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Potential Target Genes in the Development of Atrial Fibrillation: A Comprehensive Bioinformatics Analysis

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Background: Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide. Although it is not life-threatening, the accompanying rapid and irregular ventricular rate can lead to hemodynamic deterioration and obvious symptoms, especially the risk of cerebrovascular embolism. Our study aimed to identify novel and promising genes that could explain the underlying mechanism of AF development.

Material/Methods: Expression profiles GSE41177, GSE79768, and GSE14975 were acquired from the Gene Expression Omnibus Database. R software was used for identifying differentially expressed genes (DEGs), and Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were subsequently performed. A protein-protein interaction network was constructed in Cytoscape software. Next, a least absolute shrinkage and selection operator (LASSO) model was constructed and receiver-operating characteristic curve analysis was conducted to assess the specificity and sensitivity of the key genes.

Results: We obtained 204 DEGs from the datasets. The DEGs were mostly involved in immune response and cell communication. The primary pathways of the DEGs were related to the course or maintenance of autoimmune and chronic inflammatory diseases. The top 20 hub genes (high scores in cytoHubba) were selected in the PPI network. Finally, we identified 6 key genes (*FCGR3B*, *CLEC10A*, *FPR2*, *IGSF6*, *S100A9*, and *S100A12*) via the LASSO model.

Conclusions: We present 6 target genes that are potentially involved in the molecular mechanisms of AF development. In addition, these genes are likely to serve as potential therapeutic targets.

Keywords: **Atrial Fibrillation • Biological Markers • Immunity, Active**

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Background

Atrial fibrillation (AF) is the most prevalent (0.51%) and persistent heart rhythm disorder globally [1]. AF, increases the risk of blood clots causing thromboembolism, confers a nearly 5-fold increased risk of a debilitating stroke, and is a major risk factor for cardiovascular outcomes, including stroke [2,3]. Given its asymptomatic nature, many cases of AF go undetected until complications occur. Early detection of AF increases the chances of preventing stroke and other complications [4]. Therefore, it is imperative to explore the molecular mechanisms of AF pathogenesis as a means of improving the early diagnosis and treatment interventions of the disease.

Changes in genetic expression in AF are gradually gaining research attention [5,6]. Using the expression profiles of AF-associated target genes as a guide to examine the pathogenic sites of genetic variation and target gene regulation could be an effective approach [7,8]. Population studies show that a positive family history of AF increases the risk of developing AF among first-degree relatives by 30% [9,10]. The search for AF-associated genetic loci is propelled by the existing knowledge on the heritability of AF in the general population. Several genes, including some related to ion channel function, have been revealed to be associated with AF [11]. Ion channel-related genes associated with AF are primarily related to potassium channels. Previous studies have identified specific potassium channel genes or subunits that are associated AF. Monogenic AF pedigrees revealed that mutations leading to the gain or loss of function of *KCNQ1*, which encodes the potassium channel α subunit, are likely to be involved in the initiation and maintenance of AF [12]. Studies on *KCNE1* suggested that these AF-related genes are associated with decreased I_{Ks} current density and prolonged duration of atrial action potential [13,14]. Analysis of a genome cohort with sporadic AF identified that *KCNJ3* and *KCNJ5* were associated with AF through a gain-of-function mutation in the I_{KACH} channel [15]. Other studies have found that the *CRP* gene promoter associated with triallelic polymorphism is a potential genetic predictor of thromboembolic stroke in AF patients [16,17]. In addition, the redistribution and density change of gap junction channels trigger changes in the corresponding conduction velocity and anisotropic conduction, thus creating the re-entry loop of arrhythmias [18]. Several studies have explored the contribution of connexins to AF. At the preclinical stage, heterogeneity and decreased expression of connexins have been observed in AF [19]. Indeed, deletion of mouse homologues of AF-related regions in mice led to reduced expression of Cx43 [7]. Studies have also linked the expression of tumor-related genes with AF, and these genes often function as sentinel molecules in monitoring inflammatory responses and tissue homeostasis [20]. For example, the action potential duration in atrial myocytes was significantly shortened after the knockdown of esophageal cancer-related

gene-4 (*ECRG4*) [21]. Knockdown of *ECRG4* activated inflammatory pathways, as well as the genes associated with cardiac remodeling, which may shed light on the maintenance of re-entrant circuits in AF [22]. However, a causal relationship between *ECRG4* and AF has not been established in vivo. Although many genes potentially related to AF have been explored, detailed molecular mechanisms behind the initiation, perpetuation, and maintenance of AF remain elusive because of the complex nature of AF pathogenesis and the focus on single families in previous studies. Currently, the understanding and applicability of genes associated with AF are imperfect.

In the present study, based on a comprehensive bioinformatics analysis, we identified DEGs between sinus rhythm (SR) and AF samples, and further elucidated their potential molecular mechanisms and pathology in AF. This study adds several new candidate genes and related molecular pathways to those already associated with AF in previous studies. In future studies, these candidate genes and pathways could be investigated more closely to identify new and clear gene targets and potentially provide guidance for subsequent clinical studies.

Material and Methods

Data Information and Processing

The gene expression profiles of the GSE41177, GSE79768, and GSE14975 datasets were retrieved from the National Center for Biotechnology Information Gene Expression Omnibus database (NCBI GEO, <http://www.ncbi.nlm.nih.gov/geo>). The datasets contained data from AF patients with persistent AF for >3 months and SR patients without AF and not using any anti-arrhythmia drugs, with the latter serving as a control group. The GSE41177 dataset comprised 32 atrial appendage tissues from patients with persistent AF and 6 cases with SR. The GSE79768 and GSE14975 datasets consisted of atrial appendage tissues from 14 AF and 12 SR cases and 5 AF and 5 SR cases, respectively. The microarray data from GSE41177, GSE79768, and GSE14975 were based on the GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array, HG-U133_Plus_2). The raw data were processed and analyzed in R (version 3.6.2). First, the raw data underwent background correction with the limma package (<http://www.bioconductor.org/packages/limma/>). Then, a robust multichip average was created and perfect matches from the raw data were log₂ transformed. Afterwards, batch normalization and data merging for the 3 datasets was conducted using the *sva* package (<http://www.bioconductor.org/packages/sva/>).

