Original Article

Heart Diseases Associated Genes

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Abstract

Background: Heart diseases are complex pathophysiologic conditions involving biomarkers. Understanding the mechanisms by which a gene selectively triggers intracellular molecular responses provide insight into the complex processes implicated in heart diseases. The aim of this study was to predict heart diseases associated genes.

Materials and Methods: A number of computational methods have been developed for human gene prioritization. In this study, we used Beegle and KEGG pathway databases and two online services for gene prioritization and analysis of genes related to heart disease.

Results: Over 200 genes and 5 key signaling pathways related to human heart diseases were found. The processes in which gene mutations trigger a response in cells leading to cardiac conditions involve multiple pathways.

Conclusion: The genes related to heart diseases could be CRP, NPPB, IL-6, ACE2 and GATA4 with high scores and the researchers should find the diagnostic biomarker between them.

Keywords: Genes, Heart diseases, System biology

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Introduction

Heart disease accounts for a high percentage of morbidity and mortality worldwide. Several factors contribute to the progress of cardiac disorders including age, gender, low-density cholesterol, inflammation, hypertension, total cholesterol, hypercholesterolemia, alcohol consumption, diabetes, obesity, and smoking[1]. The risk of heart disease however cannot be explained only via these factors. Severity of these illnesses can be estimated more accurately via genetic factors[2]. So far, a number of computational methods have been developed for prioritization of human genes. In this investigation, online databases and literature review were used to identify and prioritize genes involved in heart disease. Beegle and KEGG pathway databases were used to facilitate this. Beegle is an online service that automatically analyzes literature to find the genes most related to a particular query and prioritize a set of candidate genes. Beegle was given the query heart disease. As per literature review, Beegle was first used to rank the genes related to heart disease. Pathways involving these genes were then further investigated. KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database provided a systematic analysis of gene functions and the graphical plot of molecular interactions, reactions and relation networks.

Methods

In addition to ranking, the genes related to the query, Beegle provided further information including supporting publications[15]. This service was available at http://beegle.esat.kuleuven.be/. For this purpose, KEGG pathway database was used. KEGG was publicly available at https://www.genome.jp/kegg/pathway.html.
According to data extracted from this server, five pathways for heart diseases were found.

Results

Gene analysis: According to Beegle webserver, over 200 genes related to heart disease were found. The most important genes with the highest ranks were listed in table-1. C-reactive protein had the highest rank.

Pathway analysis: The cellular elements of cardiovascular system are composed of several specific receptors and complex intracellular pathways. They provide appropriate responses to extracellular stimuli. In this part of the study, using KEGG pathway database, five major signaling pathways in cardiac and vascular cells was identified. These pathways provide a general overview of major genes associated with cardiovascular disease.

Fluid shear stress and atherosclerosis: Shear stress described as the frictional force of blood on the endothelial layer of a vessel. This force contributes to morphological changes of blood vessel walls as well as complex biological responses[3]. Shear stress can also up-regulate the expression of genes implicated in the anti-atherosclerotic function of endothelial cells[4].

Hypertrophic cardiomyopathy (HCM): HCM is one of the most common inherited heart disorders. It characterized by left ventricular hypertrophy with histological features such as myocyte hypertrophy, interstitial fibrosis and myofibrillar disarray. Over 400 different mutations have been identified to cause myofilament sensitivity to Ca2+ in HCM[5].

Arrhythmogenic right ventricular cardiomyopathy

Table 1: Genes related to heart disease with higher ranks according to Beegle.

Gene symbol	Gene name
CRP	C-reactive protein, pentraxin-related
NPPB	natriuretic peptide B
IL-6	interleukin 6
ACE2	angiotensin I converting enzyme 2
GATA4	GATA binding protein 4
AGER	advanced glycosylation end product-specific receptor
AGTR1	angiotensin II receptor, type 1
SIRT1	sirtuin 1
HMOX1	heme oxygenase (decycling) 1
NKX2-5	1482
LGALS3	lectin, galactoside-binding, soluble, 3
NOS3	nitric oxide synthase 3 (endothelial cell)
TNNT2	troponin T type 2 (cardiac)
ADM	Adrenomedullin
GHRL	ghrelin/obestatin prepropeptide
RYR2	ryanodine receptor 2 (cardiac)
TTR	Transthyretin
SCN5A	sodium channel, voltage gated, type V alpha subunit
TNN13	troponin I type 3 (cardiac)
NPPC	natriuretic peptide C

