Polymorphisms of lipid metabolism enzyme-coding genes in patients with diabetic dyslipidemia

Aslı Tetik Vardarlı, Ece Harman[1], Vildan Bozok Çetintaş, Meral Kayıkçıoğlu, Egemen Vardarlı[2], Ayhan Zengi[3], Ali Şahin Küçükaslan, Zuhal Eroğlu*

Departments of Medical Biology and *Cardiology, Faculty of Medicine, Ege University; İzmir-*Turkey*
[1]Department of Internal Medicine, Division of Endocrinology and Metabolism Disease, Faculty of Medicine, Katip Çelebi University; İzmir-*Turkey*
[2]Department of Neurology, Tınaztepe Hospital; İzmir-*Turkey*
[3]Department of Endocrinology and Metabolism, Isparta Public Hospital; Isparta-*Turkey*

Abstract

Objective: The polymorphisms/mutations of genes encoding proteins and enzymes involved in lipoprotein metabolism play important roles in the development of diabetic dyslipidemia. The aim of our study was to investigate the effects of *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), *PON1* (rs662), and *MNSOD* (rs4880) gene polymorphisms on lipid metabolism and diabetic dyslipidemia.

Methods: This case-control study included 217 patients with diabetic dyslipidemia and 212 healthy age- and gender-matched individuals. Genomic DNA isolation was performed from blood samples, and genotype analysis was performed using melting curve analysis on a LightCycler® 480 Instrument. The chi-square test was used to compare genotype distribution and allele frequencies between the groups.

Results: Significant associations were observed between *LPL* (rs320) (p<0.001), *LIPC* (rs2070895) (p<0.001), *SCARB1* (rs5888) (p<0.001), *LCAT* (rs2292318) (p<0.001), *CETP* (rs708272) (p<0.001), *ADIPOQ* (rs1501299) (p=0.01), *RETN* (rs3745367) (p<0.001), and *MNSOD* (rs4880) (p<0.001) polymorphisms and diabetic dyslipidemia. However, no association was observed between PON1 (rs662) polymorphisms and diabetic dyslipidemia (p=0.611).

Conclusion: *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), and *MNSOD* (rs4880) polymorphisms play an important role in basic molecular metabolism in diabetic dyslipidemia. Therefore, these polymorphisms may be used as a predictive marker for diabetic dyslipidemia in high-risk patients. *(Anatol J Cardiol 2017; 17: 313-21)*

Keywords: diabetes mellitus, dyslipidemia, lipid metabolism, genetic polymorphisms

Introduction

Diabetes mellitus is a metabolic disorder with a complex etiology resulting from the disturbance of insulin secretion/action and is characterized by carbohydrate, fat, and protein metabolism dysfunction (1). Dyslipidemia occurs in conjunction with insulin resistance and is considered to be one of the most important risk factors for cardiovascular (CV) disease (2). Quantitative and qualitative changes in the properties of lipoproteins, the degradation of lipoprotein metabolism, genetic predispositions, and environmental factors are the main etiologic mechanisms of diabetic dyslipidemia. Recent studies have shown that the polymorphisms or mutations of genes that encode proteins and enzymes involved in lipoprotein metabolism may play an important role in the development of diabetic dyslipidemia (3–5). Therefore, determining genetic profiles associated with diabetic dyslipidemia is gaining importance in terms of reducing the risk of micro- and macrovascular complications.

Roles of enzymes and enzyme-coding candidate genes in cholesterol metabolism

Lipoprotein lipase (LPL) is a key enzyme in lipoprotein metabolism. It hydrolyzes triglycerides from very-low-density lipoproteins and separates lipoproteins from the circulation (6, 7). This enzyme is coded by the *LPL* gene, and several genetic variants of *LPL* have been associated with plasma lipoprotein levels (7, 8). Lecithin–cholesterol acyltransferase (LCAT) catalyzes the esterification of free cholesterol in the blood (9). Both common and rare *LCAT* gene mutations/polymorphisms have been found to affect high-density lipoprotein (HDL) levels (6). Adipo-

Address for correspondence: Dr. Meral Kayıkçıoğlu, Ege Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İzmir-*Türkiye*
E-mail: meral.kayikcioglu@ege.edu.tr
Accepted Date: 17.11.2016 **Available Online Date:** 03.03.2017

DOI:10.14744/AnatolJCardiol.2016.7142

nectin is a cytokine that inhibits adipose-specific expression in the blood (10). Resistin, encoded by the *RETN* gene, plays a key role in glucose homeostasis; *RETN* has been described as one of the candidate genes for type 2 diabetes mellitus (11, 12). Serum paraoxonase/arylesterase 1 (PON1) is an enzyme that protects low-density lipoproteins from oxidation and is responsible for the antioxidant properties of HDL (13). Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein that regulates the exchange of triglycerides by transferring esterified cholesterol from HDL to apo-B-containing particles (14). *CETP* also plays an important role in the regulation of HDL cholesterol levels (6, 14). *CETP* gene polymorphisms have been associated with HDL cholesterol concentrations in many reports (14, 15). Scavenger receptor class B member 1 (SRB1), encoded by the *SCARB1* gene, is an HDL receptor involved in reverse cholesterol transport (16). Hepatic lipase (LIPC) is an enzyme that regulates the metabolism of low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and HDL particles and plays a crucial role in the selective uptake of cholesterol esters from HDL (17). Recent studies have reported that polymorphisms of the promoter region of the *LIPC* gene influence the regulation of insulin sensitivity and type 2 diabetes development (17, 18). Oxidative stress also plays an important role in the pathogenesis of insulin resistance. Increased reactive oxygen species (ROS) levels lead to insulin resistance in type 2 diabetes (19). Manganese-dependent superoxide dismutase (MnSOD, SOD2) is a member of the most important family of superoxide dismutases and may prevent damage from ROS-induced hyperglycemia, oxidative stress, and ionizing radiation. It has been reported that the polymorphism of the *MNSOD* gene leads to differences in protein function (20).

