Association of *LPL* and *ADRB2* polymorphisms with the risk of developing hypertriglyceridemia

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Abstract. The measurement of lipid metabolism indicators is an integral part of the assessment and control of the risk of developing atherosclerosis and cardiovascular diseases. Triglyceride levels are of particular importance as they are the main component of fat cells. The objective of the present study was to determine the association between hypertriglyceridemia and the polymorphisms of genes of β2-adrenergic receptor (ADRB2) and lipoprotein lipase (LPL). The present study was a case-control study. A total of 460 subjects participated in the study. Plasma total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, apolipoprotein B and apolipoprotein A1 levels were examined in all subjects. Quantitative PCR was performed to detect the LPL rs328, ADRB2 rs1042714 gene polymorphisms, which were found to be previously associated with susceptibility to obesity-related phenotypes and dyslipidemia. The results revealed a significant association of the rs1042714 polymorphism of the ADRB2 gene with triglyceride levels (P=0.04). The C allele and the association of the C/C and C/G genotypes of the rs1042714 polymorphism of the ADBR2 gene were more frequent in individuals with elevated triglyceride levels compared with those with normal triglyceride levels. The G allele and the G/G genotype of the rs1042714 polymorphism of the ADBR2 gene were protective and were associated with a reduced risk of developing hypertriglyceridemia (odds ratio, 0.72; 95% CI, 0.52-0.98 P=0.038). The LPL rs328 alleles were not associated with a significantly increased risk of developing hypertriglyceridemia. On the whole, the findings of the present study indicated that the ADRB2 rs1042714 allele G was associated with a decreased risk of developing hypertriglyceridemia. Polymorphisms of the LPL rs328 gene were not associated with hypertriglyceridemia and haplotype combinations were not associated with hypertriglyceridemia.

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Introduction

The diagnosis of lipid metabolism is part of the assessment and control of the risk of atherosclerosis and cardiovascular diseases (CVD); in this context, levels of triglycerides are of particular importance, as they are a major component of fat cells (1). Triglycerides are mainly found in chylomicrons, very low-density lipoproteins (VLDLs) and the intermediate fraction of lipoproteins (2). Lipoproteins are formed from nuclei that consist of triglycerides and cholesterol esters, and are surrounded by phospholipids, free cholesterol on the outside (1,3). The lipid part is associated with apolipoproteins, which are specific proteins that determine the physical and biological properties of lipoproteins. The solubility of lipids in plasma is achieved by apolipoproteins (2). Lipid transport involving lipoproteins consists of the transport of triglycerides from the intestine and liver to adipose tissue and muscle, and the transport of cholesterol to peripheral tissues for the cell membrane biosynthesis of steroid hormones and to the liver for synthesis (1). The triglycerides that are derived from food in the intestine are hydrolyzed into free fatty acids, and mono- and diglycerides, and are further absorbed with exogenous cholesterol in enterocytes and are transported through lymphatic vessels to the liver (1). Lipoprotein lipase (LPL) found in adipocytes and muscles hydrolyzes triglycerides into glycerol and free fatty acids; chylomicrons are then formed, which contain an intermediate fraction of lipoproteins (1). Endogenous triglycerides, which are synthesized in the liver, are then incorporated into low density lipoproteins (LDLs), together with cholesterol and apolipoproteins (1). Numerous animal and human studies have conclusively confirmed a negative association between intramuscular triglycerides and insulin sensitivity, suggesting a functional association between fatty acid levels and the pathogenesis of insulin resistance (4).

In a recent study, it was demonstrated that high triglyceride levels and a high triglyceride-glucose index were often observed in males who had a higher body mass index (BMI) and waist/hip ratio, as well as a higher blood pressure (5). Other authors recommend determining the triglyceride levels before and after treatment, taking into account the patient's

genotype (6). According to the results of these studies, 65 putative gene-environment interactions potentially caused by quantile-dependent expression of triglycerides were found. A significantly greater reduction in triglyceride levels was found following fenofibrate treatment in 44 LPL mutation carriers compared to 247 non-carriers of hypertriglyceridemia (6).

In a study on the genetic determinants of dyslipidemia and metabolic disorders, a panel of targeted sequencing 'LipidSeq' was developed, which allows the simultaneous assessment of monogenic and polygenic forms of dyslipidemia (7). The LipidSeq sequencing panel targets 69 genes and 185 single nucleotide polymorphisms (SNPs) associated with dyslipidemia and metabolic disorders. The developers of this panel found that the 3,262 patients studied had a majority of hypertriglyceridemia (40.1%), familial hypercholesterolemia (40.1%) and hypercholesterolemia (28.3%). According to their results, the LPL gene was associated with familial hypercholesterolemia and hypertriglyceridemia. They also described new variants of the polygenic nature of dyslipidemia, some of which were previously considered to be predominantly monogenic, thus revealing new mechanisms of disease development (7).

