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Peroxisome Proliferator-activated Receptor-alpha (*PPARA*) and – Gamma (*PPARG*) Polymorphisms as Risk Factors for Dyslipidemia and MetS in Turkish Adults

Filiz Guclu-Geyik[1], Evrim Komurcu-Bayrak[1,2], Gunay Can[3], Nihan Erginel-Unaltuna[1]

[1]Department of Genetics, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkiye
[2]Departments of Medical Genetics, Istanbul Faculty of Medicine, Istanbul University Istanbul, Turkiye
[3]Department of Public Health, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkiye

ORCID ID: F.G.G. 0000-0003-4257-9930; E.K.B. 0000-0003-1271-1208; G.C. 0000-0001-5815-6700; N.E.U. 0000-0003-0562-0455

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ABSTRACT

Objective: Dyslipidemia and metabolic syndrome (MetS) are complex diseases affected by environmental factors such as lifestyle and genetic predisposition. The genes encoding peroxisome proliferator-activated receptor-gamma (*PPARG*) and alpha (*PPARA*) are crucial in the development of dyslipidemia and MetS. We aimed to investigate the relation of these genes with dyslipidemia and MetS in the Turkish adult population.

Materials and Methods: The Turkish Adult Risk Factor (TARF-TEKHARF) cohort was randomly selected, and a cross-sectional analysis was performed. The *PPARA* rs1800206 C>G genotypes were determined in a sample of 339 unrelated Turkish adults by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and 12% polyacrylamide gel electrophoresis (PAGE) methods. The PPARG rs1801282 C>G genotypes were determined in a sample of 436 unrelated Turkish adults by a PCR-RFLP method.

Results: Both single nucleotide polymorphisms (SNPs) minor alleles were related to a risk of dyslipidemia. Logistic regression analysis showed a significantly increased risk for dyslipidemia in G allele carriers of rs1800206 C>G (Odds Ratio (OR)= 3.26; 95% CI= 1.16-9.12), and in G risk allele carriers of rs1801282 (OR= 1.85; 95% CI= 1.07-3.19), after adjustment for age, gender, lipid-lowering medication usage, physical activity and smoking status. Regarding MetS risk in the TARF study group, the G-allele of rs1800206 PPARA gene exhibited a significant OR of 3.75, after adjustment for gender, age, smoking status, and physical activity.

Conclusion: The G alleles of the studied SNPs in the *PPARA* and *PPARG* genes are related to increased dyslipidemia risk. Furthermore, The G allele of the *PPARA* gene is related to increased MetS risk.

Keywords: Dyslipidemia, metabolic syndrome, *PPARA*, *PPARG* and Turkish adults

INTRODUCTION

Cardiometabolic disorders are common public health issues, including metabolic syndrome (MetS), dyslipidemia, diabetes mellitus (DM), obesity, and hypertension (HT). The prevalence of MetS and dyslipidemia increases worldwide, with age and with changes in people's lifestyle (such as lack of physical activity and nutritional changes) in different ethnic groups and genders (1-4). MetS is a complicated disease characterized by the cluster co-existence of many cardiovascular risk factors. It is described by the co-instantaneous presence of abdominal obesity, disrupted glucose tolerance, atherogenic dyslipidemia, hypertension, and insulin resistance (5-7). This combination also leads to the development of DM and/or cardiovascular diseases (8). The dyslipidemia refers to a condition characterized by

Corresponding Author: Filiz Geyik **E-mail:** gfiliz@istanbul.edu.tr
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elevated levels of triglycerides (TG), total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), as well as low high-density lipoprotein cholesterol (HDL-C) levels. Environmental and genetic variables combine to determine the complicated etiology of dyslipidemia and MetS.

