International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Screening and Verification COPD-OSA Overlap Syndrome Core Genes Using Bioinformatics

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Background: When obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) coexist in a patient, it is called overlap syndrome (OS). However, the molecular mechanisms underpinning OS are unclear. To address this, we explored potential OS mechanisms using bioinformatics.

Methods: OSA and COPD gene expression datasets were obtained from the Gene Expression Omnibus (GEO) database. Differential expression and weighted gene co-expression network analyses (WGCNA) were performed to identify common differentially expressed genes (DEGs) in OSA and COPD, and perform functional enrichment analysis. DEGs were validated in an external COPD gene expression dataset using receiver operating characteristic (ROC) curves and box plots. Positive results were initially identified as core genes, and were then validated by analyzing core genes in healthy controls, patients with OSA alone and patients with OS using RT-qPCR.

Results: Through differential expression gene analysis, 9 common DEGs for OSA and COPD were identified. Through WGCNA analysis, 128 common key module genes for OSA and COPD were identified. By taking the intersection of the identified 9 DEGs and the 128 common key module genes from WGCNA, 5 key genes were determined. Preliminary validation in the external gene expression dataset for COPD revealed that *GRM8* was a potential hub gene for OS. Compared with the control group, the expression of *GRM8* was significantly downregulated in the COPD group ($P = 0.019$). The diagnostic value was evaluated using the ROC curve, and the results showed that the AUC was 0.857 (95% CI: 0.614–1.000). Finally, RT-qPCR confirmed that the expression levels of *GRM8* in OSA and OS were significantly lower than those in the healthy control group ($P < 0.05$), and it was a hub gene significantly associated with OS.

Conclusion: Our research identified hub gene that may provide new directions for further mechanistic research on OS.

Keywords: overlap syndrome, chronic obstructive pulmonary disease, obstructive sleep apnea, bioinformatics, glutamate metabotropic receptor 8, *GRM8*

Introduction

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are respiratory diseases with a high clinical prevalence. OSA is characterized by repeated upper airway collapse during sleep, leading to upper airway stenosis or complete obstruction, followed by intermittent decreases in blood oxygen saturation.[1] COPD is characterized by chronic respiratory symptoms and irreversible persistent airflow limitation, with or without structural lung abnormalities.[2] Both have similar characteristics and interact with each other, and when they simultaneously coexist in a patient, the condition is called COPD-OSA overlap, or overlap syndrome (OS). David C. Flenley[3] first proposed this concept in 1985.

International epidemiological studies have shown that OSA prevalence in the general population is approximately 9%–38%, and is closely related to obesity, age, and gender, and affects approximately 200 million individuals

Received: 17 March 2025
Accepted: 18 July 2025
Published: 26 July 2025

worldwide.[4] As a common disease, COPD has a global prevalence of approximately 7.6%–10%.[2] In terms of common overlap syndrome (OS) prevalence, and due to differences in study populations, prevalence rates can vary greatly. Shawon et al[5] in their 2017 systematic review, reported that overall OS prevalence in the general population was low, ranging from 1%–3.6%, but that this prevalence was significantly increased in individuals with OSA or COPD alone. In patients with OSA, the OSA-COPD overlap prevalence ranges from 7.6%–55.7%, and among patients with COPD, the COPD-OSA overlap prevalence ranges from 2.9%–65.9%. Although ranges are wide, they represent a significantly higher prevalence compared to that observed in the general population.[6] In a study involving 355 patients, patients with OS for COPD and moderate to severe OSA had the highest death risks, and their all-cause mortality was significantly higher than that for patients with OSA or COPD alone.[7]

Genetic studies have shown that OSA has significant family aggregation and polygenic inheritance tendencies, and its onset is closely related to genetic factors such as craniofacial structure, fat distribution, and neural regulation.[8] COPD also has a clear genetic basis.[9] Genome-wide association studies (GWAS) have identified susceptible gene loci including *CHRNA3/5* and *HHIP*, among which the population attributable risk of the rs8034191 allele reaches 12.2%.[10] The latest research indicates that OSA and COPD may interact through inflammatory pathways (such as systemic inflammation caused by intermittent hypoxia) and genetic mechanisms.[11] However, systematic studies on their common genetic basis are still lacking, and further research is needed to reveal their shared genetic structure and molecular mechanisms.

OS is becoming more common in clinical practice and is usually accompanied by cardiovascular diseases, such as systemic and pulmonary hypertension.[12] When compared with patients with either disease alone, OS has a poor prognosis and a heavier disease burden on a patient's body. Currently, the molecular mechanisms underpinning OS are unclear, but with rapid microarray and high-throughput sequencing technology development, bioinformatics has been widely used to study the mechanisms underpinning various comorbidities, and can effectively mine biologically significant genes from data. Previous studies have identified novel biomarkers for OSA and established a reliable diagnostic model through bioinformatics. The identified transcriptional changes may contribute to revealing the pathogenesis, mechanisms, and sequelae of OSA.[13] Other studies have screened for biomarkers related to COPD based on bioinformatics and machine learning, providing new insights into the early diagnosis, prevention, and treatment of COPD.[14] However, there are currently no bioinformatics studies on COPD complicated with OSA. All existing studies focus on either COPD or OSA alone, and there is still a lack of research on the molecular mechanisms of OS. This study is the first to conduct a preliminary exploration of the molecular mechanisms of OS through bioinformatics and experimental verification, providing a new direction for the pathophysiological research of OSA complicated with COPD. In this study, we used bioinformatics to explore common differentially expressed genes (DEGs) between OSA and COPD, which could help clarify potential OS molecular mechanisms. Our study provides guidance on potential OS gene targets and a theoretical basis for the early clinical diagnosis and treatment of OS.

Materials and Methods

Data Downloads

OSA and COPD gene expression profiles were downloaded from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). The OSA (GSE135917) gene expression dataset contained two study groups. To prevent possible effects of positive pressure ventilation therapy on outcomes, we selected the first study arm in the dataset. The experimental design involved total RNA isolation from the subcutaneous fat of patients and controls, including 10 subjects with OSA and eight healthy controls. The COPD (GSE38974) gene expression dataset included two study groups, smokers without any evidence of COPD and smokers with COPD; mRNA expression in lung tissue was detected in 59 samples, including 17 normal controls and 42 smokers with COPD. Also, to evaluate diagnostic efficiency and perform external dataset validation, we downloaded a COPD dataset (GSE106986), and selected mRNA expression data for five non-smoker tumor-free tissue samples (control group) and 14 COPD tumor-free lung tissue samples.