Identification of DEGs

Gene annotation was conducted before the analysis of the DEGs between AF and SR samples. The probe identification

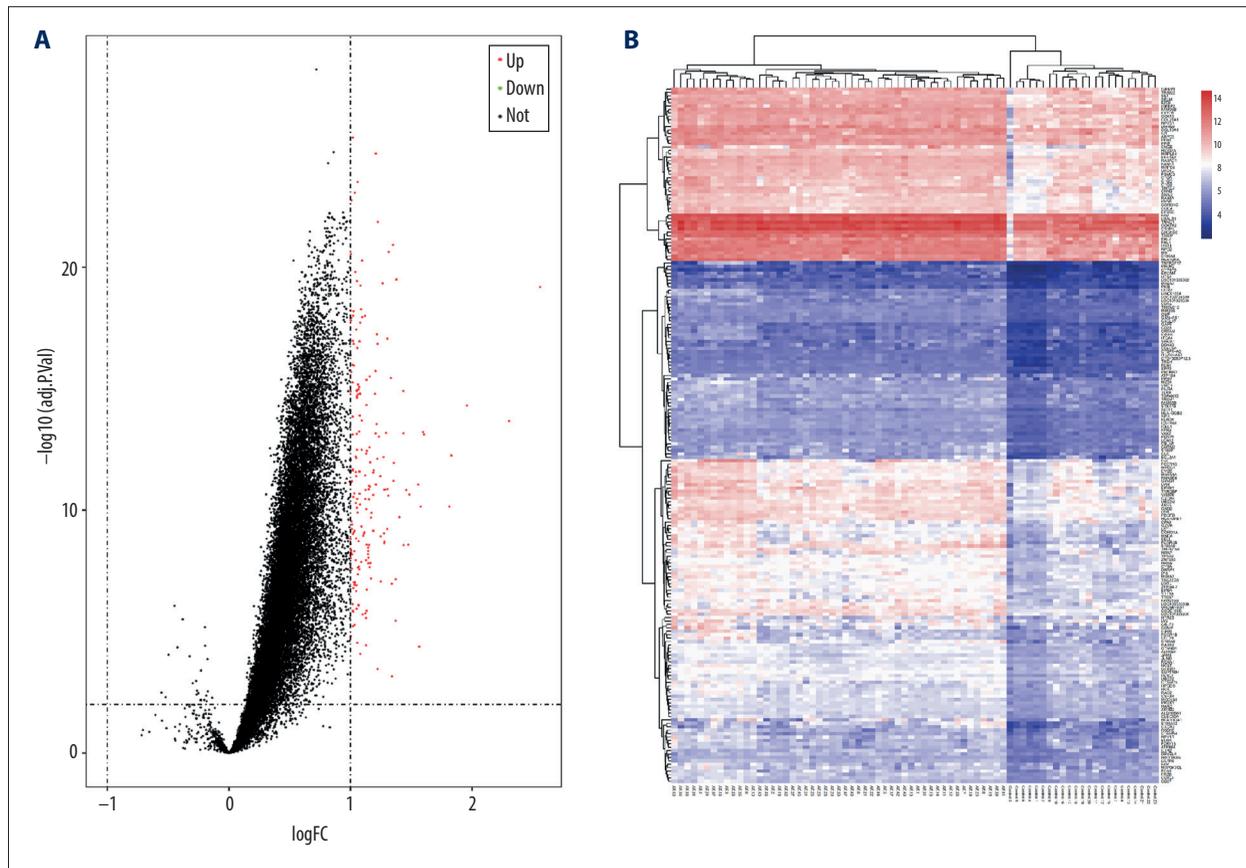


Figure 1. (A) Volcano plot of potential differentially expressed genes (DEGs). Red dots denote upregulated genes; green dots denote downregulated genes. (B) Heat maps for the DEGs between atrial fibrillation (AF) and sinus rhythm (SR).

numbers of the merged data were matched with the gene symbols using the affy package (<http://www.bioconductor.org/packages/affy/>). If multiple probes were mapped to the same gene, the median of the expression value was selected as the gene expression value. Next, we utilized the limma package to identify the DEGs, and the cutoff criteria were set at an adjusted P -value (adj. P) < 0.05 and an absolute value of log fold change ($|\log_2 FC|$) > 1 . We apply adj. P to correct false positives. The data for the listed DEGs were processed and plotted in a heatmap and volcano plots using the pheatmap and ggplot2 R packages, respectively.

