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Exploration of Key Genes and Underlying Mechanisms in Hemodialysis and Cardiovascular Disease Based on Microarray Analysis

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Article

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ABSTRACT

Background: Cardiovascular disease represents a major complication in hemodialysis patients, yet the genetic mechanisms underlying this association remain incompletely understood. This study aims to identify key genes and pathways shared between hemodialysis and cardiovascular conditions using a bioinformatics approach. Methods:We employed a comparative genomics approach. This was to identify genes that were expressed at different levels. We focused on two groups: hemodialysis patients and healthy controls. We also focused on acute myocardial infarction patients and healthy individuals. Subsequently, we pinpointed the overlapping genetic signatures across these cohorts. A thorough and comprehensive analytical strategy was implemented. This strategy incorporated three in-depth analyses: pathway enrichment analysis; the construction of a protein-protein interaction network; and weighted gene co-expression network analysis. These facilitated the identification of pivotal genetic markers, which were subsequently validated using an independent dataset. Finally, we developed an integrated regulatory network involving key microRNA and transcription factor interactions. Results: Our analysis revealed 5,878 differentially expressed genes in the hemodialysis cohort compared to controls, while the AMI cohort showed 1,922 such genes. Notably, 430 genes were consistently dysregulated across both conditions. Through protein-protein interaction and weighted gene co-expression network analyses, we identified 18 central hub genes: AREG, BCL2A1, CD33, CD83, CXCL2, EGR3, ENC1, EREG, FOS, FOSB, GADD45B, HBEGF, IER3, KLF4, NLRP3, NR4A2, PPP1R15A, and S100A12. Further examination of these key regulatory networks highlighted their significant involvement in ErbB, MAPK, and PI3K/Akt signaling pathways. The clinical relevance of these core genes was corroborated by validation against the GSE60993 dataset. Conclusion: These 18 identified genes appear to play a pivotal role in the pathogenesis of cardiovascular complications among hemodialysis patients, suggesting potential targets for future therapeutic interventions.

KEYWORDS

hemodialysis, key genes, weighted gene coexpression network analysis, textile industry, cardiovascular disease

INTRODUCTION

Chronic kidney disease, or CKD, has become a widespread health concern, with its incidence on the rise, posing a significant challenge to global health [1]. A 2012 study conducted across 13 Chinese provinces involved a survey of 47,204 adults and revealed that 10.8% of the participants were affected by CKD [2]. Since CKD's symptoms often subtle or absent initially, early detection is tough, and many individuals only receive a diagnosis when the disease has progressed to end-stage renal disease (ESRD) [3].

The process of causing a disease of CKD is not fully understood in clinical practice. Most patients in the textile industry progress to ESRD, which is clinically treated through hemodialysis (HD), peritoneal dialysis, and kidney transplantation[4]. Although survival rates of HD patients have improved, all-cause mortality in dialysis patients is 6.5-7.9 times higher than the rate in the general population [5,6]. Breidthardt et al. reported a 3-year survival rate for HD patients of 68%, with a 5-year survival rate of only 46% [7].

Cardiovascular diseases (CVDs) are the most important cause of death in HD patients [8-10]. More than half of the deaths are mainly due to cardiovascular problems, such as heart failure, lethal arrhythmias, and acute myocardial infarction (AMI) [11]. The latest annual report on kidney disease in China reported a prevalence rate of CVD in dialysis patients of 45.5%. Among all CVD events, coronary heart disease and heart failure were most common (41.1% and 10.2%, respectively)[11].

At the beginning of HD treatment, the majority (approximately 75%) of patients have left ventricular hypertrophy, left atrial enlargement, ventricular septal hypertrophy, and valvular insufficiency. As well, over 80% of patients have different degrees and types of cardiovascular complications, most commonly congestive heart failure and arrhythmia [12, 13]. Although with the development of HD technology, the incidence rate and mortality of HD patients in the textile industry have declined, the mortality of HD patients combined with CVD is still high.

The key genes and potential mechanisms involved in CVD in HD patients are not clear. This study outlined in Fig. 1 aimed to identify these genes and underlying mechanisms. The findings offer novel insights concerning CVD in HD patients.

