Chasing the cardiomyopathy modifier genes: Integrative computational analysis interweave the missing links in cardiomyopathy diseasome

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Abstract

Background Cardiomyopathies are genetic disorders resulting in an abnormal heart phenotype due to intrinsic cardiac muscle malfunction, which leads to heart failure. These are chronic disorders contributing more than 36% of heart failure in the patients. Cardiomyopathies also show co-morbidity with other diseases that frequently affect the elderly. Apart from this, many drugs used for treating other unrelated diseases cause cardio-toxicity and lead to cardiomyopathies. Unravelling the cross-talk between them is essential for useful characterization, subtyping, and better treatment of the cardiomyopathies.

Results In this work, we applied a systems biology-based analysis to explore the associations between cardiomyopathies and other morbidities. For this, we built a cardiomyopathy disease-disease network based on the combine biological data relevant to cardiomyopathies. For this, we make use of publicly available genetic, non-coding, drug and PPI datasets related to cardiomyopathies and network science tools to identify new modifiers genes that may have a role in cardiomyopathies. These modifier genes are further enriched using mouse phenotype data. Lastly, we highlight key modifier genes that may be potentially associated with cardiomyopathies. Many predicted genes link cardiomyopathies to neoplasms, metabolic and neurological disorders; some of these have been explained as case studies in this analysis.

Conclusions Traditional one drug–one target–one disease outlook alone in drug discovery is inefficient. We hereby develop an integrative approach based on primary cardiomyopathy target genes to discover new targets that provide clues in drug re-purposing, possible off-targets and hidden genetic overlap between cardiomyopathies and other morbidities. We report potential modifier genes like *NOTCH4, SIRT1* that may be investigated for role in cardiomyopathy and other diseases.

Keywords

Diseasome, cardiomyopathy, systems biology, protein-protein interaction, gene ontology, human phenotype ontology, network science, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, modifier genes

Background

Cardiomyopathies are severe and chronic health issues across the world. These are complex heart muscle disorders compounded by genetic and environmental factors. Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) have an estimated prevalence of 1:500 and 1:250 in the general population [1, 2, 3, 4]. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is succeeding primary form with an estimated prevalence of one in 2000–5000 [5]. Restrictive cardiomyopathy and other forms are very rare and uncommon. Cardiomyopathies share overlapping genetic and phenotypic features with other diseases. Newer studies have revealed that several drugs, including anti-cancer, antiretroviral and antipsychotic, have shown the potential risk of cardiotoxicity and drug-induced cardiomyopathies

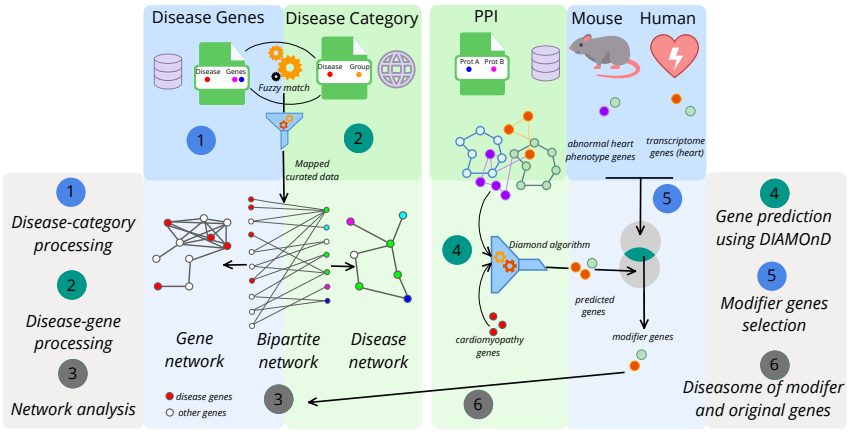

Figure 1. Schematic of modifier genes identification flowchart

[6, 7, 8, 9, 10, 11]. Genome-wide association (GWAS) and candidate gene analysis approaches have reported many common genetic variants that might be one of the plausible reasons for toxicity or induced cardiomyopathy [12, 13, 14, 15].

The emergence of network science has allowed us to understand better complex systems like social interactions, protein-protein interactions, and diseases [16, 17, 18, 19]. Disease networks analytics can apprise of disease epidemiology [20, 21]. In this direction, the first genotype-based human disease network was built based on commonly shared genes that showed the global organization of diseases and functional modules [22].Successively, many such studies have been carried out to infer co-morbidity between diseases. That has allowed to an eased conception of the relative risks of diseases and characteristics of their shared architecture [23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. Inclusion of discoveries from disease networks has found a place in therapeutic innovation and disease drug re-purposing [34, 35, 36, 37, 38, 39].

