

Bioinformatic Gene Analysis for Potential Molecular Link Between Sleep Disorders and Atrial Fibrillation: Uncovering Novel Diagnostic Candidates

Zupei Miao^{1,2}, Tao Chen², Xu Lu², Tingting Song², Yang Li^{2,*}, and Jun Guo^{2,*}

1 Postgraduate School, Medical School of Chinese People's Liberation Army (PLA), Beijing 100039, China;

2 Department of Cardiology, The Sixth Medical Center, Chinese PLA General Hospital, Beijing 100048, China;

*Correspondence: guojun301@126.com

CITATION

Zupei M, Tao C. et al. Bioinformatic Gene Analysis for Potential Molecular Link Between Sleep Disorders and Atrial Fibrillation: Uncovering Novel Diagnostic Candidates. *Psycho-Oncologie*.

ARTICLE INFO

Received: January 30, 2026

Accepted: January 30, 2026

Available online: February 4th, 2026

COPYRIGHT



Copyright © 2025 by author(s).

Psycho-Oncologie is published by PicoMed Publishing Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license.

<https://creativecommons.org/licenses/by/4.0/>

Abstract: Background: Atrial fibrillation (AF) is one of the most prevalent cardiac arrhythmias in clinical practice, and its incidence is increasing year by year. Meanwhile, exploratory results have suggested that sleep disorders may be a cause of AF. However, the underlying mechanism remains uncertain. Therefore, our study aimed to identify co-expressed genes to investigate the relationship between AF and sleep disorders in terms of molecular link via bioinformatics analysis. Methods: AF dataset GSE79768 and sleep time loss dataset GSE80612 were downloaded from the Gene Expression Omnibus (GEO) database. And we used multiple bioinformatics strategies and machine learning algorithms to screen candidate hub genes. These techniques included identifying differentially expressed genes (DEGs), weighted gene correlation network analysis (WGCNA), gene set enrichment analysis (GSEA), Gene Ontology (GO) terms, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, and machine learning methods including least absolute shrinkage and selection operator (LASSO) regression analysis. Then, the core genes were validated by using external datasets, GSE41177 for AF and GSE135917 for sleep disorder, and diagnostic value was assessed by the area under the receiver operating curve (ROC). Results: From the 950 overlapped DEGs and 35 genes in the overlapped WGCNA core modules, 20 common genes were identified in AF and short sleep samples. GSEA analysis indicated that peroxisome pathway and oxidative phosphorylation pathway were significantly enriched in AF and short sleep samples respectively, and GO analysis showed that the significant enrichment pathways include peptide disulfide oxidoreductase activity. In addition, six core genes (GLRX, PRKCI, NDRG3, RPL27A, TLN1, and SMA4) were screened out via LASSO algorithm. Among them, only one gene, GLRX, could be potential diagnostic biomarker for sleep disorder related AF, as evidenced by the receiver operating curve (ROC) curves in external validation datasets. The C5.0 and decision tree algorithms were employed to further screen for important genes, also highlighting the potential role of GLRX in the relationship between AF and sleep time loss. Conclusions: Collectively, these findings provide novel insights into the potential sleep disorders related genes associated with AF. GLRX may play a significant role in the occurrence of sleep time loss related AF.

Keywords: atrial fibrillation; sleep disorders; differentially expressed genes; bioinformatics; GLRX

1. Introduction

Atrial fibrillation (AF) is one of the most prevalent sustained cardiac tachyarrhythmias in clinical practice with significant health and socioeconomic impacts, and its incidence is increasing year by year. The prevalence of AF is predicated to reach approximately 17.9 million people in Europe and around 6 to 12 million people in the United States by year 2060^[1]. It usually manifests as palpitations, chest pain, dizziness, and shortness of breath. Some people may even experience syncope^[2]. Experimental and clinical data suggest that the pathophysiology of AF is highly complex and involves numerous important factors, including inflammation, oxidative stress, calcium overload, and myofibroblast activation, among others^[3]. Due to the numerous pathogenic factors of AF, the clinical prevention and treatment of this disease remain one of the difficult challenges in cardiovascular field.

Sleep is a complex process. The heart rhythm during sleep is influenced by the autonomic nervous system and various pathological states^[4]. Modern society, with its omnipresent technology, control of light, and countless competing interests for time, along with the cultural trend of de-emphasizing the importance of sleep, has resulted in widespread sleep deprivation. Sleeping problems including sleep deprivation or restriction, insomnia, and obstructive sleep apnea (OSA), are an increasingly recognized issue in the general population worldwide^[5]. The growing disconnect between sleep needs and sleep attainment has serious adverse effects on mental health, body metabolism, the immune system, and cardiovascular health^[6].

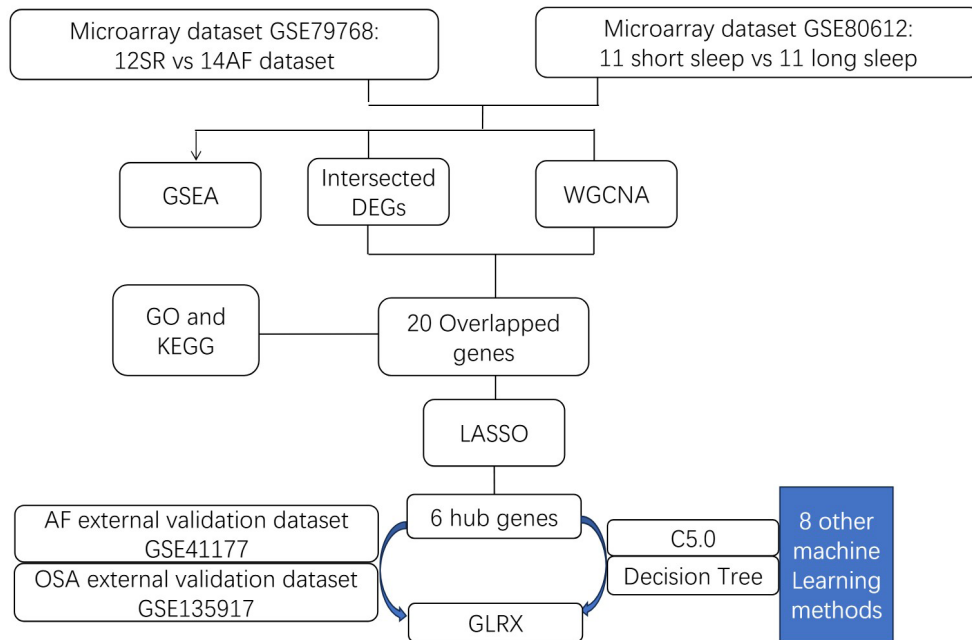
Epidemiological studies suggested that sleep disorders can multiply the incidence of AF^[7]. A meta-analysis in America in 2018 reported that compared to patients without OSA, the overall pooled OR of recurrent AF in patients with OSA was 1.70 (95% CI, 1.40–2.06, $I^2 = 0$)^[8]. Another study in 2022 led by Zhen-ni Chen in China once again confirmed that sleep-disordered breathing was significantly associated with the risk of postoperative AF in patients who underwent cardiac surgery (OR $\frac{1}{4}$ 1.49; 95% CI, 1.30–1.70; $p < 0.001$)^[9]. Negar Morovatdar also reported that short sleep duration and insomnia were related to a higher risk of AF occurrence (HR = 1.58 and HR = 1.33 respectively)^[10].

The mechanism of association between sleep disorders and atrial fibrillation has not been fully elucidated. Existing studies suggest that it may affect cardiac structure and electrical remodeling through oxidative stress, inflammatory response and autonomic nervous function changes, but the underlying molecular mechanism still needs to be further explored. In recent years, the rapid development of bioinformatics technology provides a new way to reveal complex disease mechanisms. Scholars such as Lu Peng pointed out that elucidation of the potential link between the two diseases at the molecular level is crucial for optimizing clinical management and developing targeted therapeutic strategies^[11]. Traditional biological research is limited in gene interaction network analysis,

but the application of high-throughput methods such as RNA sequencing, gene chip and microarray technology makes it possible to screen disease-related genes and signaling pathways on a large scale. For example, Kun Li et al. predicted miRNA and mRNA associated with OSA through microarray analysis ^[12]; Cao Yuanyuan's team identified potential biomarkers of OSA and its comorbidities ^[13]. However, there are still obvious shortcomings in existing studies: on the one hand, most studies have small sample size and limited mRNA types, which limits the exploration of new biomarkers and pathogenesis; On the other hand, the clinical value of incorporating mRNA markers into traditional risk models has not been fully validated. In addition, studies on the molecular association between sleep disorders and atrial fibrillation are still lacking, especially systematic analysis of specific genetic markers of OSA with different severity and the interaction of differentially expressed genes with heart failure/atrial fibrillation signaling pathways. Future studies still need to integrate multiple omics data, combined with large sample cohort validation, to reveal the core mechanism of sleep disorders-related atrial fibrillation, and provide theoretical support for precision medicine. Therefore, the objectives of this study include exploring the possible association between sleep disorders and AF, as well as using a bioinformatics framework to further explore the molecular mechanisms underpinning it.

In this study, we identified the commonly differentially expressed genes (DEGs) of AF and short sleep through bioinformatics analysis. We downloaded the expression profile data of left atrial samples from patients with and without valvular AF, as well as peripheral blood leukocyte (PBL) samples from 11 monozygotic twin pairs with different habitual sleep durations from the Gene Expression Omnibus (GEO) public databases. Subsequently, differential expression analysis was conducted to obtain DEGs, and weighted gene correlation network analysis (WGCNA) was performed to identify common genes in highly clustered modules of AF and short sleep. Gene set enrichment analysis (GSEA), functional enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed to investigate the biological functions associated with the DEGs. Afterward, the least absolute shrinkage and selection operator (LASSO) algorithm was used to screen the hub genes, which were then validated in external AF and OSA datasets and other machine learning methods. The flow-chart illustrates the design and workflow of the entire study (**Figure 1**).

A



B

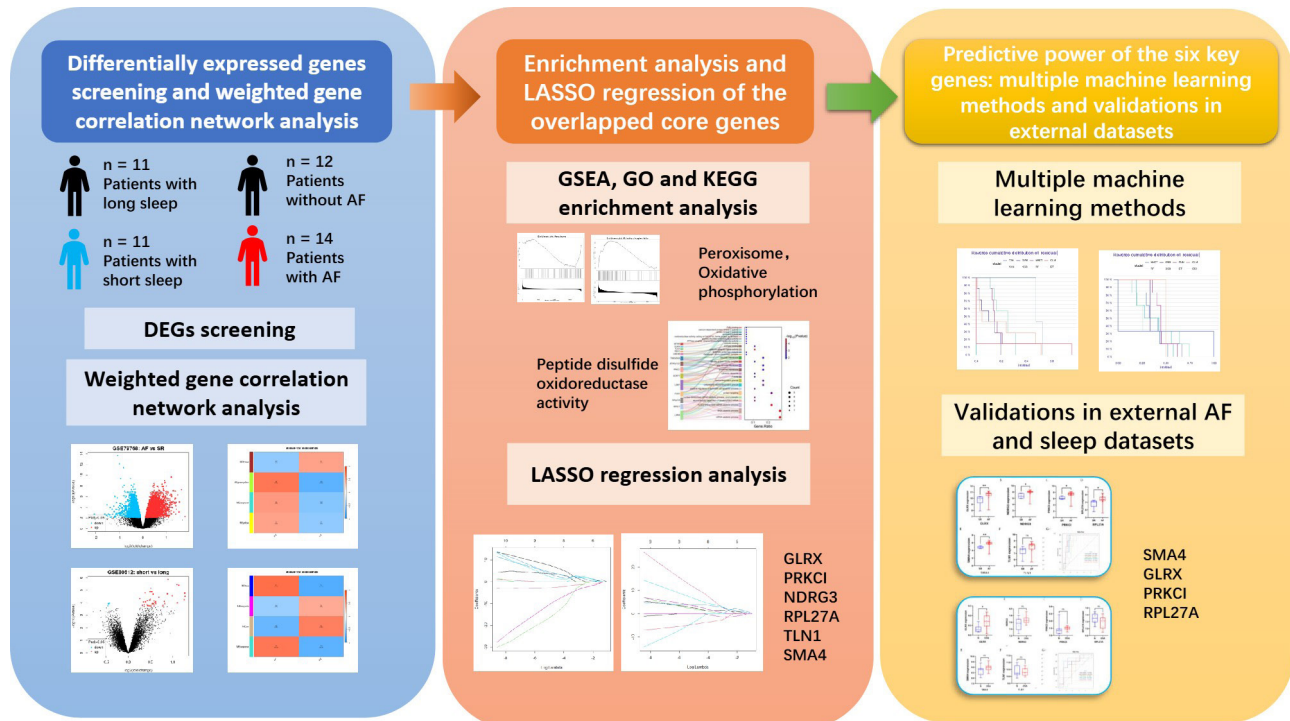
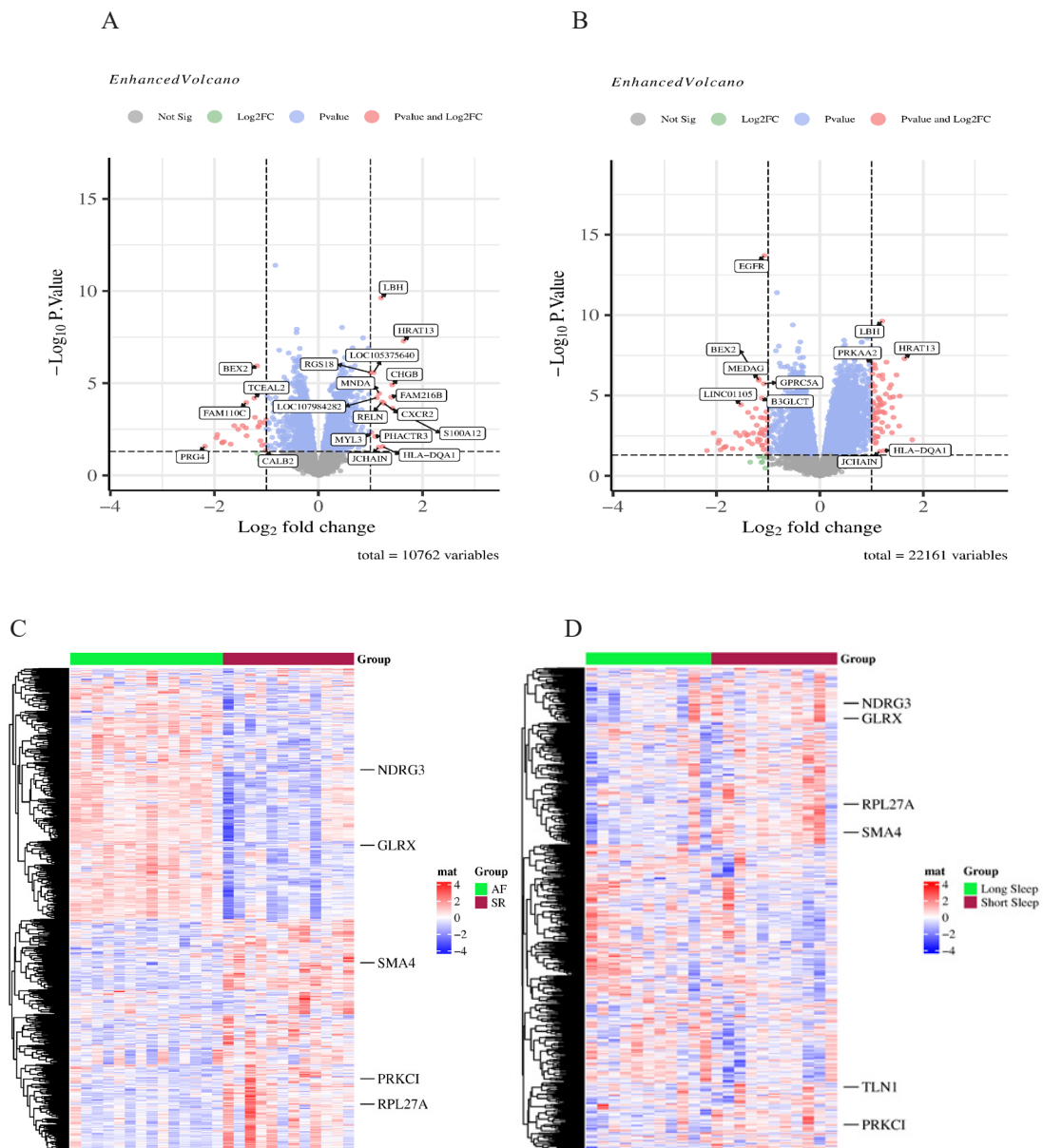