The LPL gene encodes for LPL, which hydrolyses triglycerides in circulating cholesterol high-density lipoproteins (HDLs) and chylomicrons, providing free fatty acids and monoacylglycerol for utilization by surrounding target tissues, particularly skeletal muscle, heart muscle and adipose tissue (8). A key enzyme in human lipid metabolism is LPL, which regulates the metabolism of triglyceride-rich lipoproteins (chylomicrons and HDL) by hydrolyzing their cores into free fats and monoacylglycerols. LDL variants are key determinants of triglyceride and HDL concentrations, and in turn, high triglyceride levels combined with low HDL levels lead to a propensity to develop arterial hypertension, glucose intolerance and abdominal obesity, which form the metabolic syndrome (9). Hypertriglyceridemia, one of the common symptoms of LPL deficiency and dysfunction, may be a risk factor for dyslipidemia, type 2 diabetes, arterial hypertension, ischemic heart disease and Alzheimer's disease. LPL gene-induced dyslipidemia and antioxidant stress dysfunction may be an intermediate process in the development of these diseases (10).

The β2-adrenergic receptor (ADRB2) gene encodes a β2-adrenoreceptor, which is activated by adrenaline and causes increased glycogenosis in muscle, increases insulin and glucagon secretion, increases heart contraction, and thereby affects lipid and carbohydrate metabolism (11). In a previous study which examined the association of ADRB2 gene polymorphisms with cardiovascular risk in Swedish males, it was found that the Arg16Gly polymorphism was significantly associated with predominantly abdominal obesity and an elevated systolic blood pressure, whereas the Glu27Glu polymorphism was associated with elevated leptin and triglyceride levels, but not with other indicators, including obesity (12). Given the regulatory role and the possible impact of LPL Ser447Ter (13,14) and ADRB2 Gln27Glu (15) on the development of hypertriglyceridemia, it was suggested that these polymorphisms may be potential risk factors for hypertriglyceridemia.

The indigenous population of the Republic of Kazakhstan-the Kazakh population has a centuries-old gene pool that differs from the gene pools of other populations (16). According to some authors, the Kazakh population is anthropologically similar to the Mongoloid race and occupies an intermediate position between the European and Asian populations (16). To enrich the population genetics database of the Kazakh group and taking into account the pathogenesis of hypertriglyceridemia, the present study selected LPL Ser447Ter, ADRB2 Gln27Glu.

The present study investigated the association between LPL Ser447Ter, ADRB2 Gln27Glu, and the level of triglycerides in the Kazakh population.

Materials and methods

Study population. The present study examined a total of 460 subjects of Kazakh ethnicity, aged 18 to 65 years, residing in Semey, Kazakhstan, during the period between 2018 and 2020 (17,18). In a previous study, the authors investigated the associations of four SNPs with the risk of hyperinsulinemia and insulin resistance (17). In the present study, the effects of two SNPs on the risk of dyslipidemia were examined. The exclusion criteria included cancer, cardiovascular and renal failure, mental diseases, pregnancy, or lactation. Each participant was informed of the purpose and methods of the study and signed a written informed consent to participate in the study (according to the Declaration of Helsinki of the World Medical Organization, 1964). The Ethics Committee of Semey Medical University approved the research protocol (Protocol no. 11 from 09.27.2017).

Data collection. Demographic and clinical characteristics were recorded, including systolic and diastolic arterial blood pressure, height, weight, BMI and waist circumference. Arterial blood pressure was measured twice following 5 min of rest with the subjects in a seated position. BMI was defined as the weight (kg)/height (m^2). Fasting venous blood samples were obtained from all participants in the morning.

SNP selection. SNPs were searched using the data from the 1000 Genomes Browser project (https://www.ncbi.nlm.nih.gov/genome/gdv/browser/genome/?id=GCF_000001405.40) and The Text-mined Hypertension, Obesity and Diabetes candidate gene database (T-HOD). The 1000 Genomes Browser Project includes an extensive international pool of human genome polymorphisms to study the association between genotype and phenotype (17,18). The candidate gene database T-HOD includes all gene polymorphisms that have been studied for hypertension, obesity and diabetes (19). References for tag SNPs, as well as positions and genotyping information are presented in the Table I.

DNA analysis. Whole blood samples were obtained from each of the participants and were collected into vacuum tubes with K2/K3 EDTA. The present study examined two genes, LPL Ser447Ter and ADRB2 Gln27Glu for genetic research. Genomic DNA was extracted from blood samples (40 ng) using a ready-made commercial kit (GeneJET Mini kit; Thermo Fisher Scientific, Inc.). The DNA concentration was evaluated using the Qubit 4 Fluorometer (Thermo Fisher Scientific, Inc.). The extracted DNA was frozen and stored at -20˚C.

All 460 blood samples were genotyped using quantitative PCR (qPCR) using CFX 96 (Bio-Rad Laboratories, Inc.) with mixed primers and TaqMan samples. A total of 20 μl TaqMan

Table I. Description of two SNPs and primers.