DEG Identification

The original gene expression matrix was normalized using R (4.0.4) software. Then, principal component analysis (PCA) and cluster analysis were used to assess sample validity in datasets. The `limma" R package was then used to screen for DEGs in GSE135917 and GSE38974 datasets. GSE135917 DEGs were screened and *P* values adjusted to <0.05 and |logFC| ≥ 1 values. GSE38974 DEGs were screened and *P* values adjusted to <0.05 and |logFC| ≥ 1 values. DEG PCA and cluster analysis graphs, heatmaps, and volcano graphs were drawn in R software. We used the online Venn diagram tool to intersect GSE135917 and GSE38974 DEGs and identify common DEGs. R software was used to draw Venn diagrams.

Weighted Gene Co-Expression Network Analysis (WGCNA)

The WGCNA R package was used to construct a weighted co-expression network. First, an appropriate soft threshold power was selected based on approximate scale-free topology criteria. The pickSoftThreshold function was used to analyze network topology and calculate soft threshold power, and a network was constructed using the automatic network construction function. Secondly, a hierarchical clustering tree was established based on similarity and difference coefficients between genes for module detection. Gene significance and module membership were defined to quantify any correlations between modules and clinical features. Modules were ranked according to the absolute value of module importance, and any modules that were strongly associated with specific cell subtypes were selected as hub modules.

Functional Enrichment Analysis

To explore Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) annotations, the Database for Annotation, Visualization, and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/) was used to explore functions between genes of interest, with an adjusted *P*<0.05 value set as the standard cutoff. GO annotations contained three sub-ontology categories (biological process (BP), cellular component (CC), and molecular function (MF)), which were used to identify biological characteristics of genes and gene sets in organisms. KEGG provided high-level gene functions and utilities in biological systems. All results were visualized in R.

Core Gene Selection

Receiver operating characteristic (ROC) curves and box plots were used to verify gene intersections and preliminarily screen out core genes.

Clinical Samples

This study has been reviewed and approved by the Scientific Research Ethics Committee of Wuxi People's Hospital. All patients were from Wuxi People's Hospital in Wuxi City, Jiangsu Province, China. Sleep monitoring was conducted on the general population and patients with COPD. The analysis results of patients' nighttime sleep of ≥7 h monitored by a sleep breathing monitor were collected. The diagnosis and severity assessment of OSA were carried out according to the "Primary Diagnosis and Treatment Guidelines for Adult Obstructive Sleep Apnea (2018)".Inclusion criteria: (1) Aged 18–80 years, regardless of gender; (2) Normal healthy individuals with a monitored AHI < 5 events/h were included in the healthy control group, and patients previously diagnosed with COPD at Wuxi People's Hospital in Jiangsu Province were included in the COPD group; (3) Among patients with a monitored AHI ≥ 5 events/h, those with only OSA were included in the simple OSA group, and patients previously diagnosed with COPD at Wuxi People's Hospital in Jiangsu Province were included in the OS group. Exclusion criteria: (1) Patients with acute asthma disease, pulmonary tuberculosis, respiratory failure, or in the acute exacerbation period of COPD; (2) Patients who were bed - ridden for a long time and had concurrent severe liver, kidney, or cardiovascular and cerebrovascular diseases; (3) Patients with mental or nervous system diseases who could not cooperate; (4) Patients who could not participate in sleep breathing monitoring for other reasons.

Table 1 Primer Sequences

Primer Name	Sequence
Human *GRM8* -F	CGAGGGAAAGCGATCAGCC
Human *GRM8* -R	CCCATCCACCCGTATGGAA
Human actin beta-RT-F	AGCGAGCATCCCCCAAAGTT
Human actin beta-RT-R	GGGCACGAAGGCTCATCATT

RNA Extraction and RT-qPCR

The Novozymes VeZol-Pure Total RNA Isolation Kit/RNA Extraction Kit (Vazyme, Nanjing, Jiangsu Province, China) was used to extract RNA from peripheral blood samples, after which reverse transcription reactions were conducted using the Vazyme HiScript II RT SuperMix for qPCR kit (Vazyme, Nanjing, Jiangsu Province, China). Parameters included: incubation at 25°C for 5 min, heating at 50°C for 15 min, heating at 85°C for 2 min, and incubation at 4°C. First strand cDNA was stored at −40°C. qPCR was performed on cDNAs from reverse transcription reactions using the 2×Q3 SYBR qPCR Master mix (Universal) reagent kit (Tolo Biotech, Shanghai, China). RT-qPCR primers were designed using PrimerPremier5.0 software (Table 1).

Statistical Methods

Experimental RT-qPCR data are presented as the mean ± standard error of the mean (SEM). SPSS 27.0 was used to analyze the data, and the differences between different experimental groups were determined using one-way analysis of variance, with *P*-values corrected using Bonferroni method. All other analyses were performed using R.

Results

DEG Identification

Based on PCA (Figures 1A and 2A) and sample clustering results (Figures 1B and 2B), no abnormal samples were detected in GSE135917 and GSE38974 datasets. Using established criteria, we determined DEGs. The OSA groups had 26 and 206 up- and down-regulated genes, respectively, while the COPD group had 205 and 229 up- and down-regulated genes, respectively. Then, heatmaps (Figures 1C and 2C) and volcano maps (Figures 1D and 2D) were separately constructed. Intersections in Venn diagrams yielded nine common DEGs for OSA and COPD (Figure 3).

Identifying Common Key Module Genes Using WGCNA

We identified four and seven key modules from GSE135917 and GSE38974 datasets, respectively. After separately calculating correlations between modules and OSA and COPD, we plotted corresponding module trait relationship heatmaps (Figures 4A and 5A), with each module containing correlation coefficients and corresponding P-values. The turquoise module was related to OSA and the red module to COPD, and were considered the most relevant key modules related to diseases, respectively. Dendrogram of all differentially expressed genes of OSA and COPD was clustered based on the measurement of dissimilarity. The color band showed the results obtained from the automatic single-block analysis (Figures 4B and 5B). Using the pickSoftThreshold function in WGCNA, the optimal soft threshold power for the GSE135917 sample was 16, while for GSE38974, it was 10 (Figures 4C and 5C). By overlapping key OSA and COPD modules, 128 common key module genes were obtained (Figure 6).

Functional Enrichment Analysis

We conducted functional enrichment analysis on these 128 common key module genes, which were shared by OSA and COPD groups from WGCNA results. The bubble plot of GO and KEGG were drawn (Figure 7). See Tables 2 and 3 for detailed results.

