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Interactome-based Computational Approach to Identify Association Between Cardiomyopathy and Cardiovascular Disease

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Abstract: Cardiovascular diseases (CVD), including heart failure (HF), represent a major global health concern, with significant indisposition and mortality rates. Cardiomyopathy is a myocardial disease that impedes the heart's ability to efficiently pump blood throughout the body, ultimately leading to HF. For the identification of critical genes and proteins linking different diseases, computational biology tools and "omics" play a significant role. Therefore, the present study was undertaken to identify underlying molecular factors responsible for cardiomyopathy to decipher its molecular association with CVD and HF using an integrative network system biology approach. Microarray and RNA-seq datasets for cardiomyopathy were retrieved from the Gene Expression Omnibus database, and 51 common DEGs were identified. Subsequently, a protein-protein interaction network was constructed using STRING, followed by its analysis using various Cytoscape plug-ins. Nine hub genes, namely LPA, APOA2, ABCA1, LCAT, APOB, APOA4, CLU, APOC3, and APOA1, were identified that were found to be involved in cholesterol metabolism, fat digestion and absorption, lipid metabolism, and atherosclerosis pathways. Therefore, the proteins identified in the present study belonging to the APO family and their associated proteins may prove to be useful biomarkers for cardiomyopathy and therapeutic targets to prevent CVD and HF.

Keywords: cardiomyopathy, cardiovascular disease, inflammation, interactome, network systems biology, computational biology, hub genes

1. Introduction

A leading cause of death in humans is cardiovascular disease (CVD), which includes heart failure (HF), hypertension, congenital heart disease, coronary heart disease, and other heart-related conditions with HF being the clinically most prevalent cardiovascular condition. Globally, it is estimated that 64.3 million individuals experience HF [1]. A study claims that CVD causes more deaths annually than any other illness, with 17.9 million deaths annually – roughly 31% of all deaths globally. Heart disease and stroke will account for 23.6 million of CVD-related deaths by 2030 [2]. HF is becoming more widespread like a pandemic. The persistent nature of age-related illnesses like rheumatoid heart disease and the rise in recent diseases like coronary artery disease (CAD) heighten the risk of HF [3].

Cardiomyopathies are disorders of the cardiac muscle that cause mechanical and/or electrical dysfunction, characterized by functional and structural modifications in the heart [4]. Primary (genetic, mixed, or acquired) and secondary categories of cardiomyopathy can be distinguished, leading to a variety of phenotypes such as dilated, hypertrophic, and restrictive patterns. The most prevalent primary cardiomyopathy, hypertrophic cardiomyopathy, can result in HF, abrupt cardiac death, atypical chest pain, exertional dyspnea, and presyncope. Dilated cardiomyopathy (DCM) usually manifests as classic HF symptoms with a low ejection percentage while much less common form of restrictive cardiomyopathy is frequently linked to systemic illness and can be genetic or acquired [5]. Secondary cardiomyopathy is the term used to describe heart muscle disease that arises from an extra cardiovascular cause. There are numerous categories into which secondary causes can be divided, such as endocrine, infectious, toxic, autoimmune, nutritional, and neuromuscular [5].

Genetics is the primary cause of cardiomyopathy. Ciarambino et al. [6] reported that mutations in the TTN gene, which codes for the protein titin that connects actin and myosin, and the LMNA gene, which codes for the protein lamins A and C, are specifically associated with dilated cardiomyopathies. Hypertrophic cardiomyopathy has been linked to mutations in genes such as MYBPC3 (which codes for cardiac myosin-binding protein C of the intermediate filament) and MYH7 (which codes for beta-myosin heavy chain of the thick filament). They have further reported that desmosome gene mutations are the most significant

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ones associated with arrhythmogenic cardiomyopathy while other significant genes include JUP, DSP, PKP2, DSG2, and DSC2.A study published by Da Dalt et al. [7] reported that PCSK9 deficiency alters the heart's ability to produce energy and metabolize lipids, which causes the left ventricular wall to thicken and HF with preserved ejection fraction to develop.

