by GeneMANIA.
**Abbreviations**: PCD, programmed cell death; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; QTL, quantitative trait loci.

In the CC class, the most significantly enriched pathways were associated with intracellular transport and communication, specifically involving vesicles, cytoplasmic vesicles, and intracellular vesicles. The MF category highlighted significant enrichment in binding activities, such as drug binding, carbohydrate derivative binding, anion binding, signaling receptor binding, and ATP binding. Additionally, KEGG pathway analysis revealed that the target genes were mainly enriched in the adherens junction, MAPK signaling pathway, PI3K-Akt signaling pathway, and ErbB signaling pathway. Moreover, 10 interacting proteins and 20 interacting proteins of the targets were predicted using the STRING and GeneMANIA database, respectively.

## Candidate Drug Prediction

Table S47 presents the top 5 candidate chemical compounds identified after FDR correction in association with six target genes. The analysis highlighted Bisphenol A (CTD 00000312), Lapatinib (CTD 00004348), and NVP-TAE684 (CTD 00004657) emerged as the most significant candidates. Specifically, Bisphenol A was related to SFRP1, ERBB3, IDUA, MAPK3, and FGFR1, whereas Lapatinib and NVP-TAE684 were linked to ERBB3 and MAPK3. Additionally, most target genes were found to interact with Bisphenol A and resveratrol (CTD 00002483).

## Molecular Docking

To identify binding sites and evaluate the interactions between the candidate drugs and the proteins encoded by their respective target genes, molecular docking was conducted to calculate the binding energies of each interaction. Among the analyzed complexes (Figure 8 and Table S48), MAPK3 bound to NVP-TAE684 (−10.4 kcal/mol), HSPA1B to EINECS 250–892-2 (−10.2 kcal/mol), ERBB3 to Lapatinib (−9.8 kcal/mol), IDUA to Bisphenol A (−7.9 kcal/mol),