Members of the nuclear hormone receptor superfamily 1, peroxisome proliferator-activated receptors (PPARs) are transcription factors that are activated by ligands and play a crucial role in the regulation and continuation of energy balance (9,10). In humans, PPAR has three isotypes: PPAR-alpha (PPARα), PPAR-gamma (PPARγ) and PPAR-delta (PPARδ). These isotypes have various target genes, biological functions, and roles, and they each bind to different ligands. Each isotope is encoded by different genes. PPARα is encoded by the PPAR-alpha *(PPARA*) gene, which is located on human chromosome 22q12.2-13.1 (11). It affects carbohydrate and lipid metabolism through regulation of the expression of genes related to the transportation, β oxidation, and catabolism of triglycerides (12-14).

The PPAR-gamma (PPARG) gene, located on chromosome 3p25.2, modulates the transcription of several genes related to adipocyte separation and insulin-mediated glucose absorption in a variety of tissues (15). PPARγ controls glucose metabolism by lowering free fatty acids and increasing the activity of insulin (16).

Recently, a growing number of studies have shown that *PPARA* and *PPARG* gene polymorphisms may be genetic markers for complex diseases such as MetS, DM, obesity, and hyperlipidemia, which develop as a result of disorders of glucose and lipid metabolism. The Human *PPARA* and *PPARG* genes contain thousands of polymorphic loci, among them two exonic polymorphisms (rs1801282 and rs1800206) in *PPARG* and *PPARA* genes, respectively, were reported to be significantly associated with MetS, dyslipidemia, DM and obesity in different populations worldwide. The rs1801282 (also named rs1805192) polymorphism in *PPARG* gene is a C to G transversion at position 34 in exon 2 (NM_001354668.2, c.34C>G), leading to a substitution of alanine from proline at codon 12 (p.Pro12Ala), which has been shown to regulate the transcriptional activity of the *PPARG* (17) and is linked to distorted insulin sensitivity (18).

The rs1800206 missense polymorphism is located at position 484 in exon 5 (NM_005036.6, c.484C>G) of the *PPARA* gene and causes an amino acid change from leucine to valine at codon 162 (p.Leu162Val), which has functional effects on PPARα activity (19-22).

The associations between the rs1801282 and rs1800206 polymorphisms and their implications in MetS, dyslipidemia, obesity, DM, and HDL-C and LDL-C metabolism have been documented in Caucasian, Asian, and American populations, in several case-control, GWAS, and meta-analysis studies. However, the findings are still controversial (23-34). The influence of *PPARG* (rs1801282) and *PPARA* (rs1800206) polymorphisms, if any, on dyslipidemia and MetS is unknown for the Turkish adult population. As a result, we focused on examining the association between the rs1800206 C>G polymorphism at the *PPARA* and rs1801282 C>G polymorphism at the *PPARG* locus with dyslipidemia and MetS in the TARF study (TEKHARF), which is composed of Turkish adults.

MATERIALS AND METHODS

Study Subjects

The Turkish Adult Risk Factor Study (TARF-TEKHARF) design and methodology have previously been detailed (35). In summary, participants were chosen at random from residents of seven distinct locations in Turkiye and they participated in five surveys that were conducted between 2005 and 2009. A survey was used to collect information on the patient's prior history, as well as an assessment of the cardiovascular system and blood sampling.

The study encompassed unrelated individuals who provided a written agreement to take part in the investigation after being made aware of its purpose. *PPARG* and *PPARA* genotypes were examined in unselected individuals 436 and 339, respectively. The inclusion of different numbers of individuals in the study for two single nucleotide polymorphisms (SNPs) is due to the fact that 97 individuals could not be genotyped for *PPARA*. The Istanbul University Ethics Committee agreed to the study protocol (Date of last version: February 18, 2009/No:2005/446 and date of first version: May 04, 2005/No:2005/446).

Risk Variable Measurement

Obesity parameters (weight, height, waist circumference, and body mass index (BMI) calculation) and other variables (blood pressure, cigarette and alcohol use, physical activity) have previously been detailed (36).

