Construction and Analysis of the IncRNA-miRNA-mRNA Network Based on Competing Endogenous RNA in Atrial Fibrillation

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Background: Accumulated studies have revealed that long non-coding RNAs (lncRNAs) play critical roles in human diseases by acting as competing endogenous RNAs (ceRNAs). However, functional roles and regulatory mechanisms of lncRNA-mediated ceRNA in atrial fibrillation (AF) remain unknown. In the present study, we aimed to construct the IncRNA-miRNA-mRNA network based on ceRNA theory in AF by using bioinformatic analyses of public datasets.

Methods: Microarray data sets of GSE115574 and GSE79768 from the Gene Expression Omnibus database were downloaded. Twenty-one AF right atrial appendage (RAA) samples and 22 sinus rhythm (SR) subjects RAA samples were selected for subsequent analyses. After merging all microarray data and adjusting for batch effect, differentially expressed genes were identified. Gene Ontology (GO) categories and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were carried out. A ceRNA network was constructed.

Result: A total of 8 lncRNAs and 43 mRNAs were significantly differentially expressed with fold change >1.5 (p < 0.05) in RAA samples of AF patients when compared with SR. GO and KEGG pathway analysis showed that cardiac muscle contraction pathway were involved in AF development. The ceRNA was predicted by co-expressing LOC101928304/LRRC2 from the constructional network analysis, which was competitively combined with miR-490-3p. The expression of LOC101928304 and LRRC were up-regulated in myocardial tissue of patients with AF, while miR-490-3p was down-regulated.

Conclusion: We constructed the LOC101928304/miR-490-3p/LRRC2 network based on ceRNA theory in AF in the bioinformatic analyses of public datasets. The ceRNA network found from this study may help improve our understanding of IncRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of AF.

Keywords: competing endogenous RNA, long non-coding RNAs, network, atrial fibrillation, bioinformatic analysis
INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia characterized by irregular high-frequency excitation and contraction of the atria, and is a major contributor to stroke, heart failure and sudden death (1–3). Approximately 1–2% of the common population suffer from AF, with the prevalence up to over 10% for individuals aged ≥80 years (1, 2, 4, 5). However, there is a lack of effective therapy for AF in general, largely because the pathophysiologic mechanism underlying AF remains unclear. The underlying pathogenesis of AF is multiplex, including electrical remodeling, structural remodeling, Ca2+ handling abnormalities and autonomic nervous system changes (6).

Previous studies have identified that non-coding RNAs (ncRNAs) play a critical role in the pathogenesis of AF by regulating core proteins and pivotal pathways (7). Long non-coding RNAs (lncRNAs) are a class of endogenous ncRNAs whose length are >200 nucleotides with no protein-coding potential (8). A number of studies have demonstrated that lncRNAs are involved in multiple biological processes by regulating genes of transcriptional, posttranscriptional, and epigenetic levels (9). Dysregulations of lncRNA expressions and functions have been implicated in the development and progression of many diseases including cancer, neurodegeneration diseases and cardiovascular diseases (10–12).

Competing endogenous RNA (ceRNA) is a novel regulation mechanism in which lncRNA can competitively combine with miRNAs through microRNA response elements (MREs), thus inhibiting gene silencing by isolating miRNAs from messenger RNAs (mRNAs) (13–15). This regulation mechanism has been observed in some cardiovascular diseases. For example, lncRNA PEL was shown to function as a ceRNA to competitively bind regulating core proteins and pivotal pathways (16). Let-7d and contribute to cardiac fibrosis (17). PEL was shown to function as a ceRNA to competitively band regulating core proteins and pivotal pathways (16). Let-7d and contribute to cardiac fibrosis (17).

TABLE 1 | The characteristics of datasets in this study.

| GSE series | GSE115574 | GSE79768 |
|------------|-----------|-----------|
| Platform   | GPL570    | GPL570    |
| Total      | 30        | 13        |
| AF         | 14        | 7         |
| SR         | 16        | 6         |
| Country    | Turkey    | Taiwan    |
| Contributors | Deniz GC et.al | Tsai F et.al |

GSE, gene expression omnibus; AF, atrial fibrillation; SR, sinus rhythm.

Subjects were selected. Finally, a total of 21 AF and 22 SR samples were included for subsequent analyses.

