ORIGINAL ARTICLE

Identification of potential novel biomarkers and therapeutic targets involved in human atrial fibrillation based on bioinformatics analysis

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KEY WORDS
atrial fibrillation, bioinformatics analysis, biomarkers, differentially expressed genes, miRNA

ABSTRACT

BACKGROUND Atrial fibrillation (AF) is the most common arrhythmia. However, exact molecular mechanism of AF remains unclear.

AIMS Our study aimed to identify underlying biomarkers and pathways involved in AF based on bioinformatics analysis.

METHODS The GSE79768 human heart tissue dataset was obtained from the Gene Expression Omnibus (GEO) database. A total of 26 heart tissue samples including 14 AF atrium heart tissue samples and 12 sinus rhythm heart tissue samples were used to identify the differentially expressed genes (DEGs). The functional enrichment analysis, protein-protein interaction network, and miRNA-targeted gene regulatory network analysis were performed.

RESULTS A total o f 260 DEGs were identified in the AF and sinus rhythm groups, including 150 up-regulated and 110 down-regulated genes. Functional and pathway enrichment analyses of DEGs indicated that they were mainly involved in inflammatory response, immune response, and receptor-mediated endocytosis. In addition, *CXCR4, CXCR2, C3, CXCL11, CCR2, AGTR2, CXCL1*, and others were the hub nodes in the protein-protein interaction network and module analysis revealed that these hub nodes were also significantly enriched in the inflammatory response, cytokine-cytokine receptor interaction, chemokine signaling, and neuro-active ligand-receptor interaction pathways. Furthermore, miRNA-targeted regulatory network analysis showed that 58 miRNA were involved in 61 regulatory relationships including 9 up-regulated and 5 down-regulated genes.

CONCLUSIONS This study identified a series of key genes, including *CXCR4, CXCR2, CXCL11, CCR2, LRRK2, IL1B, C3, CXCL1*, and important miRNAs such as miR-3123, miR-548g-3p, and miR-9-5p, along with pathways that were most closely related to human AF. Our results may provide a novel molecular mechanism and potential therapeutic targets for AF.

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INTRODUCTION Atrial fibrillation (AF) is the most common arrhythmia. Its incidence is about 1% to 2% in the general population and increases with age.[1,2] The prevalence of AF has been predicated to reach around 6 to 12 million people in the United States by 2050 and 17.9 million people in Europe by 2060.[3] It is a major risk factor of stroke and heart failure.[4,5] As populations continue aging and AF increases morbidity and mortality of stroke and heart failure, AF will cause substantial public health and economic burden.[6] Despite many advances in the understanding of AF mechanisms and despite the development of some relatively effective treatment options, such as catheter ablation and warfarin, the prevalence of AF is still high and estimated to increase further. In addition, the exact molecular mechanism of AF remains uncertain. Therefore, it is crucial to better understand the pathogenesis and mechanism of the disease.

WHAT'S NEW?

We applied bioinformatics analysis to explore the potential mechanism of atrial fibrillation. A total of 260 differentially expressed genes were successfully identified in the atrial fibrillation and sinus rhythm groups, including 150 up-regulated and 110 down-regulated genes. The hub genes were mainly enriched in the following biological processes: inflammatory response, cytokine-cytokine receptor interaction, chemokine signaling, and neuroactive ligand-receptor interaction. We also found that miR-3123 up-regulated *LRRK2* and *P2RY14*, and miR-548g-3p up-regulated *CCR2* and *CXCR4*. The identified key genes, pathways, and critical miRNA may provide potential novel therapeutic targets for atrial fibrillation.

Gene mutations involved in cardiac ion channels, structure proteins, and transcription factors were found to be associated with AF.[7] MiRNAs are a novel class of endogenous noncoding RNAs which play a key role in the gene expression regulatory network at the post-transcriptional level.[8] Several studies demonstrated that miRNAs take part in the genesis of AF by regulating electrical and structural remodeling in the atrium.[9] As the body of data about gene expression profiles has increased rapidly in recent years, we take the advantage of bioinformatics analysis to identify the key genes, miRNAs, and pathways in AF. Based on the bioinformatics analysis in this study, novel biomarkers for the diagnostic workup of AF as well as therapeutics for treatment may be provided.

