Network-based computational approach to identify genetic links between cardiomyopathy and its risk factors

Md. Nasim Haider¹, M. Babul Islam¹, Utpala Nanda Chowdhury¹, Md. Rezanur Rahman², Fazlul Huq⁴, Julian M.W. Quinn⁵, Mohammad Ali Moni⁴,⁵

¹Department of Electrical and Electronic Engineering, University of Rajshahi, Rajshahi 6205, Bangladesh
²Department of Computer Science and Engineering, University of Rajshahi, Rajshahi 6205, Bangladesh
³Department of Biochemistry and Biotechnology, School of Biomedical Sciences, Khwaja Yusuf Ali University, Sirajganj 6751, Bangladesh
⁴School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia
⁵Bone Biology Division, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia

E-mail: mohammad.moni@sydney.edu.au

Abstract: Cardiomyopathy (CMP) is a group of myocardial diseases that progressively impair cardiac function. The mechanisms underlying CMP development are poorly understood, but lifestyle factors are clearly implicated as risk factors. This study aimed to identify molecular biomarkers involved in inflammatory CMP development and progression using a systems biology approach. The authors analysed microarray gene expression datasets from CMP and tissues affected by risk factors including smoking, ageing factors, high body fat, clinical depression status, insulin resistance, high dietary red meat intake, chronic alcohol consumption, obesity, high-calorie diet and high-fat diet. The authors identified differentially expressed genes (DEGs) from each dataset and compared those from CMP and risk factor datasets to identify common DEGs. Gene set enrichment analyses identified metabolic and signalling pathways, including MAPK, RAS signalling and cardiomyopathy pathways. Protein–protein interaction (PPI) network analysis identified protein subnetworks and ten hub proteins (CDK2, ATM, CDT1, NCOR2, HIST1H4A, HIST1H4B, HIST1H4C, HIST1H4D, HIST1H4E and HIST1H4L). Five transcription factors (FOXC1, GATA2, FOXL1, YY1, CREB1) and five miRNAs were also identified in CMP. Thus the authors' approach reveals candidate biomarkers that may enhance understanding of mechanisms underlying CMP and their link to risk factors. Such biomarkers may also be useful to develop new therapeutics for CMP.

1 Introduction

Cardiomyopathy (CMP) is a group of diseases affecting the structure and functioning of the heart, and includes conditions where the heart is affected by ventricular hypertrophy, dilation or fibrotic dysplasia that cause mechanical and electrical dysfunction. CMP may be either cardiac-specific or a part of generalised systemic disorders, but many of these conditions result in cardiovascular damage or progressive heart failure [1]. CMP is the third most prevalent cause of heart failure in the USA [1]. In 2015, about 2.6 million people worldwide were affected by cardiomyopathy and myocarditis [2]. Currently, the most commonly occurring form of CMP is dilated CMP which affects five in 100,000 adults and 0.57 in 100,000 children [3].

The etiology of the cardiomyopathy involves genetic, infectious, metabolic and environmental factors [1]. Lifestyle risk factors include severe obesity, alcohol consumption (AC), long-term high blood pressure, coronary heart disease, and sarcoidosis, but the molecular mechanisms behind the development of CMP and how these risk factors contribute to the progression of the CMP is not well understood. However, we can use our knowledge of CMP risk factors to identify key factors in CMP development by determining the altered gene expression patterns the risk induces that are also seen CMP-affected heart tissues. Using an integrative gene-network-based approach we can then identify candidate causative pathways that can be further examined [4, 5].