Data Pre-processing
Robust multi-array average (RMA) algorithm and log2-transformed were performed for background correction and normalization. The averages of the probe sets of values were calculated as the expression values for the same gene with multiple probe sets. Furthermore, human genome reference hg38 (GRCh38.p13) was utilized to annotate series matrix files to determine transcript biotype and to convert the probe IDs into gene symbols. After merging all microarray data, empirical Bayes frameworks was used to adjust for the batch effects.

Differentially Expressed Genes Analysis
A differential expression analysis on merged GEO series based on paired-sample t-tests between AF and SR samples, were performed using “Limma” package of R software. The Benjamini and Hochberg (BH) method was introduced to adjust the raw P-values into a false discovery rate to avoid the multi-test problem. The adjust p < 0.05 and the gene expression fold change (FC) value >1.5 or ≥2/3 (|log2 FC| ≥0.58), were set as the thresholds for identifying DEGs including mRNA and LncRNA between the AF and SR sample. Moreover, up-regulated or down-regulated DEGs were visualized as heat map plots.

Functional and Pathway Enrichment Analyses of DEGs Among ceRNA Network
To better understand the biological function and characteristics of DEGs among ceRNA network, Gene Ontology (GO, http://geneontology.org/) (18) and Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp/) (19) were performed using the “clusterProfiler” package of R software. GO terms and KEGG pathways that met the criterion of adjusted p < 0.05 and Q value <0.5, were considered as significantly enriched (18, 19).

cRNA Network Construction
To constructed LncRNA-miRNA-mRNA networks, first, the differentially expressed LncRNAs and mRNAs with |log2 FC| ≥0.58 were selected. The LncRNA-miRNA interactions were predicted by using Mircode (http://www.mircode.org), which provided human miRNA target predictions based on the comprehensive GENCODE gene annotation. Furthermore, predicted miRNAs were utilized to construct miRNA-mRNA networks.
interaction using the tools of TargetScan (http://www.targetscan.org/mamm_31/), Mirdb (http://mirdb.org/), MiRTarBase (http://mirTarBase.cuhk.edu.cn/), and MirDIP (http://ophid.utoronto.ca/mirDIP/). The mRNAs predicted by three or above datasets, were used to identify the potential miRNA targets. Since lncRNAs can function as endogenous miRNA sponges and regulate the translation of targeted mRNAs, the expression of lncRNAs and mRNAs should be positively correlated (14). Subsequently, the initial ceRNA network was constructed on the basis of the differentially expressed lncRNAs, predicted miRNAs and mRNAs using the Cytoscape 3.7.2 software (http://cytoscape.org/).

Validation of the Expression of miRNAs Among ceRNA Network

In the ceRNA network, the expression of miRNAs should be negatively correlated with lncRNAs and mRNAs (14). The gene expression profile GSE28954 was downloaded from the GEO database and expression profiling arrays were generated using platform GPL10850 [Agilent-021827 Human miRNA Microarray (V3)]. Additionally, the GSE28954 dataset including 10 RAA sample (4 AF and 6 SR) was used to identify differential expression miRNAs. Any miRNAs were deemed as differentially expressed if adjusted $p$-values were $< 0.05$ and fold changes were $\geq 1.5$ or $\leq 2/3$. Subsequently, significantly down-regulated miRNAs, up-regulated miRNAs and lncRNAs were used to construct final ceRNA network. Moreover, Funrich software (http://www.funrich.org/) was used to functional enrichment for differential expression miRNAs.

RESULTS

LncRNA and mRNA Expression Profile

Gene expression levels of merged GEO series that have been adjusted for batch effects were standardized; and the results of pre- and post-standardized are showed in Supplementary Figure 1. A total of 8 lncRNAs and 43 mRNA were significantly differentially expressed with a fold change $> 1.5$ ($p < 0.05$) in RAA samples of AF patients when compared with SR. The up- and down-regulated differently expressed lncRNAs and mRNAs are listed in Tables 2, 3. Among the 8 lncRNAs, 4 were up-regulated and the remaining were down-regulated. Among the 43 mRNAs, 14 and 39 were up-regulated and down-regulated, respectively. The heat maps of the 8 lncRNAs distinctly separated AF from controls were showed in Figure 1.

