ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20221016

Investigation of associations between apolipoprotein A5 and C3 gene polymorphisms with plasma triglyceride and lipid levels

Emre Taşkin[1*], Hasan Bağci[2], Muhammed Kamil Turan[3]

SUMMARY

OBJECTIVE: The aim of this study was to determine frequency and associations between *APOA5* c.56C>G, -1131T>C, c.553G>T, and *APOC3* -482C>T and *SstI* gene polymorphisms with hypertriglyceridemia.

METHODS: Under a case-control study model, 135 hypertriglyceridemic and 178 normotriglyceridemic control participants were recruited. Polymerase chain reaction and restriction fragment length polymorphism methods were utilized for genotyping. Statistical calculations were performed by comparing allele and genotype frequencies between groups. Clinical characteristics were compared between groups and intra-group genotypes.

RESULTS: *APOC3* gene -482C>T and *SstI* polymorphic genotypes and allele frequencies were significantly higher in hypertriglyceridemic group (genotype frequencies, p=0.035, p=0.028, respectively). Regression analysis under unadjusted model confirmed that *APOC3* -482C>T and *SstI* polymorphisms were significantly contributing to have hypertriglyceridemia (p=0.02, odds ratio [OR]=1.831 (95% confidence interval [CI] 1.095–3.060); p=0.04, OR=1.812 (1.031–3.183), respectively). *APOA5* c.56C>G was in complete linkage disequilibrium with *APOA5* c.553G>T polymorphism (D'=1).

CONCLUSION: For the first time in a population sample from Turkey, among the five polymorphisms of *APOA5* and *APOC3* genes investigated, *APOC3* -482C>T and *SstI* polymorphisms were associated with elevated serum TG levels, while *APOA5* c.56C>G, -1131T>C, and c.553G>T polymorphisms were not.

KEYWORDS: Apolipoprotein A-V. Apolipoprotein C-III. Lipids. Apolipoproteins. Genetic variation.

INTRODUCTION

Hypertriglyceridemia (HTG) is characterized by significantly elevated serum triglyceride (TG) levels[1]. HTG was directly associated with coronary artery disease (CAD) risk[2]. Genetic factors are known to be responsible for increased serum lipid levels, especially TG. *APOA5* gene is the latest discovered gene that influences serum TG levels. It was shown that *APOA5* overexpressing mice displayed significantly lower serum TG levels, while *APOA5* knockout mice displayed significantly higher serum TG levels[3]. It was also reported that combined effect of *APOA5* -1131T>C and c.56C>G polymorphic alleles on elevated serum TG levels was twice as influential compared to normal alleles[4]. Apolipoprotein C-III (apoC-III) was discovered much earlier than apoA-V and influences serum lipid levels by inhibiting lipoprotein lipase enzyme (LPL)[5]. ApoC-III is a component of mainly high-density lipoproteins (HDL) and TG-rich lipoproteins while apoA-V is a component of HDL and very low density lipoproteins (VLDL).

Association of *APOA5* and *APOC3* genes with serum TG levels was shown in various ethnicities around the world[2,6-10]. However, there are also reports showing that there is no association between *APOC3* and *APOA5* with serum lipid levels[11]. These conflicting results may arise from selection criteria of the study sample, ethnic differences, and environmental factors like population lifestyle habits.

METHODS

Study subjects

Unrelated 135 hypertriglyceridemic and 178 normolipidemic control Caucasians were recruited from a hospital of Ondokuz Mayıs University, Samsun, Turkey, and Ünye community health care center number 1, Ordu, Turkey. Assoc. Prof. Dr. (MD) M. Kamil Turan contributed by referring and diagnosing the patients and clinical specimens based on the patient's clinical laboratory characteristic results. Inclusion criteria for control group was having fasting TG level under 2.26 mmol/L and for case group above 2.26 mmol/L. Individuals who were relatives, using lipid lowering medication, and had any CAD or any metabolic disease were excluded. All participants signed the informed written consent for participation in the study. The study was approved