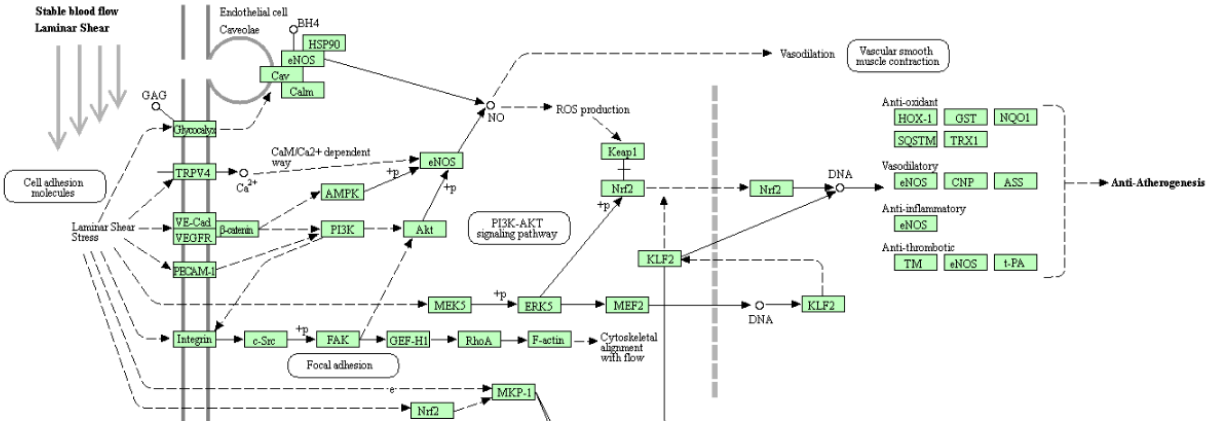

Figure 1. Fluid shear stress and related genes in recorded pathway.

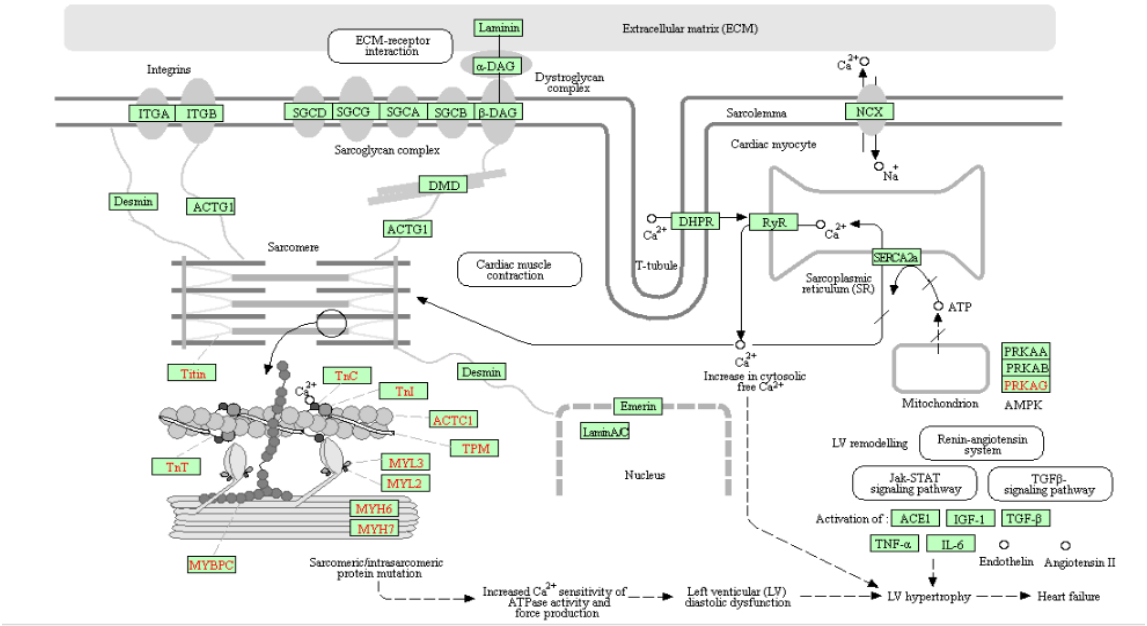

Figure 2. Hypertrophic cardiomyopathy and related genes in confirmed pathway.

