Identification of Potential Gene Interactions in Heart Failure Caused by Idiopathic Dilated Cardiomyopathy

ABCDEF
Huijuan Huang
Beibei Luo
Boqun Wang
Qianwen Wu
Yuming Liang
Yan He

Corresponding Author: Yan He, e-mail: hyxjwxy@126.com
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Background: Many heart failure (HF) cases are caused by idiopathic dilated cardiomyopathy (IDCM). This study explored the mechanisms of the development and progression of HF caused by IDCM.

Material/Methods: The gene expression profiles of 102 samples were downloaded from the GEO database (GSE5406). Differentially expressed genes (DEGs) were identified through GO analysis and a KEGG pathway analysis, respectively. A protein–protein interaction (PPI) network was constructed and analyzed to screen potential regulatory proteins. In addition, MCODE and a cytoHubba plugin were used to identify the module and hub genes of DEGs. Finally, transcription factors (TFs) were predicted using PASTAA. We did not perform whole-exome sequencing (WES) for detecting mitochondrial DNA (mtDNA).

Results: A total of 197 DEGs were screened, and 3 modules, and 4 upregulated and 11 downregulated hub genes were screened. The GO analysis focused on the terms and 12 KEGG pathways were enriched. The FOS, TIMP1, and SERPINE1 hub genes, as well as some key TFs, demonstrated important roles in the progression of HF caused by IDCM. CEBPD, CEBOB, CDC37L1, and SRGN may be new targets for HF in IDCM patients.

Conclusions: The identified DEGs and their enriched pathways provide references for exploring the mechanisms of the development and progression of HF patients with IDCM. Moreover, modules, hub genes, and TFs may be useful in the treatment and diagnosis of HF patients with IDCM. However, mtDNA was not investigated.

MeSH Keywords: Gene Expression Profiling • Heart Failure • Transcriptome

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Background

Despite the significant developments that have been made regarding the physiopathology of heart failure (HF), HF remains an increasing global epidemic, with an estimated >37.7 million individuals affected globally [1]. Among HF cases, idiopathic dilated cardiomyopathy (iDCM) has a high mortality rate and many patients are under the age of 10 years [2]. Additionally, iDCM accounts for approximately 50 000 hospitalizations and 10 000 deaths each year, and is responsible for about 25% of all cases of HF [3]. iDCM is characterized pathologically by left ventricle dilation, functionally by progressive contractile failure, and histologically by cardiomyocyte hypertrophy, the loss of myofibrils, and interstitial fibrosis [4]. However, its mechanism is not fully understood. The pathogenesis of HF arising from different etiologies varies [5]; thus, it is important to provide treatment targeted to the relevant etiology, especially in cases of iDCM with diversity pathogenesis.

Improving the outcome of patients with iDCM remains challenging for clinicians. Studies that focus on the treatment of iDCM-caused HF include urgent screening biomarkers that can make precise diagnoses. Syndecan-4 may be a useful biomarker for predicting adverse effects in iDCM patients, hepatocyte growth factor can be significantly increased in advanced HF patients with iDCM, and desmin (DES) is a good marker of HF development in patients with iDCM [6-8]. However, the cause of iDCM is unknown, more studies are needed that focus on its treatment in order to improve the outcome of HF patients with iDCM and to precisely diagnose the disease based on the screening of biomarkers. Therefore, to understand the mechanism, it is crucial to screen biomarkers with high specificity and sensitivity.

In this study, which was based on bioinformatics, samples of GSE5406 were used to analyze differential expression genes (DEGs), the enrichment of GO terms or pathways, and protein–protein interaction (PPI) in HF patients with iDCM in order to predict potential targets. We also analyzed the modules of each PPI network and sought to determine possible hub genes using cytoHubba and a network analyzer. We explored the functions of these modules. Finally, the common genes of the 3 methods were selected as the hub genes. Based on these hub genes, the key transcription factors (TFs) became evident.