[1]Bandırma Onyedi Eylül Üniversitesi, Medical Faculty, Department of Medical Genetics – Bandırma, Turkey.
[2]Ondokuz Mayıs Üniversitesi, Medical Faculty, Department of Medical Biology – Samsun, Turkey.
[3]Karabük Üniversitesi, Medical Faculty, Department of Medical Biology – Samsun, Turkey.
*Corresponding author: emretaskin@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Ondokuz Mayıs University. Project number: TB404.
Received on November 18, 2022. Accepted on December 20, 2022.

by the ethics committee of Ondokuz Mayıs University, Faculty of Medicine, with registration number 100, Date: 20.4.2005.

Genotyping

A 2 mL of venous blood was drawn to EDTA-containing tubes after overnight fasting. Genomic DNA was extracted from whole blood by salting-out method described previously and stored in TE solution at -20°C[12]. Before genotyping procedures, extracted DNA was diluted with pure water to yield optimum polymerase chain reaction (PCR) amplification. Genotyping of all single nucleotide polymorphisms (SNPs) was carried out using PCR and restriction fragment length polymorphism (RFLP) assay. For the sake of simplicity, used PCR primers and restriction enzymes were not given here, although primers for PCR and enzyme names for RFLP can be shared upon request. All PCR reactions were performed in 25 µL of total volume over 30–35 cycles depending on the polymorphism and primer and may be shared upon request. PCR amplicons were digested with RFLP enzymes overnight at 37°C. 2 µL of amplicons and restriction fragments were visualized in 2% standard agarose gel electrophoresis that stained with ethidium bromide under computerized UV system.

Biochemical analysis

Blood TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), and LDLC levels were measured after overnight fasting with automated hospital analyzer instruments of biochemistry laboratory. Hormone levels were measured using the Siemens ADVIA Centaur® XP electrochemiluminescence assay.

Statistical analysis

Statistical analyses were performed using SPSS (SPSS Inc., IL, Chicago) software. Continuous variables were expressed as mean±standard deviation (SD). Statistically significance alpha level was p=0.05. The Kolmogorov-Smirnov test was used to determine normally distributed data. Genotype and allele frequencies were determined by gene counting. Differences of genotype and allele frequencies between groups were evaluated by chi-square analysis. Mann-Whitney U test and Student's t-test were used to test significant differences in clinical characteristics. ANOVA test was used to evaluate differences in lipid levels between genotypes. Logistic regression analysis was used to evaluate the effect of polymorphisms on having HTG. Haplotype analysis and pairwise linkage disequilibrium (LD) were calculated using the SHEsis software (http://analysis.bio-x.cn). Haplotypes with frequencies less than 0.03 were excluded. LD values equal to 1 are accepted as complete LD.

RESULTS

A comparison of clinical characteristics is shown in Table 1. HTG group had significantly higher TC and body mass index (BMI) levels compared to controls (p<0.05). Mean HDLC level of control group was significantly higher than HTG group since subjects in control group had more balanced serum lipid composition compared to HTG group (p<0.05). There was no significant difference between groups in terms of age and male-female ratio.

Genotype and allele frequencies are given in Table 2. All these *APOA5* polymorphic (c.56C>G, -1131T>C, and c.553G>T) genotype allele frequencies were not significantly different between groups (p>0.05 for all). Among all subjects, only one heterozygous c.553G>T polymorphism participant was detected, while the homozygous polymorphic genotype was not detected at all. However, polymorphic genotype and allele frequencies of both *APOC3* gene -482C>T and *SstI* polymorphisms were significantly higher in HTG group compared to control group (genotype frequencies, p=0.035, p=0.028, respectively).

