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Increased risk of premature coronary artery disease in Egyptians with ABCA1 (R219K), CETP (TaqIB), and LCAT (4886C/T) genes polymorphism

Tarek A. Abd El-Aziz, MD, Rasha H. Mohamed, PhD*, Hoda A. Hagrass, MD

Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt (Dr Abd El-Aziz); Department of Biochemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt (Dr Mohamed); and Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt (Dr Hagrass)

KEYWORDS:
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BACKGROUND: Epidemiological studies have shown a strong inverse relationship between high-density lipoprotein (HDL) cholesterol (HDLc) levels and coronary artery disease (CAD), and a low concentration of plasma HDLc is considered an independent risk factor for premature atherosclerosis. Mutations in ATP-binding cassette A1 transporter (ABCA1), cholesteryl ester transfer protein (CETP), and lecithin: cholesterol acyltransferase (LCAT) reduce HDLc in humans.

OBJECTIVE: To date, no study had tested the association between these polymorphisms and premature CAD (PCAD) in the Egyptian population. Here we searched for ABCA1 (rs2230806), CETP (rs708272), and LCAT (rs5923) mutations in the Egyptian population and investigated the possible association between these gene polymorphisms and PCAD. We aimed to investigate the association between ABCA1, CETP, and LCAT gene polymorphisms and PCAD in Egyptians.

METHODS: A total of 235 Egyptians—116 with documented PCAD (PCAD group) and 119 controls—were enrolled in the study.

RESULTS: Mutation carriers with low HDLc had an elevated risk of PCAD (odds ratio [OR] = 11.38 for ABCA1 mutation carriers, $P = .000$; OR = 5.41 for CETP mutation carriers, $P = .000$; OR = 5.92 for LCAT mutation carriers, $P = .000$). Moreover, mutations in ABCA1, CETP, and LCAT were significantly associated with hyperlipidemia in this study.

CONCLUSION: These observations show that the R allele of ABCA1, the B1 allele of CETP, and the T allele LCAT genes are associated with PCAD in Egyptians. They have more considerable effect on patients with low HDLc.

Coronary artery disease (CAD) is a leading cause of morbidity and mortality all over the world, affecting millions of people in both developed and developing countries.[1] Despite much investigation, the causes are not yet fully understood. Traditional risks such as hypertension, diabetes mellitus, smoking, and hyperlipidemia can only explain approximately two-thirds of the observed clinical events. This has continued the interest in other biochemical and genetic factors that might contribute to the etiology of CAD.[2] Epidemiological studies have

* Corresponding author. 28 Elglaa Street, Zagazig, Egypt.
E-mail address: drhussieny2009@yahoo.com
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shown a strong inverse relationship between high-density lipoprotein (HDL) cholesterol (HDLc) levels and CAD, and a low concentration of plasma HDLc is considered an independent risk factor for premature atherosclerosis.[3] Identifying strong genetic causes of low HDLc and determining their frequencies in the general population are therefore crucial for understanding the risk factors of low HDLc in humans and for facilitating the direct interrogation of the relationship between changes in HDLc and the likelihood of CAD.

Among the proposed atheroprotective functions of HDL is the process of reverse cholesterol transport in which cholesterol from the periphery is transported to the liver for excretion.[4] HDL particle formation and maturation are controlled in large part by ATP-binding cassette A1 transporter (ABCA1), cholesteryl ester transfer protein (CETP), and lecithin: cholesterol acyltransferase (LCAT).