Cardiomyopathies have been part of many disease networks analysis [22, 25, 40]. However, no studies exclusively focus on cardiomyopathies in depth using network science to map its interaction with other diseases, common interacting genes, and pathways. Sarcomere proteins are the major drivers for cardiomyopathy phenotypes. Mutations in genes like *MYBPC3* and *MYH7* are the most frequent and cover more than 70% of cases. Moreover, genes involved in energy metabolism and signalling also contribute to cardiomyopathies. Apart from well-known genes implicated in cardiomyopathies, there is a group of other genes referred to as modifier genes that affect these disorders [41]. According to Hamilton et al. [42], modifier refers to a genetic variant that can change the phenotypic outcome of an independent 'conditioning' variant at another locus. Modifier genes are suitable candidates for novel biomarkers, finding drug toxicity and missing links between distinct disorders. In this direction, our study is the first large scale exploration of modifier genes in cardiomyopathy. It considers HCM, DCM, ARVC, RCM and all other significant forms of cardiomyopathies.

This study deploys an integrative systems biology network-based comprehensive analysis to understand cardiomyopathies complexities and shared genetic architecture. To achieve that, we performed comprehensive mining of publicly available genetic, PPI, mouse phenotype, miRNA and drug targets data related to cardiomyopathies and used network tools to infer the networks. Next, we develop genetic, drug toxicity/drug re-purposing as well as small RNA regulatory diseasome networks to infer modifier genes that will help identify novel modifiers for drug targets, drug re-purposing and morbidity of cardiomyopathies. These genes are enriched using mouse cardiovascular abnormality gene knock out data.

Lastly, we highlight essential modifier genes that link other morbidities to cardiomyopathies (Table 2). The aim is to unravel new mechanisms governing the regulation of lined disease pairs. We have identified modifier genes like (*NOTCH4, SIRT1, SYNE1, FGFR1, ATP2A2* etc.) involved in cardiomyopathies and other diseases.

1 Analyses

1.1 Genetic wiring of cardiomyopathy diseasome network genes with other pathophysiological disorders

1.1.1 Cardiomyopathy associated diseasome network and gene network

We found 383, 904, 3143, and 357 gene-disease associations from OMIM, ClinVar, and DisGeNet, and HumSavar, respectively, by retaining only distinct diseases. The final non-redundant dataset contains 4406 disease phenotypes. From these, cardiomyopathy genes sharing diseases were focused on for a detailed understanding of cardiomyopathy diseasome interactions. Two disorders are connected if they share at least one common gene. Further, this dataset was filtered based on each disease having at least one cardiomyopathy gene. This exclusion criterion led to the bipartite network having 146 diseases and 1929 genes. Disease projection of bi-partite network generated genetic human disease network having 146 diseases with 1193 distinct associations. These diseases belonged to many categories like metabolic, cardiovascular, neoplasms, musculoskeletal and nervous system etc. Many similar diseases in close vicinity were anticipated, such as hypertrophic cardiomyopathy and long QT syndrome or schizophrenia and bipolar disorder. Concurrently there were surprises, such as dilated cardiomyopathy and Alzheimer's disease being close together.
The degree (k) distribution of cardiomyopathy diseasome network (Fig. 3) highlights that most diseases are linked to only a few other diseases. In contrast, a few phenotypes such as dilated cardiomyopathy (k = 96) and hypertrophic cardiomyopathy (k = 63) are associated with many distinct disorders due to bias towards them. The gene projection of bi-partite network for cardiomyopathy gene network consists of 1929 genes and highlights many exclusive to cardiomyopathies genes like *MYLK2, ALPK3, CSRP3,*