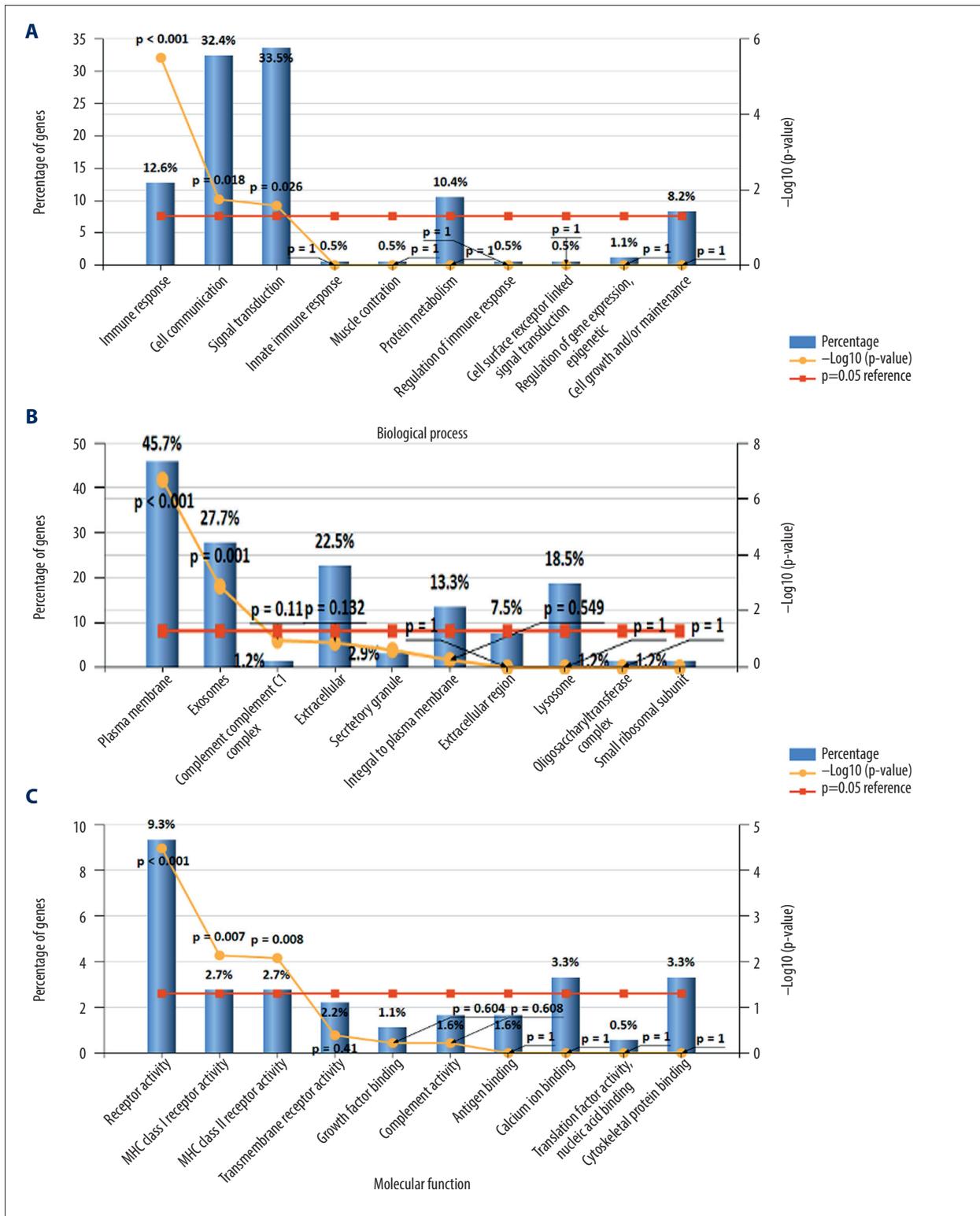
Gene Ontology and Pathway Enrichment Analysis

Based on the analysis of DEGs, added potential functional annotations in Functional Enrichment analysis tool (Funrich) were performed. Gene Ontology (GO) term enrichment analysis, included biological process (BP), cellular component (CC), and molecular function (MF). In addition, the Database for Annotation, Visualization, and Integrated Discovery (DAVID, version 6.8, <https://david.ncifcrf.gov/>) was applied to analyze the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment. DAVID is a biological information database

with gene annotation, gene symbol conversion, visualization, and integrated discovery function, and it provides comprehensive and systematic biological function annotation information of genes. Subsequently, we visualized the KEGG pathway analyses using the ggplot2 R package. The cutoff criterion was set at adj. $P < 0.05$.

Analysis of Protein-protein Interaction Networks of DEGs

The protein-protein interaction (PPI) networks of the DEGs were analyzed using the STRING online database (version 10.5; <http://string-db.org/>) to predict PPIs and protein functional associations. A confidence score of ≥ 0.4 was set as the threshold. After that, Cytoscape software (version 3.7.2; <http://cytoscape.org/>) was used to analyze and visualize the biological networks and node degrees of DEGs. The cytoHubba plugin (version 0.1) was utilized to identify the PPI networks. Based on the 4 filtering algorithms (Stress, Closeness, EcCentricity, and MCC), the top 20 hub genes obtained by each algorithm were used. Subsequently, co-expression of the hub genes and enrichment genes in the pathways was identified and presented in a Venn diagram.