Definitions

A body mass index of 30 kg/m^2 or more was considered obese. The combined presence of high triglyceride (>150 mg/dL) and low HDL-C (<40/<50 mg/dL; male/female) levels were referred to as dyslipidemia (37). A blood pressure reading of at least 140 mmHg over 90 mmHg, as well as the usage of antihypertensive medication, were considered hypertension.

According to the American Diabetes Association's guidelines (38), a person was diagnosed with diabetes if their plasma fasting glucose level was 126 mg/dL or their 2-hour postprandial glucose level was 200 mg/dL, and if they reported using diabetes medication now (39).

When three of the five National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria were identified, a person was diagnosed with MetS (37).

Genetic Analyses

SNPs Genotyping

The genomic DNA extraction method has been previously detailed (36). The *PPARA* rs1800206 C>G (Leu162Val) genotype was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and 12% polyacrylamide gel electrophoresis (PAGE) methods. The mismatch PCR technique was used to genotype the rs1800206 C>G polymorphism. The mutant allele primer was designed to have a HinfI restriction site that was removed in the presence of C at position 484. The sequences of the primers used were as follows: *PPARA* forward primer: 5′- ACT CAA GCT GGT GTA TGA CA -3′, *PPARA* reverse primer: 5′- TGTGTGACATCCCGACAGAAT -3′. When digesting the PCR product with HinfI, the mutant allele yields two fragments of 93 bp and 20 bp, while the normal allele yields a fragment of 113 bp in PAGE. PCR-RFLP was used for the *PPARG* rs1801282 C>G (Pro12Ala) genotype determination as previously reported (40).

Statistical Analyses

SPSS version 21 was used to perform all statistical analyses. Pearson's Chi-square test was used to compare genotype and allele distributions. To the expected genotype distribution, the Hardy Weinberg equilibrium (HWE) was calculated. A dominant model (specified as CC vs. CG+GG) was used to assess genotype-phenotype associations for both polymorphisms due to the small number of people with the GG genotype.

For categorical variables, the Chi-square test was applied, while two-tailed t-tests and analysis of variance tests were employed for continuous variables. Covariance analysis utilized logistic regression models. p-values <0.05 were considered significant.

RESULTS

PPARG rs1801282 and *PPARA* rs1800206 Genotypes and Allele Distribution

Table 1 describes the details of the genotyped SNPs, including genomic, cDNA and amino acid positions. *PPARA* and *PPARG* genes are located at chromosome positions 22q13 and 3p25, respectively. A genotype distribution of rs1801282 was found in 436 individuals of the TARF study cohort (Table 1). The minor allele frequency (MAF) of the rs1801282 G allele in the Turkish adults was 0.08 and the frequencies of genotypes were in HWE ($p > 0.05$).

The genotype distribution of the rs1800206 *PPARA* polymorphism was 95.6% (n=323), 4.7% (n=16) and 0% (n=0) for the CC, CG and GG genotypes respectively in the Turkish adults (n=339), the G allele frequency was 0.02 (Table 1). The genotype frequencies of the rs1800206 polymorphism were in HWE ($p > 0.05$).

Effects of the *PPARG* rs1801282 and *PPARA* rs1800206 Polymorphisms on Dyslipidemia and MetS

The distribution of the genotype frequencies of *PPARG* rs1801282 C>G between the groups of dyslipidemia and non-dyslipidemia were significantly different in the study group, with the genotypes CC+CG being more frequent in dyslipidemia compare with non-dyslipidemia individuals *(*p=0.043*)* (Table 2). Table 3 shows that, in logistic regression analysis, after adjusting for gender, age, lipid lowering medication usage, smoking status, and physical activity, the rs1801282 G allele has a strong association with dyslipidemia in the adult Turkish population. (OR=1.85, p=0.028).

