Genetic Mutations that Cause Coronary Artery Disease

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Abstract

Coronary heart disease is the leading cause of death in industrialized societies. A wide range of clinical symptoms such as angina pectoris, myocardial infarction, and sudden cardiac death are visible in respective patients. The genetic basis and heritability of the disease has recently been identified by examining family lineages in patients. However, understanding the genetic causes of coronary artery disease due to the heterogeneity of clinical symptoms and the pathophysiological processes involved is very complex due to the interplay of genetic and environmental factors. This review article explains the heterogeneity factors involved in coronary artery disease for a better explanation of genetic studies which can lead to a better understanding of the inherited mechanisms of the disease. Such studies could reveal the association of common variants in candidate genes as well as the association of a large number of effective gene loci with the risk of coronary heart disease. Large-scale gene sequencing and applied studies provide a better understanding of the biological risk factors and help better understand the biology of the disease and provide valuable insights into new therapeutic approaches. In addition, such review studies make it possible to conduct genetic tests with a medical approach to identify subgroups of patients at risk for coronary artery disease and use them for prevention and treatment purposes.

Key words: Coronary Artery Disease/ Genetic Markers / Mutation

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Extended Abstract

Introduction: Coronary artery disease (CAD) and myocardial infarction (MI) have been identified as the leading cause of death in developed countries (1, 2). Although the disease is commonly associated with risk factors such as smoking, sedentary lifestyle, and diet, it is strongly related to genetic predisposition. Based on demographic and sister-brother studies, it is estimated that 40-60% of the predisposition of CAD may be associated with genetic factors (3).

Detection of the genes involved in CAD: So far, most efforts have been focused on identifying familial patterns of disease and distinct genetic factors, including finding the genes involved in CAD. Sequencing of the human genome (completed in 2003), the rapid reduction of genotyping costs, and the sharing of data through international cooperation have played an important role in such efforts.

Family Studies: Careful family studies, by linkage analysis in families with early-onset CAD forms, provided the first opportunity to understand the causes of monogenic CAD. The inherited pattern of high cholesterol and premature CAD is called familial hypercholesterolemia (4, 5).

Evaluation of the candidate genes in which the mutation causes CAD includes the following mutations in the LDL receptor gene (LDLR) gene, mutations in the apolipoprotein B (ApoB) gene, and gain of function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) (6-8).

Association studies for common variants: Although CAD has a specific inherited pattern of disease, it is a complex disorder. Genotype chips designed to identify most genetic variations between individuals are the cornerstones for association studies (CVAS) as well as genome-related studies (GWAS) (9-12). Since the identified variants are very common, it is possible to compare the frequency of each of these variants in patients and control individuals. The results of such assessments were yielded in several parts. First, the vast majority of these variants have an allele frequency of less than 5% in the population and were associated with a relatively low risk of CAD, generally accounting for 30-40% of CAD heredity. Second, most of these variants were outside the protein-coding area. Third, the identified genetic loci to date are associated with biological aspects of CAD risk (13).

Association studies for rare variations: High-scale genetic sequencing has reduced costs and provided the conditions for the rare variant association studies (RVAS). Such variants typically do not exist in microarray genotyping chips, because the chips are designed to detect only common variants in the population. In addition, rare variants do not occur frequently and; therefore, cannot be estimated in statistical tests. However, determining the complete sequence of genomes and total exons in a large number of patients can increase the validity of statistical tests for RVAS (14, 15).

Low-Density Lipoprotein Receptor (LDLR): In the body, the main and responsible receptor for removing LDL-C from blood circulation is hepatic LDLR. LDL-C binds to LDLR and forms the LDL-C / LDLR complex, which is inside the covered vesicles with the clathrin entered to the cell by endocytosis. After transfer to the cytoplasm, LDL-C is separated from LDLR and exposed to further degradation, and LDLR is rapidly returned to the cell surface. The LDL-C absorption mechanism by LDLR is a very specific process and is influenced by various genetic and environmental factors (16, 17).

Apolipoprotein B (ApoB): Larger ApoB lipoprotein particles may have lower atrogenic properties than smaller, denser LDL counterparts. Therefore, measurement of ApoB levels in LDL particles is a better prediction of atrogenesis than total serum ApoB levels, although not documented in all published studies, ApoB is thought to be a good marker of lipoprotein disorders. Also, previous studies show that ApoB blood levels serve as a better marker in patients with CVD than HDL-C and LDL-C (18-20).

Proprotein convertase subtilisin/kexin type 9 (PCSK9): In the 1960s and 1970s, it was found that bioactive secretory proteins (hormones and enzymes) were initially made as inactive precursors and became active products after limited proteolytic digestion. This explanation suggests that the conversion of an inactive precursor to a functional product is done by a special group of proteases called proprotein convertase. Binding of PCSK9 to LDLR destroys this receptor, resulting in increased LDL-C and increased risk of atherosclerosis. As a result, PCSK9 emerged as a promising treatment strategy for the treatment of hypocholesterolemia and atherosclerosis (21-23).

Ionic channels: Coronary blood flow disorder can lead to CAD. Ionic channels are a major factor in the regulatory mechanism, and some specific variants in ion channel encoding genes may affect coronary blood flow. Polymorphism in the ion channel genes is also known to be one of the leading causes of diabetes, which is among the strongest risk factors for cardiovascular diseases. Examination of the clinical effects of these SNPs has shown that polymorphism in the nitric oxide synthase gene (NOS3), which encodes endothelial NOS (eNOS), is associated with ischemic heart disease (24, 25).

GWAS and CAD analysis: To detect gene loci responsible for atherosclerosis, large-scale genome-wide association studies (GWAS) are being performed. GWAS analysis allows the exact genotype to detect up to 1 million SNPs simultaneously (26). It seems that

the genetic risk of CAD is more associated with the number of hereditary risk variants than with the strength of each genetic variant alone. However, most of the SNPs identified by GWAS are not in coding exons, and the main mechanisms of this association are less obvious (27).

Pharmacogenomics: Pharmacogenomics includes the study of the effect of genetic diversity on drug response and the use of genetic data to facilitate the study of the efficacy and safety of drug therapies. Genetic differences in response to a drug may reflect a variation in the dose of the drug in the target recipient (pharmacokinetics) or a variation in the target of drug that results in different responses to drug-equivalent concentrations (pharmacodynamics). Many pharmacogenomic interactions with cardiovascular agents have been investigated, such as statins, clopidogrel, and warfarin (28, 29).

Conclusion: Given the complex genetic background of coronary artery disease, it makes sense to examine family history in early medical evaluation. The large-scale genomic studies and the identification of several genetic predisposing sites to CAD have made it possible to understand the main and non-primary risk factors and identify new biological mechanisms in the pathogenesis of coronary atherosclerosis.

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