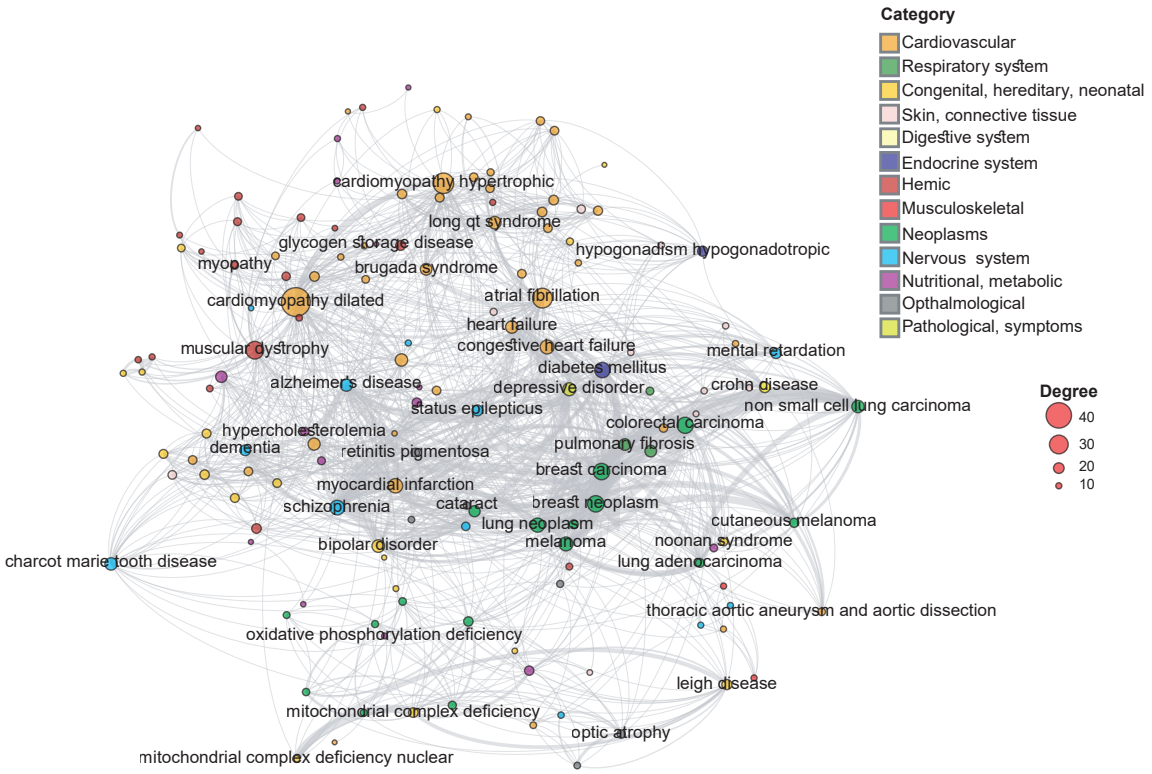

Figure 2. Cardiomyopathy specific diseasome network
In diseasome network each node means a distinct disorder, and it is colored based on the its disease class. The name of the 12 disease classes are shown on the right. A link between disorders are colored in gray. The size of each node is proportional to the number of genes in the disorder. The name of disorders with >20 associated genes are labelled in the network.

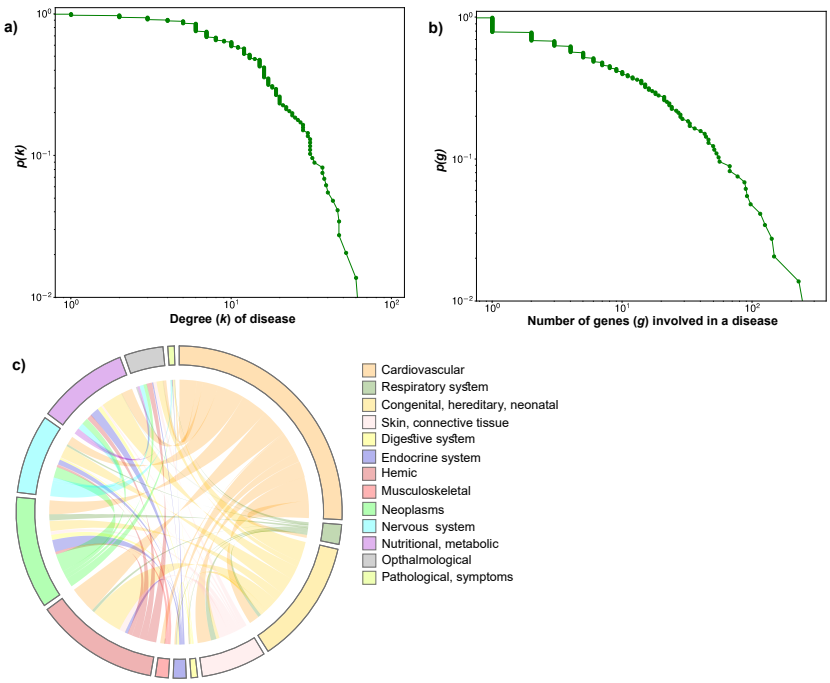

Figure 3. Cardiomyopathy diseasome network category wise interactions : Cardiomyopathy diseasome network shows complex interaction with other disorders at genetic level. a) Distribution of the degree k (number of other disorders that share common genes with a particular disorder) of all disorders in cardiomyopathy diseasome. The green dots represent the logarithmically binned data. b) Distribution of the number of genes g that are implicated in a particular disorder in the cardiomyopathy diseasome. c) Circosplot of disorders in each disease classes in the cardiomyopathy diseasome network. The name of the 12 disease classes are shown on the right and colored accordingly.

TRIM63, CALR3. On the other hand, *LMNA* and *SCN5A* were part of many diseases.

1.1.2 Cardiomyopathy diseasome genes are essentiality

We used the phenotype lethality of the corresponding mouse orthologs and genes in the human cell viability data to predict the cellular essentiality of cardiomyopathy diseasome genes. A disease gene was defined as "essential" if its mouse ortholog gene knockout leads to lethality, and also cell lines viability dataset also records as essential. Human cell-viability essential genes (451) and mouse lethal phenotype orthologs genes (1185) comparison analysis show that most disease genes constitute cell viability nonessential genes that justify that most essential genes are embryonic lethal. Out of 1929 disease genes, only 54 genes were lethal in mouse and essential for cell viability (Supplement fig2. file). Amongst them, only *DOLK* and *SDHB* were involved in cardiomyopathies.

1.1.3 Gene-ontology of cardiomyopathy diseasome associated genes

Genes implicated in disease are localized in specific neighbourhoods within the interactome [18]. As a result, the set of genes implicated in the same disorder should share similar cellular and functional characteristics, as annotated in GO. For example, HCM arises from mutations in a set of genes encoding proteins involved in sarcomeric architecture. To check this, we calculated each disorder's GO homogeneity, as mentioned in the earlier study [22]. We observe a significant difference in GH (Gene ontology homogeneity) concerning random controls in all three branches (Fig. 4. In random control, the same number of genes were picked randomly in the GO annotation data, GO homogeneity was measured for them. We iterated this 100 times to reach statistical significance.