The aim of this study was to identify the genotype distributions of enzyme-coding genes involved in the cholesterol pathway and the development of diabetic dyslipidemia in a group of patients from a single outpatient diabetes clinic in Turkey. These enzyme-coding genes included *LPL*, *LIPC*, *SCARB1*, *LCAT*, *CETP*, *ADIPOQ*, *RETN*, *PON1*, and *MNSOD*.

Methods

Study population

Our case-control study group initially consisted of 250 patients with diabetic dyslipidemia who were consecutively admitted to the Endocrinology and Metabolic Disease outpatient clinic of Ege University School of Medicine between 2007 and 2011. This study also included 225 age- and gender-matched healthy individuals. Control subjects were recruited from healthy volunteers whose routine health checkup was within normal limits. The diagnosis of diabetes was based on the presence of fasting blood glucose (FBG) levels of >126 mg/dL and/or postprandial glucose levels of >200 mg/dL and hemoglobin A1c (HbA1c) levels of >6.5%. The presence of diabetic dyslipidemia was defined as triglyceride levels of >200 mg/dL and/or HDL levels of <45 mg/dL. During the analysis, 13 control subjects were excluded due to elevated FBG levels (>126 mg/dL) indicating diabetes mellitus and 33 patients were excluded from the study group due to normal FBG levels. The remaining 429 subjects (217 diabetics and 212 healthy subjects) constituted the study population. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all subjects.

The clinical characteristics of the groups were retrospectively obtained from patient charts. Biochemical analysis included HbA1c, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and FBG levels measured by an Olympus AU2700 automated analyzer (Toshiba, Tokyo, Japan). All participants' peripheral venous blood samples were collected into EDTA-containing tubes and were stored at –20°C until genomic DNA isolation was performed.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a MagNA Pure LC instrument and MagNA Pure LC DNA Isolation Kit (Roche Applied Science, Mannheim, Germany). The analysis of *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), *PON1* (rs662), and *MNSOD* (rs4880) gene polymorphisms was performed using specific primers and a simple probe mix with a LightCycler-FastStart DNA Master Hybridization Probes Kit (Roche Applied Science). All experiments were performed in a LightCyclerTM 480 Instrument (Roche Applied Science) according to the protocol provided by the manufacturer (TIB MOLBIOL, Berlin, Germany). All polymorphisms were detected in the F2 channel. Alleles were identified by the specific melting temperature of the resulting amplicons, as individuals with two copies of the wild-type genotype show a single melting peak, individuals with heterozygous alleles show two melting peaks, and individuals with two copies of the polymorphic genotype show a single melting peak for all polymorphisms. Among the patients with diabetic dyslipidemia, errors occurred in the analysis of *LPL* (rs320) in 1 patient, in the analysis of *LIPC* (rs2070895) and *ADIPOQ* (rs1501299) in 2 patients, and in the analysis of *PON1* (rs662) in 3 patients; therefore, these 5 patients were not included in the final statistical analysis.

Biochemical analyses were compared between the patients with diabetic dyslipidemia and the control group according to the genotypic status of *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), *PON1* (rs662), and *MNSOD* (rs4880) gene polymorphisms.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS, Chicago, IL, USA). Data are presented as percentages for discrete variables and as mean ± standard deviation (SD) for continuous variables. Comparisons between the groups were made using Student's t-test, and discrete variables were compared by chi-square analysis. Distribution analy-

ses of the variables were performed using the Kolmogorov–Smirnov test. A p value of <0.05 (two-sided) was regarded to be statistically significant.

Results

This study consisted of 217 patients with diabetic dyslipidemia (133 females and 84 males) and 212 unrelated healthy individuals (122 females and 90 males). The comparison of clinical characteristics and biochemical parameters between the groups is shown in Table 1. FBG, total cholesterol, triglyceride, and LDL cholesterol levels were significantly higher in the diabetic dyslipidemia group than in the control group (p<0.001), while HDL cholesterol levels were significantly lower in the diabetic dyslipidemia group. Within our patient group, those with diabetic dyslipidemia were treated with oral antidiabetics, insulin, and lipid-lowering drugs (Table 1).

LPL (rs320) TT, TG and GG genotype distributions were 10.1%, 38%, and 51.9% in the diabetic dyslipidemia group and 69.8%, 25.5%, and 4.7% in the control group, respectively. Patients with diabetic dyslipidemia had a higher frequency of the polymorphic GG genotype of *LPL* (rs320) than control subjects (p<0.001) (Table 2).

GG, GA and AA genotype distributions of the *LIPC* (rs2070895) gene were 0.5%, 21.4%, and 78.1% in the diabetic dyslipidemia group and 73.6%, 21.4%, and 3.8% in the control group, respectively. Patients with diabetic dyslipidemia showed a higher frequency of the polymorphic AA genotype of *LIPC* (rs2070895) than control subjects (p<0.001) (Table 2).

The frequencies of the CC, CT, and TT *SCARB1* (rs5888) genotypes were 30.9%, 39.2%, and 30% in the diabetic dyslipidemia group and 79.6%, 18.9%, and 2.8% in the control group, respectively. Patients with diabetic dyslipidemia had higher frequencies of the *SCARB1* (rs5888) CT and TT genotypes than control subjects (p<0.001) (Table 2).

LCAT (rs2292318) CC, CT, and TT genotypes were found in 0%, 17.9%, and 82.1% of patients with diabetic dyslipidemia and in 69.1%, 30.9%, and 0% of the control subjects, respectively. Genotype analysis revealed that patients with diabetic dyslipidemia showed a higher frequency of the polymorphic TT genotype of *LCAT* (rs2292318) than control subjects (p<0.001), while control subjects had a higher frequency of the CC genotype than patients with diabetic dyslipidemia (p<0.001) (Table 2).

For the *CETP* (rs708272) gene, the frequencies of the GG, GA and AA genotypes were 31.3%, 51.6%, and 17.1% in the diabetic dyslipidemia group and 70.8%, 25%, and 4.2% in the control group, respectively. The frequency of the AA genotype was significantly higher in patients with diabetic dyslipidemia than in control subjects (p<0.001) (Table 2).