Figure 1. The workflow of the entire study(A) and the main results(B)

2. Results

2.1. Identification of DEGs

Based on GEO2R, we identified 5,344 upregulated and 4,545 downregulated DEGs in the GSE79768 dataset related to AF, and a total of 1,651 (911 up, 740 down) short sleep-related DEGs were obtained from GSE80612. The volcano plots of GSE79768 and GSE80612 were manifested in **Figure 2A** and **Figure 2B**, respectively. Then, the top 1000 DEGs of the GSE79768 and GSE80612 datasets are represented by heatmaps, respectively (**Figure 2C, D**). The 950 overlapping genes between AF-related DEGs and short sleep-related DEGs were shown in the Venn diagram (**Figure. 2E**).



E

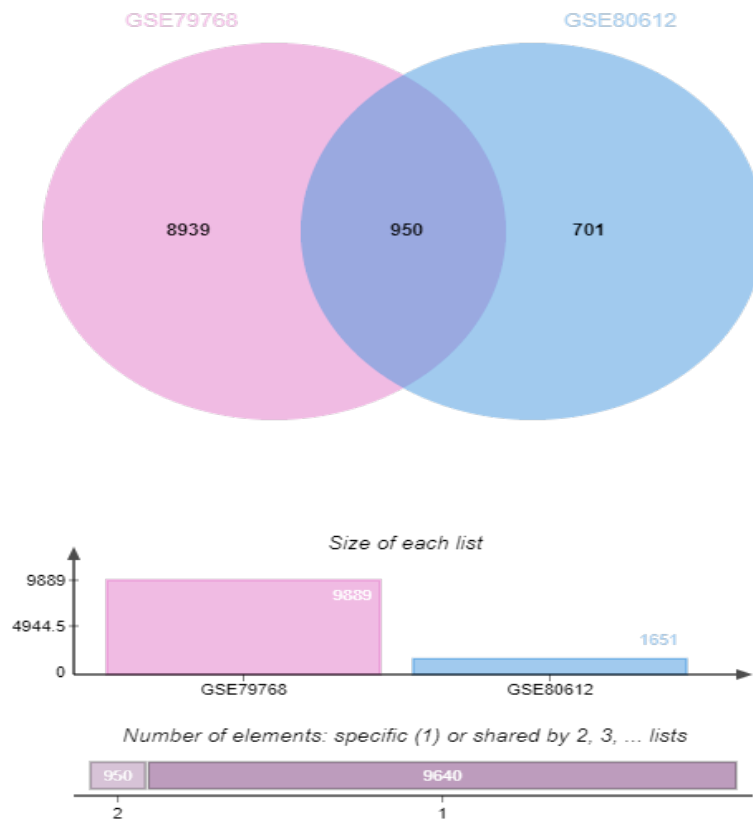
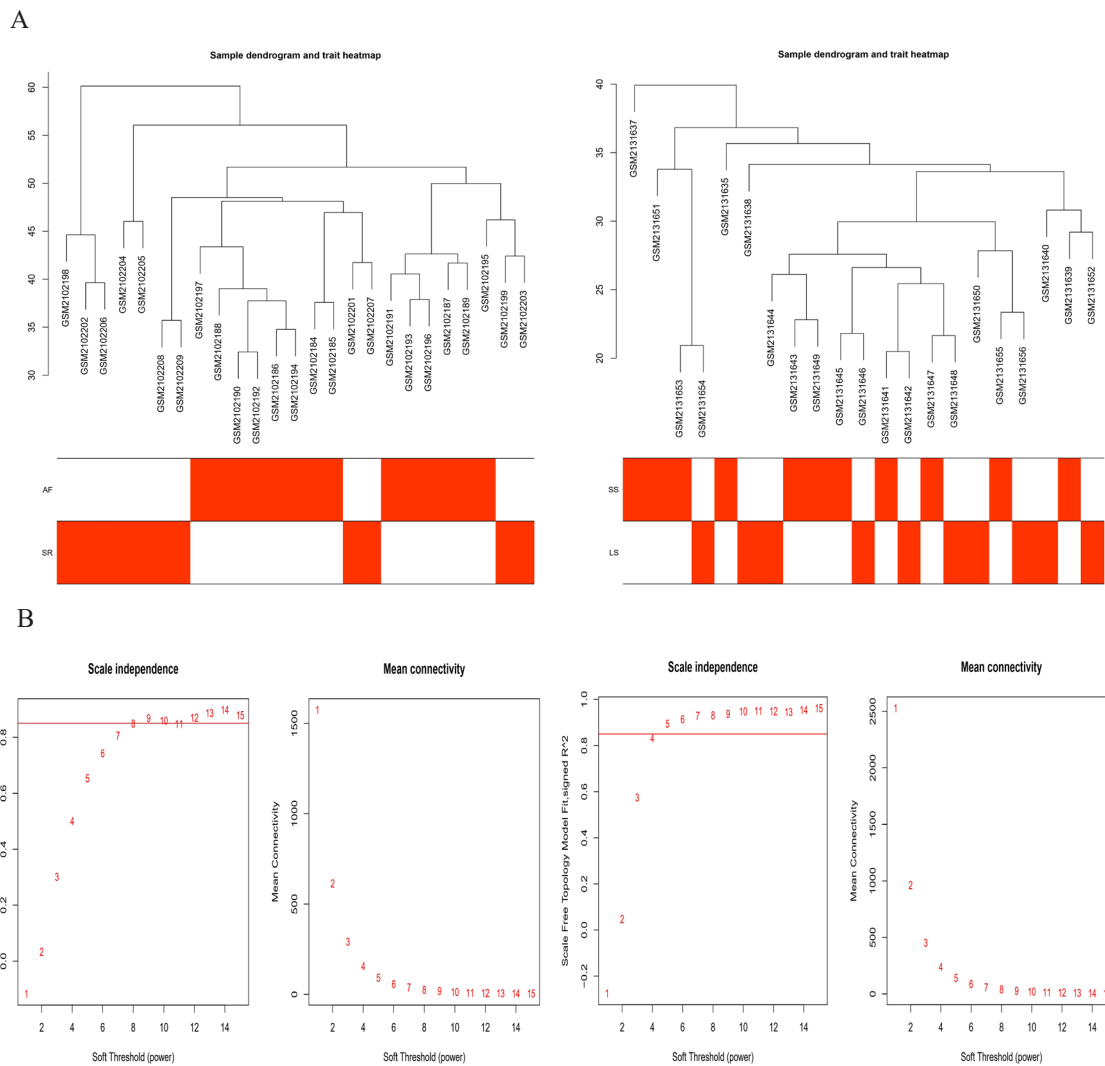


Figure 2. DEGs representation by volcano plot diagrams, heatmaps and Venn diagram. (A) The volcano plot of DEGs in GSE79768. (B) The volcano plot of DEGs in GSE80612. (C-D) The heat maps of the top 1000 DEGs in GSE79768 and GSE80612 were shown, respectively. (E) Venn diagram of DEGs from GSE79768 and GSE80612. AF, atrial fibrillation; SR, sinus rhythm; DEGs, differentially expressed genes.

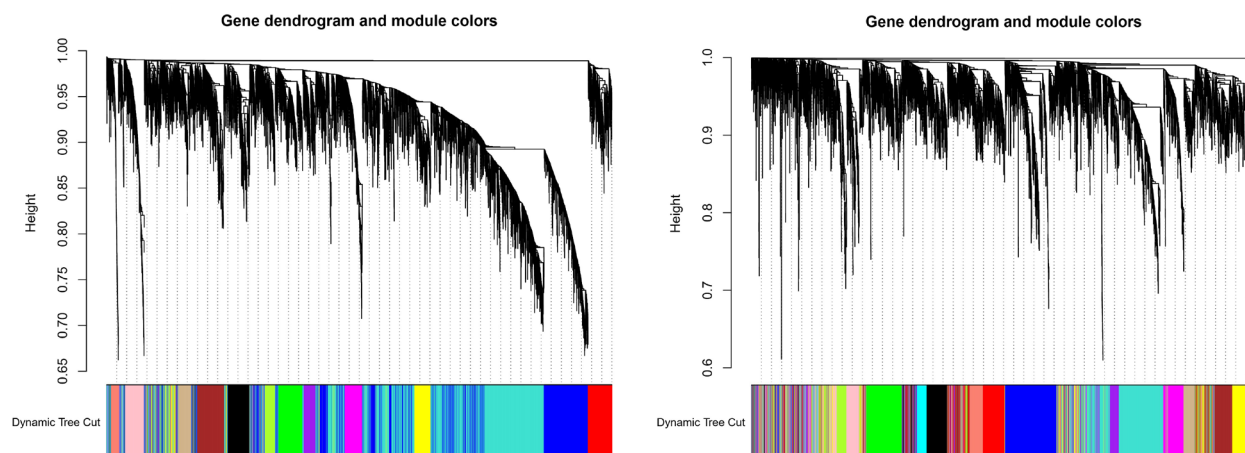
2.2. Construction and module analysis of the WGCNA

WGCNA was used to identify differentially expressed co-expressed gene clusters between AF and short sleep duration. AF dataset (GSE79768) and the short sleep dataset (GSE80612) were used for the WGCNA analysis. Outliers were identified using sample clustering, and GSM2102200 and GSM2131636 were removed from GSE79768 and GSE80612, respectively. The dendrogram was used to cluster samples in the merged mRNA dataset (**Figure 3A**). According to the approximate scale-free topology criterion, $\beta = 4$ was chosen to determine the soft threshold in the AF model, and $\beta = 8$ was chosen to determine the soft threshold in the short sleep model (**Figure 3C-D**). Cluster dendrograms of the co-expression of AS and OSA were shown in Figure 3B, E. There are four significantly defined models in both the atrial fibrillation and short sleep models (**Figure 3F**). Among the AF modules, the blue module and turquoise module had the strongest positive correlation with AF ($R = 0.7$ and $R = 0.68$ respectively), and the green-yellow module had the strongest positive correlation with the oc-

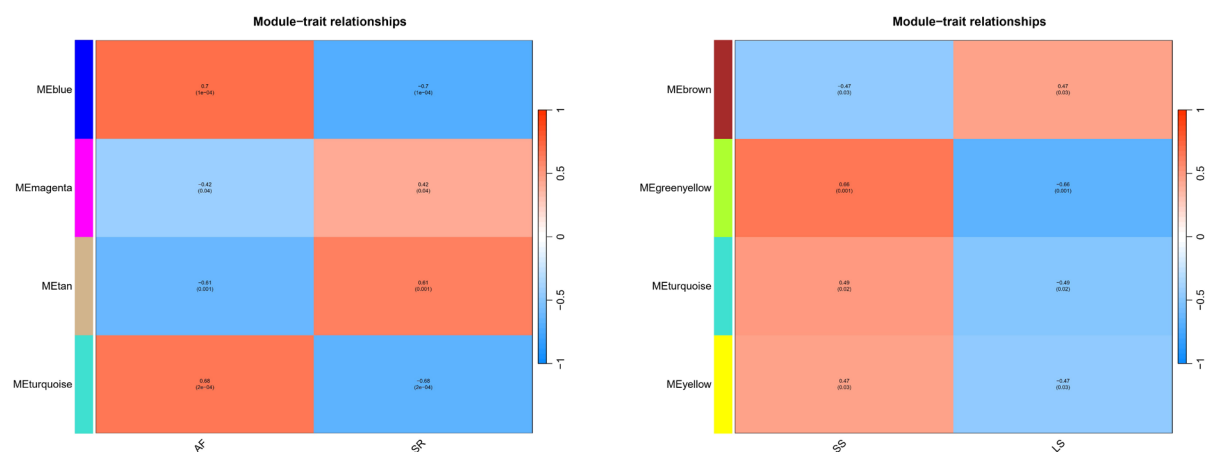
currence of short sleep ($R = 0.66$). The scatter plots of module membership (MM) vs. gene significance (GS) in the blue, turquoise, and green-yellow modules, revealing a correlation of 0.69 ($p < 1e-200$), 0.7 ($p < 1e-200$), and 0.67 ($p = 3.8e-39$) respectively, demonstrated a high correlation between the gene modules and clinical traits, as shown in **Figure 3G**. The two modules (blue and turquoise) genes of AF and the yellow-green module of short sleep were recognized as the key module genes for AF and short sleep, respectively. We then conducted a Venn analysis between the two disease groups (**Figure 3H**). The analysis indicated that 35 genes were shared as key module genes.