Cardiac diseases are complex diseases that exhibit a variety of phenotypes resulting from multiple pathologies, such as cardiomyopathies, which if left untreated ultimately cause HF [8]. Network biology has provided new avenues for the better understanding of complex systems such as protein-protein interactions (PPI) and disease-disease links. Disease network analysis facilitates and projects a basic understanding of the relative risks of diseases and features of their shared architecture, which is useful in the field of disease epidemiology [9]. The fields of clinical medicine and cardiology have benefited greatly from the advances in systems biology, which have led to a better understanding of molecular systems, complex biological networks, and biological constructs [10]. Some studies have reported genes associated with either cardiomyopathy or different types of CVD. Si [11] reported an association of RPS4Y1 and MYH6 genes with cardiomyopathy based on a PPI network of transcriptome data. In a recent study, Yan et al. [12] have identified genes namely C3, F5, FCGR3A, APOB, PENK, LUM, CHRDL1, FCGR3A, CIQB, and FMOD, in cardiomyopathy using a bioinformatics approach. The mechanism underlying the molecular association of cardiomyopathy and HF is poorly understood. Network-centric approaches to study interactomes of diseases provide an opportunity to identify critical targets that can act both as biomarkers and therapeutic targets which must be studied using a network systems biology approach for their better understanding [13]. Therefore, the present study was undertaken to identify underlying molecular factors and pathways responsible for cardiomyopathy which may lead to CVD using an integrative network system biology approach.

2. Research Methodology

2.1. Data collection

NCBI GEO database was used for the retrieval of multiple omics datasets (GSEs) to collect RNA-seq and microarray data related to cardiomyopathy. The inclusion criteria for both datasets were selected as follows: (i) three control and three experimental samples; (ii) platforms owned by Affymetrix, Illumina, or Agilent manufacturers; (iii) human datasets. Studies using gene therapies or interfering molecules like siRNAs or miRNAs and manipulated datasets were not included.

2.2. Preprocessing microarray data and DEG identification

The microarray dataset GSE120895 [14], consisting of 47 DCM patients and 8 healthy controls, was based on the Platform GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The gene expression profile was downloaded using the R platform's GEOquery package [15]. For downstream analysis, the following packages were used: (i) affy for Affymetrix-derived datasets [16]; (ii) rma method [17] in the affy package to correct background, normalize, and summarize expression values for each probe set of the dataset; (iii) limma [18] and Biobase [19] packages for differential gene expression analysis. DEGs were identified with the threshold set as $P < 0.05$. The DEGs with log2FC < -1 were considered as down-regulated genes, while the DEGs with log2FC > 1 were considered as up-regulated genes. To identify DEGs between cardiomyopathy patients and control samples and to control the false discovery rate (FDR) of the test statistics, moderated *t*-test and Benjamini–Hochberg (BH) method were applied, respectively. The volcano plot of the DEGs was generated using RStudio.

2.3. Preprocessing RNA-Seq data and DEG identification

The gene expression profile of RNA-Seq dataset GSE230585, on account of GPL21697 Platform NextSeq 550 (*Homo sapiens*), including 11 samples of patients with hypertrophic cardiomyopathy and 5 heart-healthy donors, was obtained from the NCBI GEO database. DESeq2 R package [20] was used for the differential gene expression analysis. The DEGs between samples were determined by the threshold set as $|\log2FC| \geq 1$ with the BH for FDR correction of $p < 0.05$ followed by the construction of a volcano plot using RStudio.

2.4. PPI network construction and analysis

Interactions among the DEGs were examined with the STRING database [21] followed by an analysis of the interaction network using Cytoscape 3.10.1 software [22] and its various plug-ins namely CytoCluster [23], Molecular Complex Detection (MCODE) [24] and CytoHubba [25].

