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Role of Modifier Genes in Idiopathic Cardiomyopathies

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But however far we may proceed in analysing the genotypes into separable genes or factors, it must always be borne in mind, that the characters of the organism their phenotypical features are the reaction of the genotype in toto. The Mendelian units as such, taken per se are powerless.
Wilhelm Johannsen, 1923

1. Introduction

Cardiomyopathies are chronic diseases of heart muscle, in which the muscle is abnormally enlarged, thickened, and/or stiffened (1). According to American Heart Association, “Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure related disability” (1). Within this broad definition, WHO (1995) and International Society & Federation of Cardiology has classified cardiomyopathies into four types:

- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)
- Restricted cardiomyopathy (RCM)
- Arrhythmogenic right Ventricular cardiomyopathy

2. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is the third most common cause of heart failure after coronary artery disease and hypertension with an estimated prevalence of 1:2500 (1, 2). DCM is characterized by a progressive course of ventricular dilatation and systolic dysfunction clinically. The life expectancy is limited and varies according to the underlying etiology. Myocarditis, immunological abnormalities, toxic myocardial damage, and genetic factors are all assumed to be causes. The familial occurrence of DCM, mostly as an autosomal dominant trait, is more common than generally believed. As a matter of fact, 20–30% of all cases of DCM are caused by genetic mutations in sarcomeric and non sarcomeric genes. In the past decade, major progress has been achieved by investigating families with

inherited DCM. The analysis of candidate genes led to the discovery of cardiac α -actin, the first DCM-causing gene. In the first report on MYH7 mutations as cause of familial DCM, two different missense mutations were identified in 2 out of 21 families with heritable pure DCM without other organ manifestations. In addition, several groups have described patients who exhibit a conversion from a hypertrophic cardiomyopathy (HCM) to a DCM phenotype. Mutations in TNNT2 seem to lead to complete penetrance and a high proportion of patients die suddenly at younger ages whereas patients with mutations in MYH7 may have a more benign disease course. Mutations in genes encoding sarcomere, cytoskeletal, and nuclear proteins, as well as proteins involved in regulation of Ca^{2+} metabolism have been found to be associated with DCM (6-16). When considering the contribution of all known DCM genes, it is estimated that mutations in known disease genes are the cause of inherited DCM in approximately 20% of cases. This low proportion reflects a more complicated genetic etiology than assumed.

3. Hypertrophic cardiomyopathy

HCM is a mendelian trait with an autosomal dominant pattern of familial inheritance whose clinical diagnosis is based on the identification of increased wall thickness of left ventricle in absence of loading conditions (hypertension and valve disease) (17, 18). Mostly based on studies performed until the late 1980s, HCM was originally described and perceived as a rare disease. Later subsequent studies revealed HCM as an epidemiologically relevant, widespread, yet infrequently diagnosed condition. These studies, however, were run according to different designs: some utilized echocardiography as a screening tool of large populations and should thus be considered as true prevalence studies, while others reported data from large group of subjects referred to echocardiography according to different criteria and protocols. Thus, this latter group of studies may have underestimated the prevalence of HCM as small fraction of the originally screened individuals was subsequently referred to echocardiography. From these studies HCM emerges as an important global disease affecting approximately 1:500 individuals worldwide, and is the most common cause of sudden death in the young (3).

The disease seems to be sporadic in ~ 50% of cases but the incomplete penetrance of the phenotype in carriers of some mutations could lead to underestimation of the percentage of familial cases. It is now known that HCM is genetically heterogeneous and caused by mutation in any one of the genes that encode contractile proteins of the cardiac sarcomere, involving thick filaments and thin filaments and in cardiac myosin binding protein C - the structural network that joins thick and thin filaments (17, 19-22). Hundreds of mutations in more than a dozen genes that encode protein constituents of the sarcomere have been identified in HCM (23, 24). MYH7, MYBPC3, TNNT2 and cardiac troponin T (TNNT2) are the most prevalent disease genes, but mutations have also been found in α -tropomyosin (TPM1), cardiac actin (ACTC), cardiac troponin C (TNNT1), essential myosin light chain (MYL3), regulatory myosin light chain (MYL2), α -cardiac myosin heavy chain (MYH6), titin (TTN), γ 2 subunit of the protein kinase A (PRKAG2). The prognosis of HCM varies considerably with respect to the reported mutations.

4. Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is an uncommon myocardial disease characterized by increased stiffness of ventricles leading to impaired filling of blood in the presence of

normal wall thickness and systolic function. Most affected individuals have severe signs and symptoms of heart failure. RCM may present with interventricular conduction delays, heart block, or skeletal muscle disease. However, the diagnostic criteria for restriction are not universally accepted, and the morphology generally overlaps with HCM, often making the diagnosis difficult.

Previously, RCM was believed to be of idiopathic origin unless otherwise associated with inflammatory, infiltrative or systemic disease but now the results of recent molecular genetic investigations have revealed that a substantial proportion of RCM (not associated with systemic disease) is caused by mutations in sarcomeric disease genes that have been associated with HCM and DCM (25-29).

5. Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic Right Ventricular cardiomyopathy/Dysplasia (ARVD) is a cardiomyopathy characterized by progressive degeneration and fibrous-fatty replacement of right ventricular myocardium, by arrhythmias with a left branch block pattern and by increased risk of sudden death in juveniles. The prevalence of ARVD has been estimated to be 1 in 5,000. Several forms of dominant arrhythmogenic right ventricular cardiomyopathy/dysplasia have been identified so far: ARVD1 (14q24.3), ARVD2 (1q42), ARVD3 (14q11-q12), ARVD4 (2q32), ARVD5 (3p23), ARVD6 (10p12-p14) and ARVD7 (10q22). Mutations in the genes encoding the cardiac ryanodine receptor were detected in patients affected with ARVD2.11 (30, 31). Attempts to identify genes involved in other dominant ARVDs were so far unsuccessful.

6. Modifier genes

In many genetic disorders in which a primary disease-causing locus has been identified, evidence exists for additional trait variation due to genetic factors. These findings have led to studies seeking secondary 'modifier' loci. Identification of modifier loci provides insight into disease mechanisms and may provide additional screening and treatment targets. Genetic background, often referred to as the modifier genes, do not cause the disease but simply affects the severity of its phenotypic expression particularly in case of autosomal dominant disorders in which age-dependent onset and variable expressivity are characteristic. The final phenotype is the result of interactions between the causal genes, genetic background (modifier genes), and probably the environmental factors.

One of the major features of cardiomyopathies is a wide phenotypic heterogeneity among affected subjects, which is characterized by variable degree or distribution of hypertrophy and prognosis in HCM patients and variable penetrance of disease in DCM patients carrying same mutations. Part of this can be explained by locus heterogeneity but genetic studies have revealed the presence of clinically healthy individuals carrying the mutant allele, which is, in first-degree relatives, associated with a typical phenotype of the disease. This variable expressivity suggests the existence of modifier genes or polymorphisms, which modulate the phenotypic expression of the disease. Obvious candidate modifier genes encode proteins implicated in cardiac growth and hypertrophy. Several components of the renin-angiotensin-aldosterone system (RAAS) and adrenergic signaling pathways have been analyzed in patients with idiopathic cardiomyopathies. In fact genetic variations in these genes might be one explanation for the well known inter-individual variations in drug responses (ACE inhibitors and beta blockers) in patients.

In this chapter, we have provided information on association of several candidate genes with clinical phenotype of cardiomyopathies. We identified studies of modifier genes from PubMed search using the MESH terms 'cardiomyopathy and genetics or genetic polymorphisms, or MESH terms Modifier genes and cardiomyopathy or heart failure, limiting results to the English language publications on studies in human adults. We further identified specific polymorphisms of interest noted in earlier reviews and performed additional PubMed searches based on these candidate genes. Our aim was to collate the existing body of knowledge on common genetic polymorphisms and their relationship to phenotypic expression of cardiomyopathy. We have included information on individual study size and design, as well as the strength of statistical association. We tried to remove bias in the selection of research articles by selecting maximum number of studies and from different ethnic groups and by reviewing both published and unpublished (where ever possible) data. The reference lists of all articles obtained were examined to identify additional studies. All titles and abstracts from the search process were examined. The retrieved studies were examined and included if: 1) the patients were well characterized for cardiomyopathies i.e. LVEF $\leq 40\%$ for DCM and LVH (septal thickness) $>13\text{mm}$ for HCM and 2) Results were compared with well categorized control samples.