Material and Methods

Data source

The gene expression profile of GSE5406 was downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/) using the platform GPL96 ([HG-U133A] Affymetrix Human Genome U133A Array; Affymetrix, Inc., Santa Clara, CA, USA). A total of 102 individuals were analyzed in this study. RNA samples for this dataset were extracted from explanted left ventricular (LV) myocardia of 86 patients with systolic HF due to iDCM (iDCM-HF), and 16 unused donor hearts with normal LV functions at the time of harvest were used as controls [9]. By applying whole-exome sequencing (WES), mitochondrial DNA (mtDNA) mutation in patients were identified, but we did not perform WES in this data source.

Data processing

The expression matrix retrieved from the GEO database was pre-processed using the robust multiarray analysis (RMA) method (http://www.bioconductor.org/). The probe ID for each gene was then converted to a gene symbol using hgu133a.db, org.Hs.eg.db, and the annotate package in Bioconductor (http://www.bioconductor.org/). If a gene's symbols corresponded with multiple probes' IDs, the expression level of that gene was represented by the mean of the probes [10].

Identification of DEGs

A Linear Models for Microarray Data (LIMMA) package of R was used to identify the DEGs in the iDCM-HF samples compared with the normal LV samples [12]. The DEGs were selected with a threshold of |log2(fold change)|>0.589(fold change>1.5) and p<0.05. A heatmap and volcano plot were used to plot the samples and the DEGs using the pheatmap package in R.

Functional enrichment analysis

To further explore the biofunctions of the DEGs, a GO analysis and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were used. clusterProfiler (http://www.bioconductor.org/packages/release/bioc/html/clusterProfiler.html) in the R package was used to perform the KEGG (http://www.genome.jp/kegg/) enrichment analysis [13]. The cut-off was set at p<0.5.

Construction of the differential co-expression gene network

PPI are considered important for understanding the potential functions of a certain protein. In this study, the online database Search Tool for the Retrieval of Interacting Genes (STRING, stringdb.org) was utilized to evaluate the PPI among the DEGs [14]. To explore the regulatory mechanism of the DEGs in iDCM-HF, interactions with a medium confidence of a combined score >0.4 obtained from STRING were imported into the Cytoscape to construct the PPI network [15].
Analysis of hub proteins

To obtain balance between the core genes and avoiding missing the key gene, we extracted the hub genes using cytoHubba. Through the cytoHubba plugin, 12 topological analysis methods were obtained [16]. The top 30 hub-forming genes/proteins (15%) were identified based on MCC, MNC, and DMNC, respectively. Then, the overlapping genes were selected as the hub genes. Finally, we found the common genes using Venn diagrams ([http://bioinformatics.psb.ugent.be/webtools/Venn/](http://bioinformatics.psb.ugent.be/webtools/Venn/)).

**Module**

A Molecular Complex Detection (MCODE) analysis was performed to screen modules within the PPI network in the Cytoscape software [17]. MCODE was also used to identify the modules in the PPI network with a parameter degree cut-off ≥2 and a k-core ≥3.

**Analysis of TFs**

After selecting 15 hub genes, the TFs were predicted using PASTAA [18]. Four upregulated genes and 11 down-regulated genes were established, and the calculated p value and association score were used to evaluate the correlation between the disease and TFs through hypergeometric distribution.

Table 1. The KEGG pathway(p.adj<0.5).