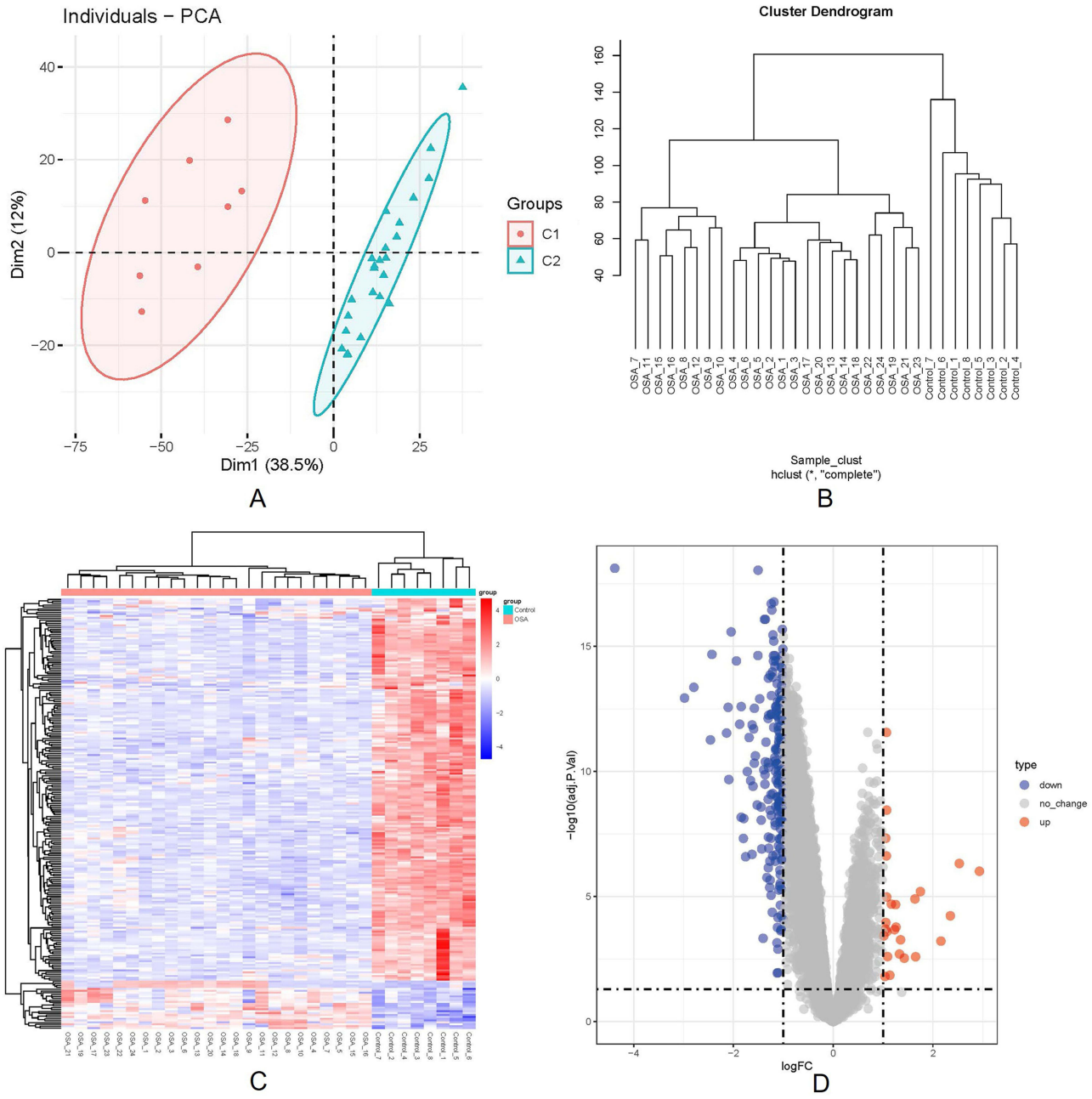

Figure 1 Differentially expressed gene identification in GSE135917. (**A**) Principal Component Analysis results, with red C1 representing the normal control group and green C2 representing the OSA group. (**B**) Sample clustering results. (**C**) Heatmap showing expression levels gradually increasing from blue to red. (**D**) Volcano plot, with blue on the left indicating down-regulated genes and red on the right indicating up-regulated genes. The dashed line above the vertical axis represents $P<0.05$, and the two dashed lines on the horizontal axis represent |log FC| ≥ 1.

Preliminary Core Gene Identification

By intersecting the nine DEGs and 128 common genes, five common genes (*MYH11, BCHE, SOSTDC1, GRM8, OGN*) were identified (Figure 8). We then used an external COPD dataset (GSE106986) to perform ROC curve and box plot validation analyses (Figure 9). In the GSE106986 sample, glutamate metabotropic receptor 8 (*GRM8*) showed significant differences between control and COPD groups. ROC curve results showed that the area under the curve was 0.857 and the 95% confidence interval was 0.614–1.000, which indicated that *GRM8* had a certain diagnostic value for COPD. Therefore, we preliminarily considered *GRM8* as a core OS gene.

