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Correlation of *ITGB3* Gene rs5918T>C and *APOA1* Gene rs1799837C>T Variants with Serum Lipid Profiles in Turkish Cypriot Patients with Coronary Artery Disease

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SOUHRN

Cíl: Vztah mezi hypercholesterolemií, zvláště zvýšenými hodnotami cholesterolu v lipoproteinech o nízké hustotě (LDL-C) a ischemickou chorobou srdeční (ICHS), je potvrzen důkazy z předchozích epidemiologických studií. Důležité bylo popsání souvislosti mezi genetickým polymorfismem a hodnotami lipidů v plazmě. Cílem této studie bylo zkoumat vztah mezi variantami rs5918 T>C genu pro ITGB3 a variantou rs1799837 C>T genu pro APO-A1 na jedné straně a metabolismem lipidů v séru na straně druhé.
Pacienti a metody: Do této studie bylo zařazeno celkem 100 jedinců s ICHS a 250 zdravých jedinců. U každého účastníka bylo provedeno základní biochemické vyšetření včetně stanovení koncentrace glukózy v séru, celkového cholesterolu (total cholesterol, TC) v séru, hodnot HDL-C, LDL-C a triglyceridů. Pro genotypizaci polymorfismů genů pro ITGB3 a APO-A1 byla použita polymerázová řetězová reakce s následnou analýzou polymorfismu délky restrikčních fragmentů (restriction fragment length polymorphism, RFLP).
Výsledky: Pokud se týče genotypu a distribuce alel polymorfismu rs5918 T>C genu pro ITGB3, vyskytovala se alela C častěji ve skupině s ICHS než v kontrolní skupině (p = 0,001). Ve skupině s ICHS byla navíc pozorována statisticky významná souvislost mezi genotypem rs5918 ITGB3 a hodnotami celkového cholesterolu v genotypu CC na jedné straně a TC v séru a cholesterolu v lipoproteinech o vysoké hustotě (HDL-C) (p = 0,0006, resp. p = 0,016). Nicméně ani v kontrolní skupině, ani ve skupině s ICHS nebyla nalezena statisticky významná spojitost mezi polymorfismem rs1799837 C>T genu pro APO-A1 a biochemickými parametry.
Závěr: Výsledky prokázaly, že varianta rs5918 T>C genu pro ITGB3 by mohla být z klinického hlediska významná jako genetický marker zvýšené vnímavosti k rozvoji ICHS. Alelu C varianty rs5918 genu pro ITGB3 by tak bylo možno navrhnout pro screening potenciálního rozvoje ICHS u populace kyperských Turků, kteří se dostaví na kontrolu k lékaři.

Keywords:
APO-A1
Coronary artery disease
HDL-C
ITGB3
LDL-C
Polymorphism
Turkish Cypriot

ABSTRACT

Aim: The relationship between hypercholesterolemia, particularly elevated low density lipoprotein-cholesterol (LDL-C) levels and coronary artery disease is recognized by the evidence from previous epidemiologic studies. Importantly, genetic polymorphisms on different genes have been reported to be associated with plasma lipid levels. In this particular study, we aimed to investigate the relationship between the *ITGB3* gene rs5918 T>C and *APO-A1* gene rs1799837 C>T markers and serum lipid metabolism.

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Patients and methods: A total of 100 subjects with CAD and 250 healthy subjects were involved in the current study. A basic biochemical analysis, including serum glucose, total serum cholesterol, HDL-C, LDL-C and triglycerides, was performed for each participant. Genotyping for the *ITGB3* gene and *APO-A1* gene polymorphisms was performed by polymerase chain reaction followed by restriction fragment length polymorphism (RFLP) analysis.

Results: With respect to the genotype and allele distributions of *ITGB3* rs5918 T>C polymorphism, the frequency of the C allele was higher in the coronary artery disease (CAD) group compared to the control group (p = 0.001). Moreover, there was a statistically significant association detected between *ITGB3* rs5918 CC genotype and serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) (p = 0.0006, p = 0.016, respectively) in CAD group. However there was no statistically significant association was identified between the *APOA1* rs1799837 C>T polymorphism and biochemical parameters in control and CAD group.

