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Interpretation of Coronary Artery Disease through Environmental/Genetic Risk Factors and Contributing Genes: A Comprehensive Review

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Abstract

Coronary artery disease is considered as major cause of death all over the world. Although it is associated with traditional risk factors like age, gender, hypertension, diabetes, smoking, such phenotypes also have strong association with genetic background. Here we reviewed the available data concerned to CAD traditional as well as genetic markers along with contributing genes and their interactions with environment. CAD as a polygenic disease possess about 50%-60% heritability causing difficulty in understanding its genetic architecture. Besides, complicated pathophysiological processes including both genetic and environmental interactions may increase or decrease the CAD risk depending upon the expression of concerned genes. In future, adequate genetic markers may be identified presenting risk profile to prevent CAD.

Keywords: Coronary artery disease; Pathophysiology; Emanating risk factors; Genetics of CAD; Genetic risk factors; Contributing genes; Environmental interactions

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Introduction

CAD is considering as major cause of death now a day, contributing about deaths of 17 million people annually all over the world. In China, because of CAD approximately 700,000 deaths set down every year. As CAD is complex, polygenic and multifactorial, it effects by a range of environmental disclosure and genetic diversity which may include age, gender, hypertension, diabetes, cigarette smoking, family history, and dyslipidemia [1]. Life style has strong association with CAD, as strong physical activity conducted per week or twice a week is associated with considerably lower CAD risk as compared to those performed no or less activity. However, persistent strong activity has no association with superior results [2]. Based on sibling and population studies, it is approximated that 40-60% of vulnerability to CAD is accredited to hereditary factors [3]. The pathophysiology in CAD includes various metabolic processes specifically inflammatory cells accumulation as well as lipid accumulation. Previously, in various populations, about 400 loci and genes have been identified in the susceptibility to CAD by Genome-Wide Association Studies (GWASs). Among these 400 CAD genes, several genes belong to the lipid level [4]. Translational and observational epidemiology research cracks have brought about remarkable betterment in enhancing the perception of the morbid physiology of CAD. The obviation and treatment plans developed by this understanding decrease >50% age-adjusted death rate of CAD in USA from 1980 to 2000. However, in spite of all this progress, CAD is still the leading cause of death [5].

Literature Review

Genetic testing is available increasingly now a days, it become possible the identification of genetic markers which represent the risk of CAD and their use in clinical practice. Today, the genetic marker measurement is non-invasive, making detection of CAD genetic predisposition easier. The measurement of such markers is easier for screening of high-risk individual in early life. Unlike circulating biomarkers such as cholesterol and triglycerides, genetic markers do not fluctuate. For prevention strategies, it is good to have screening in time (lifestyle and drug modification). Early risk factor modifications can prevent or postpone the disease [6]. It is sensible to assess the genetic variations having association with changing risk factors like lipid levels and blood

pressure. For effective CAD treatment therapies, it is important to improve understanding about numerous epigenetic, as well as genetic cues developing heart failure [7].

CAD can be prevented by inciting adherence to healthy lifestyle in population –for instance, avoiding obesity, not smoking, regular exercise and healthy diet. Additional medication can be used by increased-risk individuals to lower LDL cholesterol level (for instance, statins), decrease blood pressure, or prevent blood clot formation (for instance, aspirin). A procedure of placing a stent or bypass narrowed vessels by open-heart surgery can be followed to restore blood flow. Because of considerable risk of outbreak in high-risk individuals, medical therapies are strengthening day by day [8].

Risk factors for CAD

Typically CAD risk factors include hyperlipidemia, hypertension, smoking, family history, diabetes mellitus etc. The contribution of these traditional risk factors to CAD is only 50%. For providing a precise CAD risk assessment, a well-planned biochemical, clinical and genetic studies in CAD risk developing subjects and in CAD patients are mandatory (9). Here we will discuss only emanating and genetic risk factors.

Emanating/Proceeding risk factors for CAD

Despite a number of traditional risk factors, about 50% of CAD is still unexplained. Thus, researchers suggested some emerging risk factors contributing CAD. Some emerging RFs as oxidative stress, antioxidant system, Advanced Glycation End Products (AGES), along with novel risk factors like homocysteine, lipoprotein (a), fibrinolytic factors and coagulation, high sensitivity C-creative protein (hs-CRP) and inflammatory markers are linked to high CAD risk. DNA damage is recognized as an emanating risk factor for CAD and atherosclerosis [9].

