The impact of common polymorphisms in \textit{CETP} and \textit{ABCA1} genes with the risk of coronary artery disease in Saudi Arabians

Cyril Cyrus\textsuperscript{1*}, Chittibabu Vatte\textsuperscript{1}, Awatif Al-Nafie\textsuperscript{2}, Shahanas Chathoth\textsuperscript{1}, Rudaynah Al-Ali\textsuperscript{2}, Abdullah Al-Shehri\textsuperscript{2}, Mohammed Shakil Akhtar\textsuperscript{2}, Mohammed Almansori\textsuperscript{2}, Fahad Al-Muhanna\textsuperscript{2}, Brendan Keating\textsuperscript{3} and Amein Al-Ali\textsuperscript{1}

Abstract

Background: Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide. Many genetic and environmental risk factors including atherogenic dyslipidemia contribute towards the development of CAD. Functionally relevant mutations in the dyslipidemia-related genes and enzymes involved in the reverse cholesterol transport system are associated with CAD and contribute to increased susceptibility of myocardial infarction (MI).

Method: Blood samples from 990 angiographically confirmed Saudi CAD patients with at least one event of myocardial infarction were collected between 2012 and 2014. A total of 618 Saudi controls with no history or family history of CAD participated in the study. Four polymorphisms, rs2230806, rs2066715 (\textit{ABCA1}), rs5882, and rs708272 (\textit{CETP}), were genotyped using TaqMan Assay.

Results: \textit{CETP} rs5882 (OR = 1.45, \(P < 0.005\)) and \textit{ABCA1} rs2230806 (OR = 1.42, \(P = 0.017\)) polymorphisms were associated with increased risk of CAD. However, rs708272 polymorphism showed protective effect (B1 vs. B2: OR = 0.80, \(P = 0.003\) and B2B2 vs. B1B1: OR = 0.68, \(P = 0.012\)) while the \textit{ABCA1} variant rs2066715 was not associated.

Conclusion: This study is the first to report the association of these polymorphisms with CAD in the population of the Eastern Province of Saudi Arabia. The rs5882 polymorphism (\textit{CETP}) showed a significant association and therefore could be a promising marker for CAD risk estimation while the rs708272 polymorphism had a protective effect from CAD.

Keywords: Gene polymorphism, CAD, \textit{CETP}, \textit{ABCA1}, TaqMan Assay

Background

Coronary artery disease (CAD) is one of the leading causes of morbidity and disability and the most common cause of mortality worldwide equally among men and women. CAD is a disease burden in both high- and low-income countries [1, 2]. A study conducted on 17,232 people from Saudi Arabia revealed that 5.5 \% had been diagnosed with CAD, with a higher prevalence in urban populations (6.2 \%) compared to rural populations (4 \%) [3]. Platelet aggregation and thrombus formation following the rupture of coronary atherosclerotic plaque is the major cause of myocardial infarction (MI) [4–6].

Many extrinsic and intrinsic risk factors, including hypertension, dyslipidemia, obesity, smoking, age, lack of exercise, and diabetes, are established risk factors for MI [7]. Atherogenic dyslipidemia is characterized by abnormal levels of triglycerides, low- and high-density lipoprotein (LDL-C and HDL-C) [8–10]. Functionally relevant mutations in the dyslipidemia-related genes and gene encoding enzymes involved in the reverse cholesterol transport system have been reported to be associated with high-density lipoprotein-cholesterol (HDL-C) levels [11–13]. Epidemiological and clinical studies have demonstrated a contradictory association between HDL-C concentrations and cardiovascular risk [10, 14, 15]. The anti-atherogenic effect of HDL-C may act through several mechanisms, such as anti-oxidation of low-density lipoprotein. This study is the first to report the association of these polymorphisms with CAD in the population of the Eastern Province of Saudi Arabia. The rs5882 polymorphism (\textit{CETP}) showed a significant association and therefore could be a promising marker for CAD risk estimation while the rs708272 polymorphism had a protective effect from CAD.