Logistic regression analysis results are shown in Table 3. Compatible with the chi-square association analysis as shown in Table 2, none of the three *APOA5* polymorphisms had an effect on having HTG under both additive and dominant models (p>0.05). However, in the unadjusted model, both *APOC3* -482C>T and *SstI* heterozygous polymorphic genotypes significantly contribute to have HTG (p=0.02, odds ratio [OR]=1.831 (95% confidence interval [CI]=1.095–3.060); p=0.04, OR=1.812 (1.031–3.183), respectively). In the adjusted model (adjusted for age and sex), heterozygous polymorphic genotype of *APOC3* -482C>T was also contributing to having HTG with a greater OR than the unadjusted model (p=0.01, OR=2.065 (95%CI 1.187–3.592). However, significant contribution of APOC3 *SstI* polymorphism on having HTG was disappeared in the adjusted model with a borderline alpha

Table 1. Basic characteristics of subjects.

	HTG	Controls	p-value
Gender (M/F)	70/65	58/78	>0.05
Age (years)	46.07±11	43.93±11	>0.05
TG (mmol/L)	3.61±1.38	1.34±0.48	<0.05
TC (mmol/L)	5.50±1.08	4.54±0.91	<0.05
HDLC (mmol/L)	1.01±0.24	1.18±0.33	<0.05
LDLC (mmol/L)	2.85±1.00	2.74±0.74	>0.05
BMI (kg/m^2)	28.72±3.94	26.64±4.15	<0.05

Standard deviation is given after ± symbol. TG: triglyceride; TC: total cholesterol; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; BMI: body mass index.

Table 2. Comparison of genotypes and allelic frequencies of *APOA5* and *APOC3* polymorphisms between HTG and control groups.

		HTG	Controls	p-value
APOA5 c.56C>G n (%)	CC	102 (78.5)	115 (85.8)	0.286
	CG	26 (20.0)	18 (13.4)	
	GG	2 (1.5)	1 (0.8)	
Allele frequencies C/G		0.88/0.12	0.93/0.07	0.11
APOA5 -1131T>C n (%)	TT	62 (79.5)	43 (71.7)	0.536
	TC	13 (16.7)	13 (21.7)	
	CC	3 (3.8)	4 (6.7)	
Allele frequencies T/C		0.88/0.12	0.82/0.18	0.21
APOA5 c.553G>T n (%)	GG	132 (99.2)	135 (100)	0.496
	GT	1 (0.8)	0 (–)	
	TT	0 (–)	0 (–)	
Allele frequencies G/T		0.992/0.008	1/0	*
APOC3 -482C>T n (%)	CC	44 (33.8)	66 (49.3)	**0.035**
	CT	72 (55.4)	59 (44.0)	
	TT	14 (10.8)	9 (6.7)	
Allele frequencies C/T		0.62/0.38	0.71/0.29	**0.018**
APOC3 SstI n (%)	CC	68 (59.6)	84 (73.7)	**0.028**
	CG	44 (38.6)	30 (26.3)	
	GG	2 (1.8)	0 (–)	
Allele frequencies C/G		0.79/0.21	0.87/0.13	**0.025**

Bold indicates statistically significant p-values. *Not available.

significance level (p=0.06). In the unadjusted model, both -482C>T and *SstI* polymorphisms were more effective than additive model on having HTG (p=0.01, OR=1.897 (95%CI 1.154–3.117); p=0.03, OR=1.894 (1.082–3.317), respectively). Similarly, both polymorphisms were still effective with greater odd ratios in the adjusted model (p=0.01, OR=2.052 (95%CI 1.205–3.494); p=0.04, OR=1.851 (1.022–3.352), respectively).

DISCUSSION

The vast majority of previous *APOA5* and *APOC3* polymorphism studies were mainly focused on the association of the disease with CAD. However, the direct involvement of *APOA5* and *APOC3* polymorphisms in the development of CAD remained controversial, possibly due to too many influential factors involved in CAD that are uncontrollable in a case-control study. Thus, it may be more effective to know whether *APOA5* and *APOC3* are involved in HTG. In addition, studies that include nonalcoholic fatty liver disease (NAFLD), which may occur as a result of excess TG accumulation, investigated the possible relations between genetic factors and NAFLD. In one of these studies, it was reported that genetic mutations as well as oxidative stress may lead to necrotic inflammation in the liver[13]. They also added that mostly genetic background of the individuals is significant in the development of NAFLD. Additionally, Toman et al.[14] reported that obesity, a condition that is related to elevated serum TG and cholesterol levels, may cause NAFLD. However, it was also reported that obesity may be protective in patients with lung lobectomy[15].