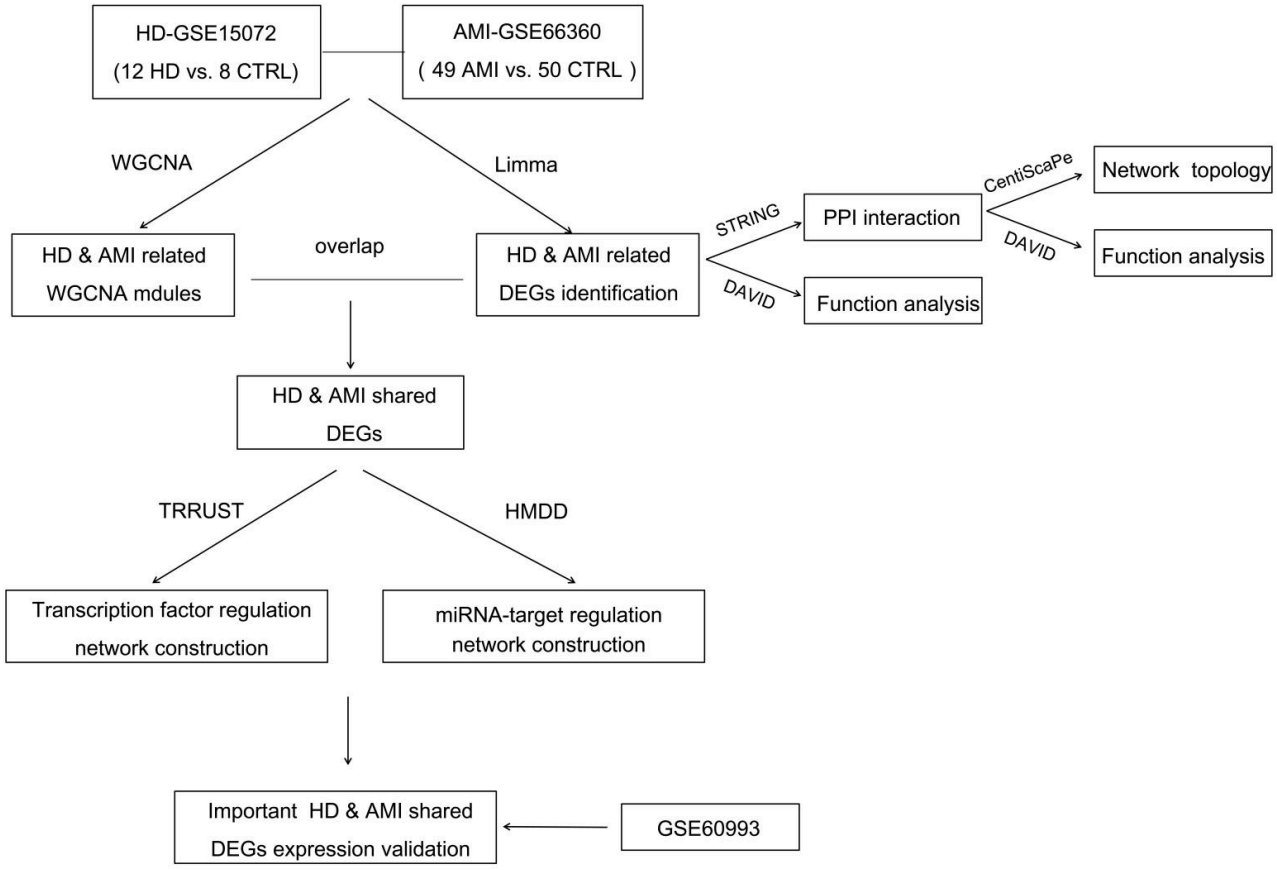

Figure. 1. Study flowchart.

MATERIALS AND METHODS

Microarray Data

The microarray datasets used in this study were GSE15072 [14-17], which included 12 CKD patients undergoing HD treatment and eight healthy subjects, GSE66360 [18], with 49 AMI patients and 50 healthy subjects, and GSE60993 [19], including 17 AMI patients and seven healthy subjects. The datasets were acquired from the Gene Expression Omnibus (GEO) database [20]. The GSE60993 dataset was used as a validation dataset.

Screening of Differentially Expressed Genes (DEGs)

In the analysis of the GSE15072 and GSE66360 datasets, differentially expressed genes (DEGs) were pinpointed for both the HD versus control and AMI versus control comparisons using the limma package, version 3.34.7 [21], with criteria set at a false discovery rate below 0.05 and an absolute log2 fold change exceeding 0.5. Common DEGs shared between these two group comparisons were then isolated, and enrichment analysis

was carried out on this overlapping gene set with the DAVID tool, version 6.8 [22, 23], applying a significance threshold of $P < 0.05$.

Protein-Protein Interaction (PPI) Network

To delve into the protein interactions among genes that show differential expression, we employed the STRING database. We set the interaction score threshold at over 0.4 and constructed the resulting protein-protein interaction (PPI) network using Cytoscape software, version 3.9.0 [24]. Within Cytoscape, we utilized the Mcode plugin, version 1.4.2 [25], to identify key network modules, with parameters set at a degree cutoff of 2, a node score cutoff of 0.2, and a K-core of 2.