The GG, GT, and TT genotypes of *ADIPOQ* (rs1501299) were detected at frequencies of 60.5%, 32.1%, and 7.4% in the diabetic dyslipidemia group and 73.6%, 23.1%, and 3.3% in the control group, respectively. The TT genotype was significantly more common in the diabetic dyslipidemia group (p=0.01) (Table 2).

Table 1. Characteristics and biochemical parameters of patients with diabetic dyslipidemia and control subjects

	Patients with diabetic dyslipidemia Mean±SD n=217	Control subjects Mean±SD n=212	*P*
Gender, female/male	133/84	122/90	–
Age, years	53.2±9.8	52.8±9.2	–
Fasting glucose, mg/dL	161.9±72.5	87.7±11.6	<0.001
Total cholesterol, mg/dL	219.3±61.8	178.2±20.7	<0.001
Triglycerides, mg/dL	231.6±255.8	109.5±25.9	<0.001
HDL cholesterol, mg/dL	48.5±13.6	63±8.9	<0.001
LDL cholesterol, mg/dL	131.6±42.3	117±17.9	
Lipid-lowering drugs, n, %	68 (31.3%)	–	
Oral antidiabetics, n, %	20 (9.2%)	–	
Insulin, n, %	29 (13.4%)	–	

HDL - high-density lipoprotein; LDL - low-density lipoprotein

The distributions of the GG, GA, and AA genotypes of *RETN* (rs3745367) were 19.4%, 46.5%, and 34.1% in the diabetic dyslipidemia group and 57.5%, 35.4%, and 7.1% in the control group, respectively. The frequency of the polymorphic AA genotype was significantly higher among patients with diabetic dyslipidemia than among control subjects (p<0.001) (Table 2).

For *PON1* (rs662), frequencies of the AA, AG, and GG genotypes were 51.4, 40.7%, and 7.9% in the diabetic dyslipidemia group and 56.1%, 36.3%, and 7.5% in the control group, respectively. No significant differences emerged between patients with diabetic dyslipidemia and control subjects (p=0.611) (Table 2).

The distributions of the *MNSOD* (rs4880) CC, CT, and TT genotypes were 46.5%, 34.6%, and 18.9% in patients with diabetic dyslipidemia patients and 77.4%, 19.3%, and 3.3% in control subjects, respectively. The differences between patients with diabetic dyslipidemia and control subjects were statistically significant (p<0.001) (Table 2).

In the control group, *CETP* (rs708272) and *PON1* (rs662) gene polymorphisms showed a negative correlation with triglycerides (r=–0.137, p=0.047) and HDL cholesterol (r=–0.158, p=0.022) levels, respectively, whereas no significant correlation was observed between *LPL* (rs320), *LCAT* (rs2292318), *ADIPOQ* (rs1501299), *RETN* (rs3745367), *LIPC* (rs2070895), *SCARB1* (rs5888), or *MNSOD* (rs4880) gene polymorphisms and lipid parameters including total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels (p>0.005). Furthermore, no significant association was observed between these gene polymorphisms and HbA1c or FBG levels in control subjects.

In the diabetic dyslipidemia group, *SCARB1* (rs5888) and *ADIPOQ* (rs1501299) gene polymorphisms showed a weak positive correlation with FBG (r=0.172, p=0.011) and HDL cholesterol (r=0.176, p=0.010) levels, respectively. However, no significant association was found between *LPL* (rs320), *LIPC* (rs2070895),

Table 2. Genotype distributions and allele frequencies of *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), *PON1* (rs662), and *MNSOD* (rs4880) gene polymorphisms in the study groups

Gene/SNP	Genotype/ haplotype	Patients with diabetic dyslipidemia n (%)	Control subjects n (%)	*P*
LPL (rs320) T495G	Wild type (TT)	22 (10.1)	148 (69.8)	<0.001
	Heterozygote (TG)	82 (38)	54 (25.5)	
	Polymorphic (GG)	112 (51.9)	10 (4.7)	
	T	126	350	
	G	164	74	
LIPC (rs2070895) G250A	Wild type (GG)	1 (0.5)	156 (73.6)	<0.001
	Heterozygote (GA)	46 (21.4)	48 (21.4)	
	Polymorphic (AA)	168 (78.1)	8 (3.8)	
	G	48	360	
	A	382	64	
SCARB1 (rs5888) C1050T	Wild type (CC)	67 (30.9)	166 (79.6)	<0.001
	Heterozygote (CT)	85 (39.2)	40 (18.9)	
	Polymorphic (TT)	65 (30.0)	6 (2.8)	
	C	219	372	
	T	215	52	
LCAT (rs2292318) C511T	Wild type (CC)	0 (0)	150 (69.1)	<0.001
	Heterozygote (CT)	38 (17.9)	67 (30.9)	
	Polymorphic (TT)	174 (82.1)	0 (0)	
	C	38	367	
	T	67	386	
CETP (rs708272) G279A	Wild type (GG)	68 (31.3)	150 (70.8)	<0.001
	Heterozygote (GA)	112 (51.6)	53 (25)	
	Polymorphic (AA)	37 (17.1)	9 (4.2)	
	G	248	353	
	A	186	71	
ADIPOQ (rs1501299) G276T	Wild type (GG)	130 (60.5)	156 (73.6)	=0.01
	Heterozygote (GT)	69 (32.1)	49 (23.1)	
	Polymorphic (TT)	16 (7.4)	7 (3.3)	
	G	329	361	
	T	101	63	
RETN (rs3745367) G299A	Wild type (GG)	42 (19.4)	122 (57.5)	<0.001
	Heterozygote (GA)	101 (46.5)	75 (35.4)	
	Polymorphic (AA)	74 (34.1)	15 (7.1)	
	G	185	319	
	A	249	105	
PON1 (rs3745367) Q192R	Wild type (AA)	110 (51.4)	119 (56.1)	0.611
	Heterozygote (AG)	87 (40.7)	77 (36.3)	
	Polymorphic (GG)	17 (7.9)	16 (7.5)	
	A	307	315	
	G	121	109	
MNSOD (rs4880) Ala16Val	Wild type (CC)	101 (46.5)	164 (77.4)	<0.001
	Heterozygote (CT)	75 (34.6)	41 (19.3)	
	Polymorphic (TT)	41 (18.9)	7 (3.3)	
	C	277	369	
	T	157	55	

ADIPOQ - adiponectin; CETP - cholesterol ester transfer protein; LCAT - lecithin–cholesterol acyltransferase; LIPC - hepatic lipase; LPL - lipoprotein lipase; MNSOD - manganese-dependent superoxide dismutase; PON1 - paraoxonase; RETN - resistin; SCARB1 - scavenger receptor class B member 1.
Statistical analysis was performed using SPSS 18.0. The chi-square test was used to compare the genotype distribution and allele frequencies between the groups. The level of significance was accepted as $P<0.05$.