Integrative network-based or multi-omics analyses are an increasingly common approach used to identify disease-associated biomarkers and therapeutic targets [6]. Such an approach is now commonly used for elucidating molecular mechanisms in different diseases such as Alzheimer's disease [7–12], Parkinson's disease [13–15], multiple sclerosis [16], respiratory system diseases [17], colorectal cancer [18] and Thyroid cancers [19–21]. Therefore, in this study, a system biology-based approach was used to identify molecular biomarker transcripts (i.e. miRNAs), and proteins (hub proteins) and pathways in CMP using CMP-associated risk factors to clarify the genes that may be causative factors for the progression of CMP (Fig. 1). For this purpose, we first identified DEGs, genes whose expression is altered in CMP affected tissues and in risk-factor exposed tissues; these DEGs that were common between CMP and particular CMP-associated risk factors were then identified. These common DEGs, were then studied for their involvement in human biomolecular networks such as protein–protein interaction (PPI) networks to identify central signalling molecules (hub proteins) and molecular pathways. This resulted in the identification of candidate genes that could mediate influences of the CMP risk factors, and these were then cross-validated using gold benchmarking datasets OMIM and dbGaP gene-disease association databases to identify those candidates with known pathological involvement.

2 Materials and methods

2.1 High-throughput microarray gene expression datasets

We analysed gene expression microarray datasets to identify the molecular association of different factors with CMP at the molecular level. All the datasets used in this study were collected from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus [22], and employed Affymetrix Human DNA arrays unless otherwise stated. The utilised gene expression datasets with accession numbers GSE4172, GSE1144, GSE4806, GSE12654, GSE20950, GSE25220, GSE44456, GSE48964, GSE56960 and GSE68231 were analysed in this study. The CMP dataset (GSE4172) was obtained by gene expression profiling of human inflammatory CMP [23]. The ageing (AG) dataset (GSE1144) was obtained by analysing gene expression in skeletal muscle tissue characterised by loss of metabolic and contractile...
We performed a differential gene expression analysis of the CMP dataset (GSE4172), ageing (GSE1144), smoking (GSE4806), depression (GSE12654), high RM consumption (GSE25220), IR (GSE20950), chronically high AC (GSE44456), morbid obesity (GSE48964), HCD (GSE56960) and HFD datasets (GSE68231) have been obtained from NCBI-GEO.

To identify regulatory transcription factors (TFs) that regulate the DEGs at the transcriptional level, TF-target gene interactions were identified from miRTarBase based on topological parameters [37–39]. We reconstructed a PPI network around the proteins encoded by the DEGs using protein interactome database STRING [40]. The PPI network was analysed by Cytoscape (v3.5.1) [41, 42]. An undirected graph representation was used for the PPI network, where the nodes indicate proteins and the edges symbolise the interactions between the proteins. We performed a topological analysis using Cyto-Hubba plugin [43, 44] in Cytoscape to identify highly connected proteins (i.e. hub proteins) in the network and the degree metrics were employed [45, 46].
The diseasome association networks centred on the CMP were built to identify statistically significant associations among these risk factors (Figs. 2 and Table 1). Notably, FAM208B was commonly dysregulated for CMP, AG, HFD and IR. CMP shared 18 DEGs (ESCO2, HIST1H4A, HIST1H4B, HIST1H4C, HIST1H4D, HIST1H4E, HIST1H4F, HIST1H4H, HIST1H4I, HIST1H4J, HIST1H4K, HIST1H4L, HIST2H4A, HIST2H4B, HIST4H4, ITGB1, PIEZ1, ZO2, SNTA1) and five miRNAs (mir-335-5p, mir-26b-5p, mir-34a-5p, mir-92a-3p, and mir-17-5p) were detected from the DEGs–TFs and DEGs–miRNAs interactions (Fig. 4). The DEGs shared GABRB1 and HMGA2 dysregulated genes with HFD and RM. Moreover, CMP and HFD shared CCNF, TNPO2 and PPP2R1B dysregulated genes with AG, DEP and SM, respectively.