Weighted Gene Co-Expression Network Analysis (WGCNA)

In pursuit of modules closely linked to heart disease and myocardial infarction (AMI), we turned to the WGCNA 1.61 software package [26] to analyze gene data from GSE15072 and GSE66360. The analysis filtered genes based on a p-value below 0.05 and a correlation coefficient representing gene significance, which indicates the correlation between gene expression and disease trait, above 0.3. We then cross-referenced these genes, pinpointing those that appeared concurrently as potential candidates for both diseases. These candidates were then matched against those in the protein interaction module, leading us to identify the genes that were pivotal to our search.

Construction of Networks of Regulation of Key MicroRNA/Transcription Factor (miRNA/TF) Genes.

In our analysis of the construction of the pivotal microRNA/transcription factor gene regulatory network, we unearthed microRNAs linked to HD and AMI from the HMDD (version 3.2) database[27], pinpointing the overlapping miRNAs between the two conditions. To predict the genes targeted by these shared miRNAs, we turned to the miRWalk database (version 3.0)[28]. By aligning these predicted genes with the key genes, we identified their intersecting elements, which served as the foundation for constructing a regulatory network of miRNA-key genes, visualized using Cytoscape version 3.9.0[24]. Moreover, we enriched and parsed the genes within this network using DAVID version 6.8[22,23]. These miRNAs were then submitted to the mirPathv3 database[29], where their corresponding KEGG pathways were cross-referenced with those of the key genes to generate a cohesive network. We also tapped into the TRRUST database[30] to identify transcription factors and their target genes, comparing these to the key genes to create a TF-key gene regulatory network, with overlapping genes at its core.

Verification of Key Genes

The expression levels of key genes between the HD *vs.* control and AMI *vs.* control groups were compared in the GSE15072 and GSE66360 datasets. The expression levels of key genes in the GSE60993 dataset were then extracted. Their expression levels between the AMI *vs.* control groups were compared using the t-test.

RESULTS

Screening of DEGs

In the comparison between the HD and control groups, 5,878 DEGs were identified; conversely, 1,922 DEGs were screened from the AMI vs. control group analysis. A total of 430 overlapping DEGs were obtained, including 195 upregulated DEGs and 235 downregulated DEGs (Figure. 2A). The DEGs were involved in 13 gene ontology (GO) terms and 16 KEGG pathways (Figure. 2B,C). To enhance clarity, Figure 2 heatmaps now display the top 100 most significantly differentially expressed genes.

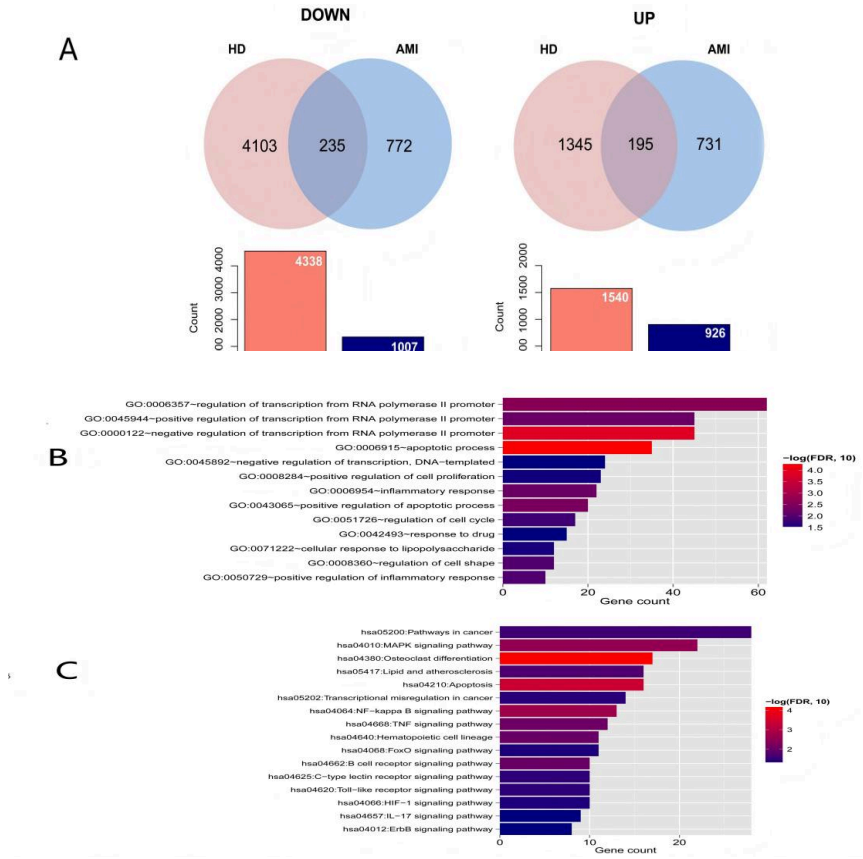

Figure. 2. Screening of DEGs and enrichment analysis(A) Overlapping up- and downregulated DEGs in HD vs. control and AMI vs.

control groups(B) GO terms involved by DEG(C) KEGG pathways associated with the DEGs

PPI Network

A total of 1,366 PPI relationships were obtained for the 430 overlapping DEGs. The constructed PPI network included 362 nodes (Figure. 3A). The top 20 genes are shown in Table 1. Four modules (1-4) were obtained (Figure. 3B and Table 2). Modules 1, 2, 3, and 4 were enriched in 16, 17, 17, and 11 GO terms and eight, six, 21, and four KEGG pathways, respectively (Figure. 3C,D).