Gene	Tag SNP	Chromosome	Major/minor alleles	Forward	Reverse
LPL Ser447Ter	rs328	8:19962213	C/G	FAATAAGAAGTCA GGCTGGTGA	RTTATTCTTCAGTCCGAC CACT
ADRB2 Gln27Glu	rs1042714	5:148826910	C/G	FCGTCACGCAGG AAAGGGACGA	RGCAGTGCGTCCTTTCCC TGCT

SNPs, single nucleotide polymorphisms; LPL, lipoprotein lipase; ADRB2, β2-adrenergic receptor.

Table II. Comparison of the clinical characteristics of the patients.

	Sex		
	Males (n=231), median (Q_1,-Q_3)	Females (n=229), median (Q_1,-Q_3)	P-value
Age, years	48 (39-57)	45 (38-53)	0.03[a]
BMI, (kg/m^2)	26.42 (23.87-29.35)	25.86 (22.65-28-41)	0.04[a]
Healthy weight, (n)	83 (18.04%)	102 (22.17%)	0.12[b]
Overweight, (n)	107 (23.26%)	86 (18.69%)	
Obese, (n)	41 (8.92%)	41 (8.92%)	

Data are presented as the median (Q1-Q3) for age and BMI. Data were analyzed using the [a]Mann-Whitney test or [b]χ2 test. P-values <0.05 were considered to indicate a statistically significant difference. BMI, body mass index.

Genotyping Mastermix reagent and 10 ng DNA were used as a template with a final volume of 25 μl in 96-well plates. The amplification program included a pre-denaturation step at 95˚C for 3 min followed by 48 cycles of reaction at 95˚C for 10 sec and 60˚C for 40 sec for SNP [reagents for ADRB2 Gln27Glu (rs1042714), manufactured by Syntol *ADRB2* Gln27Glu (rs1042714) FCGTCACGCAGGAAAGGGACGA (forward) and *ADRB2* Gln27Glu (rs1042714) RGCAGTGCGTCCTTTCCC TGCT (reverse)]. For SNP LPL Ser447Ter (rs328), the amplification program included a pre-denaturation step at 93-denaturation step at 95˚C for 3 min followed by 48 cycles of reaction at 95˚C for 10 sec and 60˚C for 1 min followed by 35 reaction cycles at 93˚C for 10 sec, 64˚C for 10 sec and 72˚C for 20 sec (LPL Ser447Ter (rs328) reagent from Lytech Co. Ltd. *LPL* Ser447Ter (rs328) FAATAAGAAGTCAGGCTGGTGA (forward) and *LPL* Ser447Ter (rs328) RTTATTCTTCAGTCCGACCACT (reverse). Data were analyzed using the $2^{-\Delta\Delta Cq}$ method (20).

Concentration measurements. Total cholesterol, triglycerides, HDL, LDL, apolipoprotein B and apolipoprotein A1 levels were measured using Cobas 8000 analyzers (Roche Diagnostics GmbH) according to instructions of the manufacturer. Reference values were as follows: Total cholesterol, 2.9-5.2 mmol/l; HDL, 0.78-2.2 mmol/l; LDL, 2.33-5.31 mmol/l; triglycerides, 1.7-2.25 mmol/l; apolipoprotein A1, 1.04-2.02 g/l (for males) and 1.08-2.25 g/l (for females); apolipoprotein B, 0.66-1.33 g/l (for males) and 0.6-1.17 g/l (for females).

Statistical analysis. All statistical analyses were performed using IBM SPSS Statistics Version 20 (International Business Machines Corp.) and SNPStat (SNPStats: your web tool for SNP analysis). All variables were examined to determine whether they were normally distributed. Non-parametric tests were used for non-normally distributed data. These were the Mann-Whitney test for comparisons between two groups and the Kruskal-Wallis test for co-dominant, dominant, and recessive models for differences in phenotypic variables for genotype. The χ^2 test and logistic regression analysis were used for comparing differences in allele frequencies of SNPs between subjects with hypertriglyceridemia (was defined using the dichotomous qualitative trait of triglycerides, ≤2.25 and triglycerides, >2.25) and the control subjects. In a single test, P<0.05 was considered to indicate a statistically significant difference. Following Bonferroni's correction for multiple testing, again, P<0.05 was considered to indicate a statistically significant difference.

Results

Comparisons of the study subjects and general information. The study population comprised 231 males [age: Median (Q_1-Q_3), 48 years (39-57)]; and 229 females [age: Median (Q_1,-Q_3), 45 years (38-53)], P=0.03. Males had a significantly higher BMI than females [median (Q_1,-Q_3), 26.42 (23.87-29.35) and median (Q_1,-Q_3), 25.86 (22.65-28-41)], respectively P=0.04. In total, 83 males (18.04%) and 102 females (22.17%) had a healthy weight, 107 males (23.26%) and 86 females (18.69%) were overweight, and 41 males (8.92%) and 41 females (8.92%) were obese (P=0.12) (Table II). The demographic and laboratory finding of the study population between two

Table III. Comparison of the triglyceride levels between the two groups as regards clinical characteristics.