In a study from Morocco where the case group was composed of CAD patients, under the dominant model, *APOA5* c.56C>G polymorphism was found to be associated with elevated TG and TC levels (p<0.05 for both)[16]. This result may be comparable with ours due to multifactorial nature of CAD, since when all subjects are included, it may be accepted as a population sample. c.56C>G polymorphism of the *APOA5* gene was reported to be associated with HTG also in a Caucasian population sample previously[17]. However, like ours, there are studies that did not find any association between c.56C>G and HTG in several ethnicities[16]. In intragroup comparisons, we detected a borderline significant TC decrease of CG+GG genotypes compared to CC genotype in HTG group under dominant model, which may be explained by lipid-raising effect of this polymorphism (p=0.043) (data not shown). G allele of the c.56C>G is very less frequent in Asian ethnicity (0.01–0.03), while it does not exist in Korean ethnicity[18]. In our study, the G allele frequency of c.56C>G was 0.12 in HTG group and 0.07 in control group, displaying a similar general population sample frequency to Asian and Korean populations. As expected, the G allele frequency of our cohort was higher from Asian ethnicity, closer to Eastern ethnicities.

The C allele frequency of -1131T>C polymorphism was 0.3 in Chinese and Japan ethnicities, while it was 0.1 in Caucasian ethnicity[18,19]. In our study, the C allele frequency of -1131T>C was 0.12 in HTG group and 0.18 in control group, displaying an overall frequency between Asian and Caucasian ethnicities, with an insignificant p-value of 0.21. In a Spanish population sample, the C allele of the APOA5 -1131T>C polymorphism was not associated with elevated serum TG levels. In Chinese population, polymorphic C allele carriers of -1131T>C showed approximately 25% higher serum TG level compared to non-carriers, where this difference was 27% and significant in our study (p=0.004)[11]. The C allele frequency of *APOA5* -1131T>C in various ethnicities around the globe differs between 13 and 41%[20]. In our study, T allele frequency was below 1%, which

Table 3. Binary logistic regression analysis.

Additive model					
Genotype		Unadjusted		Adjusted[a]	
		OR (95%CI)	p-value	OR (95%CI)	p-value
APOA5 c.56C>G	CC	1		1	
	CG	1.629 (0.844–3.143)	0.15	1.655 (0.824–3.324)	0.16
	GG	2.255 (0.201–25.237)	0.51	2.012 (0.179–22.629)	0.57
APOA5 -1131T>C	TT	1		1	
	TC	0.694 (0.293–1.642)	0.4	0.745 (0.285–1.944)	0.55
	CC	0.520 (0.111–2.443)	0.41	0.371 (0.060–2.305)	0.29
APOA5 c.553G>T	GG	1		1	
	GT	*	*	*	*
	TT	*	*	*	*
APOC3 -482C>T	CC	1		1	
	CT	1.831 (1.095–3.060)	**0.02**	2.065 (1.187–3.592)	**0.01**
	TT	2.333 (0.930–5.856)	0.07	1.982 (0.751–5.231)	0.17
APOC3 SstI	CC	1		1	
	CG	1.812 (1.031–3.183)	**0.04**	1.768 (0.972–3.215)	0.06
	GG	*	*	*	*
Dominant model					
Genotype		Unadjusted		Adjusted[a]	
		OR (95%CI)	p-value	OR (95%CI)	p-value
APOA5 c.56C>G	CC	1		1	
	CG+GG	1.662 (0.876–3.153)	0.12	1.678 (0.853–3.301)	0.13
APOA5 -1131T>C	TT	1		1	
	TC+CC	0.653 (0.298–1.432)	0.29	0.648 (0.269–1.559)	0.33
APOA5 c.553G>T	GG	1		1	
	GT+TT	*	*	*	*
APOC3 -482C>T	CC	1		1	
	CT+TT	1.897 (1.154–3.117)	**0.01**	2.052 (1.205–3.494)	**0.01**
APOC3 SstI	CC	1		1	
	CG+GG	1.894 (1.082–3.317)	**0.03**	1.851 (1.022–3.352)	**0.04**