3.2 Molecular pathway and functional analysis

To clarify the biological roles of the identified common DEGs between CMP and other risk factors, we performed gene ontology analysis to identify the biological process, cellular component and molecular functions enriched by the DEGs (Table 2). There was a total of 741 significant gene ontology groups including leukocyte adhesion to vascular endothelial cell (GO:0061756), cellular reaction to reactive nitrogen species (GO:1902170), mesoderm formation (GO:0007170), cAMP-mediated signalling (GO:0019933), morphogenesis of an epithelium (GO:002009), negative regulation of response to biotic stimulus (GO:0028321), leukocyte tethering or rolling (GO:0059011), establishment of epithelial cell apical/basal polarity (GO:0045198), regulation of osteoblast proliferation (GO:003688), mesodermal cell differentiation (GO:0048333) were identified.

The significantly altered molecular pathways were identified in CMP and other risk factors. A total of 61 pathways were found to be over-represented among several groups out of which some significant pathways are shown in Table 2. The amino acid metabolism pathway such as alanine metabolism pathways, different signalling pathways such as MAPK and RAS signalling pathways, ECM pathways, and alcoholism came into prominence as signalling pathways.

3.3 Identification of regulatory biomolecules

We studied the regulators of the common DEGs utilising DEGs–TFs and DEGs–miRNAs interactions analyses, presented in Table 3. We identified DEG–TFs interactions (Fig. 4) and DEGs–miRNAs interactions (Fig. 5) and detected central regulatory biomolecules (TFs and miRNAs) using topological parameters. As shown in Table 3, 31 TFs (FOXC1, GATA2, FOXL1, YY1, and CREB1) and five miRNAs (mir-335-5p, mir-26b-5p, mir-34a-5p, mir-92a-3p, and mir-17-5p) were detected from the DEGs–TFs and DEGs–miRNAs interaction networks, respectively. These biomolecules regulate genes at transcriptional and post-transcriptional levels.

The FOXC1 is a TF that plays a critical role in early cardiomyogenesis [48]. It is also required for the morphogenesis process of cardiac outflow tract [58]. The TF GATA2 expression is high in the thoracic aorta and GATA2 variants are associated with early-onset familial coronary artery disease [49]. FOXL1 is a TF whose elevated expression is associated with good outcomes in human pancreatic ductal adenocarcinoma [50] but does not have a known association with cardiac diseases. The activity of YY1 TF is increased in human heart failure [51]. CREB over-expression is associated with cardiac failure suggesting it plays a significant role in cardiac hypertrophy [52].

miRNAs (miRNAs) are short single-stranded RNA molecules (~22 nucleotides long) that regulate the expression of genes at post-transcriptional stage. miRNAs are being considered as potential sources of biomarkers for complex disease including neurodegenerative disease and cancers. Therefore, we have identified those miRNAs controlling the DEGs to provide insights into the regulatory biomolecules. Among the miRNAs, mir-335-5p was identified as upregulated in experimental heart failure by experimental animals [53]. Sun et al. [54] also predicted mir-335-5p is implicated in hypertrophic CMP pathway by microarray analysis. Jia et al. [54] showed mir-26b-5p was associated with suppression of proliferation and enhance the apoptosis in multiple myeloma cells. It has been proposed the mir-34a-5p could prevent autophagic cell deaths in ischemic hearts and in this way can improve the myocardial injury [55, 60]. The inhibition of mir-92a-3p leads to increase blood vessel growth and recovery of damaged tissues in myocardial infarction mice models, which suggest it may be an important therapeutic target in ischaemic heart disease [56]. The mir-17-5p has been suggested as important prognostic biomarkers in cancer, including hepatocellular carcinoma [57].

3.4 PPI network analysis

The PPI network was constructed using all the distinct 236 differentially expressed genes that were common between the CMP and the risk factors (Fig. 6). The topological analysis using degree matrices was used to identify highly connected proteins clusters. Each node in the network represents a protein and an edge indicates the interaction between two proteins. We detected ten hub proteins (CDK2, ATM, CDF1, NCOR2, HIST1H4A, HIST1H4B, HIST1H4C, HIST1H4D, HIST1H4E and HIST1H4L) in PPI analysis. These hub proteins may be potential drug targets.