MATERIALS AND METHODS

Data sourcing

The GSE79768 human heart tissue dataset was downloaded from the Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (NCBI).[10] A total of 26 human heart tissues were included in this study, including 14 AF samples and 12 sinus rhythm (SR) samples. Patients in the SR group were older than in the AF group (mean [SD] age, 62 [13.59] years and 48.91 [12.8] years, respectively; P <0.05). There were 5 men and 5 women in the SR group, and 5 men and 6 women in the AF group. Paired right and left specimens of atrial appendages were obtained from patients undergoing surgery for mitral valve or with coronary artery disease. In the AF group, more patients presented with rheumatic heart disease. However, in the SR group, more patients had hypertension and coronary artery disease. All samples were sequenced on the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array (Affymetrix, Santa Clara, California, United States).

Identification of differentially expressed genes

Raw CEL profiles were downloaded from the GEO database and processed using the Affy package (version 3.2, New York, New York, United States) in the R software (version 2.9, New York, New York, United States), including background correction and data standardization.[11] Then, gene symbols were annotated according to the annotation files provided by the platform and nonmatched probes were removed. For different probes matched to one certain gene, the mean value of different probes was calculated as the final expression value of this gene. Following this, DEGs were screened between AF and SR samples with the Bayes method using the limma package in the R software.[12] DEGs were considered as P values of less than 0.05 and log |fold change (FC)| higher than 0.585.

Functional enrichment analysis of differentially expressed genes

The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a public database of biological systems that integrates genomic, chemical, and systemic functional information.[13] The Gene Ontology (GO) is a community-based bioinformatics resource that provides information about gene sets grouped into families of: molecular function (MF), biological function (BF), and cellular component (CC).[14] In this study, the DAVID online tool[15] was used to perform KEGG pathway and GO functional enrichment analyses of DEGs. Significant enrichment was considered as a gene count of 2 or more and a P value of less than 0.05.

Construction of the protein–protein interaction network

According to the STRING database,[16] interactions among DEG-encoded proteins were predicted with a threshold of medium confidence of 0.4 or more. Based on this, interaction relationships among proteins were visualized using Cytoscape (version 3.2, NIGMS, Bethesda, Maryland, United States).[16] Moreover, the degree centrality was calculated and used as a topology index to assess the node (protein) score in the protein–protein interaction (PPI) network. The higher score the node obtained, the more importance the node presented in the network, and could be used as the hub protein in this network. In addition, the KEGG pathway and GO functional enrichment of the top 20 nodes in the PPI network were also performed using the DAVID online tool.

Construction of the miRNA-targeted gene regulatory network

For further investigation, miRNAs targeting the top 20 nodes in the PPI network were predicted using the miRDB online tool[17] with the cutoff target score of 85 or higher. Next, the miRNA-targeted regulatory network was visualized using Cytoscape.

Statistical analysis

Data were expressed as mean (SD) and were analyzed using the SPSS software, version 17.0 (IBM, New York, New York,

United States). A *P* value of less than 0.05 was considered significant. The ethics approval was not required for this study.

RESULTS Identification of differentially expressed genes Finally, a total of 260 DEGs were identified between the AF and SR groups, including 150 upregulated genes and 110 downregulated genes. Bidirectional clustering heat map of DEGs presented that these DEGs could obviously distinguish the AF samples from the SR samples (FIGURE 1A). A volcano plot of DEGs is presented in FIGURE 1B. According to log|FC| value, the top 10 upregulated and downregulated DEGs were separately tabulated in TABLE 1.

Functional enrichment results of differentially expressed genes After DEG identification, KEGG pathway enrichment analyses of both upregulated and downregulated DEGs were performed (TABLE 2 and FIGURE 2). Specifically, the upregulated DEGs were significantly enriched in 5 KEGG pathways, including the intestinal immune network for IgA production (P = 0.005), cytokine-cytokine receptor interaction (P = 0.01), and renin-angiotensin system (P = 0.01). Moreover, the upregulated DEGs were significantly enriched in 21 GO terms, including 11 BP terms (inflammatory response, etc), 7 CC terms (antigen binding, etc), and 3 MF terms (integral component of membrane, etc) (FIGURE 3A). For down-regulation, DEGs were significantly enriched in 6 KEGG pathways such as cytokine-cytokine receptor interaction (P = 0.004), tumor necrosis factor signaling pathway (P = 0.01), and nucleotide-binding, oligomerization domain–like receptor signaling pathway (P = 0.03). In addition, downregulated DEGs were significantly enriched in 26 GO terms, including 11 BP terms (inflammatory response, etc), 8 CC terms (extracellular exosome, etc), and 7 MF terms (hemoglobin binding, etc) (FIGURE 3B).