Functional Enrichment Analyses: GO and KEGG Pathway Analyses

To further investigate the biological functions of the 43 differential expressed mRNA, functional enrichment analyses were performed (Table 4). GO enrichment analysis revealed that differential expressed mRNA were enriched in five biological processes (adjusted $p < 0.05$ and Q value $< 0.05$), but not in the AF associated process. Pathway analyses showed that differential expressed mRNA were enriched in 4 biological processes including bile secretion, cardiac muscle contraction, insulin secretion, protein digestion and absorption. The up-regulated ATP1B4 and down-regulated TRDN were enriched in cardiac muscle contraction (adjusted $p = 0.0360$ and $Q = 0.0278$). Cardiac muscle contraction was found to indicate AF development, which was line with a previous study (20).

Construction of ceRNA Network

Using the Mircode, we obtained 335 miRNAs. Furthermore, we obtained 77019 mRNAs based on the tools of TargetScan, Mirdb, MiRTarBase and MirDIP. By using the Cytoscape, we found that a total of 7 lncRNAs, 91 miRNAs and 28 mRNAs were involved in the ceRNA-miRNA-mRNA network (Figure 2). Based on the ceRNA theory (14), the screened lncRNAs and mRNAs were both up-regulated (Table 5).

Validation of the Expression of miRNAs Among ceRNA Network

To further validate the ceRNA network of AF, we analyzed miRNA microarrays GSE28954 from the GEO data and results showed that eight differentially expressed miRNAs were identified (Table 6). After combining with the findings from

### TABLE 2 | The up-regulated and down-regulated differently expressed lncRNAs in merged data.

| LncRNA         | FC  | AveExpr | t    | P Value | Adjust P value | B    |
|---------------|-----|---------|------|---------|----------------|------|
| **Up-regulated** |     |         |      |         |                |      |
| TRDN-AS1      | 2.2933 | 5.0081  | 5.5285 | $<0.0001$ | 0.0019         | 4.9934 |
| UNCSB-AS1     | 1.9265 | 5.9359  | 4.8713 | $<0.0001$ | 0.0066         | 3.0102 |
| LINCO0702     | 2.1401 | 6.1239  | 3.8955 | 0.0003   | 0.0323         | 0.1999 |
| LOC101928304  | 1.6665 | 7.3767  | 4.8761 | $<0.0001$ | 0.0066         | 3.0243 |
| **Down-regulated** |   |         |      |         |                |      |
| LINC00844     | 0.4813 | 8.1024  | $-4.7081$ | $<0.0001$ | 0.0089         | 2.5262 |
| MUM1L1        | 0.5784 | 6.0297  | $-3.9796$ | 0.0003   | 0.0286         | 0.4158 |
| LOC100507477  | 0.6137 | 5.6490  | $-4.9845$ | $<0.0001$ | 0.0057         | 3.3483 |
| GGTA1P        | 0.6632 | 7.7114  | $-4.8667$ | $<0.0001$ | 0.0065         | 3.0559 |

FC, fold change; AveExpr, average expression, defined as average log2-expression level for that gene across all the arrays and channels in the experiment; B, The B-statistic is the log-odds given that the gene is differentially expressed.
### TABLE 3 | The up-regulated and down-regulated differently expressed mRNA in merged data.