Conclusion: The results demonstrated that rs5918 T>C variant within the *ITGB3* gene might have a clinical importance as a genetic marker which increases the susceptibility to CAD. Therefore, the *ITGB3* gene rs5918 C allele may be offered as a screening option for CAD in Turkish Cypriot population who come in for medical check-up.

Introduction

Among the group of cardiovascular disorders, coronary artery disease (CAD) is the most commonly reported all around the world.[1,2] Among the modifiable risk factors, abnormal lipid metabolism plays a critical role in the pathogenesis of CAD.[2] According to the World Health Organization (WHO) statistics, 17.9 million people die each year from CVDs, which accounts for nearly 31% of all global deaths.[1]

Over more than a decade, it has been shown that serum concentrations of blood lipids are associated with increased risk of developing cardiovascular diseases.[3] Genetic variants on several genes are believed as one of the most significant determinants of the concentration of serum lipids and CAD.[4] The product of the *ITGB3* gene (OMIM 173470) which is located on chromosome 17 long (q) arm at 21.32 position is a protein known as integrin beta III, which is also noted as platelet glycoprotein IIIa, GP3A, GPIIIa or antigen CDG1, is a surface protein found in various tissues, and has an active role in cell surface mediated signaling and adhesion. A single base change at position 1565 in exon 2 of *ITGB3* gene (T to C) (rs5918T>C) results substitution of leucine (PlA1) amino acid for proline amino acid (PlA2) at a residue 33 of the β3 subunit of the platelet glycoprotein IIIa.[5] This polymorphism causes different spatial orientation and conformational change of protein in fibrinogen binding region.[1,6] Several mechanisms have been documented about the role of the fibrinogen in CVD, essentially when it binds to activated platelets via glycoprotein IIb/IIIa, it contributes to platelet aggregation.[6,7]

According to Shabana et al.[1] the *ITGB3* gene rs5918T>C polymorphism has a significant role in the progression of coronary artery disease and coronary thrombosis due to a key event in acute coronary syndrome. Additionally, it has been demonstrated that there is a strong association of *ITGB3* with triglycerides in non-Hispanic blacks.[3] In earlier studies, it has been shown that PlA2 variant was associated with an increased risk of coronary heart disease. Importantly, some reports suggest that PlA1/A2 heterozygotes are more prone to develop thrombotic diseases, while, PlA1/A1 homozygotes may be prone to develop early atherosclerosis.[6] A study which was undertaken by Khatami et al.,[6] showed that (PIA1/PIA2) polymorphism in the *ITGB3* gene is associated with CAD in the Iranian population.

Apolipoprotein A-1 *(APOA1)* gene (OMIM 107680) which is located on chromosome 11 long (q) arm at 23.3 position.[4] Also it is a crucial apolipoprotein component of HDL-C which is essential for normal HDL-C synthesis (F. Wang et al., 2019; Rosales et al., 2019). It has been indicated that inter-individual variants in plasma *APOA1* and HDL are mostly affected by a common polymorphism of a cytosine (C) to thymine (T) substitution (C/T) at -75 bp (rs1799837) in the promoter region.[4]

Genetic variants and mutations in the *APOA1* gene may reduce HDL-C levels therefore the risk of developing premature CAD may be increased.[8] In light of the evidence from previous studies, the association of "T" allele (minor/mutant allele) carriers have undoubtedly higher TG levels while other studies showed there is no association between "T" allele carriers and TG.[4] Interestingly, various studies have shown that the rs1799837 SNP is associated with higher plasma HDL-C levels in carriers of the TT genotype.[9]

Despite many genetic markers have been studied previously, *APOA5* (rs662799 T>C), *APOA5* (rs2075291 G<T), *APOA5* (rs3135507 G>A).[10] *NOS3* c.894G>T and 27-bp VNTR polymorphisms.[11] *CDKN2B-AS1* (rs4977574 A>G), *CDKN2B-AS1* (rs1333040 C>T).[12] ACE INDEL polymorphism.[13] FV Leiden (G1691A), Factor V R2 mutation (FVR2) (H1299R), *PTH* (G20210A), *FXIII* (V34L), β-fibrinogen (–455 G>A), *PAI-1* (4G/5G), *HPA1* (a/b), *MTHFR* [C677T] and [A1298C], *ACE* (I/D), *Apo B* (R3500Q), and *Apo E* (14) rs5918T>C and rs1799837C>T have not been previously investigated in the Turkish Cypriot population. Therefore, this study is the first study which aimed to investigate the association of the *ITGB3* gene rs5918T>C and the *APO-A1* gene rs1799837C>T markers with serum lipid metabolism in cardiovascular patients in the population of Turkish Cypriots.