(ARVC): ARVC is an inherited cardiomyopathy with autosomal dominant inheritance pattern[6]. So far, several genetic mutations have been identified that play a critical role in ARVC.

Dilated cardiomyopathy (DCM): DCM is a myocardial disease characterized by the enlargement of the right or left ventricle, or both. The prevalence is estimated to be 1 in 2500-3000 and increases with age[7]. Familial DCM is the inherited form of DCM caused by several mutations, which mostly occur in genes encoding mitochondrial, cytoskeletal, nucleoskeletal, and calcium-handling proteins.

Myocarditis: Myocarditis is defined as an inflammatory heart disease that results from both viral and non-viral etiologies. Viral myocarditis is more prevalent[8]. Many virus types can produce myocarditis. Among them are: coxsackie virus B3 (CVB3), parvoviruses, echoviruses, adenovirus, influenza H1N1, Epstein–Barr, mumps, rubella, varicella, measles , yellow fever, Zika , polio, hepatitis A and C, rabies, and human immunodeficiency viruses.

Discussion

Heart disease is a complex condition in which several factors and biomarkers are involved. Understanding the mechanisms by which a gene selectively induces intracellular molecular responses, provides insight into complex processes causing heart conditions. Heart

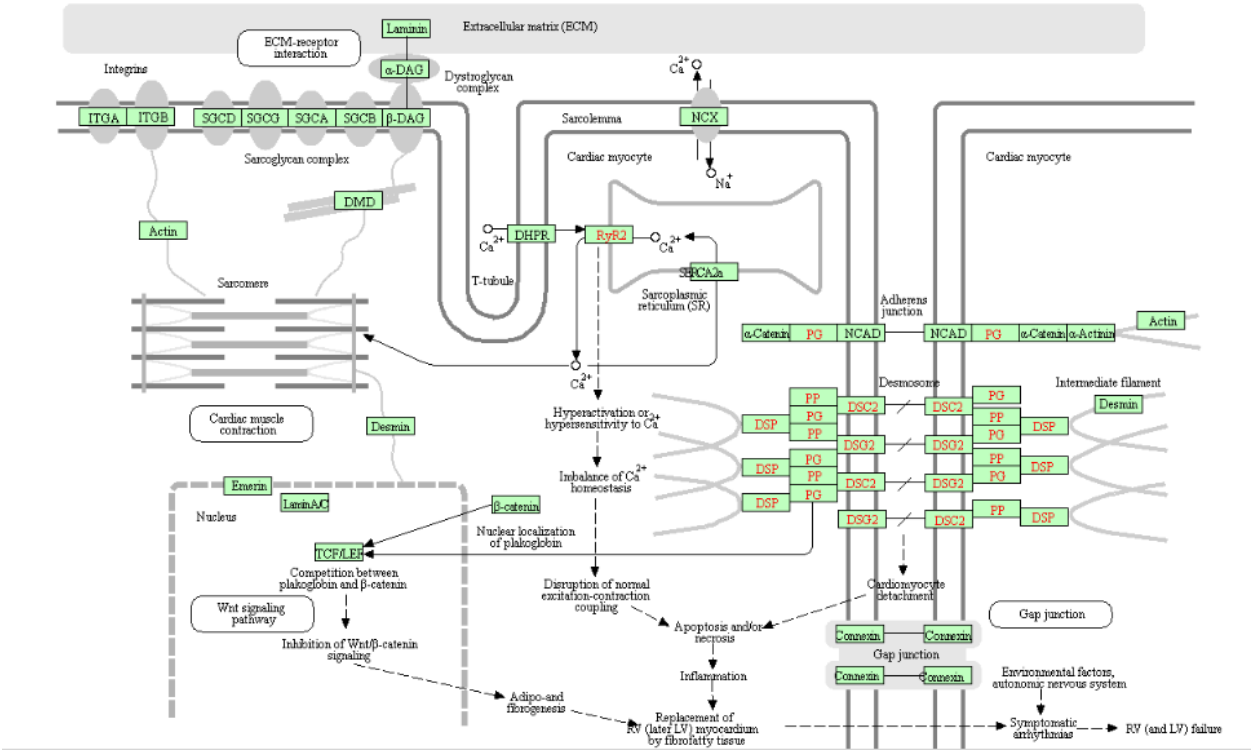

Figure 3. Arrythmogenic right ventricular cardiomyopathy (ARVC) and related genes in annotated pathway.