3.5 Identification of candidate drugs

A protein–drug interaction network was analysed and we found GABRB1, GRIA3, SLC6A2, GAD2, GAD2, CACNB1, NTRK2, and GMR5 proteins had interaction with 5 drugs/compounds (Ethanol, Amoxapine, L-Glutamic Acid, Amitripityline, Acamprosate) as shown in Fig. 8.

4 Discussion

In this study, the molecular mechanisms that may link CMP and associated risk factors were investigated. We performed an analysis of gene expression data from CMP tissue analysis and from the risk factors in order to identify the common DEGs shared by CMP and the risk factors. This identified CMP affected tissues shared with 81 genes with tissues and cells affected by HFD exposure; similarly there were shared DEGs seen for AG (48 genes) and SM (32 genes), the conditions that shared most DEGs with CMP. To clarify the biological relevance of the identified DEGs, GO and molecular pathways analysis was performed which revealed pathways with significantly altered activity. Among such pathways, MAPK signalling cascades have been reported to be prominent in the pathogenesis of cardiovascular disease [61–63]. Another pathway, RAS signalling, plays a critical role in cardiac hypertrophy, which suggests complexity in developing meaningful therapy for individuals with these RASopathies [64]. Clinical and genetic studies have also revealed close relationships between cell adhesion proteins and the occurrence of various CMPs [65], thus indicating the important role of focal adhesion pathways in CMP. Related to this, extracellular matrix alterations may be a significant factor in the pathogenesis of dilative CMP [66]. Moreover, molecular pathways hypertrophic CMP, arrhythmogenic right ventricular CMP, dilated CMP pathways were notably and consistently seen to be enriched in CMP.

Analysis of PPIs can provide some detailed insights into the central mechanism behind the diseases [9, 11, 12]. Therefore, we reconstructed the PPI networks around the protein encoded by the DEGs. Based on our topological analysis, we detected ten hub proteins (CDK2, ATM, CD1, NCOR2, HIST1H4A, HIST1H4B, HIST1H4C, HIST1H4D, HIST1H4E and HIST1H4L) involved in the CMP. A brief description of hub proteins, their gene ontology and features are presented in Table 4. Among the hubs, CDK2 involved in the regulation of myocardial ischaemia and reperfusion injury [67, 74]. The hub protein apical transverse motion (ATM) is associated with electromechanical dys synchrony in adult dilated CMP [68]. The ATM protein involved in CMP associated with obesity and IR [75]. The hub protein CD1 is associated with genotoxic stress, which results in aberrant cell proliferation leading to cancer formation [69], but its association with the CMP is not known. Another hub protein, NCOB2 has been reported to be associated with non-alcoholic fatty liver disease [70], which is one of the prominent risk factors for cardiovascular disease. Yin et al.
have reported the dysregulation of HIST1H4B in rat cardiomyocytes. The other hub proteins, HIST1H4A, HIST1H4D, HIST1H4E and HIST1H4L were not reported to CMP yet. These identified hubs proteins might be considered as candidate biomarkers or, if their biological role is confirmed, as potential drug targets.

Based on the network-based approach, our analyses revealed novel relationships between CMP and other susceptibility/causative factors. This study identified potential biomarkers, which may be candidates for the development of prognostic strategies and treatments. Since the common pathways may indicate ways by which the risk factors influence CMP, such pathways and their hub genes identified in this study may have important pathogenic roles in CMP. To examine this and so to validate the results of this systems biology approach, we also analysed the DEGs associated with CMP and each of the risk factors with OMIM databases and dbGAP databases using the valid gold benchmark the disease-gene associations (Table 5). The DEGs of nine risk factors were identified as showing suggestive links that may promote CMP development and progression. This analysis furnishes new hypotheses that may point the way to establishing mechanistic links between the CMP and the various risk factors that we examined.