Characteristic	Triglycerides (mmol/l)		P-value
	≤2.25 (n)	≥2.25 (n)	
Age, years	46 (38-55)	48 (41-56)	0.055[a]
Sex (total)	336	124	0.88[b]
Male	168	63	
Female	168	61	
BMI (kg/m^2)	25.94 (23.12-28.4)	27.14 (23.76-29.74)	0.007[a]
Total cholesterol (mmol/l)	3.34 (2.41-2.53)	3.45 (2.66-2.17)	0.1[a]
HDL (mmol/l)	0.92 (0.76-1.18)	1.12 (0.96-1.2)	0.01[a]
LDL (mmol/l)	1.8 (1.3-2.53)	1.88 (1.31-2.2)	0.91[a]
Apolipoprotein B (g/l)	0.92 (0.76-1.14)	1.12 (0.96-1.29)	0.0001[a]
Apolipoprotein A1 (g/l)	1.5 (1.33-1.72)	1.47 (1.28-1.65)	0.17[a]

Data are presented as the median (Q1-Q3) for age, sex, BMI, total cholesterol, triglycerides, HDL, LDL, apolipoprotein B and apolipoprotein A1. P-values <0.05 were considered to indicate statistically significant differences. Data were analyzed using the [a]Mann-Whitney test or [b]χ^2 test. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table IV. Frequency of genotypes and alleles of each gene polymorphism in total, triglycerides ≤2.25, and triglycerides ≥2.25.

Gene polymorphism	Genotypes			Allele		P-value[a]
LPL Ser447Ter	C/C	C/G	G/G	C	G	0.33
Total	354	86	20	794	126	
Triglycerides ≤2.25, no. of patients	263	61	12	587	41	
Triglycerides ≥2.25, no. of patients	91	25	8	207	85	
ADRB2 Gln27Glu	C/C	C/G	G/G	C	G	0.04
Total	227	191	42	645	275	
Triglycerides ≤2.25, no. of patients	172	140	24	484	188	
Triglycerides ≥2.25, no. of patients	55	51	18	161	87	

[a]Data were analyzed using the χ^2 test. LPL, lipoprotein lipase; ADRB2, β2-adrenergic receptor.

groups are presented in Table III. The group with hypertriglyceridemia had a significantly higher BMI (kg/m^2) than the group with normal levels of triglycerides. The mean levels of HDL (mmol/l) and apolipoprotein B (g/l) were significantly higher in the group with hypertriglyceridemia. There were no statistically significant differences between the two groups as regards the levels of total cholesterol, LDL and apolipoprotein A1 (Table III).

Genotype and allele analysis LPL Ser447Ter and ADRB2 Gln27Glu genes polymorphisms. The present we genotyped all 460 subjects. Only LPL Ser447Ter deviated from the Hardy-Weinberg equilibrium (P=0.0001). The frequencies of the C/C, C/G and G/G genotypes of LPL Ser447Ter were 76.95, 18.69 and 4.36%, respectively (Table IV). The frequencies of the C/C, C/G and G/G genotypes of ADRB2 Gln27Glu were 49.35, 41.52 and 9.13%, respectively (Table IV). The present study found a significant association of the Gln27Glu (rs1042714) polymorphism of the ADRB2 gene with triglycerides levels (P=0.04; Table III). When analyzing the link between SNPs and the level of triglycerides, it was found that risk of developing hypertriglyceridemia was significantly associated with ADRB2 Gln27Glu [odds ratio (OR), 0.72; 95% confidence interval (CI), 0.52-0.98; P=0.038]; the values for the C/G and G/G genotypes were as follows: OR, 0.88; 95% CI, 0.56-1.36; and OR, 0.42; 95% CI, 0.21-0.84, respectively (Table V).

Logistic regression analysis between the levels of triglycerides and LPL Ser447Ter and ADRB2 Gln27Glu gene polymorphisms. Logistic regression analysis revealed that the risk of developing hypertriglyceridemia was significantly lower in carriers of the ADRB2 Gln27Glu G allele than in those with the C/C genotype (C/G + C/C vs. G/G: Adjusted OR, 0.42; 95% CI, 0.21-0.84; P=0.05 in the codominant model) (Table V). As shown in Table V, the C allele and the association of the C/C and C/G genotypes of the Gln27Glu (rs1042714) polymorphism of the ADBR2 gene were more frequent in individuals with elevated triglyceride levels compared with those with normal triglyceride levels.

Table V. Genotype and allele frequencies of 2 SNP associations with response levels of triglycerides.