Keywords: Gene polymorphism, CAD, \textit{CETP}, \textit{ABCA1}, TaqMan Assay

* Correspondence: ccyrus@uod.edu.sa
1Institute for Research and Medical Consultation, University of Dammam, P.O.Box 1982, Dammam 31441, Kingdom of Saudi Arabia
Full list of author information is available at the end of the article

© 2016 Cyrus et al. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
lipoprotein-cholesterol (LDL-C) and anti-inflammation and inhibition of vascular endothelial cell apoptosis.

The reverse cholesterol transport system plays a vital role in these processes [16], as it is involved in the transportation of cholesterol from the peripheral tissues to the liver, where cholesterol is secreted into bile. ATP-binding-cassette A1 (ABCA1), apolipoprotein A-1 (ApoA-1), and cholesteryl ester transfer protein (CETP) play important roles in the reverse cholesterol transport system [17]. Certain ABCA1 polymorphisms have been reported to be associated with HDL-C concentrations, which in turn indicate increased cardiovascular risk [18]. The potential atherogenicity of CETP relates to its ability to transfer cholesteryl esters from the anti-atherogenic HDLs to the pro-atherogenic VLDL and LDL proteins. Mutations in the CETP gene give rise to less functional protein, which reduces the transfer of cholesteryl esters, and consequently HDL levels are elevated [19]. ABCA1 and CETP variants including rs2230806, rs2066715, and rs5882, have been associated with increased HDL-C concentrations and rs708272 with a decreased risk for CAD [20, 21].

The objective of the present study is to evaluate the association of the two ABCA1 polymorphisms, rs2230806 [R219K: c.656G>A (p.Arg219Lys)] and rs2066715 [V825I: c.2473G>A (p.Val825Ile)], and two CETP polymorphisms, rs5882 [R219K: c.1264G>A (p.Arg219Lys)] and rs2066715 [V825I: c.118+279G>A], with the risk of CAD in the population of the Eastern Province of Saudi Arabia.

## Results

Demographical and clinical data of cases and the control group, including age, sex, clinical manifestations, and biochemical parameters, are shown in Table 1. Patients were classified into subgroups based on their hypertension and diabetes status. Hypertension and diabetes were more prevalent in the patient group compared to the control group.

All genotype frequencies of the control group were consistent with Hardy-Weinberg equilibrium. The distribution of analyzed genotype polymorphisms are shown in Table 2. Since all the four SNPs had a G>A transition substitution, the genotypes are denoted with the amino acid change, except for Taq1B alleles, which are designated by B1 and B2. The genotype analysis showed overall heterozygous polymorphism predominance in rs2230806 of ABCA1, rs5882, and rs708272 of CETP (Table 2).

The CETP rs708272 polymorphism showed a significantly lower risk for CAD (B1B2+B2B2 vs. B1B1: OR = 0.68, 95 % CI 0.55–0.85, P = 0.0006 and B2B2 vs. B1B1: OR = 0.68, 95 % CI 0.50–0.92, P = 0.012). There was also a significant variation of B1B2 genotypes among patients and controls (OR = 0.68, 95 % CI 0.54–0.86, P = 0.001). Genotyping for the rs5882 polymorphism in CETP exon-14 showed that the frequency of VI genotype was higher in cases than in controls (52.8 vs. 48.0 %). Our analysis revealed that CETP rs5882 polymorphism is associated with an increased risk of CAD in our Saudi population study dataset (V1+I vs. VV: OR = 1.42, 95 % CI 1.11–1.82, P = 0.005; II vs. VV: OR = 1.37, 95 % CI 1.02–1.82, P = 0.031). Allele frequency analysis of the B2 allele of rs708272 of CETP (OR = 0.80, 95 % CI 0.69–0.92, P = 0.003) and the K allele of rs2230806 of ABCA1 (OR = 1.17, 95 % CI 1.01–1.35, P = 0.029) showed a significant difference between the two tested groups (Table 2). The mutant KK genotype of rs2230806 of ABCA1 is found to be associated with an increased risk of CAD (RR vs. KK: OR = 1.42, 95 % CI 1.06–1.91, P = 0.017). There were no significant differences in allele and genotype frequencies of rs2066715 polymorphisms in ABCA1 between the patient and control groups. The power of the study observed was 100 % for protective effect at odds ratio of 0.5 and 94.9 % at 0.7 for Taq1B, and for the other three SNPs (R219K, V825I, and I405V), the results ranged from 45.48 to 96.9 % for an odds ratio of 1.2–1.5.