| mRNA   | FC    | AveExpr | t      | P Value | Adjust P Value | B       |
|--------|-------|---------|--------|---------|----------------|---------|
| **Up-regulated** |       |         |        |         |                |         |
| DNAJA4 | 1.5251| 6.5447  | 7.2648 | <0.0001 | 0.0001         | 10.2856 |
| DHR59  | 2.3195| 8.4284  | 7.1253 | <0.0001 | 0.0001         | 9.8654  |
| ANGPTL2| 1.5611| 6.7732  | 6.2432 | <0.0001 | 0.0005         | 7.1793  |
| FRMD3  | 1.5410| 7.8567  | 5.9835 | <0.0001 | 0.0009         | 6.3838  |
| CHGB   | 2.3222| 7.9284  | 5.8236 | <0.0001 | 0.0012         | 5.8944  |
| LBH    | 1.7619| 7.6184  | 5.6304 | <0.0001 | 0.0017         | 5.3041  |
| RPL3L  | 2.1094| 7.2044  | 5.1515 | <0.0001 | 0.0041         | 3.8500  |
| COLQ   | 2.3222| 7.9284  | 5.0006 | <0.0001 | 0.0057         | 3.9364  |
| COL21A1| 1.5923| 6.7335  | 4.7384 | <0.0001 | 0.0089         | 2.6156  |
| DHRS9  | 2.3195| 8.4284  | 4.1370 | <0.0001 | 0.0232         | 0.8736  |
| ANGPTL2| 1.5611| 6.7732  | 4.4534 | <0.0001 | 0.0140         | 1.8121  |
| FHOD2  | 1.7130| 5.9668  | 4.4534 | <0.0001 | 0.0141         | 1.7860  |
| PRIMA1 | 1.2225| 4.0392  | 4.1332 | <0.0001 | 0.0232         | 0.8630  |
| RELN   | 2.3546| 7.1304  | 3.8306 | <0.0001 | 0.0358         | 0.0219  |
| HOXA1  | 1.6400| 5.9306  | 3.6332 | <0.0001 | 0.0469         | −0.5107 |
| **Down-regulated** |       |         |        |         |                |         |
| C1orf105| 0.4957 | 6.6784 | −4.6479| <0.0001 | 0.0100         | 2.3488  |
| GOS2   | 0.6187| 9.3051  | −4.5603| <0.0001 | 0.0120         | 2.0917  |
| SCAR45 | 0.6410| 7.2144  | −4.5603| <0.0001 | 0.0120         | 2.0917  |
| TN11   | 0.3292| 6.7636  | −4.4634| <0.0001 | 0.0140         | 1.8121  |
| VIT    | 0.5843| 5.1497  | −4.4554| <0.0001 | 0.0141         | 1.7860  |
| BEX2   | 0.5819| 8.2081  | −4.3737| <0.0001 | 0.0160         | 1.5495  |
| PRIMA1 | 0.6659| 6.9603  | −4.3647| <0.0001 | 0.0160         | 1.5236  |
| CACNA2D2| 0.6092 | 7.1702 | −4.2543| <0.0001 | 0.0186         | 1.2069  |
| SFRP5  | 0.5573| 6.3132  | −4.2466| <0.0001 | 0.0186         | 1.1850  |
| SOXDC1 | 0.5526| 5.3729  | −4.2146| <0.0001 | 0.0186         | 1.1706  |
| SYT13  | 0.6506| 4.9698  | −4.2277| <0.0001 | 0.0192         | 1.1311  |
| TMEM132C| 0.6557 | 6.1435 | −4.1234| <0.0001 | 0.0236         | 0.8353  |
| TMEM176A| 0.6291 | 8.0699 | −4.0289| <0.0001 | 0.0266         | 0.5700  |
| CTN3   | 0.6533| 6.2783  | −4.0121| <0.0001 | 0.0275         | 0.5332  |
| IPX3   | 0.6642| 7.3042  | −3.9392| <0.0001 | 0.0306         | 0.3206  |
| MFAP4  | 0.6284| 7.9084  | −3.8971| <0.0001 | 0.0323         | 0.2042  |
| KCNN2  | 0.6305| 6.0473  | −3.8486| <0.0001 | 0.0349         | 0.0711  |
| ART3   | 0.6384| 8.6506  | −3.8262| <0.0001 | 0.0359         | 0.0098  |
| SUSD4  | 0.6213| 5.8862  | −3.8150| <0.0001 | 0.0362         | −0.0208 |
| BCHE   | 0.6113| 6.4957  | −3.7419| <0.0005 | 0.0408         | −0.2192 |
| CLSTN2 | 0.6348| 5.8874  | −3.6521| <0.0007 | 0.0459         | −0.4605 |
| CPLX3  | 0.5812| 6.6010  | −3.6176| <0.0008 | 0.0485         | −0.5522 |
| MGC24103| 0.6030 | 5.3526 | −3.9094| <0.0003 | 0.0316         | 0.2382  |
| REC114 | 0.6487| 4.9716  | −5.8065| <0.0001 | 0.0012         | 5.8422  |
| TRDN   | 0.6624| 6.5037  | −4.9370| <0.0001 | 0.0061         | 3.2060  |
| SLC7A11| 0.6358| 4.7243  | −4.8509| <0.0001 | 0.0069         | 2.9495  |
| BLM    | 0.6175| 6.1317  | −4.8269| <0.0001 | 0.0073         | 2.8779  |

**FC**, fold change; **AveExpr**, average expression, defined as average log2-expression level for that gene across all the arrays and channels in the experiment; **B**, The B-statistic is the log-odds given that the gene is differentially expressed.