Table 1. Network properties of cardiomyopathy specific diseasome network

Disease	Degree	DC	BC	CC	Clustering
Dilated Cardiomyopathy	96	0.662	0.293	0.744	0.158
Hypertrophic Cardiomyopathy	63	0.434	0.156	0.62	0.167
Atrial Fibrillation	60	0.414	0.063	0.612	0.258
Muscular Dystrophy	52	0.359	0.055	0.594	0.268
Breast Carcinoma	47	0.324	0.021	0.592	0.398
Breast Neoplasm	47	0.324	0.022	0.592	0.404
Colorectal Carcinoma	46	0.317	0.044	0.578	0.361
Diabetes Mellitus	43	0.297	0.027	0.558	0.393
Schizophrenia	40	0.276	0.025	0.551	0.406
Myocardial Infarction	39	0.269	0.017	0.571	0.457
Lung Neoplasm	38	0.262	0.011	0.571	0.495
Congestive Heart Failure	37	0.255	0.026	0.556	0.459
Melanoma	37	0.255	0.015	0.569	0.491
Depressive Disorder	33	0.228	0.007	0.543	0.545
Bipolar Disorder	32	0.221	0.009	0.539	0.504
Heart Failure	31	0.214	0.012	0.503	0.516
Non Small Cell Lung Carcinoma	31	0.214	0.007	0.556	0.568
Long QT Syndrome	31	0.214	0.017	0.531	0.394
Charcot Marie Tooth Disease	31	0.214	0.023	0.533	0.402
Left Ventricular Non Compaction	31	0.214	0.009	0.533	0.48

DC: Degree Centrality, BC: Betweenness Centrality, CC: Closeness centrality

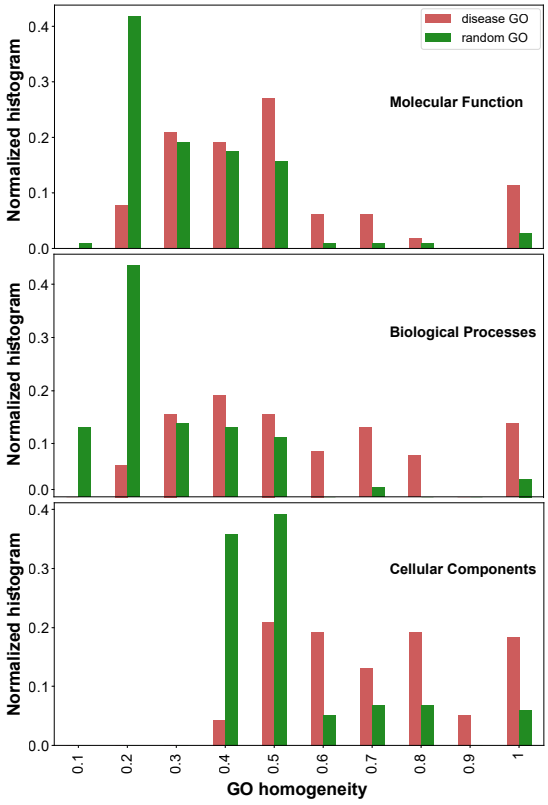

Figure 4. Gene Ontology Homogeneity: The GO homogeneity measure of cardiomyopathy associated disorders for the GO categories biological process (Left), cellular component (Center), and molecular function (Right). Red bars represent the actual disease specific histogram and the green bars show the random control, calculated for each disease by choosing the same number of genes randomly.