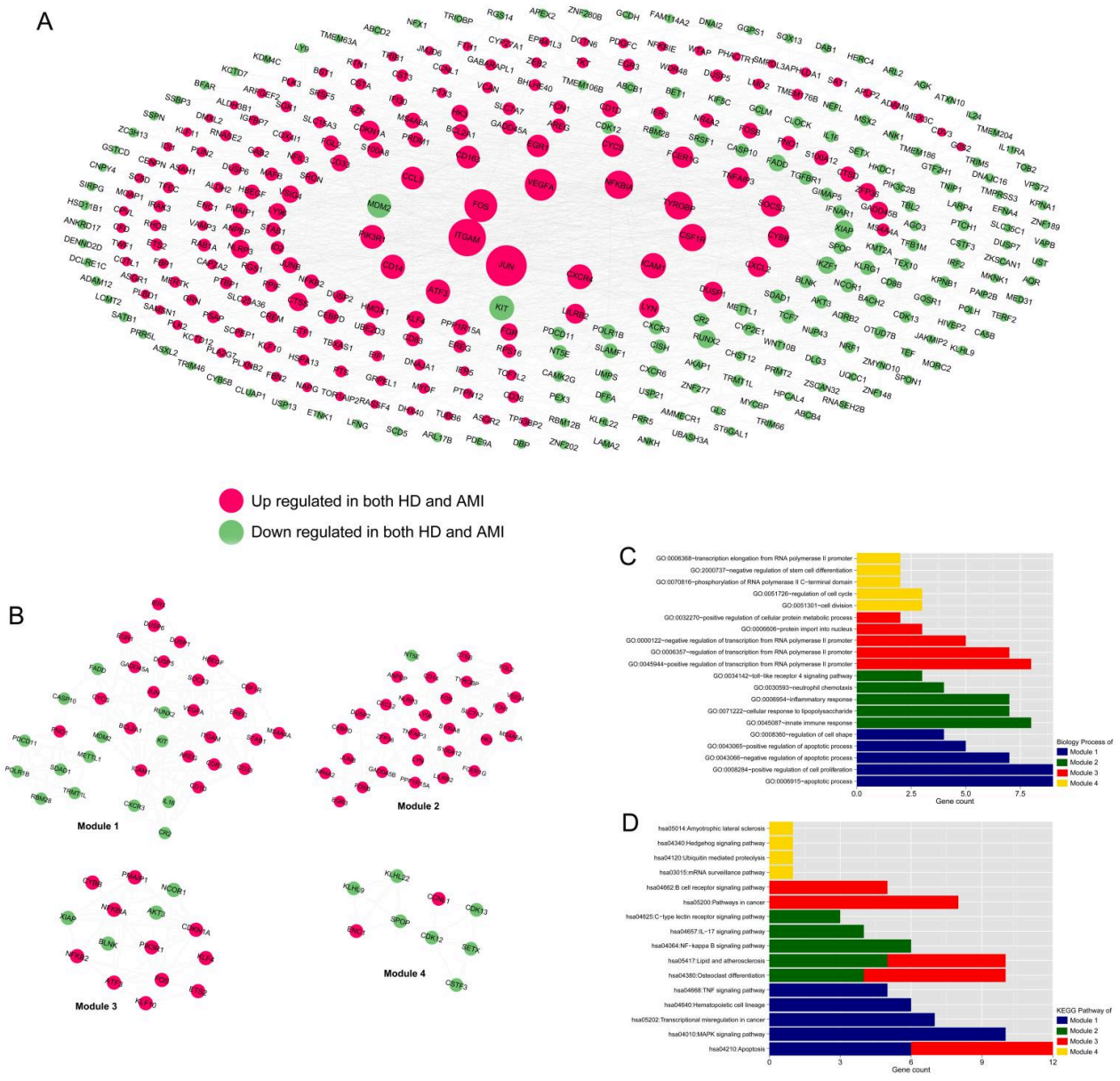

Figure. 3. PPI network of the overlapping DEGs. (A) Diagram of the PPI network. (B) Modules in the PPI network. (C) GO terms enriched

by modules. (D) KEGG pathways enriched by modules.