Material and methods

Study design and participants

The study protocol was approved by the Near East University Ethics Review Board (NEU/2016/36/382) and informed

consent was obtained from all patients and control individuals. Each subject was provided with a detailed questionnaire form to collect information about their personal characteristics, including age, ethnicity, socio-economic background and health status. The current study included 438 Turkish Cypriot individuals. The participant who has history of smoking, hypertension, obesity (BMI >30), diabetes, dislipidemia, and family background were exluded from this study. The Turkish Cypriot race was identified as living on the island as well as being born to parents who have been living at least past three generations. However, participants were selected from among whole island according to their or parents residence before 1974. Furthermore, due to the small size of island population and large numbers of kinship in the Northern Cyprus, the subjects which are relatively related were eliminated from the study. Three hundred forty-five healthy subjects, having no clinical evidence of family/history of stroke or transient ischemic attacks constituted the control group and 93 patients with angiography confirmed CAD who were diagnosed by a cardiologist comprised the CAD group. The controls and CAD groups were matched according to their sex, age, and socio-economic background. Blood samples were collected from all participants and biochemical analysis was performed for total cholesterol, glucose, LDL-cholesterol, HDL-cholesterol, and triglycerides. Additionally, blood pressure measurements were also performed. Basic biochemical analysis protocol has been applied for each individual. Antecubital venous blood was collected from each individual and samples were centrifuged within 2 h of collection. Total serum cholesterol, HDL-C (high density lipoprotein cholesterol), LDL--C (low density lipoprotein cholesterol), triglycerides (TG) and serum glucose were analyzed at the Near East University Hospital Biochemistry Laboratory. Moreover, the subjects who are under any medication that might alter the serum level parameters were eliminated from the study group.

Genotyping

Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) from 350 individuals fromm the Turkish Cypriot population. QIAamp DNA Blood Mini Kit (Qiagen Inc.,Valencia, CA, USA) was used for DNA extraction. Genotypes for *ITGB3* gene (rs5918T>C) and *APOA1* gene (rs1799837C>T) polymorphisms were determined by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) following the same primers and conditions in earlier studies.[15,16] Polymerase chain reaction (PCR) was performed in a total reaction volume of 25 µl in 200 µl tubes on an Applied Biosystems Veriti Thermal Cycler. The reaction mixture included PCR Master Mix (2X) (Thermo Scientific Waltham, CA, USA), 10nM of forward and reverse primers (Thermo Scientific Waltham, CA, USA) and 10 ng of the genomic DNA. Fragments obtained from PCR-RFLP were separated in 3% agarose gels. Then gels were visualized by ethidium bromide staining. By using UV-treated solutions, designated pipettes, and pipette tips, a class II laminar hood and DNA/DNAse free plasticware and reagents, the risk of contamination was decreased to minimum. Genotypes were determined according to presence or absence of restriction sites and alleles were designated with respect to actual base change according to the dbSNP (https://www.ncbi.nlm.nih.gov/SNP) and Ensembl (http://www.ensembl.org/) websites.

Statistical analysis

The commercial software program (Graphpad Software, Inc. California, USA) was used for statistical analysis. The data were expressed as mean ± standard deviation (SD) for normally distributed continuous variables. Intergroup differences in continuous variables were determined by the Student's unpaired *t* test, where a *p*-value (two-tailed) of less than 0.05 was considered as statistically significant. Genotype distributions and allele frequencies were measured by the gene-counting method and the Pearson's goodness of fit Chi square (χ^2) method was applied to check their compliance to the Hardy-Weinberg equilibrium. The association between the case–control status and each polymorphism was assessed by the odds ratio (OR) and its corresponding 95% confidence interval (CI), where a *P* value of < 0.05 was considered to be statistically significant. For each polymorphism, one-way ANOVA (analysis of variance) was used to evaluate the impact of the designated genotypes on biochemical parameters.