Model	Genotype	Triglycerides ≤2.25, no. of patients	Triglycerides ≥2.25, no. of patients	OR (95% CI)	P-value	AIC	BIC
LPL Ser447Ter							
Codominant	C/C	91	263	1.00	0.34	542	558.6
	C/G	25	61	0.84 (0.50-1.42)			
	G/G	8	12	0.51 (0.20-1.30)			
Dominant	C/C	91	263	1.00	0.27	540.9	553.3
	C/G-G/G	33	73	0.76 (0.47-1.23)			
Recessive	C/C-C/G	116	324	1.00	0.19	540.5	552.8
	G/G	8	12	0.53 (0.21-1.34)			
Overdominant	C/C-G/G	99	275	1.00	0.62	541.9	554.3
	C/G	25	61	0.88 (0.52-1.47)			
Log-additive		-	-	0.77 (0.53-1.11)	0.17	540.3	552.7
ADRB2 Gln27Glu							
Codominant	C/C	55	172	1.00	0.05	538.3	554.8
	C/G	51	140	0.88 (0.56-1.36)			
	G/G	18	24	0.42 (0.21-0.84)			
Dominant	C/C	55	172	1.00	0.19	540.5	552.9
	C/G-G/G	69	164	0.76 (0.50-1.15)			
Recessive	C/C-C/G	106	312	1.00	0.018	536.6	549
	G/G	18	24	0.45 (0.23-0.86)			
Overdominant	C/C-G/G	73	196	1.00	0.92	542.2	554.6
	C/G	51	140	1.02 (0.67-1.55)			
Log-additive		-	-	0.72 (0.52-0.98)	0.038	537.9	550.3

The data were adjusted by sex. LPL, lipoprotein lipase; ADRB2, β2-adrenergic receptor; OR, odds ratio; 95% CI, 95% confidence interval.

Conversely, the G allele and the G/G genotype are more common in the group with normal TG levels. The C allele and C/C and C/G genotypes of the Gln27Glu (rs1042714) polymorphism of the ADBR2 gene were associated with an increased risk of developing hypertriglyceridemia in the study sample. By contrast, the G allele and the G/G genotype of the Gln27Glu (rs1042714) polymorphism of the ADBR2 gene were protective and were associated with a reduced risk of hypertriglyceridemia (OR, 0.72; 95% CI, 0.52-0.98; P=0.038) in this sample. Genotyping of the Gln27Glu (rs1042714) polymorphism of the ADRB2 gene revealed that in a recessive model, C/C and C/G increased the risk of hypertriglyceridemia in the study sample, whereas the presence of the G/G genotype reduced the risk of hypertriglyceridemia 0.45-fold (OR, 0.45; 95% CI, 0.23-0.86; P=0.018).

Multiple-SNP analysis. Multiple-SNP analyses were performed between the two SNPs for gene-gene interactions, and the D' value between LPL Ser447Ter (rs328) and ADRB2 Gln27Glu (rs1042714) was 0.003 (P=0.56) (Table VI). The haplotype containing two SNPs was not associated with the risk of developing hypertriglyceridemia. The results of the haplotype analysis are shown Table VII.

Table VI. Multiple-SNP analyses between the two SNPs for gene-gene interactions.

	SNP	*LPL Ser447Ter*
D statistic	*ADRB2 Gln27Glu*	0.003
D' statistic		0.03
r statistic		0.019
P-values		0.56

Discussion

The levels of triglycerides are dependent on genetic and exogenous factors (race, age, sex, dietary habits and physical activity) (2). A small increase in the levels of triglycerides reflects an increase in the concentration of LDL and its residues and, in some cases, an increase in the concentration of LDL and HDL (2). The levels of triglycerides can also be used to assess therapy to reduce the risk of atherosclerotic CVDs and cardiovascular events (21), as the reduction in plasma triglyceride levels is due to a reduction in triglycerides in lipoproteins. Elevated levels of triglycerides are more often

Table VII. Haplotype association with response levels of triglycerides.

Haplotype		Frequency			
LPL Ser447Ter	*ADRB2 Gln27Glu*	Triglycerides ≤2.25, no. of patients	Triglycerides ≥2.25, no. of patients	OR (95% CI)	P-value
C	C	0.6309	0.5452	1.00	-
C	G	0.2427	0.2895	0.72 (0.51-1.03)	0.074
G	C	0.0894	0.104	0.78 (0.45-1.36)	0.39
G	C	0.0371	0.0613	0.54 (0.25-1.15)	0.11

The data were adjusted by sex. Global haplotype association P-value: 0.1. LPL, lipoprotein lipase; ADRB2, β2-adrenergic receptor; OR, odds ratio; 95% CI, 95% confidence interval.

accompanied by low HDL and high LDL levels; therefore, the determination of the levels of triglycerides is critical in assessing the risk of cardiovascular events (1).