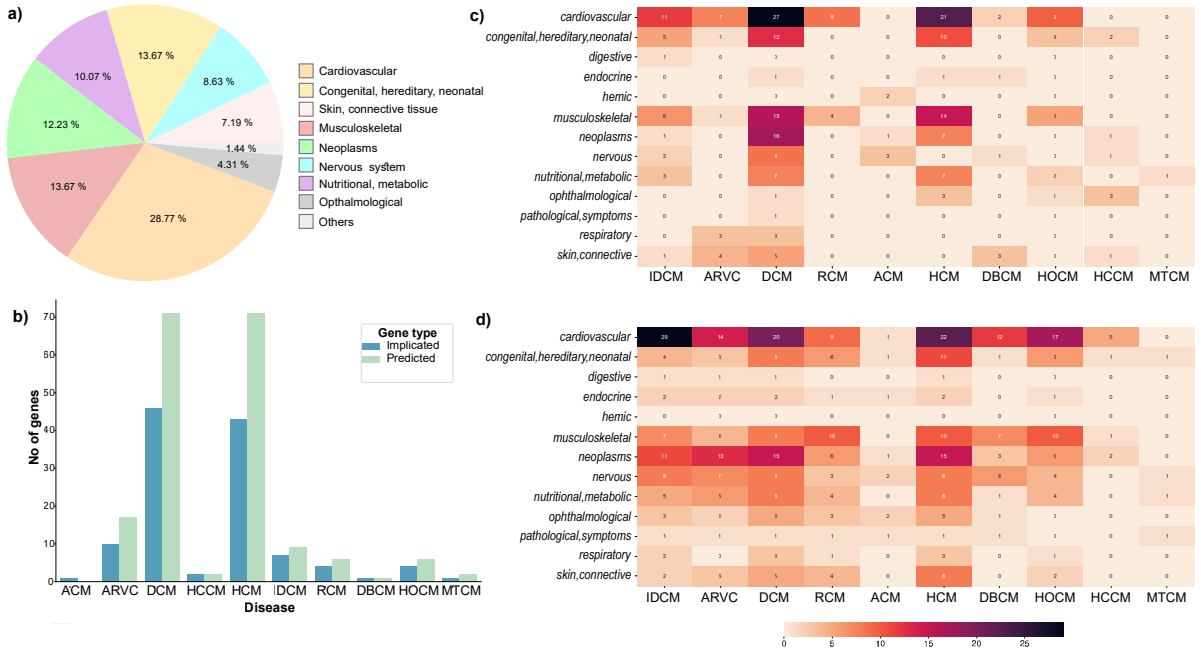

Figure 5. Characteristics of the cardiomyopathy associated disease categories. a) A pie chart showing the proportion of diseases a disorder class occupies in the cardiomyopathy diseasome network. b) A histogram showing no. of original genes and predicted new genes implicated in each cardiomyopathy. c) A heatmap showing no. of diseases in the disorder classes corresponding to each cardiomyopathy. d) A heatmap showing no. of diseases in the disorder classes corresponding to each cardiomyopathy after inclusion of modifier genes.

1.2 Cardiomyopathy diseasome genetic landscape links neoplasms, metabolic and musculoskeletal diseases

1.2.1 Cardiomyopathy exclusive diseasome associations

The disease-disease interaction data was further reduced to include only the cardiomyopathy associations in the disease network. This focused analysis shows that these disorders belonged to cardiovascular, neoplasm, metabolic and neural categories (Fig. 5). Dominant category belonged to the cardiovascular system occupying 28.7% associations followed by musculoskeletal and congenital each sharing 13.67% interactions. Neoplasms also contributed surprising a large share in cardiomyopathies interaction (12.2%). Genetic interactions between most neoplasms and cardiomyopathies were due to RAF1 gene. Metabolic disorders were the next significant contributors (10.0%). Among cardiomyopathies, dilated cardiomyopathy links to the most diverse disease categories.

1.2.2 Protein-protein interaction of cardiomyopathy genes and mouse phenotype gene helps in the identification of underlying modifier genes

We exploited primary PPI datasets from HPRD, IntAct, MINT, CORUM and Phosphosite for comprehensive protein-protein interaction knowledge of gene product interactions [43, 44, 45, 46, 47]. The integrated set of PPIs contains 131984 interactions between 14123 proteins. Out of 1929 disease gene products, 1353 form a giant cluster in the PPI network, and this cluster is statistically significant compared to a random network (z-score = 18.762709 & p-value = 0.000100). To find the relationship between PPI and the number of diseases of a gene, we compared the correlation between protein-protein interactions and diseases. There was a mild correlation of 0.29 between PPI and number of diseases of a gene (supplement fig). Based on corroboration of several studies that have shown that genes associated with a specific disease cluster in specific regions rather than scattered randomly, we used the DIAMOnD algorithm that exploits this pattern for finding modifier genes [48, 49]. The DIAMOnD executes a methodological analysis of the human PPI network to unravel new disease-linked genes by exploring the connectivity significance. This algorithm was used for each cardiomyopathy separately, and fifty times (with a maximum of 2000) new genes compared to the original implicated genes were predicted. We used IMPC (international mouse

Table 2. Disease association of predicted modifier genes that are screened based on mouse phenotype genes.