The genotype frequencies of *PPARA rs1800206 C>G* polymorphism were obviously significantly different in individuals with both dyslipidemia and MetS in the TARF study population (p=0.023 and p=0.024, respectively), the

Table 1. Description, genotypic, and allelic frequencies of the two polymorphisms in PPARs genes studied in this study

Gene	Description of SNPs			Genotype frequency			Allele frequency		
	Genomic position	cDNA and amino acid position	rsID	CC % (n)	CG % (n)	GG % (n)	C %	G %	*p**
PPARG	chr3:12351626 (GRCh38.p14)	c. 34C>G (p.Pro12Ala)	rs1801282	83.4 (366)	15.9 (70)	0.7 (3)	0.9134	0.0866	0.8614
PPARA	chr22:46218377 (GRCh38.p14)	c.484C>G (p.Leu162Val)	rs1800206	95.3 (323)	4.7 (16)	0 (0)	0.9764	0.0236	0.6563

*Frequencies are computed using the Chi-square test

Table 2. Association analysis of the *PPARG* rs1801282 and *PPARA* rs1800206 genotypes with metabolic and clinical status, including risk factors for cardiovascular diseases.

Characteristics	***PPARG* rs1801282 (n=436)**			***PPARA* rs1800206 (n=339)**		
	Genotypes			**Genotypes**		
	CC	**CG +GG**	**p**	**CC**	**CG +GG**	**p**
Age (years)	51.32 ± 13.0 (366)	50.71 ± 12.4 (70)	0.722	51.27 ± 13.1 (323)	50.56 ± 12.2 (16)	0.835
Waist circumference (cm)	92.9 ± 12.3 (344)	94.5 ± 13.1 (69)	0.371	92.9 ± 12.5 (304)	97.0 ± 8.5 (16)	0.066
Body mass index (kg/m^2)	28.38 ± 4.7 (3339	29.38 ± 5.8 (66)	0.198	28.59 ± 4.8 (292)	29.11 ± 3.5 (169)	0.587
Systolic BP (mmHg)	129.83 ± 23.4 (345)	130.25 ± 20.2 (69)	0.880	129.41 ± 21.7 (305)	125.75 ± 15.5 (16)	0.382
Diastolic BP (mmHg)	82.32 ± 13.3 (345)	83.87 ± 13.0 (69)	0.378	82.53 ± 12.8 (305)	82.56 ± 13.7 (16)	0.993
Apolipoprotein A-I (mg/dL)	131.97 ± 28.8 (226)	126.27 ± 26.03 (48)	0.181	131.71 ± 28.18 (2129)	118.57 ± 38.9 (13)	0.253
Apolipoprotein B (mg/dL)	108.05 ± 34.2 (207)	112.57 ± 32.2 (44)	0.406	109.2 ± 33.8 (196)	115.5 ± 29.5 (12)	0.539
Total Cholesterol (mg/dL)	188.38 ± 41.7 (346)	187.58 ± 44.6 (69)	0.886	186.59 ± 40.6 (306)	200.2 ± 50.9 (16)	0.309
HDL-Cholesterol (mg/dL)	42.81 ± 12.6 (346)	40.38 ± 10.9 (69)	0.106	42.52 ± 12.6 (306)	39.17 ± 8.4 (16)	0.149
LDL-Cholesterol (mg/dL)	114.66 ± 35.3 (342)	114.95 ± 37.6 (69)	0.954	113.41 ± 33.9 (304)	126.46 ± 48.9 (16)	0.308
Triglycerides † (mg/dL)	128.8 ± 1.76 (346)	141.2 ± 1.69 (69)	0.232	128.8 ± 1.74 (306)	120.2 ± 1.72 (16)	0.263
C-reactive protein,† mg/L	2.23 ± 2.9 (221)	2.23 ± 4.4 (40)	0.971	2.23 ± 3.1 (209)	2.23 ± 1.6 (8)	0.598
Glucose (mg/dL)	100.53 ± 30.6 (336)	97.89 ± 27.9 (67)	0.349	101.5 ± 32.5 (305)	88.89 ± 10.5 (16)	**0.000**
Insulin (IU/L)	0.90 ± 0.292 (206)	1.00 ± 0.306 (46)	**0.044**	0.92 ± 0.296 (215)	0.87 ± 0.298 (10)	0.566
HOMA Index †	1.90 ± 1.61 (193)	2.34 ± 2.1 (45)	0.084	2.04 ± 2.1 (202)	1.54 ± 1.9 (10)	0.232
Clinical status **Prevalence, % (n)**						
Sex						
Male	49.7 (192)	44.3 (31)	0.404	94.4 (153)	5.5 (9)	0.488
Female	50.3 (184)	55.7 (39)		96.0 (170)	4.0 (7)	
Obesity						
No	83.8 (217)	16.2 (42)	0.812	95.0 (188)	5.0 (10)	0.878
Yes	82.8 (116)	17.1 (24)		94.5 (104)	5.5 (6)	
Type 2 Diabetes						
No	83.4 (322)	16.6 (64)	0.406	94.6 (284)	5.3 (16)	0.140