https://doi.org/10.2147/COPD.S528703

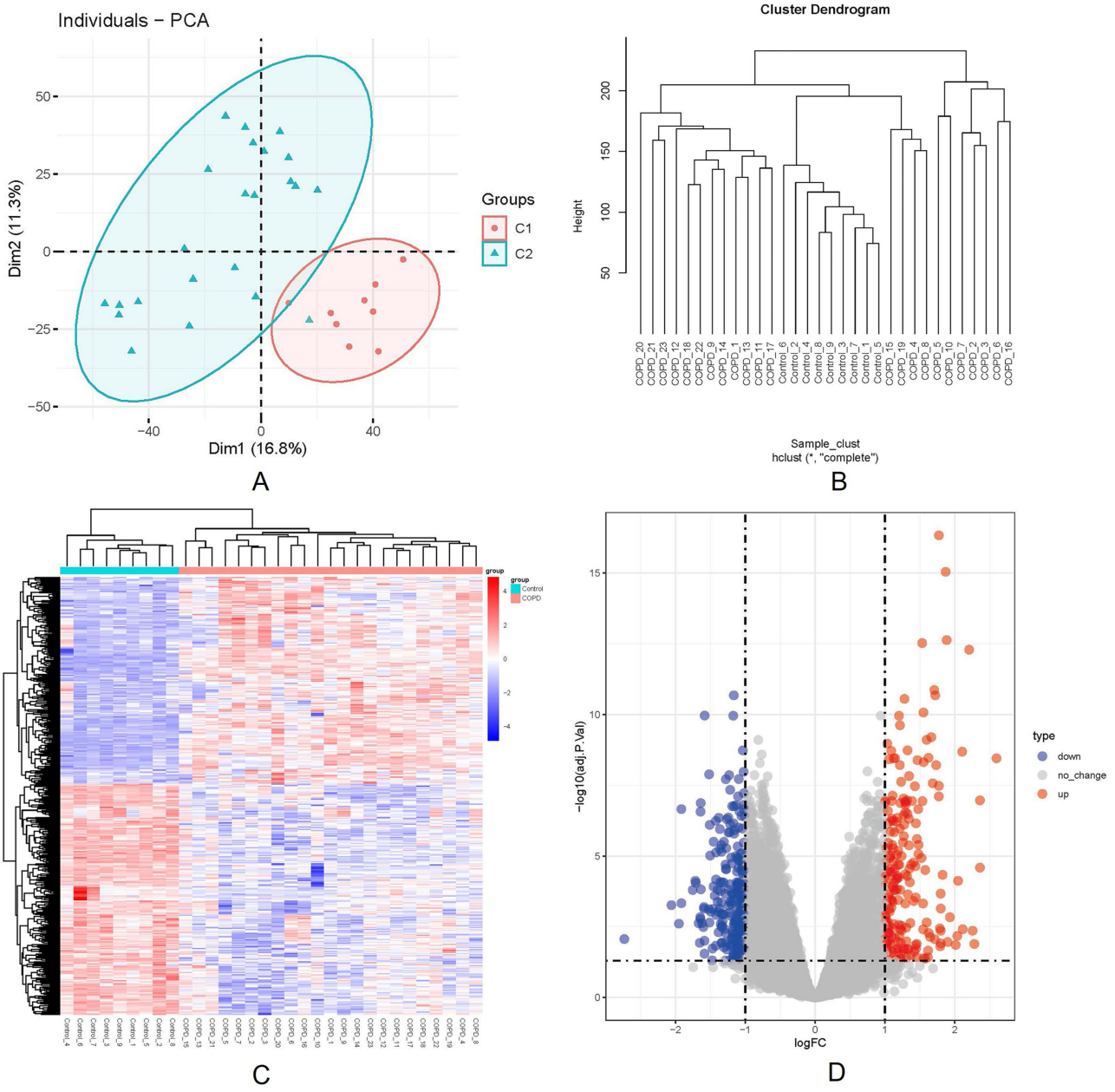

Figure 2 Differentially expressed gene identification in GSE38974. (**A**) Principal component analysis results, red C1 represents the normal control group, and green C2 represents the COPD group. (**B**) Sample clustering results. (**C**) Heatmap showing expression levels gradually increasing from blue to red. (**D**) Volcano plot, with blue on the left indicating down-regulated genes and red on the right indicating up-regulated genes. The dashed line above the vertical axis represents $P<0.05$ and the two dashed lines on the horizontal axis represent |logFC| ≥ 1.

Core Gene Expression Comparisons in Peripheral Blood Samples

Due to a lack of a suitable external OSA dataset, we validated OSA using 30 clinical samples, including eight (healthy control group), eight (simple OSA group), six (COPD group), and eight (OS group). The clinical characteristics of 30 participants are shown in Table 4. RT-qPCR results (Figure 10) showed significant differences ($P<0.05$) in *GRM8* levels

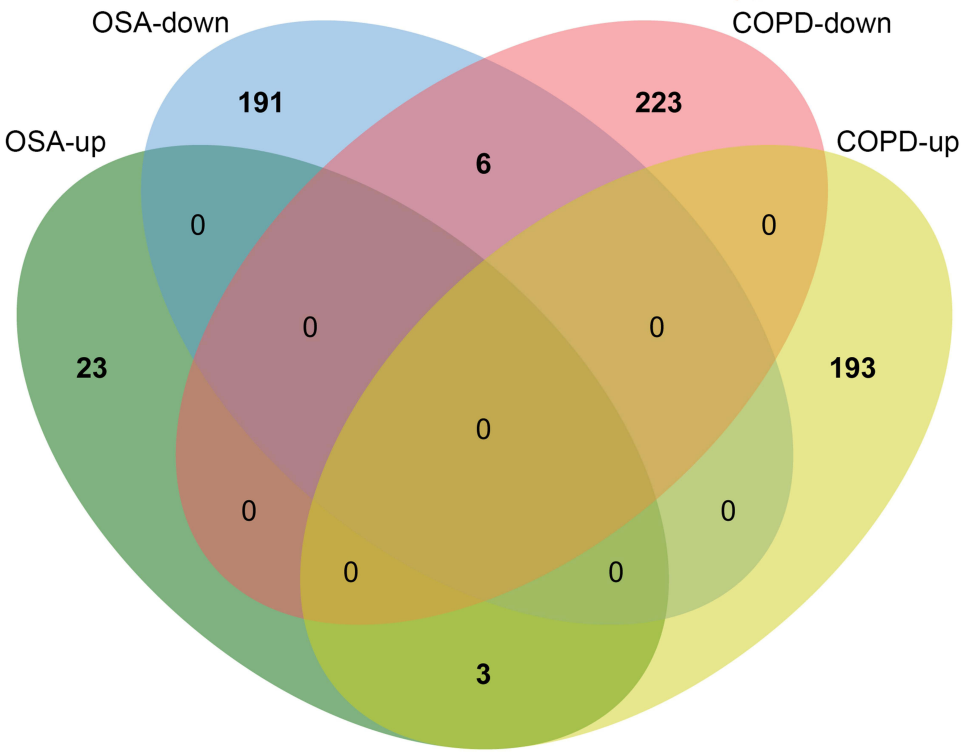

Figure 3 Venn diagram showing differentially expressed genes between OSA and COPD groups. Different colors represent up- and down-regulated differentially expressed genes in OSA and COPD groups, respectively, and the numbers represent intersecting genes.