A joint analysis of two SNPs of both ABCA1 and CETP is shown in Table 3. All the combinations of the CETP variants exhibited no association, except B1B1+VI (OR = 1.7, 95 % CI 1.0–2.9, P = 0.048). On the other hand, for ABCA1, RK+VV and RK+V lacked an association (Table 3). A sex-based analysis revealed a higher frequency of B1B1 genotype in men and women with CAD compared to their respective controls (Table 4). There was no statistical significance in the distribution of ABCA1 genotypes in the female cohort whereas in the male cohort genotypes KK (OR = 1.8, P = 0.001) of rs2230806 and VI (OR = 2.17, P = 0.041) of rs2066715 showed a significantly higher risk for CAD. In the CETP, rs5882 polymorphisms II (OR = 1.98, 95 % CI 1.38–2.85, P = 0.0002) revealed a significantly higher risk for CAD in the male cohort. In the male and female cohorts, rs708272 B1B2 and B2B2 genotypes showed a protective effect for CAD, respectively. The rs2230806 and rs2066715 of ABCA1 did not show any significant differences in allele and genotype frequencies among cases and controls.
### Table 2: Association between ABCA1 and CETP genotypes and alleles with CAD

| SNP         | Genotype/alleles | Cases (N = 990) | Control (N = 618) | OR (95 % CI) | P value |
|-------------|------------------|-----------------|-------------------|--------------|---------|
| rs2230806 (R219K) | RR               | 291             | 195               | Ref          |         |
|             | RK               | 473             | 317               | 0.9 (0.79–1.25) | 0.999   |
|             | KK               | 226             | 106               | 1.42 (1.06–1.91) | 0.017   |
|             | RK+KK            | 699             | 423               | 1.10 (0.89–1.37) | 0.359   |
|             | R(G)             | 1055            | 707               | Ref          |         |
|             | K(A)             | 925             | 529               | 1.17 (1.01–1.35) | 0.029   |
| rs2066715 (V825I) | VV               | 945             | 597               | Ref          |         |
|             | VI               | 45              | 21                | 1.35 (0.79–2.29) | 0.26    |
|             | II               | 0               | 0                 | –             | –       |
|             | VI+II            | 45              | 21                | 1.35 (0.79–2.29) | 0.26    |
|             | V(G)             | 1935            | 1215              | Ref          |         |
|             | I(A)             | 45              | 21                | 1.34 (0.79–2.26) | 0.27    |
| rs5882 (V422I) | VV               | 178             | 147               | Ref          |         |
|             | VI               | 523             | 297               | 1.45 (1.12–1.88) | 0.005   |
|             | II               | 289             | 174               | 1.37 (1.02–1.82) | 0.031   |
|             | VI+II            | 812             | 471               | 1.42 (1.11–1.82) | 0.005   |
|             | V(G)             | 879             | 591               | Ref          |         |
|             | I(A)             | 1101            | 645               | 1.14 (0.99–1.32) | 0.058   |
| rs708272 (TaqIB) | B1B1             | 376             | 183               | Ref          |         |
|             | B1B2             | 454             | 321               | 0.68 (0.54–0.86) | 0.001   |
|             | B2B2             | 160             | 114               | 0.68 (0.50–0.92) | 0.012   |
|             | B1B2+V           | 614             | 435               | 0.68 (0.55–0.85) | 0.0006  |
|             | B1+B2           | 108             | 75                | 0.97 (0.56–1.66) | 0.913   |
|             | B2B2+V           | 55              | 45                | 0.82 (0.45–1.50) | 0.527   |