Yes	88 (44)	12 (6)		100.0 (39)	0.0 (0)	
Metabolic syndrome						
No	86.5 (192)	13.5 (30)	0.141	**97.8 (174)**	**2.2 (4)**	**0.024**
Yes	81.3 (174)	18.7 (40)		**92.5 (149)**	**7.5 (12)**	
Dyslipidemia						
No	**85.8 (248)**	**14.2 (41)**	**0.043**	**96.9 (216)**	**3.10 (7)**	**0.023**
Yes	**77.7 (98)**	**22.2 (28)**		**90.9 (90)**	**9.10 (9)**	
Hypertension						
No	84.3 (220)	15.7 (41)	0.810	96.1 (199)	3.9 (8)	0.353
Yes	83.4 (146)	16.6 (29)		93.9 (124)	6.1 (8)	
Diabetes medication usage	91.4 (32)	8.6 (3)	0.209	100 (25)	0.0 (0)	0.248
Lipid lowering medication usage	100 (17)	0.0 (0)	0.066	92.9 (15)	7.1 (1)	0.662
Alcohol consumption	5.8 (20)	11.6 (8)	0.081	5.6 (17)	6.3 (1)	0.909
Low Physical activity	31.3 (108)	21.7 (15)	0.112	27.2 (83)	43.8 (7)	0.151
Smoking status	44.0 (152)	42.0 (29)	0.765	42.9 (131)	43.75 (7)	0.651

Strong relationships are bolded and deemed significant at $p < 0.05$.

Dichotomous variables are shown as percentages, and continuous variables are shown as mean ± SD. Means were compared using a two-tailed t test, and percentages were compared using a chi-square test.

BP; blood pressure

† Log-transformed variables expressed in geometric values.

Table 3. Adjusted association by logistic regression of *PPARG* rs1801282 and *PPARA* rs1800206 genotypes with dyslipidemia and MetS.

Genotypes	Risk of Dyslipidemia		Risk of MetS	
	OR (95%CI)	p*	OR (95%CI)	p**
***PPARG*, rs1801282**				
CC (n=345)	1		1	
CG + GG (n=69)	**1.85 (1.070 - 3.197)**	**0.028**	1.46 (0.852 - 2.522)	0.168
***PPARA*, rs1800206**				
CC (n=305)	1		1	
CG + GG (n=16)	**3.26 (1.165 - 9.128)**	**0.024**	**3.75 (1.156 - 12.167)**	**0.028**

Odds ratios were calculated regarding the presence of the minor allele. CI: Confidence interval, OR: odds ratio, n: Number of individuals, p* age, gender, physical activity, currently smoking, lipid lowering medication usage, p** age, gender, physical activity, smoking status.

Table 4. Association analysis of the of *PPARG* rs1801282 and *PPARA* rs1800206 interaction with dyslipidemia and MetS.