Results

Demographic, clinical and laboratory characteristics of the studied subjects

The personal characteristics and biochemical parameters of the subjects, from whom blood samples were obtained are shown in **Table 1**. The subjects composed of 350 Turkish Cypriot individuals including 100 patients with CAD and 250 Turkish Cypriots as the control group. The CAD group showed no statistically significant difference from the control group with respect to age, gender and low--density lipoproteins-cholesterol (LDL-C) (*p* >0.05), whereas, fasting plasma glucose levels, serum concentration

Table 1 – General characteristics of all studied subjects

parameters	Control	CAD	Two-tailed *p*-value
	n = 250	n = 100	0.052
Age (years)	57.5 ± 15.5	62.0 ± 12.0	
Sex	37.6% F	45% F	0.201
	62.4% M	55% M	
Glucose (mg/dl)	94.7 ± 16.2	128.0 ± 47.1	<0.0001
Cholestrol (mg/dl)	178.2 ± 39.0	204.5 ± 44.9	0.001
HDL-C (mg/dl)	52.7 ± 12.4	43.9 ± 16.3	<0.0001
LDL-C (mg/dl)	122.5 ± 39.1	135.7 ± 34.7	0.053
Triglyceride (mg/dl)	117.3 ± 76.1	160.7 ± 82.3	0.003

CAD – coronary artery disease; n – number of subjects; F – female; M – male; HDL-C – high-density lipoprotein-cholesterol; LDL-C – low density lipoprotein-cholesterol; TG – triglyceride. Data are represented as mean ± standard deviation (SD).

Table 2 – Genotype distributions and allele frequencies for the *ITGB3* rs5918 T>C and *APOA1* rs1799837 C>T among the studied groups

Genotype	Groups		Genotype	Groups	
	Control	CAD		Control	CAD
ITGB3 rs5918 T>C	(N: 250)	(N: 100)	APOA1 rs1799837 C>T	(N: 250)	(N:100)
TT	190	64	**CC**	150	63
TC	52	25	**CT**	91	29
CC	8	11	**TT**	9	8
X2	3.3	9.2	**X2**	1.14	
***p*-value**	0.69	0.002	***p*-value**	0.285	
T allele	432	153	**C allele**	391	155
C allele	68	47	**T allele**	109	45
T allele frequency	0.86	0.76	**C allele frequency**	0.78	0.78
C allele frequency	0.14	0.24	**T allele frequency**	0.22	0.22
***p* value**	0.001		***p* value**	0.839	
OR	1.951		**OR**	1.041	
95% CI	1.288-2.955		**95% CI**	0.702-1.544	

CAD – coronary artery disease; CI – confidence interval; N – number of subjects; OR – odds ratio; χ^2– Chi square; p <0.05, reaches statistical significance.

Table 3 – Comparisons of ITGB3 rs5918 T>C and APOA1 rs1799837 C>T polymorphisms with clinical parameters within both studied groups

Clinical parameters	rs5918			ANOVA *p*-value	rs1799837			ANOVA *p*-value
Control	TT	TC	CC		CC	CT	TT	
Glucose (mg/dL)	89.1 ± 5.8	96.1 ± 25.0	99.1 ± 17.8	0.664	93.9 ± 57.0	98.3 ± 33.3	88.1 ± 50.2	0.479
Cholestrol (mg/dL)	199.0 ± 36.6	202.7 ± 46.3	207.8 ± 42.3	0.878	194.7 ± 47.5	203.4 ± 45.0	213.6 ± 32.5	0.465
HDL-C (mg/dL)	55.6 ± 11.0	53.1 ± 12.8	49.0 ± 9.6	0.339	39.9 ± 13.3	49.6 ± 21.0	42.0 ± 6.5	0.295
LDL-C (mg/dL)	120.0 ± 29.3	131.6 ± 31.9	132.3 ± 37.1	0.719	125.2 ± 42.1	125.3 ± 40.2	102 ± 38.0	0.648
Triglyceride (mg/dL)	101.3 ± 37.0	125.5 ± 100.0	153.1 ± 155.5	0.503	173.6 ± 87.0	155.1 ± 78.8	149.0 ± 102.5	0.780
Clinical parameters				**ANOVA *p*-value**				**ANOVA *p*-value**
CAD	TT	TC	CC		CC	CT	TT	
Glucose (mg/dL)	124.7 ± 38.4	164.4 ± 87.1	103.3 ± 29.7	0.138	128.8 ± 57.0	120.9 ± 33.3	135.3 ± 50.2	0.844
Cholestrol (mg/dL)	165.0 ± 15.2	190.4 ± 44.6	267.6 ± 66.1	**0.0006**	188.0 ± 43.6	196.7 ± 47.5	153.6 ± 51.0	0.344
HDL-C (mg/dL)	38.5 ± 11.7	42.9 ± 16.8	66.5 ± 9.9	**0.016**	53.9 ± 13.7	51.6 ± 12.4	55.3 ± 12.1	0.607
LDL-C (mg/dL)	123.2 ± 40.7	105.2 ± 14.1	154.6 ± 53.0	0.184	124.1 ± 37.9	131.8 ± 36.6	145.0 ± 32.2	0.314
Triglyceride (mg/dL)	150.0 ± 85.5	166.0 ± 85.0	175.5 ± 30.4	0.887	106.3 ± 43.7	149.2 ± 164.1	81.7 ± 22.3	0.098