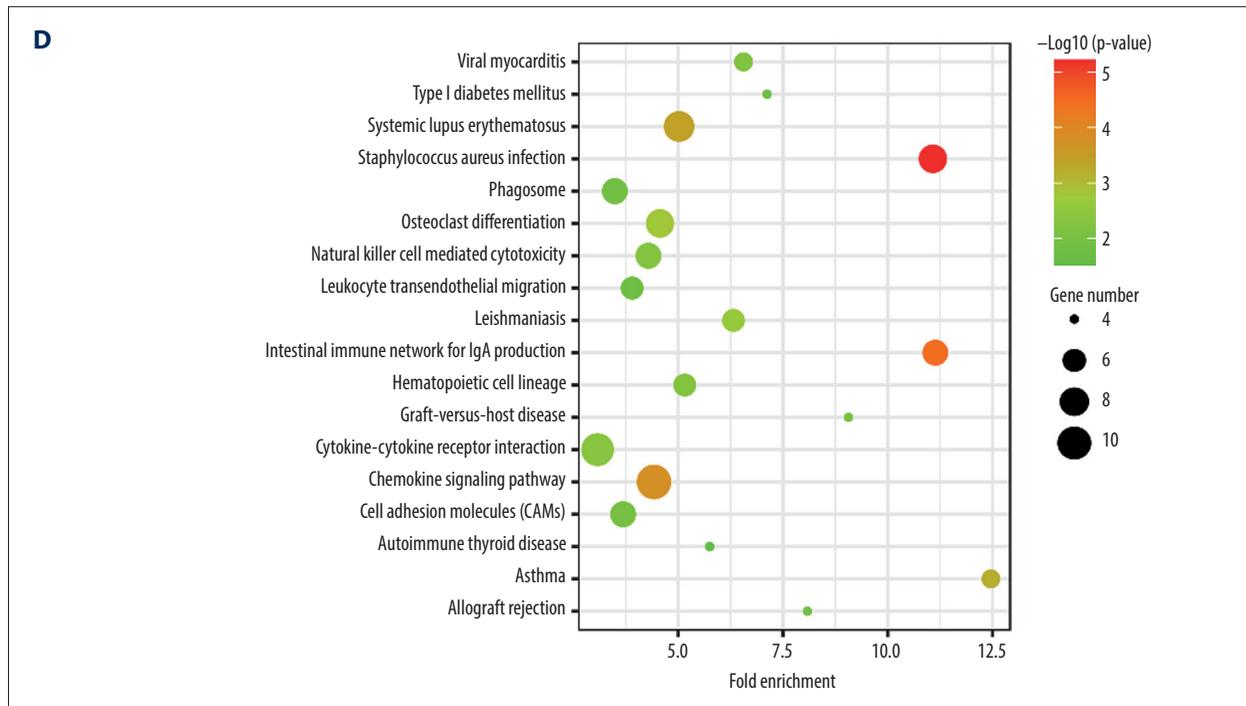


Figure 2. Biological functions based on Gene Ontology (GO) analysis of the differentially expressed genes (DEGs): (A) biological process (BP); (B) cellular component (CC), and (C) molecular function (MF). (D) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the DEGs.

Construction of the LASSO Model And ROC Curve Analysis

Based on the hub genes, we constructed a least absolute shrinkage and selection operator (LASSO) model because of its strong predictive value using the glmnet package (<http://www.bioconductor.org/packages/glmnet/>). Then, the expression data of the hub genes, based on the ratio 7: 3, were randomly allocated to the training and testing sets. The receiver-operating characteristic (ROC) curve was plotted using the pROC package in R. The value of ROC area under the curve (AUC) was obtained to assess the sensitivity and specificity of the key genes screened by the LASSO model.

Results

Identification of DEGs in AF

We obtained the microarray datasets GSE41177, GSE79768, and GSE14975 from the GEO database. The datasets contained 51 AF and 23 SR samples. With the cutoff criteria set at adj. $P < 0.05$ and $|\log_2 FC| > 1$, we identified 204 DEGs (Figure 1). Compared with the control SR differential genes in the datasets, AF-related genes were mostly upregulated. The expression heatmaps of the DEGs are shown in Figure 1A, 1B. These genes were well clustered between the AF and control cases.

GO Term Enrichment Analysis of DEGs

We identified the DEGs for the GO analysis using the Funrich software, and the DEGs were examined based on 3 categories: BP, CC, and MF. In the BP group, the DEGs were mainly enriched in immune response, cell communication, and signal transduction; in the CC group, the DEGs were primarily enriched in plasma membrane and exosomes; and in the MF group, the enrichment of the DEGs was mostly in the receptor activity, MHC class I receptor activity, and MHC class II receptor activity (Figure 2A-2C, Table 1).

Signaling Pathway Enrichment Analysis

The KEGG pathway enrichment analysis was performed for the DEGs, and the results are shown in Figure 2D and Table 2. Enrichment of the DEGs was mainly in the *Staphylococcus aureus* infection, intestinal immune network for IgA production, systemic lupus erythematosus, asthma, and viral myocarditis.

PPI Network and Hub Genes Identification

Using the STRING database and Cytoscape software, we constructed 4 PPI networks for the DEGs as shown in Figure 3A-3E. Furthermore, the top 20 hub genes of each dataset were identified using the 4 algorithms (Stress, Closeness, Eccentricity, and MCC) of the cytoHubba plugin. Among these hub genes,

Table 1. Significantly enriched GO terms in AF.