Protein–protein interaction network analysis The PPI network was constructed according to the STRING database, including 125 nodes and 236 interaction pairs (Supplementary material, *Figure S1A*). The top 20 nodes involved in the PPI network were summarized in TABLE 3. Subsequently, functional enrichment analyses of the top 20 nodes were conducted. The results revealed that the top 20 nodes were apparently enriched in 8 KEGG pathways, such as cytokine-cytokine receptor interaction (P <0.001), chemokine signaling pathway (P <0.001), and neuroactive ligand-receptor interaction (P = 0.003) (TABLE 4); and 42 GO terms, including 33 BP terms (inflammatory response, etc), 6 CC terms (extracellular space, etc), and 3 MF terms (chemokine activity, etc) (Supplementary material, *Figure S1B* and TABLE 4).

miRNA-targeted regulatory network Furthermore, miRNA was predicted to target top 20 nodes in the PPI network using the miRDB. Then, the regulatory network was visualized using Cytoscape, including 9 upregulated genes, 5 downregulated genes, 58 miRNAs, and 61 regulatory relationships were found (Supplementary material, *Figure S2*). What is more, our analysis

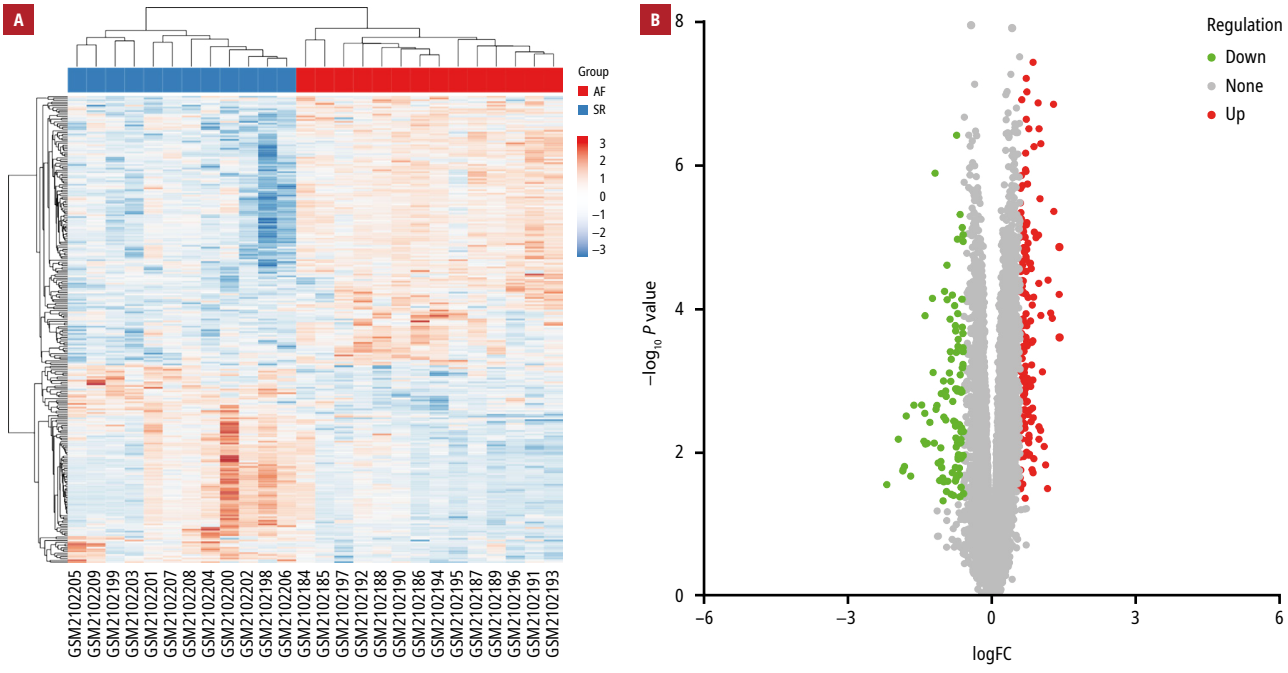

FIGURE 1 Heat map (**A**) and volcano plots (**B**) of differentially expressed genes. Abbreviations: AF, atrial fibrillation; logFC, log fold change; SR, sinus rhythm