Disease A	Disease B	Mouse cardiovascular phenotype gene	Human heart transcriptome gene
Restrictive cardiomyopathy	Cataract	BFSP1	Absent
Arrhythmogenic right ventricular cardiomyopathy	lung neoplasm	CDKN1A	PRKN,FGFR1
Beck	Dilated cardiomyopathy	CDKN1C	Absent
Dilated cardiomyopathy	Retinitis pigmentosa	DHX38	Absent
Hypertrophic cardiomyopathy	Charcot Marie tooth disease	DYNC1H1	Absent
Idiopathic cardiomyopathy	Distal myopathy	DYSF	ACTN2
Restrictive cardiomyopathy	Muscular dystrophy	DYSF	SGCG,TTN,SYNE1
Hypertrophic cardiomyopathy	Paraganglioma	EPAS1	Absent
Hypertrophic cardiomyopathy	Depressive disorder	ESR2	ABCB1,FGFR1
Dilated cardiomyopathy	Schizophrenia	ESR2,NOTCH4	FGFR1,ATP2A2,ERBB4,ABCB1,TNIK,NOTCH4
Hypertrophic cardiomyopathy	Schizophrenia	ESR2,NOTCH4	FGFR1,ATP2A2,ERBB4,ABCB1,TNIK,NOTCH4
Dilated cardiomyopathy	Heart failure	HIF1A	PPARGC1A,ATP2A2
Hypertrophic cardiomyopathy	Heart failure	HIF1A	PPARGC1A,ATP2A2
Idiopathic cardiomyopathy	Hypercholesterolemia	MYBPC3	MYBPC3
Restrictive cardiomyopathy	Hypercholesterolemia	MYBPC3	MYBPC3
Arrhythmogenic right ventricular cardiomyopathy	Breast neoplasm	MYH9	FGFR1,ERBB4,KDR,STAT3,IGF1R,SORBS1,FLT1,GSN
Breast neoplasm	Hypertrophic obstructive cardiomyopathy	MYH9	ARID1B
Breast neoplasm	Idiopathic cardiomyopathy	MYH9	Absent
Breast neoplasm	Restrictive cardiomyopathy	MYH9	Absent
Arrhythmogenic right ventricular cardiomyopathy	Melanoma	PDGFRA	FLT1,ERBB4
Arrhythmogenic right ventricular cardiomyopathy	Gastrointestinal stromal tumor	PDGFRA	Absent
Hypertrophic cardiomyopathy	Gastrointestinal stromal tumor	PDGFRA	Absent
Hypertrophic cardiomyopathy	Mental retardation	PPP2R5D,CRBN,DYNC1H1	ARID1B,CRADD,TNIK
Aortic aneurysm	Diabetic cardiomyopathy	PRKG1	Absent
Diabetic cardiomyopathy	Thoracic aortic aneurysm and aortic dissection	PRKG1	Absent
Dilated cardiomyopathy	Diabetes mellitus	SIRT1	PPARGC1A,ATP2A2
Aortic aneurysm	Dilated cardiomyopathy	TGFBR2	Absent
Dilated cardiomyopathy	Thoracic aortic aneurysm and aortic dissection	TGFBR2	Absent
Dilated cardiomyopathy	Loeys Dietz syndrome	TGFBR2	Absent
Hypertrophic cardiomyopathy	Thoracic aortic aneurysm and aortic dissection	TGFBR2	Absent
Hypertrophic cardiomyopathy	Loeys Dietz syndrome	TGFBR2	Absent
Hypertrophic cardiomyopathy	Colorectal carcinoma	TGFBR2,LEF1,ESR2	DLC1,ABCB1,KDR

phenotypic consortium) [50] cardiovascular abnormality data for identification of modifier genes. Mapping of these genes to human orthologs (HGNC) led to 615 genes. The DIAMoND algorithm predicted genes were mapped to these 615 genes for identification of cardiomyopathy specific modifier genes. This stringent filtering increases the robustness of the network.

1.2.3 Modifier genes as a medium to associate cardiomyopathies to other morbidities

Based on implicated genes and predicted genes, we categorized disease links into two categories: a) established associations and b) predicted associations from modifier genes (for more details see supplementary table). Apart from the original 69 cardiomyopathies associations to other disorders, additional 139 interactions were predicted using modifier genes as linkage.

1.2.4 Drug-targets and miRNA datasets as a medium to associate cardiomyopathies to other morbidities

We conceptualized the drug-based disease network by therapeutic links among diseases that may convey the underlying similarities among diseases. Drug based cardiomyopathy diseasome network consists of 391 nodes and 18994 edges. Neoplasms and nervous system disorders dominate this network. Apart from intragroup connectivity, many diseases have strong inter category disease connectivity. Such resemblance could convey related biological pathways, co-morbidities, or new indications for drugs.
There is an increasingly new interest in post-transcriptional regulation's molecular mechanism, emphasizing non-coding RNAs in cardiomyopathies [51, 52, 53]. We visualized cardiomyopathy specific miRNA diseasome network by retaining miRNAs whose at least one target gene was present cardiomyopathy genes list. miRNA associated cardiomyopathy diseasome network consists of 935 nodes and 187479 edges.

1.3 Cardiomyopathy modifier genes case studies

Our study predicts many novel modifier genes that have been implicated in schizophrenia, neoplasms, Alzheimer's and hypogonadism hypogonadotropic etc. We performed a literature search to assess the biological relevance of the results. Twenty-two genes of modifier genes interactions also showed cardiovascular abnormalities in mouse phenotypes. In contrast, forty-nine modifier genes were expressed in heart tissue, as mentioned in [54]. *ATP2A2* [55], *IGF1R* [56], *FGFR1* [57], *PDGFRA* [58], *CDKN1C* [59], *SYNE1* [60, 61], *NOTCH4* [62], *SIRT1* [63] etc. have been reported in numerous studies as cardiomyopathies relevant. *ATP2A2* gene links acrokeratosis verruciformis disease to HCM and DCM. *IGF1R* is associated with Alzheimer's disease and ARVC, DCM. *SYNE1* is implicated in bipolar disorders and idiopathic cardiomyopathy. Disease-associated with *NOTCH4* includes schizophrenia and may be linked to HCM and DCM. Similarly, *SIRT1* is implicated in diabetes mellitus and may be a modifier in DCM.
SIRT1 is a multi-functional protein involved in controlling DNA repair, tissue regeneration, cell survival, inflammation, signalling, and circadian rhythms [64, 64, 65, 66]. We predicted link between cardiomyopathy and diabetes mellitus with *SIRT1* as a common gene. Previous works[67] have shown *SIRT1* in protecting pancreatic β-cells from cytokine toxicity. In another study, Lan Cui et al.[68] indicated that *EPO* might activate *SIRT1* to enhance mitochondrial function and protect against DOX-induced cardiotoxicity. One of the latest studies by [69] demonstrated that Resveratrol-mediated *SIRT1* activation attenuated tesaglitazar-induced cardiac dysfunction.