7. Renin Angiotensin System genes as modifiers in idiopathic cardiomyopathies

The classical renin-angiotensin system (RAS) consists of renin, angiotensin-converting enzyme, angiotensinogen and its receptors. Renin is synthesized in the kidney, stored in the afferent arterioles and released in response to hemodynamic, neurogenic, and ionic signals. Renin, has a very high specificity for its substrate angiotensinogen (AGT). Renin cleaves AGT to release the amino terminal decapeptide angiotensin I (Ang I). Angiotensin-converting enzyme (ACE), which is expressed endothelially, then cleaves Ang I to release the two carboxy terminal amino acids. The resulting octapeptide is designated angiotensin II (Ang II). Ang I is biologically inactive while Ang II is a potent vasoconstrictor. The members of RAS pathway acting as modifier genes will be described in this chapter.

8. Angiotensin Converting Enzyme (ACE)

Angiotensin I-converting enzyme (ACE), is a dipeptidyl peptidase transmembrane-bound enzyme (32). A soluble form of ACE in plasma is derived from the plasma membrane-bound form by proteolytic cleavage of its COOH-terminal domain. There are two distinct isoforms of ACE: somatic and testicular. They are transcribed from a single gene at different initiation sites. The somatic form of ACE is a large protein (150–180 kDa) that has two identical catalytic domains and a cytoplasmic tail. It is synthesized by the vascular endothelium and by several epithelial and neural cell types. The testicular form of ACE is a 100- to 110-kDa protein that has a single catalytic domain corresponding to the COOH-terminal domain of somatic ACE and is only found in developing spermatids and mature sperm where it may play a role in fertilization. It has two primary functions:

- ACE catalyses the conversion of AngI to AngII, a potent vasoconstrictor
- ACE degrades bradykinin, a potent vasodilator, and other vasoactive peptides, (33)

These two actions make ACE inhibition a goal in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy, and type 2 diabetes mellitus. Inhibition

of ACE (by ACE inhibitors) results in the decreased formation of AngII and decreased metabolism of bradykinin, leading to systematic dilation of the arteries and veins and a decrease in arterial blood pressure. In addition, inhibiting AngII formation diminishes AngII-mediated aldosterone secretion from the adrenal cortex, leading to a decrease in water and sodium reabsorption and a reduction in extracellular volume (34).

Genetic variations in ACE gene have been reported to be associated with many cardiovascular diseases including cardiomyopathies. An insertion or deletion of a 287bp DNA fragment in the ACE gene (ACEI/D) has been found to be an important modifier which may influence the clinical phenotype in cardiomyopathies. ACE I/D polymorphism has been shown to be associated with left ventricular hypertrophy (LVH) in untreated hypertension, complications of atherosclerosis (35) and HCM (36- 40). D allele was shown to be associated with increased risk of cardiomyopathy in Asian Indians; HCM patients with DD genotype were found to be more susceptible to disease (38). D allele carrying genotypes (DD, ID) were also found to be associated with higher mean septal thickness as compared to II genotype in HCM patients, however, the difference was not significant ($P>0.05$). DCM patients with ID genotype also showed significantly decreased left ventricular ejection fraction (LVEF) indicating a possible association of D allele in pathogenesis of DCM. It has been suggested that DD genotype may be an important biomarker of HCM and presence of the ACE gene I/D polymorphism may be an important marker to identify those individuals with HCM who are likely to have more progressive disease, and therefore at higher risk of adverse clinical outcomes (38, 39). DD-ACE is considered a 'pro-LVH' modifier in HCM (41). DD genotype has been shown to be associated with increased tissue levels of ACE resulting in increased AngII which may lead to increased hypertrophy and fibrosis.

9. Angiotensinogen (AGT)

AGT is an inactive peptide of Renin-Angiotensin System that is produced constitutively and released into the circulation mainly by the liver. Gene for AGT is located on chromosome 1 and codes for 452 amino acids. The first 12 amino acids are the most important for activity. Angiotensinogen is converted into bioactive Angiotensin II, mainly by the action of Renin and ACE.