LCAT (rs2292318), *CETP* (rs708272), *RETN* (rs3745367), *PON1* (rs662), or *MNSOD* (rs4880) gene polymorphisms and lipid parameters, plasma glucose levels, or HbA1c levels (p>0.005).

Discussion

To the best of our knowledge, no previous studies have reported the effects of *LPL* (rs320), *LCAT* (rs2292318), and *PON1* (rs662) gene polymorphisms in patients with diabetic dyslipidemia. Our study is the first comprehensive study to provide evidence on possible associations between *LPL* (rs320), *LIPC* (rs2070895), *SCARB1* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), and *MNSOD* (rs4880) gene polymorphisms and diabetic dyslipidemia in Turkish adults.

According to our results, heterozygote and polymorphic genotype rates in patients with diabetic dyslipidemia were found to be 38% TG and 51.9% GG for *LPL*, 21.4% GA and 78.1% AA for *LIPC*, 39.2% CT and 30% TT for *SCARB1*, 17.9% CT and 82.1% TT for *LCAT*, 51.6% GT and 17.1% TT for *CETP*, 32.1% GT and 7.4% TT for *ADIPOQ*, 46.5% GA and 34.1% AA for *RETN*, and 34.6% CT and 18.9% TT for *MNSOD*.

LPL, *LIPC*, *SCARB1*, *LCAT*, and *CETP* proteins play important roles in the endogenous and exogenous pathways of lipoprotein metabolism. Genetic and environmental factors such as obesity, dyslipidemia, and blood glucose and blood insulin levels are defined as risk factors for the development of type 2 diabetes. Therefore, the determination of the relationship between *LPL* T495G gene polymorphisms and risk factors associated with diabetes mellitus is becoming more important in understanding the etiology of type 2 diabetes. In our study, the frequency of heterozygous and polymorphic genotypes of the T495G polymorphism was observed in 38% and 51.9% of patients with diabetic dyslipidemia, respectively. Daoud et al. (7) determined TG and GG genotype frequencies to be 35.8% and 19%, respectively, in Saudi Arabian patients with coronary artery disease (CAD). They also found lower TG and GG frequencies than those in our population in their subgroups of patients with CAD having diabetes (53.04% and 28.15%, respectively) and dyslipidemia (45.88% and 24.35%, respectively). The systemic overexpression of the *LPL* gene may initiate a tissue-specific insulin signaling cascade, causing insulin resistance in skeletal muscles as well as other metabolic tissues and eventually leading to the development of type 2 diabetes mellitus. *LPL* activity is also sensitive to environmental factors such as hormonal regulation. We believe that the *LPL* GG genotype has utility as a biomarker for type 2 diabetes. Qi et al. (8) reported that even in patients with a normal lipid profile, the GG genotype of *LPL* T495G was significantly associated with an increased risk of developing type 2 diabetes. Individuals with the GG genotype have higher pre-heparin *LPL* levels and lower triglycerides levels than those with the TT genotype. Ariza et al. (21) reported that T495G *LPL* gene variants have a lowering effect on triglyceride levels (p<0.005) and that this polymorphism has a protective effect against the development of hypertriglyceridemia (p=0.042). In summary, the *LPL* T495G polymorphism may regulate the magnitude of dyslipidemia, but its effects on lipid metabolism are not yet clearly understood.

HDL cholesterol levels are associated with the *LCAT* enzyme due to the important physiological function of *LCAT*; however, only a few large studies have determined a significant relationship between *LCAT* gene polymorphisms and HDL cholesterol levels (9, 22). In our study, the CT and TT genotypes were detected in 17.9% and 82.1% of patients with diabetic dyslipidemia, respectively. Ghanei et al. (9) reported that *LCAT* activity is significantly decreased in patients with type 2 diabetes mellitus. The *LCAT* rs2292318 polymorphism may result in a decreased enzyme activity of *LCAT*. As there are few studies on rs2292318, its effect on *LCAT* enzyme activity is unknown. Paré et al. (22) showed a significant relationship between the TT genotype of the *LCAT* rs2292318 polymorphism (7.6%) and increased HDL cholesterol levels in patients with CAD. In recent studies, 5 *LCAT* polymorphisms (Gly230Arg, P143L, rs4986970, rs5922, and rs2292318) have been associated with HDL cholesterol levels, though the findings were not entirely consistent with each other (6). To determine the effects of the *LCAT* rs2292318 genetic polymorphism on HDL cholesterol levels and enzyme activity, rare and frequent genetic variations of this polymorphism should be investigated in genome-wide association studies.

To date, the direct effects of the *SCARB1* C1050T gene polymorphism could not be fully explained by in vivo studies. Constantineau et al. (16) have investigated the effects of the C1051T polymorphism on SRB1 protein expression and function by an in vitro study. They concluded that the C1050T variant of *SCARB1* affects the secondary structure and protein translation of SRB1, leading to reduced protein expression and function. Roberts et al. (23) determined an association between high HDL cholesterol levels and C1050T polymorphism in women (<50 years old), but any association between lipid levels and the C1050T polymorphism in men was not examined. We determined a positive correlation between FBG and the *SCARB1* rs5888 variant in patients with diabetic dyslipidemia. However, no association was found between other lipid parameters and the C1050T polymorphism in the diabetic dyslipidemia group. Stanislovaitiene et al. (24) reported that *SCARB1* TT genotype frequency (9.4%) was significantly lower in the oldest male myocardial infarction group than in the control group (22.3%). McCarthy et al. (25) also reported that the rs5888 variants of *SCARB1* were associated with insulin resistance (p=0.0003), particularly in women. In our study, we revealed the *SCARB1* C1050T polymorphism to be a risk factor for the development of diabetic dyslipidemia, regardless of gender.