Tables 5, 6, we found that LOC101928304/miR-490-3p/LRRC2 was consistent with the ceRNA mechanism. The expression of LOC101928304 and LRRC2 were up-regulated in myocardial tissue of patients with AF, while miR-490-3p was down-regulated. LOC101928304 was positively correlated with LRRC2 (Supplementary Figure 2).
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**FIGURE 1** | Heatmap of IncRNAs profile comparisons between atrial fibrillation and control. Each row represents a sample and each column represents a single gene. Pink color represents AF samples and blue color presents SR samples. The color scale shows the relative gene expression level in certain slide: green indicates low relative expression levels; red indicates high relative expression levels.

**TABLE 4** | Significant enriched GO terms and pathways of differential expressed mRNA.

| Term | Genes | P value | Adjust P value | Q value |
|------|-------|---------|----------------|---------|
| GO terms | | | | |
| GO:0001941 Postsynaptic membrane organization | RELN/SLC7A11/CLQ | <0.0001 | 0.0082 | 0.0057 |
| GO:0043113 Receptor clustering | RELN/SLC7A11/CLQ | <0.0001 | 0.0107 | 0.0075 |
| GO:0072578 Neurotransmitter-gated ion channel clustering | RELN/SLC7A11 | 0.0001 | 0.0157 | 0.0110 |
| GO:0050807 Regulation of synapse organization | RELN/SLC7A11/CLQ/CLSTN2 | 0.0001 | 0.0157 | 0.0110 |
| GO:0050803 Regulation of synapse structure or activity | RELN/SLC7A11/CLQ/CLSTN2 | 0.0001 | 0.0157 | 0.0110 |
| KEGG pathway | | | | |
| hsa04976 Bile secretion | ATP1B4/KCNN2 | 0.0028 | 0.0360 | 0.0278 |
| hsa04260 Cardiac muscle contraction | TRDN/ATP1B4 | 0.0040 | 0.0360 | 0.0278 |
| hsa04911 Insulin secretion | ATP1B4/KCNN2 | 0.0040 | 0.0360 | 0.0278 |
| hsa04974 Protein digestion and absorption | COL21A1/ATP1B4 | 0.0048 | 0.0360 | 0.0278 |

**DISCUSSION**

In this bioinformatics study, we integrated gene expression profiles of 46 AF samples and 31 SR samples from 2 GEO datasets. We identified 8 IncRNAs and 43 mRNA were significantly differentially expressed with fold change $>$1.5 ($p < 0.05$). Furthermore, the LOC101928304/miR-490-3p/LRRC2 network based on ceRNA theory was constructed in AF. The expression of LOC101928304 and LRRC2 were up-regulated in myocardial tissue of patients with AF, while miR-490-3p was down-regulated.

Recently, the pathological functions of IncRNAs and miRNAs in cardiovascular disease have been recognized, making them potential candidates as therapeutic targets and biomarkers. However, AF-related IncRNAs and miRNAs still required further research. Recent studies have investigated the expression profiles of IncRNA in AF patients (20–25). For instance, Xu et al. detected the expression levels of IncRNAs in AF in elderly patients, which showed that IncRNAs were closely involved in the pathogenesis of AF (26). Moreover, an increasing number of reports indicate that IncRNAs can regulate protein-coding genes in mammals through the ceRNA network (27), where IncRNAs function as miRNA sponges to upregulate the expression of their targets (28). For instance, Liu et al. identified LINC00964 as a key IncRNA in AF susceptibility- and persistence-associated ceRNA networks (29). By integrating three microarray datasets and construction of a ceRNA network, the study by Wu et al. discovered that HCG11, KRBOX1-AS1, ACBD5 and RAD52 may compete with WEE1 for has-miR-17-5p to affect the development of AF (30). However, given the sparse existing evidence in the literature, the ceRNA mechanisms related to AF remained largely obscure and required further investigation.