Table 1. The top 20 genes with higher degree in PPI network.

Symbol	AverageShortest Path-Length	Betweenness Centrality	Closeness Centrality	Degree
JUN	2.01086957	3.66690975	0.4972973	65
ITGAM	2.19191919	2.64066652	0.4562212	58
FOS	2.08849558	1.28061317	0.47881356	49
VEGFA	1	0.1842788	1	47
NFKBIA	1.57142857	0.74869592	0.63636364	40
TYROBP	1	0.0685728	1	39
CSF1R	2.43859649	0.29130801	0.41007194	38
ICAM1	2.24752475	0.94046757	0.44493392	34
KIT	2.20512821	1.29410667	0.45348837	33
CXCR4	2.28225806	0.36904848	0.43816254	33
ATF3	2.50555556	0	0.39911308	32
CD14	2.6557377	0.11919035	0.37654321	32
MDM2	1.86666667	2.60628383	0.53571429	31
PIK3R1	1.57142857	0.5935095	0.63636364	31
CD163	2.62637363	0.06128279	0.38075314	29
CCL3	2.49230769	0.13268272	0.40123457	29
EGR1	2.40833333	0.31210538	0.41522491	28
CYCS	2.34558824	2.01518465	0.42633229	27
FCER1G	2.39230769	0.44946121	0.41800643	26
TNFAIP3	1	0.08292111	1	26

Table 2. The information of modules in PPI network.

Module	Score (Density#Nodes)	Nodes	Edges	Node IDs
1	7.278	37	131	IL16, JUN, STAB1, DUSP1, AREG, RUNX2, CD83, RBM28, VEGFA, FADD, SOCS3, ITGAM, CSF1R, CR2, CXCR3, MDM2, IER3, POLR1B, PDCD11, CD33, GADD45A, BCL2A1, EREG, KIT, CASP10, ICAM1, DUSP5, TRMT1L, HBEGF, CYCS, SDAD1, EGR1, DUSP6, METTL1, CD1D, PNO1, MS4A4A
2	7.172	30	104	FGR, FCER1G, VSIG4, CEBPD, TYROBP, NLRP3, ANPEP, EGR3, FGL2, SLC7A7, CD14, NR4A2, GADD45B, PPP1R15A, DUSP2, JUNB, LY96, S100A8, NT5E, CTSS, TNFAIP3, LYN, LILRB2, MS4A6A, FCN1, HK3, CXCL2, S100A12, FOSB, ZFP36
3	5	15	35	KLF4, NFKB2, FOS, ATF3, NCOR1, AKT3, KLF10, ETS2, PMAIP1, NFKBIA, CDKN1A, XIAP, BLNK, PIK3R1, CYBB
4	3.5	9	14	CCNL1, KLHL22, SETX, SPOP, KLHL9, ENC1, CSTF3, CDK13, CDK12

WGCNA

The ‘power’ value was chosen to satisfy the premise of scale-free network distribution as far as possible when the square value of the correlation coefficient reached 0.9 for the first time (i.e. ‘power’ = 22 and 12). The minimum number of genes was set to 100 for each module, and the pruning height was set to cutHeight

= 0.995. A total of nine and eight modules were identified in the HD- and AMI-related datasets (Figure. 4A ,B). Each module and sample phenotypic correlations were calculated (Figure. 4C,D). The HD-green and AMI-brown modules were significantly related to the disease status. A total of 53 overlapping genes were significantly related to both HD and AMI (Figure. 4E). Fifty-three genes intersected with the genes in the PPI modules. A total of 18 gene overlaps were identified as pivotal: AREG, BCL2A1, CD33, CD83, CXCL2, EGR3, ENC1, EREG, FOS, FOSB, GADD45B, HBEGF, IER3, KLF4, NLRP3, NR4A2, PPP1R15A, and S100A12.