CAD – coronary artery disease; HDL-C – high-density lipoprotein-cholesterol;; LDL-C – low-density lipoprotein-cholesterol. Values are represented as mean ± standard deviation. *p <0.05, reaches to statistical significance.

of total cholesterol (TC), and the serum concentration of triglycerides (TG) were significantly higher in the CAD group compared to those in the control group (p <0.001, p = 0.001, p = 0.003, respectively). Additionally, the serum concentrations of high-density lipoprotein-cholesterol (HDL-C) was significantly lower in the CAD group compared to those in the control group (p <0.001).

Genotype and allele distributions of the ITGB3 *and* APOA1 *gene polymorphisms in the studied groups*

The allele and genotype frequency distributions of *ITGB3* rs5918 T>C and *APOA1* rs1799837 C>T gene polymorphisms among the control and CAD group are demonstrated in **Table 2**. Regarding the genotype and allele distributi-

ons of *ITGB3* rs5918 T>C, the results showed statistically significant in the CAD patients ($\chi^2 = 9.2$, $p = 0.002$) and not significant ($\chi^2 = 3.3$, $p = 0.69$) in the control group. Therefore, determining CAD risk factors, C allele was more frequent in CAD group compared to the control group ($p = 0.001$, odd ratio [OR] = 1,951, 95% CI = 1.288–2.955). However, in *APOA1* rs1799837 C>T, the allele frequency was equal for C allele and G allele in control group and CAD group ($p = 0.839$, OR = 1,041, 95%CI 0.702–1.544).

Comparison of ITGB3 *and* APOA1 *gene polymorphisms with clinical parameters within both studied groups*

The distribution of all biochemical parameters according to the *ITGB3* and *APOA1* genotypes among the control group and CAD group are shown in **Table 3**.

ANOVA standard weighted-means analysis for independent samples (df:2) was performed to determine the association between *ITGB3* rs5918 T>C and *APOA1* rs1799837 C>T polymorphisms and biochemical parameters. Data are expressed as mean ± standard deviation (SD). According to the analysis, *ITGB3* rs5918 T>C variant showed significant association in serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) values in CAD group. Importantly, the statistically significant association has been observed between *ITGB3* rs5918 CC genotype and serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) ($p = 0.0006$, $p = 0.016$, respectively). On the other hand, no statistically significant association was found between the *APOA1* rs1799837 C>T SNP and biochemical parameters in control and CAD group.

Discussion

Among the group of cardiovascular diseases, coronary artery disease (CAD) is the most commonly observed cardiovascular disease all around the World.[17] While gender, age, family history, diabetes mellitus, sedentary lifestyle, hypertension, stress, obesity, smoking, and dyslipidemia are known as some of the important risk factors for CAD,[1,6] the most common etiological factor of coronary artery disease is atherosclerosis.[18] In addition to these, a number of polymorphisms on several genes have been previously shown to play a critical role in serum lipid concentrations.[19] This particular study was focused on evaluating the association of the *ITGB3* rs5918 T>C and the *APOA1* rs1799837 C>T gene polymorphisms with serum lipid metabolism in cardiovascular patients in Turkish Cypriot population. To our knowledge, this is the first study investigating the effect of *ITGB3* rs5918 T>C and *APOA1* rs1799837 C>T polymorphisms in Turkish Cypriot population which will also offer valuable insights to understand the susceptibility of the Turkish Cypriot population to diseases such as cardiovascular conditions, dyslipidemia and hypercholesterolemia.