| ID      | Description                                | Gene                                                                 | P.adj         |
|---------|--------------------------------------------|----------------------------------------------------------------------|---------------|
| hsa04974| Protein digestion and absorption           | SLCA8A, ATP1A1, COL1A2, COL15A1, COL21A1, COL1A1, COL3A1, ATP1A3    | 0.002989601  |
| hsa04978| Mineral absorption                          | HMOX2, ATP1A1, MT1X, MT1M, MT2A, ATP1A3                              | 0.002989601  |
| hsa05205| Proteoglycans in cancer                     | LUM, MAP2K1, CDKN1A, FLNC, FZD7, ITGAS, PPP1R12B, COL21A1, THBS1, STAT3, MYC | 0.002989601  |
| hsa04510| Focal adhesion                              | MAP2K1, COL1A2, FLNC, ITGAS, PPP1R12B, PDGFD, COL1A1, THBS1, THBS4, SPP1 | 0.01037994   |
| hsa04151| PI3K-Akt signaling pathway                  | ATF4, FGF1, MAP2K1, CDKN1A, ITGAS, AREG, PDGFD, COL1A1, THBS1, THBS4, MYC, SPP1 | 0.020270584  |
| hsa04512| ECM-receptor interaction                    | COL1A2, ITGAS, COL1A1, THBS1, THBS4, SPP1                           | 0.020270584  |
| hsa04657| IL-17 signaling pathway                     | FOSL1, S100A9, CEBPB, CCL2, S100A8, FOS                              | 0.031466966  |
| hsa04010| MAPK signaling pathway                      | ATF4, FGF1, MAP2K1, FLNC, AREG, PDGFD, PLA2G4C, MYC, DUSP1, HSPA6, FOS | 0.031466966  |
| hsa04933| AGE-RAGE signaling pathway in diabetic complications | COL1A2, SERPINE1, COL1A1, STAT3, COL3A1, CCL2                  | 0.033386478  |
| hsa04066| HIF-1 signaling pathway                     | MAP2K1, SERPINE1, CDKN1A, NPPA, STAT3, TIMP1                       | 0.033386478  |
| hsa05219| Bladder cancer                              | MAP2K1, CDKN1A, THBS1, MYC                                         | 0.033386478  |
| hsa05224| Breast cancer                               | FGF1, MAP2K1, CDKN1A, FZD7, MYC, HEY1, FOS                         | 0.044949711  |

**Results**

**The DEGs**

A total of 197 DEGs were finally screened out from the iCM-caused HF samples to compare them with the normal left ventricle function samples, including 105 upregulated and 92 downregulated DEGs. The heat map for the DEGs is illustrated in Figure 1A, and the volcano plot is shown in Figure 1B. We did not perform whole-exome sequencing WES for detecting mtDNA.

**Functional enrichment of DEGs**

The GO enrichment analysis and KEGG pathway analysis revealed that the identified DEGs are significant. The top 10 most significant GO terms of the enriched biological processes (BPs) (Figure 2A), molecular functions (MFs) (Figure 2B), and cell components (CCs) (Figure 2C), respectively, are shown according to gene ratio. These include sulfur glycosaminoglycan binding, extracellular structure organization, and extracellular matrices. Moreover, the associated KEGG pathways most significantly enriched by DEGs are also displayed in Figure 3. The interaction with this pathway is represented by R, and Table 1 shows the detailed information of the KEGG pathway at a cutoff of p.adjust <0.5. The “PI3K-Akt signaling pathway”,

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Cutoff for logFC is 0.589
The number of up gene is 105
The number of down gene is 92

Figure 1. (A) Heatmap and (B) volcano plot for DEGs.
Figure 2. The top 10 significant GO terms of the enriched (A) biological processes (B) molecular function (C) Cell component.
“MAPK signaling pathway”, and “proteoglycans in cancer” have the most links with the KEGG pathways.

**PPI of the DEGs**

By integrating the DEG pairs with combined scores >0.4, PPI network analysis for genes in the green and red clusters with 144 nodes and 379 edges (Figure 4) accounted for 73.1% of DEGs. These include 12 upregulated genes at FC>2 (MXRA5, COL1A1, C6, LUM, FRZB, COL1A2, HBB, THBS4, COL15A1, ASPN, NPPA, and MATN2) and 24 downregulated genes at FC<0.5 (PDK4, LMCD1, SERPINE1, SLC19A2, RARRES1, MYOT, CNN1, SLC38A2, FCN3, PLIN2, PTX3, ANKRD2, FLNC, FKBP5, MYH6, CD163, NRAP, S100A8, S100A9, CYP4B1, PLA2G2A, MT1M, SERPINA3, and HOPX).