In the present study, the level of triglycerides was associated with a higher BMI, and higher apolipoprotein B and HDL levels. These results are similar to those of other researchers (1). The association of abdominal obesity with triglyceride levels is explained by the involvement of adipocytes in triglyceride metabolism. Plasma triglyceride concentrations reflect apolipoprotein B-containing lipoproteins (22). Similar findings have been reported in other studies; for example, Ference *et al* (23) argued that the effect of triglycerides on the risk of atherosclerotic CVD was related not to triglyceride itself, but to the concentration of apolipoprotein B-containing lipoproteins. Some authors have argued that increased lipogenesis in the liver result in hypertriglyceridemia, which decreases HDL levels (24). This is also consistent with the data of other researchers. Patwardhan *et al* (25) found that triglyceride and HDL levels were associated with the initial manifestations of insulin resistance. They argued that the timely treatment of dyslipidemia may be a prevention for insulin resistance (25).

Xie *et al* (10) reviewed the molecular structure, expression and function of the LPL gene for its association with dyslipidemia, type 2 diabetes, arterial hypertension, ischemic heart disease and Alzheimer's disease. They found that the insufficient synthesis or dysfunction of LPL reduced the hydrolysis of chylomicrons and VLDL, interfered with lipid consumption and led to the accumulation of lipoproteins in plasma (10). Liu *et al* (26) demonstrated that in the presence of the Ser447Ter polymorphism of the LPL gene, there was a high concentration of triglycerides and/or a low concentration of HDL, which was associated with a high systolic blood pressure and pulse pressure in patients with arterial hypertension. When studying the role of genes in the development of arterial hypertension Chen *et al* (27) found that polymorphisms of the LPL gene not only contributed to the development of arterial hypertension, but also influenced the increase in triglyceride levels. Matsunaga *et al* (28) noted that the heterozygous rs328 genotype of the LPL gene polymorphism was more common in patients with hypertriglyceridemia. They argued that multiple gene variations and environmental factors were the main causes of severe hypertriglyceridemia (29). In the presents study, it was found that the LPL Ser447Ter alleles were not associated with a statistically increased risk of hypertriglyceridemia.

Some authors have investigated the association between the Gln27Glu (rs1042714) polymorphism of the ADRB2 gene and obesity-related parameters (30) and found it to be associated with levels of triglycerides and HDL. A recent study demonstrated that the ADRB2 homozygous Gln27Glu variant was associated with type 2 diabetes, a risk factor that may have been associated with the risk of visceral fat accumulation and the development of type 2 diabetes in males, but not in females (29). In the present study, it was found that alleles of the Gln27Glu polymorphism (rs1042714) of the ADRB2 gene were associated with a high risk of developing hypertriglyceridemia. El-Menyar *et al* (31) stated that patients with the homozygous G/G genotype of the ADRB2 gene were more likely to have acute coronary syndrome with severe coronary artery stenosis. In addition, patients with type 2 DM with the G/G genotype of the ADRB2 gene had an increased risk of significant coronary stenosis (31).

The present study focused only on the association between ADRB2 Gln27Glu and triglycerides level. It was found that a higher risk of developing hypertriglyceridemia was associated with the ADRB2 Gln27Glu-C allele, but not with the G/G genotype. It was also found that a lower risk of developing hypertriglyceridemia was related to the ADRB2 Gln27Glu-G allele and the recessive model of the ADRB2 Gln27Glu polymorphism (C/C + C/G vs. G/G) was associated with a lower risk of developing hypertriglyceridemia (OR, 0.45; 95% CI, 0.23-0.86; P=0.0018). At the same time, polymorphisms of the LPL Ser447Ter (rs328) gene were not associated with hypertriglyceridemia in the present study population. There was no significant gene interaction between LPL Ser447Ter and ADRB2 Gln27Glu. These data are consistent with the aforementioned researches. As previously reported, SNP ADRB2 Gln27Glu affects the levels of triglycerides and HDL (30). A recent study demonstrated that ADRB2 Gln27Glu homozygous variant is associated with type 2 diabetes mellitus (30). In males it was a risk factor that possibly influences the accumulation of visceral fat and the development of type 2 diabetes mellitus, but not in females.

In identifying the major candidate genes that increase the risk of obesity, Lee *et al* (32) found that the ADRB2 gene polymorphism in combination with smoking and overeating

was strongly associated with obesity, and the chance of developing obesity was 11.7-fold higher in smokers compared to non-smokers. In evaluating the combined effect of rs9930501, rs9930506 and rs9932754 polymorphisms of the FTO gene, and the rs1042713 and rs1042714 polymorphisms of the ADRB2 gene on risk of obesity and cardiometabolic parameters, Tan and Mitra (15) demonstrated that individuals with a high frequency of risk alleles were more likely to be obese compared to those who had fewer risk alleles.