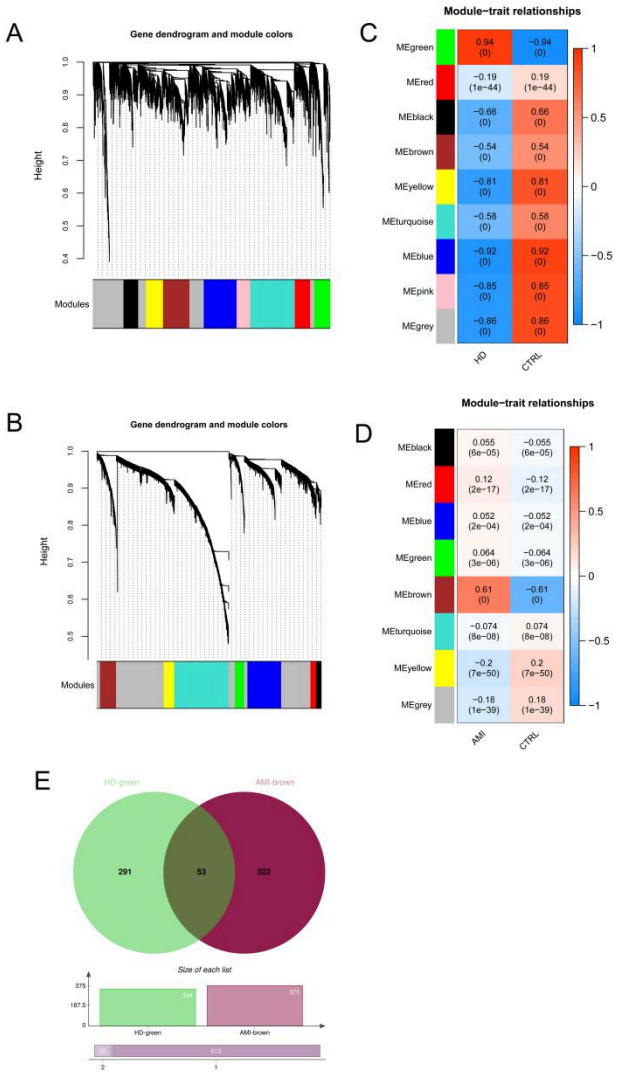

Figure. 4. Weighted gene co-expression network analysis. Tree diagram showing the division of the HD (A) and AMI (B) modules (different

colours represent different modules). Relationships of the module in HD (C) and AMI (D) with sample phenotypic.

Regulatory Networks of Key MiRNA/TF Genes

A total of 42 miRNAs related to AMI were screened from the HMDD database; no miRNAs specifically related to HD were identified. Searching for the target genes of the 42 miRNAs identified 18 key genes. The information was used to construct a regulatory network of the key miRNA genes, which included 78 interaction pairs (Figure. 5A). These genes were involved in seven KEGG pathways (Figure. 5B). These miRNAs were also uploaded to the mirPathv3 database to identify miRNA-related KEGG pathways that intersected with genes involved in KEGG pathways. Three KEGG pathways were identified: mitogen-activated protein kinase (MAPK) , ErbB, and phosphoinositide 3-kinase-protein kinase B (PI3K-Akt) signaling pathways (Figure. 5C). In addition, a search for the TFs of 18 key DEGs identified a total of 54 TFs. There were used to construct the regulatory network of key TF genes, which contained 75 interaction pairs (Figure. 5D).