2.5. Functional and pathway enrichment analysis

KEGG pathway analysis and functional annotation were done using the enrichment tool, Enrichr [26]. It uses Clustergrammer to visualize high-dimensional data as a hierarchically clustered matrix with colored matrix cells and produces dynamic heatmaps of enriched terms as columns and user input genes as rows.

3. Results

3.1. Identification of DEGs

The Microarray dataset and the RNA-seq dataset with accession numbers GSE120895 and GSE230585 respectively were preprocessed followed by data normalization to identify the DEGs. A total of 859 DEGs were identified in the microarray dataset (GSE120895) out of which 7 genes were up-regulated and 852 genes were down-regulated (Figure 1(A)). RNA-seq dataset (GSE230585) had 973 DEGs out of which 639 were up-regulated and 334 were down-regulated genes (Figure 1(B)). Fifty-one common DEGs associated with cardiomyopathy were identified using Venn diagram from the two datasets (Figure 1(C)).

3.2. PPI and modular analysis

The PPI network of the 51 genes previously identified from the DEG analysis was constructed in STRING (Figure 2(A)) and had 48 nodes (representing the genes) and 32 edges (representing the interactions between the genes) with enrichment *P*-value of less than 1.0e-16, indicating high degrees of gene interaction. The interaction network was further built in STRING to identify interacting partners of the 51 proteins and the resulting network

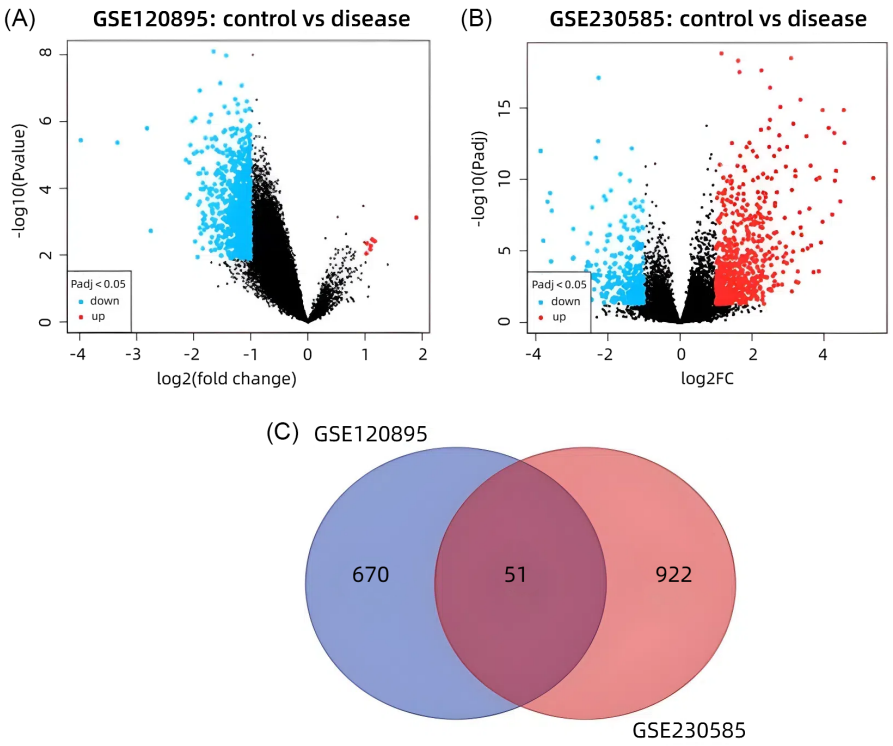


Figure 1. Volcano plot for up- and down-regulated genes for datasets GSE120895 (A) and GSE230585; (B) blue color represents down-regulated genes, red color represents up-regulated genes, while black color represents non-significant genes based on the cutoff criteria: adjusted *P*-value <0.05 and |log2FC|>1; (C) Venn diagram representing common DEGs among the microarray and RNA-seq datasets

having 98 nodes and 486 edges was imported to Cytoscape for further analysis (Figure 2(B)).