	Dyslipidemia		MetS	
	p	**OR (95% CI)**	**p**	**OR (95% CI)**
Age	0.506	1.00 (0.98 - 1.02)	**0.003**	1.03 (1.01 - 1.05)
Gender	0.520	0.80 (0.42 - 1.54)	0.424	1.27 (0.70 - 2.32)
Smoking status	0.134	1.65 (0.85 - 3.18)	0.386	1.31 (0.76 - 2.45)
Physical activity	0.508	0.81 (0.44 - 1.49)	0.593	1.16 (0.66 - 2.06)
Rs1801282				
G allele	**0.020**	**2.09 (1.12 - 3.88)**	0.054	1.84 (0.99 - 3.46)
Rs1800206				
G allele	**0.025**	**3.29 (1.16 - 9.29)**	**0.028**	**3.76 (1.15 - 12.26)**

Odds ratios were calculated regarding the presence of the minor allele. CI: Confidence interval, OR: odds ratio, n: Number of individuals; strong relationships are bolded and deemed significant at $p < 0.05$

genotypes CG+GG being more common in dyslipidemia than in non-dyslipidemia individuals and in MetS than in non-MetS individuals (Table 2). The logistic regression analysis demonstrates a significant association between the rs1800206 G allele and dyslipidemia after adjusting for gender, age, smoking status, physical activity, and use of lipid-lowering medications (OR=3.26, p=0.024) (Table 3). In logistic regression analysis, the G-allele had a significant OR of 3.75 for MetS risk in the TARF population after adjustment for age, gender, physical activity and smoking status (p=0.028).

We further investigated a genotype interaction between *PPARG* rs1801282 C>G and *PPARA* rs1800206 C>G polymorphisms for the risk of dyslipidemia and MetS. The *PPARA* rs1800206 G allele showed a significant OR of 3.76 (p= 0.028) for the risk of MetS, and an OR of 3.29 (p=0.025) for the risk of dyslipidemia after adjustment for gender, age, physical activity, smoking status and *PPARG* rs1801282 G (Table 4). The *PPARG* rs1801282 G allele showed borderline significance for the risk of MetS (OR=1.84, p=0.054) and a significant risk for dyslipidemia (OR=2.09, p=0.020) after adjustment for gender, age, physical activity, smoking status and *PPARA* rs1800206 G (Table 4).

Effects of the *PPARG* rs1801282 and *PPARA* rs1800206 Polymorphisms on Metabolic Variables

We investigated the relation between *PPARGG rs1801282* C>G polymorphism and baseline characteristics (anthropometric and biochemical variables) of the TARF population (Table 2). In a crude analysis, there were no differences between HDL-C, LDL-C, total-C, triglycerides, C-reactive protein, glucose, HOMA index, apoB and apoA-1 concentrations and PPARG rs1801282 C>G genotypes, whereas there were substantial associations with insulin (p=0.044) (t-test). In analysis of covariance (ANCOVA) analysis, those with the CG+GG genotype did not exhibit significantly higher insulin levels (mean ± SD, 1.00 ± 0.306) compared with the CC carriers (mean ± SD, 0.90 ± 0.292) when adjusted for gender, age, smoking status, DM medication usage and physical activity (p>0.05).

We examined the relationship between the *PPARA* gene's rs1800206 C>G polymorphism and anthropometric and biochemical factors in the TARF population. A crude analysis revealed no differences with other variables, although there were statistically significant relationships with fasting glucose levels (p<0.001). When gender, age, physical activity, smoking status, and use of diabetes medication were taken into account, the significance of this association with regard to glucose concentrations was lost (p>0.05).