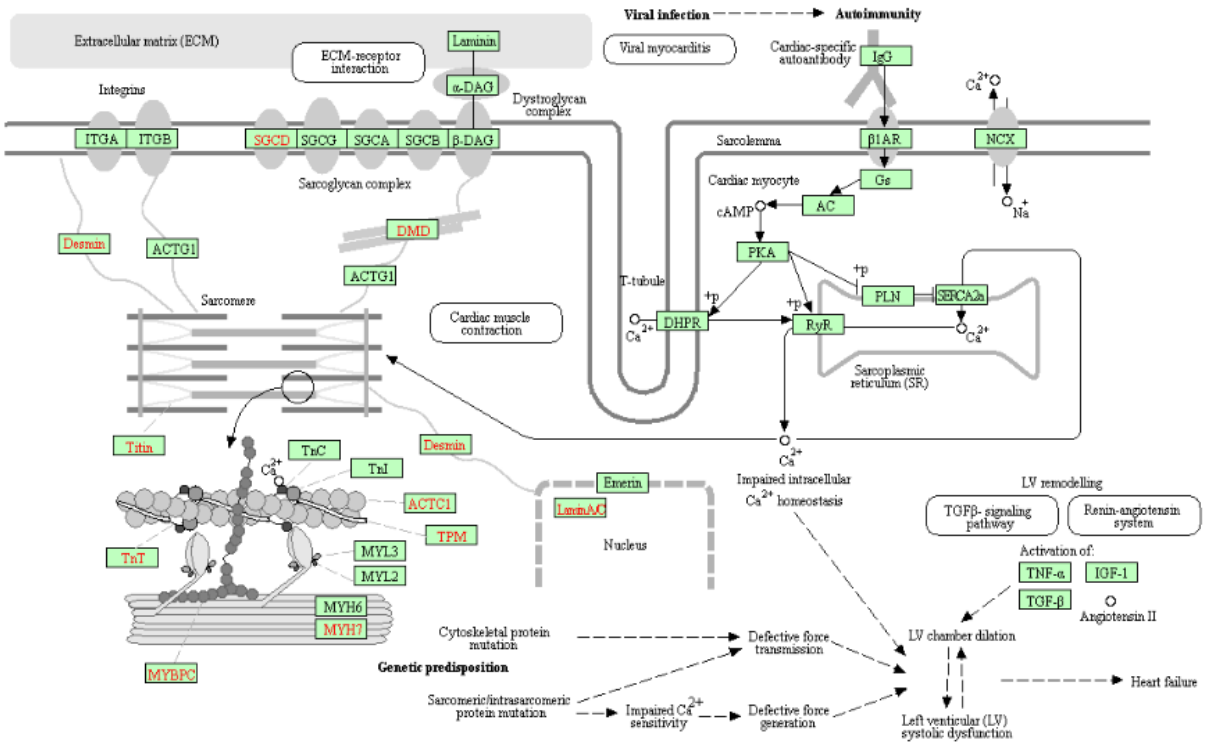

Figure 4. Dilated cardiomyopathy (DCM) and related genes in recorded pathway.

disease associated genes lead to one of two different pathologies: hypertrophy (HCM) and dilation (DCM). In hypertrophy, wall thickness is increased without chamber expansion; however, in dilation, walls are