5 Conclusion

In this study, the genetic association of CMP with various diseases was identified from comprehensive transcriptomics analyses incorporated with human biomolecular networks to reveal candidate biomarkers at RNA level (transcripts and miRNAs) and protein levels (hub proteins); identified as potential key signalling and regulatory biomolecules in CMP; we also identified possible molecular pathways with CMP involvement. Protein–drug interaction studies revealed eight gene products that had detectable in silico interaction with four compounds including, Amoxapine, L-Glutamic Acid, Amitriptyline and Acamprosate, which are all compounds already available for therapeutic use apart from glutamate, with is a nutrient and neurotransmitter. Thus, new gene-based recommendations for disease diagnosis and possible...
treatment were demonstrated in this study. The molecular signatures and repurposing of the drugs presented in this study may thus deserve attention for use in further experimental studies of CMP.

| Category                                      | GO ID      | Term/pathway                                      | Genes                        | Risk factors | P-value   |
|------------------------------------------------|------------|---------------------------------------------------|------------------------------|--------------|-----------|
| gene ontology biological process              | GO:2000146 | negative regulation of cell motility              | NF1, SRGAP2C, SRGAP2, NF2,   | DEP, SM      | 4.62×10^-7 |
|                                               | GO:0070828 | heterochromatin organisation                       | MTHFR, HMGA2                 | HFD, RM      | 9.07×10^-5 |
|                                               | GO:2000257 | regulation of protein activation cascade           | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 1.35×10^-4 |
|                                               | GO:0030334 | regulation of cell migration                       | NF1, SRGAP2C, SRGAP2, NF2,   | DEP, SM      | 1.37×10^-4 |
|                                               | GO:0030449 | regulation of complement activation                | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 1.40×10^-4 |
|                                               | GO:0002920 | regulation of humoral immune response              | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 1.61×10^-4 |
|                                               | GO:0002697 | regulation of immune effector process              | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 1.66×10^-4 |
|                                               | GO:0002673 | regulation of acute inflammatory response          | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 2.08×10^-4 |
|                                               | GO:0070613 | regulation of protein processing                    | IGHG3, IGHG4, IGHG1, IGHG2, C4BPA | AG, HCD     | 2.58×10^-4 |
|                                               | GO:1902531 | regulation of intracellular signal transduction    | CDC42, PAK1, F2RL1, ATM, HIPK2, CDK2, NF2, SRGAP2, PML, ARHGAP35 | AG, SM      | 5.20×10^-4 |
| gene ontology                                  | GO:0005887 | integral components of plasma membrane             | SLC14A1, KCNJ15, TSPAN5, PTGFR | HCD, OB     | 1.10×10^-2 |
| cellular component                             | GO:0030424 | axon                                              | NTRK2, PAK1, NF1, KCNB1, KCNC2 | AG, DEP, RM | 1.79×10^-2 |
|                                               | GO:0071437 | invadopodium                                       | PK1, EZR                     | AG, IR      | 1.81×10^-2 |
|                                               | GO:0030425 | dendrite                                           | KCNB1, KCNC2, NF1            | DEP, RM     | 3.21×10^-2 |
|                                               | GO:0005856 | cytoskeleton                                       | CDC42, TPM3, RARA, SPTBN1, LRRFIP1 | AG, OB     | 3.60×10^-2 |
| gene ontology molecular function              | GO:0005096 | GTPase activator activity                         | SRGAP2C, SRGAP2, NF1, ARHGAP35, SRGAP2B | SM, DEP    | 6.51×10^-4 |
|                                               | GO:0030695 | GTPase regulator activity                         | SRGAP2C, SRGAP2, NF1, ARHGAP35, SRGAP2B | SM, DEP    | 9.41×10^-4 |
|                                               | GO:0015204 | urea transmembrane transporter activity           | SLC14A1, SLC14A2              | DEP, HCD, SM | 1.05×10^-3 |
|                                               | GO:0042887 | amide transmembrane transporter activity           | SLC14A1, SLC14A2              | DEP, HCD, SM | 1.35×10^-3 |
|                                               | GO:0004955 | prostaglandin receptor activity                   | PTGFR, PTGER3                 | OB, AG      | 3.30×10^-3 |
|                                               | GO:0015467 | G-protein activated inward rectifier potassium channel activity | KCNJ15, KCNJ4 | HCD, SM     | 3.84×10^-3 |
|                                               | GO:0022838 | substrate-specific channel activity                | SLC14A1                      | DEP, HCD    | 4.19×10^-3 |
|                                               | GO:0005249 | voltage-gated potassium channel activity          | KCNB1, KCNC2, KCNJ15         | RM, HCD     | 6.88×10^-3 |
|                                               | GO:0005242 | inward rectifier potassium channel activity       | KCNJ15, KCNJ4                | HCD, SM     | 7.68×10^-3 |
|                                               | GO:0003680 | AT DNA binding                                     | HMGA2                        | RM, HFD     | 1.15×10^-2 |
Table 2  Some significant KEGG pathways those are common among inflammatory CMP and other risk factors such as SM (smoking), IR, AC, HCD (high caloric diet), RM (high red meat intake), depression, HFD (high fat diet), obesity and ageing

