EDITORIAL ARTICLE

The influence of gene polymorphisms on evolution of atherosclerosis.

Vana Kolovou[1], Genovefa Kolovou[2]

1. Chemist, MSc, PhD student, Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece
2. Cardiology Department, Head of OutPatients Clinics, Preventive Cardiology and LDL Apheresis Service, Onassis Cardiac Surgery Center, Athens, Greece

Corresponding author: Genovefa Kolovou MD, PhD, FESC, SFASA, FACS, FRSH Tel: 00302109493520Fax: 00302109493336e-mail: genovefa@kolovou.com

The evolution of atherosclerosis is influenced by environmental risk factors such as dyslipidemia, arterial hypertension, diabetes mellitus and smoking, which are significantly related to cardiovascular (CV) disease and by genetic factors [1, 2]. Genetic factors may explain approximately 50% of the risk for CV disease [2].

Also genetic factors contribute to the variation of human life span by around 25%, which is believed to be more profound after 85 years of age [3]. According to the genetic influence to longevity, the nonagenarians and centenarians may represent a particularly informative study population in the search for traits of genes associated with longevity. Several research teams are working on genes involved in oxidative stress, lipid and glucose metabolism, inflammation, DNA damage and repair, axis of growth hormone and insulin like growth factor and others [4]. The results are still conflicting and it may be suggested that the combination of numerous fixed genetic variants will be necessary for someone to achieve exceptional longevity [5].

Case-control studies[2] have shown, on average, a 2- to 3-fold increase in risk for coronary artery disease (CAD) in first-degree relatives of affected individuals. Decades ago, Rissanen reported [2] that the younger the patient at the diagnosis of a first myocardial infarction (MI), the more common was CAD present in his parents and siblings. Also, arterial hypertension and dyslipidemia were more frequent among the relatives of the youngest patients and diminished with advancing age of the patient [2]. Furthermore, in families with early onset of CAD (< 46 years old) heritability was estimated to be 92-100%, whereas in families of delayed onset cases heritability ranged from 15-30% [2]. Therefore, genetic screening in cases with early CV disease may prove useful.

Studies of genes are not easily replicated (often due to inadequate sample size). For example, to detect a minor allele frequency of ≥ 5% with an odds ratio for risk of ≥1.3 and 90% power, an estimated 14 000 individuals (9 000 patients and 5 000 healthy controls) are required [6]. Humans have 20 000-25 000 genes [6]. Notable progress has been made towards understanding the development and outcome of CV disease through genetic information. Therefore, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) considered a family history of CAD in a first-degree relative before the age of 60 years as an independent risk factor for early MI [7].

Atherosclerosis has been widely evaluated in apolipoprotein E knockout mouse [8] (an animal model where a similar pathological process to that in humans occurs over a short period of time) and the results indicate a strong genetic component to atherosclerosis [9]. Using the candidate gene approach, numerous studies have used genes implicated with known risk factors for atherosclerosis, for example dyslipidemia. Genes involved in lipid metabolism which are frequently studied are for: low density lipoprotein receptor [10, 11], cholesteryl ester transport protein (CETP) [12], apolipoproteins (A-5 or B or C-III or E) [13-16], hepatic lipase [13, 17], lipoprotein lipase [17], peroxisome-proliferator-receptor-α [18], ABCA1 [19], NFκB, cytochrome P450 (CYP) [20] and others.

For example, CETP may have pro- or anti-atherogenic properties depending upon the lipid-metabolic setting [21]. High density lipoprotein (HDL) particles are influenced by CETP activity; CETP promotes the exchange of cholesteryl esters for triglycerides (TG) between HDL particles and TG-rich lipoproteins [22]. Ordovas et al [23] suggested that

increased HDL-cholesterol levels resulting from lower CETP activity seems to be associated with a lower risk of coronary heart disease in men. The nuclear factor kappa B (NFκB) gene is a regulator of the genes that encode cytokines and cell-adhesion molecules, and induce the expression of growth factors and other factors involved in stress responses, cell proliferation and cell cycle progression [24]. Lee at al [25] reported increased levels of NFκB in senescent cells in association with increased oxidative stress. Furthermore, Leychenko et al [26] demonstrated that NFκB activation plays a role in mediating vascular endothelial growth factor (VEGF) and coordinates the hypertrophic response of cardiomyocytes during pressure overload-induced hypertrophy (hypertension and heart disease are influencing ageing).

ATP-binding cassette transporter A1 (ABCA1) mediates the transport of cholesterol and phospholipids from cells to lipid-poor apolipoproteins. Animals and human studies documented that defects in the ABCA1 pathway are significant determinants of CAD [27]. Inactivation of *ABCA1 gene* in macrophages increases atherosclerotic lesions in hyperlipidemic mice [28], and overexpressing human ABCA1 in transgenic mice retards atherogenesis [29]. The *ABCA1 gene* encodes ABCA1 protein, which is expressed in liver, macrophages, intestines, lungs etc. Several *ABCA1 gene* polymorphisms were identified such as *rs2230806 (R219K)*, *rs2230808 (R1587K)* and *rs4149313 (I883M*).

The cytochrome P450 proteins are monooxygenases that beside others catalyze reactions involved in drug metabolism. The protein is localized in the endoplasmic reticulum and its expression is induced by glucocorticoids and some pharmacological agents. The CYP3A5 gene is part of a cluster of cytochrome P450 genes in chromosome 7q21.1. There are substantial CYP3A expression differences between individuals, which contribute greatly to variation in oral bioavailability and systemic clearance of CYP3A substrates. Recently, the researchers are focused on the pharmacogenetics. Pharmacogenetic studies have as target to correlate specific gene polymorphisms with drug effectiveness.

Concerning the impact of CYP gene polymorphism on the effectiveness of statin treatment, the results are still unclear.

In conclusions, the evaluating genetic association with atherosclerosis is a promising tool for primary and secondary prevention. Additionally, understanding the manner by which genetics influence the response to hypolipidemic treatment may help to reach most favorable results, particularly that effect may vary in different ethnicities, patient categories or environments.

Furthermore, the association between CAD and gene polymorphisms involved in lipid metabolism remains the subject of debate owing to differences in results. Many studies involved a limited number of participants. Furthermore, the studies varied markedly by including different populations (e.g. age, sex and ethnicity), sampling strategies and genotyping procedures. Additionally, lipid profile can be influenced by several environmental factors such as smoking status, eating habits, associated customs (fasting periods), sedentary life style, body composition, gender and others. The most important factors influencing the lipid profile include the sex hormone status and age. Evidently, atherosclerosis is a multifaceted disease, and there is a need for extensive and costly research before genetics are introduced in every day clinical practice.

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