eMethods. Study Analyses

GWAS data quality control

Each of the five Open Genome-wide Association study (GWAS) datasets[1-3] of Respiratory Diseases utilized in this work was subjected to stringent quality control; the inclusion criteria and specifics of the quality control processes were reported in detail in the original publication. Additionally, we only use any data for data analysis following additional, stringent quality control using the techniques listed below: (1) Only bialleles were present for genes in the 1000 Genomes Project (1KGP) Phase 3 reference panel of the European reference population that had a minor allele frequency (MAF) greater than 0.01; (2) After matching, SNPS without a rsID or with a duplicate rsID is removed; (3) chromosomal positions of all SNPS are matched to those in the hg19 human reference genome.

Global AND Local genetic correlation analysis

To determine the polygenicity of each respiratory trait, we first assessed the GWAS heritability of each variable using univariate linkage disequilibrium score regression(LDSC)[4]. Using bivariate LDSC, a global genetic correlation analysis (ranging from -1 to 1) was additionally carried out to determine the shared genetic components among the five respiratory illnesses. By building a regression relationship between the LD score and the results of the GWAS test, LDSC calculates the heritability of a single trait or the genetic association of two characteristics. The LD score was calculated using European ancestry reference data (https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2) from 1000G and was limited to 1.2 million HapMap3 SNPs (http://ldsc.broadinstitute.org/static/media/w_hm3.noMHC.snplist.zip) with good data quality control. SNPS in the MHC region were disregarded because complex LD interactions have an impact on the assessment of genetic correlations. We did not restrict intercept terms in univariate and bivariate LDSC analyses since we did not know the extent of sample overlap. Instead, we used intercept terms to determine whether population stratification existed in a single trait GWAS or whether there was a possibility of sample overlap between two GWAS datasets.

Furthermore, we estimated genetic correlations between five respiratory disorders using High Definition Likelihood (HDL)[5] and compared them to LDSC estimates. Due to the fact that HDL bases its estimates on LD information from across the genome, it has a lower variance than LDSC. Our HDL estimates are based on the reference panel of UK Biobank imputed HapMap3 SNPs(https://github.com/zhenin/HDL/wiki/Reference-panels).

The global genetic correlations that LDSC and HDL assess are Inferred from compiled data on all genome variants. However, due to the intricacy of disease association and genetic variation, The amount and direction of each region's contribution to genetic correlation varied, and there were also considerable differences in the genetic correlation between the two traits across regions. Particularly, opposing regional genetic correlations may cancel one another, reducing the global genetic correlation of traits and hiding any potential pleiotropic effects. Therefore, we estimated the genetic associations in locally independent regions of the genomic[6] pairwise in five respiratory disorders using the Local Analysis of Variant Association (LAVA). LAVA was performed on 2,495 separate LD blocks previously divided, with LD estimates based on a 1000G EUR reference.

Multi-trait pleiotropy analysis using CPASSOC

Cross Phenotype Association (CPASSOC)[7] is a Meta-analysis that combines the effect values of a

SNP in multiple traits, calculates a summary statistic, and provides a P-value to indicate whether the site is significantly associated or not. Through hypothesis tests (H0, H1), CPASSOC identifies multiple validity associations. H0: Zmeta =Z1+Z2+Z3=0 (Z1=Z2=Z3=0), H1: Zmeta=Z1+Z2+Z3≠0 (Z1≠0 | Z1≠2 | Z3≠0). It is statistically proven that the SNP is related to at least one trait when H0 is rejected（$P < 5\times10^{-8}$）. By incorporating data from several GWAS, CPASSOC enhanced the sample size in order to find new relevant SNPS. The SHet estimates produced by CPASSPC were based on Meta-analysis and thus allowed for the existence of heterogeneous effects among several features. A Z-score correlation matrix of independent SNPS is also used by CPASSOC to account for the impact of sample overlap on outcomes. Only SNPS that appeared in all five GWAS were included in our analysis. $P_{CPASSOC}<5\times10^{-8}$ SNPS are regarded as significant pleiotropic SNPS.

Genomic Loci Characterizationand Functional Annotation

Based on the findings of CPASSOC, we discovered the probable pleiotropy locus using Functional mapping and annotation of genetic associations (FUMA)[8]. The SNPs that met the requirements $P_{CPASSOC}<5\times10^{-8}$ and LD $r^2<0.60$ are considered as independent significant SNPs, while SNPs that satisfy the criteria $r^2<0.1$ are regarded as Lead SNPs. If the Lead SNPs are less than 500kb apart, it is identified as a locus. Within each loci, the SNP with the smallest p-value is the Top SNP. The SNP function was annotated using data from the Phase 3 reference panel of the European Reference Population 1000 Genomes Project (1KGP). Then, we used FUMA to calculate the RegulomeDB score and the Combined Annotation Dependent Depletion (CADD) score, and SNPS with a CADD value greater than 12.37 were regarded as possibly deleterious variations. You can also keep examining functional annotations, channels, and organizational expressions using additional FUMA tools. Finally, in order to acquire the genetic loci of a single GWAS, we annotated the original GWAS of 5 respiratory disorders using the same parameters through FUMA. We compared the pleiotropic loci produced by CPASSOC with five single traits using the beginning and ending loci of the loci in an effort to discover additional association sites. A polygenic locus is regarded as a novel pleiotropic locus if it does not overlap in any single trait GWAS.