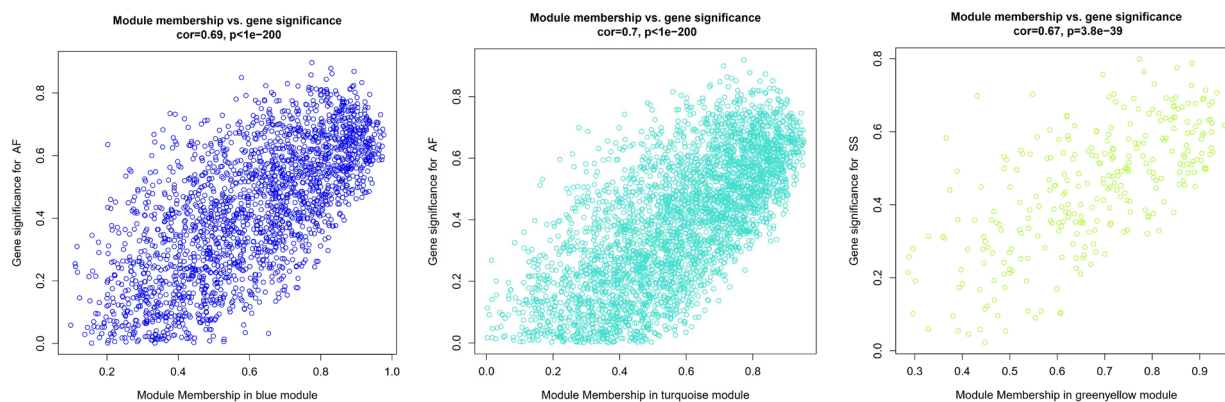
C



D



E



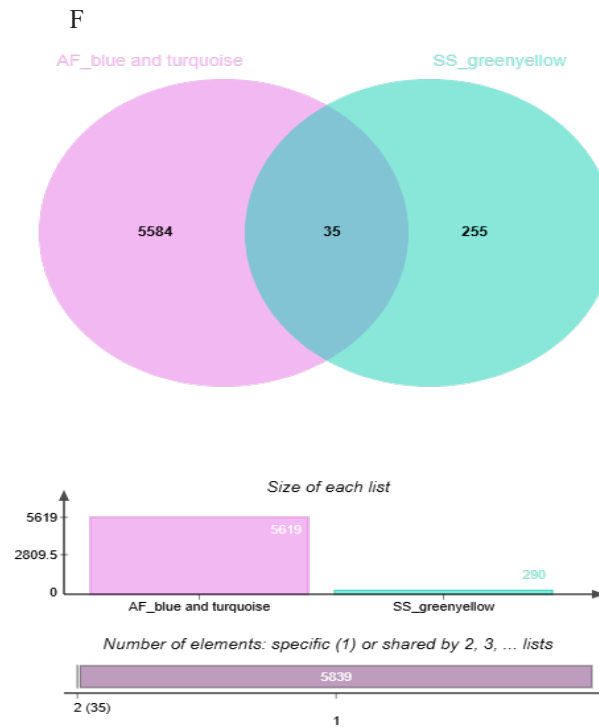
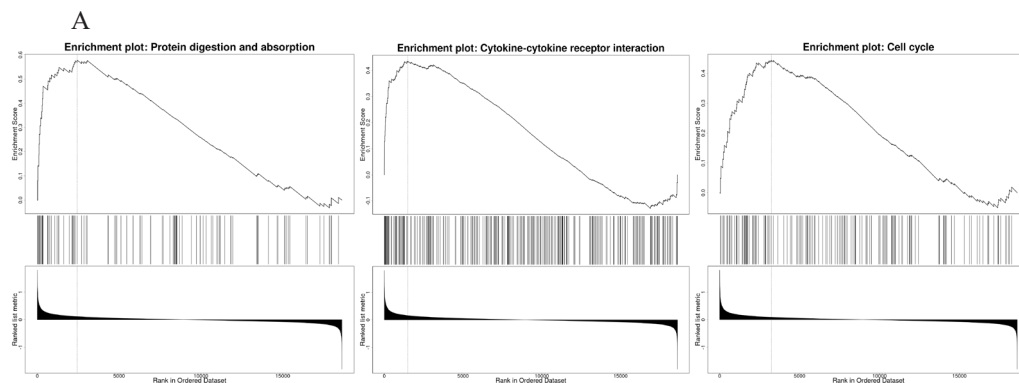


Figure 3. Weighted gene correlation network analysis. (A) The dendrograms of the samples and the heatmaps of the clinical traits. (B) Soft threshold power analysis. The red line corresponds to 0.85. (C) Gene clustering trees. (D) Correlation between modules and clinical traits in AF and short sleep. (E) Scatter plots of the blue, turquoise and green-yellow modules' module membership (MM) vs. gene significance (GS), with a correlation coefficient (cor) of 0.69, 0.7 and 0.67 respectively. (F) Venn diagram showing the overlap of 35 genes in the AF and short sleep modules. AF, atrial fibrillation; SS, short sleep

2.3. GSEA analysis

GSEA indicated that peroxisome pathway was significantly enriched when comparing AF samples to sinus rhythm (SR) samples in dataset GSE79768 (**Figure 4B-C**) and oxidative phosphorylation pathway was significantly enriched when comparing the short-sleep (SS) samples to the long-sleep (LS) samples in dataset GSE80612 (**Figure 5A, C**).



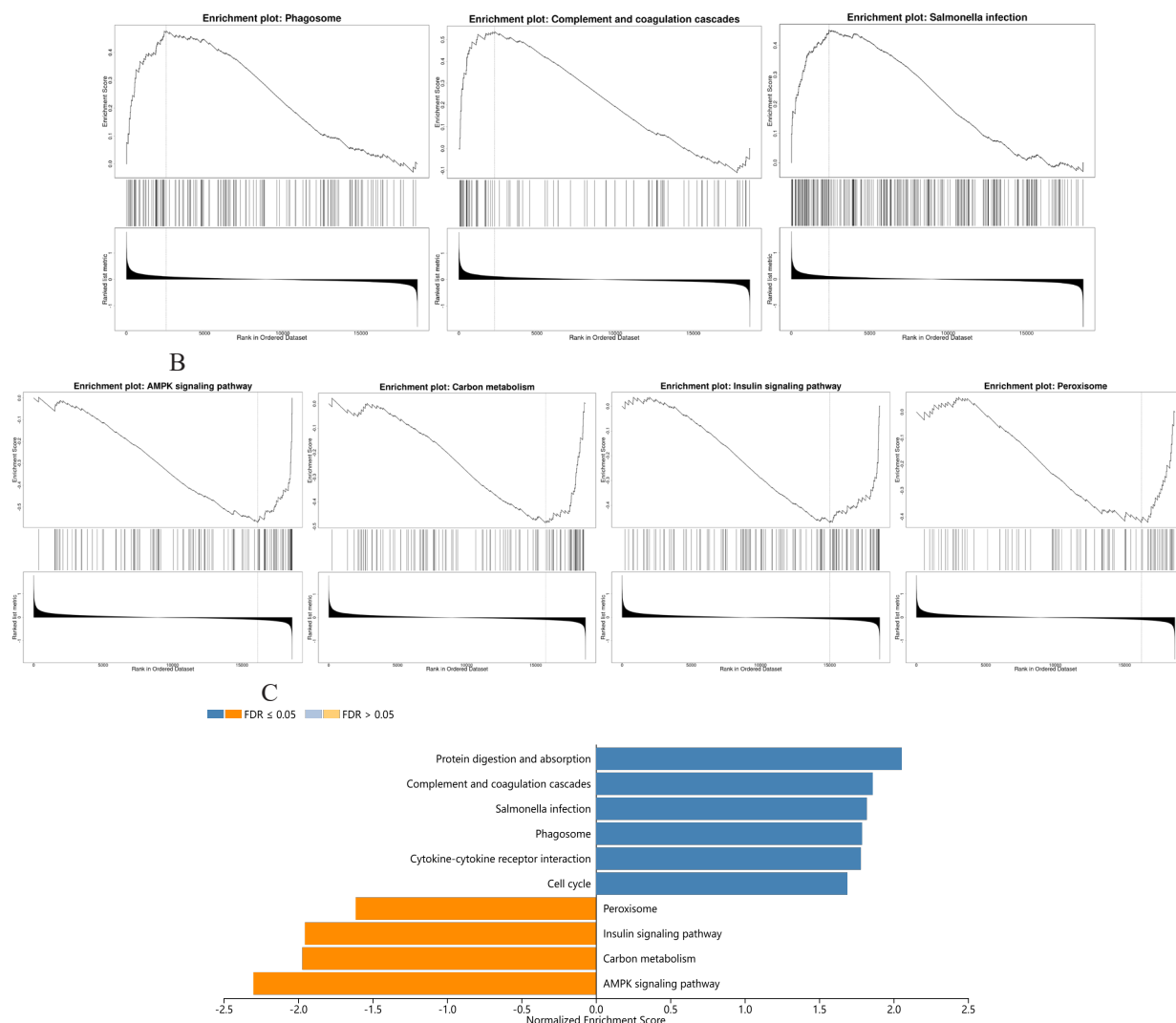
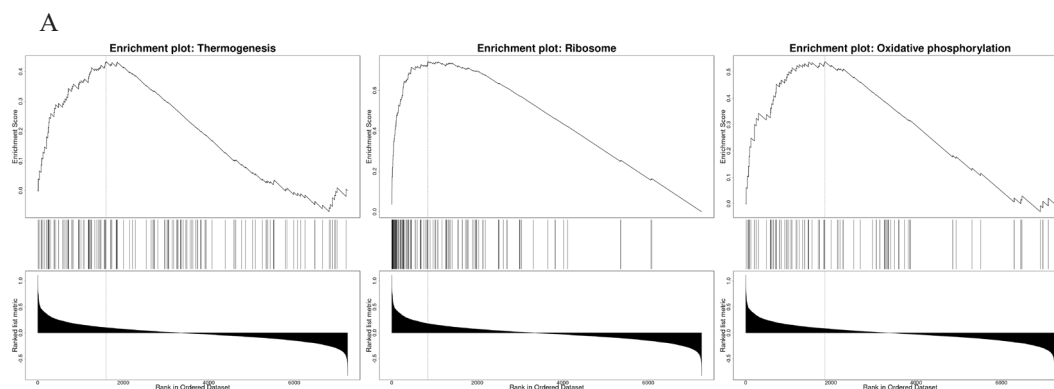


Figure 4. Pathway maps of the GSEA of dataset GSE79768. (A) Genes in dataset GSE79768 showed significant positive enrichment in pathways including Protein digestion and absorption, Complement and coagulation cascades, Salmonella infection, Phagosome, Cytokine-cytokine receptor interaction, and Cell cycle. (B) Genes in dataset GSE79768 showed significant negative enrichment in pathways including Peroxisome, Insulin signaling pathway, Carbon metabolism, and AMPK signaling pathway. (C) Bar plot of the significant GSEA results of dataset GSE79768. GSE79768 yielded mainly ten biological features.