| KEGG ID | Pathway                              | Genes in pathway            | Risk factors |
|---------|--------------------------------------|-----------------------------|--------------|
| hsa00410| beta-Alanine metabolism              | CNDP1, GAD2                 | AC, RM       |
| hsa04010| MAPK signalling pathway              | CACNB1, CDC42, NTRK2, AK1, FGFR2, NF1 | AG, DEP     |
| hsa04014| RAS signalling pathway              | CDC42, AK1, FGFR2, NF1      | AG, DEP      |
| hsa04510| focal adhesion                       | CDC42, PAK1, ITGB7, LAMA4, ARHGPAP35 | AG, SM     |
| hsa05032| morphine addiction                  | PDE1A, GABBR1, GNB5         | OB, RM       |
| hsa05200| pathways in cancer                   | CDC42, TPM3, PTGER3, RARA, FGFR2, KITLG, LAMA4, CDK2, PML | AG, SM |
| hsa05202| transcriptional misregulation in cancer | RARA, ATM, ITGB7, HMGA2, GRIA3 | AG, RM     |
| hsa05410| hypertrophic cardiomyopathy (HCM)    | CACNB1, TPM3, ITGB7, ITGB1, ITGA4, SLC8A1 | AG, HFD |
| hsa05412| arrhythmogenic right ventricular cardiomyopathy (ARVC) | CACNB1, ITGB7, ITGB1, ITGA4, SLC8A1 | AG, HFD |
| hsa05414| dilated cardiomyopathy              | CACNB1, TPM3, ITGB7, ITGB1, ITGA4, SLC8A1 | AG, HFD |

Fig. 4  Differentially expressed genes and TF interactions were analysed to identify the TFs that regulate the differentially expressed genes in CMP

Table 3  Summary of transcriptional and/or post-transcriptional regulators (TFs and microRNAs) of the differentially expressed genes