Oxidative stress

A high level of reduction potential in the cell, or a low level of reducing capacity by redox couples in the cell is called as oxidative stress. An imbalance betwixt the reactive oxygen production and detoxification of reactive intermediates by biological systems or resulting damage repair is the main cause of oxidative stress. Because of their non-specific and high reactive nature, ROS can strike lipid membranes and other biomolecules. Cellular membrane damage is the crucial toxic effect by excessive ROS, the process called as lipid peroxidation. Double bonds; i.e., in PUFAs and guanine bases of DNA are the preferential targets of chemical reactions. Oxidation of LDL by ROS is thought to be an important step for progression and initiation of atherosclerosis. Because of ROS overproduction, increased oxidative stress in CAD is observed, which can cause reduced antioxidant capacity. ROS exist normally with the biochemical antioxidant balance in aerobic cells [10].

Antioxidant system

A molecule which is capable of oxidation inhibition of any other molecule is termed as antioxidant. Antioxidants are endogenous or exogenous compounds that acts in various ways, as scavenging ROS and their precursors, ROS formation inhibitor and metal ions binding needed to catalyse ROS generation. Increased lipid peroxidation occurs because of suppression of scavenging mechanisms and enhanced processes of generation of free radicals. Recently, enhanced oxidative stress or impaired defense of antioxidants has been regarded as contributing factor for progression and initiation of CAD complications [11]. Antioxidants reduce the severity and risk of the atherosclerosis by lipid peroxidation inhibition. This framework suggests that in conjunction with plasma lipid and lipoprotein estimation, antioxidant–oxidant profile evaluation in individuals will significantly contribute to prophylaxis, risk assessment and CAD management.

Advanced Glycation End Products (AGES)

For searching molecular mechanism and by-products of metabolism performing pathogenic role, increased level of Advanced Glycation End Products (AGEs) represent a critical risk factor for CAD progression in both of these cases. AGEs interaction with transmembrane receptor cell, RAGE in smooth muscle and endothelial cells also in platelets, causes activation of intracellular signaling which results in endothelial injury, function modulation of vascular muscle cell and platelet activity alteration. Furthermore, AGEs tissue accumulation affects treatment approaches involved in being stent restenosis [12]. AGEs represent a condemnatory family of particles that plays a vital role in pathophysiology of CAD. As they directly implicate in atherosclerosis, vascular stiffness and intracellular signaling modulation with damaging effects in response of endothelial cells, platelet activity and VSMCs function, AGEs are considered as vital risk factors of cardio metabolism. Additionally, the interference of AGEs with the treatment predisposes subjects to a stubborn cardiovascular risk that emphasizes the need of improving analytical measurements, biomarker potential establishment and their integration for risk stratification of subjects and in decision of treatment. The symbiotic action of nutritive AGEs to the endogenous load indicates the necessity for lifestyle modification in prevention and therapeutic plan of myocardial ischemia along with its complications, with selective AGE modulating drugs [13].

DNA damage

Modern studies regarding DNA damage provides new perception about atherosclerotic pathogenesis leading to the progression of new therapeutic approaches. Resent evidences indicate that oxidative DNA damage represents a potential link between atherosclerotic oxidative theory and its inflammatory nature. Various atherosclerosis supporting animal models indicates that oxidative DNA damage plays a vital role in the formation and atherosclerotic complications. Human researches also support atherosclerotic mutational hypothesis. It is suggested by authors that xenobiotic induces DNA damage at increased level that plays a vital role in early atherogenesis phases [14]. Various responses are produced by DNA damage, including apoptosis, DNA repair and senescence. These damages if not repaired, cause mutations that can cause diseases. In order to get protection from genome instability along with its harmful consequences, subjects have

developed various DNA repair systems [15]. The increased DNA damage is due to enhanced imbalance between antioxidant and oxidant defense production in subjects possessing metabolic syndrome. Metabolic syndrome produces increased oxidative stress and is an important contributing factor of CAD [16].