Category	GO term	Genes
BP	Immune response	HLA-DQB2; FCGR3B; IGLL1; CLEC10A; LST1; LILRA6; CD27; C1QC; IGSF6; CD28; LGALS1; IFI6; TREM1; FCN1; FCER1G; HLA-DPB1; CLC; CRTAM; C1QB; HLA-DRA; C1QA; TNFRSF17; HLA-DQA1
	Cell communication	PDAP1; CTNNB1; RLN1; PROKR2; OMP; ARRB2; RAB8A; PREX1; RCAN1; CMTM2; MS4A2; FPR2; S100A9; S100A12; RAB8B; JAM3; PROK2; PILRA; ARF5; RGS18; HRAS; CLEC5A; FRZB; CD1E; HCK; S100A8; PDGFD; HCST; TSPAN15; TLR8; CSF3R; CBLN1; STK17B; CXCR4; EPCAM; NPY1R; TYROBP; RAC2; CXCR2; GNB2; SELL; UTS2; TXNIP; PPBP; MIF; IL1R2; S100P; IGFBP2; ITGA4; GPR34; FAP; IGFBP3; TNNC1; BLNK; CCL19; CHGB; LY96; CRLF1; HTR2B
	Signal transduction	PDAP1; CSF2RA; CTNNB1; RLN1; PROKR2; OMP; ARRB2; RAB8A; PREX1; RCAN1; CMTM2; MS4A2; FPR2; S100A9; S100A12; RAB8B; JAM3; PROK2; PILRA; ARF5; RGS18; HRAS; CLEC5A; FRZB; CD1E; HCK; S100A8; PDGFD; HCST; TSPAN15; TLR8; CSF3R; CBLN1; MS4A7; STK17B; CXCR4; EPCAM; NPY1R; TYROBP; RAC2; CXCR2; GNB2; SELL; UTS2; P2RY13; TXNIP; PPBP; MIF; S100P; IGFBP2; ITGA4; GPR34; FAP; IGFBP3; TNNC1; BLNK; CCL19; CHGB; LY96; CRLF1; HTR2B
CC	Plasma membrane	CSF2RA; CTNNB1; HLA-DQB2; PROKR2; ARRB2; KLRD1; RAB8A; PREX1; CYBA; CLEC10A; CMTM2; MS4A2; CCDC109B; RABAC1; MCOLN1; FPR2; LST1; S100A9; LILRA6; TREH; CD27; S100A12; RAB8B; JAM3; PILRA; ARF5; HRAS; IGSF6; CLEC5A; FRZB; HCK; S100A8; HCST; SIDT1; TLR8; CSF3R; CBLN1; CD28; STT3A; PPIB; CXCR4; EPCAM; LGALS1; NPY1R; CLIC4; TYROBP; RAC2; SET; CXCR2; CCR2; SELL; UTS2; TREM1; EVI2B; FCN1; P2RY13; FCER1G; HLA-DPB1; C16orf54; CLC; CORO1A; IL1R2; TMED2; S100P; CRTAM; FXYD1; ITGA4; GPR34; VAMP8; FAP; IGFBP3; HLA-DRA; FCGR1B; BLNK; ATP1B4; LY96; HTR2B; TNFRSF17; HLA-DQA1
	Exosomes	CTNNB1; ALYREF; ALDH16A1; RPN1; RAB8A; GLIPR2; EIF3I; COTL1; CORO1C; S100A9; TREH; RAB8B; C1QC; PILRA; ARF5; HRAS; S100A8; PFN1; S100A4; TSPAN15; VMO1; PPIB; CXCR4; EPCAM; LGALS1; CLIC4; RAC2; MNDA; GNB2; EVI2B; FCN1; HLA-DPB1; EIF2S3; COL15A1; EEF1A2; EIF5A; CORO1A; MIF; TMED2; ARPC3; S100P; ITGA4; C1QB; VAMP8; HLA-DRA; CHGB; HLA-DQA1; LYZ
MF	Receptor activity	FCGR3B; KLRD1; CLEC10A; MS4A2; LST1; LILRA6; CD27; PILRA; CLEC5A; TLR8; CD28; TYROBP; TREM1; FCER1G; IL1R2; ITGA4; TNFRSF17
	MHC class I receptor activity	HLA-DQB2; SET; HLA-DPB1; HLA-DRA; HLA-DQA1
	MHC class II receptor activity	HLA-DQB2; SET; HLA-DPB1; HLA-DRA; HLA-DQA1

SPI1, *HCK*, *TLR8*, *FPR2*, *RAC2*, *IGSF6*, *CSF3R*, *CXCR4*, *S100A8*, *S100A9*, *FCGR3B*, *TYROBP*, *S100A12*, and *CLEC10A* exhibited the highest degree of association with AF and are listed in the Venn diagram (Figure 3F).

Validation of the Diagnostic Value of Key Genes

The construction of a LASSO model was based on the A gene expression profile of the 14 hub genes (Figure 4A). Based on the model, 6 genes were identified according to the regression coefficients that were not equal to zero. ROC curve analysis (Figure 4B, 4C) identified the AUC for *FCGR3B*, *CLEC10A*, *FPR2*, *IGSF6*, *S100A9*, and *S100A12* in AF patients and normal controls; in the training set, the AUC values were 0.9981 (95% confidence interval [CI], 0.993-1), 0.9944 (95% CI, 0.9821-1), 0.987 (95% CI, 0.9655-1), 0.9481 (95% CI, 0.8566-1), 0.9852

(95% CI, 0.9616-1), and 0.9981 (95% CI, 0.993-1); in the test set, the AUC values were 0.8762 (95% CI, 0.7271-1), 0.9714 (95% CI, 0.9079-1), 0.981 (95% CI, 0.9358-1), 0.8857 (95% CI, 0.7092-1), 0.8952 (95% CI, 0.7517-1), and 0.9429 (95% CI, 0.825-1).

Discussion

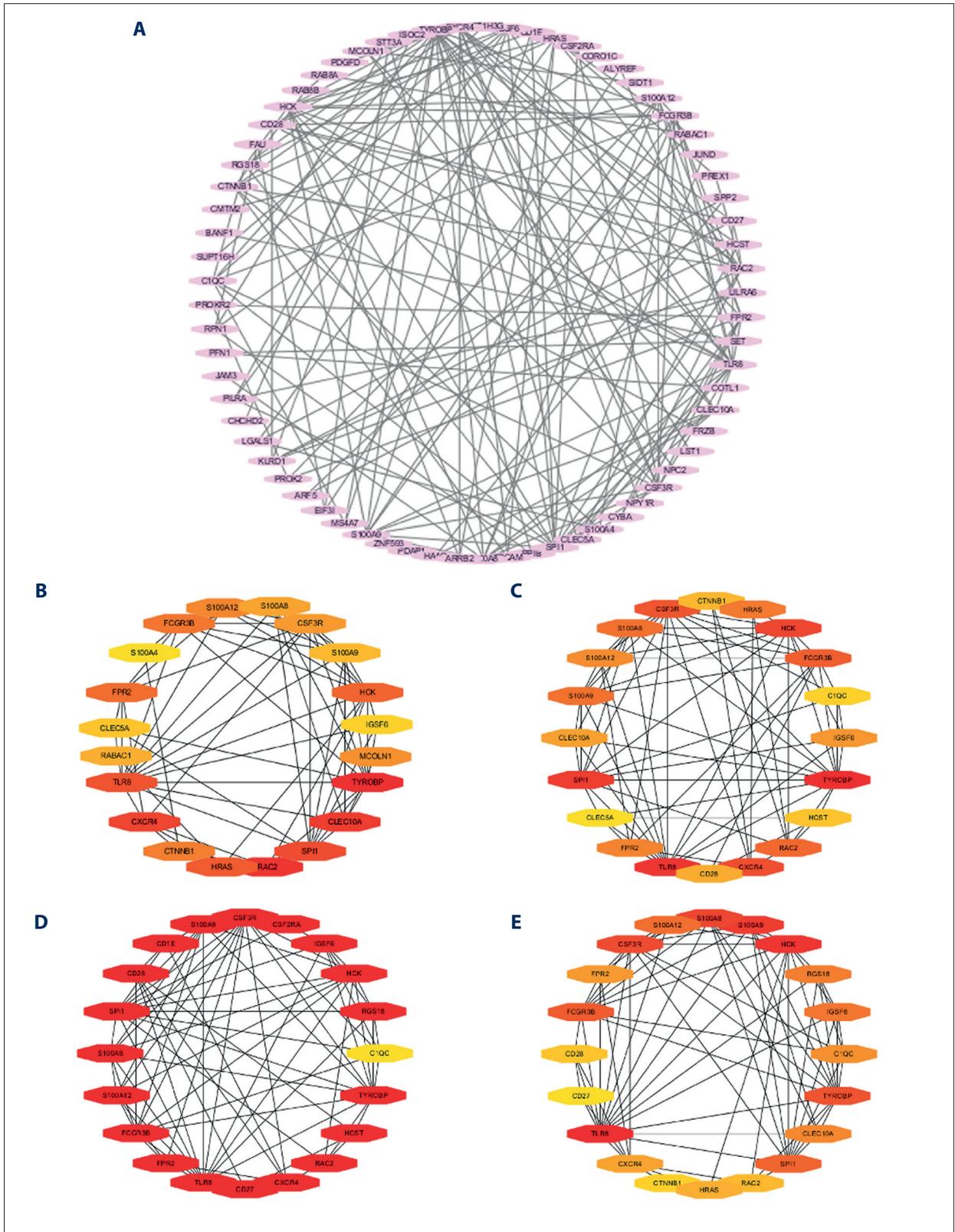
The initiation and development of AF are regulated by the expression of many genes. Here, we systematically investigated gene expression profiles obtained from AF microarray studies. Gene expression data were downloaded from 3 GEO datasets in the GCBI. To better explore the DEGs, we identified the potential and remarkable DEGs, biological pathways, and processes based on comparisons between AF and normal SR samples.