CETP plays an important role in the regulation of HDL cholesterol concentrations. Carlquist et al. (15) reported that the frequencies of the GG, GA and AA genotypes of *CETP* rs708272 were 32.9%, 50.3%, and 16.8%, respectively, in patients with CV diseases. We also found very similar genotypic frequencies (31.3% GG, 51.6% GA, and 17.1% AA). However, Dixit et al. (14) demonstrated that the prevalence of the AA mutant

genotype of *CETP* rs708272 was higher in patients with type 2 diabetes than in those without diabetes, whereas no association was observed between the rs708272 polymorphism and type 2 diabetes mellitus. They also found that the heterozygous genotype of *CETP* increased the risk of type 2 diabetes-induced hypertension (p=0.028), while the wild-type genotype had a protective effect against disease development (p=0.038) (14). Population studies in Singapore (China, Malaysia, and Indies) demonstrated that the AA polymorphic genotype was associated with higher HDL cholesterol concentrations (26). As our study, also Indian patients have a higher frequency of the A allele, they have low HDL cholesterol levels than Malaysian and Chinese individuals. Our results also support of the results obtained by Yılmaz et al. (27) who indicated that polymorphic gene carriers in the control group show a negative correlation between *CETP* (rs708272) gene polymorphism and triglyceride concentrations. Furthermore, Ağırbaşlı et al. (28) determined an association between the *CETP* (rs708272) polymorphism and low HDL cholesterol phenotype in children. However, this result was not as strong as that in adults. Contrary to the findings of Yılmaz et al. (27), we did not find any association between the *CETP* rs708272 polymorphism and biochemical parameters such as triglyceride or HDL cholesterol levels in our diabetic dyslipidemia patient group. A recent study demonstrated that a *CETP* rs708272 gene variant is associated with low HDL cholesterol phenotype in Turkish children (28, 29). As our patient population was on lipid-lowering drugs, insulin, and oral antidiabetics, the effects of polymorphisms on lipid parameters and glucose might be masked by drug treatments. We also suspect that these discrepancies in the results of various studies in the same population are attributable to differences between selected patient groups' baseline characteristics and gene–gene and gene–environment interactions. Similar to our study, Yılmaz et al. (27) also demonstrated that the *CETP* rs708272 polymorphism was associated with an increased risk of developing type 2 diabetes mellitus in Turkish patients.

LIPC plays an important role in the metabolism of LDL, IDL, and HDL particles. The common polymorphisms of the *LIPC* gene change the *LIPC* enzymatic activity by approximately 20–30% of the individual variation (18). Population studies have indicated that lipid and lipoprotein abnormalities are messengers for developing type 2 diabetes and that *LIPC* plays a central role in insulin resistance in dyslipidemia. Regarding the *LIPC* (rs2070895) G250A polymorphism, AA (78.1%) genotype carriers significantly outnumbered GA (21.4%) and GG (0.5%) genotype carriers among our patients with diabetic dyslipidemia. Although *LIPC* levels were not measured, we can assume that polymorphic genotypes (AA) increase *LIPC* levels by causing the accumulation of visceral fat (17).

Adiponectin, resistin, *PON1*, and *MnSOD* proteins have crucial roles in glucose homeostasis. To date, studies have not fully elucidated how the *ADIPOQ* (rs1501299) G276T polymorphism affects insulin sensitivity and type 2 diabetes development. Şenol et al. (30) found the frequencies of G276T genotypes in patients with CAD to be 65.5% GG, 29.1% GT, and 5.5% TT in Turkish patients, which is comparable to the results of our study. Cnop et al. (31) and Tschritter et al. (32) demonstrated in large studies that plasma adiponectin concentrations are positively correlated with HDL cholesterol levels and negatively correlated with triglyceride levels. In our patient group, we found a positive correlation between *ADIPOQ* G276T polymorphisms and HDL concentrations. Therefore, adiponectin may have a direct role in HDL catabolism by promoting HDL assembly in the liver. Various studies have indicated that adiponectin levels are affected by multigenic control, particularly genetic variability in the *ADIPOQ* gene, contributing to the regulation of the protein (33, 34). Hara et al. (35) and other previous studies have shown that GG *ADIPOQ* gene variants had a greater effect on adiponectin levels, leading to insulin resistance and the progression of glucose intolerance to type 2 diabetes (10, 36). Contrary to these results, Ramya et al. (37) and Tsai et al. (38) demonstrated that TT genotypes were significantly associated with type 2 diabetes in Indian and Taiwan Chinese Han populations, respectively. Tu et al. (39) reported that *ADIPOQ* polymorphisms confer genetic susceptibility for type 2 diabetes in East Asians. *ADIPOQ* gene polymorphisms (rs2241766 and rs1501299) were also associated with an increased risk of developing type 2 diabetes mellitus in the Chinese Han population in a meta-analysis (38). Consistent with our results, various studies have concluded that the TT genotype plays an important role in the pathogenesis of type 2 diabetes.

In recent years, resistin was defined as a new potential signaling molecule proposed to link obesity and diabetes mellitus (11). Our results revealed that the *RETN* G299A polymorphism AA genotype (34.1%) was significantly associated with an increased risk of diabetic dyslipidemia compared to the control group. Ma et al. (12) concluded that obesity and the AA genotype were associated with an increased risk of type 2 diabetes. In contrast, Fehmann et al. (40) and Ochi et al. (41) did not detect any association between the *RETN* G299A polymorphism and type 2 diabetes mellitus. Furthermore, rs3745367 and rs1423096 *RETN* variants were significantly associated with resistin levels in a genome-wide association study conducted by Chung et al. (10). However, rs1423096 variants in the downstream region of *RETN* seem to be more associated with an increased risk of type 2 diabetes than the rs3745367 variant (42). These discrepancies could be attributed to ethnic differences between the selected populations.