Previous studies have found an association between LOC101928304 and cardiovascular diseases. Qiu et al. found that LOC101928304 were related with the functions of blood circulation and heart contraction using high-throughput sequencing of IncRNAs in myocardial tissues collected from patients with dilated cardiomyopathy (DCM) and normal heart donors (31). They also confirmed that LOC101928304 were downregulated in DCM tissues by using real-time PCR (31).
Likewise, one study reported that miR-490-3p played a key role in different acute and chronic cardiovascular disease processes (32). Downregulation of miR-490-3p expression in atherosclerosis patients, and miR-490-3p which enhanced cell proliferation and migration of vascular smooth muscle cells and human umbilical vein endothelial cells in atherosclerosis (33, 34). The inhibition of miR-490-3p could promote autophagy to reduce myocardial ischemia reperfusion (IR) injury by upregulating ATG4B (35). Qiang et al. investigated that miR-490-3p was downregulated in patients with chronic heart failure (HF), which might provide novel targets for prevention and treatment of chronic HF (36). Cao et al. revealed that miR-490-3p was down-regulated in AF, which had a potential diagnostic value to distinguish patients with AF from healthy controls (37).

First, we constructed the ceRNA network based on lncRNA and mRNA, and predicted the corresponding miRNA. In subsequent verification, we carried out an exploratory analysis because the sample size was limited. Under these circumstances, even if its adjusted $P > 0.05$, we still have reason to believe that miR-490-3p has potential to be part of the ceRNA network that could be
combined with published literature, which should be further verified in subsequent experimental studies. Taken together, our findings were consistent with results from previous studies in that miR-490-3p may participate in the ceRNA network of LOC101928304.

LRRC2 located in chromosome three common eliminated region one, is a member of the leucine-rich repeat-containing family of proteins that have been implicated in various biological pathways. Recently, LRRC2 has been reported to correlate with transcripts associated with cardiac remodeling, thereby playing critical roles in the processes of cardiomyocyte hypertrophy and mitochondrial abundance (38). RNAi-mediated LRRC2 knockdown in a rat-derived cardiomyocyte cell line resulted in enhanced expression of canonical hypertrophic biomarkers as well as increased mitochondrial mass in the context of increased PGC-1α expression (38). LRRC2 partially localized to the mitochondrion and regulated by the mitochondrial master regulator PGC-1α (38). Most notably, mitochondrial dysfunction and cardiomyocyte hypertrophy increase the heterogeneity of atrial electrical conduction, leading to change in atrial structure and potentially facilitating the development of AF (39). The expression of PGC-1α was significantly decreased in AF model of rabbits with rapid pacing, indicating that mitochondrial biosynthesis was impaired in AF (40). LRRC2 may be a mediator of mitochondrial and cardiac function, which involve the PGC-1α-dependent mitochondrial abundance regulation mechanism, thereby ultimately facilitating the development of AF. Nevertheless, a more thorough understanding of LOC101928304/miR-490-3p/LRRC2 pathway in AF is necessary.

Discovering ncRNA-disease associations may help generate diagnostic and therapeutic tools for diseases. However, since uncovering associations via experimental studies are resource and time consuming, bioinformatic analyses for the identification of ncRNAs associated with AF are a helpful approach for preliminary exploration. In our study, we constructed a novel lncRNA-miRNA-mRNA network (LOC101928304/miR-490-3p/LRRC2) based on the ceRNA theory, which may therefore provide insights into the ceRNA regulatory mechanisms in the atrial fibrillation (AF) model.

**Table 5** The ceRNA network of AF with up-regulated lncRNA and mRNA.

| lncRNA     | miRNA          | mRNA       | lncFC | mFC  |
|------------|----------------|------------|-------|------|
| UNC5B-AS1  | hsa-miR-125a-5p| LBH        | 1.9265| 1.7619|
| UNC5B-AS1  | hsa-miR-125b-5p| LBH        | 1.9265| 1.7619|
| LIN00702   | hsa-miR-143-3p | LRRC2      | 2.1401| 1.6346|
| LIN00702   | hsa-miR-181a-5p| PHILDA1    | 2.1401| 1.7130|
| LOC101928304| hsa-miR-204-5p | ANGPTL2    | 1.6665| 1.5611|
| LOC101928304| hsa-miR-211-5p | ANGPTL2    | 1.6665| 1.5611|
| LOC101928304| hsa-miR-214-3p | COLQ       | 1.6665| 2.5338|
| LOC101928304| hsa-miR-218-5p | RELN       | 1.6665| 2.3546|
| LIN00702   | hsa-miR-27a-5p | RELN       | 2.1401| 2.3546|
| LOC100702  | hsa-miR-27b-3p | RELN       | 2.1401| 2.3546|
| LOC101928304| hsa-miR-361-5p | COLQ       | 1.6665| 2.5338|
| LOC101928304| hsa-miR-375    | PHILDA1    | 1.6665| 1.7130|
| TRDN-AS1   | hsa-miR-375    | PHILDA1    | 1.6665| 1.7130|
| LOC101928304| hsa-miR-490-3p | LRRC2      | 1.6665| 1.6346|
| UNC5B-AS1  | hsa-miR-670-5p | LBH        | 1.9265| 1.7619|
| LOC101928304| hsa-miR-761    | COLQ       | 1.6665| 2.5338|

lncFC, lncRNA fold change; mFC, mRNA fold change.