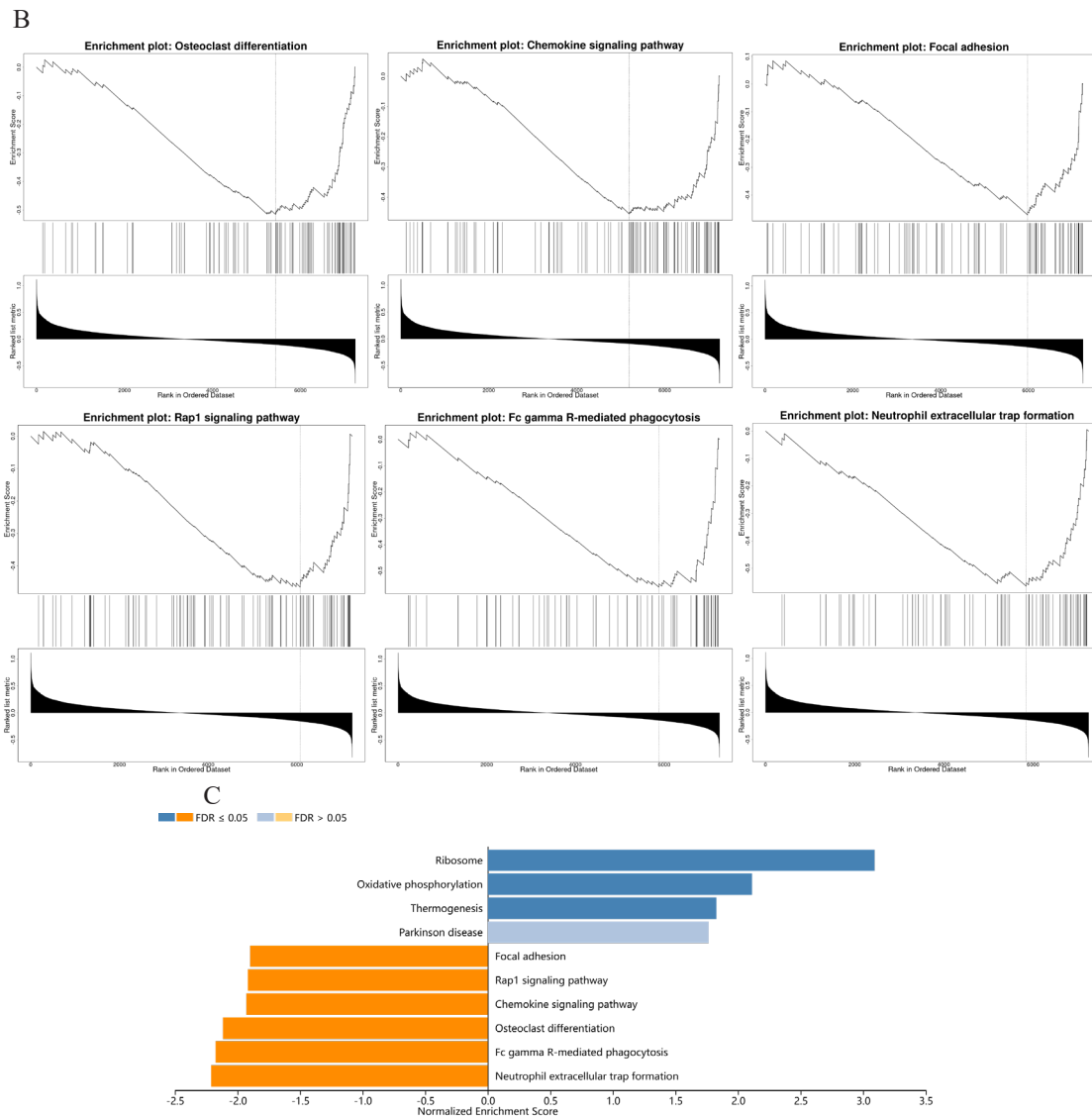
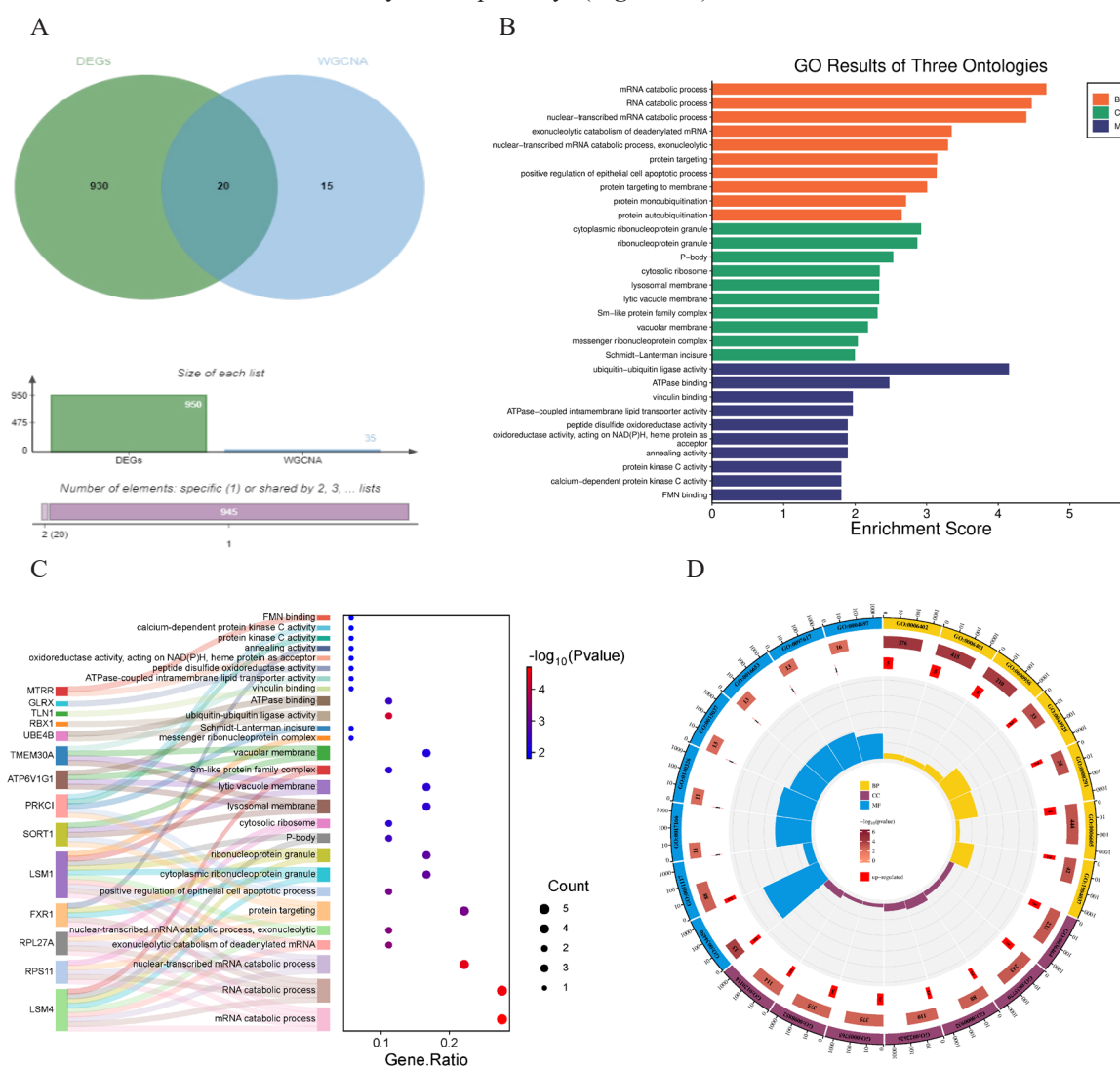


Figure 5. Pathway maps of the GSEA of dataset GSE80612. (A) Genes in dataset GSE80612 showed significant positive enrichment in pathways including Ribosome, Oxidative phosphorylation, and Thermogenesis. (B) Genes in dataset GSE80612 showed significant negative enrichment in pathways including Focal adhesion, Rap1 signaling pathway, Chemokine signaling pathway, Osteoclast differentiation, Fc gamma R-mediated phagocytosis, and Neutrophil extracellular trap formation. (C) Bar plot of the significant GSEA results of dataset GSE80612. GSE80612 yielded mainly nine biological features.

2.4. Functional enrichment analysis

We used a Venn plot and found that there were 20 overlapping genes between the 950 co-DEGs and the 35 WGCNA core modules key gene (Figure 6A). GO and KEGG pathway analysis were performed to identify the potential biological functions of the common genes in short sleep and AF samples. In the GO analysis results, 150 biological process (BP) terms, 35 cellular component (CC) terms, and 31 molecular function (MF) terms were identified. P value <

0.05 signified threshold significance. Overall, 5 genes were primarily abundant in BP term “mRNA catabolic process”, 3 genes were located in the “cytoplasmic ribonucleoprotein granule” of CC term, and 4 genes were abundant in the MF term “ubiquitin-ubiquitin ligase activity” as indicated in Figure 6B. We also draw a Sankey-dot plot of the most significant pathways in GO enrichment analysis on Weishengxin platform, which showed that GLRX was distributed in peptide disulfide oxidoreductase activity pathway (Figure 6C). The cyclic graph corresponding to the GO enrichment was shown in Figure 6D. Furthermore, the results of KEGG enrichment analysis indicated that the common genes of co-DEGs and co-WGCNA were implicated in several critical pathways, namely, RNA degradation, platelet activation, and the ubiquinone and other terpenoid-quinone biosynthesis pathways (Figure 6E).



E

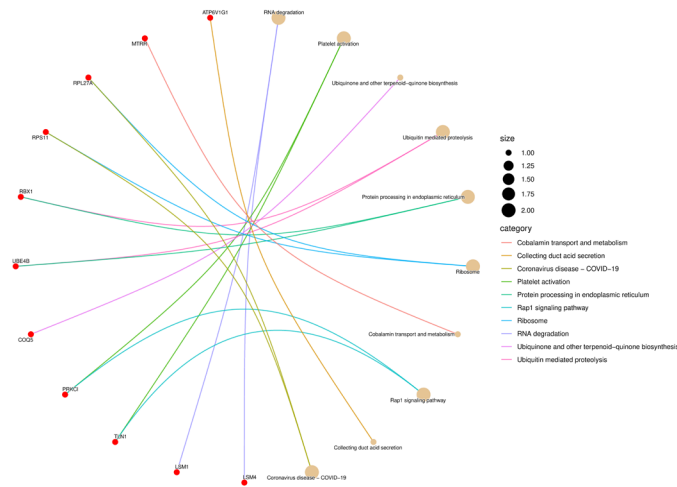
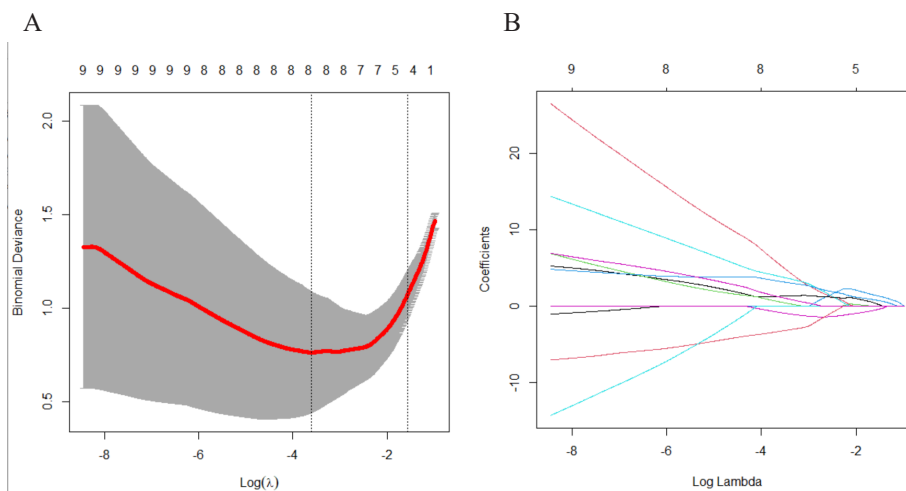


Figure 6. GO term and KEGG pathway analysis for DEGs significantly associated with AF and short sleep. (A) The Venn diagram shows that 20 key genes overlap between the genes screened by DEGs and those screened by WGCNA. (B) GO enrichment analysis of the 20 key common genes of AF and short sleep. (C) The Sankey-dot plot of the most significant pathways in GO enrichment analysis. (D) The cyclic graph corresponding to the GO enrichment. (E) The circular plot illustrates the top 10 entries for KEGG enrichment analysis of the 20 common genes.

2.5. Potential shared diagnostic genes selection by LASSO

The LASSO model was used to narrow down the range of possible shared genes among the 20 robust hub common genes in the AF dataset (**Figure 7A, B**) and the short sleep dataset (**Figure 7C, D**). 9 candidate genes were identified based on the AF dataset GSE79768 (Supplementary **Table 1**), while 15 candidate genes were identified based on the short sleep dataset GSE80612 (Supplementary **Table 2**). Six overlapped key genes were mined using the Venn diagram: GLRX, PRKCI, NDRG3, RPL27A, TLN1, and SMA4 (**Figure 7E**). To better summarize their biological functions, the common candidate genes identified by LASSO were presented in Supplementary **Table 3**.



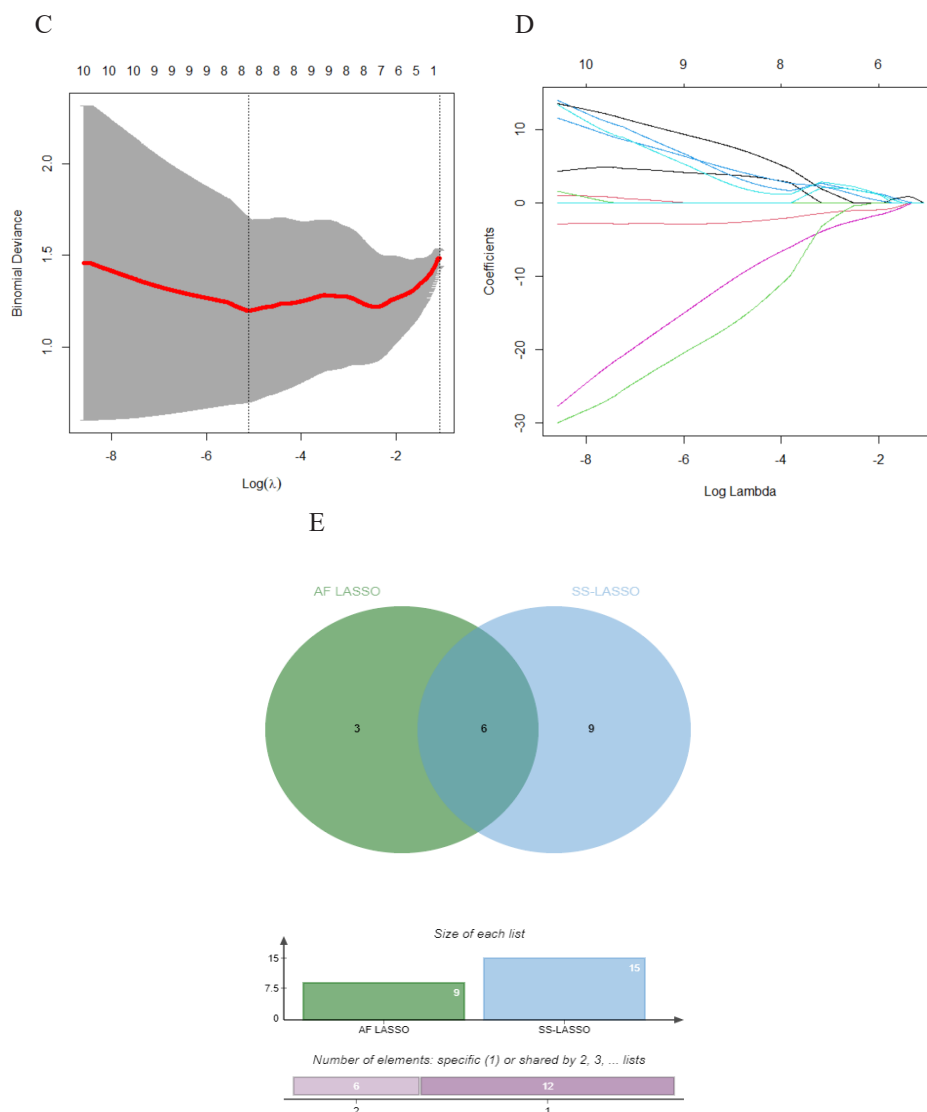


Figure 7. Selection of potential shared diagnostic genes by LASSO. (A) The partial likelihood deviation curve of the minimum number of signature genes in GSE79768 dataset. (B) The ten-fold cross-validation for tuning parameter selection in the LASSO model in GSE79768. Each curve corresponds to a single gene. (C) The partial likelihood deviation curve of the minimum number of signature genes in GSE80612 dataset. (D) The ten-fold cross-validation for tuning parameter selection in the LASSO model in GSE80612. (E) Venn diagram showing the common key biomarkers screened by LASSO of GSE79768 and GSE80612. LASSO, Least Absolute Shrinkage and Selection Operator.