Given the importance of AGT as a substrate for generation for vasoconstrictive AngII, it has been used as a therapeutic target in heart failure (HF). Genetic variations of this gene have been suggested to represent a predisposing factor to heart failure. Two single nucleotide polymorphisms (SNPs) in AGT (T174M and M235T) have been shown to be associated with HF; for example, an increased frequency of the AGT T235 allele and the AGT 235TT genotype has been reported in HCM associated HF. Rigat et al (1990) have studied AGT polymorphism in 111 healthy volunteers and 58 HF patients with a documented left ventricular ejection fraction (LVEF) $\leq 40\%$ within the previous 6 months. And observed mutant T allele (T235) to be more prevalent in HF group as compared to healthy controls ($P = 0.0025$, OR 2.02, 95% CI 1.24, 3.30); AGT haplotype (174M and 235T) was also found to be associated with the HF phenotype ($P = 0.0069$) (45). An evaluation of gene-gene interactions revealed significant interaction between AGT (T235) and ACED polymorphisms in the HF group ($P = 0.02$, OR 2.12, 95% CI 1.11, 4.06) suggesting that AGT/ACE gene combination may play an important role in disease predisposition (43). Since polymorphisms of the ACE gene can modulate the circulating AngII levels (42), thus co occurrence of risk alleles of both ACE and AGT genes could be associated with left ventricular hypertrophy (LVH).

AngII, along with pressure overload, has been shown to play a key role in myocardial fibrosis (one of the key features in HCM) by regulation of synthesis of fibrillar collagen in cardiac fibroblasts (44). However, several studies failed to find an association between AGT M235T polymorphism and risk of heart failure (45, 46). Thus, role of these genetic polymorphisms as determinants of disease phenotype (i.e. LVH) still remains to be confirmed.

10. Angiotensin Receptors (AGTR)

AGTRs are a class of G protein-coupled receptors. There are two types of angiotensin receptors: Angiotensin Receptor Type1 (AGTR1) and Angiotensin Receptor Type2 (AGTR2). AGTR1 and AGTR2 receptors share a sequence identity of ~30%, but have a similar affinity for AngII, which is their main ligand.

The AGTR1 receptor belongs to the G protein-coupled receptor (GPCR) superfamily and is primarily coupled through G proteins to the activation of phospholipase C and calcium signaling. The AGTR1 receptors mediate virtually all of the known physiological actions of AngII in cardiovascular, renal, neuronal, endocrine, hepatic, and other target cells. These actions include the regulation of arterial blood pressure, electrolyte and water balance, thirst, hormone secretion, and renal function. The gene coding for AGTR1 is located on chromosome 3 and codes for 359 amino acids. A single nucleotide polymorphism A1166C in 3' UTR of AGTR1 gene has been found to be associated with increased left ventricular mass without hypertension (47). Arthur et al showed that the AGTR1 genotype influenced the magnitude of LVH in subjects with HCM and it was significantly higher in patients carrying risk 'C' allele genotypes than in AA homozygotes, so proposed that A/C1166 polymorphism could modulate the phenotypic expression of hypertrophy in subjects with HCM and may explain why individuals with the same HCM mutation show a significant variability in the magnitude of LVH (48).

11. Adrenergic receptor genes as modifiers in idiopathic cardiomyopathies

Adrenergic receptors mediate the central and peripheral actions of the neurohormones epinephrine and norepinephrine. Stimulation of adrenergic receptors by catecholamines released from sympathetic branch of autonomic nervous system results in a variety of effects such as increased heart rate, regulation of vascular tone and bronchodilation. In the central nervous system, adrenergic receptors are involved in many functions including memory, learning, alertness and the response to stress.

β -Adrenoceptors (β -AR) are expressed in many cell types throughout the body and play a pivotal role in regulation of cardiac, pulmonary, vascular, endocrine and central nervous system. Although originally adrenergic receptors were divided into two types: α and β , but later on depending on the pharmacological differences these were further divided into many subtypes.