Clustering was performed using two different Cytoscape plug-ins, CytoCluster and MCODE, to identify and validate the significant clusters to further identify the critical hub genes. ClusterONE (Clustering with Overlapping Neighborhood Expansion) is an algorithm of CytoCluster plug-in, that was used to identify highly overlapping regions, i.e., cluster modules based on a *P*-value of <0.05 [13] while MCODE detects clusters on the basis of topology, i.e., a maximum number of nodes and edges. Ten clusters were obtained following analysis of the imported PPI network from STRING (Figure 2(B)) with CytoCluster, out of which only 2 clusters were significant (Table 1(A)). Both these clusters were merged and had 51 genes which were analyzed with the CytoHubba plug-in of Cyctoscape using Maximal Clique Centrality scoring method, and nine hub genes, namely Lipoprotein (a) (LPA), apolipoprotein A2 (APOA2), ATP-binding cassette transporter A1 (ABCA1), lecithin cholesterol acyl transferase (LCAT), APOB, apolipoprotein A-IV (APOA4), clusterin (CLU), APOC3, and apolipoprotein A-I (APOA1), were found (Table 2, Figure 3(A)). To validate the hub genes, the imported PPI network (Figure 2(B)) was also analyzed with MCODE which returned 5 cluster modules out of which only 2 clusters were selected that had a significant number of nodes and edges (Table 1(B)). These two clusters having 40 genes were merged and analyzed with CytoHubba, and the nine hub genes obtained (Table 2, Figure 3(B)) were identical to the results of CytoCluster and CytoHubba, thereby validating the genes obtained using two different analysis approaches.

3.3. Gene enrichment

The diseasome association network for the 9 hub genes identified in the present study for cardiomyopathy was constructed using STRING and a highly connected PPI network was obtained (Figure 4). To further understand the biological roles of the common hub genes between cardiomyopathy, KEGG pathway analysis was carried out, and all the genes identified in the present study were found to be involved in cholesterol metabolism, fat digestion and absorption, lipid and atherosclerosis, and PPAR signaling pathway and showed a direct or indirect association with CVDs with may result in HF (Figure 5 and Table 3).

4. Discussion

In the present study to identify underlying molecular factors responsible for cardiomyopathy which may lead to HF, 9 proteins were identified from the interactome obtained from the analysis of the DEG associated with both the medical conditions. Common causes of HF have been identified as atrial fibrillation, myocardial infarction, ischemic heart disease, valvular heart disease, and cardiomyocytes [27]. All the proteins identified in the study (Table 3) are involved in pathways involved in metabolism, absorption, or transport of fatty acids with most of them belonging to apolipoprotein family.

The primary structural and functional protein constituent of high-density lipoprotein (HDL), or good cholesterol in plasma, is APOA1 which constitutes about 70% of it. It is known for regulating cholesterol trafficking and protecting against CVD.