Multitrait colocalization analysis

We apply hypothesis Prioritisation in multi-trait Colocalization (HyPrColoc) using the R package hyperbolic 1.0 based on the pleiotropic loci acquired by FUMA annotation. With the help of the Bayesian split clustering method HyPrColoc, it is possible to identify the causal variation that is shared by each pleiotropic loci across a number of traits. HyPrColoc categorized qualities into groups based on distinct pleiotropic loci, with traits within each group sharing a chance SNP. The last colocalization loci among them is the posterior prob>0.7.

Candidate gene analysis

We kept looking into the biological basis of the pleiotropy loci indicated above. First, we compared all of the pleiotropy loci discovered by CPASSOC to the locations of 19,427 protein-coding genes in NCBI build 37.3. The cross-overlapping loci were taken into consideration as potential candidate genes for shared risk. Following that, the potential pleiotropic genes were examined using a gene-based[9] association method called multimarker analysis of

GenoMic annotation (MAGMA). To determine the link between this gene and the investigated trait, MAGMA combines SNP-related data in the gene (5kb) region using a multivariate regression model. The GRCh37 assembly created by NCBI served as the basis for the gene's location and border. The 1000 Genomes Project (1KGP) Phase 3 reference panel for the European reference population calculated the level of differentiation (LD), and potential confounding factors like gene size and gene density were utilized as covariates. After Bonferroni correction, $P < 0.05$ is a significant result.

Gene expression and tissue specificity are not taken into consideration by MAGMA, and SNPS are expected to affect traits through changing gene expression levels. We used Functional Summary-based Imputation (FUSION) to perform transcriptome-wide association (TWAS)[11]analyses, lung and whole blood tissues which were provided based on GTEx (v. 8)[10], on the original GWAS for each trait, and screened candidate genes for traits at the transcriptome level. We then combined the results of single-trait TWAS to see if there was gene sharing between the two tissues. To uncover plasma protein-trait relationships, we similarly conducted whole proteome association studies (PWAS) utilizing plasma protein cis-PQTL data from European populations. We then compared the PWAS results for five traits to assess cross-trait protein expression. After BH correction was applied, $P<0.05$ in each tissue was considered significant.

Biological pathway, GTEx tissue, and SNP-heritability enrichment

We used MAGMA gene-set analysis to perform Gene Set for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway databases Gene Set Enrichment Analysis (GSEA) [9] in order to further study some of the biological implications of these shared genes. MAGMA's gene set analysis is built on the basis of genetic analysis, which is enriched using the full distribution of SNP p values. From MsigDB V2023.1, the gene set for GO and KEGG was derived.

Additionally, we used the phenotype-cell-gene Association (PCGA) analytic platform (https://pmglab.top/pcga/#/) to carry out tissue/single cell-specific enrichment[13-15] in order to clarify the tissue/cell specificity of pleiotropic SNP data discovered by CPASSOC. GTEx v8 was used to generate the tissue results, while datasets from PanglaoDB, Human Cell Landscape, and Allen Brain Atlas as well as PanlaoDB for mice were used to generate the single-cell results.

Mendelian randomization analysis

To investigate the connection between the five phenotypes, we conducted a bidirectional two-sample MR analysis. The primary approach makes use of Random Effects Inverse Variance Weighted (IVW), which performs a Meta-analysis on the Wald ratio value of each SNP to determine the total impact value. Furthermore, when instrumental factors are heterogeneous, it is possible to provide results estimation that is more accurate. Likewise, we used MR-Egger regression[16] and weighted median[17] as the replenishment of the IVW. To further guarantee the accuracy of the findings, we applied the sensitivity analysis listed below: (1) Horizontal pleiotropy is examined using the MR-Egger intercept test[16], and heterogeneity is calculated using Cochran's Q statistic. (2) Determine whether a single SNP is responsible for the putative causal influence between two traits using the leave-one-out method (3) Determine whether the directionality of the estimated causal relationship between two traits is true using the MR Steiger directionality test (4) The F statistic is employed to assess the IVs' intensity. It is thought that the analysis results may be

weakly biased by an instrumental variable if it is less than 10;(5) For the main finding, a significant threshold (q value＜0.05) is a P-value less than 0.05 after a false discovery rate (FDR) correction (BH technique).

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