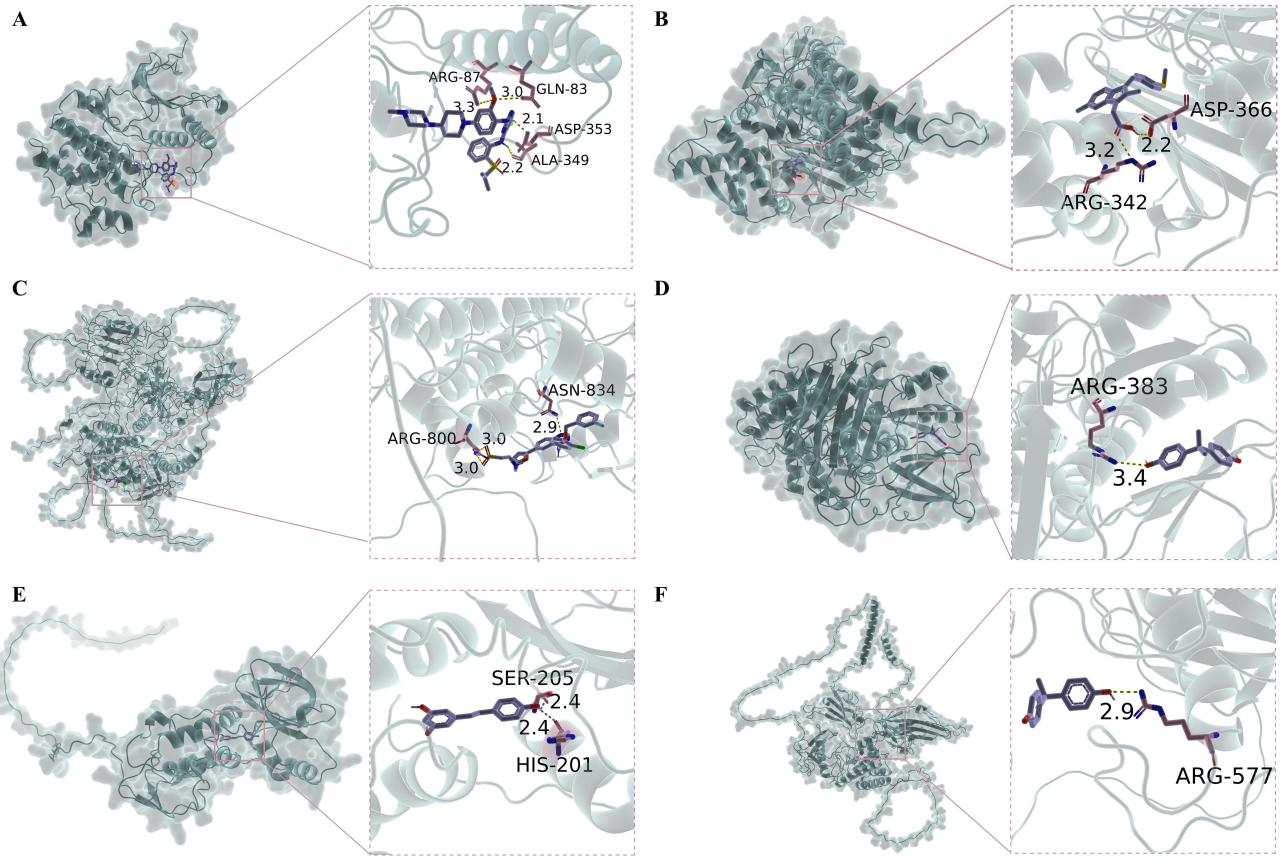


**Figure 8** Docking results showing the lowest binding energies for proteins encoded by identified PCD-related genes with candidate chemical compounds. (**A**) MAPK3 docked with NVP-TAE684, (**B**) HSPA1B docked with EINECS 250–892-2, (**C**) ERBB3 docked with Lapatinib, (**D**) IDUA docked with Bisphenol A, (**E**) SFRP1 docked with Resveratrol, and (**F**) FGFR1 docked with Bisphenol A.
**Abbreviation**: PCD, programmed cell death.


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SFRP1 to Resveratrol (−7.7 kcal/mol), and FGFR1 to Bisphenol A (−6.6 kcal/mol) exhibited the lowest binding energies observed for these proteins, suggesting highly stable binding.

## Discussion

In this study, we comprehensively utilized multi-omics data and applied MR analysis to identify putative causal PCD-related genes, as well as to elucidate the underlying mechanisms involved in asthma, COPD, and lung function parameters. Through the integration of GWAS data with mQTLs, eQTLs, and pQTLs derived from peripheral blood, we identified six PCD-related genes along with their regulatory elements associated with respiratory traits. Specifically, ERBB3 was linked to COPD in never-smokers, SFRP1 to FEV1, FGFR1 to FEV1/FVC, HSPA1B to non-allergic asthma, MAPK3 to overall COPD, and IDUA to overall asthma. These genes are involved in distinct PCD pathways, with ERBB3, SFRP1, FGFR1, and HSPA1B implicated in apoptosis, MAPK3 in autophagy, and IDUA in lysosome-dependent cell death. To examine the potential pleiotropic effects and evaluate possible drug side effects of these targets, we conducted a PheWAS analysis. Additionally, enrichment analysis and PPI network construction were performed to elucidate the biological relevance of these targets. Finally, we predicted and molecularly docked drugs corresponding to these targets, underscoring their druggable potential.

ERBB3 encodes for a transmembrane receptor tyrosine kinase and is a member of the ERBB family of receptor tyrosine kinases (RTKs). A previous MR study reported that elevated gene expression of ERBB3 exerts a protective factor against spirometry-defined COPD, whereas our findings specifically identify multi-omics levels of ERBB3 as a protective factor for COPD in never-smokers. Moreover, our study further extended and refined this finding through the integration of multi-omics. A study characterizing a cohort of smokers revealed that bronchial epithelial expression of ERBB3 is elevated in current smokers, irrespective of their COPD status, suggesting that the ERBB receptor may be a key regulator of epithelial responses to cigarette smoke exposure.[40] Additionally, ERBB3 signaling has been implicated in regulating mucin overproduction induced by cigarette smoke,[41] which in turn contributes to the irreversible airflow limitation in COPD.[42] However, evidence from patients with chronic systolic heart failure indicates that ERBB3 inhibits TNF-α production in nonclassical monocytes,[43] while in COPD, TNF-α plays a pivotal role in promoting lung inflammation.[44] The phenome-wide analysis further indicates that elevated ERBB3 expression is associated with reduced inflammation. Thus, we suspect that the function of ERBB3 in COPD could differ depending on smoking status, while further investigations are needed.