Several different subtypes of β -ARs have been reported in the myocardium and many functionally relevant polymorphisms in the genes encoding for these receptor subtypes have been identified (49). The β 1-AR is the dominant subtype and represents 70-80% of β -ARs in the non failing heart (50); β 2-AR represents 20-40% (51). In vascular smooth muscle the majority of β -ARs are β 2AR. Desensitization and downregulation of adrenergic receptors are principal mechanism observed in heart failure. Desensitization is the mechanism by which cells decrease effector responses, despite the presence of ligands; this is usually due to

defect in G-protein coupling. In heart failure, both β 1-AR and β 2-AR are significantly desensitized due to uncoupling of receptor from its respective signaling pathways (52, 53). Several SNPs in both β 1-AR (ADRB1) and β 2-AR (ADRB2) genes have been examined for association with HF. Two (ADRB1) SNPs Ser49Gly and Arg389Gly have been commonly studied for association with HF (54). Cinzia et al. showed that the β 1-AR Gly49 variant and the β 2-AR Gly16Gly genotypes were significantly and independently associated with the DCM phenotype (55). We have examined association of ADRB2 Gln27Glu polymorphism in modulating the phenotypic variability in patients diagnosed with idiopathic cardiomyopathies in Asian Indian patients and observed that HCM patients with mutant Glu27 allele had lower mean septal thickness as compared to carriers of wild type allele but the results lacked statistical significance ($p > 0.05$). DCM patients with 27Glu allele also showed decreased LVEF indicating a possible role of this polymorphism in pathogenesis of DCM. Another polymorphism (ADRB2 Q27E), however, was not found to be associated or influence phenotypic variability of the idiopathic cardiomyopathies in the same cohort (unpublished data). In vitro studies have indicated that these SNPs result in variation in the receptor coupling to stimulatory G (Gs)-protein or agonist-promoted receptor downregulation (56-60). Unlike the β 1-AR, the β 2-AR does not undergo down regulation in failing myocardium, but may account for about 40% of surface receptors (61). It has been proposed that changes in the expression or properties of the β -adrenergic receptors due to single nucleotide polymorphism (SNPs) might influence cardiovascular function or may contribute to the pathophysiology of several disorders like hypertension, congestive heart failure, asthma, obesity or type 2 diabetes mellitus.

12. Other modifier genes in cardiomyopathies

Recently several other genes such as ACE2, Calmodulin III and TnnI3K have been also studied for their role as modifier genes in cardiomyopathies.

13. Angiotensin Converting Enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2) is a homolog of ACE, and hydrolyzes Ang I to produce Ag-(1-9), which is subsequently converted into Ang-(1-7) by a neutral endopeptidase and ACE. ACE2 releases Ang-(1-7) more efficiently than its catalysis of Ang-(1-9). Thus, the major biologically active product of ACE2 is Ang-(1-7), which is considered to be a beneficial peptide of the RAS cascade in the cardiovascular system (62, 63). ACE2 is present in a wide variety of cells including heart (64-68). ACE2 is a carboxy-monopeptidase with a preference for hydrolysis between a proline and carboxy-terminal hydrophobic or basic residues, differing from ACE, which cleaves two amino acids from AngI. ACE inhibitors have no direct effect on ACE2 activity. As a result, ACE2 is a central enzyme in balancing vasoconstrictor and proliferative actions of AngII with vasodilatory and antiproliferative effects of Ang-(1-7) (66, 69).

Genetic variants in the ACE2 have been recently shown to be associated with left ventricular mass, and LVH in hemizygous men (70). Two mutant alleles of ACE2 SNPs (rs2106809 and rs6632677) have been also found to be associated with increased risk of HCM. An ACE2 haplotype comprising of mutant alleles of these two SNPs was found to be associated with 1.59 fold increased risk of HCM in male patients (71). These observations suggest that ACE2 genotypes may be important determinants of quantum of LVH in patients with HCM.

14. Calmodulin gene

Proteins involved in hypertrophic pathways or mediators of Ca^{2+} signaling in cardiomyocytes are promising candidates as modifier genes (72, 73). Calmodulin (CaM) is a ubiquitous, highly conserved Ca^{2+} sensor involved in the regulation of a wide variety of cellular events. Many of the actions of Ca^{2+} are mediated through its interaction with calmodulin (CaM), which serves as an intracellular sensor for Ca^{2+} ions and plays a major role in Ca^{2+} homeostasis. Thus, any genetic variant that directly affect CaM gene expression and/or function would be expected to impact on the intracellular Ca^{2+} concentration. In humans, CaM is encoded by a multigene family consisting of three members, CALM1, CALM2, and CALM3, which are located on chromosomes 14q24–q31, 2p21.1–p21.3, and 19q13.2–q13.3.22. A -34 T>A polymorphism in the 5'-flanking region of human CALM3 gene has been shown to be differently distributed between familial HCM (FHC) patients and controls and between affected and healthy carriers of an FHC mutation indicating that -34 T>A CALM3 polymorphism is a potential modifier gene for FHC in patients carrying a mutation in either the MYH7 or MYBPC3 gene (74).