[a]Adjusted for age, gender, and BMI. *Since there was only one heterozygote and no homozygous polymorphic genotype in both HTG and control groups, the p-value cannot be calculated. Bold indicates statistically significant p-values.

is an extremely low percentage compared to Chinese studies. We detected only one heterozygous participant and did not detect a nonhomozygous polymorphic genotype among all subjects (particularly in HTG group). This finding is compatible with the nonexistence of *APOA5* c.553G>T polymorphism in Caucasians[17].

In Chinese population, T allele of *APOC3* -482C>T polymorphism was found to be associated with increased serum TG and decreased HDLC levels (p=0.012 and p=0.012, respectively)[21]. However, this population sample was recruited from healthy subjects, unlike our case-control study design; thus, we cannot directly compare our results. We have also checked whether polymorphic genotypes of -482C>T have an influence on serum lipid levels and BMI in both HTG and control groups and interestingly observed that under additive model, this polymorphism was showing a significant TG-lowering effect in the HTG group (p=0.025) and BMI-lowering effect in the control group (p=0.017) (data not shown). This result is not compatible with previously reported results and may be explained by intergenic interactions like LD with other polymorphisms.

APOC3 *SstI* polymorphism was associated with increased serum TG levels in Bogalusa Heart Study, whose participants were from the USA with a large sample size[22]. Polymorphic allele frequency was detected at 30–43% in Chinese, 25–48% in Japanese, and 16% in Indians[23]. However, there are also studies in European populations that did not encounter any association between APOC3 *SstI* polymorphism and serum TG levels[24]. We have detected an association between APOC3 *SstI* polymorphism and HTG, with a significantly higher frequency of polymorphic genotypes in HTG group than in controls (p=0.028). We have also confirmed by regression analysis that there is a significant effect of *APOC3 SstI* polymorphism on having HTG under dominant model under both unadjusted and adjusted models (p=0.03, OR=1.894 (95%CI 1.082–3.317); p=0.04, OR=1.851 (95%CI 1.022–3.352), respectively).

Haplotype analysis showed that none of the haplotype frequencies were significantly different between case and control groups (p>0.05, all) (data not shown). A weak LD (D'=0.29) between *APOA5* 1131T>C and *APOC3* 482C>T was observed in a Chinese population[21]. Similar to the mentioned Chinese sample, in our study, the D' value between *APOA5* -1131T>C and *APOC3* -482C>T was very weak (D'=0.03). It was reported that *APOC3* -482C>T with *APOA5* c.56C>G, *APOA5 -1131C>T*, and *APOC3 SstI* has strong LD[25]. Our result was compatible with the abovementioned study, with a strong LD between *APOC3* -482C>T and *APOC3 SstI* (D'=0.87). Yin et al.[23] reported that in a Chinese population sample, *APOC3 SstI* was in LD with *APOA5* -1131T>C (r^2=0.359). In our study, *APOA5* c.56C>G and *APOA5* c.553G>T showed complete LD (D'=1) (data not shown). The other strong LD were observed between *APOA5* c.553G>T and *APOC3* -482C>T (D'=0.96), APOA5 c.553G>T and *APOC3 SstI* (D'=0.99), and *APOC3* -482C>T and *APOC3 SstI* (D'=0.87) (data not shown).

Limitations of this study that should be addressed are lack of serum apoA-V and apoC-III protein measurements and relatively small sample size due to low cost.