Secreted frizzled-related protein 1 (SFRP1) exhibits inhibitory effects on WNT/β-catenin signaling,[45] a pathway critical for lung development.[46,47] Previous research has shown that the activation of the canonical WNT/β-catenin pathway promotes the proliferative capacity of pulmonary epithelial cells, suggesting its crucial component in epithelial cell repair mechanisms.[48–50] According to our study, genetically predicted multi-omics levels of SFRP1 are associated with reduced FEV1. Experimental evidence has shown that the selective upregulation of SFRP1 in human emphysema activates destructive mechanisms, leading to the loss of lung tissue.[45] A pronounced decrease in nuclear β-catenin levels has been observed in the lung tissue of COPD patients.[51] Additionally, in murine models of emphysema, treatment with lithium chloride, a recognized modulator of WNT/β-catenin activity, effectively reduced airspace enlargement and mitigated emphysema progression.[51] Our findings partially coincide with these studies, reinforcing the potential role of SFRP1 in FEV1 decline.

Fibroblast growth factors (FGFs) are critical mediators of chronic inflammation, fibrosis, and tissue repair across various contexts, including pulmonary tissues.[52] Their biological effects are primarily initiated through interactions with four high-affinity receptors, namely FGF receptor (FGFR).[52] Findings from this study revealed that multi-omics levels of FGFR1 are associated with an increase in the FEV1/FVC. FGF10 has been shown to restore pulmonary glycocalyx integrity, mitigate endothelial apoptosis, and alleviate smoke-induced COPD through the activation of FGFR1 signaling pathways.[53] Additionally, FGF-1 has shown protective and therapeutic effects in addressing pulmonary fibrosis driven by Transforming Growth Factor (TGF)-β1 by inhibiting myofibroblast formation. These effects involve stimulating the proliferation of alveolar epithelial cells (AECs), modulating TGF-β1 signaling, and regulating FGFR1 expression, which was found elevated in AECs but decreased in fibroblasts.[54]

HSPA1B, a member of the Hsp70 family,[55] functions as a stress-inducible protein essential for maintaining cellular homeostasis,[56] potentially through protective mechanisms that defend cells against DNA damage.[57] Based on the current findings, methylation of cg21080034 may reduce the expression of HSPA1B, consequently lowering the risk of non-allergic asthma. However, the effect of HSPA1B protein abundance levels on non-allergic asthma is inconsistent with its gene expression

levels, possibly due to factors such as post-translational modifications,[58] PPI,[59] or isoform effects.[60] Non-allergic asthma is predominantly characterized by inflammation mediated by neutrophils.[61] HspA1A, regarded as completely analogous to HSPA1B in human tissues,[62] facilitates autonomous apoptosis in primary bone marrow-derived neutrophils.[63] This process, along with the subsequent clearance of apoptotic neutrophils, is associated with the termination of inflammation.[64]

Mitogen-activated protein kinase 3 (MAPK3), also called extracellular regulated kinases 1, serine/threonine kinase, is activated downstream in the MAPK signaling cascade and constitutes the final step in this crucial pathway.[65] Cigarette smoke has been shown to promote the production of matrix metalloproteinase-1 (MMP-1),[66,67] which contributes to the development of pulmonary emphysema.[68] However, this contrasts with the findings of our study, which revealed that hypomethylation of cg00192773 is associated with a decreased risk of COPD through the upregulation of MAPK3 expression. The MAPK pathway integrates mesenchymal and epithelial signals necessary for respiratory tract development.[69] The disruption of normal MAPK cascade function has been associated with the pathogenesis of various conditions,[70] such as neurodegenerative[71] and autoimmune diseases.[72] Previous MR studies have identified MAPK3 as a potential protective target for heart failure[73] and ulcerative colitis.[74] Additionally, MR analysis is thought to reflect the cumulative impact of lifelong exposure to MAPK3 levels rather than the influence of exposure confined to a specific time window.[75] Further research is needed to clarify the findings.

α-L-iduronidase (IDUA) is essential for the sequential breakdown of glycosaminoglycan (GAG).[76] Mutations in the IDUA gene frequently lead to mucopolysaccharidosis type I (MPS I), an autosomal recessive lysosomal storage disorder (LSD), which is a destructive genetic condition.[76] According to this study, multi-omics levels of IDUA are associated with an increased risk of asthma. Respiratory involvement is a common feature across most MPS types, with many manifestations stemming from GAG deposits and resulting in prominent airway obstruction.[77] Furthermore, a successful enzyme replacement therapy (ERT) for MPS I has been reported, in which participants received weekly intravenous administration of the study drug or placebo for 26 weeks. This intervention led to an improvement in vital capacity (VC), with an observed 11% increase compared to baseline levels.[78]