Genetics of CAD

The long-acknowledged CAD familial clustering recommends that genetics of organisms play a vital role in the development of CAD, with its heritability estimated approximately 50% - 60%. To understand CAD genetic architecture has become costly and difficult because of its heterogeneity and fundamental multi-decade complicated pathophysiological processes which involve both environmental and genetic interactions. The CAD clinical heterogeneity clarify spectrum of diseases in the genetic studies which provides an overview of historical understanding and heritability estimation of CAD [17]. Understanding of CAD genetic basis provides an insight regarding the disease pathogenesis as well as underpinning for development of therapeutic and preventive strategies [18]. Population-based as well as clinical studies have suggested that genetics play a vital role in development of CAD. The CAD family clustering phenomenon was reported in 1960s and 1950s [17]. It is estimated that CAD heritability in male twin is 57% (50%-59%) and in female twin is 38% (25%-50%) [19]. The effect of genetics is obvious at the age of 36 to 86 years [20]. The genetic risk factors have no dependence with typical risk factors for disease. The traditional risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, obesity, physical activity, tobacco, and C-reactive protein are familiar to possess their own complicated genetic components having individual values of heritability, estimated in twins studies [17] **(Figure 1).** The collective effect of environmental factors, age, and genetic factors determine the atherosclerotic CAD development with its complications [21].

Genetic Factors

Familial Hypercholesterolemia (FH)

The key monogenic disease-causing susceptibility to CAD and atherosclerosis is Familial Hypercholesterolemia (FH). FH is a most common disorder of genetics, and is marked by high level of Low Density Lipoprotein cholesterol (LDL-C). FH is a genetic disease and even single mutation can cause an elevated risk for premature MI and development of atherosclerotic plaque [22].

The diagnosis of FH is done by family history and circumferential blood lipid profile. However, genetic screening still has not been adopted universally not mandatory, but recommended in Norway, United Kingdom, and Netherland. Not all FH mutation carriers exhibit severely elevated level of cholesterol. A study represents that about 27% of individuals have normal concentrations of LDL-C (suggesting partial penetrance of mutation). While among individuals who were diagnosed with acute hypercholesterolemia, having level of LDL-C greater than 4.91 mmol/L (190 mg/dL), only 2% of them were FH mutation carriers. These data represent that the monogenic disorders results for only a small portion of diseases related to atherosclerotic diagnosed cases. Most of the cases are polygenic, which results from complicated interactions among epigenetic, environmental, and genetic factors [23].

Several gene mutations responsible for the development of FH and resultantly CAD, involved are, mutations in the genes of LDL receptor (*LDLR*), apolipoprotein B (*ApoB*), protein convertase subtilisin/kexin type 9 (*PCSK9*), ATP binding cassette sub-family G (*ABCG*) member 8 (*ABCG8*) or member 5 (*ABCG5*), and LDLR adaptor protein 1 (*LDLRAP1*) **(Figure 2)** [24].

Low-Density Lipoprotein Receptor (LDLR)

Hepatic LDLR is a principal receptor which is responsible for LDL-C clearance from blood flow. A complex of LDLR/LDL-C is formed by binding of LDL-C with LDLR, which undergoes endocytosis within the clathrin coated vesicle. After translocation to cytoplasm, LDLR separates from LDL-C, and undergoes further degradation, LDLR recycles rapidly, and then folds back rapidly to cell surface [25]. The LDL-C uptake mechanism by LDLR is a specified process, which is influenced by different environmental and hereditary factors. Familial hypercholesterolemia and its outcomes can be

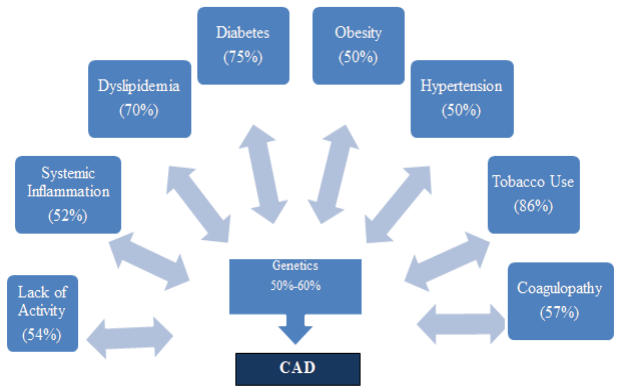

Figure 1 The genetic factors contribution is illustrated either directly or through traditional risk factors for the manifestation and development of CAD [17].