2.6. Identification of hub AF-SS-DEGs via machine learning

Eight other machine learning algorithms were used to screen hub AF-short sleep DEGs in order to identify significant genes in the short sleep population with AF: random forest (RF), support vector machine (SVM), extreme gradient boosting (XGBoost), decision tree, k-nearest neighbor (kNN), neural networks (NNET), general linear model (GLM), and C5.0 algorithms. Following the integration of the outcomes from decision tree, C5.0 and LASSO (Table. 1, Table. 2)

algorithms, we ultimately identified the most critical gene: GLRX, by using Venn diagram (**Figure 8F**). The reverse cumulative residual distribution of each machine learning model in GSE79768 and GSE80612 were displayed in **Figure 8B** and **Figure 8C** respectively, and the residuals of each machine learning model were presented in boxplots (**Figure 8D, E**).

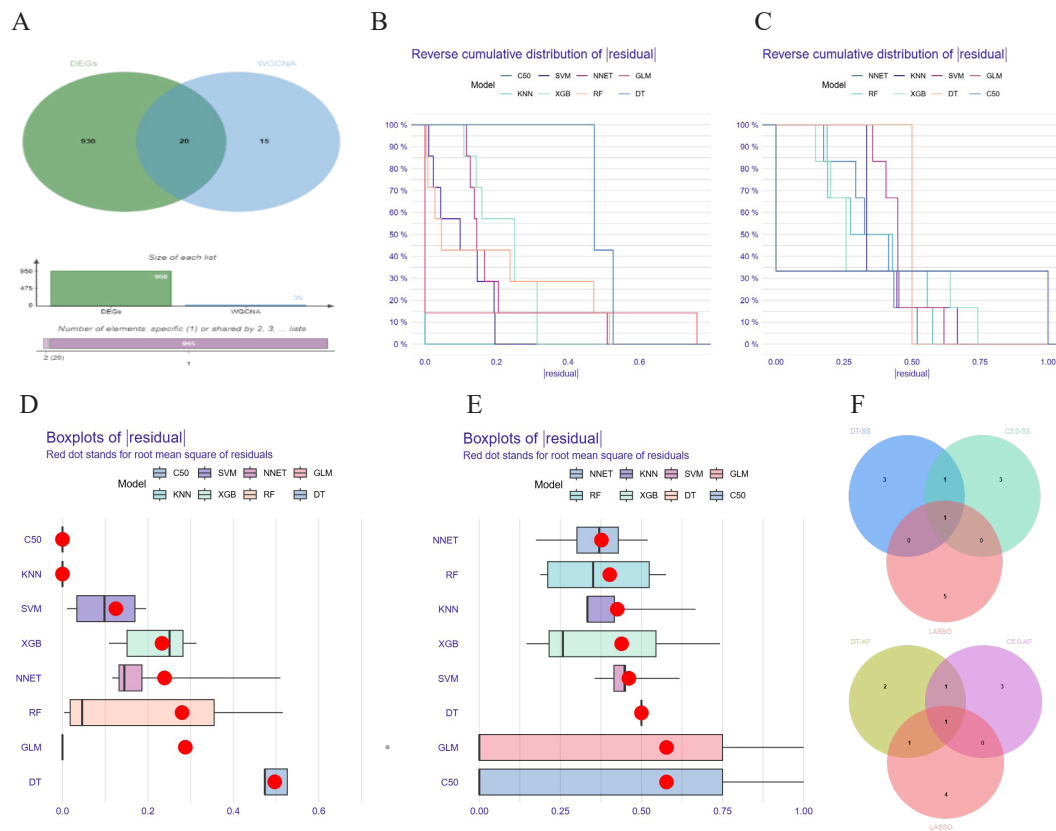


Figure 8. Construction of RF, SVM, XGBoost, Decision Trees, kNN, Neural Networks (NNET), GLM, and C5.0 machine learning models. (A) The overlapping genes between DEGs and WGCNA. (B) The reverse cumulative residual distribution of each machine learning model in AF dataset GSE79768. (C) The reverse cumulative residual distribution of each machine learning model in short sleep dataset GSE80612. (D) The residuals of each machine learning model in GSE79768 were presented in boxplots. (E) The residuals of each machine learning model in GSE80612 were presented in boxplots. (F) Venn diagram illustrating the intersection of genes selected as AF-short sleep markers using LASSO, decision tree, and C5.0 algorithms.

2.7. Differential expression and ROC analysis of the common biomarkers

Subsequently, the diagnostic value of each candidate hub gene was revalidated using the other validation datasets GSE135917 (OSA) and GSE41177 (AF). In GSE135917, differential expression analysis showed significant differences ($p < 0.05$) in GLRX (**Figure 9A**); however, the remaining five genes were not statistically significant (**Figure 9B-F**). In AF validation set, GSE41177, the expression levels of GLRX, SMA4, NDRG3, PRKCI, and RPL27A differed significantly between AF and SR samples (Figure 10A-E). However, SMA4, PRKCI

and RPL27A were raised in AF group in GSE41177, while they were reduced in AF group in GSE79768. The difference of TLN1 in AF and control groups was not statistically significant in the validation dataset (**Figure 10F**). Notably, in validation datasets, there were significant differences in GLRX expression in both the OSA and AF groups compared to control groups.

Moreover, ROC curves were displayed, and the area under the curve (AUC) was computed to distinguish patients with AF or OSA from the controls. We research the prediction effects of GLRX, SMA4, TLN1, RPL27A, NDRG3, and PRKCI in OSA and AF datasets. The AUC values of SMA4, GLRX, PRKCI, and RPL27A are > 0.7 in the OSA dataset GSE135917(**Figure 9G**), and the AUC values of all six genes are > 0.7 in the AF dataset (**Figure 10G**).

The above results indicated that only GLRX shows favorable diagnostic value in both the OSA and AF datasets among the six core genes.

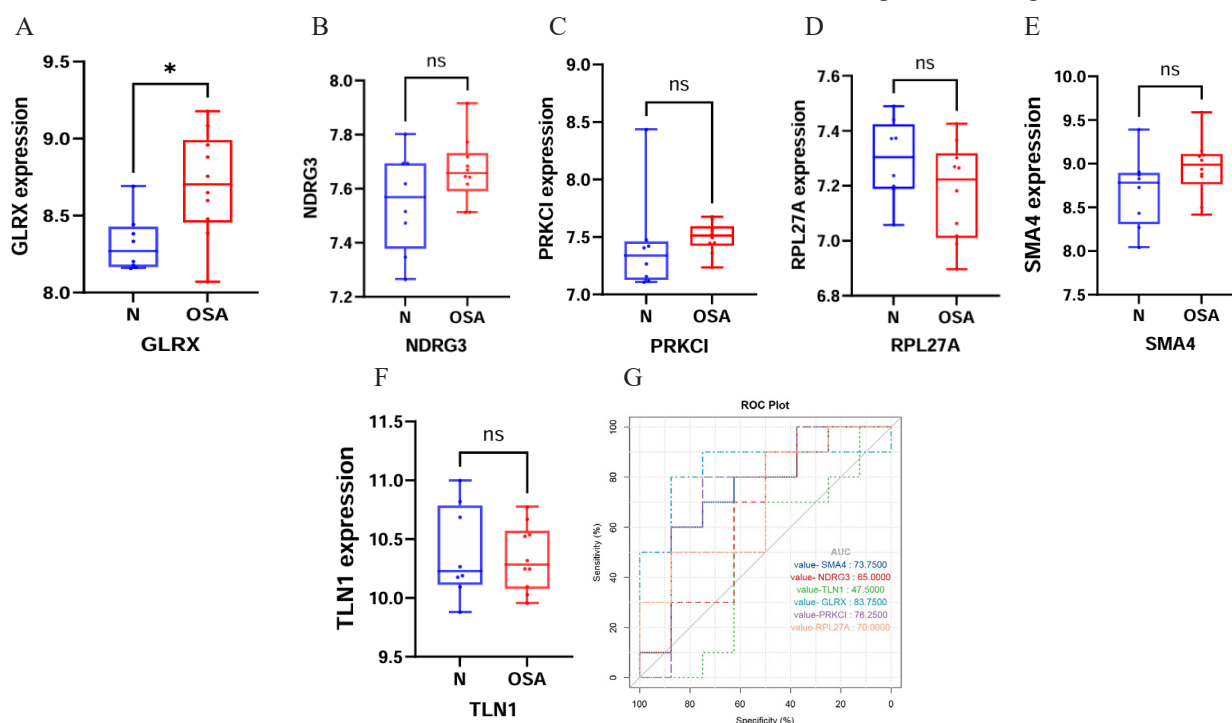


Figure 9. The candidate gene expression levels and their diagnostic values in the validation dataset GSE135917. (A-F) Expression levels of GLRX, NDRG3, PRKCI, RPL27A, SMA4, and TLN1 in GSE135917. (G) ROC curves of GLRX, NDRG3, PRKCI, RPL27A, SMA4, and TLN1 genes in GSE135917.

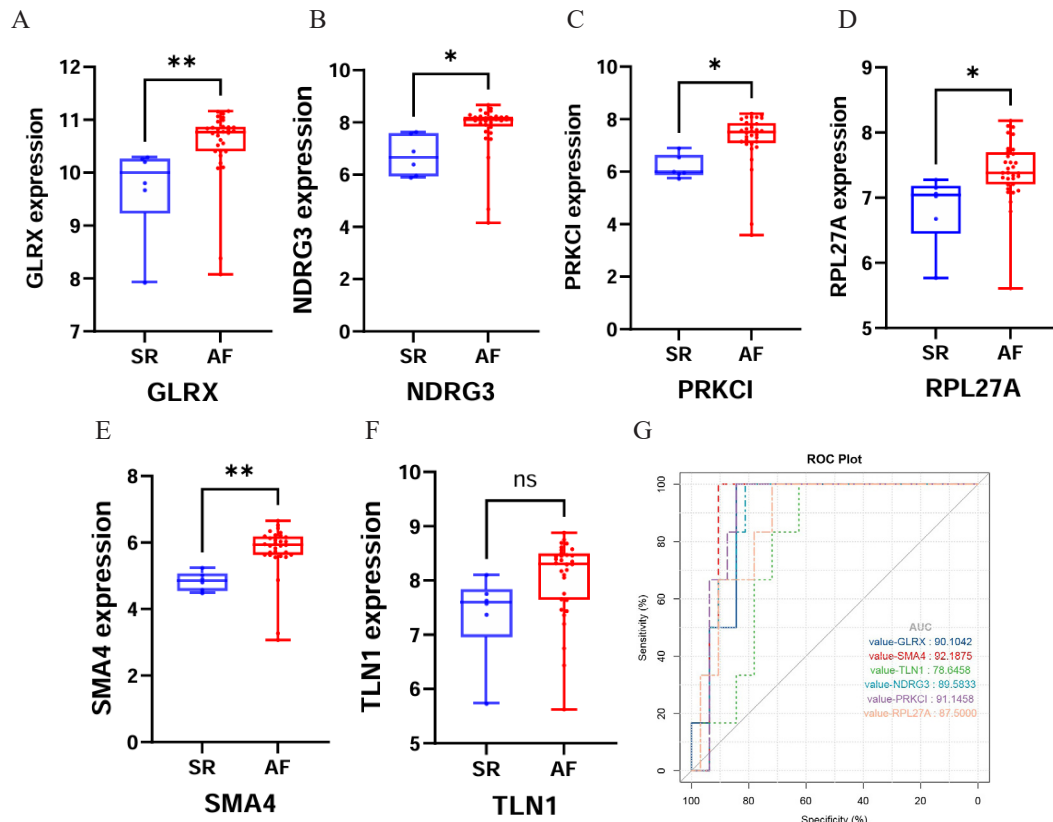
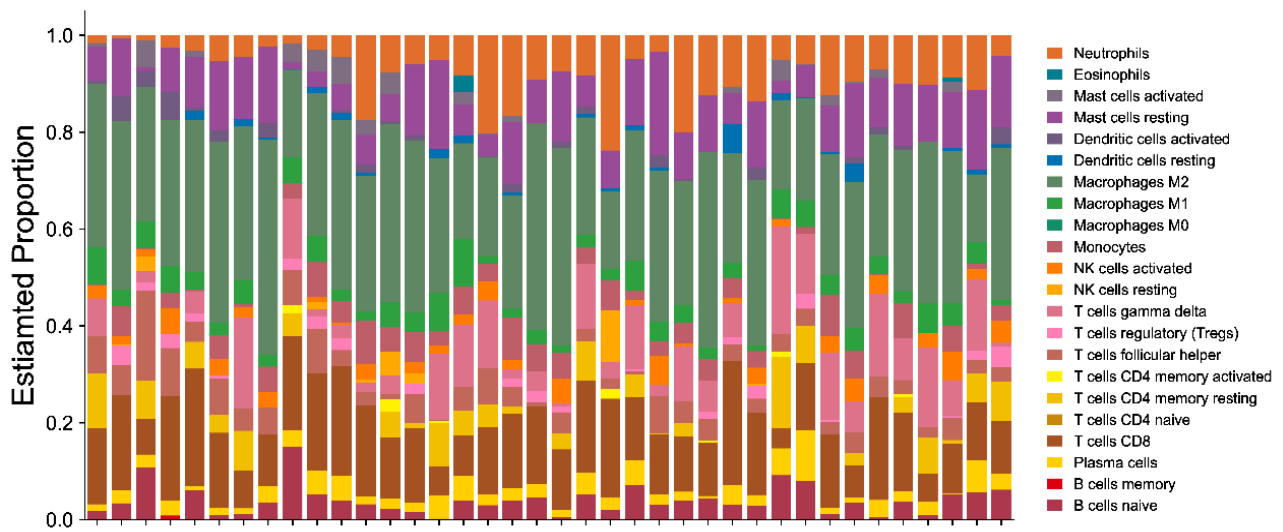


Figure 10. The candidate gene expression levels and their diagnostic values in the validation dataset GSE41177. (A-F) Expression of GLRX, NDRG3, PRKCI, RPL27A, SMA4, and TLN1 in GSE41177. (G) ROC curves of GLRX, NDRG3, PRKCI, RPL27A, SMA4, and TLN1 genes in GSE41177.