Table 2. Significantly enriched pathways in AF.

Rank	Pathway	Genes
1	<i>Staphylococcus aureus</i> infection	C1QA; C1QB; FPR2; HLA-DPB1; FCGR3B; C1QC; HLA-DQA1; HLA-DRA
2	Intestinal immune network for IgA production	CXCR4; TNFRSF17; ITGA4; HLA-DPB1; HLA-DQA1; HLA-DRA; CD28
3	Chemokine signaling pathway	HRAS; PPBP; RAC2; GNB2; ARRB2; CXCR4; PREX1; HCK; CCR2; CCL19; CXCR2
4	Systemic lupus erythematosus	C1QA; C1QB; HLA-DPB1; FCGR3B; HIST1H3G; C1QC; HLA-DQA1; HLA-DRA; CD28
5	Asthma	FCER1G; MS4A2; HLA-DPB1; HLA-DQA1; HLA-DRA
6	Osteoclast differentiation	CYBA; JUND; LILRA6; SPI1; FHL2; FCGR3B; BLNK; TYROBP
7	Leishmaniasis	CYBA; ITGA4; HLA-DPB1; FCGR3B; HLA-DQA1; HLA-DRA
8	Cytokine-cytokine receptor interaction	IL1R2; PPBP; CXCR4; CCR2; CCL19; TNFRSF17; CSF3R; CXCR2; CSF2RA; CD27
9	Natural killer cell mediated cytotoxicity	HRAS; RAC2; FCER1G; FCGR3B; KLRD1; TYROBP; HCST
10	Hematopoietic cell lineage	IL1R2; CSF3R; ITGA4; CD1E; CSF2RA; HLA-DRA
11	Viral myocarditis	RAC2; HLA-DPB1; HLA-DQA1; HLA-DRA; CD28
12	Graft-versus-host disease	HLA-DPB1; HLA-DQA1; HLA-DRA; CD28
13	Cell adhesion molecules (CAMs)	SELL; ITGA4; HLA-DPB1; JAM3; HLA-DQA1; HLA-DRA; CD28
14	Allograft rejection	HLA-DPB1; HLA-DQA1; HLA-DRA; CD28
15	Phagosome	CYBA; CORO1A; COMP; HLA-DPB1; FCGR3B; HLA-DQA1; HLA-DRA
16	Type I diabetes mellitus	HLA-DPB1; HLA-DQA1; HLA-DRA; CD28
17	Leukocyte transendothelial migration	CYBA; RAC2; CXCR4; ITGA4; JAM3; CTNNA1
18	Autoimmune thyroid disease	HLA-DPB1; HLA-DQA1; HLA-DRA; CD28

GO analysis revealed that a considerable number of the co-expressed DEGs were primarily associated with immune response, cell communication, signal transduction, plasma membrane, exosomes, receptor activity, MHC class I receptor activity, and MHC class II receptor activity. Previous studies indicated that the immune response can be a complex and powerful factor in the pathophysiological process of AF and its concomitant complications [23,24]. The major immune cells found in the left atrial appendages of patients with AF were immunologically active monocytes and macrophages, suggesting a pro-inflammatory state characterized by increased infiltration of iNOS-positive, but Arg1-negative immune cells [25,26]. AF-induced cardiac injury processes of the myocardium initiate a cardiac immune response as shown by damage-associated molecular patterns (DAMPs), such as extracellular matrix and reactive oxygen species [27]. The pattern recognition receptor then initiates recognition of DAMPs, before the activation of innate and adaptive immune cells. This immune process forms a long-term feedback loop and promotes the formation of permanent forms of AF [28]. Inflammation and immune response

are dependent on the onset and maintenance of AF, which is in turn dependent on inflammation and immune response. In addition, a clinical phenomenon that AF promotes inflammation supports a vicious cycle of “AF begets AF” [29]. The results of our pathway analysis showed that the DEGs identified were mainly associated with the course or maintenance of autoimmune diseases and chronic inflammatory diseases. Multiple systems of systemic lupus erythematosus (SLE), a chronic inflammatory autoimmune disease, may be an independent risk factor for AF since SLE has cardiac manifestations. Recent studies have shown that the disease status of SLE is independently associated with AF after adjusting for age, sex, race, and coronary artery disease [30]. Moreover, systemic inflammation and disease pathways of chronic inflammatory diseases are considered as pathogenic contributors to the initiation and development of AF [31,32]. Chemokines guide the migration and activation of systemic leukocytes and may influence AF development [33]. Some studies have suggested that the level of inflammatory cytokines/chemokines is related to the progression of AF to myocardial fibrosis [34]. The