### Table 3: Association between joint analysis of two SNPs of ABCA1 gene and CETP gene with CAD

| Gene | Genotype | Cases (N = 990) | Controls (N = 618 ) | OR | 95 % CI | P value |
|------|----------|-----------------|---------------------|----|---------|---------|
| ABCA1| RR+VV    | 256             | 186                 | Ref |         |         |
|      | RR+VI    | 35              | 9                   | 2.82 | 1.32–6.02 | 0.007 |
|      | RK+VV    | 463             | 305                 | 1.10 | 0.86–1.39 | 0.419 |
|      | RK+VI    | 10              | 12                  | 0.60 | 0.25–1.43 | 0.252 |
|      | KK+VV    | 226             | 106                 | 1.54 | 1.14–2.08 | 0.004 |
| CETP | B1B1+V   | 46              | 31                  | Ref |         |         |
|      | B1B1+VI  | 180             | 71                  | 1.70 | 1.0–2.90 | 0.048 |
|      | B1B1+II  | 150             | 81                  | 1.24 | 0.73–2.11 | 0.41 |
|      | B1B2+W   | 77              | 71                  | 0.73 | 0.41–1.27 | 0.27 |
|      | B1B2+VI  | 269             | 175                 | 1.03 | 0.63–1.69 | 0.888 |
|      | B1B2+II  | 108             | 75                  | 0.97 | 0.56–1.66 | 0.913 |
|      | B2B2+W   | 55              | 45                  | 0.82 | 0.45–1.50 | 0.527 |
|      | B2B2+VI  | 74              | 51                  | 0.97 | 0.54–1.74 | 0.939 |
|      | B2B2+II  | 31              | 18                  | 1.16 | 0.55–2.42 | 0.692 |
association with an increased risk for CAD in the female cohort compared to the control subjects.

Discussion

CAD is a multifactorial disease mediated through a complex association of environmental and genetic factors with ethnicity demonstrated to be an important determinant of disease variability. The strength of the current study is the selection of CAD patients from similar ethnic backgrounds. In the present study, two common genetic variations in each ABCA1 and CETP gene were studied with reference to their effect on CAD. We tested four SNPs, namely rs2230806 (R219K), rs2066715 (V825I), rs5882 (V422I), and rs708272 (TaqIB) for their association with CAD. CETP, located on chromosome 16q21, plays a crucial role in lipid metabolism, and numerous SNPs in this gene have been reported to alter the plasma HDL-C levels and function of CETP [22, 23]. Among the CETP SNPs, rs708272 is the one that is most studied. Therefore, we investigated the association of two SNPs of this gene and their risk for CAD in the Saudi population.

Our overall results showed that the heterozygous and mutant of rs708272 polymorphism may confer protection against CAD (B1B2: OR = 0.68, \( P = 0.001 \); B2B2: OR = 0.68, \( P = 0.012 \)) while those of rs5882 increased the risk of CAD (VI: OR = 1.45, \( P = 0.005 \); II: OR = 1.37, \( P = 0.031 \)). Earlier studies had suggested that the CETP variant rs5882 causes low CETP and is associated with higher HDL and possibly with increased CAD among hypertriglyceridemia men [24, 25]. In contrast, in many recent studies, the rs5882 polymorphism lacked any association with CAD [26–29]. ABCA1 encodes an important protein that facilitates the formation of HDL-C and regulates the efflux of lipids from peripheral cells into lipid-poor ApoA1 particles, stimulating reverse cholesterol transport. [30] The association between the ABCA1 gene polymorphisms and CAD has been the focus for many studies [31–33]. The rs2230806 is the most common polymorphism of ABCA1; the possible role of rs2230806 in cardiovascular diseases is still debatable as numerous studies have reported divergent results [34, 35]. The results of our study revealed that the K variant of rs2230806 (\( P = 0.029 \)) is associated with CAD, which is in line with Zargar et al. [36]. The rs2066715 of ABCA1 is not associated with an increased risk of CAD. The frequency of the rare allele of rs2066715 (0.02) showed a unique distribution compared to the 1000 genome database (0.113) and Han Chinese (0.44) population [37]. The K allele frequency of rs2230806 (R219K) polymorphism in our study was 0.47 reported in earlier studies [18, 38, 39]. The K allele frequency reported in our study is in line with other reports, namely a European ancestry study which reported a K allele frequency of 0.26–0.46 and a study on Dutch men with proven CAD, which reported a frequency of 0.46 [40, 41].