2 Discussion

Cardiomyopathies, heart muscle disorders are no restricted to sarcomeric protein-coding genes. Involvement of metabolic, signalling associated, and other modifier genes also influence these phenotypes. Many studies have shown that disease co-morbidities arise due to shared genes [23, 24]. These shared genes may not be directly associated; therefore, an integrative, disease-specific network can unravel these hidden key genes to gain more insights into the disease co-morbidity and drug toxicity. In this study, we present cardiomyopathy focused diseasome network that examines all major cardiomyopathies in detail. In our approach, we use systems biology principles to link cardiomyopathies to other diseases or morbidities through shared genes, drug targets, and miRNAs that provide insights about modifier genes, drug toxicity, and non-genetic regulation. Genetic data (OMIM, ClinVar, DisGeNet and HumSavar) provide a credible source of disease and its genes. We present cardiomyopathy exclusive diseasome with 146 disorders and 1929 associated genes that show many pathophysiological disorders from neurological, musculoskeletal, metabolic and neoplasms. Human cell viability and mouse phenotype lethality data give an insight into the nature of the genes involved in these diseases. Our analysis shows that most disease genes are nonessential for cell viability and are consistent with other studies [citation]. The network also highlights that most genes involved in the diseasome are not essential for cell viability and are also connected to a few diseases only. Protein-protein interaction data (HPRD, MINT, IntAct, CORUM and Phosphosite) outlines functional connectivity amongst genes. It helps identify close interactors/related genes (directly interacting gene products in PPI) genes implicated as modifiers. PPI and mouse phenotype data can fill the missing link between two non-obvious diseases. Similarly, gene ontology (GO) terms convey the molecular level information genes in diseases. Majority of genes in disease are involved in the same

biological process or are part of the same cellular component. We used mouse phenotype data and heart tissue transcriptome data to validate modifiers' role in cardiovascular abnormalities. This analysis led to the identification of new modifiers linking cardiomyopathies to other disorders. Our integrated approach demonstrates the power of network study to find novel modifier genes linking distinct disorders. *SIRT1, SYNE1, NOTCH4, ATP2A2* and *IGF1R* look promising modifiers for cardiomyopathies. Later we looked at common drug and miRNAs that have gene targets in two different diseases. Drug based diseasome networks highlight the therapeutic interconnectivity of different diseases. Many of these diseases belong to different categories. The separate disease-disease network was constructed for miRNA set. Many studies demonstrate that microRNAs carry out similar functions by targeting either the same gene or functionally related genes [70, 71]. microRNA associated diseasome network will be resourceful in deciphering the roles of microRNAs in disease associations.
Despite our best effort, some diseases may be assigned the wrong category. This study's primary limitation is the initial data noise, which may remain in the outcome even after processing. Further, the disease associations are based on either common shared genes, drug or miRNA only and may miss physical co-morbidity. In future, we would like to study structural and *in-silico* point mutational analysis of these modifiers in cardiomyopathies.

3 Potential implications

Our study's approach to identifying links between cardiomyopathies and other pathophysiological disorders may also be extended to another disease-specific network to understand interesting modifier genes. The predicted modifiers reported in this study may also be taken up further for experimental and clinical validations.

4 Methods

4.1 Diseases-gene association data sources

Genes and diseases association data were downloaded from OMIM(v2018), ClinVar(2020), HumSaVar(2020) and DisGeNet(2020) datasets. Custom python scripts were used for the pre-processing of each dataset. From the OMIM dataset, only '(3)' marked diseases were selected for curated data. Similarly, in DisGeNet, diseases with a score above 0.4 were considered. HGNC gene symbols were assigned to each gene for a consistent and more accurate name. Synonymic or alternative gene names were reduced to the HGNC gene primary symbol, as reported in HGNC (June 2020 release). All disease-gene datasets were merged and manually curated for a comprehensive non-redundant disease-gene data. Similar diseases, disease sub-types or the same disease with different names were merged (d-2 hydroxyglutaric aciduria and l-2 hydroxyglutaric aciduria were merged together and named hydroxyglutaric aciduria).

4.2 Diseases-category association data sources

MeSH 2020 (2020), GARD (2020), and MeSH 2020 (2020), GARD (2020), and Literature [22] data were integrated for the categorization of diseases. When mapping MeSH terms, we only used the portions of the vocabulary from Diseases[C]. A custom python script was used to process the disease phenotype data. The category names were assigned according to significant organ systems based on MeSH 2020, and similar types were merged, thus restricting the number of the category to 12. A different 'multiple' group was created to cater to diseases belonging to multiple categories. If a disorder was part of many categories, the dominant type was assigned. In the case of multiple dominant categories, it was assigned to the 'multiple' category. Some diseases may be misassigned to a category as categorization of diseases is still a research problem.