So far, several variants of the *ITGB3* gene have been identified.[6] In the current study, the allele and genotype frequencies of the *ITGB3* rs5918 T>C polymorphism were determined in a group of patients with CAD and control group. Minor Allele Frequency (MAF) was higher (MAF: 0.24 C) when compared with European and global MAF (EUR MAF: 0.13 C; global MAF: 0.09) (Ensembl Genome Browser (http://www.ensembl.org). Earlier studies including Egyptian population pinpointed that the *ITGB3* rs5918 T>C variant has a strong association with the etiology of CAD.[2] In contrast, it has been indicated that the carriage of the *ITGB3* rs5918 T>C polymorphism is not a major risk factor for the development of myocardial infarction in Iranian patients with premature CAD.[20] Furthermore, it has been found that there is a strong association between the *ITGB3* rs5918 T>C with triglycerides in non-Hispanic blacks who are one of the major ethnic groups in the US population.[3]

In another study, the researchers investigated the association between the PlA2 (C) allele and acute coronary syndrome (ACS) in a case control study of 71 Caucasians patients with a diagnosis of MI or unstable angina. It has been documented that the PlA2 (C) allele was overexpressed in patients with CAD compared to 68 healthy controls (39.4% versus 19.10%; $p = 0.01$, respectively).[21] Considerably, in our study, the frequency of the C allele was more frequent in CAD group compared to the control group ($p = 0.001$) and a significant association has been observed between *ITGB3* rs5918 CC genotype and serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) ($p = 0.0006$, $p = 0.016$, respectively).

More importantly, as it is known *ITGB3* is a membrane receptor for fibrinogen and von-Willebrand factor which has a critical role in platelet aggregation.[22] Although newer antiplatelet drugs were developed, acetylsalicylic acid is still one of the most commonly used antiplatelet agent all around the world to prevent thrombotic events in patients with cardiovascular diseases.[4] However, many patients have had adverse situations in spite of acetylsalicylic acid intake which is also known as "aspirin resistance" (AR), the AR term indicates that a mechanistic reason limits acetylsalicylic acid's efficiency.[23]

There is limited evidence for the biological reasons that explain the anti-platelet effect of acetylsalicylic acid in patients, the mechanisms involved in AR are likely to be multifactorial.[24] For instance, diabetes mellitus, hyperlipidemia, severe unstable angina, heart failure, and obesity are some of the risk factors associated with increased lipid peroxidation and overproduction of isoprostanes which may lead to the development of AR.[24] Additionally, by understanding the role of genetic variation or polymorphisms in drug response can be useful to discover if an individual will develop an altered clinical effect.[25]

Undas et al.[26] suggested that individuals homozygous for the *ITGB3* rs5918 CC genotype have a higher risk of developing myocardial infarction (MI) and aspirin resistance. Therefore, testing for genetic polymorphisms before prescribing drug therapy could be a valuable strategy to identify additional risk factors. Screening patients with cardiovascular disease for antiplatelet polymorphisms may help optimize treatment options and improve outcomes.[21]

Similarly, the allele and genotype frequencies of the *APOA1* rs1799837 C>T polymorphism were analyzed in a cohort of patients with coronary artery disease (CAD) and a control group. Although *APOA1* polymorphisms have been widely studied in various diseases, their as-

sociation with cardiovascular diseases remains controversial. Liao et al.[27] reported that individuals carrying the *APOA1*-75 T allele had a lower risk of developing CAD, as this variation was significantly associated with increased serum HDL-C levels in a Chinese Han population (p <0.001). In contrast, Wang et al. (2017) found no significant association between the *APOA1* rs1799837 C>T polymorphism and HDL-C levels in a study involving interactions between *APOA1* single nucleotide polymorphisms (SNPs) and obesity subtypes in the Chinese population.

Moreover, Villard et al.[9] explored the impact of genetic variants involved in the biogenesis, maturation, and intravascular remodeling of high-density lipoprotein (HDL) particles on plasma efflux capacity. Their study also found no significant association between the *APOA1* rs1799837 C>T variant and plasma HDL-C levels. In line with these findings, our current study did not observe a significant association between the *APOA1* rs1799837 C>T polymorphism and serum lipid concentrations.