In their study, Wang *et al* (33) compared Han, Uyghur and Kazakh males, in terms of BMI, waist circumference, systolic blood pressure, diastolic blood pressure and HDL. They stated that Kazakh males had the highest BMI, waist circumference, blood pressure, HDL and lowest triglyceride levels among the three groups (33). In the present study, BMI also differed between the hypertriglyceridemia and healthy triglycerides groups. In addition, the levels of HDL, apolipoprotein B and BMI were significantly higher in the hypertriglyceridemia group than in the healthy triglyceride group. This can b explained by the high meat and carbohydrate intake and low fruit and vegetable intake in the Kazakh population. A high-calorie diet leads to dyslipidemia. No significant gene interaction was also found between LPL Ser447Ter and ADRB2 Gln27Glu.

There were several limitations to the present study. First, the significance of the association with hypertriglyceridemia was only observed for the recessive model (P=0.018) and the allele frequency of the LPL Ser447Ter gene. The P-value of 0.038 of the genetic predisposition to hypertriglyceridemia in the subjects with a C allele, was higher than the significance level estimated from Bonferroni's correction (P=0.025). Moreover, the LPL Ser447Ter polymorphism was associated with the dichotomous categorization of triglycerides groups as a qualitative trait.

On this basis, the C allele and the C/C and C/G genotypes of the Gln27Glu (rs1042714) polymorphism of the ADBR2 gene were associated with an increased risk of developing hypertriglyceridemia in the study sample. In turn, the G allele and G/G genotype of the Gln27Glu (rs1042714) polymorphism of the ADBR2 gene was associated with a reduced risk of developing hypertriglyceridemia in the present study sample. According to the results, the Ser447Ter (rs328) polymorphism of the LPL gene was not informative as a genetic determinant of the risk of dyslipidemia in this sample.

In conclusion, the present study indicates that the ADRB2 Gln27Glu polymorphism is associated with a risk of developing hypertriglyceridemia. In the Kazakh population, the ADRB2 Gln27Glu allele G was associated with a decreased risk of developing hypertriglyceridemia, whereas the LPL Ser447Ter alleles exhibited no association. The findings suggested that the levels of triglycerides were associated with higher levels of BMI, apolipoprotein B and HDL. However, further investigations are required to confirm these findings in a larger population in prospective longitudinal research.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AS and MM were the major contributors to the research, and performed the sequencing data analysis and were responsible for the clinical samples. NA, AS, AN, ZZ, DK and MM made substantial contributions to the conception and design of the study. AS and MM contributed to the qPCR analysis. MM, NA, ZZ and were responsible for the whole project. AS, DK and MM were involved in the writing of the manuscript. AS, MM, DK confirm the authenticity of all the raw data. NA, AN, DK and ZZ given final approval of the version to be published. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided written informed consent to participate in the study (according to the Declaration of Helsinki of the World Medical Organization). The Ethics Committee of Semey Medical University approved the research protocol (Protocol no. 11 from 27.09.2017).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Solnica B, Sygitowicz G, Sitkiewicz D, Cybulska B, Jóźwiak J, Odrowąż-Sypniewska G and Banach M: 2020 Guidelines of the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA) on laboratory diagnostics of lipid metabolism disorders. Arch Med Sci 16: 237-252, 2020.
2. Zhu JR, Gao RL, Zhao SP, Lu GP, Zhao D and Li JJ: 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriat Cardiol 15: 1-29, 2018.
3. Lim SY, Steiner JM and Cridge H: Lipases: It's not just pancreatic lipase! Am J Veterinary Res 83: 348-358, 2022.
4. Gilbert M: Role of skeletal muscle lipids in the pathogenesis of insulin resistance of obesity and type 2 diabetes. J Diabetes Investig 12: 1934-1941, 2021.
5. Yan Y, Wang D, Sun Y, Ma Q, Wang K, Liao Y, Chen C, Jia H, Chu C, Zheng W, *et al*: Triglyceride-glucose index trajectory and arterial stiffness: Results from Hanzhong Adolescent Hypertension Cohort Study. Cardiovasc Diabetol 21: 33, 2022.
6. Williams PT: Gene-environment interactions due to quantile-specific heritability of triglyceride and VLDL concentrations. Sci Rep 10: 4486, 2020.