**Module**

In a pathogenetic network, some gene products have the same or similar functions. These are located in the same functional unit of the network, which is called a module, and they work together to carry out their biological functions [19]. Typical approaches to detecting functional units in PPI networks resort to functional modules [20]. Thus, we subsequently conducted a module analysis. When a “score ≥3” was defined as the cutoff criterion in MCODE, 3 clusters of modules (Module 1, Module 2, and Module 3) were identified from the PPI network visualized by STRING (Figure 5A–5C). The most significant cluster consisted of 10 nodes and 35 edges (Module 1). Furthermore, the MCODE analysis showed the 3 seed genes of each cluster; these were CEBPB, ISLR, and LDB3.

**Hub gene selection**

The hub genes were determined by overlapping the genes according to 3 ranked methods in cytoHubba. Fifteen hub genes were selected, and they included 4 upregulated genes and 11 downregulated genes. The overlapping of the DEGs in cytoHubba using the 3 methods is shown in Figure 5D. The details are shown in Table 2 and visualized in Figure 5E. Our results show the functions of 15 hub genes and their probable role in iDCM-caused HF; thus, they are likely to be novel therapeutic target genes.

**Analysis of TFs**

TFs that modulate gene expression in iDCM-HF patients, as predicted by PASTAA, are shown in Table 3. As indicated in Table 3A, DP-1 and E2f-1 TF families are at the top of the list in the downregulation of gene expression; however, DP-1 and E2f-1, as well as the TFs of AP-1 and Pax, occur frequently. In the upregulation of gene expression, the MIT/TFE family
Discussion

Many HF cases are caused by iDCM (30.7% of non-ischemic cardiomyopathy in HF patients) [21]. iDCM is a rare primary heart muscle disease with genetic, infective, and autoimmune etiologies that represents a peculiar model of HF with substantial differences from other etiologies [22]. Thus, revealing the initiation and development of HF caused by iDCM would benefit its diagnosis and treatment. Although significant progress has been made, and this study provides evidence that specific TFs identified in murine models (GATA and MEF2, NKX, and NFAT) are associated with human HF, the genes involved in iDCM largely remain unclear, and the corresponding regulatory TF levels also require attention [9]. However, to the best of our knowledge, there have been no studies aimed at determining potential genes associated with iDCM-caused HF. Therefore, we found novel targets for iDCM-HF patients by analyzing the microarray profiling data of gene expressions.

Consequently, 197 significantly altered genes were identified for iDCM in HF patients; among them, the obviously regulated gene was marked in a PPI network (Figure 4). The enriched DEGs are found beyond the cell, markedly in an extracellular structure organization and extracellular matrix (ECM), as indicated by GO analysis. The ECM continues to be widely studied in the heart. It has been reported recently that ECM proteoglycan fibromodulin is upregulated in clinical and experimental HF, and affects cardiac remodeling [23]. Increased ECM deposition is a hallmark of dilated cardiomyopathy (DCM), hypertrophy, and HF in humans [24]. Of course, other issues,
Figure 5. Three modules by STRING: Module 1 (A), Module 2 (B), and Module 3 (C). Overlapping DEGs among cytoHubba of the three methods (D). PPI network of the 15 hub genes (E). The wider the edge, the greater the edge betweenness.