An analysis of the effect of a combination of ABCA1 genotypes on CAD showed that the RR+VI genotype was significantly associated with a high risk of CAD (OR = 2.82, 95 % CI 1.32–6.02, \( P = 0.007 \)). However, an analysis of the effect of the combination of CETP genotypes on CAD showed no significant pattern. All other combinations lacked a significant association with an OR ranging from 0.73 to 1.24, except for B1B1+VI (OR = 1.7, \( P = 0.048 \)). The prevalence of CAD was higher in males (M:F 708:282) than in females in the present study. Homozygous mutant and heterozygous of rs5882 in men and women were strongly associated with an increased risk of CAD, while the other two ABCA1 polymorphisms showed no significant association with CAD (OR = 0.73–1.13) in the female cohort. Also, heterozygosity of rs708272 alleles was strongly associated with an increased risk of CAD (OR = 0.65, \( P = 0.002 \)), a homozygous carriage of rs5882, the rarer variants II causing amino acid

---

**Table 4** Association between ABCA1 and CETP genotypes and CAD in male and female cohorts

| Genotype | Male cohort | | | Female cohort | | |
|----------|-------------|-----------------|---|-----------------|---|
|          | Cases (n = 708) | Control (n = 423) | OR (95 % CI) | \( P \) value | Cases (n = 282) | Control (n = 195) | OR (95 % CI) | \( P \) value |
| R219K RR | 212 | 137 | Ref | | 79 | 58 | Ref |
| RK       | 337 | 229 | 0.95 (0.72–1.24) | 0.718 | 136 | 88 | 1.13 (0.73–1.74) | 0.566 |
| KK       | 159 | 57 | 1.80 (1.24–2.61) | 0.001 | 67 | 49 | 1.0 (0.60–1.65) | 0.987 |
| V825I VV | 676 | 414 | Ref | | 269 | 183 | Ref |
| VI       | 32  | 9  | 2.17 (1.02–4.60) | 0.041 | 13  | 12  | 0.73 (0.32–1.65) | 0.458 |
| V422I VV | 123 | 103 | Ref | | 55  | 44  | Ref |
| VI       | 376 | 232 | 1.35 (0.99–1.84) | 0.052 | 147 | 65  | 1.80 (1.10–2.96) | 0.018 |
| II       | 209 | 88  | 1.98 (1.38–2.85) | 0.0002 | 80  | 86  | 0.74 (0.45–1.22) | 0.246 |
| TaqIB B1B1 | 261 | 124 | Ref | | 115 | 59  | Ref |
| B1B2     | 340 | 247 | 0.65 (0.49–0.85) | 0.002 | 114 | 74  | 0.79 (0.51–1.21) | 0.282 |
| B2B2     | 107 | 52  | 0.97 (0.65–1.45) | 0.91  | 53  | 62  | 0.43 (0.27–0.71) | 0.0008 |
substitutions showed a strong association with an increased risk of CAD (OR = 1.98, \( P = 0.0002 \)) among the male cohort. The \textit{CETP} rs5882 polymorphism was found to be associated with an increased risk for CAD in the overall study population and also in the male and female cohorts, which is in contrast to a recent study which reported that this polymorphism is associated with a decreased risk of CAD and MI [42].

Studies conducted in other populations have correlated the genotypes of \textit{ABCA1} and \textit{CETP} and risk of CHD with respect to its effect on HDL-C. A study of 119 patients in Korea showed that the B1B1 genotype of the \textit{CETP} TaqIB polymorphism was associated with low HDL-C levels in females and non-smoking males and may be an independent genetic risk factor for CAD [43]. In the present study, the B2 allele of the \textit{CETP} rs708272 polymorphism was associated with a reduced risk of CAD mediated by elevated HDL-C concentrations. However, Borggreve et al. in their prospective population-based study (PREVENT study) on 8141 Caucasians demonstrated that the B2 and I alleles of the rs708272 (TaqIB) and rs5882 (V422I) of the \textit{CETP} gene were not associated with a decreased risk for CAD, despite their HDL-C-raising effect suggesting that the risk may be independent of the gene’s influence on HDL-C levels [44]. Thus, the association of polymorphic \textit{CETP} genotypes with a decreased cardiovascular risk seems to be independent of their effect on HDL-C levels [45–47].