4.3 Disease-Gene-category Association

The in-house algorithm, 'i-EAGLE', was used for Disease-Gene-Category analysis. It assigned the best category for disease using partial and full ratio match from fuzzy logic using a cut-off of 70% similarity for the safe category assignment. Assigned categories were further manually curated for any discrepancies. Around 30% of diseases were randomly picked for manual curation. Only those disease, where at least one cardiomyopathy gene was present, were retained for further analysis.

4.4 Diseasome network and Gene network construction

The bipartite network between disease and genes was constructed from the previous data with disorders as one category of nodes and genes another type. A disease-gene pair were linked if the gene was part of that disease. Then cardiomyopathy diseasome network was obtained by projecting the network on disease nodes. The degree (k) distribution of cardiomyopathy diseasome was calculated using networkx. Node size is proportional to the number of genes in the disease, and edge width is proportional to the common in both diseases. Nodes are coloured according to categories of diseases. Similarly, the cardiomyopathy gene network was constructed by projecting the bipartite network on gene nodes. This whole analysis was done using networkx module in python.

4.5 Gene ontology of diseasome

Molecular function, cellular component and biological processes for disease genes were obtained from the UniProt database. For this, all genes in the full diseasome were mapped to UniProt gene symbol. In this analysis, 4923 out of 4995 disease genes mapped to UniProt primary gene map. The GO analysis was applied to each disease linked to cardiomyopathies only. The statistical significance of the dominant GO in each disorder was compared against the random condition. In this, the GO homogeneity (GH) of each disorder was measured as the maximum fraction of genes in the same disease with the same GO terms. It is defined as

$$GH_i = max_j \frac{n_{ji}}{n_i} \tag{1}$$

wherein this case n_i denotes the number of genes in the disorder i that have any GO annotations, and n_{ji} the number of genes with a specific GO term j. GH_i was calculated separately for biological process (BP), molecular function (MF), and cellular component (CC).

4.6 Essential and non-essential genes analysis

Cell lines viability and mouse phenotype lethality data used in the previous study was used for essential and nonessential genes classification [72]. Data was processed, and cardiomyopathy diseasome associated genes were mapped to it.

4.7 Protein-protein interaction network analysis

Human protein-protein interaction (PPI) data (HPRD, MINT, and IntAct) were integrated with other interactions (protein complex and kinase substrate) from CORUM and Phosphosite databases for comprehensive interaction data. Cardiomyopathy diseasome genes were mapped on this comprehensive PPI data to find a diseasome specific PPI network.

4.8 Gene prediction and cardiovascular phenotype validation

Fifty times the original genes implicated in each cardiomyopathy were predicted from PPI using the diamond algorithm. Mouse cardiovascular abnormality phenotype genes were downloaded from IMPC. From cardiovascular data, heart-specific phenotypes genes were filtered manually for further analysis.Mouse genes and heart tissue-specific transcriptome genes were used as validation for predicted genes from the

PPI network. If any of these genes involved other diseases, we called them putative candidates linking both diseases.

4.9 Drug-target and MiRNA based disease interactome analysis

Drugs and its targets data were downloaded from DrugBank 2018 and DrugCentral 2020 [73, 74]. The files were parsed using a python script, and only human-specific data were used for further analysis. This data was used for finding drug target genes linking two diseases. We subsequently constructed a hypothetical human diseasome based on common miRNA targeting genes from different diseases. Diseasome network was constructed to incorporate putative miRNA targets in cardiomyopathy diseases.

5 Availability of supporting data and materials

Available upon request to authors

6 Declarations

6.1 List of abbreviations

ACM: Amyloid Aardiomyopathy ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
CORUM: The comprehensive resource of mammalian protein complexes
DBCM: Diabetic Cardiomyopathy
DCM: Dilated Cardiomyopathy
GARD: The Genetic and Rare Diseases
GWAS: Genome-wide association
HCCM: Histocoid Cardiomyopathy
HCM: Hypertrophic Cardiomyopathy
HGNC: HUGO Gene Nomenclature Committee
HOCM: Hypertrophic Obstructive Cardiomyopathy
HPO: human Phenotype Ontology
HPRD: The Human Protein Reference Database
IDCM: Idiopathic Cardiomyopathy
i-EAGLE: intelligent-Enhanced Automatic Gene-Disease Lexicon Enabler
MeSH : Medical Subject Headings
MINT: The Molecular INTeraction Database
MTCM: Mitochondrial Cardiomyopathy
OMIM: Online Mendelian Inheritance in Man
PPI: Protein-Protein Interaction
RCM: Restrictive Cardiomyopathy

6.2 Ethical Approval (optional)

Not applicable

6.3 Consent for publication

Not applicable

6.4 Competing Interests

The authors declare that they have no competing interests.

6.5 Author's Contributions

P.K.C. conceptualized the study, performed data analysis and visualization, wrote the codes, and wrote the manuscript R.S. supervised, provided resources and helpful discussions

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