OPEN ACCESS
Freely Available Online

JOURNAL OF HYPERTENSION AND CARDIOLOGY
ISSN NO: 2329-9487

Research

DOI: 10.14302/issn.2329-9487.jhc-21-3742

Some Regulation Mechanisms of Candidate Genes for Human Cardiovascular Diseases

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Summary

Cardiovascular disease is actually a major cause of mortality, illness and hospitalization worldwide. Several risk factors have been identified that are strongly associated with the development of cardiovascular disease. Public prevention strategies have relied predominately on managing environmental factors that contribute to cardiovascular disease, such as obesity, smoking and lack of exercise. The understanding of the role of genetics in cardiovascular disease development has become much more important to link genetics with the onset of disease and response to therapy. This seeks to examine how genes can predispose individuals to cardiovascular disease and how this knowledge might be applied to more comprehensive preventive strategies in the future. In addition, the review explores possibilities for genetics in cardiovascular disease treatment, particularly through the use of identified driver genes and gene therapy. To fully understand the biological implications of these associations, there is a need to relate them to the exquisite, multilayered regulation of protein expression and regulatory elements, mutation, microRNAs and epigenetics. Understanding how the information contained in the DNA relates to the operation of these regulatory layers will allow us not only to better predict the development of cardiovascular disease but also to develop more effective therapies.

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Keywords: Cardiovascular disease, candidate gene, regulation mechanism, human

Received: Feb 10, 2021 **Accepted:** Feb 27, 2021 **Published:** Mar 13, 2021

Editor: Sasho Stoleski , Institute of Occupational Health of R. Macedonia, WHO CC and Ga2len CC, Macedonia.

Introduction

Cardiovascular diseases (CVDs) are a group of diseases of the heart and blood vessels. CVDs are the leading cause of death worldwide [1, 2]. For example, 1 in 3 deaths in the United States are caused by CVDs [1]. In Europe alone, CVD causes over 4.3 million deaths each year [3]. It is also responsible for an estimated 17.5 million deaths in 2005, representing 30% of all deaths [4]. [5] stated that 30% of all global death was attributed to cardiovascular disease. Despite South Asian subcontinent accounts only 20% of the world's population, the CVDs burden is estimated at 60% of the world's CVDs. This may be attributed to a combination of genetic predisposition and environmental factors [6].

The pathogenesis of CVDs is complex, influenced by genetic, environmental and lifestyle factors [7], despite significant disparities related to socio-economic strata and gender [8]. Different fields of cardiovascular medicine has been dramatic progress in diagnosis, prevention and treatment [9, 10], which in turn reduced global and cause-specific mortality [11-13].

Epigenetics has been initially studied in CVD patients for its prominent role in inflammation and vascular involvement [14, 15]. Furthermore, epigenetic studies in cardiovascular medicine revealed a significant number of modifications affecting the development and progression of CVD. In addition, epigenomics are also involved in cardiovascular risk factors such as smoking [16, 17], diabetes, hypertension [18], high cholesterol [3] and age [19].

Even though substantial advances in medical management, prognosis of CVD remains poor, and identification of mechanisms and potential therapeutic approaches are still a priority of considerable importance [3].

However, studies of CVD heritability are confounded by the fact that several other risk factors, such as blood pressure, lipid levels and diabetes, are themselves under genetic control [20]. Nonetheless, several studies have noted that family history is an independent risk factor [21].

CVDs are studied in a mechanistic, genetic and biochemical contexts that include genomic [22], gene expression and proteomic studies [23].

Therefore, the Objectives of this Review Paper Were

- To review research findings and facts on regulation mechanisms of candidate genes for human cardiovascular diseases
- To review nature and prevalence of cardiovascular diseases and its types for human.