\textbf{Conclusion}

This study is the first to report the association of these polymorphisms with the development of CAD in a Saudi population. A significant association of \textit{CETP} rs5882 and \textit{ABCA1} rs2230806 polymorphism with CAD was observed marking these polymorphisms as risk factors. The rs708272 showed a protective effect for CAD, and rs2066715 of \textit{ABCA1} gene lacked any association with CAD, whereas the joint effect of the \textit{ABCA1} gene (RR+VI and KK+VV) conferred a higher risk for CAD. A sex difference subsists with a higher prevalence of CAD among males (M:F 708:282). Female heterozygous and male homozygous for the rs5882 were shown to have an increased risk of CAD.

\textbf{Methods}

\textbf{Study population}

Patients reporting to the cardiac clinic at King Fahd Hospital of the University, Al-Khobar, and other major hospitals in the Eastern Province of Saudi Arabia were screened, and angiographically confirmed CAD cases with at least one event of MI (N = 990) were enrolled in this study. A total of 618 age-matched normal Saudi controls with no history or family history of CAD were recruited from the blood banks of the same hospitals. This study was approved by the Ethical Committee of the University of Dammam. Signed written informed consent was obtained from all participants.

\textbf{Genotyping}

Blood samples (5 ml) were obtained from 1608 subjects in EDTA-coated tubes and DNA was extracted using QIAamp DNA isolation kit (Qiagen, Germany) as per the manufacturer’s instructions. Allele-Specific TaqMan® PCR procedures were used to detect the genetic variants rs2230806, rs2066715, rs708272, and rs5882.

\textbf{Statistical analysis}

The difference between cases and controls was evaluated using \textit{t} test for continuous variables and Chi-square test for discrete variables. Allele frequencies were estimated by direct counting of the test allele divided by the total number of alleles. To assess the risk for CAD, odds ratio was determined by univariate analysis. All statistical analyses were performed using SPSS software (version 19). The power of the study was calculated using online software sampsize.sourceforge.net.

\textbf{Competing interests}

The authors declare that they have no competing interests.

\textbf{Authors’ contributions}

CC, CV, and SC designed the study, performed the assay, and drafted the manuscript. AAS and MA provided the CAD patient samples, AAN and FAM provided the age- and sex-matched controls. MSA and RAA collected all medical data of the individual participant from the hospital records. CV performed the statistical analyses. BK was involved in drafting the manuscript for important intellectual content. AAA and FAM provided critical review of the manuscript. All authors made significant intellectual contributions and have read and reviewed the manuscript. All authors read and approved the final manuscript.

\textbf{Acknowledgements}

The authors acknowledge the King Abdulaziz City for Science and Technology (KACST) for funding the for the current research grant (LGP 32-44). We thank Mr. Geoffrey James Tam Moro and Mr. Florentino Jr Mata for the technical support.

\textbf{References}

1. Kubo M, Kiyohara Y, Kato I, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke. 2003;34(10):2349–54.
2. Gaziano TA, Bitton A, Anand S, et al. Growing epidemic of coronary heart disease in low-and middle-income countries. Curr Probl Cardiol. 2010;35(2):72–115.
3. Al-Nozha MM, Arafa MR, Al-Mazrou YY, et al. Coronary artery disease in Saudi Arabia. Saudi Med J. 2004;25(9):1165–71.
4. Yamada Y, Izawa H, Ichihara S, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med. 2002;347(24):1916–23.
5. Licastro F, Chiapelli M, Porcellini E, et al. Gene-gene and gene-clinical factors interaction in acute myocardial infarction: a new detailed risk chart. Curr Pharm Des. 2010;16(7):783–8.