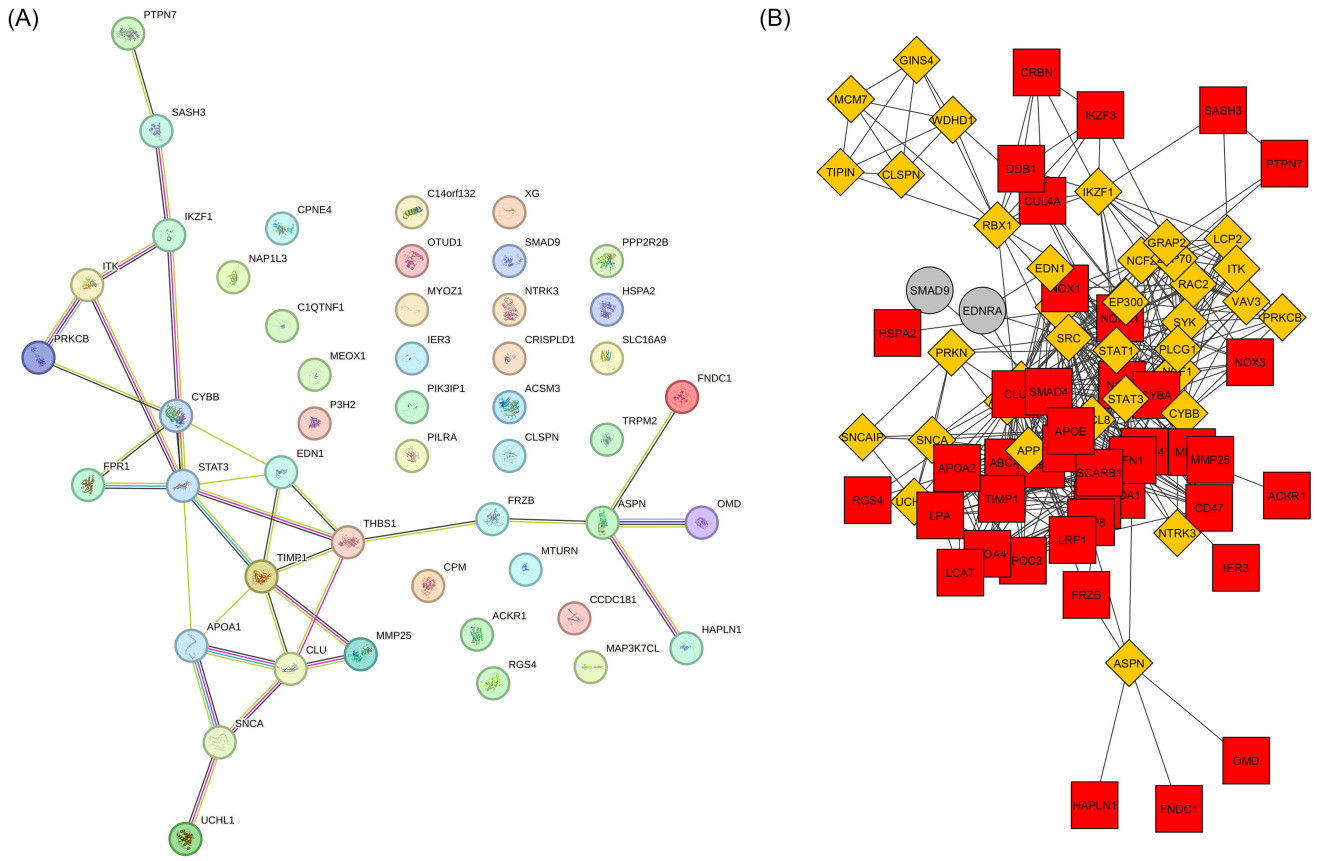
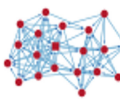


Figure 2. (A) Protein–protein interaction network generated using STRING having 48 nodes and 32 edges; (B) representation of interacting partners of the 48 proteins generated from STRING having 98 nodes and 486 edges, in Cytoscape

Table 1. Selection of two ClusterOne (A) and MCODE; (B) clusters based on *P*-value of <0.05 and high number of nodes, respectively

(A) ClusterOne		(B) MCODE			
Clusters	Details	Clusters	Nodes	Edges	Score
	Nodes: 32 Density: 0.500 Quality: 0.70 *P*-value: 0.000		20	94	9.895
	Nodes: 19 Density: 0.509 Quality: 0.439 *P*-value: 0.008		20	72	7.579

Gordon et al. [28] also reported its role in modulating inflammatory and immune responses. It facilitates the efflux of cholesterol from tissues into the liver for excretion as a cofactor for LCAT, which is required for the synthesis of most plasma cholesteryl esters [29]. LCAT is a key enzyme in the metabolism of HDL and is essential for the reverse cholesterol transport that occurs in macrophages [30]. It has been reported that LCAT activity may be linked to increased formation of triglyceride-rich lipoproteins (TRLs), which in turn reduces the size of LDL particles in patients at high risk for atherosclerotic cardiovascular disease [30]. The second major protein constituting 20% of high-density lipoprotein cholesterol (HDL-C) particles is APOA2, which has been reported to have an antagonistic effect on the efflux of cholesterol from cells by regulating the enzymes involved in the remodeling of HDL-C, a known risk factor for CAD [31].