Literature Review

Nature and Prevalence of Cardiovascular Diseases

The most prevalent CVDs include ischaemic heart disease (heart attack), cerebrovascular disease (stroke), hypertension, inflammatory heart disease and rheumatic heart disease in that order of prevalence [24]. These five major CVDs are linked to over 16 million deaths annually, with heart attacks alone affecting 12.7% of the global population, followed by stroke, which affects 9.6% of the global population. The numbers of CVD associated deaths per year are much higher in certain regions than others which were 1,106,000, 1,760,000 and 503,000 per year in Americas, Europe and Africa respectively [24].

Types of cardiovascular Disease

Cardiovascular disease includes coronary artery diseases (CAD) such asangina and myocardial infarction (commonly known as a heart attack) [2]. Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease (CHD), valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, andvenous thrombosis [25].

CHD is one of CVD which is the most common type of birth defect, affecting 1% of all live births, and is the leading non-infectious cause of death in the first year of life [26]. It has been recognized that environmental factors during fetal development increase risk of CHD, including viral infections with rubella [27], chemical teratogens like retinoic acid, lithium, dilantin [28] and halogenated hydrocarbon [29] and maternal diseases including diabetes and systemic lupus erythematosus [30].

In humans, heart development begins at 15 to 16 days of gestation with the migration of precardiac stem cells, in five steps:(1) migration of precardiac cells from the primitive streak and assembly of the paired cardiac crescents at the myocardial plate, (2) coalescence of the cardiac crescents to form the primitive heart tube, establishing the definitive heart, (3) cardiac looping, assurance of proper alignment of the future cardiac chambers, (4) septation and heart chambers formation, and (5) development of the cardiac conduction system and coronary vasculature [31, 32].

The establishment of left-right asymmetry is very important to the normal development of heart [33]. Secreted FGF, BMP, Nodal, and Wnt act as input signal of symmetric cardiac morphogenesis, BMP2, FGF8, Shh/ Ihh, and Nodal function as positive regulators, whereas Wnt and Ser are negative regulators [34, 35]. The cardiogenic plate-specific expressed genes NKX2.5, SRF, GATA4, TBX5, and HAND2, compose the core regulatory network of cardiac morphogenesis, controlling heart looping, left-right symmetry and chambers formation. SRF regulates the differentiation of coronary vascular smooth muscle cells [36].

Specific genes such as the NOTCH receptor, Jagged (JAG), WNT, transforming growth factor beta 2 (TGF ß2) and bone morphogenic proteins have been implicated in cardiac neural crest development in the mouse [37]. Complex signal pathways are implicated in the crosstalk between endocardium and myocardium to form endocardial cushion and heart valves, including VEGF, NFATc1, Notch, Wnt/ß-catenin, BMP/TGF-ß, EGF, erbB, NF1 signal pathways [32, 38]. Foxn4 driver gene is expressed in the atrioventricular canal and binds to a *tbx2* enhancer domain to drive transcription of *tbx2b* in the atrioventricular canal defects frequent in humans [39].

Mutation in FBN1 gene encoding extracellular matrix protein fibrillin 1, responsible for Marfan's syndrome [40]. When a specific mutation in the fibrillin 1 (FBN1) gene causes Marfan's syndrome in a family, carriers of the same mutation can display variable clinical manifestations [41].

However, more recent studies suggest that microfibrils normally bind the large latent complex of the cytokine transforming growth factor β (TGF-β) and that failure of this event to occur results in increased TGF-β activation and signaling. Now, investigators are exploring the hypothesis that blocking TGF-β signaling will ameliorate the growth of aortic aneurysms in Marfan's syndrome.

For further examples of therapeutic approaches derived from the study of Mendelian disorders, we refer the reader to a recent review on this topic [42].

Rare mutations in FBN1 cause the thoracic aortic aneurysms and dissections seen in Marfan's syndrome, whereas common SNPs in the introns of FBN1 are the top association result in a GWAS for spontaneous, non-syndromic thoracic aortic aneurysm and dissection [43]. Rare mutations in SCN5A, KCNQ1, KCNH2, KCNE1, and KCNJ2 cause monogenic long QT syndrome, where-as common SNPs in these five genes are associated with QT interval measured on electrocardiograms in the population [44].