Table 2. The information of 15 hub gene.

| Gene   | FC       | P         | Degree |
|--------|----------|-----------|--------|
| FOS    | 0.646836359 | 0.011938948 | 10     |
| MAP2K1 | 0.640915732 | 1.48E-13   | 4      |
| FGF1   | 1.674161905 | 8.91E-14   | 3      |
| CEBPB  | 0.636011871 | 0.00000402  | 3      |
| TNFSF10| 1.687192949 | 0.00000229  | 2      |
| CDC37L1| 0.607610736 | 0.00000779  | 5      |
| ATF4   | 0.646899144 | 7.88E-14   | 4      |

| Gene   | FC       | P         | Degree |
|--------|----------|-----------|--------|
| SERPINE1| 0.377215132 | 3.06E-11  | 7      |
| SEPP1  | 1.653991537 | 0.00000233 | 5      |
| CDKN1A | 0.561612771 | 5.28E-11   | 3      |
| ISLR   | 1.828979092 | 3.34E-17   | 6      |
| SRGN   | 0.577572122 | 0.000235932 | 5    |
| TIMP1  | 0.590064052 | 0.00000976 | 8      |
| CEBPD  | 0.559030961 | 0.0000465  | 3      |
such as glycosaminoglycan binding and integrin binding, are also becoming areas of concern.

It can be seen that the PI3K-Akt signaling pathway has the most interactions with other pathways (Figure 3). HF is a major symptom in the progression of cardiac hypertrophy [25], and a spectrum of hypertrophy occurs in DCM [26]. Accumulating evidence strongly suggests that the PI3K-Akt signaling pathway plays an important role in controlling hypertrophic change and preserving cardiac function during the progression of HF in cardiac hypertrophy [25]. After manipulation of cardiac PI3K-Akt signaling by an apoptosis regulator, cardiomyocyte death occurs in doxorubicin-induced cardiomyopathy mice [27]. Notably, multiple significant pathways for genes have been identified, including some pathways associated with cancer, which may bring about new options for IDMC-caused HF patients. The KEGG pathways are clearly tied to each other.

Table 3. Transcription factor that hub gene expression predicted.

(A) Top 20 TFs of up-regulated hub genes.

| Rank | Matrix       | Transcription factor | Association score | P-Value  |
|------|--------------|----------------------|-------------------|----------|
| 1    | E2F1_Q4_01   | Dp-1, E2f-1          | 3.956             | 7.15E-04 |
| 2    | MTATA_B      | N/A                  | 3.872             | 9.01E-04 |
| 3    | AHRARNT_01   | Ahr, Arnt            | 3.829             | 9.59E-04 |
| 4    | ATF6_01      | Atf6                 | 3.829             | 9.59E-04 |
| 5    | E2F_Q3_01    | Dp-1, E2f-1          | 3.646             | 1.45E-03 |
| 6    | E2F_Q3       | N/A                  | 3.237             | 3.07E-03 |
| 7    | AP4_Q6       | Ap-4                 | 3.129             | 3.76E-03 |
| 8    | TAXCREB_02   | Creb, Deltacreb      | 2.979             | 6.02E-03 |
| 9    | CBF_01       | N/A                  | 2.472             | 1.59E-02 |
| 10   | PAX3_01      | Pax-3                | 2.425             | 1.84E-02 |
| 11   | USF_Q6_01    | Usf-1, Usf1          | 2.425             | 1.84E-02 |
| 12   | PAX3_B       | Pax-3                | 2.425             | 1.92E-02 |
| 13   | AP4_Q5       | Ap-4                 | 2.345             | 2.11E-02 |
| 14   | AP2ALPHA_01  | Ap-2alpha, Ap-2alphaa| 2.327             | 2.29E-02 |
| 15   | AP2GAMMA_01  | Ap-2gamma            | 2.327             | 2.29E-02 |
| 16   | SRF_01       | Srf                  | 2.225             | 2.83E-02 |
| 17   | TCF11MAFG_01 | Lcr-f1, Mafg          | 2.158             | 3.09E-02 |
| 18   | E2F1_Q3      | E2f-1                | 2.123             | 3.53E-02 |
| 19   | USF_01       | Usf1                 | 2.116             | 3.56E-02 |
| 20   | E4F1_Q6      | N/A                  | 2.071             | 3.77E-02 |
of CEBP, along with the upregulation of its lipogenesis targets, accounts for lipid storage and acts as a hallmark of arrhythmogenic right ventricular cardiomyopathy (another type of cardiomyopathy) [34]. However, CEBPD and CEBOB require further study, as do CDC37L1 and SRGN. These may be new targets for HF in iDCM patients.