According to a study, APOA2 independently predicts the risk of CVD and the need for future revascularization in patients with stable hearts suggesting that APOA2 is directly linked to the burden and progression of atherosclerosis rather than cardioprotection in humans [31]. The smaller apolipoprotein APOA3 is mostly found on TRLs and HDL in the bloodstream, with a smaller amount on LDL [32]. According to recent research, APOC3 levels on lipoproteins may increase their atherogenicity and act as a risk indicator for CVD in people [33]. Lipid-binding apolipoprotein A-IV (APOA4) is found on HDLs, chylomicron remnants, and in lipid-free form and is reported to regulate a variety of physiological processes, including lipid absorption and metabolism, anti-atherosclerosis, platelet aggregation, and thrombosis [34]. APOB is an apolipoprotein that forms a crucial part of VLDLs and the metabolites LDLs and IDLs by providing a framework, that is essential to preserve the lipoprotein's structural stability [35].

LPA is a modified LDL particle and has physiological roles in wound healing, tissue repair promotion, and vascular remodeling. Its elevated plasma concentration is an independent predictor of atherosclerotic CVD and peripheral arterial disease [36].

Table 2. Top 9 dysregulated genes and their expression values

Gene symbol	LogFC	AveExpr	*t*	P-value	Adj.P-value	B	Direction
LPA	−1.48308	6.756596	−3.44763	0.00108	0.03007	−0.92127	Down
LCAT	2.579948	1.019443	3.82005	0.00257	0.042554	−1.40249	UP
CLU	1.263447	4.097684	2.21768	0.03118	0.144357	−3.79878	UP
ABCA1	−1.445242	4.500200	−4.50207	3.49E-05	0.008551	2.19224	Down
APOA1	−1.135203	3.828202	−3.61844	0.00064	0.025039	−0.44848	Down
APOA2	−1.228575	4.159338	−3.616529	0.00067	0.025534	−0.45587	Down
APOA4	−1.799703	4.660992	−3.635174	0.000679	0.025534	−0.46190	Down
APOC3	−2.644425	1.723289	−3.840097	0.00072	0.025986	−0.47700	Up