Coronary Artery Disease (CAD)

PTPRC, FYB and FCER1G have been identified as key drivers of an inflammatory gene signature underlying multiple diseases (including CAD) [45]. Key driver genes such as SGK1, SIK1 and SLC10A6 (sodium metabolism and hypertension), MT2A and TSC22D3 (glucocorticoid signaling), GADD45G, ERRFI1, GPRC5A, and EGFR (cell growth and apoptosis), and CEBPB, CEBPD, and KCNA5 (heart development and function) [46].

MEF2A disease-causing gene for CAD and MI is highly expressed in the endothelium susceptible to inflammation and the formation of an atherosclerotic plaque, which may result in thrombosis, MI, and sudden death [47].

Familial combined hyperlipidemia (FCHL) is present in patients of CAD which is elevated serum total cholesterol or triglycerides. *USF1* encodes a transcriptional factor belonging to the basic helix-loophelix leucine zipper family and regulates genes involved in glucose and lipid metabolism, including ABCA1 and apolipoproteins CIII, AII, and E [48]. Also dysregulated biological processes such as cholesterol metabolism and transport can eventually lead to CAD [49].

Cerebrovascular Disease (Stroke)

The work that reported a positive association between a mutation of human ANP gene and the risk of stroke [50]. CREBBP gene is mentioned in connection with pathophysiological changes in cerebral vessels predisposing to stroke [51].

There are associations of migraine and stroke with NOS3, EDN and EDNRB regulatory genes [52]. A candidate gene can be suggested as possibly related to variation in stroke risk. In addition PDE4D6 gene is associated with cardiovascular disease [53].

Some findings have been reported that HDAC9 associated with large vessel disease [54] and PITX2 and ZFHX3 related to car-dioembolic stroke [55] and a PITX2 variant and cardioem-bolic stroke [54]. ANP is a well-known physiologically important cardiovascular peptide that exerts natriuretic, diuretic, and vasorelaxant proper-ties, and it is expressed in cardiac and cerebral tissues [56]. In the search for stroke-related genes, another experimental model was investigated, the SHR with MCAO-induced ischemic stroke [57].

Rheumatic Heart Disease (RHD)

Polymorphisms within the promoter region of the FCN2 gene are associated with plasma levels of this protein in chronic RHD patients and probably prolong the time of infection or repeated streptococcal infections [58].

The interleukin 1 (IL-1) gene cluster located on chromosome 2 includes the genes expressing the proinflammatory cytokines IL-1a and IL-1b and their inhibitor IL-1 receptor antagonist (IL-1RA). The ratio of IL-1RA to IL-1 is important in determining the duration and intensity of the inflammatory response [59]. The absence or misrepresentation of two alleles of VNTR from the IL-1RA gene results in a strong inflammatory response. RHD patients with severe carditis had low frequencies of one of these alleles, suggesting the absence of inflammatory control [60].

Mannose-binding lectin is encoded by *MBL2* gene, located on the chromosome [61]. It is considered an acute-phase reactant [62], whose levels can increase up to threefold during the acute-phase response, mainly due to up-regulation by acute-phase mediators [63]. *MBL2* is a highly polymorphic gene, exhibiting variants responsible for large variations in both MBL levels and functional activity [64].

Cardiomyopathy

It is shown that dilated cardiomyopathy tissues contain elevated levels of p53 and its regulators MDM2 and HAUSP compared to non-failing hearts [65]. Also, regulation of MDM2 is critical in cardiac endocardial cushion morphogenesis during heart development [66]. It is also shown that GRB2 plays a role in the signaling pathway for cardiac hypertrophy and fibrosis [67].