7. Dron JS, Wang J, McIntyre AD, Iacocca MA, Robinson JF, Ban MR, Cao H and Hegele RA: Six years' experience with LipidSeq: Clinical and research learnings from a hybrid, targeted sequencing panel for dyslipidemias. BMC Med Genomics 13: 23, 2020.
8. Petrie JR, Guzik TJ and Touyz RM: Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms. Can J Cardiol 34: 575-584, 2018.
9. Beisiegel U: Lipoprotein metabolism. Eur Heart J 19 (Suppl A): A20-A23, 1998.
10. Xie C, Wang ZC, Liu XF and Yang MS: The common biological basis for common complex diseases: Evidence from lipoprotein lipase gene. Eur J Hum Genet 18: 3-7, 2010.
11. Olefsky JM and Glass CK: Macrophages, inflammation, and insulin resistance. Ann Rev Physiol 72: 219-246, 2010.
12. Rosmond R, Ukkola O, Chagnon M, Bouchard C and Björntorp P: Polymorphisms of the beta2-adrenergic receptor gene (ADRB2) in relation to cardiovascular risk factors in men. J Intern Med 248: 239-244, 2000.
13. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, *et al*: Discovery and refinement of loci associated with lipid levels. Nat Genet 45: 1274-1283, 2013.
14. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, *et al*: Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466: 707-713, 2010.
15. Tan PY and Mitra SR: The combined effect of polygenic risk from FTO and ADRB2 Gene variants, odds of obesity, and post-hipcref diet differences. Lifestyle Genomics 13: 84-98, 2020.
16. Sikhayeva N, Talzhanov Y, Iskakova A, Dzharmukhanov J, Nugmanova R, Zholdybaeva E and Ramanculov E: Type 2 diabetes mellitus: Distribution of genetic markers in Kazakh population. Clin Interv Aging 13: 377-388, 2018.
17. Shakhanova A, Aukenov N, Nurtazina A, Massabayeva M, Babenko D, Adiyeva M and Shaimardonov N: Association of polymorphism genes LPL, ADRB2, AGT and AGTR1 with risk of hyperinsulinism and insulin resistance in the Kazakh population. Biomed Rep 13: 35, 2020.
18. 1000 Genomes Project Consortium; Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA and Abecasis GR: A global reference for human genetic variation. Nature 526: 68-74, 2015.
19. Dai HJ, Wu JCY, Tsai RTH, Pan WH and Hsu WL: T-HOD: A literature-based candidate gene database for hypertension, obesity and diabetes. Database (Oxford 2013: bas061, 2013.
20. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 25: 402-408, 2001.
21. Bastien M, Poirier P, Lemieux I and Després JP: Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 56: 369-381, 2014.
22. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, *et al*: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J 41: 111-188, 2020.
23. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, *et al*: Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA 321: 364-373, 2019.
24. Lechner K, McKenzie AL, Kränkel N, Von Schacky C, Worm N, Nixdorff U, Lechner B, Scherr J, Weingärtner O and Krauss RM: High-risk atherosclerosis and metabolic phenotype: The roles of ectopic adiposity, atherogenic dyslipidemia, and inflammation. Metab Syndr Relat Disord 18: 176-185, 2020.
25. Patwardhan V, Khadilkar A, Chiplonkar S and Khadilkar V: Dyslipidemia and Fat Distribution in Normal Weight Insulin Resistant Men. J Assoc Physicians India 67: 26-29, 2019.
26. Liu A, Lee L, Zhan S, Cao W, Lv J, Guo X and Hu Y: The S447X polymorphism of the lipoprotein lipase gene is associated with lipoprotein lipid and blood pressure levels in Chinese patients with essential hypertension. J Hypertens 22: 1503-1509, 2004.
27. Chen P, Jou YS, Fann CS, Chen JW, Chung CM, Lin CY, Wu SY, Kang MJ, Chen YC, Jong YS, *et al*: Lipoprotein lipase variants associated with an endophenotype of hypertension: Hypertension combined with elevated triglycerides. Hum Mutat 30: 49-55, 2009.
28. Matsunaga A, Nagashima M, Yamagishi H and Saku K: Variants of Lipid-related genes in adult japanese patients with severe hypertriglyceridemia. J Atheroscler Thromb 27: 1264-1277, 2020.
29. Gonzalez Sanchez JL, Proenza AM, Martinez Larrad MT, Ramis JM, Fernandez Perez C, Palou A and Serrano Ríos M: The glutamine 27 glutamic acid polymorphism of the beta2-adrenoceptor gene is associated with abdominal obesity and greater risk of impaired glucose tolerance in men but not in women: A population-based study in Spain. Clin Endocrinol (Oxf) 59: 476-481, 2003.
30. Apalasamy YD, Ming MF, Rampal S, Bulgiba A and Mohamed Z: Gender-dependent association of a β(2)-adrenergic gene variant with obesity parameters in malaysian malays. Asia Pac J Public Health 27: NP154-NP165, 2015.
31. El-Menyar A, Rizk NM, Asim M, Al-Thani H, Elgendy A and Al-Suwaidi J: Association of β-adrenergic receptor gene polymorphisms with acute coronary syndrome and cardiovascular risk factors in an arab population. Angiology 67: 762-771, 2016.
32. Lee S, Kim CM, Kim HJ and Park HS: Interactive effects of main genotype, caloric intakes, and smoking status on risk of obesity. Asia Pac J Clin Nutr 20: 563-571, 2011.
33. Wang Y, Zhang J, Ma Y, Song X, Li S, Zhan X and Wu L: Different lipid profiles, insulin sensitivity, and insulin resistance among Han, Uygur, and Kazak men with normal glucose tolerance in Xinjiang, China. Lipids Health Dis 17: 209, 2018.