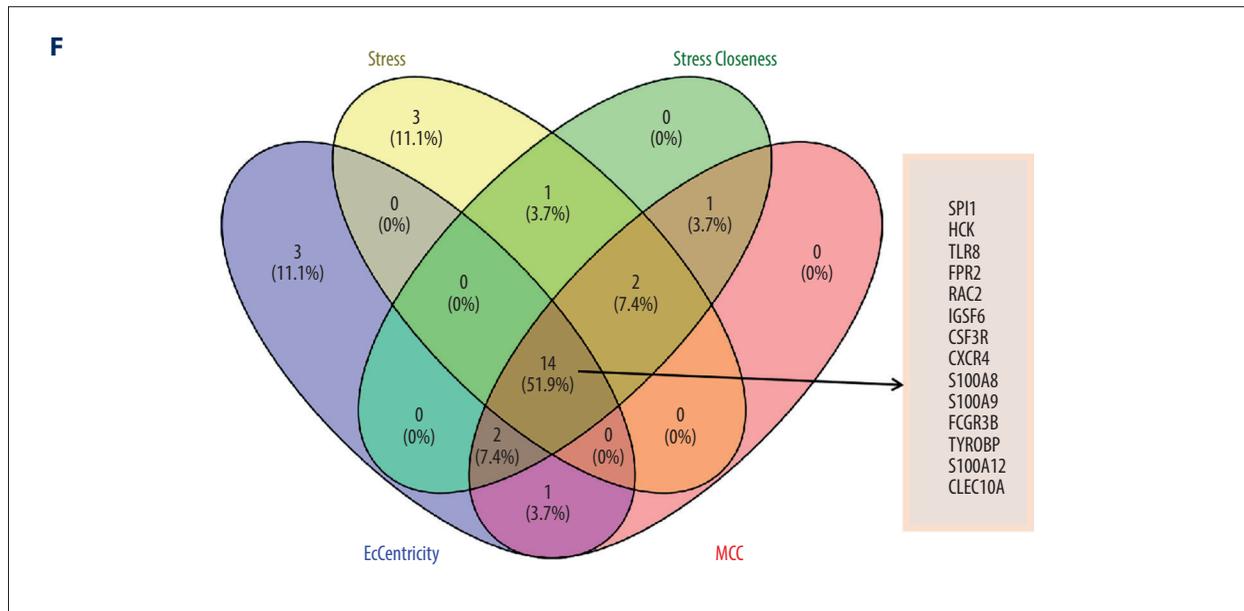


Figure 3. (A) Protein–protein interaction (PPI) networks of the differentially expressed genes (DEGs). The top 20 genes in cytoHubba plugins: (B) Stress, (C) Closeness, (D) EcCentricity, and (E) MCC. (F) Venn diagrams of the top 20 genes.

expression of cytokines in AF promotes the degree of the recruitment of immune cells [35]. As a classic way related in immune reaction, transforming growth factor (TGF)- β and interleukin (IL)-6 were expressed more frequently in the atria of macrophages after migration in AF [36].

Further analysis of the co-expression genes in the PPI network and LASSO model identified 6 key genes (*FCGR3B*, *CLEC10A*, *FPR2*, *IGSF6*, *S100A9*, and *S100A12*) as the most significance. Among the key genes, *FCGR3B* showed a closer association with AF. *FCGR3B* encodes a low-affinity receptor for the Fc portion of gamma immunoglobulins (IgG) known as Fc γ RIIIb (CD16b). The Fc γ RIIIb can bind either the monomeric or aggregated IgG, and it may function to capture dedicated immune complexes in the peripheral circulation [37]. On neutrophils, Fc γ RIIIb regulates immune responses [38]. Our findings provide strong evidence that recruitment of neutrophils, particularly polymorphonuclear neutrophils, promotes the development of AF [39,40]. Human Fc γ RIIIb lacks intracellular signaling motifs and is anchored in the cell membrane via a glycosphatidyl inositol anchor [41]. In addition, intracellular signaling promotes phagocytosis of antibody-opsonized microbes by human neutrophils through Fc γ RIIIb in collaboration with other associated Fc γ R [42]. In the rapid adhesion of neutrophils to endothelial cells, Fc γ RIIIb binding immune complexes remains an important link [43]. Thus, this gene is involved in the recruitment and activation of polymorphonuclear neutrophils at the site of inflammation [44].

Although the potential role of *FCGR3B* in autoimmunity has been extensively investigated, its role in AF development

remains unclear [45]. The protein interacts with the Fc portion of the IgG molecule involved in immune regulation. Moreover, the variation of *FCGR3B* copy numbers is associated with susceptibility to several autoimmune diseases [46]. Importantly, *FCGR3B* could be linked to cardiovascular disorder of the myocardium and coronary heart disease [47]. In addition, CD16⁺ monocytes have been shown to be involved in atrial remodeling in the pathophysiology of AF [48]. Therefore, the *FCGR3B* gene could be a potential biomarker for AF.