Limitations

This study has several limitations. Firstly, it is volunteer--based, and the sample size is relatively small. Secondly, CAD is a multifactorial disease involving various genetic and environmental influences, which makes identifying significant associations between candidate genes and disease risk more challenging. Thirdly, considering the unique and underexplored genetic profile of the Turkish Cypriot population, these polymorphisms might exhibit different effects on plasma lipid levels compared to other populations. Nonetheless, despite the small sample size, our study adds important preliminary data to the literature. For instance, the *ITGB3* gene rs5918 C allele could serve as a useful screening marker for Turkish Cypriots during routine medical check-ups, enabling personalized lifestyle modifications based on genetic susceptibility.

Furthermore, the absence of comprehensive polymorphic data for many genes in the Turkish Cypriot population underscores the need for additional studies. Future research should focus on larger cohorts and incorporate more detailed biochemical and genetic analyses to strengthen the findings and explore additional candidate gene associations.

Conclusion

Overall, our study highlights the potential role of the *ITGB3* rs5918 T>C and *APOA1* rs1799837 C>T polymorphisms in determining serum lipid concentrations. Notably, individuals with the *ITGB3* rs5918 CC genotype exhibited higher total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels. These findings suggest that the *ITGB3* rs5918 T>C variant may contribute to an increased susceptibility to CAD, providing insights for further investigation in diverse genetic populations.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Shabana NA, Ashiq S, Ijaz A, et al. Genetic risk score (GRS) constructed from and ALDH2 genes is associated with the risk of coronary artery disease in Pakistani subjects. Lipids Health Dis 2018;17:224.
2. Fawzy MS, Toraih EA, Aly NM, Fakhr-Eldeen A, Badran DI, Hussein MH. Atherosclerotic and thrombotic genetic and environmental determinants in Egyptian coronary artery disease patients : a pilot study. BMC Cardiovasc Disord. 2017 Jan 13;17(1):26.
3. Chang MH, Yesupriya A, Ned RM, Mueller PW, Dowling NF. Genetic variants associated with fasting blood lipids in the U.S. population: Third National Health and Nutrition Examination Survey. BMC Med Genet. 2010 Apr 20;11:62.
4. Rai H, Sinha N, Finn J, Agrawal S, Mastana S. Association of serum lipids and coronary artery disease with polymorphisms in the apolipoprotein AI-CIII-AIV gene cluster. Cogent Med. 2016 Dec 31;3(1):1266789.
5. Komsa-Penkova R, Golemanov G, Tsankov B, Ivanov P, Beshev L, Tonchev P. Rs5918ITGB3 Polymorphism, Smoking, and BMI as Risk Factors for Early Onset and Recurrence of DVT in Young Women. Clin Appl Thromb Hemost. 2017 Sep;23(6):585-595.
6. Khatami M, Heidari MM, Soheilyfar S. Common rs5918 (PlA1/A2) polymorphism in the ITGB3 gene and risk of coronary artery disease. Arch Med Sci Atheroscler Dis. 2016 Apr 27;1(1):e9-e15.
7. Bridge KI, Philippou H, Ariëns RAS. Clot properties and cardiovascular disease. Thromb Haemost. 2014 June;112(11):901–908.
8. Wang F, Ji Y, Chen X, Song Y, Huang S, Zhou C, et al. ABCA1 variants rs2230806 (R219K), rs4149313 (M8831I), and rs9282541 (R230C) are associated with susceptibility to coronary heart disease. J Clin Lab Anal. 2019 Jul;33(6):e22896.
9. Villard EF, El Khoury P, Frisdal E, Bruckert E, Clement K, Bonnefont-Rousselot D, et al. Translational Science Genetic Determination of Plasma Cholesterol Efflux Capacity Is Gender-Specific and Independent of HDL-Cholesterol Levels. Arterioscler Thromb Vasc Biol. 2013 Apr;33(4):822-8.
10. Fahrioğlu U, Ergören MÇ. The Association Between APOA5 Gene Polymorphisms and Plasma Lipids in the Turkish Cypriot Population: A Possible Biomarker for Preventing Cardiovascular Diseases. Biochem Genet. 2018 Jun;56(3):176-187.
11. Ergoren MC, Turkgenc B, Teralı K, Rodoplu O, Verstraeten A, Van Laer L, et al. Identification and characterization of a novel FBN1 gene variant in an extended family with variable clinical phenotype of Marfan syndrome. Connect Tissue Res. 2019 Mar;60(2):146-154.
12. Temel SM, Ergören MC. The association between the chromosome 9p21 CDKN2B-AS1 gene variants and the lipid metabolism: A pre-diagnostic biomarker for coronary artery disease. Anatol J Cardiol. 2019 Jan; 21(1): 31–38. Published online 2018 Dec 7.
13. Temel SG, Ergoren MC, Yilmaz I, Oral HB. The use of ACE INDEL polymorphism as a biomarker of coronary artery disease (CAD) in humans with Mediterranean-style diet. Int J Biol Macromol. 2019 Feb 15;123:576-580.
14. Conkbayir C, Fahrioglu Yamaci R, Gencer P, Barin B, Yucel G, Yildiz CE, et al. Impact of genetic defects on coronary atherosclerosis among Turkish Cypriots. Heart Surg Forum. 2017 Oct 30;20(5):E223-E229.
15. Martínez-Quintana E, Chirino R, Nieto-Lago V, Pérez-Jiménez P, López-Ríos L, Rodríguez-González F. Prognostic value of ACE I/D, AT1R A1166C, PAI-I 4G/5G and GPIIIa a1/a2 polymorphisms in myocardial infarction. Cardiol J. 2014;21(3):229-37.
16. Yin RX, Li YY, Lai CQ. Apolipoprotein A1/C3/A5 haplotypes and serum lipid levels. Lipids Health Dis. 2011 Aug 19;10:140.
17. Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet. 2017 Jun;18(6):331-344.