15. Cardiac Troponin I-interacting kinase

Cardiac troponin I-interacting kinase (Tnni3k) is a novel cardiac specific protein kinase that interacts with cardiac Troponin I (cTnI) (75). A yeast two hybrid interaction screen with a C-terminal fragment of Tnni3k identified several additional sarcomeric proteins as putative binding partners such as cardiac α -actin and myosin binding protein C (76). Wheeler et al showed that a 3784(C>T) polymorphism in intron 19 in Tnni3k coding gene activates a cryptic splice site, generating an aberrant transcript that undergoes NMD (Nonsense Mediated Decay), leading to drastically reduced mRNA levels and an apparent absence of Tnni3k protein. Their study showed that Tnni3k might modulate sarcomere function through interactions with key components of the sarcomeric complex (77). However, the role of TNNI3K polymorphisms in modulating phenotype of cardiomyopathy patients is not well studied and needs to be examined in different ethnic populations.

16. Modifier genes as potential therapeutic interventions in cardiomyopathies

Cardiomyopathies are emerging as a frequent cause of hospitalization and mortality among men and women world wide. Traditional risk factors and mutations in causal genes alone cannot fully account for the inter-individual variation in the prevalence and penetrance of the disease in general population. Identification of modifier loci provides insight into disease mechanisms and may provide additional screening and treatment targets.

Recent studies suggest that pharmacologic blockade of modifier genes could confer beneficial effects in cardiomyopathies, such as relief in symptoms (syncope, dyspnea, LVEF etc.). ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and beta blockers are now part of routine therapy for hypertension, heart failure and myocardial infarction (MI). They reduce the risk of all cardiovascular events and all-cause mortality by reducing blood pressure makes it easier for the heart to pump blood and can improve heart failure.

Apart from the pharmacological modulations of modifier genes, many trials on gene therapy and animal models of the disease are on going which will provide better understanding of the pathophysiology of cardiomyopathies and will also help in better patient management. For example, pharmacologic interventions in transgenic animal

models of HCM aimed at the potential modifier genes have highlighted the role of modifier genes in the pathogenesis of morphologic and histological phenotypes in HCM. Lim et al showed that blockade of AGTR1 in the cardiac troponin T-Q92 transgenic mouse model reduced interstitial collagen volume by 49% and expression of collagen (I) mRNA and transforming growth factor, a known mediator of profibrotic effects of angiotensin II, by approximately 50% (78). Because interstitial fibrosis is considered a major risk factor for SCD and ventricular arrhythmias in human patients with HCM (69, 79), it illustrates that interventions aimed at the modifier genes could reduce the severity of the phenotype (myocardial fibrosis, LVH, risk of SCD) and mortality in idiopathic cardiomyopathies.

To conclude, along with identification of mutations in causal genes, delineation of genetic variations in modifier genes is needed to understand the pathogenesis of the cardiomyopathies and for symptomatic treatment of the patients. This approach will be helpful for personalized medicine as etiology and severity of idiopathic cardiomyopathies is highly variable in patients.

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Atherosclerotic Cardiovascular Disease

Edited by Dr. Ksenija Pesek

ISBN 978-953-307-695-9

Hard cover, 124 pages

Publisher InTech

Published online 03, October, 2011

Published in print edition October, 2011

Cardiovascular diseases (CVD) are still one of the leading causes of death in the world. The book *Atherosclerotic Cardiovascular Disease* is a contribution to the application of new knowledge in the area of cardiovascular diseases. The book comprises six chapters divided in three subsections, starting with the General Considerations of Cardiovascular Disease, through Diagnostic Techniques, and Specific Therapy.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Madhu Khullar, Bindu Hooda and Ajay Bahl (2011). Role of Modifier Genes in Idiopathic Cardiomyopathies, *Atherosclerotic Cardiovascular Disease*, Dr. Ksenija Pesek (Ed.), ISBN: 978-953-307-695-9, InTech, Available from: <http://www.intechopen.com/books/atherosclerotic-cardiovascular-disease/role-of-modifier-genes-in-idiopathic-cardiomyopathies>

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