PON1 is an HDL-associated antioxidant enzyme that prevents LDL oxidation (43). According to the genotype analysis of *PON1* Q192R polymorphisms, the diabetic dyslipidemia and control groups were 40.7% and 36.3% heterozygous and 7.9% and 7.5% polymorphic, respectively. The R allele frequencies of the *PON1* Q192R polymorphism widely vary between distinct ethnic groups; rates in Italy, Sardinia, Ethiopia, Benin, and Ecuador were reported to be 31.3%, 24.8%, 40.8%, 61.2%, and 78.9%, respectively (44). Ghanei et al. (9) reported that the QQ (AA) homozygote and R

(G) alleles were associated with myocardial infarction in dyslipidemia cases, whereas only the R (G) allele was associated with myocardial infarction in patients with diabetes (p<0.05). Alegria-Torres et al. (45) identified the Q192R polymorphism of the *PON1* gene as a risk factor for insulin resistance and metabolic syndrome in Mexican children. The study determined that for this population, the R allele of the *PON1* Q192R polymorphism was not an independent risk factor for the development of myocardial infarction (p<0.005) (46). Gamboa et al. (13), Pérez-Herrera et al. (47), Rojas-García et al. (48), and other studies in Chinese, Afro-American, and other Mexican populations demonstrated that individuals with the *PON1* 192RR genotype had lower levels of HDL cholesterol than 192QQ genotype carriers. These results are similar to those in our control group. Hence, these data suggest that *PON1* polymorphisms affect HDL cholesterol levels Although we did not find significant differences in the *PON1* Q192R genotype distribution and allele frequencies between patients and control subjects, in the control group, we observed a negative correlation between the Q192R polymorphism and HDL cholesterol levels. This result may support the protective effect of *PON1* Q192R gene polymorphisms on HDL cholesterol levels in healthy individuals.

Increased levels of ROS and endogenous antioxidants are related to various diseases such as Parkinson's, Alzheimer's, CV disease, pulmonary disease, diabetes, ocular disorders, and cancer, as well as aging and radiation damage (49). Nakanishi et al. (19) investigated the effects of the *MNSOD* Ala16Val polymorphism on the development of type 2 diabetes mellitus. Of 523 nondiabetic cases, only 65 developed type 2 diabetes during the 9.9-year-follow-up period. However, the number of homozygous TT genotype carriers (n=55) was higher than that of CC genotype carriers (n=10) in patients with type 2 diabetes mellitus. Therefore, they concluded that the *MNSOD* Ala16Val polymorphism plays an important role in the development of diabetes (p=0.041) (19). Li et al. (20) also demonstrated that *MNSOD* rs4880 gene variants confer an increased risk of type 2 diabetes mellitus to the Chinese Han population, whereas Nomiyama et al. (50) reported that Ala16Val allele frequency differences were not statistically significant between diabetic and nondiabetic patients in the Japanese population. Mitochondrial oxidative stress plays a key role in beta cell dysfunction, insulin resistance, and glucose tolerance, which leads to diabetes mellitus (20). Our data suggest that *MNSOD* Ala16Val polymorphisms impacts oxidative metabolism and increases the risk of diabetic dyslipidemia.

Study limitations

The main limitation of our study was the lack of whole-gene sequencing for *LPL*, *LIPC*, *SCARB1*, *LCAT*, *CETP*, *ADIPOQ*, *RETN*, and *MNSOD* genes. However, all studied SNPs were well-known mutations associated with either dyslipidemia and/or CV disease.

Conclusion

LPL (rs320), *LIPC* (rs2070895), *SCARB* (rs5888), *LCAT* (rs2292318), *CETP* (rs708272), *ADIPOQ* (rs1501299), *RETN* (rs3745367), and *MNSOD* (rs4880) gene polymorphisms can be used as markers for the early detection of diabetic dyslipidemia. We believe that further studies are necessary to determine the effects of other enzyme-coding gene polymorphisms and interactions on plasma lipid concentrations. Although the exact molecular mechanisms of diabetic dyslipidemia are not yet fully understood, our study results will guide further investigations to elaborate the development of diabetic dyslipidemia.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – A.T.V., E.H., A.Z., Z. E., V.B.Ç.; Design – A.T.V., Z.E.; Supervision – A.T.V., Z.E., M.K.; Materials – E.H., E.V.; Data collection &/or processing – A.T.V., E.H., A.Ş.K., E.V., M.K.; Analysis &/or interpretation – A.T.V., M.K.; Literature search – A.Z., A.Ş.K., V.B.Ç.; Writing – A.T.V., M.K.; Critical review – A.Z., Z.E., V.B.Ç., E.V., A.Ş.K.

References

1. http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf.
2. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab 2009; 5: 150-9. [CrossRef]
3. Corella D, Ordovas JM. Single nucleotide polymorphisms that influence lipid metabolism: Interaction with Dietary Factors. Annu Rev Nutr 2005; 25: 341-90. [CrossRef]
4. Manica-Cattani MF, Cadoná FC, Oliveira Rd, Silva Td, Machado AK, Barbisan F, et al. Impact of obesity and Ala16Val MnSOD polymorphism interaction on lipid, inflammatory and oxidative blood biomarkers. Open Journal of Genetics 2012; 2: 1- 8. [CrossRef]
5. El-Shala AS, Pashaa HF, Rashad NM. Association of resistin gene polymorphisms with insulin resistance in Egyptian obese patients. Gene 2013; 515: 233-8. [CrossRef]
6. Boes E, Coassin S, Kollerits B, Heid IM, Kronenberg F. Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: a systematic in-depth review. Exp Gerontol 2009; 44: 136-60.
7. Daoud MS, Ataya FS, Fouad D, Alhazzanı A, Shehata AI, Al-Jafari AA. Associations of three lipoprotein lipase gene polymorphisms, lipid profiles and coronary artery disease. Biomed Rep 2013; 1: 573-82.
8. Qi Y, Liu J, Wang W, Wang M, Sun J, Liu J, et al. The HindIII polymorphism in the lipoprotein lipase gene predicts type 2 diabetes risk among Chinese adults. Clin Chim Acta 2011; 412: 1229-33. [CrossRef]
9. Ghanei A, Esfananian F, Esteghamati A, Behjati J, Hamidi S, Nakhjavani M. Lecithin cholesterol acyltransferase activity is decreased in type 2 diabetes mellitus. Acta Medica Iranica 2007; 45: 481-6.
10. Chung HK, Chae JS, Hyun YJ, Paik JK, Kim JY, Jang Y, et al. Influence of Adiponectin Gene Polymorphisms on Adiponectin Level and Insulin Resistance Index in Response to dietary intervention in overweight-obese patients with impaired fasting glucose or newly diagnosed type 2 Diabetes. Diabetes Care 2009; 32: 552-8. [CrossRef]
11. McTernan PG, McTernan CL, Chetty R, Jenner K, Fisher FM, Lauer MN, et al. Increased resistin gene and protein expression in human abdominal adipose tissue. J Clin Endocrinol Metab 2002; 87: 2407.