2.8 Immune cell infiltration analysis in AF and OSA validation datasets

We further analyzed the proportion of immune-infiltrating cells by using CIBERSORT on Weishengxin Platform. The bar charts visualizing the distribution of 22 types of immune cells in AF and OSA individual samples were showed in Figure 11. Compared with the control group, the samples in AF group had higher proportions of neutrophils and gamma delta T cells (**Figure 12A**), while samples in the OSA group accounted for higher proportions of resting mast cells and CD8⁺ T cells (**Figure 12B**).

A



B

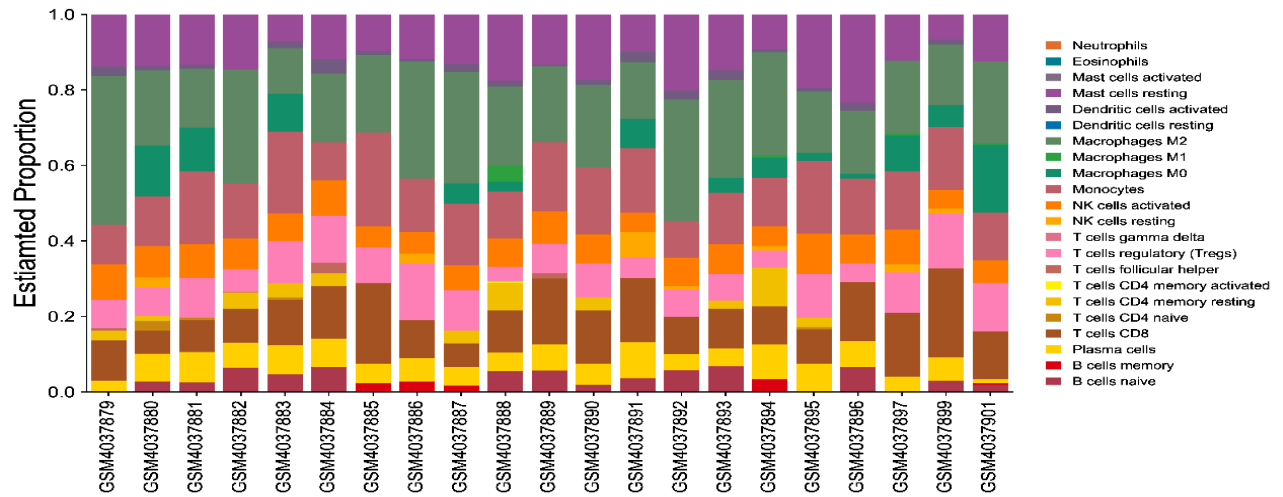


Figure 11. Analysis of immune cell filtration in AF dataset GSE41177(A) and GSE135917(B).

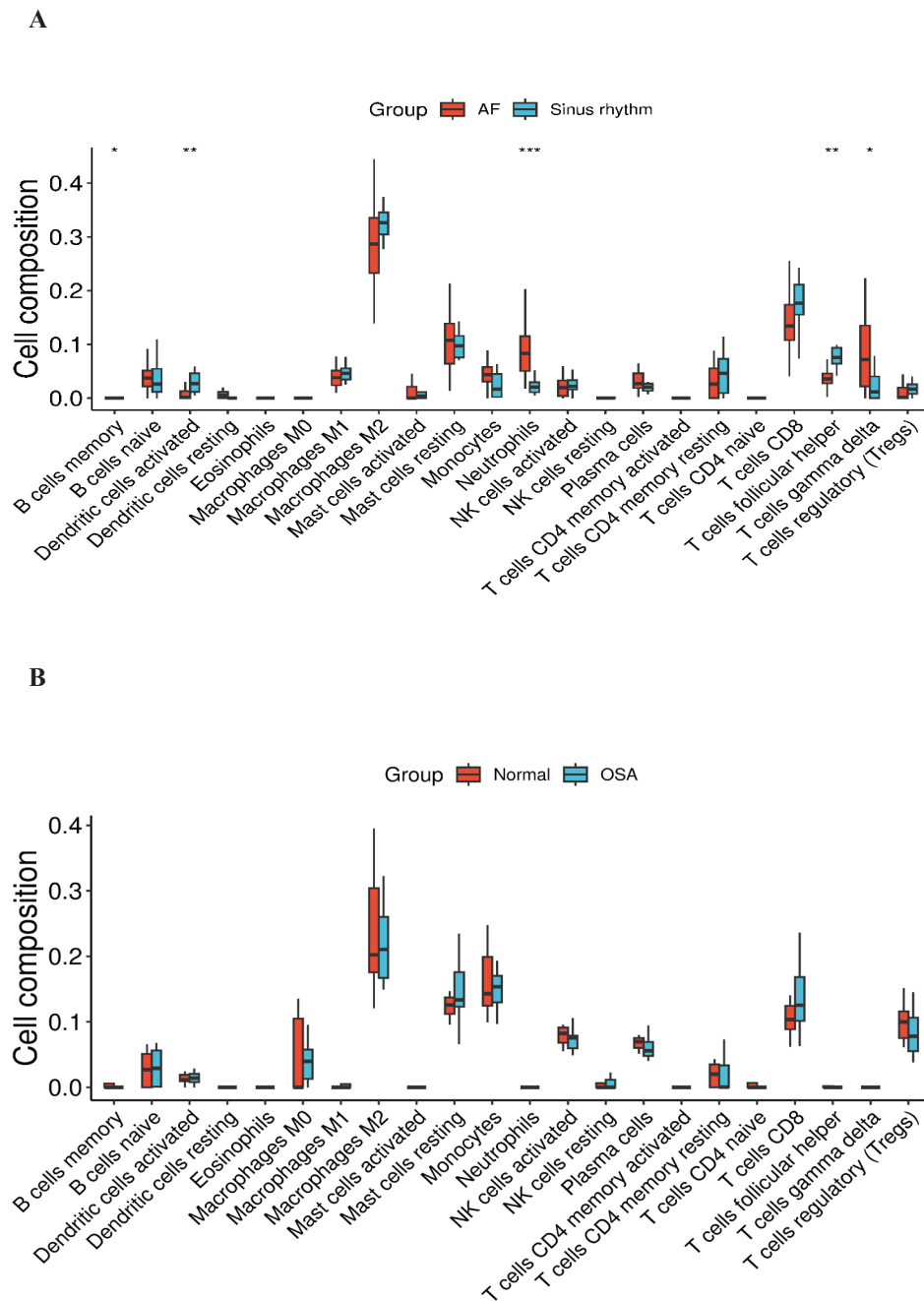


Figure 12. The box plots visualizing the distribution of infiltrating immune cells in different groups for AF (A) and OSA (B).

3. Discussion

In recent years, the number of people suffering from sleep problems has increased globally, and previous studies have shown a close association between sleep disorders and the occurrence of atrial fibrillation^[14]. We assume that sleep

disorders and AF share a common mechanism of response to systemic injury. However, there is little research on this mechanism at the molecular level. At present, there are two relevant studies that can be found, one of which is MAO Ting's study on the mechanism of action of Tiaoganyiqidingji prescription in the treatment of paroxysmal atrial fibrillation complicated with OSAHS in Traditional Chinese medicine ^[15]. This study found that Tiaoganyiqidingji palpitation prescription in the treatment of paroxysmal atrial fibrillation complicated with OSAHS was mainly related to TNF signaling pathway, PI3K Akt signaling pathway, HIF signaling pathway, apoptosis, cytokine-cytokine receptor interaction and other signaling pathways. In another paper, Junqing Liang et al. used the public database related to sleep and atrial fibrillation to screen out that the transcription factor Y-box binding protein 1 (YBX1) may play a key role in linking sleep deprivation and AF through inflammatory processes and immune responses ^[16]. More research is needed to further validate the above studies or to discover new core molecules and pathways, thereby providing more theoretical support for precision medicine. Hence, we conducted a systematic bioinformatic analysis to explore the possible shared pathways in sleep disorders and AF, along with new potential diagnostic biomarkers in sleep disorder related AF. It turns out that the occurrence of sleep disorders and AF may both be related to common pathways, including peroxisome, oxidative phosphorylation, and peptide disulfide oxidoreductase activity, with Glutaredoxin (GLRX) as one of the key shared genes that steadily increases in both sleep disorder and AF participants, showing significant diagnostic value. Our study is the first to integrate WGCNA with multiple machine learning algorithms to identify GLRX as a novel shared diagnostic biomarker for both sleep disorders and AF, which has not been reported previously. Notably, we chose to investigate gene expression in monozygotic twins, minimizing the influence of factors other than sleep duration as much as possible.

We obtained hub differential genes by taking the intersection of DEGs from the short sleep and AF datasets. The results of GSEA indicated that peroxisome pathway and oxidative phosphorylation pathway were enriched in AF datasets and short sleep datasets respectively. GO enrichment analysis of these common differential genes revealed that pathways including peptide disulfide oxidoreductase activity also play important roles in the occurrence of both AF and sleep loss. And notably, all these pathways mentioned above have something to do with oxidative stress response, which is consistent with the key gene GLRX.

A total of 35 genes overlapped in the strongest positive modules of the WGCNA for sleep disorders and AF. Thus, these genes may be involved in the common pathogenesis of sleep disorders and AF. We identified 20 shared diagnostic gene biomarkers based on the intersection of DEGs and modular hub genes using the Venn diagram. To narrow the range of potentially shared diagnostic genes among the 20 DEGs, we used the LASSO algorithm. Using LASSO regression, six shared key genes were detected: GLRX, PRKCI, NDRG3, RPL27A, TLN1, and SMA4.

GLRX (also known as glutaredoxin) is an important thiol-disulfide oxidoreductase in cells that regulates redox reactions, supports cell growth, and inhibits apoptosis. It belongs to the thioredoxin (Trx) family and catalyzes glutathione-dependent redox reactions, facilitates iron-sulfur cluster assembly, participates in redox signaling, and is indirectly involved in the detoxification of reactive oxygen species (ROS) ^[17]. Owing to these functions, GLRX is associated with the development of various human diseases, including infections, diabetes, cardiovascular and cerebrovascular diseases, cataracts, acquired immune deficiency syndrome, tumours, and autoimmune diseases ^[18]. In recent years, the protective function of GLRX, in synergy with other antioxidant enzymes, in eye diseases have been elucidated ^[19]. It has also been shown that GLRX overexpression is involved in the malignant progression of cervical cancer and can be used as a potential molecular marker for the diagnosis and prognosis prediction of cervical cancer ^[20]. However, in terms of cardiovascular disease, the function of GLRX varies in different tissues in different studies. In cardiomyocytes, a study showed that GLRX alleviated OSA-induced atrial fibrillation by reducing oxidative stress ^[21] and inhibiting autophagy through the caspase-8/3 apoptosis pathway and JNK/c-Jun signaling pathway ^[22]. While in plasma, the study of Hongxin Zhang suggests that plasma GLRX may be involved in the occurrence and development of carotid atherosclerosis ^[23]. It is reported that GLRX may have a bidirectional effect on cardiovascular disease by regulating redox status and apoptosis ^[15]. In ischemia/reperfusion injury and cardiac hypertrophy, low concentrations of ROS can activate related pathways and play a cardioprotective role, while excess ROS can lead to cell damage and death ^[24]. Additionally, GLRX proteins are also involved in regulating various signaling pathways, such as the Akt pathway and the NF- κ B pathway. The role of GLRX in atrial fibrillation is rarely discussed in the literature. However, the occurrence and development of atrial fibrillation are closely related to oxidative stress and Akt signaling pathways. It is reasonable to suspect that GLRX may also play a bidirectional role in atrial fibrillation. Apart from the aspect of oxidative stress, there are also studies suggesting that GLRX may contribute to the occurrence of atrial fibrillation through pathological processes such as cardiac remodeling and autonomic nerve imbalance. In terms of cardiac remodeling, animal experiments have shown that mice with the GLRX gene knocked out have significantly reduced cardiac hypertrophy when stimulated by Ang II. GLRX may also promote metabolic cardiomyopathy, leading to cardiac contractile dysfunction and fibrosis ^[25]. In terms of the impact on the autonomic nervous system, experimental studies on the heart have shown that the activity of GLRX promotes the pathological process mediated by Ang II. Since Ang II serves as a key hub connecting the regulation of the body fluids and the excitation of the sympathetic nerve, GLRX, by enhancing the signaling pathway of Ang II (such as activating growth-promoting signals like Ras and Akt), may indirectly exacerbate the excessive activation of the sympathetic nerve driven by Ang II, thereby disrupting the balance of the autonomic nervous system ^[26].