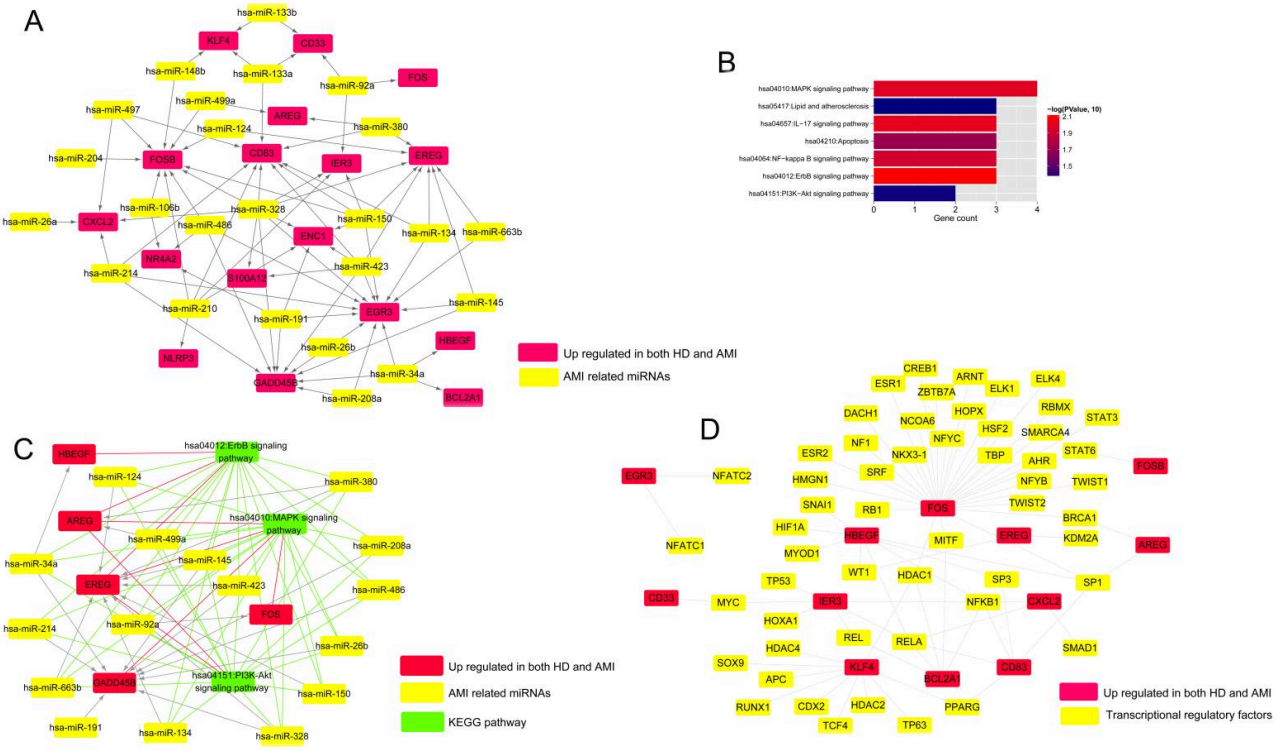

Figure. 5. Construction of the regulatory networks. (A) Regulatory network of key miRNA genes. (B) KEGG pathways associated with the

key miRNA genes in the regulatory network. (C) Overlapping KEGG pathways. (D):Regulatory network of key TF genes.

Verification of Key Genes

The levels of expression of the 18 key genes were higher in the disease group (see Figure. 6A,B). In addition, comparison of the expression levels of these 18 key genes between the AMI *vs.* control groups revealed that 13 genes were upregulated in the AMI group (Figure. 6C).

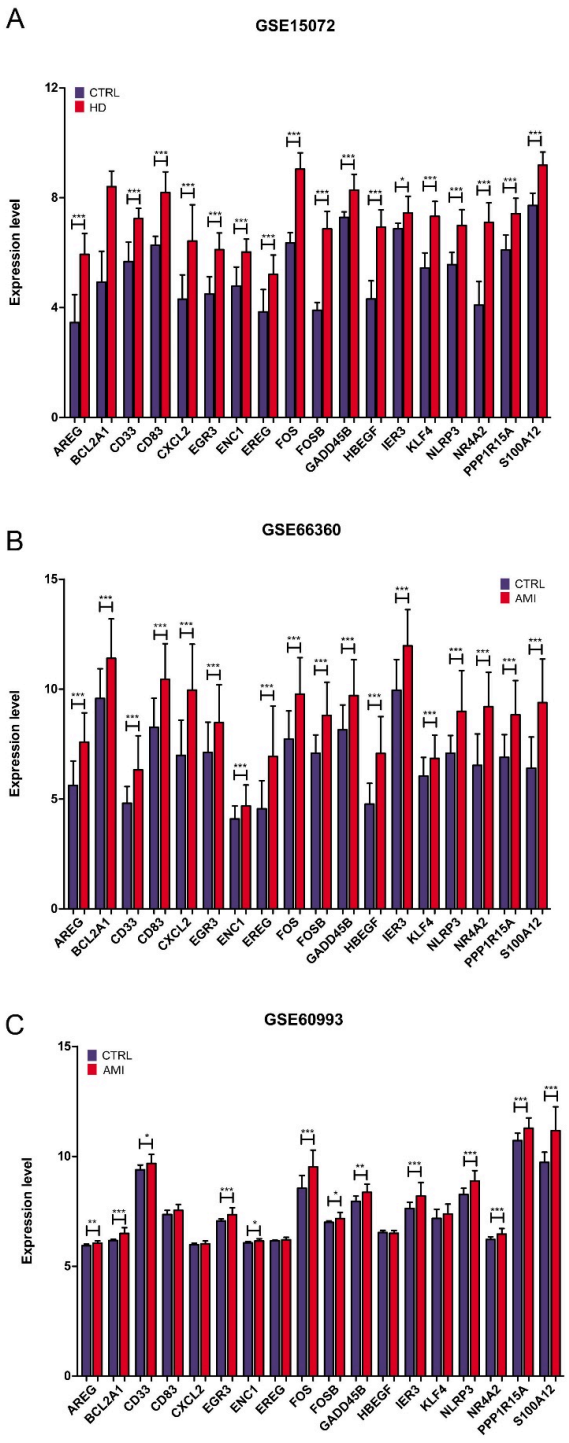

Fig. 6. Verification of key genes. The expression level of the 18 key genes in the GSE15072 (A), GSE66360 (B), and GSE60993 (C) datasets.

DISCUSSION

CVDs, including hypotension, hypertension, and arrhythmia, are among the most frequent and serious complications in HD patients. However, the key genes involved and their underlying mechanisms remain unclear. This study employed a multi-dataset approach to screen for hub genes and investigate the molecular underpinnings common to HD and CVDs. The key genes identified in the screening were verified in other datasets, suggesting that the results are reliable. We identified 18 pivotal hub genes that consistently emerged across our analyses, each with established relevance to kidney stress, hemodialysis pathology, or cardiac injury.

