Sampaio and Magalhães, Int J Cardiovasc Res 2020, 9:7
DOI: 10.37532/icrj.2020.9(7).420

International Journal of Cardiovascular Research

Editorial

A SCITECHNOL JOURNAL

Cardiovascular Risk Determined by Genetic Polymorphisms and Epigenetics

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Abstract

Several risk factors for the development of cardiovascular disorders, such dyslipidemias, can trigger phenomena such as atherosclerosis, coronary disease and even infarction. The adoption of healthy lifestyle habits such a low calorie diet with low cholesterol content, rich in unsaturated fatty acids, fibers and antioxidants such as flavonoids and omega-3, abandonment of alcohol and tobacco and physical exercise are some of the most recommended approaches to decrease serum cholesterol and triglyceride concentrations, as well as increase the liver production of High Density Lipoprotein (HDL). However, for some patients, even maintaining a healthy lifestyle, serum lipids levels remain higher than those considered safe, being refractory to conventional treatments with statins, fibrates, sequestering resins, and inhibitors of intestinal cholesterol absorption, for example. In these cases, it has been suggested the involvement of genotypic conditions, both genetic polymorphism or epigenetics, being necessary more specific diagnostic and management designs. Thus, the present editorial for the International Journal of Cardiovascular Research aims to reinforce this area of knowledge, encourage researchers to invest in works focused on this theme and describe a theoretical framework to be considered in clinical practice.

Keywords

Single nucleotide polymorphisms; Dyslipidemias; Autosomal inheritance

Introduction

Disorders of serum lipid metabolism, also known as dyslipidemias, as well as other cardiovascular risk factors such as hypertension, diabetes, obesity and metabolic syndrome may have genetic causes associated with mutations and autosomal inheritance, making laboratorial monitoring and clinical anamnesis difficult, and the adoption of traditional management strategies ineffective. Polymorphic individuals may present mutations that cause the deletion of genes that encode transporter proteins, transmembrane receptors and enzymes involved in the metabolism pathways of lipoproteins and cholesterol. For example, one of the main known genetic disorders is familial hypercholesterolemia, which is caused by mutations in the Low-Density Lipoprotein (LDL) receptor genes, which recognize Apolipoprotein B (APO-B), making it impossible to use these lipid particles in peripheral tissues and accumulating cholesterol in the circulation [1].

Other genetic conditions are associated with the occurrence of dyslipidemia. Studies show, for example, that rare mutations p.M404 V and p.V333 M in the Lecithin Cholesterol Acyltransferase (LCAT) gene cause the suppression of the activity of this enzyme, reducing the esterification of cholesterol on HDL particles, leading to hypoalphalipoproteinemia [2]. Still in this sense, familial chylomicronemia syndrome is often associated with several types of hypertriglyceridemia phenotypes, and caused by variants of homozygous or biallelic function of Lipoprotein Lipase (LPL) gene, as well apolipoproteins APO-C2 and APO-A5, Lipase Maturation Factor 1 (LMF1) and Glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1 (GPIHBP1) genes [3]. Other example is the dysbetalipoproteinemia, characterized by the accumulation of remaining lipoprotein particles. Most patients with this condition are homozygous for apolipoprotein ε2 variant, which is associated with decreased binding of apolipoprotein E to the LDL receptor [4]. Several other familial dyslipidemias are known; however, they need to be further investigated to identify the genes and nucleotides targeted by mutation, the most common phenotypes, and the possible management strategies for these rare cases.

In the last years, many researcher groups focused on correlate the severity of cardiovascular diseases with genetic polymorphisms in dyslipidemic and diabetic patients in distinct populations worldwide. Recently, a study with Vietnamese children showed that the carriers of the C allele on APO-A5 rs662799 have 75% higher risks to develop dyslipidemia and 53% to develop hypertriglyceridemia than subjects that don't have this allele [5]. This variant allele displayed a correlation with major triglyceride levels in Chinese women with coronary disease [6].

Polymorphisms related to the translation of other proteins can also help in the detection of other cardiovascular risk factors. Proteins that are not directly involved in lipidic metabolism deserves highlighting in role of cardiovascular research. In occident, Brazilian people with polymorphism DD in Angiotensin Converting Enzyme (ACE) gene revealed seven more odds to hypertension development compared with II allele carriers [7]. Vitamin D receptor polymorphism rs2228570 is appointed as a great risk factor to dyslipidemia and, consequently, cardiovascular disease deployment, for having a strong correlation with serum cholesterol associated with LDL and HDL (respectively, LDL-c and HDL-c) levels. In mutant allele carriers, the receptor can't interact correctly with its binders, producing low levels of serum vitamin D and a deficient regulation of lipidic metabolism [8].

Another factor that can interfere in determining cardiovascular risk is epigenetics, which represents a phenomenon of change in the hereditary phenotypic expression of genetic records, without changes in DNA nucleotides sequence. Epigenetics shows that genetic inheritance is also determined by environmental factors, determining susceptibility to diseases. Several epigenetic processes, including DNA methylation, histone modification and non-coding RNA expression have been demonstrated as mechanisms for development of cardiovascular diseases, such as congenital cardiomyopathy, heart failure, systemic arterial hypertension and atherosclerosis [9].

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Received: October 06, 2020 **Accepted:** October 27, 2020 **Published:** November 03, 2020

doi: 10.37532/icrj.2020.9(7).420

For example, the study of epigenetics has been applied in determining cardiovascular risk in childhood, showing that maternal health status, such as high cholesterol, diabetes and obesity, can determine the occurrence of growth retardation, low birth weight, post-natal excessive growth and metabolic changes, with subsequent appearance of risk factors for cardiovascular disease, such as dyslipidemia and atherosclerosis in early childhood [10]. Other studies demonstrate that the transcription of an antisense lncRNA called ANRIL, whose expression is regulated by epigenetics, is linked to the risk of type 2 diabetes, coronary artery disease, coronary calcium score, myocardial infarction and stroke [11]. Additionally, it has been described the association between global leukocyte DNA methylation and cardiovascular risk in postmenopausal women [12]. There are countless possibilities that must be explored and that brings a new panorama that transcends the determination of risk, but that, in the future, can be applied in the prevention of diseases at a very early stage.

Therefore, it is necessary to study and describe epigenetic changes and which are the most important target genes. In addition, epigenetics is also associated to modifiable cardiovascular risk factors, such as smoking, exposition to environmental mutagens and pharmacotherapy. Thus, it has been suggested that some drugs can indirectly reduce cardiovascular risk, beside their direct mechanisms of action. Recent studies show that some antidiabetic drugs, as well as blockers of renin-angiotensin-aldosterone system, exert effects epigenetics in addition to their hypoglycemic and antihypertensive functions, respectively [13], causing cumulative protective effects. This information can lead to a more rational and targeted drug use, identifying factors related to the prescription of more specific treatments and individual contraindications.

One of the major challenges in this theme is the development of panels of polygenic markers based on Single Nucleotide Polymorphisms (SNP), aiming new diagnostic tools with high positive predictive values and able to accurately correlate the occurrence of variant genes and the severity of the dyslipidemia and/or other condition. To counter this problem, it is necessary to encourage multicenter studies, with populations of diverse ethnicities and lifestyle habits and with different types of cardiovascular diseases. Indeed, these studies will eventually increase the knowledge on the effects of genetic alterations on susceptibility and development of cardiovascular disease, allying to development of personalized therapies and new diagnostic techniques.

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