TABLE 1 Top 20 upregulated and downregulated differentially expressed genes

DEGs	logFC	*P* value	Adjusted *P* value
Upregulated			
TRDN-AS1	1.636580	5.97×10^{-8}	9.57×10^{-5}
S100A12	1.422056	2.47×10^{-4}	6.76×10^{-3}
CHGB	1.418162	1.36×10^{-5}	1.29×10^{-3}
FAM216B	1.397223	6.20×10^{-5}	3.12×10^{-3}
B3GALT2	1.287522	4.35×10^{-6}	7.78×10^{-4}
DHRS9	1.280910	1.41×10^{-7}	1.42×10^{-4}
CXCR2	1.254837	1.33×10^{-4}	4.80×10^{-3}
RELN	1.222239	1.13×10^{-4}	4.39×10^{-3}
LBH	1.204157	2.66×10^{-10}	2.68×10^{-6}
MNDA	1.167431	3.92×10^{-5}	2.42×10^{-3}
JCHAIN	1.155933	3.10×10^{-2}	1.26×10^{-1}
LYZ	1.116696	1.45×10^{-2}	7.92×10^{-2}
PHACTR3	1.085895	8.05×10^{-3}	5.53×10^{-2}
NRAP	1.049841	7.39×10^{-4}	1.26×10^{-2}
TCIM	1.017547	4.98×10^{-7}	2.28×10^{-4}
ZNF208	1.017184	1.22×10^{-4}	4.59×10^{-3}
MYL3	1.013453	4.82×10^{-3}	3.98×10^{-2}
RGS18	1.000141	2.90×10^{-6}	6.09×10^{-4}
PKIB	0.980199	3.09×10^{-7}	1.95×10^{-4}
ATP1B4	0.978339	6.38×10^{-3}	4.80×10^{-2}
Downregulated			
PRG4	−2.181992	2.73×10^{-2}	1.16×10^{-1}
MSLN	−1.942843	6.38×10^{-3}	4.80×10^{-2}
ITLN1	−1.850739	1.76×10^{-2}	8.92×10^{-2}
HP	−1.844829	1.69×10^{-2}	8.70×10^{-2}
SLPI	−1.816258	1.53×10^{-2}	8.17×10^{-2}
UPK1B	−1.778626	3.03×10^{-3}	2.97×10^{-2}
SYT4	−1.686477	2.08×10^{-2}	9.86×10^{-2}
PRR9	−1.619296	2.15×10^{-3}	2.44×10^{-2}
CXCL1	−1.457485	2.14×10^{-3}	2.43×10^{-2}
BNC1	−1.411299	6.80×10^{-3}	5.00×10^{-2}
KLK11	−1.393466	2.79×10^{-3}	2.84×10^{-2}
FAM110C	−1.387659	1.23×10^{-4}	4.61×10^{-3}
AADAC	−1.380442	7.45×10^{-3}	5.25×10^{-2}
FLRT3	−1.343362	7.28×10^{-3}	5.18×10^{-2}
LRRN4	−1.287621	3.72×10^{-3}	3.38×10^{-2}
TCEAL2	−1.235198	7.03×10^{-5}	3.37×10^{-3}
ACTA1	−1.220157	7.55×10^{-4}	1.28×10^{-2}
IL1B	−1.197718	7.23×10^{-3}	5.15×10^{-2}
BEX2	−1.179566	1.28×10^{-6}	4.05×10^{-4}
DNER	−1.160800	2.45×10^{-3}	2.64×10^{-2}

Abbreviations: DEGs, differentially expressed genes; others, see FIGURE 1

TABLE 2 Kyoto Encyclopedia of Genes and Genomes pathway analysis of upregulated and downregulated differentially expressed genes