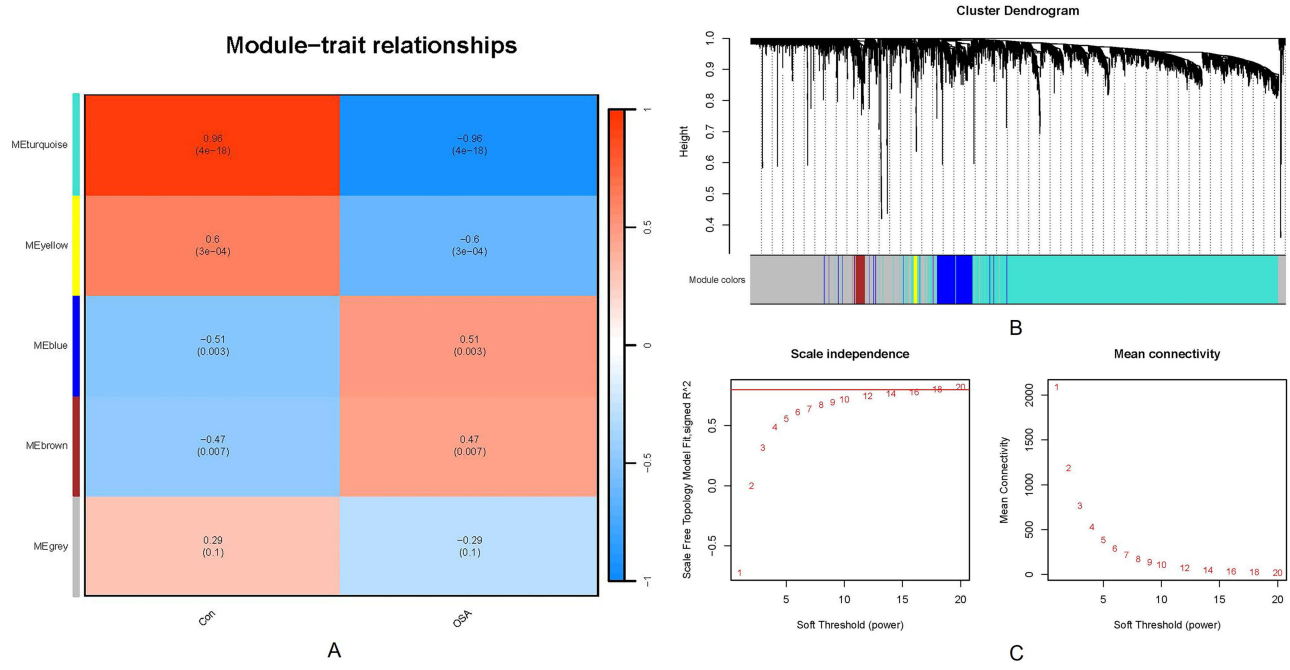

Figure 4 Weighted gene co-expression network analysis of GSE135917. (**A**) Module trait relationship heatmap. (**B**) Hierarchical clustering map. (**C**) The left panel shows the determination of the optimal soft threshold, and the right panel shows the network connections under various soft thresholds.

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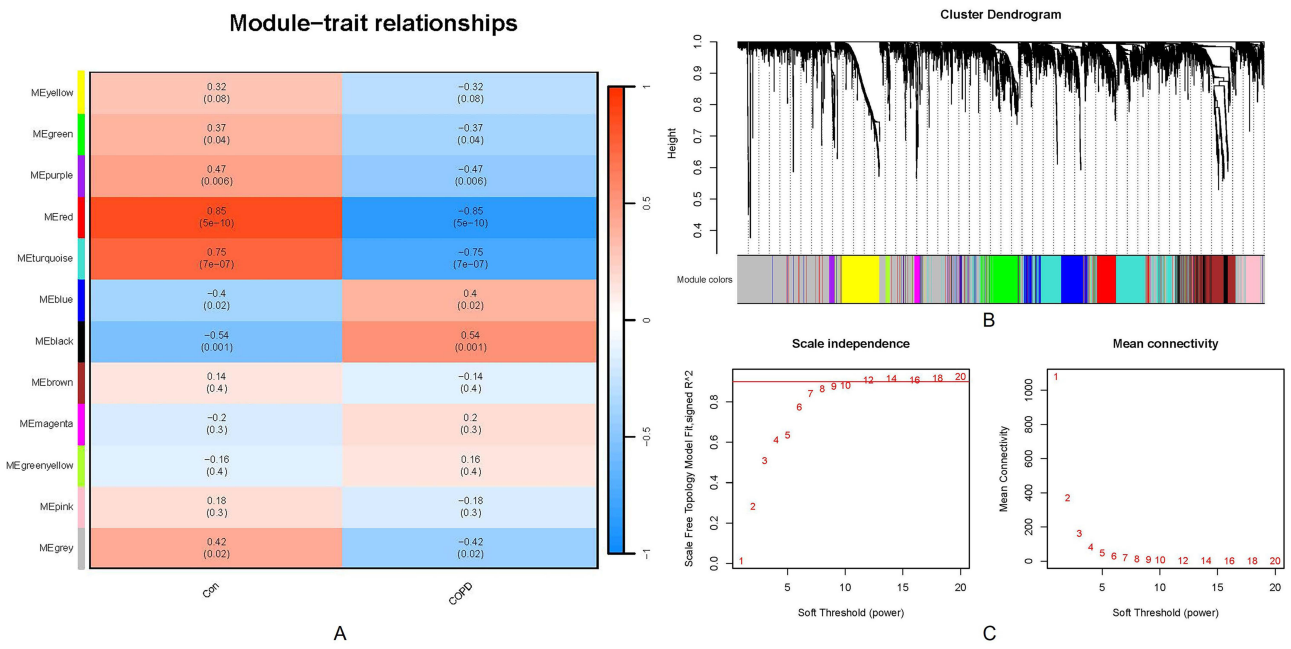

Figure 5 Weighted gene co-expression network analysis of GSE38974. (**A**) Module trait relationship heatmap. (**B**) Hierarchical clustering map. (**C**) The left panel shows the determination of the optimal soft threshold, and the right panel shows the network connections under various soft thresholds.

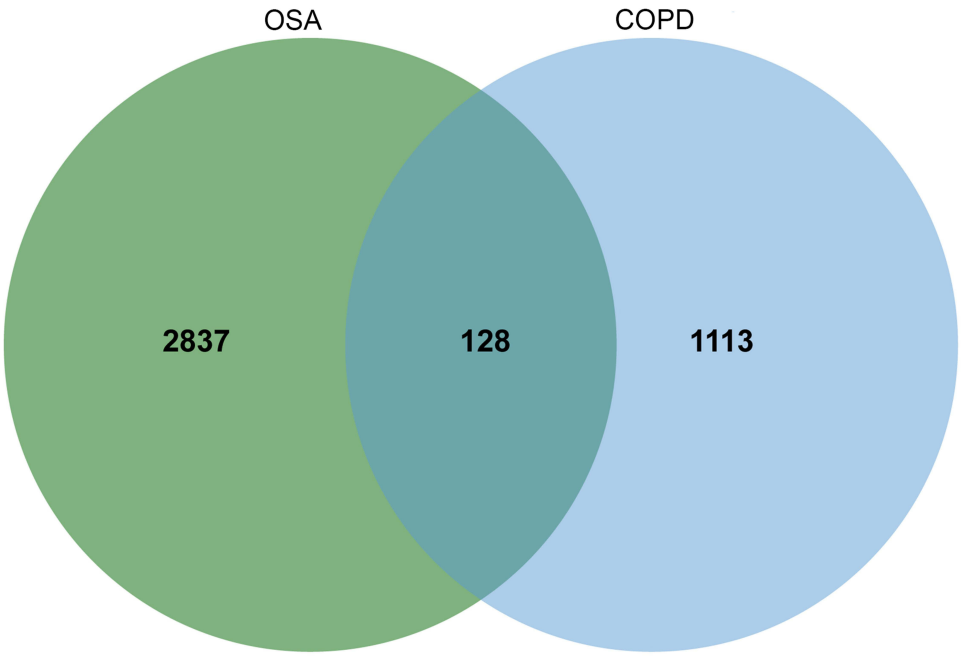

Figure 6 Venn diagram showing weighted gene co-expression network analysis intersection results for GSE135917 and GSE38974 datasets. The green circle (left) represents OSA dataset results and the blue circle (right) represents COPD dataset results.