CLEC10A is one of the members of the c-type lectin domain family 12, which serves as a characteristic galactose lectin on macrophages and dendritic cells. CLEC10A can be activated through Toll-like receptor signaling and increase the secretion of various cytokines, including tumor necrosis factor- α , IL-8, and IL-10 [49]. In addition, lectin has been linked to the development of AF, and it can particularly predict thrombosis and left atrial appendage remodeling in patients with AF [50]. A synergistic interaction exists between lectin and TGF- β 1, which can induce AF by activating the TGF- β 1/Smad pathway in patients with AF [51]. Formyl peptide receptors (FPRs) belong to a G-protein-coupled chemokine receptor family and include 3 subtypes (FPR1, FPR2, and FPR3) that play important roles in host defense and inflammation [52]. FPR2 is involved in the initiation and resolution of inflammation. Similarly, the FPR2 signaling has important vascular effects through the inflammatory response [53,54].

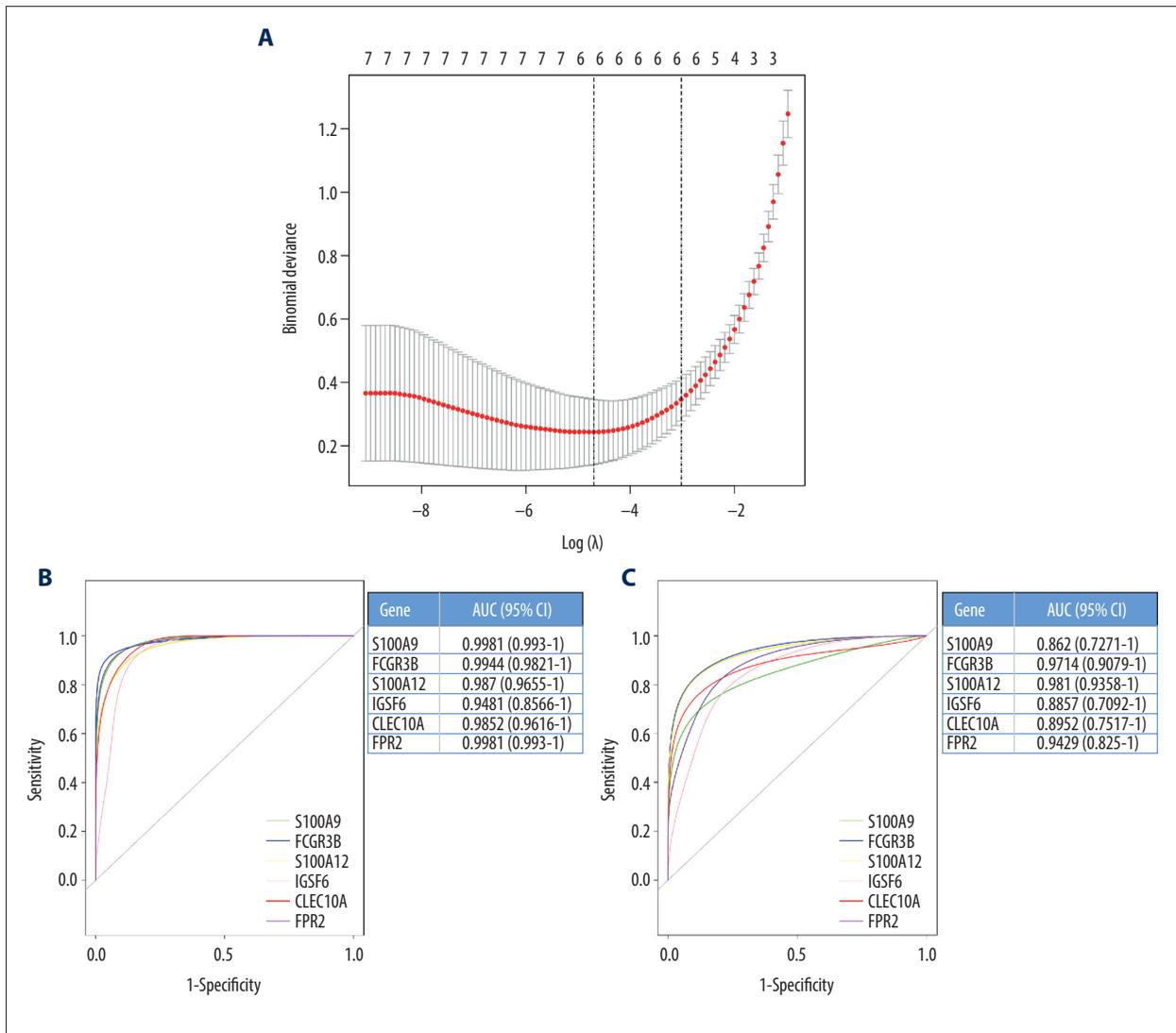


Figure 4. (A) Least absolute shrinkage and selection operator (LASSO) regression analysis of the hub genes. (B) Receiver-operating characteristic (ROC) curve of the hub genes in the training cohort. (C) ROC curve of the hub genes in the testing cohort.

Conclusions

In summary, we used bioinformatics analysis tools to delineate the pathomechanism of AF based on DEGs. Autoimmune and chronic inflammatory pathways, neutrophil chemotaxis, and immune response were confirmed to play roles in the development of AF. In addition, 6 genes, including *FCGR3B*, *CLEC10A*, *FPR2*, *IGSF6*, *S100A9*, and *S100A12* were identified as potential AF biomarkers. Our findings pave the way for further research on AF occurrence and development.

There are some limitations of our study. First, the clinical atrial tissue samples were not analyzed in the laboratory. Therefore, future studies on the mechanism of AF occurrence and development should incorporate such samples. In addition, given the current limited datasets, the sample sizes were relatively small and a multicenter study involving a larger sample size is needed. Further investigation is required to determine whether the 6 key genes (*FCGR3B*, *CLEC10A*, *FPR2*, *IGSF6*, *S100A9*, and *S100A12*) activate any of the pathways or other mechanisms known to induce AF in humans.

Conflict of Interest

None.

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