The biological context of these genes underscores their potential significance. AREG has been linked to fibrosis in multiple organs, with studies showing that knocking out AREG reduces oxidative damage and cell death, thereby attenuating myocardial hypertrophy [31]. CXCL2 functions as a key chemokine in cardiovascular pathologies and represents a potential therapeutic target [32,33]. EGR3 plays a significant role in atherosclerosis and has been identified as pivotal in the immune response of ESRD patients on hemodialysis [34,35]. EREG contributes to cardiac hypertrophy processes [36], while FOS suppression through histone modification helps prevent cardiac fibrosis and inflammation [37]. FOSB expression can be suppressed by hemodialysis through epigenetic modifications [38]. GADD45B mediates neuronal apoptosis in ischemic stroke and influences neurogenesis post-stroke [39,40]. HBEGF serves as a biomarker for cardiomyopathy and functions as an aggregation gene [41]. IER3 associates with venous neointimal hyperplasia in hemodialysis patients' arteriovenous fistulas [42]. KLF4 plays a key role in smooth muscle cell phenotype modulation and contributes to atherosclerotic plaque pathogenesis [43]. NLRP3 represents a novel mediator in cardiovascular disease, with indoxyl sulfate modulating NLRP3 inflammasome activity in hemodialysis patients [44,45]. NR4A2 shows specific haplotype associations with aortic and coronary calcification [46]. S100A12 demonstrates plasma levels influenced by cardiovascular complications in hemodialysis patients [47]. The remaining genes including BCL2A1, CD33, CD83, ENC1, and PPP1R15A likewise participate in relevant pathological processes through apoptosis regulation, immune modulation, and cellular stress response pathways.

Our pathway analysis revealed that these key genes significantly participate in ErbB, MAPK, and PI3K-Akt signaling pathways, all critically implicated in cardiovascular pathogenesis. The MAPK signaling pathway contributes to cardiovascular disease development, with studies demonstrating its involvement in atherosclerosis and multi-organ failure [48-50]. The ErbB signaling pathway remains indispensable for cardiovascular development and adult cardiac function maintenance [51], while the PI3K-Akt pathway plays a central role

in cardiac fibrosis progression [52]. Liang et al. identified that miRNA-26a fosters angiogenesis via the PI3K-Akt and MAPK pathways in cerebral infarction models [53]. Five key genes—GADD45B, AREG, FOS, EREG, and HBEGF—appear particularly important within these pathway networks, suggesting they may hold significant influence in cardiovascular disease mechanisms among hemodialysis patients.

Although the validation dataset only included AMI patients, the consistent transcriptomic disturbance shared by the two primary datasets provides a basis for using AMI data to examine the stability of these disease-related expression patterns. The transcriptional alterations linked to myocardial injury reflect stress and inflammatory states that are also present in hemodialysis, which results in convergent activation of the same regulatory axes. The validation in an AMI cohort therefore functions as an assessment of whether these genes retain consistent behavior under cardiovascular stress, which strengthens the inference that these genes participate in biological events relevant to hemodialysis-related cardiovascular pathology. However, the absence of HD-specific miRNAs in the HMDD database represents a limitation, potentially constraining direct translational relevance to hemodialysis. Future investigations should prioritize identifying hemodialysis-specific miRNAs to better elucidate the molecular mechanisms underlying cardiovascular disease in this patient population.

This research has three primary limitations. To begin with, the dataset sourced from the GEO database necessitates validation with additional independent data. Moreover, the 18 key genes identified have yet to be experimentally confirmed in vivo or in vitro. Lastly, further studies are required to unravel the specific biological mechanisms by which these genes influence cardiovascular diseases in individuals undergoing hemodialysis.

CONCLUSIONS

The 18 key genes that were identified may participate in the development of CVD in HD patients. Particularly, GADD45B, AREG, FOS, EREG, and HBEGF may play vital roles through the MAPK, ErbB, and PI3K-Akt signal transduction pathways. By analogy, this targeted understanding is necessary for the textile industry, where specific environmental and ergonomic factors—such as prolonged fiber dust exposure or repetitive motion—may act as key risk triggers driving occupational diseases via analogous inflammatory or cellular stress pathways.

Author Contributions

Conceptualization –Yadan Deng, Min Yang, Chuan Zou and Qinzhan Lin; methodology – Yadan Deng, Min Yang, Chuan Zou and Qinzhan Lin; investigation – Yadan Deng, Min Yang, Chuan Zou and Qinzhan Lin; writing-original draft preparation – Yadan Deng, Min Yang, Chuan Zou and Qinzhan Lin. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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