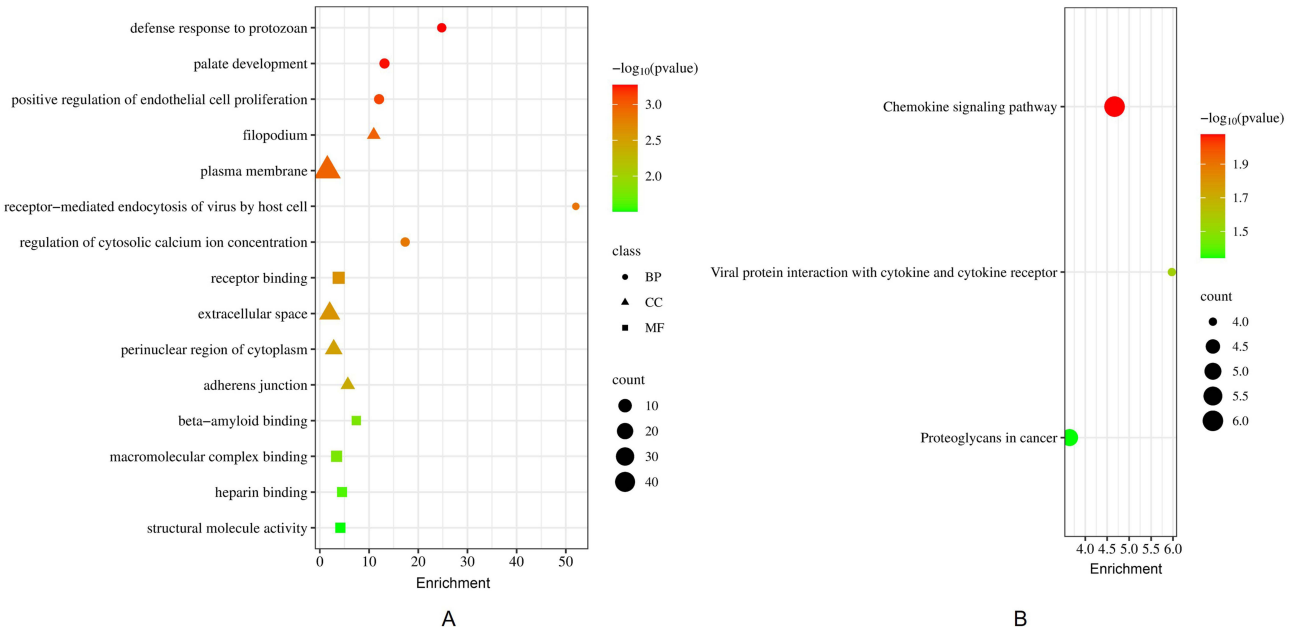

Figure 7 Functional enrichment analysis. (**A**) Gene Ontology pathway enrichment analysis of key module genes shared by OSA and COPD. The color changes in the bubble chart correspond to different *P*-values, with different shapes representing biological processes, cellular components, and molecular functions. Bubble size represents the number of genes. (**B**) The bubble plot shows the Kyoto Encyclopedia of Genes and Genomes pathways involved in OS, with bubble size indicating gene numbers.

between healthy control and simple OSA groups. We also conducted clinical sample validation on OS, with RT-qPCR results (Figure 10) showing significant differences ($P<0.05$) in *GRM8* levels between healthy control and OS groups. Therefore, we identified *GRM8* as a core gene in OS.

Table 2 Results of GO Enrichment Analysis

Class	Name	*P* value	Number of Genes
BP	Defense response to protozoan	<0.001	4
BP	Palate development	<0.001	5
BP	Positive regulation of endothelial cell proliferation	<0.001	5
BP	Receptor-mediated endocytosis of virus by host cell	0.001	3
BP	Regulation of cytosolic calcium ion concentration	0.001	4
CC	Filopodium	0.001	5
CC	Plasma membrane	0.001	47
CC	Extracellular space	0.003	22
CC	Perinuclear region of cytoplasm	0.003	12
CC	Adherens junction	0.004	6
MF	Receptor binding	0.002	9
MF	Beta-amyloid binding	0.017	4
MF	Macromolecular complex binding	0.017	7
MF	Heparin binding	0.025	5
MF	Structural molecule activity	0.031	5

Table 3 Results of KEGG Pathway Enrichment Analysis

Pathway	*P* value	Number of Genes
Chemokine signaling pathway	0.008	6
Viral protein interaction with cytokine and cytokine receptor	0.028	4
Proteoglycans in cancer	0.045	5

https://doi.org/10.2147/COPD.S528703

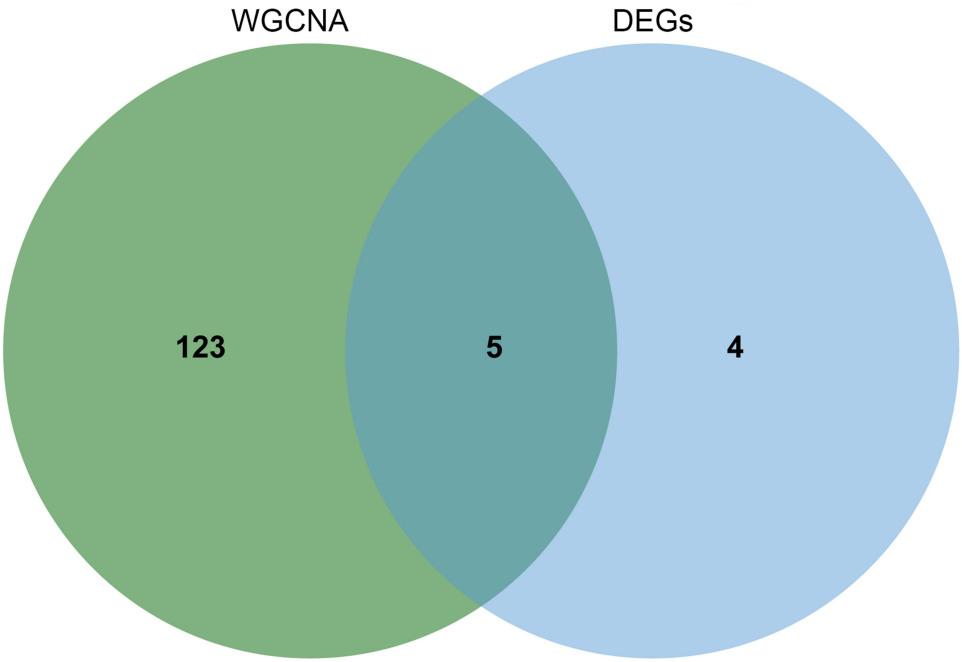

Figure 8 Venn diagram showing common key module gene and common DEGs intersection in WGCNA. The green circle (left) represents WGCNA intersection genes and the blue circle (right) represents DEG intersections.