In our study, it seems that GLRX has negative effects on the occurrence of both sleep disorders and AF. Therefore, we speculate that the increase of GLRX in samples of sleep disorders and atrial fibrillation may exert a decompensated negative damaging effect in the progression of OSA and atrial fibrillation by indirectly regulating ROS. Although tissues differ, previous studies [22-24] indicate that GLRX is involved in systemic oxidative stress regulation, supporting its potential as a cross-tissue biomarker. The crucial point is that when myocardial cells are damaged under pathological conditions, this redox enzyme GLRX may leak passively into the blood or distant adipose tissues, thereby influencing the systemic inflammatory response. This is the first time that GLRX has been identified and reported as a potential diagnostic biomarker for these two diseases, a finding that has never been mentioned in previous studies. This study may provide new insights for future research on the connective mechanisms of both sleep disorders and AF.

PRKCI (protein kinase C Iota) is a serine/threonine protein kinase, an atypical protein member of the PKC family, and it plays a key role in various cellular processes, particularly during tumour development [27]. PRKCI plays a key role in promoting tumor cell proliferation, migration, and invasion by activating the PI3K/AKT and Wnt/ β -catenin pathways in various malignant tumours [28]. PRKCI regulates the cell cycle and tumour progression in lung squamous cell carcinoma [29] and is involved in the formation of the tumour immunosuppressive microenvironment in hyperserous ovarian cancer [30]. According to available data, there are few studies on PRKCI in cardiovascular diseases, and further literature searches in related fields may be needed to obtain more detailed information.

NDRG3 (N-Myck downstream regulatory gene 3) is involved in cell differentiation [31]. NDRG3 enhances the adaptability of tumour cells to hypoxia by inhibiting apoptosis, promoting angiogenesis, and stimulating cell proliferation in hypoxic environments. In cardiovascular field, the decreased expression of NDRG3 may be related to cardiovascular diseases such as hypertension [32]. In terms of atrial fibrillation, there is no direct evidence showing the role of NDRG3, but the study by Ga Young Lee1 found that NDRG family members play a role in inhibiting aerobic glycolysis and the PI3K-Akt-mTOR signaling pathway [33].

RPL27A is a gene associated with the development of obesity [34], while TLN1 (Talin-1), an oncogene linked to tumorigenesis and cancer progression [35], encodes an intracellular adapter protein critical for integrin-mediated cell adhesion to the extracellular matrix. In the cardiovascular system, TLN1 is highly expressed in cardiomyocytes and essential for cardiac function, with studies showing that heart-specific TLN1 knockout mice maintain normal baseline heart function but exhibit reduced cardiac hypertrophy response and improved cardiac function under pathological conditions, as observed in human failing hearts with upregulated TLN1 expression [36]. Additionally, TLN1 deficiency may impair platelet aggregation, neutrophil adhesion/migration, and affect blood coagulation

and inflammatory responses^[37]. Although the role of TLN1 in atrial fibrillation is not explicitly stated, its involvement in cardiovascular cell adhesion and signaling suggests potential participation in atrial fibrillation pathology. Similarly, SMA-4 may regulate cardiovascular development and function through gene expression modulation, and while its role in atrial fibrillation remains unclear, it is hypothesized to influence cardiac electrophysiological stability and myocardial cell structure.

We then validated these six genes with two validation datasets, collected atrial samples from patients with AF and subcutaneous fat samples from patients with OSA, and found that only the GLRX gene was consistently increased in both AF and OSA patients and has a high diagnostic value ($AUC > 0.7$). Furthermore, among the results of screening core genes by eight other machine learning methods, the intersection of the decision tree and the C5.0 algorithms also contains the GLRX gene, once again verifying the communal role GLRX plays in sleep disorders and atrial fibrillation.

Our study has certain limitations. First, although we explore the common systemic changes in GLRX in sleep disorder and AF, the direct connection within specific tissues remains unexplored. Second, the small sample size raises the possibility of bias, so larger cohorts in future work are absolutely necessary. While the discoveries require further clinical or experimental validations, our computational model provides a strong rationale and a specific hypothesis for future investigations into the potential molecular links between sleep disorders and atrial fibrillation. We plan to seek more datasets to include the samples of blood in both AF patients and sleep disorder participants, and include clinical and experimental validations in the following researches to confirm these results.

4. Materials and Methods

4.1. Data sourcing

The GEO database (<http://www.ncbi.nlm.nih.gov/geo/>) provided all of the gene expression datasets used in this study. Four human datasets (GSE79768, GSE80612, GSE41177, and GSE135917) were selected for this study. These datasets were profiled using microarrays of atrial samples, peripheral blood leukocyte samples, and subcutaneous fat samples. Among them, GSE79768 and GSE41177 included atrial tissue from participants with AF and SR. In GSE79768, 13 patients receiving valvular surgery were included (7 with AF and 6 with SR)^[38], while GSE41177 contained 16 AF patients and 3 patients with SR receiving valvular surgery^[39]. In addition, GSE80612 and GSE135917 were downloaded from the NCBI (National Center of Biotechnology Information) GEO database, both of which included gene expression data for patients with 15 different sleep situations. The GSE80612 dataset contained 11 monozygotic healthy twin pairs discordant for habitual sleep duration^[40], and GSE135917

contained 10 patients with OSA and 8 control individuals ^[41]. The study flowchart is shown in **Figure 1**.

4.2. Identification and classification of DEGs

By using the GEO2R software (<http://www.ncbi.nlm.nih.gov/geo/geo2r>), a tool provided by the GEO database that relies on the R package “limma”, AF-related DEGs were screened from the GSE79768 dataset, and short sleep-related DEGs were also obtained from the GSE80612 dataset. Genes with $p < 0.05$ and $|\log_2 \text{FC}| > 0.5$ were considered DEGs. Overlapping DEGs were extracted and visualized for further analysis using the Jvenn tool. Finally, with the help of the GEO2R and Hiplot (<https://hiplot.com.cn/>) websites, volcano maps and heat maps of the DEGs were created.

4.3. Weighted Gene Co-expression Network Analysis

Construction and module analysis of weighted gene co-expression network analysis is a bioinformatics analysis method used to describe gene association patterns among different samples. Co-expression networks corresponding to the clinical features of DEGs in AF and short sleep were constructed using the WGCNA R package. First, duplicate columns and missing values were removed, and hierarchical cluster analysis was performed using the cluster function in R software to exclude outlier samples. Then, the “pickSoftThreshold” function in the WGCNA package was used to screen the appropriate soft-power threshold β for automatic network construction, and the minimum value of the degree of independence over 0.85 was used. The results were clustered via a topological overlap matrix analysis, and the analysis included module assignments tagged by color and module eigengenes. Overlapping genes in the hub modules were extracted and visualized for further analysis by using the Venn diagrams.

4.4. Gene set enrichment analysis

GSEA is a method used to determine whether a prioritized set of defined genes is statistically significant ^[42]. It is usually used in conjunction with the Molecular Signatures Database (MsigDB) to study the biological function of genes ^[43]. In this study, we analyzed gene sets and expression matrices of short sleep and AF using GSEA enrichment(<http://www.webgestalt.org/>) to explore possible regulatory pathways. False Discovery Rate (FDR)<0.05 was defined as statistically significant.

4.5. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis

GO integrates the world’s largest source of information about gene functions and serves as the basis for large-scale molecular biology and genetic experimental computational analysis in biomedical research. It describes the biological functions in the following three parts: CC, BP, and MF ^[44]. To understand the function of DEGs in AF patients and participants with different sleep durations,

GO analysis of the overlapping genes of the co-DEGs and genes in the core modules in WGCNA of AF and short sleep was performed. The KEGG database has powerful graphical functions that help researchers understand metabolic pathways ^[45], and the DAVID database (<https://david.ncifcrf.gov/>) offers a systematic set of functional annotation tools ^[46]. Hence, we performed a KEGG pathway enrichment analysis to predict the potential functions of the robust common genes. The enriched terms with $P < 0.05$ were considered statistically significant. Both GO and KEGG pathway enrichment analysis were performed on Weishengxin platform (<https://www.bioinformatics.com.cn/>).

4.6. Identification of shared genes by Least Absolute Shrinkage and Selection Operator

We used Venn diagrams to identify the intersecting genes of WGCNA and DEGs. LASSO is a regression analysis technique that uses a machine learning prediction method incorporating feature selection. By penalizing the number of variables in the regression model, the coefficients of unimportant variables can be reduced to 0 and excluded. The “glmnet” package in R was used to perform LASSO regression to filter the best predictors of AF and short sleep in the overlapping genes of the aforementioned WGCNA and DEGs based on the short sleep dataset GSE80612 and the AF dataset GSE79768.

4.7. Identification of shared genes by multiple machine learning approaches

To filter the best predictors of AF and short sleep in the overlapping genes of the common genes identified by the LASSO algorithm, we then used 8 other machine learning approaches on the common DEGs in both the GSE79768 and GSE80612 datasets by using R software. These machine learning methods included RF, SVM, XGBoost, decision trees, kNN, NNET, GLM, and C5.0 algorithms.

4.8. Candidate biomarker expression levels and their diagnostic value

GraphPad Prism 9.5 was used to compare the differential expression of characteristic genes between sleep disorder or AF and control samples in the validation datasets (GSE41177 for AF, GSE135917 for OSA). Boxplots were used to show differences in gene expression. In addition, the ROC curve analysis was performed using the open-source network tool Hiplot to visualize the diagnostic value of each individual gene, along with the calculation of the AUC.

4.9 Immune cell infiltration analysis

The CIBERSORT method on Weishengxin Platform were used to evaluate immune infiltration profiles of 22 immune cell types in samples in AF dataset GSE41177 and OSA dataset GSE135917, with $p < 0.05$ considered significant. Comparative analysis of immune cell distributions in AF and OSA datasets was

also performed in box plots.

4.10. Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.5 and R software (R version 4.4.1). Comparisons between two groups were carried out with two-tailed Student's t-test or Mann–Whitney U-test. The area under the ROC curve (AUC) represented diagnostic performance. For all assessments, a p-value < 0.05 was considered statistically significant, except where a certain p value has been provided.

5. Conclusions

Our study identified GLRX as a potential diagnostic biomarker for sleep disorders related AF, offering promise for novel diagnostic candidates and potentially more detailed molecular mechanisms and potential therapeutic targets for AF^[47].

Funding:

This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The datasets GSE79768, GSE80612, GSE41177 and GSE135917 for this study can be found in the GEO datasets (<http://www.ncbi.nlm.nih.gov/geo/>).

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AF	Atrial fibrillation
GEO	Gene Expression Omnibus
DEGs	Differentially Expressed Genes
WGCNA	Weighted Gene Correlation Network Analysis
GSEA	Gene Set Enrichment Analysis
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
LASSO	Least Absolute Shrinkage And Selection Operator
ROC	Receiver Operating Curve
OSA	Obstructive Sleep Apnea
PBL	Peripheral Blood Leukocyte

SR	Sinus Rhythm
SS	Short Sleep
LS	Long Sleep
BP	Biological Process
CC	Cellular Component
MF	Molecular Function
RF	Random Forest
SVM	Support Vector Machine
XGBoost	Extreme Gradient Boosting
kNN	k-Nearest Neighbor
NNET	Neural Networks
GLM	General Linear Model
TNF	Tumor Necrosis Factor
GLRX	Glutaredoxin
ROS	Reactive Oxygen Species
PRKCI	Protein Kinase C Iota
NDRG3	N-Myck Downstream Regulatory Gene 3
TLN1	Talin-1
NCBI	National Center of Biotechnology Information

References

1. Schnabel, R.B.; Yin, X.; Gona, P.; Larson, M.G.; Beiser, A.S.; McManus, D.D.; Newton-Cheh, C.; Lubitz, S.A.; Magnani, J.W.; Ellinor, P.T.; et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015, 386, 154-162, [http://doi: 10.1016/S0140-6736\(14\)61774-8](http://doi: 10.1016/S0140-6736(14)61774-8).
2. Zheng, P.; Zhang, W.; Wang, J.; Gong, Q.; Xu, N.; Chen, N. Bioinformatics and functional experiments reveal that MRC2 inhibits atrial fibrillation via the PPAR signaling pathway. *J Thorac Dis*. 2023, 15, 5625-5639, <http://doi: 10.21037/jtd-23-1235>.
3. Hu, F.; Zheng, L.; Liu, S.; Shen, L.; Liang, E.; Ding, L.; Wu, L.; Chen, G.; Fan, X.; Yao, Y. Avoidance of vagal response during circumferential pulmonary vein isolation: effect of initiating isolation from right anterior ganglionated plexi. *Circ Arrhythm Electrophysiol*. 2019, 12, 7811, <http://doi: 10.1161/CIRCEP.119.007811>.
4. Qin, M.; Zeng, C.; Liu, X. The cardiac autonomic nervous system: a target for modulation of atrial fibrillation. *Clin Cardiol*. 2019, 42, 644-652, <http://doi: 10.1002/clc.23190>.
5. Zhu Y, Mi J. Unraveling the complex relationship between night shift work and diabetes: exploring mechanisms and potential interventions. *Front Public Health*. 2025, 13, 1539679. <http://doi: 10.3389/fpubh.2025.1539679>.
6. Gaspar, L.S.; Sousa, C.; Alvaro, A.R.; Cavadas, C.; Mendes, A.F. Common risk factors and therapeutic targets in obstructive sleep apnea and osteoarthritis: an unexpectable link? *Pharmacol Res*. 2021, 164, 105369, <http://doi: 10.1016/j.phrs.2020.105369>.
7. Shaikh, G.; Raval, R.; Shahid, H.; Pandit, M.; Kumar, A.; Khalid, M.; Khalid, A.U.; Shaikh, S.; Rahim, N.; Albshir, M.M. Association Between Sleep Duration and Atrial Fibrillation: A Narrative Review. *Cureus*. 2024, 16, e64147, <http://doi: 10.7759/cureus.64147>.
8. Congrete, S.; Bintvihok, M.; Thongprayoon, C.; Bathini, T.; Boonpheng, B.; Sharma, K.; Chokesuwattanaskul, R.; Srivali, N.; Tanawuttiwat, T.; Cheungpasitporn, W. Effect of obstructive sleep apnea and its treatment of atrial fibrillation recurrence after radiofrequency catheter ablation: A meta-analysis. *J Evid Based Med*. 2018, 11, 145-151, <http://doi: 10.1111/jebm.12313>.
9. Chen, Z.; Zhang, R.; Hu, X.; Wan, C.; Shen, Y.; Qin, J.; Gao, L.; Zhu, J. Impact of sleep disordered breathing

on postoperative atrial fibrillation in patients who underwent cardiac surgery: a meta-analysis. *Ann Med.* 2022, 54, 3177-3188, <http://doi: 10.1080/07853890.2022.2143555>.