The major strength of our study lies in the implementation of a comprehensive MR design, which effectively minimizes bias due to confounding and reverse causation. By leveraging genetic variants, we were able to estimate the causality of PCD-related protein abundance, gene methylation, and gene expression on asthma, COPD, and lung function parameters. The integration of multi-omics evidence enhanced causal inference, while colocalization analysis mitigated potential bias arising from LD. Additionally, the large-sample GWASs significantly enhanced the statistical power of our analysis. Moreover, the reproducibility of our findings across diverse datasets further validated the robustness of our results. Nevertheless, certain limitations warrant careful consideration. Firstly, the scope of the current analysis was confined to populations of European descent, necessitating further studies to confirm the generalizability of these findings across diverse ancestries. Secondly, our analysis focused on plasma protein levels in relation to asthma, COPD, and lung function. However, we were unable to evaluate protein levels in other tissues. Evaluating protein levels in additional tissues, particularly lung tissue, could offer deeper insights into the pathogenesis of these conditions. Thirdly, the limited representation of PCD-related proteins within the pQTL dataset restricted our capacity to fully explore the causality between the proteins and asthma, COPD, and lung function. Fourthly, our study focused exclusively on QTLs in cis-regions, potentially overlooking regulatory contributions from trans-regions. Although trans-acting domains likely influence disease networks, their causal relationships are complex and challenging to interpret.[19] Finally, functional experiments remain necessary to validate and further substantiate our findings.

## Conclusion

By employing a multi-omics MR method, our findings identified six PCD-related genes whose effects on asthma, COPD, and lung function are mediated by alterations at the levels of gene methylation, gene expression, and protein abundance. Based on these potential causal pathways, this study deepens the insights into these conditions and highlights potential pharmacological targets for therapeutic intervention.

## Abbreviations

COPD, chronic obstructive pulmonary disease; CRD, chronic respiratory disease; PCD, Programmed cell death; MR, Mendelian randomization; IV, instrumental variables; SMR, summary data-based MR; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; KEGG, Kyoto Encyclopedia of Genes and Genomes; MSigDB, Molecular Signatures Database; QTL, quantitative trait loci; SNP, single nucleotide polymorphism; mQTL, methylation quantitative trait loci; eQTL, expression quantitative trait loci; pQTL, protein quantitative trait loci; GTEx, Genotype-Tissue Expression; GWAS, genome-wide association study; UKB, United Kingdom Biobank; ICD-10, International Classification of Diseases, 10th Revision; GBMI, Global Biobank Meta-analysis Initiative; HEIDI, Heterogeneity in Dependent Instrument; LD, linkage disequilibrium; FDR, false discovery rate; TSMR, two sample Mendelian randomization; IVW, inverse-variance weighting; PPH4, posterior probability for H4; FUSION, Functional Summary-based Imputation; TWAS, transcriptome-wide association studies; sCCA, sparse canonical correlation analysis; ACAT, aggregate Cauchy association test; MAGMA, multi-marker analysis of genomic annotation; HPA, Human Protein Atlas; PheWAS, phenome-wide association study; GO, Gene Ontology; BP, biological process; MF, molecular function; CC, cellular component; PPI, protein-protein interaction; DSigDB, Drug Signatures Database; PDB, Protein Data Bank; RTK, receptor tyrosine kinase; SFRP1, Secreted frizzled-related protein 1; FGF, Fibroblast growth factor; FGFR, Fibroblast growth factor receptor; TGF, Transforming Growth Factor; AEC, alveolar epithelial cell; MAPK3, Mitogen-activated protein kinase 3; IDUA, α-L-iduronidase; GAG, glycosaminoglycan; LSD, lysosomal storage disorder; ERT, enzyme replacement therapy; VC, vital capacity; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

## Data Sharing Statement

All data used in this study are publicly available, and the accession numbers are included in the article/Supplementary materials.

## Ethical Approval

This study was reviewed by the Institutional Review Board (IRB) of the Affiliated Hospital of Nantong University (2025-M001). Because the research relied solely on legally and publicly available data and involved no intervention in public behavior, it meets the exemption criteria specified in Articles 32(1) and 32(2) of the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans". Accordingly, no further IRB approval was required.

## Consent for Publication

All authors contributed to the article and approved the final version of the manuscript.

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## Author Contributions

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

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## Disclosure

The authors report no conflicts of interest in this work.

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