ID	Name	Count	*P* value	Genes
Upregulated DEGs				
hsa04672	Intestinal immune network for IgA production	4	5.81×10^{-3}	*CXCR4*, *TNFRSF17*, *ITGA4*, *HLA-DRA*
hsa04060	Cytokine-cytokine receptor interaction	7	1.14×10^{-2}	*PPBP*, *CXCR4*, *CCR2*, *TNFRSF17*, *TNFRSF19*, *CXCR2*, *CXCL11*
hsa04614	Renin-angiotensin system	3	1.38×10^{-2}	*AGTR2*, *CMA1*, *ENPEP*
hsa04261	Adrenergic signaling in cardiomyocytes	5	2.26×10^{-2}	*AGTR2*, *MYL3*, *ATP1B4*, *RAPGEF4*, *SCN7A*
hsa05410	Hypertrophic cardiomyopathy	4	2.30×10^{-2}	*MYL3*, *ITGA1*, *PRKAA2*, *ITGA4*
Downregulated DEGs				
hsa05134	Legionellosis	4	1.76×10^{-3}	*CXCL1*, *C3*, *IL18*, *IL1B*
hsa04060	Cytokine-cytokine receptor interaction	6	4.23×10^{-3}	*LIF*, *CXCL1*, *CCL20*, *IL18*, *IL1B*, *BMPR1B*
hsa05143	African trypanosomiasis	3	9.51×10^{-3}	*IL18*, *IL1B*, *HPR*
hsa04668	TNF signaling pathway	4	1.20×10^{-2}	*LIF*, *CXCL1*, *CCL20*, *IL1B*
hsa04621	NOD-like receptor signaling pathway	3	2.60×10^{-2}	*CXCL1*, *IL18*, *IL1B*
hsa04610	Complement and coagulation cascades	3	3.82×10^{-2}	*C3*, *CFB*, *BDKRB1*

Abbreviations: NOD, nucleotide-binding, oligomerization domain; TNF, tumor necrosis factor; others, see TABLE 1