10. Morovatdar, N.; Ebrahimi, N.; Rezaee, R.; Poorzand, H.; Bayat, T.M.A.; Sahebkar, A. Sleep Duration and Risk of Atrial Fibrillation: a Systematic Review. *J Atr Fibrillation.* 2019, 11, 2132, <http://doi: 10.4022/jafib.2132>.

11. Peng, L.; Wang, X.; Bing, D. Identification and Validation of Prognostic Factors of Lipid Metabolism in Obstructive Sleep Apnea. *Front Genet.* 2021, 12, 747576, <http://doi: 10.3389/fgene.2021.747576>.

12. Li, K.; Chen, Z.; Qin, Y.; Wei, Y. MiR-664a-3p expression in patients with obstructive sleep apnea: A potential marker of atherosclerosis. *Medicine (Baltimore).* 2018, 97, e9813, <http://doi: 10.1097/MD.0000000000009813>.

13. Cao, Y.; Cai, X.; Zhu, Q.; Li, N. Screening and identification of potential biomarkers for obstructive sleep apnea via microarray analysis. *Medicine (Baltimore).* 2021, 100, e24435, <http://doi: 10.1097/MD.00000000000024435>.

14. Linz B, Hohl M, Lang L, Wong DWL, Nickel AG, De La Torre C, Sticht C, Wirth K, Boor P, Maack C, Speer T, Jespersen T, Schotten U, Sanders P, Böhm M, Linz D. Repeated exposure to transient obstructive sleep apnea-related conditions causes an atrial fibrillation substrate in a chronic rat model. *Heart Rhythm.* 2021, 18, 455-464, <http://doi: 10.1016/j.hrthm.2020.10.011>.

15. Mao, T. Clinical Research and Mechanism Exploration of the Formula for Regulating the Liver, Benefiting Qi and Stabilizing Palpitations in the Treatment of Paroxysmal Atrial Fibrillation Complicated with Obstructive Sleep Apnea-hypopnea Syn-drome. Ph.D. Thesis, China Academy of Chinese Medical Sciences, China, 2020, <http://doi: 10.27658/d.cnki.gzzyy.2020.000209>.

16. Liang, J.; Tang, B.; Shen, J.; Rejiepu, M.; Guo, Y.; Wang, X.; Shao, S.; Guo, F.; Wang, Q.; Zhang, L. New Insights into the Role of Inflammatory Pathways and Immune Cell Infiltration in Sleep Deprivation-Induced Atrial Fibrillation: An Integrated Bio-informatics and Experimental Study. *J Inflamm Res.* 2025, 18, 791-812, <http://doi: 10.2147/JIR.S495777>.

17. Burns, M.; Rizvi, S.H.M.; Tsukahara, Y.; Pimentel, D.R.; Luptak, I.; Hamburg, N.M.; Matsui, R.; Bachschmid, M.M. Role of Glutaredoxin-1 and Glutathionylation in Cardiovascular Diseases. *Int J Mol Sci.* 2020, 21, 6803, <http://doi: 10.3390/ijms21186803>.

18. Allen, E.M.; Mieyal, J.J. Protein-thiol oxidation and cell death: regulatory role of glutaredoxins. *Antioxid Redox Signal.* 2012, 17, 1748-1763, <http://doi: 10.1089/ars.2012.4644>.

19. Fan, Q.; Zhang, Y.; Liu, Y.; Yang, J.; Li, D.; Tang, Y.; Cai, L.; Zhao, Z.; Zhou, P.; Lu, Y. Glutaredoxin Desensitizes Lens to Oxidative Stress by Connecting and Integrating Specific Signaling and Transcriptional Regulation for Antioxidant Response. *Cell Physiol Biochem.* 2016, 39, 1813-1826, <http://doi: 10.1159/000447881>.

20. Gennigens, C.; Jerusalem, G.; Lapaille, L.; De, C.M.; Streel, S.; Kridelka, F.; Ray-Coquard, I. Recurrent or primary metastatic cervical cancer: current and future treatments. *ESMO Open.* 2022, 7, 100579, <http://doi: 10.1016/j.esmoop.2022.100579>.

21. Huang, H.; Du, J.; Sun, Y.; Hou, Y.; Gao, M. The mechanism by which hydrogen sulfide regulates oxidative stress through glutaredoxin-1 to alleviate atrial fibrillation induced by acute obstructive sleep apnea. *Journal of Shandong University (Health Sciences).* 2022, 60, 1-5+12.

22. Zhang, C.; Hou, J.; Wang, B.; Qi, X.; Li, S.; Sun, Y.; Shi, Y.; Yu, H. Grx1 inhibits the activation of the Caspase-8/3 and JNK/c-Jun apoptotic pathways in H9c2 cells induced by high glucose. *Chinese Journal of Biochemistry and Molecular Biology.* 2014, 30, 579583, <http://doi:10.13865/j.cnki.cjbmb.2014.06.009>.

23. Meena D, Huang J, Zare M, et al. Genome-wide association study and multi-ancestry meta-analysis identify common variants associated with carotid artery intima-media thickness. *medRxiv.* 2025, 4, 25325582, <http://doi: 10.1101/2025.04.11.25325582>.

24. Andreadou, I.; Efentakis, P.; Frenis, K.; Daiber, A.; Schulz, R. Thiol-based redox-active proteins as cardioprotective therapeutic agents in cardiovascular diseases. *Basic Res Cardiol.* 2021, 116, 44, <http://doi: 10.1007/s00395-021-00885-5>.

25. Bachschmid MM, Xu S, Maitland-Toolan KA, Ho YS, Cohen RA, Matsui R. Attenuated cardiovascular hyper-

trophy and oxidant generation in response to angiotensin II infusion in glutaredoxin-1 knockout mice. *Free Radic Biol Med.* 2010 Oct 15;49(7):1221-9. doi: 10.1016/j.freeradbiomed.2010.07.005.

26. Burns M, Rizvi SHM, Tsukahara Y, Pimentel DR, Luptak I, Hamburg NM, Matsui R, Bachschmid MM. Role of Glutaredoxin-1 and Glutathionylation in Cardiovascular Diseases. *Int J Mol Sci.* 2020 Sep 16;21(18):6803. doi: 10.3390/ijms21186803.

27. Yu, L.; Zheng, J.; Yu, J.; Zhang, Y.; Hu, H. Circ_0067934: a circular RNA with roles in human cancer. *Hum Cell.* 2023, 36, 1865-1876, <http://doi: 10.1007/s13577-023-00962-y>.

28. Qiu, S.; Zhang, K.; Chen, S.; Yin, S. Circular RNA PRKCI (hsa_circ_0067934): a potential target in the pathogenesis of human malignancies. *Front Oncol.* 2024, 14, 1365032, <http://doi: 10.3389/fonc.2024.1365032>. 19.

29. Bensen R, Brognard J. New Therapeutic Opportunities for the Treatment of Squamous Cell Carcinomas: A Focus on Novel Driver Kinases. *Int J Mol Sci.* 2021, 22, 2831, <http://doi: 10.3390/ijms22062831>.

30. Talbot, T.; Lu, H.; Aboagye, E.O. Amplified therapeutic targets in high-grade serous ovarian carcinoma - a review of the literature with quantitative appraisal. *Cancer Gene Ther.* 2023, 30, 955-963, <http://doi: 10.1038/s41417-023-00589-z>.

31. Azad MG, Russell TM, Gu X, Zhao X, Richardson V, Wijesinghe TP, Babu G, Guo X, Kaya B, Dharmasivam M, Deng Z, Richardson DR. NDRG1 and its family members: More than just metastasis suppressor proteins and targets of thiosemicarbazones. *J Biol Chem.* 2025, 301, 110230, <http://doi: 10.1016/j.jbc.2025.110230>.

32. Lee, G.Y.; Chun, Y.S.; Shin, H.W.; Park, J.W. Potential role of the N-MYC downstream-regulated gene family in reprogramming cancer metabolism under hypoxia. *Oncotarget.* 2016, 7, 57442-57451, <http://doi: 10.18632/oncotarget.10684>.

33. Dai, C.; Li, Q.; May, H.I.; Li, C.; Zhang, G.; Sharma, G.; Sherry, A.D.; Malloy, C.R.; Khemtong, C.; Zhang, Y.; et al. Lactate Dehydrogenase A Governs Cardiac Hypertrophic Growth in Response to Hemodynamic Stress. *Cell Rep.* 2020, 32, 108087, <http://doi: 10.1016/j.celrep.2020.108087>.

34. Volkov P, Olsson AH, Gillberg L, Jørgensen SW, Brøns C, Eriksson KF, Groop L, Jansson PA, Nilsson E, Rönn T, Vaag A, Ling C. A Genome-Wide mQTL Analysis in Human Adipose Tissue Identifies Genetic Variants Associated with DNA Methylation, Gene Expression and Metabolic Traits. *PLoS One.* 2016, 11, e0157776, <http://doi: 10.1371/journal.pone.0157776>.

35. Li, S.; Chen, A.; Gui, J.; Zhou, H.; Zhu, L.; Mi, Y. TLN1: an oncogene associated with tumorigenesis and progression. *Discov Oncol.* 2024, 15, 716, <http://doi: 10.1007/s12672-024-01593-x>.

36. Gough, R.E.; Goult, B.T. The tale of two talins - two isoforms to fine-tune integrin signalling. *FEBS Lett.* 2018, 592, 2108-2125, <http://doi: 10.1002/1873-3468.13081>.

37. Torres-Gomez, A.; Cabañas, C.; Lafuente, E.M. Phagocytic Integrins: Activation and Signaling. *Front Immunol.* 2020, 11, 738, <http://doi: 10.3389/fimmu.2020.00738>.

38. Watson, N.F.; Buchwald, D.; Delrow, J.J.; Altemeier, W.A.; Vitiello, M.V.; Pack, A.I.; Bamshad, M.; Noonan, C.; Gharib, S.A. Transcriptional Signatures of Sleep Duration Discordance in Monozygotic Twins. *Sleep.* 2017, 40, zsw019, <http://doi: 10.1093/sleep/zsw019>.

39. Gharib, S.A.; Hurley, A.L.; Rosen, M.J.; Spilisbury, J.C.; Schell, A.E.; Mehra, R.; Patel, S.R. Obstructive sleep apnea and CPAP therapy alter distinct transcriptional programs in subcutaneous fat tissue. *Sleep.* 2020, 43, zsz314, <http://doi: 10.1093/sleep/zsz314>.

40. Zhou, Z.; Sun, B.; Huang, S.; Zhao, L. Roles of circular RNAs in immune regulation and autoimmune diseases. *Cell Death Dis.* 2019, 10, 503, <http://doi: 10.1038/s41419-019-1744-5>.

41. Wang Y, Zhang J, He Y, Pan Z, Zhang X, Liu P, Hu K. The theranostic value of acetylation gene signatures in obstructive sleep apnea derived by machine learning. *Comput Biol Med.* 2023, 161, 107058, <http://doi: 10.1016/j.compbiomed.2023.107058>.

42. Ye, J.; Yang, R.; Li, L.; Zhong, S.; Jiang, R.; Hu, Z. Molecular mechanism of Danxiong Tongmai Granules in treatment of coronary heart disease. *Aging (Albany NY).* 2024, 16, 8843-8865, <http://doi: 10.18632/aging.205845>.

43. Deng X, Thompson J. An R package for survival-based gene set enrichment analysis. *PeerJ*. 2025, 13, e19489, <http://doi: 10.7717/peerj.19489>.
44. Alborzi SZ, Ritchie DW, Devignes MD. Computational discovery of direct associations between GO terms and protein do-mains. *BMC Bioinformatics*. 2018, 19, 413, <http://doi: 10.1186/s12859-018-2380-2>.
45. May, A.M.; Van, W.D.R.; Mehra, R. OSA and Cardiac Arrhythmogenesis: Mechanistic Insights. *Chest*. 2017, 151, 225-241, <http://doi: 10.1016/j.chest.2016.09.014>.
46. Tsai, F.C.; Lin, Y.C.; Chang, S.H.; Chang, G.J.; Hsu, Y.J.; Lin, Y.M.; Lee, Y.S.; Wang, C.L.; Yeh, Y.H. Differential left-to-right atria gene expression ratio in human sinus rhythm and atrial fibrillation: Implications for arrhythmogenesis and thrombogenesis. *Int J Cardiol*. 2016, 222, 104-112, <http://doi: 10.1016/j.ijcard.2016.07.103>.
47. Zupei M.; Yang L.; Tao C.; Jun G. Bioinformatic gene analysis for potential molecular links between sleep disorders and atrial fibrillation: uncovering novel diagnostic candidates. *Research on Arrhythmia*, CCCP, Beijing, China, 2025 August 15–17.