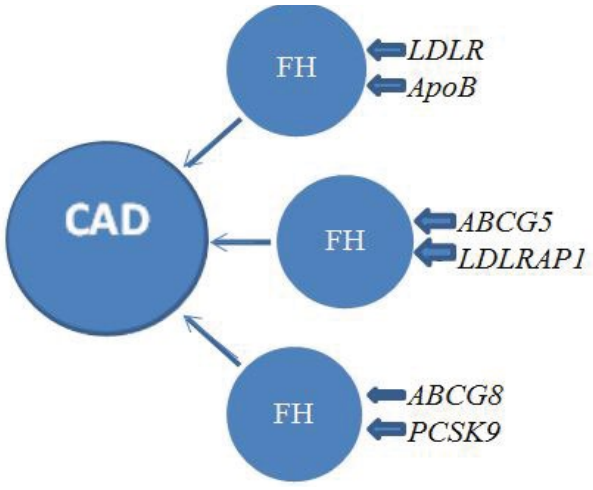

Figure 2 Candidate genes identified for FH genetic markers resultantly causing CAD [24].

due to LDLR gene mutations. There are different mutations in the gene of LDLR that can cause mild to severe FH, like mutations that can affect LDLR synthesis in endoplasmic reticulum, mutation that can disable proper LDLR transport to Golgi apparatus, mutation that can disable LDLR binding to LDL-C, mutation that can disable proper LDLR recycling [26].

LDLR Adaptor Protein 1 (*LDLRAP1*)

Recessive autosomal hypercholesterolemia is commonly a rare disorder caused by *LDLRAP1* gene mutation. *LDLRAP1* is a protein which is involved in regulation process of recycling and traffic of LDLR. Mutations in the gene of *LDLRAP1* cause defective low-density uptake of the hepatocytes, which results in hypercholesterolemia. Clinically, heterozygous genotypic patients have normal cholesterol level in circulation than homozygous genotypic patients [27].

Protein Convertase Subtilisin /Kexin Type 9 (PCSK9)

PCSK9 is a very important modulator of plasma LDL-C and LDLR levels [28]. Decrease in PCSK9 can cause significantly lower LDL-C level in individuals and protects from CAD. PCSK9 by binding to LDLR enables process of its degradation that decrease LDL-C level, and increase atherosclerosis risk. Resultantly, PCSK9 appears as a therapeutic approach for treatment of atherosclerosis and hypercholesterolemia [29].

Apolipoprotein B (ApoB)

High concentration of plasma ApoB is a very important predictor/ risk factor of CAD, as it remains attached to lipoproteins without suffering any changes. ApoB is a direct source of providing lipoprotein particles in blood circulation. The most of total plasma ApoB bounds to LDL that makes it a very good substitute of concentration of LDL particles. Higher concentration of particles of ApoB lipoprotein may be little atherogenic than denser, smaller LDL particles. Consequently, measurement of ApoB level in the LDL particles is better predictor for atherogenesis rather than ApoB level of total serum, although it is not mentioned in many published studies [30]. ApoB is taken as better marker for abnormalities of lipoprotein. In CVD patients, ApoB blood level has better description than LDL-C and HDL-C levels. The predominant constitutional apolipoprotein LDL particle is ApoB, which binds to the LDLR, and moderate uptake of hepatic LDL-C. So, it is assumed that the mutations in LDLR and ApoB affect cholesterol level, cause hypercholesterolemia and progression and development of CVD [31].