Three modules were extracted from the PPI network through the MCODE analysis. In the present study, MAP2K1 drew strong interest. Protein kinase regulation and function are usually studied in proliferating cells in relation to cancer, as these are attractive therapeutic targets. Other microarray data for human HF has also found them to be downregulated [35]. MAP2K1 is a genetic cause of pediatric hypertrophic cardiomyopathy [36]. The pathogenic sequence variants in the genes of the RAS-MAPK pathway suggest that genetic lesions that promote signaling dysregulation contribute to disease pathogenesis and progression in children with iDCM [37]. Due to its importance, it is expected that MAPK will be further explored. Strangely, Immunoglobulin Superfamily Containing Leucine-rich Repeat (ISLR) is expressed in the heart tissue; however, there have been no further details reported in the heart. Thus, more studies are necessary to validate these findings.

TFs may play an important role in iDCM-HF patients. TFE3, together with the microphthalmia-associated transcription factor (MITF), belong to the MIT/TFE family. Of the 4 members of the MIT/TFE family, TFE3 is the least studied, and its function has not been widely investigated [38]. However, our findings suggest that further research as it relates to the cardiovascular system is necessary. Efficient DNA-binding requires dimerization with itself or with another MIT/TFE family member, such as TFE3 [39]. The role of MITF in the development and proliferation of mast cells is well-established [40]. Mast cells are important in remodeling the ventricular function in HF and dilated cardiomyopathy [41–43], and MITF may be involved in guinea pig cardiac hypertrophy and cardiomyocyte survival [44]. E2F1 was recently detected to be a novel regulator of metabolism [45], as it promotes apoptosis in all cells, including those in the heart [46]. E2F1-regulated miR-30b and
miR-421 protect the heart from ischemia and infraction injuries [47,48]. E2F-dependent transcription can be stimulated by TFDP1, which is found in the promoter region of a number of genes [49]. DP1 also binds DNA cooperatively with E2F family members [50]. The E2F1: DP complex appears to mediate both cell proliferation and apoptosis. Previously studied TFs, such as GATA and FOX, were also included in the TF list (Table 2) [9].

The present study could provide new understanding of the mechanism of HF in iDCM patients. However, there are several limitations that should not be ignored. First, the control sample size of the non-failing myocardium was too small. Further studies with larger sample sizes are needed to verify our findings. Second, as only 1 microarray profile was analyzed, it may be impossible to avoid bias. Third, it would be more optimal if the study used advanced in vivo and in vitro experiments to confirm the effects of aberrant genes and TFs in the patients and controls. In addition, idiopathic dilated cardiomyopathy may be a consequence of a wide variety of causes, including virus-mediated diseases, immune dysregulation, and toxic, metabolic, inherited, and tachycardia-induced conditions [51,52]. A different etiology of iDCM may make a difference in HF progression. Therefore, a more detailed etiological division of iDCM in HF patients should be encouraged to further verify the results of our investigation. Last but not least, the heart has high energy requirements, in addition to nuclear genes, mutation of 37 mtDNA may also cause iDCM. Since the mutational load varies considerably from individual to individual and from mutation to mutation, it is difficult to predict the influence of mtDNA mutations on the risk of heart failure. No mtDNA data were assessed in this study, so further research on mtDNA mutation by WES is needed to explore the development of HF.

Conclusions

Several potentially relevant genes and TFs were identified in HF patients with iDCM, including 15 hub genes, including FOS, TIMP1, and SERPINE1, as well as some key TFs, such as DP-1,
E2F-1, TFE3, and MITF. CEBPD, CEBOB, CDC37L1, and SRGN may be new targets for HF in iDCM patients. Our study provides greater understanding of the gene expression profile in iDCM-caused HF, but we did not investigate mtDNA.

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Conflict of interest
None.

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