DISCUSSION

The relationships between the *PPARA rs1800206* C>G and *PPARG* rs1801282 C>G polymorphisms with MetS and dyslipidemia were examined in this population-based cross-sectional study using data from the Turkish adult representative TARF study. In Turkish adults, while carriage of the G allele of *PPARA* rs1800206 C>G polymorphism had exhibited significantly elevated risk for dyslipidemia (OR=3.26) and MetS (OR=3.75), carriage of the G allele of *PPARG* rs1801282 C>G polymorphism indicated significantly elevated risk only for dyslipidemia (OR=1.85).

The study's findings on the MAF of the *PRARA* gene rs1800206 C>G and PPARG rs1801282 C>G polymorphisms (2% and 8%, respectively) are comparable to those found in the 1000 Genomes Phase 3 combined population (https://www.internationalgenome.org /1000-genomes-browsers/index.html (last accessed July 2023). The minor G allele of the rs1800206 polymorphism shows a similar distribution among several populations (1-6% in African, South Asian, American, and European populations), but it has not been observed in East Asians. The distribution of the minor G allele of the rs1801282 polymorphism is similar in American, European and South Asian populations (12%), but is lower in African (1%) and East Asian (3%) populations. The MAF obtained for the two polymorphisms in this study was lower than in European populations.

Previous research has found conflicting associations between dyslipidemia or phenotypes associated with dyslipidemia and the rs1800206 C>G polymorphism of the *PPARA* gene. Bage et.al. found no significant association between rs1800206 C>G polymorphism of the *PPARA* gene and diabetic dyslipidemia among the South Indian population (30).

Gu et al. found that the G allele of rs1800206 was linked to an increased risk of dyslipidemia in 192 dyslipidemic patients compared to 628 controls in the Chinese Han population (28). In a similar study, Mazzotti et al. also found an association between the *PPARA* rs1800206 polymorphism and dyslipidemia in the 570 adult/elderly cohort from Cuiaba City (Brazilian populations) (24). Additionally, an association between rs1800206 C>G polymorphism and hypertriglyceridemia have been reported by Gu et al. in the 346 hypertriglyceridemia and 474 non-hypertriglyceridemia subjects from the prevention of MetS and multi-metabolic disorders in Jiangsu Province of China Study (26). In a Lithuanian study, it has been found that the CG genotype of the rs1800206 C>G polymorphism is associated with higher TG levels only in men with dyslipidemia (34). In diabetic patients, *PPARA* rs1800206 G allele carriers had higher HDL, apoA1, total cholesterol, and cholesterol (21). Our findings are in accordance with these positive results. The G allele of the *PPARA* rs1800206 C>G polymorphism increases the risk of dyslipidemia by 3.26-fold, regardless of age, gender, smoking status, physical activity and lipid-lowering medication usage in the adult Turkish population. PPARα activates proteins that control the binding and transport of fatty acids, and it controls genes involved in fatty acid oxidation (41) Consequently, it has been hypothesized that the rs1800206 polymorphism located in the *PPARA* gene's DNA binding domain might influence lipid metabolism, specifically TG levels (42).

The *PPARA* rs1800206 C>G polymorphism is strongly linked to the risk of MetS in addition to contributing to the development of dyslipidemia. MetS is characterized by abdominal obesity, glucose intolerance and dyslipidemia (5-7).

According to Robitaille et al., there may be a higher chance of developing certain components of the metabolic syndrome in carriers of the *PPARA* rs1800206 G allele. This suggests that the rs1800206 C>G polymorphism could regulate the relationship between dietary fat intake and abdominal obesity (29). Utjurraltta et al., identified an association between high TG and low HDL, both of which are components of the metabolic syndrome (43), and Smalinskiene et al., also found a relationship with TG as well (34). The majority of the r studies discussed above focus on the relationship between MetS components and the *PPARA* rs1800206 C>G polymorphism. Research exploring the link of this polymorphism with MetS revealed no association in the Malaysian population (31). Our study firstly examined the influence of *PPARA* rs1800206 C>G polymorphism on MetS in Turkish adults. Here, we find an independent relationship between the rs1800206 C>G polymorphism and MetS in adult Turkish individuals with an OR of 3.75.