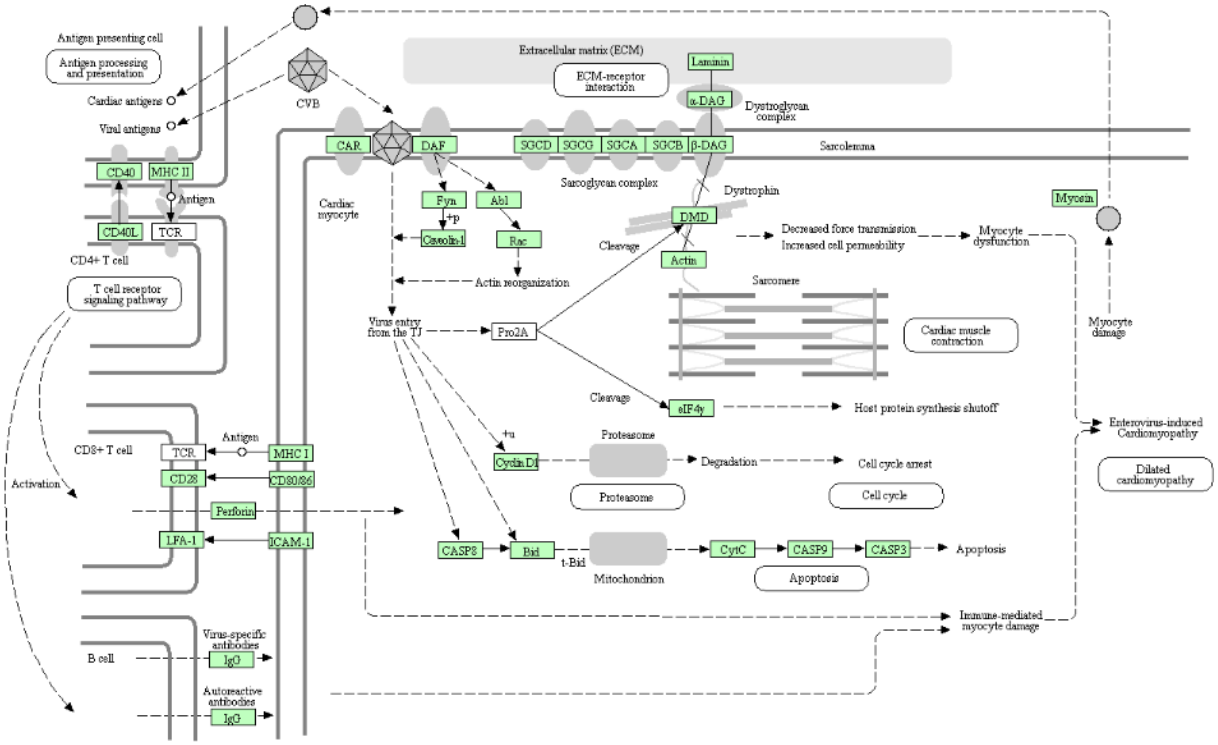

Figure 5. Viral myocarditis and related genes in recorded pathway.

normal or thin but chamber volume is increased. Furthermore a number of serum markers such as C-reactive protein (CRP), phospholipase A2 (PLA2), Nitric oxide synthase3 (NOS3), apolipoprotein C3 (APOC3), proprotein convertase subtilisin/kexin type9 (PCSK9), fibroblast growth factor23 (FGF23), interleukin-10 (IL-10), endotelin1 (EDN1), low density lipoprotein receptor (LDLR), CD39, interleukin-6 (IL-6), GATA4, and CD44 have been identified to be involved in the initiation and progression of heart disease. According to our findings, Heart disease genes that cause either HCM or DCM, include: β-cardiac myosin heavy chain (MYH7), TTN, cardiac actin (ACTC), TNNT2, α-tropomyosin (TPM1), TNNI3, and myosin light chain (MYL3 and MYL2)[9]. Mutations in sarcomere protein genes leading to DCM are different from those in HCM. Different amino acids affecting in each category-giving rise to diverse types of cellular malfunction. As mentioned earlier the development of DCM or HCM depends on the type of mutation. Some mutations result exclusively in mild left ventricular hypertrophy (HCM), while TNNT2 mutations often result in heart failure (DCM) and sudden death. Sarcomere homozygous mutations in either TNNT2 or MYH7 lead to severe hypertrophies. According to clinical genetic experiments, MYH7, TNNT2 and TPM1 mutations are involved in nearly 2 to 4% of DCM cases[10]. It is also notable that, there are a number of mutations occurring in the giant protein titin. Mutations in TTN account for about 25% of DCM cases[11]. Defects in nuclear genes such as Lamin A/C are also linked to DCM[32]. Mutations in desmosomal genes can result in myocyte hypersensitivity in response to right ventricular cardiomyopathy and mechanical stress. Also mutations in plakoglobin, desmoplakin, plakophilin-2, and RyR2 (a calcium channel in sarcoplasmic reticulum membrane of myocytes) have been found in ARVD[12]. Cell surface mechanic-sensors are sensitive to shear stress. Shear stress can induce various intracellular pathways. Many of these pathways are linked to common signaling pathways, such as the Ras/MAPK and the PI3K/Akt pathway[13]. In laminar shear stress, athero-protective proteins, such as NOS-3 become phosphorylated and up-regulated by Akt in a PI3K-dependent pathway. EDN1, a strong vasoconstrictor, is a functional partner of NOS-3 in the regulative process of laminar shear and cardiovascular