| Symbol   | Description                              | Feature                                                                 |
|----------|------------------------------------------|-------------------------------------------------------------------------|
| TFs      |                                          |                                                                         |
| FOXC1    | Forkhead Box C1                          | play critical role in early cardiomyogenesis [48]                      |
| GATA2    | GATA Binding Protein 2                   | affiliated with early onset familial coronary artery disease [49]       |
| FOXL1    | Forkhead Box L1                          | associated with good outcome in human pancreatic ductal adenocarcinoma [50] |
| YY1      | YY1 TF                                   | increased in human heart failure [51]                                  |
| CREB1    | CAMP Responsive Element Binding Protein 1| cardiac failure is afflicted with CREB [52]                            |
| microRNAs|                                          |                                                                         |
| mir-335-5p| MicroRNA 335                             | upregulated in heart failure; involved in hypertrophic cardiomyopathy pathway [53] |
| mir-26b-5p| MicroRNA 26                              | associated with suppression of proliferation and enhance the apoptosis in multiple myeloma cells [54] |
| mir-34a-5p| MicroRNA 34                              | could prevent autophagic cell deaths in ischaemic hearts and in this way can improve the myocardial injury [55] |
| mir-92a-3p| MicroRNA 92                              | increase blood vessel growth and recovery of damaged tissues in myocardial infarction [56] |
| mir-17-5p| MicroRNA 17                              | prognostic markers of hepatocellular carcinoma [57]                     |
Fig. 5 Differentially expressed genes and microRNAs interactions were analysed to identify the microRNAs that regulate the differentially expressed genes in CMP.

Fig. 6 PPI network of differentially expressed genes that were common between CMP and other risk factors.

Fig. 7 Simplified PPI network of the common differentially expressed genes between CMP and the risk factors. Ten significant hub proteins are marked as red, orange and yellow, respectively.
Table 4 Summary of hub proteins identified from PPI network

| Symbol | Description | Gene ontology | Feature |
|--------|-------------|---------------|---------|
| CDK2 | Cyclin Dependent Kinase 2 | transferase activity | involved in the regulation of myocardial ischaemia and reperfusion injury [67] |
| ATM | ATM Serine/Threonine Kinase | transferase activity | associated with electromechanical dysynchrony in adult dilated CMP [68] |
| CDT1 | Chromatin Licensing and DNA Replication Factor 1 | — | genotoxic stress which result in aberrant cell proliferation [69] |
| NCOR2 | Nuclear Receptor Corepressor 2 | sequence-specific DNA binding | associated with non-alcoholic fatty liver disease [70] |
| HIST1H4A | Histone Cluster 1 H4 Family Member A | histone binding | implicated a strong involvement of inflammatory-immune pathways [71] |
| HIST1H4B | Histone Cluster 1 H4 Family Member B | histone binding | dysregulation of HIST1H4B in rat cardiomyocytes [72] |
| HIST1H4C | Histone Cluster 1 H4 Family Member C | histone binding | hyperinsulinemic hypoglycemia familial 1 [73] |
| HIST1H4D | Histone Cluster 1 H4 Family Member D | histone binding | involved in meiosis and signalling pathways by Rho GTPases [73] |
| HIST1H4E | Histone Cluster 1 H4 Family Member E | histone binding | involved in meiosis and signalling pathways by Rho GTPases [73] |
| HIST1H4L | Histone Cluster 1 H4 Family Member L | histone binding | involved in meiosis and signalling pathways by Rho GTPases [73] |

Table 5 Gene-disease association analysis of differentially expressed genes of nine risk factors using OMIM and dbGAP databases for CMP

| Risk fac./Causes | Gene | Adjusted P-value |
|-----------------|------|-----------------|
| AG | SGCD, TNNI2, TNNC1, LDB3, TTN | 1.85×10⁻³ |
| SM | OPDR1, SMAD1, BUB1, PKP2 | 2.18×10⁻¹ |
| DEP | HNF4A, TSHR | 4.16×10⁻² |
| IR | WWOX, MCTP2, BACH2, ZNF783, PPARA | 4.62×10⁻¹ |
| RM | HMG2A, ADCY2, MYH6 | 3.34×10⁻¹ |
| AC | VWF | 2.42×10⁻¹ |
| OB | ABC9C, TFAP2A, DMD, FOS | 1.45×10⁻¹ |
| HCD | SMAD1, DSC2 | 1.02×10⁻¹ |
| HFD | AKAP13, CREBBP, TGFB3, HNF4A, HMG2A, FNM2, ADAMTS7, TGFB3 | 2.29×10⁻¹ |

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