12. Ma X, Warram JH, Trischitta V, Doria A. Genetic variants at the resistin locus and risk of type-2 diabetes in Caucasians. J Clin Endocrinol Metab 2002; 87: 4407-10. [CrossRef]
13. Gamboa R, Zamora J, Rodriguez-Perez JM, Fragoso JM, Cardoso G, Posadas-Romero C, et al. Distribution of paraoxonase PON1 gene polymorphisms in Mexican populations. Its role in the lipid profile. Exp Mol Pathol 2006; 80: 85-90. [CrossRef]
14. Dixit M, Bhattacharya S, Mittal B. Association of CETP TaqI and APOE polymorphisms with type II diabetes mellitus in North Indians: a case control study. BMC Endocr Disord 2005; 5: 7. [CrossRef]
15. Carlquist JF, Muhlestein JB, Horne BD, Hart NI, Bair TL, Molhuizen HO, et al. The cholesteryl ester transfer protein Taq1B gene polymorphism predicts clinical benefit of statin therapy in patients with significant coronary artery disease. Am Heart J 2003; 146: 1007-14.
16. Constantineau J, Greason E, West M, Filbin M, Kieft JS, Carletti MZ, et al. A synonymous variant in scavenger receptor, class B, type I gene is associated with lower SR-BI protein expression and function. Atherosclerosis 2010; 210: 177-82. [CrossRef]
17. Todorova B, Kubaszek A, Pihlajamäki J, Lindström J, Eriksson J, Valle TT, et al. The G-250A Promoter Polymorphism of the Hepatic Lipase Gene Predicts the Conversion from Impaired Glucose Tolerance to Type 2 Diabetes Mellitus: The Finnish Diabetes Prevention Study. J Clin Endocrinol Metab 2004; 89: 2019-23. [CrossRef]
18. Meng L, Ruixing Y, Yiyang L, Xingjiang L, Kela L, Wanying L, et al. Association of LIPC -250G>A polymorphism and several environmental factors with serum lipid levels in the Guangxi Bai Ku Yao and Han populations. Lipids Health Dis 2010; 9: 28. [CrossRef]
19. Nakanishi S, Yamane K, Ohishi W, Nakashima R, Yoneda M, Nojima H, et al. Manganese superoxide dismutase Ala16Val polymorphism is associated with the development of type 2 diabetes in Japanese-Americans. Diabetes Res Clin Pract 2008; 81: 381-5. [CrossRef]
20. Li JY, Tao F, Wu XX, Tan YZ, He L, Lu H. Polymorphic variations in manganese superoxide dismutase (MnSOD) and endothelial nitric oxide synthase (eNOS) genes contribute to the development of type 2 diabetes mellitus in the Chinese Han population. Genet Mol Res 2015; 14: 12993-3002. [CrossRef]
21. Ariza MJ, Sanchez-Chaparro MA, Baron FJ, Hornos AM, Calvo-Bonacho E, Rioja J, et al. Additive effects of LPL, APOA5 and APOE variant combinations on triglyceride levels and hypertriglyceridemia: results of the ICARIA genetic sub-study. BMC Med Genet 2010; 11: 66. [CrossRef]
22. Pare´ G, Serre D, Brisson D, Anand SS, Montpetit A, Tremblay G, et al. Genetic analysis of 103 candidate genes for coronary artery disease and associated phenotypes in a founder population reveals a new association between endothelin-1 and high-density lipoprotein cholesterol. Am J Hum Genet 2007; 80: 673-82. [CrossRef]
23. Roberts CG, Shen H, Mitchell BD, Damcott CM, Shuldiner AR, Rodriguez A. Variants in scavenger receptor class B type I gene are associated with HDL cholesterol levels in younger women. Hum Hered 2007; 64: 107-13. [CrossRef]
24. Stanislovaitiene D, Lesauskaite V, Zaliuniene D, Smalinskiene A, Gustiene O, Zaliaduonyte-Peksiene D, et al. SCARB1 single nucleotide polymorphism (rs5888) is associated with serum lipid profile and myocardial infarction in an age- and gender-dependent manner. Lipids Health Dis 2013; 12: 24. [CrossRef]
25. McCarthy JJ, Somji A, Weiss LA, Steffy B, Vega R, Barret-Connor E, et al. Polymorphisms of the scavenger receptor class B Member 1 are associated with insulin resistance with evidence of gene by sex interaction. J Clin Endocrinol Metab 2009; 94: 1789-96. [CrossRef]
26. Tai ES, Ordovas JM, Corella D, Deurenberg-Yap M, Chan E, Adiconis X, et al. The Taq IB and -629C>A polymorphisms at the cholesteryl ester transfer protein locus: associations with lipid levels in a multiethnic population. The 1998 Singapore National Health Survey. Clin Genet 2003; 63: 19-30. [CrossRef]
27. Yılmaz H, Agaçhan B, Karaali ZE, İsbir T. Taq1B polymorphism of CETP gene on lipid abnormalities in patients with type II diabetes mellitus. Int J Mol Med 2004; 13: 889-93. [CrossRef]
28. Ağırbaşlı M, Eren F, Ağırbaşlı D, White MJ, Williams SM. Multilocus candidate gene analyses of lipid levels in a pediatric Turkish cohort: lessons learned on LPL, CETP, LIPC, ABCA1, and SHBG. OMICS 2013; 17: 636-45. [CrossRef]
29. White MJ, Eren F, Ağırbaşlı D, Chen J, Hu T, Moore JH, et al. A systems genetics approach to dyslipidemia in children and adolescents. OMICS 2015; 19: 248-59. [CrossRef]
30. Tsai MK, Wang HMD, Shiang JC, Chen H, Wang CC, Shiao YF, et al. Sequence Variants of ADIPOQ and Association with Type 2 Diabetes Mellitus in Taiwan Chinese Han Population. The Scientific World Journal 2014; 2014: 1-7. [CrossRef]
31. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003; 46: 459-69. [CrossRef]
32. Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, et al. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 2003; 52: 239-43.
33. Comuzzie A, Funahashi T, Sonnenberg G, Martin LJ, Jacob HJ, Black AE, et al. The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. J Clin Endocrinol Metab 2001; 86: 4321-5. [CrossRef]
34. Menzaghi C, Ercolino T, Salvemini L, Coco A, Kim SH, Fini G, et al. Multigenic control of serum adiponectin levels: evidence for a role of the APM1 gene and a locus on 14q13. Physiol Genomics 2004; 19: 170-4. [CrossRef]
35. Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, et al. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. Diabetes 2002; 51: 536-40. [CrossRef]
36. Zacharova J, Chiasson JL, Laakso M. The Common Polymorphisms (Single Nucleotide Polymorphism [SNP] _45 and SNP _276) of the Adiponectin Gene Predict the Conversion From Impaired Glucose tolerance to Type 2 Diabetes The STOP-NIDDM Trial. Diabetes 2005; 54: 893-9. [CrossRef]
37. Ramya K, Ayyappa KA, Ghosh S, Mohan V, Radha V. Genetic association of ADIPOQ gene variants with type 2 diabetes, obesity and serum adiponectin levels in south Indian population. Gene 2013; 532: 253-62. [CrossRef]
38. Tsai MK, Wang HM, Shiang JC, Chen IH, Wang CC, Shiao YF, et al. Sequence Variants of ADIPOQ and Association with Type 2 Diabetes Mellitus in Taiwan Chinese Han Population. ScientificWorldJournal 2014; 2014: 650393. [CrossRef]
39. Tu Y, Yu Q, Fan G, Yang P, Lai Q, Yang F, et al. Assessment of type 2 diabetes risk conferred by SNPs rs2241766 and rs1501299 in the ADIPOQ gene, a case/control study combined with meta-analyses. Mol Cell Endocrinol 2014; 396: 1-9. [CrossRef]
40. Fehmann HC, Heyn J. Plasma resistin levels in patients with Type 1 and Type-2 diabetes mellitus and in healthy controls. Horm Metab Res 2002; 34: 671-3. [CrossRef]
41. Ochi M, Osawa H, Onuma H, Murakami A, Nishimiya T, Shimada F. The absence of evidence for major effects of the frequent SNP +299G>A in the resistin gene on susceptibility to insulin resistance syndrome associated with Japanese type-2 diabetes. Diabetes Res Clin Pract 2003; 61: 191-8. [CrossRef]