Several studies evaluated genetic contributions of the *PPARG* rs1801282 C>G polymorphism to dyslipidemia and MetS. Results for dyslipidemia and MetS have been inconsistently associated with the *PPARG* rs1801282 C>G polymorphism. Gu et al. reported that the CG and GG genotypes of rs1801282 were associated with dyslipidemia (OR=1.77 and OR=2.96, respectively) in a Chinese Han population (28). In accordance with this positive finding, our results showed association between GG genotype of this polymorphism and dyslipidemia in Turkish adults (OR=1.85). In contrast, the absence of association of the rs1801282 genotypes with diabetic dyslipidemia among South Indian patients was reported by Bage et al. (30). Barbieri et al., discovered an inverse relationship between blood TG concentrations and the G allele of rs1801282 in Caucasian participants (44). Additionally, it has been demonstrated that the G allele is linked to decreased serum total HDL levels in a Japanese population (45). Gu et al., reported the association of the GG carrier genotype of *PPARG* rs1801282 and hypertriglyceridemia in MetS (27).

Studies investigating the association between *PPARG* rs1801282 C>G polymorphism and the risk of MetS in several populations have been inconsistent. According to Tellechea et al., those with the rs1801282 G allele, particularly non-smokers, are more likely to develop MetS and insulin resistance (46). Furthermore, compared to CC homozygotes, G carriers had greater BMI, waist circumference, and fat mass in The Québec Family Study, indicating that this polymorphism may be able to modify the relationship between dietary fat intake and elements of the MetS (47). Meirhaeghe et al., showed no link between the *PPARG* rs1801282 C>G polymorphism and MetS in a large French population (48). *PPARG* rs1801282 C>G polymorphism was not directly linked to MetS, according to Yang et al.'s study that included 423 individuals with MetS and families without the condition (49). Consistent with these results, middle-aged Swedish individuals who carried the G allele in the *PPARG* gene did not exhibit statistically significant differences in fasting glucose, TG, HDL-cholesterol, waist circumference, or blood pressure when compared to GG homozygotes (50). This suggests that the rs1801282 polymorphism in the *PPARG* gene does not play a significant role in determining the prevalence of MetS. Even after stratifying by ethnicity and MetS component, a meta-analysis of ten case-control studies revealed no statistically significant association between the rs1801282 polymorphism and MetS (51). In our study, no significant difference was observed in the distribution of *PPARG* rs1801282 genotypes in MetS, but the rs1801282 G allele confers a borderline risk for MetS independent from the *PPARA* rs1800206 G allele. We suggest that differences in association studies may be caused by the effects of other genes and variations in gender, physical activity, BMI, ethnicity, sample size, and study methodology.

The study contains limitations and strengths. One limitation of this study is the absence of information in our investigation regarding potential interactions between other genetic variations and *PPARA* and *PPARG* genotypes. Another limitation is that we are unable to analyze the two sexes independently due to the small sample size. The primary strength of this research is its population-based design, which enables assessment of the genetic and environmental influences on the relevant phenotypic.

To conclude, this study demonstrated that the *PPARA* rs1800206 and *PPARG* rs1801282 C>G polymorphisms were associated in Turkish adults with increased dyslipidemia risk, independent

of age, gender, physical activity, lipid-lowering medication usage and smoking status. The G allele of rs1800206 *PPARA,* which is a significant risk factor for MetS, is the stronger risk factor for dyslipidemia than the G allele of rs1801282 *PPARG*. Furthermore, *PPARA* rs1800206 polymorphism increases the risk of MetS. This association requires additional studies in large, well-characterized study populations.

Ethics Committee Approval: The Istanbul University Ethics Committee agreed to the study protocol (Date of last version: February 18, 2009/No:2005/446 and date of first version: May 04, 2005/No:2005/446).

Informed Consent: Signed consent was obtained from the participants.

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