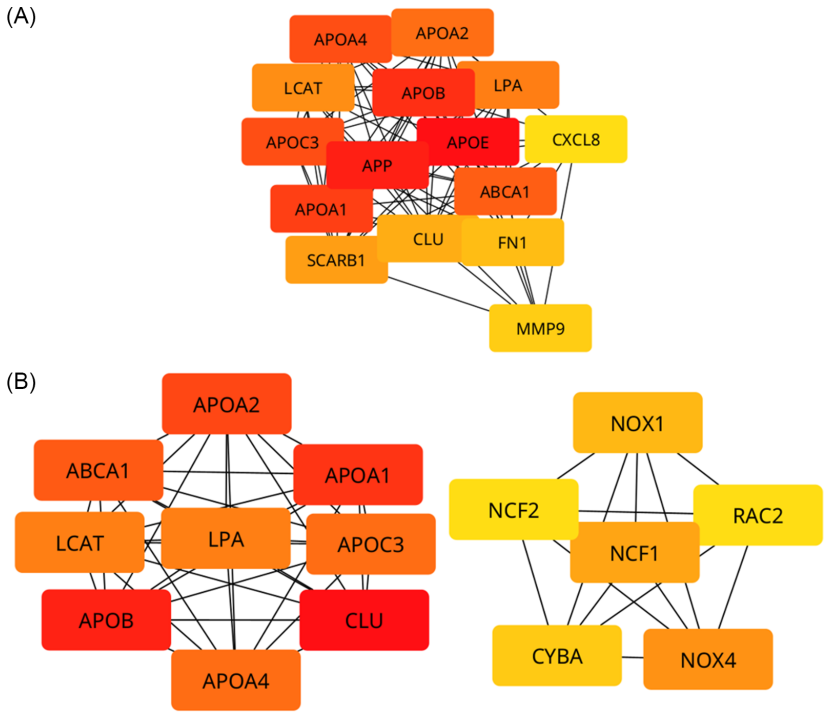


Figure 3. Graphical view of ranked hub nodes of (A) ClusterOne; (B) MCODE cluster obtained from Cytohubba with color-coding (Red – highly essential genes and Yellow – less essential genes

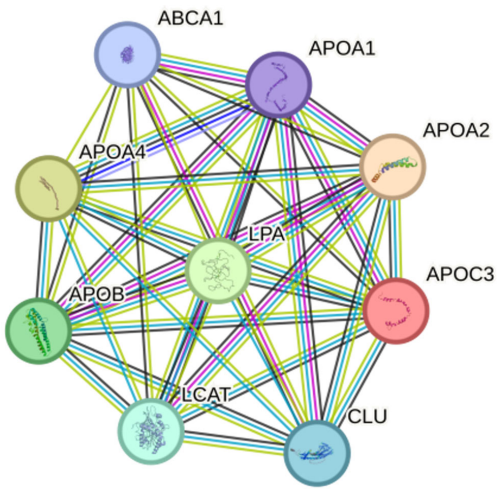


Figure 4. Interactome network of the hub genes obtained from STRING

Tsimikas et al. [37] reported that LPA is a causative mediator of calcific aortic valve disease and CVD based on pathophysiological, epidemiological, and genetic studies.

The protein known as ABCA1 is crucial for preserving cholesterol homeostasis and is known for mediating the nascent HDL biogenesis. Therefore, decreased ABCA1 function may have a significant impact on reverse cholesterol transport and cholesterol homeostasis [38]. Therapeutic strategies aimed at removing excess cholesterol from tissues and preventing CVD now have ABCA1 as a promising new target, regardless of the way numerous atherogenic factors combine to produce cholesterol deposits in arterial macrophages [38].

CLU also known as apolipoprotein J, is a ubiquitous, multifunctional glycoprotein that can be found in nearly all of the body's fluids and multiple places within the intracellular matrix and has been proposed to play a protective role during pathological stresses [39, 40]. Park et al. [41] reported that the serum level of CLU is significantly increased in subjects with type II diabetes and HF.

Table 3. KEGG pathway analysis of hub genes

Pathway	Genes in pathway	*P*-value	Enrichment score
Cholesterol metabolism	APOC3, APOA2, LPA, LCAT, APOB, APOA4, APOA1, ABCA1	7.599e-21	176031.05
Fat digestion and absorption	APOB, APOA4, APOA1, ABCA1	2.315e-9	8137.98
Vitamin digestion and absorption	APOB, APOA4, APOA1	1.269e-7	7550.44
Lipid and atherosclerosis	APOB, APOA4, APOA1, ABCA1	0.000001569	1002.34
PPAR signaling pathway	APOC3, APOA2, APOA1	0.000004019	1742.91
Complement and coagulation cascades	CLU	0.03761	97.18

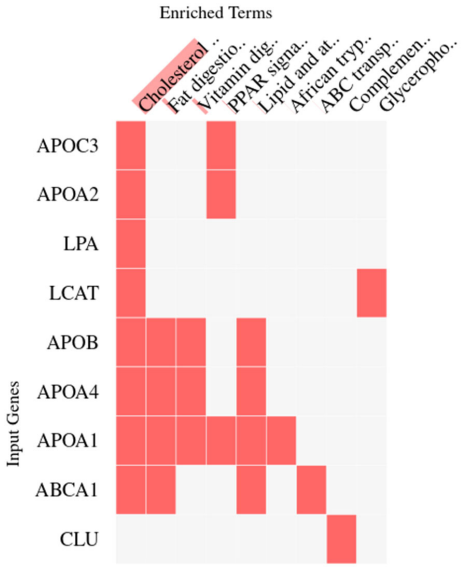


Figure 5. Heatmap showing the top 9 key hub genes involved in KEGG pathway analysis