18. Önalan MA, Bahşeliyev Ş, Beyaz MO, Öztaş DM, Önal Y, Uğurlucan M, Tireli E. Karotis endarterektomi operasyonu geçiren hastalarda alt ekstremite periferik arter hastalığı sıklığının belirlenmesi. İst Tıp Fak Derg 83 (1), 40-41 .
19. Tada H, Nohara A, Kawashiri M. Serum triglycerides and atherosclerotic cardiovascular disease: Insights from clinical and genetic studies. Nutrients. 2018 Nov; 10(11): 1789. Published online 2018 Nov 17.
20. Sheikhvatan M, Boroumand MA, Behmanesh M, Ziaee S, Cheraghee S. Integrin Beta-3 Gene Polymorphism and Risk for Myocardial Infarction in Premature Coronary Disease. Iran J Biotechnol. 2019 Apr; 17(2): e1921. Published online 2019 Apr 20.
21. Gandhi PJ, Cambria-Kiely JA. Aspirin resistance and genetic polymorphisms. J Thromb Thrombolys. 2002 Sep; 14(1):51–58.
22. Verdoia M, Cassetti E, Schaffer A, Barbieri L, Giovine GD, Nardin M, et al. Relationship between glycoprotein IIIa platelet receptor gene polymorphism and coronary artery disease. Angiology. 2015 Jan;66(1):79-85.
23. Kenneth A. Schwartz. Aspirin Resistance: A Clinical Review Focused on the Most Common Cause, Noncompliance. Neurohospitalist 2011;1:94–103.
24. Chadha DS, Sumana B, Karthikeyan G, Jayaprasad V, Arun SS. Prevalence of aspirin resistance in Asian-Indian patients with stable coronary artery disease. Catheter Cardiovasc Interv 2016;88:E126–E131.
25. Knowles JW, Wang H, Itakura H, et al. Association of polymorphisms in platelet and hemostasis system genes with acute myocardial infarction. Am Heart J 2007;154:1052–1058.
26. Undas A, Brummel K, Musial J, et al. Pl(A2) polymorphism of beta(3) integrins is associated with enhanced thrombin generation and impaired antithrombotic action of aspirin at the site of microvascular injury. Circulation 20017;104:2666–2672.
27. Liao B, Cheng K, Dong S, et al. Effect of apolipoprotein A1 genetic polymorphisms on lipid profiles and the risk of coronary artery disease. Diagn Pathol. 2015;16:102.