CONCLUSIONS

The investigated polymorphisms in this study represent divergent frequencies and associations with HTG in previous studies that were conducted with several other ethnicities. Representing a sample who live in Black Sea coast, in the current study, we show that *APOC3* polymorphisms -482C>T and *SstI* are associated with HTG. However, we did not encounter any association between *APOA5* polymorphisms c.56C>G, -1131T>C, and HTG. Additionally, the homozygous polymorphic genotype of *APOA5* c.553G>T was not seen in our cohort. Finally, *APOA5* c.56C>G and c.553G>T polymorphisms are observed in complete LD.

AUTHORS' CONTRIBUTIONS

ET: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **HB:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **MKT:** Data curation, Methodology, Resources, Writing – review & editing.

REFERENCES

1. Oh RC, Trivette ET, Westerfield KL. Management of hypertriglyceridemia: common questions and answers. Am Fam Physician. 2020;102(6):347-54. PMID: 32931217
2. Goyal S, Tanigawa Y, Zhang W, Chai JF, Almeida M, Sim X, et al. APOC3 genetic variation, serum triglycerides, and risk of coronary artery disease in Asian Indians, Europeans, and other ethnic groups. Lipids Health Dis. 2021;20(1):113. https://doi.org/10.1186/s12944-021-01531-8
3. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, et al. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001;294(5540):169-73. https://doi.org/10.1126/science.1064852
4. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. Hum Mol Genet. 2002;11(24):3031-8. https://doi.org/10.1093/hmg/11.24.3031
5. Hansen SEJ, Madsen CM, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Genetic variants associated with increased plasma levels of triglycerides, via effects on the lipoprotein lipase pathway, increase risk of acute pancreatitis. Clin Gastroenterol Hepatol. 2021;19(8):1652-1660.e6. https://doi.org/10.1016/j.cgh.2020.08.016
6. Dai W, Zhang Z, Yao C, Zhao S. Emerging evidences for the opposite role of apolipoprotein C3 and apolipoprotein A5 in lipid metabolism and coronary artery disease. Lipids Health Dis. 2019;18(1):220. https://doi.org/10.1186/s12944-019-1166-5
7. Girelli D, Piubelli C, Martinelli N, Corrocher R, Olivieri O. A decade of progress on the genetic basis of coronary artery disease. Practical insights for the internist. Eur J Intern Med. 2017;41:10-7. https://doi.org/10.1016/j.ejim.2017.03.019