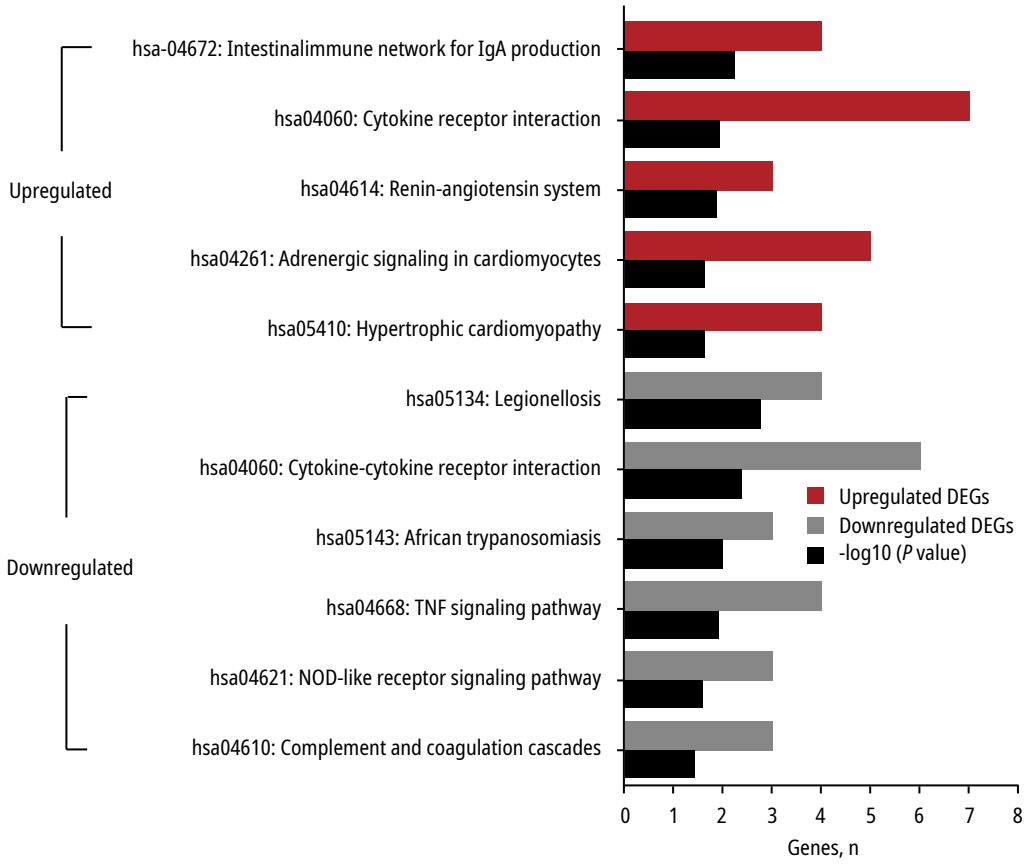

FIGURE 2 Kyoto Encyclopedia of Genes and Genomes pathway analysis of differentially expressed genes
Abbreviations: see TABLES 1 and 2

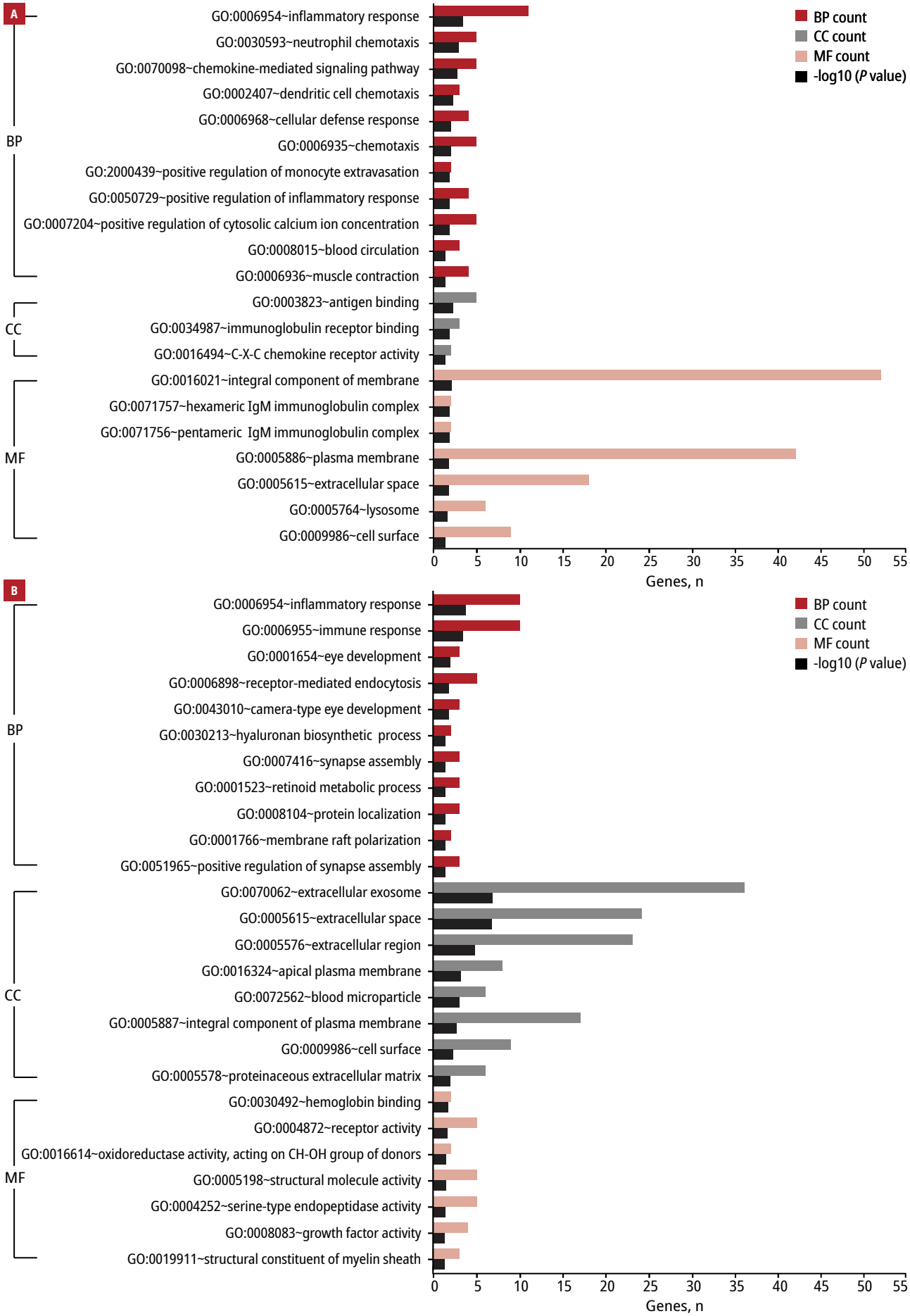

FIGURE 3 Gene Ontology (GO) analysis of differentially expressed genes (DEGs): **A** – upregulated DEGs; **B** – downregulated DEGs. DEGs were divided into 3 functional groups, including biological process (BP), cellular component (CC), and molecular function (MF).