Erdmann et al. [42] performed Genome-Wide Association Studies and reported that APOA1, APOC3, APOA4, APOB, and LPA genes, and their mutations are linked to CAD that may cause HF. Henein et al. [43] reported that in the genesis, progression, and manifestation of CVD, inflammation plays a critical role. Clinical trial and observational cohorts reported the high prevalence of residual inflammatory risk in patients with CVD. Navarro et al. [44] reported that there may be differences in the regulation of the ApoA-I/C-III/A-IV gene clusters depending on the type of response and the temporal frame of study, such as steady-state mRNA or plasma levels. They further reported that hepatic and plasma Apo C-III levels are similar, which correspond with plasma triglycerides. These findings suggest that inflammation plays a significant role in all processes related to the expression of the ApoA-I/C-III/A-IV gene cluster. The elimination of ApoA-I might heighten the inflammatory reaction and may contribute to chronic inflammation [45]. The first conclusive evidence of ApoA-IV's novel anti-inflammatory and inhibitory effect on*P*-selectin expression, which regulates leukocyte and platelet adhesive interactions, was found in a study using a murine model of DSS colitis [34].

This is the first study based on analysis of the diseasome association network obtained for cardiomyopathy that shows the association of ABCA1, LCAT, and CLU with the apolipoprotein family which is an inflammatory marker being associated with CVD. The genes identified in the present study namely LPA, APOA2, ABCA1, LCAT, APOB, APOA4, CLU, APOC3, and APOA1 were found to be involved in cholesterol metabolism, fat digestion and absorption, lipid and atherosclerosis, and PPAR signaling pathway and showed a direct or indirect association with CVDs leading to CVD which may result in HF.

5. Limitations and Recommendations

The approach used in the present study aimed to elucidate the association between cardiomyopathy and CVD. The study lacks direct clinical validation of the identified hub genes though notably, the subsequent validation of the identified genes implicated in cardiomyopathy and their relevance to CVD outcomes was analyzed through text-mining.

To further validate the biomarkers identified in the present study based on this predictive analysis using a network systems biology approach, animal and clinical studies would provide additional scientific evidence for the clinical application of these biomarkers.

The research strategy used in the present study offers a holistic understanding of the molecular factors influencing cardiomyopathy and its connection to CVDs. By adopting an interactome-based computational approach, the research advances our understanding of the complex molecular mechanisms involved in CVDs.

6. Conclusion

Cardiomyopathies are an important cause of HF, and a comprehensive understanding of their association at the molecular level can have a significant impact on disease prognosis. The hub genes identified in the present study, including LPA, APOA2, ABCA1, LCAT, APOB, APOA4, CLU, APOC3, and APOA1, emerge as potential biomarkers and therapeutic targets for cardiomyopathy and CVDs. The APO family of proteins identified in this study, together with the proteins they are linked to, may serve as helpful biomarkers for cardiomyopathy leading to CVD that may result in HF. This in turn may guide personalized therapeutic interventions for modulation of cardiomyopathy to prevent CVD and HF.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support the findings of this study are openly available in Gene Expression Omnibus at GSE120895 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE120895) and GSE230585 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE230585).

Author Contribution Statement

Tammanna R. Sahrawat: Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Muskan:** Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Rijul Sharma:** Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Suhani Dange:** Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Ritika Patial:** Formal analysis, Investigation. **S. K. Gahlawat:** Conceptualization, Resources, Data curation, Writing – review & editing, Project administration, Funding acquisition.

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