development. Thus, EDN-1 and NOS-3 are essential for maintaining vascular homeostasis[35]. EDN-1 has a critical role in both fluid shear stress and HCM pathways[14]. In addition, EDN1 promotes expression, phosphorylation, and activation of GATA4 gene in myocytes. This leads to heightened iNOS activity and therefore increased nitric oxide production. Zinc finger transcription factor GATA4 also seems to play an important role in the pathology of HCM response[15]. It has been reported that CRP, an acute phase-reactant protein, is strongly implicated in cardiac disease. This protein is often made in the liver in response to IL-6 and plays several pathophysiological roles in the inflammatory process. Elevated CRP levels in heart disease suggest this inflammatory biomarker may be directly involved in the pathogenesis of these disorders. CRP can induce apoptosis in myocardial cells, and produce ventricular injury or dysfunction resulting in HCM or DCM[38]. Studies also revealed that serum levels of IL-6 are elevated in both DCM and HCM[16]. More than 50 genes are associated with DCM including: TTN (Titin), BAG3 (BCL2-associated athanogene 3), ABCC9 (ATP-binding cassette, sub-family C, member 9), TTR (Transthyretin), TNNI3 (Troponin I type 3), TMPO (Thymopoietin), TNNC1 (Troponin C type 1), CTF1 (Cardiotrophin 1), DES (Desmin), DMD (Dystrophin), LMNA (Lamin A/C), TNNT2 (Troponin T type 2), PLN (Phospholamban)[10]. These genes often encode desmosomal proteins such as plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmoplakin (DSP) and desmocollin-2 (DSC2). Mutations in components of the cardiac desmosome result in disruption of desmosomal function, as well as heart failure[17]. Several mutations in genes encoding for non-desmosomal proteins have also been reported. These include Transforming growth factor-β3 (TGFB3), ryanodine receptor 2 (RYR2), trans membrane protein 43 (TMEM43) and sodium voltage-gated channel alpha subunit, 5 (SCN5A). In summary, myocardial failure followed by genetic disorders may lead to inflammation and cell apoptosis[18]. It has been found that inflammatory biomarkers including IL-1, IL-6 and CRP are involved in HCM. Under various forms of stress, IL-6 is expressed in myocardium. It can modulate the function of myocardium through a variety of mechanisms, including the induction of left ventricular hypertrophy, cardiomyopathy, and apoptosis in cardiac myocytes. IL-6 level elevates in response to muscle contraction and can be found in both skeletal and smooth muscle as a pro-inflammatory cytokine[19]. Endothelin-1 (EDN-1) is also increased as a potent vasoconstrictor and contributes to hypertrophy in HCM. Researchers showed that increased pressure in hypertrophied heart resulted in over-expression of EDN-1[20].

Conclusion

Single-gene abnormalities contribute to a tiny fraction of heart disease in humans. The process in which a gene mutation induces a response in cells depends on several factors including other genes. Bioinformatics analysis can be helpful in categorizing and remodeling the complex process of responses leading to heart disease. The genes related to heart diseases can be CRP, NPPB, IL-6, ACE2 and GATA4 with high scores and the researchers should find the diagnostic biomarker between them. In continue for a special heart disorder the others like eNOS3, HCM, PKP2, DSG2, TTN, BAG3, ABCC9 and CVB3 have the critical roles.

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