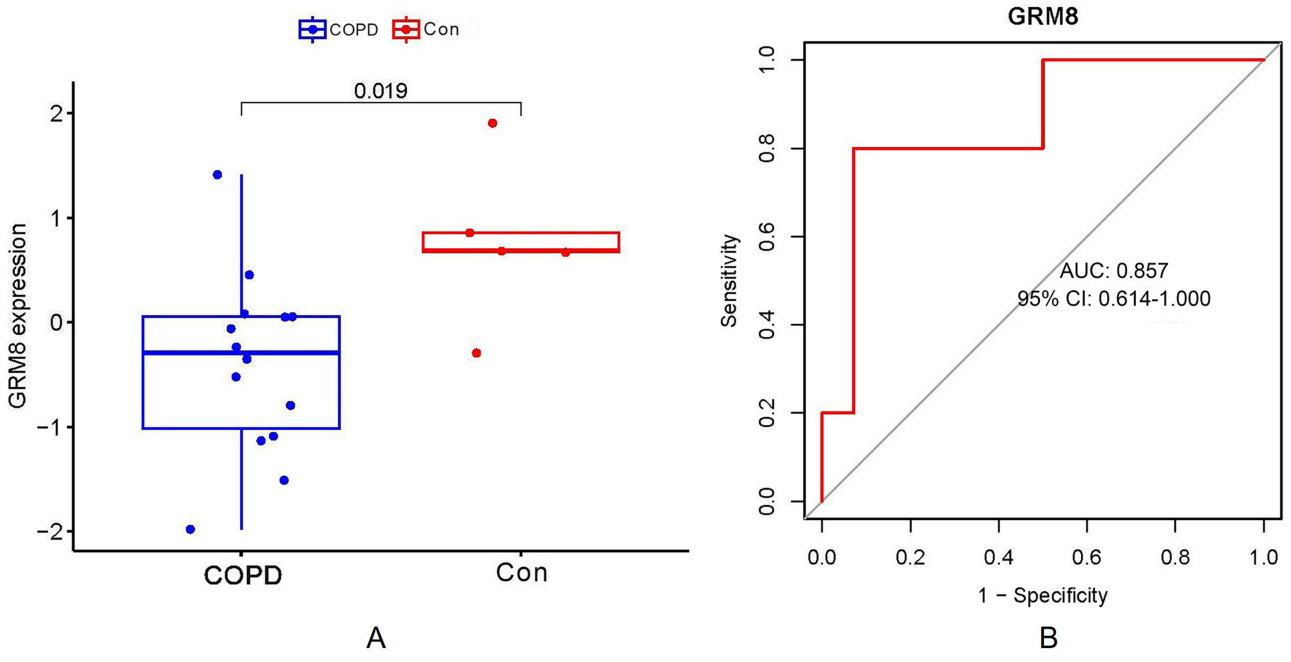

Figure 9 Verification of the external COPD dataset (GSE106986). (**A**) Box plot. Blue represents COPD group, red represents normal control group. (**B**) ROC curve of the hub diagnostic genes.

Table 4 The Clinical Characteristics of 30 Participants

Groups	Normal (n=8)	OSA (n=8)	COPD (n=6)	OS (n=8)
Ages (Y)	26.4±1.5	35.5±8.5	70.7±5.4	67.3±4.9
Male (N)	8	8	6	8
BMI (kg/m²)	19.6±1.7	27.6±2	20±1.4	27.7±3.4
Smoking (N)	0	0	6	8
Family history (N)	0	0	0	0

Abbreviations: OSA, Obstructive sleep apnea; COPD, Chronic obstructive pulmonary disease; OS, Overlap syndrome; Y, years; N, numbers.

Discussion

COPD is a serious lung disease characterized by persistent and progressive airflow obstruction due to airway and alveoli abnormalities. OSA is a sleep-related respiratory disorder characterized by obstructive sleep apnea and hypopnea and is a complication in patients with COPD. The coexistence of these two diseases can lead to increased nocturnal oxygen desaturation, which is the most significant sleep abnormality in both diseases,[15] and is due to their combined effects and mutually reinforces the influence of both diseases. Upper respiratory tract stenosis in patients with OSA can exacerbate existing hypoxia and ventilation dysfunction in patients with COPD, leading to further hypoxic burden.[16] Although research and understanding of pure COPD or OSA alone have grown, the pathogenesis of OS remains complex and understudied. Therefore, identifying common DEGs between COPD and OSA, exploring the molecular mechanisms underpinning OS, and improving early diagnosis and treatment interventions for OS are imperative.

For the first time, we used WGCNA analysis and differential expression analysis to identify the common key module genes of COPD and OSA. Through WGCNA analysis, we identified 128 common key module genes of COPD and OSA. By performing functional enrichment analysis on these common key module genes, we found that there were overlapping

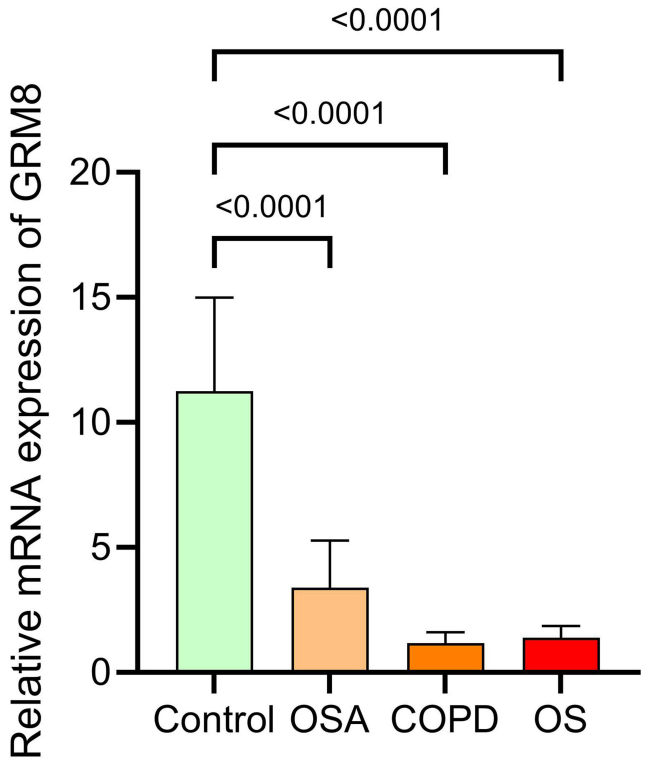

Figure 10 Clinical sample validation results. *GRM8* expression differences between healthy control, OSA, COPD, and OS groups. Vertical axis: Relative mRNA expression of GRM8.