6. Otiki T, Habashi Y, Kohno T, et al. Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction. Am Heart J. 2012;163(2):164–7.

7. Romero-Conal A, Somers WK, Sierra-Johnson J, et al. Normal weight obesity: a risk factor for cardiac metabolic dysregulation and cardiovascular mortality. Eur Heart J. 2010;31(6):737–46.

8. Vinzova R, Boissonnet CP, Acevedo M, et al. Dyslipidemia in seven Latin American cities: CARMELA study. Prev Med. 2010;50(3–4):106–11.

9. Pöös J, Custodis F, Wemer C, et al. Cardiovascular disease and dyslipidemia: beyond LDL. Curr Pharm Des. 2011;17(9):861–70.

10. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomization study. Lancet. 2012;380(9841):572–80.

11. Rejeb J, Omezzine A, Rebihi L, et al. Association of the cholesteryl ester transferprotein TaqI B2B2 genotype with higher high-density lipoprotein-cholesterol concentrations and lower risk of coronary artery disease in a Tunisian population. Arch Cardiovasc Dis. 2008;101(10):629–36.

12. van Acker BA, Botma GJ, Zwinderman AH, et al. High HDL cholesterol does not protect against coronary artery disease when associated with combined cholesteryl ester transfer protein and hepatic lipase gene variants. Atherosclerosis. 2008;200(1):161–7.

13. Hiura Y, Shen CS, Kokubo Y, et al. Identification of genetic markers associated with high-density lipoprotein cholesterol by genome-wide screening in a Japanese population: the Suita study. Circ J. 2009;73(6):1110–26.

14. Holzmann MJ, Jungner I, Walldius G, et al. Dyslipidemia is a strong predictor of myocardial infarction in subjects with chronic kidney disease. Ann Med. 2012;44(3):262–70.

15. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian randomization of HDL cholesterol, and risk of future myocardial infarction: genome wide association study. BMJ. 2012;345:e9607.

16. Porchaj J, Pelan F, Bellii N, et al. ABCA1 single nucleotide polymorphisms on high-density lipoprotein-cholesterol and overweight: the D.E.S.I.RE study. Obesity. 2006;14(11):1874–9.

17. Barter PJ, Brewer Jr HB, Chapman MJ, et al. Cholesteryl ester transfer protein, a novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol. 2003;23(2):160–7.

18. Brousseau ME, O'Connor Jr JJ, Ordovas JM, et al. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol level and lower risk of coronary heart disease endpoints in men with HDL deficiency: veterans affairs HDL cholesterol intervention trial. Arterioscler Thromb Vasc Biol. 2002;22(7):1148–54.

19. Beekholff SM, Kuvenhoven JA, Vrolijk GM, et al. CETP gene variation: relation to lipid parameters and cardiovascular risk. Curr Opin Lipidol. 2004;15:393–8.

20. Thompson A, Di Angelantonio E, Sarwar N, et al. Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. JAMA. 2008;299(23):2777–88.

21. Ridker PM, Paré G, Parker AN, et al. Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: genome wide analysis among 18245 initially healthy women from the Women’s genome health study. Circ Cardiovasc Genet. 2009;2:22–33.

22. Bruce C, Sharp DS, Tall AR. Relationship of HDL and coronary heart disease to a common amino acid polymorphism in the cholesteryl ester transfer protein in men with and without hypertriglyceridemia. J Lipid Res. 1998;39(10):1–7.

23. Gudnason V, Kakko S, Nicault C, et al. Cholesteryl ester transfer protein gene effect on CETP activity and plasma high-density lipoprotein in European populations. The EARS Group. Eur J Clin Invest. 1999;29(2):16–28.

24. Padmaja N, Ravindra KMA, Soya SS, et al. Common variants of Cholesteryl ester transfer protein gene and their association with lipid parameters in healthy volunteers of Tamilian population. Clin Chim Acta. 2007;375:140–6.

25. Parra ES, Panzoldo NB, Kaplan D, et al. The I405V and TaqIB polymorphisms of the CETP gene differentially affect sub-clinical carotid atherosclerosis. Lipids Health Dis. 2012;11:130.