TABLE 3 The top 20 nodes involved in the protein–protein interaction network

Hub-gene	Regulation	Degree
CXCR4	Up	19
IL1B	Down	18
CXCR2	Up	17
C3	Down	17
CXCL11	Up	15
CCR2	Up	15
LRRK2	Up	15
CXCL1	Down	14
CCL20	Down	14
AGTR2	Up	14
BDKRB1	Down	13
PPBP	Up	12
NPY1R	Up	12
FPR3	Up	12
P2RY14	Up	12
ACTA1	Down	12
IL18	Down	8
WT1	Down	8
CALB2	Down	7
S100A8	Up	6

TABLE 4 Kyoto Encyclopedia of Genes and Genomes pathway analysis of the top 20 differentially expressed genes

ID	Name	Count	*P* value	Genes
hsa04060	Cytokine-cytokine receptor interaction	9	2.18×10^{-8}	*CXCL1*, *PPBP*, *CCL20*, *CXCR4*, *IL18*, *CCR2*, *IL1B*, *CXCR2*, *CXCL11*
hsa04062	Chemokine signaling pathway	7	2.30×10^{-6}	*CXCL1*, *PPBP*, *CCL20*, *CXCR4*, *CCR2*, *CXCR2*, *CXCL11*
hsa05134	Legionellosis	4	2.38×10^{-4}	*CXCL1*, *C3*, *IL18*, *IL1B*
hsa04080	Neuroactive ligand-receptor interaction	5	3.19×10^{-3}	*AGTR2*, *P2RY14*, *BDKRB1*, *FPR3*, *NPY1R*
hsa04621	NOD-like receptor signaling pathway	3	7.26×10^{-3}	*CXCL1*, *IL18*, *IL1B*
hsa05132	Salmonella infection	3	1.55×10^{-2}	*CXCL1*, *IL18*, *IL1B*
hsa05323	Rheumatoid arthritis	3	1.73×10^{-2}	*CCL20*, *IL18*, *IL1B*
hsa04668	TNF signaling pathway	3	2.50×10^{-2}	*CXCL1*, *CCL20*, *IL1B*

Abbreviations: see TABLE 2

showed that miR-3123 upregulated *LRRK2* and *P2RY14*, miR-548g-3p upregulated *CCR2* and *CXCR4* (Supplementary material, *Figure S2*).

DISCUSSION Incidence and prevalence of AF is continuously increasing, and the disease usually leads to severe clinical outcomes. Understanding the genetic and molecular mechanisms of AF is of great importance to improve prognosis. The rapid development of microarray technologies provided an opportunity to explore the potential biomarkers and therapeutic targets of AF by bioinformatics analysis.

In this study, a total of 260 DEGs were identified between the AF and SR groups, including