https://doi.org/10.2147/COPD.S528703

parts in the molecular functions, biological processes, and cellular components of the genes related to COPD and OSA, indicating that the two diseases may share some common mechanisms during their occurrence and development. Through KEGG pathway analysis, we found that COPD and OSA shared some common pathways: chemokine signaling pathway, viral protein interaction with cytokine and cytokine receptor, and proteoglycans in cancer. Consistent with previous studies, the results of a clinical study by Monika et al evaluating the impact of certain comorbidities on a panel of 45 chemokines in OSA patients found that in OSA patients with COPD, elevated levels of certain pro - inflammatory cytokines such as chemokine *CCL11* may contribute to the persistence of the chronic inflammatory state and lead to further complications.[17] Our research results revealed a close association between the occurrence and development of OS and the chemokine signaling pathway. Currently, there is a lack of research on the two pathways of viral protein interaction with cytokine and cytokine receptor and proteoglycans in cancer, which may be potential research directions for OS in the future.

To further screen central genes, we used differential expression analysis technology to screen out 9 differentially expressed genes shared by COPD and OSA. These genes were intersected with the 128 common key module genes obtained by WGCNA. Finally, 5 key genes (*MYH11, BCHE, SOSTDC1, GRM8, OGN*) were obtained. Through research and verification, it was confirmed that *GRM8* is closely related to OS.

GRM8 is a G protein-coupled glutamate receptor that affects the inhibition of cyclic AMP (Adenosine monophosphate) cascade and regulates presynaptic glutamate release. In our study, *GRM8* was significantly down-regulated in OSA, COPD, and OS groups. Previous reports suggested that smoking and obesity were the most common factors in COPD patients with OSA. Bauer, Ph.D et al[18] conducted a simple exercise inhibition study on 122 European and American adults and found that the *GRM8* locus was associated with substance dependence risks, and that secondary allele deletion at candidate loci was associated with substance dependence diagnoses (eg, alcohol dependance, cocaine dependence). In a previous genome-wide association study, glutamatergic neurotransmission, involved in most aspects of normal brain function, was affected in many neuropathological conditions, and showed a significant correlation between *GRM8* and nicotine dependence and addiction susceptibility.[19] Glutamate signaling may have important roles in smoking behavior,[19] while *GRM8* down-regulation or deletion may increase nicotine addiction, thereby increasing COPD risks. Previous studies also reported that *GRM8* was associated with an increased risk of alcohol abuse, and that mechanisms affecting alcohol and other substance dependence may overlap with food appetite regulatory processes,[20] indicating a potential relationship between *GRM8* and feeding behavior. In an animal study by Oka et al,[21] it was suggested that *GRM8* may have a role in feeding behavior and metabolism via the hypothalamic pathway. A clinical study by Marcel S. Woo et al[22] reported that the major G allele rs2237781 in *GRM8* was significantly associated with increased feeding behavior inhibition scores. Therefore, low *GRM8* expression levels in patients with OS may reduce feeding restraints, affect metabolism, increase obesity risks, and increase OSA incidence rates. In our study, we found that *GRM8* tended to be further downregulated in OS patients compared with OSA alone, although this was not significant. Therefore, down-regulated *GRM8* may increase concurrent COPD risks in patients with OSA, thus providing a possible OS biomarker for early prevention and diagnosis in patients with OSA.

However, we also observed that *GRM8* levels in patients with OSA were significantly lower than in the control group, and that *GRM8* levels in patients with COPD and OS were more significantly decreased than those in the control group. A previous study by Woo et al[23] reported that *GRM8*-deficient neurons were more prone to glutamate excitotoxicity, leading to inflammation-driven neurodegeneration in related neurological diseases. This may be an indirect cause of more widespread and severe cognitive impairment in OS.[23] *GRM8* activation can counteract the excitotoxicity induced by glutamate,[24] indicating that this activation may be a valuable therapeutic approach and provide new directions and perspectives for *GRM8* as a novel therapeutic target for OS.

Our research elucidated OSA pathogenesis when combined with COPD. However, our study had some limitations. First, although genes shared by OSA and COPD were identified, their biological function and associated pathways in OS were not fully delineated. Therefore, the comprehensive molecular pathogenesis underlying these two comorbidities requires more study. Additionally, study sample size was too small, and there was some gender imbalance in case selection. OSA and COPD conditions are more common in males,[6] which is a potential study limitation. Our sample was entirely male; therefore, our data may not fully represent female patients, thereby limiting the generalizability of our

findings. However, our research still provides valuable references for clinical practice. In future research studies, it is necessary to validate through more clinical cases and more comprehensive inclusion of female patients, and to confirm through deeper functional and pathway analysis of the *GRM8* gene.

Conclusions

This study is the first to use bioinformatics methods to study the hub gene of comorbid OSA and COPD. Finally, it was found that *GRM8* is a hub gene closely related to OS. This provides a new direction for *GRM8* as a preliminary screening and diagnosis for OS in the general population. *GRM8* may provide a new perspective for exploring biomarkers of OS and potential OS mechanisms. The downregulation of *GRM8* in the diseased population also provides a possible new therapeutic target for OS.

Abbreviations

OSA, Obstructive sleep apnea; COPD, Chronic obstructive pulmonary disease; OS, Overlap syndrome; GEO, Gene Expression Omnibus; DEGs, Differentially expressed genes; DAVID, Database for Annotation, Visualization, and Integrated Discovery; WGCNA, Weighted Gene Co-expression Network Analysis; ROC, Receiver Operating Characteristic; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, Molecular Function; BP, Biological Process; CC, Cellular Component; AHI, Apnea-Hypopnea Index.

Data Sharing Statement

The data used to support these findings are included in the manuscript.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Wuxi People's Hospital. Ethical Number: KY24042.

Consent for Publication

Informed consent was obtained from all participants.

Acknowledgments

We thank the Sleep Center of Wuxi People's Hospital for providing data and information.

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 International Journal of Chronic Obstructive Pulmonary Disease has been submitted; and agree to be accountable for all aspects of the work.

Funding

No benefit of any form was received or will be received from a commercial party related directly or indirectly to the subject of this article.

Disclosure

The authors declare no conflicts of interest.

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