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Original Article

The Relationship of Leptin (+19) AG, Leptin (2548) GA, and Leptin Receptor Gln223Arg Gene Polymorphisms with Obesity and Metabolic Syndrome in Obese Children and Adolescents

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ABSTRACT

Purpose: Obesity is defined as the abnormal or excessive accumulation of fat over acceptable limits. Leptin is a metabolic hormone present in the circulation in amounts proportional to fat mass. Leptin reduces food intake and increases energy expenditure, thus regulating body weight and homeostasis. Various polymorphisms are present in the leptin gene and its receptor. These polymorphisms may be associated with obesity. This study aimed to show the association of leptin (+19) AG, leptin (2548) GA, and Gln223Arg leptin receptor polymorphisms with obesity and metabolic syndrome in Turkish children aged 6–17 years, and to conduct further investigations regarding the genetic etiology of obesity.
Methods: A total of 174 patients diagnosed with obesity and 150 healthy children who were treated at Tokat Gaziosmanpaşa Medical School Hospital between September 2014 and March 2015 were included in this study. The ages of the children were between 6 and 17 years, and anthropometric and laboratory results were recorded. Genotyping of leptin (+19) AG, leptin (2548) GA, and leptin receptor Gln223Arg polymorphisms was performed by polymerase chain reaction.
Results: An association between leptin receptor Gln223Arg gene polymorphism and obesity was detected.
Conclusion: Further studies are needed to determine the role of genetic etiologies and to indicate the role of leptin signal transmission impairment in the pathogenesis of obesity. We hope that gene therapy can soon provide a solution for obesity.

Keywords: Leptin; Obesity; Metabolic syndrome; Polymorphism; Polymerase chain reaction

INTRODUCTION

Obesity is defined as the abnormal or excessive accumulation of fat over acceptable limits. Body mass index (BMI) is the most widely accepted method for obesity screening. Abnormal BMI can be evaluated using specific percentile curves according to age and sex. Obesity is defined as a

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Conflict of Interest
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BMI at or above the 95th percentile in children aged two years or older [1]. Metabolic syndrome (MS) is an endocrinopathy associated with systemic disorders such as abdominal obesity, glucose intolerance, diabetes mellitus, dyslipidemia, and hypertension [2].

The discovery of the genetic aspect of the diseases and the major susceptibility locus, may be important in understanding the pathophysiology of obesity. New advanced molecular and biological techniques, and recent studies have provided more information regarding genetic factors that could play a role in obesity. These studies investigated genes related to energy expenditure, such as those encoding adrenergic receptors and mitochondrial uncoupling proteins [3,4].

The name leptin is driven from the Greek word Leptos, meaning thin. Leptin was first shown as a mutagenic gene product in ob/ob mutant mice. It is secreted from adipose tissue, is controlled by the hypothalamus, and regulates body weight. Although its presence was considered during the discovery of ob/ob mice in the 1950s, it was not identified until 1994 when it was discovered by Zhang et al. [5,6].

The leptin gene is located on chromosome 7 and its cytogenic location is on chromosome 7q31.3. The molecular weight of leptin is 16 kDa [7]. Leptin consists of 167 amino acids, but its mature and functional form consists of 146 amino acids. A large part is secreted by the adipose tissue. It controls eating behavior and thus plays a major role in the maintenance of metabolism [8].

The structure of the leptin receptor is similar to that of glycoprotein 130 (GP 130), a member of the interleukin-6 cytokine family. These receptors are in the form of four isoforms (LEPRα, LEPRb, LEPRc, LEPRf), all of which are encoded by the LEPR gene, set on the first chromosome with its cytogenic location on chromosome 1p31 [7,8]. The LEPR-b receptor is the longest receptor, and the mutation of this isoform is known as the Ob gene because it causes excessive obesity [8].

Leptin is found in the body in proportion to body fat mass, and it passes into the central nervous system proportional to its plasma level. The most important mechanism of its action is by the regulation of many pituitary hormones, which inhibit neuropeptide Y, released and expressed in the arcuate nucleus. It plays a significant role in increasing appetite. In addition, recent research reports that leptin interacts with other mediators through a complex communication network [9].

Many studies have shown that some polymorphisms in the LEP and LEPR genes are potentially associated with the pathophysiology of obesity, MS, and diabetes mellitus [10-12]. The conflicting results from studies conducted to assess the association of leptin and leptin receptor polymorphisms with obesity in different populations and age groups drove us to conduct a study to determine the role of leptin (+19) AG, leptin (2548) GA, and leptin receptor Gln223Arg gene polymorphisms in obesity and MS in Turkish children and adolescents.

MATERIALS AND METHODS

One hundred seventy-four obese children aged 6–17 years were included in this cross-sectional, case-control study. A total of 150 non-obese healthy individuals were enrolled in

the control group. Children with any other disease were excluded from the study. All the parents or legal guardians provided informed written consent before enrollment in the study.

All the studies and investigations were conducted at Tokat Gaziosmanpasa University, School of Medicine Hospital, Turkey. The Helsinki Declaration of the World Medical Association and its ethics standards were taken into consideration for this study. The Ethics Committee of the Tokat Gaziosmanpaşa University School of Medicine approved the study. The local ethics committee approval number was 14-KAEK- 204.