Inhibition of SMAD2 phosphorylation preserves cardiac function during pressure overload [68]. JUN gene is linked to different types of mitral valvular disease (MVD), including mitral regurgitation (MR) and mitral stenosis (MS) [69]. It is shown that c-Jun mRNA are upregulated in patients with MS compared with those with MR and that phosphorylated c-Jun N-terminal kinase in the MR group of patients is significantly greater than that in the MS group.

Congenital Heart Disease (CHD)

Mutations in components of the cardiac gene network cause of CHD

Heart development is controlled by a highly conserved network of transcription factors that connect signaling pathways with genes of muscle growth, patterning, and contractility. The core transcription factor network consists of NKX2, MEF2, GATA, TBX, and Hand. Dozens of other transcription factors contribute to cardiogenesis, in many cases by serving as accessory factors for these core regulators. Autoregulatory and cross regulatory of the cardiac gene network maintain the cardiac phenotype once the network has been activated by upstream inductive signals. Mutations in components of the cardiac gene Network cause CHD [70, 71]. For example, mutations in NKX2.5 cause a spectrum of CHDs, including atrial septal diseases (ASDs), ventral septal diseases (VSDs), and cardiac conduction abnormalities [72]. In addition, mutations in TBX5 cause the congenital disease Holt–Oram syndrome, which is characterized by truncations of the upper limbs and heart malformations [73].

Regulatory Pathway of Cardiac Genes

In mammals, four Notch family receptors have

been described: NOTCH1 up to NOTCH4; Notch ligands are encoded by the Jagged (JAG1 and JAG2) and Delta-like (DLL1, DLL3 and DLL4) gene families [37].

The formation of bicuspid aortic valve might reflect the role of Notch signaling in regulating the epithelial-mesenchymal transition required for the generation of the heart valves [37, 74]. Recently, mutations in Notch1 in humans have been shown to cause aortic valve defects Additionally, mutations in various Notch signaling pathway genes, including Jagged1, mind bomb 1, Hesr1/Hey1, and Hesr2/Hey2, result I cardiac defects, such as pericardial edema, atrial and ventricular septal defects, cardiac cushion, and valve defects [75, 76].

MicroRNA Dysfunction

MicroRNAs are natural, single-stranded, non–protein-coding small RNA molecules (∼22 nucleotides) that regulate gene expression by binding to target mRNAs and suppress its translation or initiate its degradation [77]. For example, miR-1 and miR-133 control cardiac and skeletal muscle development [78, 79]. Both genes are under the control of serum response factor, indicating that they are part of a developmental program regulated by cardiac transcription factors. It has been shown that miR-1 targets the cardiac transcription factor HAND2. Deletion of miR-1-2 results in heart defects that include VSDs; surviving mice have conduction system defects and increased cardiomyocyte proliferation. Dysregulation of miRNAs might result in congenital heart disease in human [80].

Epigenetics

Epigenetics refers to DNA and chromatin modifications that play a critical role in regulation of various genomic functions, cell differentiation and embryonic morphogenesis [81, 82]. In epigenetic, phenotypic differences in monozygous twins could result from their epigenetic differences. BAF60C (also known as SMARCD3), a subunit of Swi/Snf-like chromatin-remodelling complex BAF, physically links cardiac transcription factors to the BAF complex. Loss of BAF60C results in severe defects in cardiac morphogenesis and impaired activation of a subset of cardiac genes. The muscle-restricted histone methyltransferase SMYD1 (also known as BOP) is a crucial regulator of cardiac chamber growth and differentiation. Histone deacetylases have mostly been characterized as having an important role in heart hypertrophy and development [37].

Conclusion

Cardiovascular diseases are very important to control since it causes high mortality and morbidity. Gene prediction by different molecular markers such as SNP in genomics, proteomics level that has identified important new genes involved in various forms of cardiovascular disease. Biological validation and medical exploitation of this predictions, as well as characterization of key mechanisms responsible for disease formation and progression, are subjects of future research.

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