Adiponectin

Adiponectin is a most abundant secretory protein which is adipocyte-derived in visceral fat tissues of human. Adiponectin circulating level is negatively associated with percentage of visceral fat mass [32]. Circulating adiponectin presents 0.05% of serum protein, while concentrations in circulation are from 2-20 $\mu g/mL^{-1}$. High level of adinopectin in plasma is associated with insulin sensitivity among healthy population. Decreased level of adiponectin is a threat for developing CAD, hypertension, and diabetes. Adinopectin possess atheroprotective characteristics having inverse relationship with CAD [33]. Adinopectin level is lower in cardiovascular disease patients, and this lower level can be predictor of development of MI. Adinopectin is present as cardio protective protein, still its relation with severity of atherosclerosis and CAD predictive power remains disputed in various populations, probably because of ethnic/racial differences, environmental factors, and lifestyle. Concentrations of adiponectin in plasma might be helpful as early biomarker of risk of cardiovascular and also predictor of terrible cardiovascular events happened in CAD patients [34].

C - reactive protein (CRP)

C-reactive protein is a protein of acute phase synthesized in vascular endothelium and liver, and belongs to pentraxins family. In the atherosclerotic plaque, it exists with lipoproteins and monocytes. Increased level of CRP is related with higher CAD risk in the apparently healthy persons which has strong association with risk of lethal CAD outcomes [35] **(Tables 1 and 2).**

Environment-gene interactions and gene regulation

Now-a-days, the effects of gene-environment interactions have been identified by changing the conditions of environment. To describe environmental and genetic cardiovascular risk factors, it is necessary to discover gene regulation under controlled conditions of treatment in relevant type of cells. The molecular phenotypes measured in controlled cellular environment provide more tractable settings to investigate gene-environment interaction in absence of confounding variables. The scientists performed different experiments in the endothelial cells, which were exposed to dexamethasone, retinoic acid, selenium, and caffeine to model the environmental and genetic effects on regulation of gene in vascular endothelium, a common pathology site in the cardiovascular diseases. It was investigated that genes that are present near differentially approachable chromatin are more differentially expressed [OR = (3.41, 6.52), p <10-16]. Moreover, it was also confirmed by scientists that the environment specific change in binding transcription factor is a basic mechanism to describe cellular response to the environmental stimuli. The single nucleotide polymorphisms in the footprints of caffeine response factors are enhanced in the co-localized eQTLs causing CAD, which suggests that caffeine plays a very important role in the CAD risk. By combining eQTLs, response genes, and GWAS, scientists annotated the environmental components which can decrease or increase the risk of disease by changing gene expression of 43 genes. According to studies, the genetic risk of CAD may be amplified or buffered by each treatment, depending on gene considered or particular SNP [36,37].

Discussion and Conclusion

From the studies up till now, it is concluded that CAD is a complicated and multifactorial disease of which some factors are modifiable while others are non-modifiable. Some emerging RFs as oxidative stress, antioxidant system, Advanced Glycation End Products (AGES) are linked to high CAD risk. DNA damage is

Table 1 Genes identified as cause of coronary artery disease.

Gene mutations cause high LDL		Mutations cause low HDL		Mutation cause high TG	
Genes	Chromosomal location	Genes	Chromosomal location	Genes	Chromosomal location
LDL receptor	19p13.2	*LCAT*	16q22.1	*Apo C-II*	19q13.2
ApoB-100	2p24.1	*ABCA1*	9q31.1	*LPL*	8p21.3
LDLRAP1, ARH	1p36.1	-	-	*APOA5*	11q23.3

Table 2 Genetic variants which are associated with the reduced coronary artery disease risk [17,36].

Gene	Chromosomal location	Intermediate phenotype
PCSK9	1p32.3	↓LDL cholesterol
NPC1L1	7p13	↓LDL cholesterol
ASGR1	17p13.1	↓LDL cholesterol ↓Triglyceride-rich lipoproteins
APOC3	11q23.3	↓Triglyceride-rich lipoproteins
ANGPTL4	19p13.2	↓Triglyceride-rich lipoproteins
LPA	6q26-27	↓Lipoproteins (a)

also recognized as an emanating risk factor for CAD. Moreover, we reviewed considerable progress in understanding genetic CAD underpinnings. Significant advances in studies provided deep insight into CAD pathogenesis. These studies showed that there is a strong association between environmental and genetic risk factors and CAD. Different gene mutations have been discovered which play a vital role in amplifying or buffering genetic risk of CAD. Hopefully, future genomic approaches will identify new genes possessing CAD linked expression and generating new hypothesis related to CAD pathogenesis.

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