**Table 6** The differential expression of miRNA in AF patients compared with controls.

| miRNA          | FC    | logFC   | AveExpr | t      | P-Value | adj.P.Val | B         |
|----------------|-------|---------|---------|--------|---------|-----------|-----------|
| hsa-miR-146b-5p| 5.2289| 2.3865  | 0.1283  | 10.4588| 0.0000  | 0.0005    | 5.8165    |
| hsa-miR-21-5p  | 3.3088| 1.7263  | −0.3083 | 5.5215 | 0.0002  | 0.0608    | 0.9038    |
| hsa-miR-331-3p | 0.6302| −0.6661 | −0.0134 | −5.0775| 0.0005  | 0.0768    | 0.2909    |
| hsa-miR-490-3p | 0.3849| −1.3774 | −0.1368 | −4.6268| 0.0009  | 0.0768    | −0.3638   |
| hsa-miR-139-5p | 0.5946| −0.7500 | −0.0444 | −4.6021| 0.0009  | 0.0768    | −0.4007   |
| hsa-miR-128-2-3p| 0.6196| −0.6906 | 0.0241  | −4.5304| 0.0011  | 0.0768    | −0.5080   |
| hsa-miR-143-5p | 0.4905| −1.0278 | −0.2194 | −4.5209| 0.0011  | 0.0768    | −0.5223   |
| hsa-miR-128-3p | 0.6406| −0.6424 | −0.0031 | −4.2403| 0.0017  | 0.0930    | −0.9502   |

FC, fold change; Log2FC, log2 Fold change; AveExpr, average expression, defined as average log2-expression level for that gene across all the arrays and channels in the experiment; B, The B-statistic is the log-odds given that the gene is differentially expressed.
pathogenesis of AF. However, our study has some limitations. First, it is difficult to integrate some important factors for analyses, including regions, races and age. Given that the development of AF was caused by numerous environmental and genetic factors, our findings may be influenced by some immeasurable risk factors to an unknown extent. Additionally, specimens were obtained only from within the RAA, whereas AF is predominantly a left atrial disease. KEGG pathway analyses showed that the differently expression IncRNAs were mainly associated with cardiac muscle contraction. The up-regulated ATP1B4 and down-regulated TRDN were enriched in cardiac muscle contraction. Therefore, LOC101928304/miR-490-3p/LRRC2 may be involved in AF through other pathways. Our study may provide some new insights into the AF mechanism based on the bioinformatics analyses; however, the significantly differentially expressed IncRNAs and mRNAs would require experimental investigation of RT-PCR in clinical samples for further validation. In addition, the significantly differentially expressed IncRNAs require experimental investigations using the left atria appendage/pulmonary vein region samples for further validation. Likewise, future experimental research is needed to validate the ceRNA network of LOC101928304/miR-490-3p/LRRC2 in the pathogenesis of AF.

CONCLUSION

The LOC101928304/miR-490-3p/LRRC2 network based on ceRNA theory was constructed in AF in this bioinformatic analysis study. The novel ceRNA network found from this study may help improve our understanding of IncRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of AF.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS

XK, JZ, ZY, and GL were responsible for study conception, design of the study, data acquisition, and analysis and interpretation of results. ML was responsible for data acquisition. ML, XH, and SL took part in the discussion of the paper. XK wrote the manuscript that was reviewed and revised by GL, ZY, ML, XH, and SL. All authors gave approval of the version to be submitted.

FUNDING

This work was supported by the Medical Scientific Research Foundation of Guangdong Province of China (Grant sponsor: GL; Grant no. A2020453), the Science Foundation of Guangdong Second Provincial General Hospital (Grant sponsor: GL; Grant no.YY2018-002), and Doctoral workstation foundation of Guangdong Second Provincial general Hospital (Grant sponsor: XK; Grant no. 2021BSGZ008).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.791156/full#supplementary-material

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