The ABCA1 gene codes for a 2261 amino acid protein located on the cell membrane that facilitates the efflux of cholesterol into lipo-poor apolipoprotein A1 (apoA1) particles to form HDL.[5]Therefore, ABCA1 may be a candidate gene for the determination of plasma HDLc concentration. The ABCA1 gene, located at chromosome 9q31 spanning more than 150 kb, encompasses 50 exons. The common polymorphism in the coding region is R219K (rs2230806), which lead to an arginine→lysine substitution at exon 7.[6]

CETP facilitates the uptake of cholesterol from peripheral tissues to the liver in an antiatherogenic process known as reverse cholesterol transport. A common polymorphism of the CETP gene located in intron 1TaqIB (rs708272) has consistently been shown to influence CETP activity and HDLc levels.[7]

LCAT encodes the lecithin: cholesterol acyltransferase enzyme, which converts free cholesterol to cholesterol esters that are incorporated into discoidal HDL particles to form mature, spherical HDL.[8]The human LCAT gene is located on chromosome 16q22.1.[9]

Although loss-of-function mutations inABCA1, CETP, and LCAT are well-established to underlie low HDLc in humans,[10] previous resequencing studies of unrelated individuals with low HDLc report large variability in mutation frequencies for these genes.[11,12] It also remains unclear whether mutations in these genes also cause a concomitant increase in risk for CAD.[13] Although several human genetics and clinical-based studies support that mutations in ABCA1, CETP, and LCAT elevate risk of CAD,[14–16] others observe no CAD increase in mutation carriers despite significant reductions in HDLc,[17,18] thereby questioning the long-standing hypothesis that HDL protects against atherosclerosis.

To date, no study had tested the association between these polymorphisms and premature CAD (PCAD) in the Egyptian population. Here we searched for ABCA1 (rs2230806), CETP (rs708272), and LCAT (rs5923) mutations in the Egyptian population and investigated the possible association between these gene polymorphisms and PCAD. We aimed to investigate the association between ABCA1, CETP, and LCAT gene polymorphisms and PCAD in Egyptians.

Subjects and methods

Study population

The total population in this study consisted of 235 Egyptian individuals divided into 2 groups: 116 unrelated individuals consisting of 90 males and 26 females (mean age 42.4 ± 7.3 years) with documented PCAD (PCAD group), age at the time of CAD diagnosis 45 years or younger in men and 55 years or younger in women, and 119 unrelated control subjects with a mean age of 41.9 ± 6.4 years (63 males and 56 females). Patients with CAD were recruited from patients admitted to the cardiology section of the Zagazig University Hospital (Zagazig, Egypt). Documented CAD was diagnosed by the following criteria: stable CAD suggested by clinical evaluation and proved by coronary angiography (>50% reduction of coronary artery diameter in at least one of the major arteries) or the occurrence of myocardial infarction (MI) as defined by the World Health Organization criteria. The control subjects were randomly selected and were age-matched to PCAD patients. They had no history of CAD, MI, or stroke.

The presence of CAD risk factors was determined using the criteria of the European society of cardiology: hypertensive condition was attributed when systolic blood pressure values were > 139 mm Hg and/or diastolic blood pressure values >89 mm Hg in at least 2 separate measurements or when being medicated against hypertension; subjects were considered smokers when consuming more than 5 cigarettes per day or nonsmokers when they had never smoked or had stopped smoking at least 1 year before sample collection; obesity was defined for waist-to-hip ratio of >0.90 in men or >0.85 in women; dyslipidemia was considered for serum values of total cholesterol (TC) ≥ 200 mg/dL, triglycerides (TG) ≥ 150 mg/dL, low-density lipoprotein cholesterol (LDLc) ≥ 130 mg/dL, and HDLc ≤ 40 mg/dL in men, ≤ 50 mg/dL in women.[19]

Analyses of lipids

Blood samples were drawn from all subjects after an overnight fast. Sera were separated immediately and stored at −20°C. TC and TG were measured by routine enzymatic methods (spinreact). HDLc was determined after precipitation of the apoB-containing lipoproteins. LDLc was calculated using the Friedewald formula.[20]

Isolation of DNA

Genomic DNA was extracted from EDTA whole blood using a spin column method according to the protocol (QIAamp Blood Kit; Qiagen GmbH, Hilden, Germany).