8. Dib I, Khalil A, Chouaib R, El-Makhour Y, Noureddine H. Apolipoprotein C-III and cardiovascular diseases: when genetics meet molecular pathologies. Mol Biol Rep. 2021;48(1):875-86. https://doi.org/10.1007/s11033-020-06071-5
9. Matsunaga A, Nagashima M, Yamagishi H, Saku K. Variants of lipid-related genes in adult japanese patients with severe hypertriglyceridemia. J Atheroscler Thromb. 2020;27(12):1264-77. https://doi.org/10.5551/jat.51540
10. Dron JS, Hegele RA. Genetics of triglycerides and the risk of atherosclerosis. Curr Atheroscler Rep. 2017;19(7):31. https://doi.org/10.1007/s11883-017-0667-9
11. You Y, Wu YH, Zhang Y, Zhang L, Song Y, Bai W, et al. Effects of polymorphisms in APOA5 on the plasma levels of triglycerides and risk of coronary heart disease in Jilin, northeast China: a case-control study. BMJ Open. 2018;8(6):e020016. https://doi.org/10.1136/bmjopen-2017-020016
12. Kalousová M, Levová K, Kuběna AA, Jáchymová M, Franková V, Zima T. Comparison of DNA isolation using salting-out procedure and automated isolation (MagNA system). Prep Biochem Biotechnol. 2017;47(7):703-8. https://doi.org/10.1136/bmjopen-2017-020016
13. Toman D, Sengul I, Pelikán A, Sengul D, Vavra P, Ihnát P, et al. Hepatocellular carcinoma *versus* nonalcoholic fatty liver disease: metabolic, environmental, and genetic association? *De facto*? Rev Assoc Médica Bras. 2022;68(5):708-11. https://doi.org/10.1590/1806-9282.20220147
14. Toman D, Sengul I, Pelikán A, Sengul D, Vavra P, Ihnat P, et al. A narrative review on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis versus hepatocellular carcinoma: do you mind? Rev Assoc Médica Bras. 68(6):871-4. https://doi.org/10.1590/1806-9282.20220268
15. Tulinský L, Sengul I, Ihnát P, Ostruszka P, Toman D, Guňková P, et al. Obesity in cases undergoing the surgical procedure of lung lobectomy: risk or benefit Rev Assoc Med Bras. 2022;68(8):1090-5. https://doi.org/10.1590/1806-9282.20220526
16. Morjane I, Charoute H, Ouatou S, Elkhattabi L, Benrahma H, Saile R, et al. Association of c.56C > G (rs3135506) apolipoprotein A5 gene polymorphism with coronary artery disease in Moroccan subjects: a case-control study and an updated meta-analysis. Cardiol Res Pract. 2020;2020:5981971. https://doi.org/10.1155/2020/5981971
17. Hubacek JA, Adamkova V, Prusikova M, Snejdrlova M, Hirschfeldova K, Lanska V, et al. Impact of apolipoprotein A5 variants on statin treatment efficacy. Pharmacogenomics. 2009;10(6):945-50. https://doi.org/10.2217/pgs.09.17
18. Lai CQ, Tai ES, Tan CE, Cutter J, Chew SK, Zhu YP, et al. The APOA5 locus is a strong determinant of plasma triglyceride concentrations across ethnic groups in Singapore. J Lipid Res. 2003;44(12):2365-73. https://doi.org/10.1194/jlr.M300251-JLR200
19. Baum L, Tomlinson B, Thomas GN. APOA5-1131T>C polymorphism is associated with triglyceride levels in Chinese men. Clin Genet. 2003;63(5):377-9. https://doi.org/10.1034/j.1399-0004.2003.00063.x
20. Mahrooz A, Zargari M, Ansari V, Makhlough A, Hashemi-Sooteh MB. Association of APOA5 gene promoter region -1131T>C polymorphism (rs662799) to plasma triglyceride level in patients with type 2 diabetic nephropathy. J Clin Diagn Res JCDR. 2016;10(5):BC09-13.
21. Li GP, Wang JY, Yan SK, Chen BS, Xue H, Wu G. Genetic effect of two polymorphisms in the apolipoprotein A5 gene and apolipoprotein C3 gene on serum lipids and lipoproteins levels in a Chinese population. Clin Genet. 2004;65(6):470-6. https://doi.org/10.1111/j.1399-0004.2004.00251.x
22. Hallman DM, Srinivasan SR, Chen W, Boerwinkle E, Berenson GS. Longitudinal analysis of haplotypes and polymorphisms of the APOA5 and APOC3 genes associated with variation in serum triglyceride levels: the Bogalusa heart study. Metabolism. 2006;55(12):1574-81. https://doi.org/10.1016/j.metabol.2006.07.018
23. Yin RX, Li YY, Lai CQ. Apolipoprotein A1/C3/A5 haplotypes and serum lipid levels. Lipids Health Dis. 2011;10:140. https://doi.org/10.1186/1476-511X-10-140
24. Kee F, Amouyel P, Fumeron F, Arveiler D, Cambou JP, Evans A, et al. Lack of association between genetic variations of apo A-I-C-III-A-IV gene cluster and myocardial infarction in a sample of European male: ECTIM study. Atherosclerosis. 1999;145(1):187-95. https://doi.org/10.1016/s0021-9150(99)00066-0
25. Talmud PJ, Hawe E, Martin S, Olivier M, Miller GJ, Rubin EM, et al. Relative contribution of variation within the APOC3/A4/A5 gene cluster in determining plasma triglycerides. Hum Mol Genet. 2002;11(24):3039-46. https://doi.org/10.1093/hmg/11.24.3039