150 upregulated genes and 110 downregulated genes. In order to study the biological function of DEGs, we performed further analyses of GO, KEGG, PPI and miRNA-targeted gene regulatory network. We screened potential key genes for AF, including upregulated genes: *CXCR4*, *CXCR2*, *CXCL11*, *CCR2*, *LRRK2*, *AGTR2*, *PPBP*, *NPY1R*, *FRR3*, *P2RY14*, *SL00A8*, and downregulated genes: *IL1B*, *C3*, *CXCL1*, *CCL20*, *BDKRB1*, *ACTA1*, *IL18*, *CALB2*, *WT1*, and others. *CXCR4* belongs to the super-family of the 7-transmembrane domain, heterotrimeric G-protein-coupled receptors and is involved in cell survival, proliferation, and migration.[18] *CXCR4* is an α-chemokine receptor specific for stromal cell-derived factor 1 (SDF-1, also called CXCL12). It has been reported that plasma SDF-1 was increased in patients with AF compared with those with SR.[19] *CXCR2* is another member of superfamily of the 7-transmembrane domain, heterotrimeric G-protein-coupled receptors, and the major chemokine receptors of neutrophils. *CXCR2* is the receptor for 7 chemokines: *CXCL1*, *CXCL2*, *CXCL3*, *CXCL6*, and *CXCL8*.[20] Several studies revealed that *CXCR2* participates in tumor progression and numerous inflammatory reactions.[21] *CXCL11* is a selective ligand for *CXCR3* and is secreted by monocytes, endothelial cells, and fibroblasts.[22] CXCL11 is usually expressed at low levels in physiological conditions, but elevated by cytokine stimulation and plays an important role in immune cell migration, differentiation, and activation.[23] This mechanism may help delay the structural remodeling of AF. CCR2 is expressed on the surface of monocytes, endothelial cells, leukocytes, and smooth muscle cells. CCR2 also presents in basophils, dendritic and natural killers cells, and activated T cells.[24] *CCR2* is the main chemokine receptor of CCL2 and plays a pivotal role in several physiological and pathological processes, including the migration of endothelial cells, monocyte recruitment to inflammatory sites.[25] Han et al[26] found that CCR2 expression was increased in patients with hypercholesterolemia and promoted the chemotactic motility and recruitment of monocytes to the vessel wall and might accelerate the progression of atherosclerosis. LRRK2 belongs to the human Roco proteins family, it catalyzes 2 distinct biochemical activities, phosphotransfer and GTP hydrolysis, and is strongly associated with PD, Alzheimer disease, and immune disorders.[27] LRRK2 has been implicated in a wide range of cellular processes including mitochondrial maintenance, synaptic vesicle cycling, autophagy, lysosomal biology, and translational control.[28,29] IL1B is part of a cluster of genes on chromosome 2 coding for a family of interleukin 1 proteins. It has been shown to be an important modulator of inflammatory pathways and is involved in the pathogenesis of cardiovascular diseases.[30] CXCL1 modulates inflammation, angiogenesis, wound healing, tumorigenesis, and cell motility through regulating *CXCR2*, *CXCL1*.[31] The mammalian *WT1* gene is 50 kb in length, and there are at least 36 potential *WT1* isoforms. In the developing heart, it has been shown that *WT1* expression is mainly restricted to the epicardium. Study shows that *WT1* knockout mice have smaller ventricles, thinner epicardium, and a much more reduced coronary vascular system.[32] *WT1* also influences epicardial cell migration and myocardial proliferation through the inhibitory chemokines *CXCL10* and *CCL5*.[33]

Functional enrichment results of DEGs indicated that inflammatory response is crucial for AF. Weymann et al[34] reported that inflammatory factors such as levels of C-reactive protein (CRP) and interleukins (such as interleukin 6, 8, and 10) were increased significantly in AF and can help to predict and monitor AF. Xu et al[35] found that blood interleukin 17A level was elevated in patients with recurrent AF after catheter ablation. MiRNAs are small noncoding RNAs which regulate gene expression at post-translational level.[8,36] Based on our miRNA-targeted regulatory network analysis, we found that miR-3123 upregulated the expression of *LRRK2* and *P2RY14,* miR-548g-3p increased the *CCR2* and *CXCR4* levels. The exact mechanism of AF is still uncertain. Our study may provide new insight into the mechanism of AF. It is critical to determine risk factors for the prediction and prevention of AF. Previous studies revealed that, compared with healthy subjects, renalase,[37,38] leptin, adiponectin, tumor necrosis factor α,[39] and NT-proBNP[40] were elevated in patients with AF. Appropriate management of AF[41] and treatment based on the current theory may help to reduce the mortality of AF. Our study may provide novel potential therapeutic targets for AF.

Conclusions The present study identified a series of key genes, including *CXCR4*, *CXCR2*, *CXCL11*, *CCR2*, *LRRK2*, *IL1B*, *C3*, *CXCL1*, *CALB2*, and others. In addition, we also discovered important miRNAs such as: miR-3123, miR-548g-3p, and miR-9-5p, along with pathways that were most closely related with human AF. Our results may provide a more detailed molecular mechanism and potential therapeutic targets for AF.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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