42. Chung CM, Lin TH, Chen JW, Leu HB, Yin WH, Ho HY, et al. Common quantitative trait locus downstream of RETN gene identified by genome-wide association study is associated with risk of type 2 diabetes mellitus in Han Chinese: a Mendelian randomization effect. Diabetes Metab Res Rev 2014; 30: 232-40. [CrossRef]
43. Li J, Wang X, Huo Y, Niu T, Chen C, Zhu G, et al. PON1 polymorphism, diabetes mellitus, obesity, and risk of myocardial infarction: Modifying effect of diabetes mellitus and obesity on the association between PON1 polymorphism and myocardial infarction. Genet Med 2005; 7: 58-63. [CrossRef]
44. Scacchi R, Corbo RM, Rickards O, De Stefano GF. New data on the world distribution of paraoxonase (PON1 Gln 192 --> Arg) gene frequencies. Hum Biol 2003; 75: 365-73. [CrossRef]
45. Alegria-Torres JA, Garcia-Dominguez ML, Cruz M, Aradillas-Garciac C. Q192R Polymorphism of Paraoxonase 1 Gene Associated with insulin resistance in Mexican Children. Arch Med Res 2015; 46: 78-83. [CrossRef]
46. Aubo C, Senti M, Marrugat J, Tomas M, Vila J, Sala J, et al. Risk of myocardial infarction associated with Gln/Arg 192 polymorphism in the human paraoxonase gene and diabetes mellitus. Eur Heart J 2000; 21: 33-8. [CrossRef]
47. Perez-Herrera N, May-Pech C, Hernandez-Ochoa I, Castro-Mane J, Rojas-Garcıa E, Borja-Aburto VH, et al. PON1 Q192R polymorphism is associated with lipid profile in Mexican men with Mayan ascendancy. Exp Mol Pathol 2008; 85: 129-34. [CrossRef]
48. Rojas-Garcia AE, Solis-Heredia MJ, Pina-Guzman B, Vega L, Lopez-Carrillo L, Quintanilla-Vega B. Genetic polymorphisms and activity of PON1 in a Mexican population. Toxicol Appl Pharmacol 2005; 205: 282-9. [CrossRef]
49. Borrelli A, Schiattarella A, Bonelli P, Tuccillo FM, Buonaguro FM, Mancini A. The Functional Role of MnSOD as a Biomarker of Human Diseases and Therapeutic Potential of a New Isoform of a Human Recombinant MnSOD. BioMed Res Int 2014; 2014: 476789. [CrossRef]
50. Nomiyama T, Tanaka Y, Piao L, Nagasaka K, Sakai K, Ogihara T, et al. The polymorphism of manganese superoxide dismutase is associated with diabetic nephropathy in Japanese type 2 diabetic patients. J Hum Genet 2003; 48: 138-41.

From Prof. Dr. Arif Akşit's collections