Digital weighing (Seca Corp., Chino, CA, USA) was used to measure the body weight of the children. A portable stadiometer (Seca Corp.) was used to measure the height. BMI is defined as the body mass divided by the square of the body height (kg/m^2). If BMI was equal or over the 95th percentile, the child was categorized as "obese," and as "controlled" if the BMI was in the 5th–85th percentile. The sex- and age-specific growth curves for Turkish children proposed by Neyzi et al. [13] were used. A digital sphygmomanometer (OMRON 705IT; Omron Healthcare Co., Kyoto, Japan) and appropriate sleeves for each child were used to measure blood pressure (BP). The mean of two measurements was recorded.

Laboratory tests

Fasting blood samples of glucose, insulin, and lipid profiles were evaluated only in obese children. No laboratory tests, except for genetic analysis, were performed in the control group. Reagent kits from Roche Diagnostics adapted to the COBAS6000 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA) were used to measure serum fasting glucose, insulin, triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C).

Definition of hypertension, insulin resistance, dyslipidemia, and metabolic syndrome

BP ≥95th percentile according to age, sex, and height was defined as hypertension [14]. The following equation was used to calculate the homeostasis model assessment of insulin resistance (HOMA-IR index): HOMA-IR=Fasting insulin (μU/mL)×Fasting glucose (mg/dL)/405). The HOMA-IR cut-off point for the diagnosis of insulin resistance is 3.16 [15]. Dyslipidemia is defined as TGs ≥105 mg/dL in children <10 years of age and ≥136 mg/dL in children ≥10 years of age, and/or HDL-C <35 mg/dL [16]. When three or more of the following five criteria were met (abdominal obesity [necessary component], fasting glucose over 100 mg/dL, dyslipidemia [TG level over 150 mg/dL or HDL-C level below 40 mg/dL], and hypertension), the diagnosis of MS was made according to the modified International Diabetes Federation guidelines [17-19].

Genetic analysis

Genetic analysis of leptin (+19) AG, leptın (2548) GA, and leptın receptor Gln223Arg polymorphisms was performed in all children using polymerase chain reaction. All genetic testing was performed at the Molecular Biology and Medical Genetics Department of Tokat Gaziosmanpaşa University Medical School.

Statistical analysis

Data are expressed as mean±standard deviation or as frequency and percentage. An independent sample *t*-test was used to compare continuous normal data between the groups. The chi-square test was used to compare categorical data between groups. Statistical significance was set at $p<0.05$. Analyses were performed using IBM SPSS Statistics 19.0 (IBM Co., Armonk, NY, USA).

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RESULTS

Leptin (+19) AG, leptin (2548) GA, and leptin receptor Gln223Arg were genotyped in the obese and control groups. The clinical and laboratory characteristics of the children are presented in **Table 1**. Some of the children's DNA denatured during purification. Therefore, calculations were made with 167 obese patients for leptin (+19) AG, 134 obese patients for leptin (2548) GA, and 146 obese patients for leptin receptor Gln223Arg polymorphism. The same denaturation pattern was observed in the control group. The calculations were performed with 145 of the controls for leptin (+19) AG, 140 for leptin (2548) GA, and 150 for leptin receptor Gln223Arg polymorphisms in the control group.

According to our study, there was no relationship between leptin (+19) AG and leptin (2548) GA gene polymorphisms, and obesity (p>0.05) (**Tables 2** and **3**). The leptin receptor Gln223Arg Genom GG, AG ve AA, was 24 (16.5%), 54 (37%), and 68 (46.5%), respectively, in the obese group, and 18 (12%), 77 (51%), and 55 (37%), respectively, in the control group, indicating a relationship between the last gene polymorphism and obesity (p<0.05) (**Table 4**). There was no relationship between MS and leptin (+19) AG, leptin (2548) GA, and leptin receptor Gln223Arg polymorphism (p>0.05) (**Table 5**).

Table 1. Clinical and laboratory characteristics of study participants

Characteristic	Obese group (n=174)	Control group (n=150)	p-value
Average age (yr)	11.6±2.79	10.95±3.36	0.097
Female/Male	109 (64)/65 (36)	82 (55)/68 (45)	0.097
BMI (kg/m^2)	28.15±4.60	20.08±1.60	0.049
Height (cm)	150.76±15.17	143.56±17.84	0.041
Weight (kg)	65.9±19.96	38.99±14.80	0.035
TG (mg/dL)	111.29±64.42	-	-
Insulin (mIU/L)	19.08±12.39	-	-
Glucose (mg/dL)	88.21±12.01	-	-
HOMA-IR	4.13±3.09	-	-
HDL-C (mg/dL)	48.19±12.41	-	-
Triglyceride status (normal/high)	109 (65.3)/58 (34.7)	-	-
HOMA-IR status (normal/high)	72 (43.6)/93 (56.4)	-	-
Glucose status (normal/high)	155 (90.6)/16 (9.4)	-	-
Blood pressure status (normal/high)	93 (62.8)/55 (37.2)	-	-
HDL-C status (normal/low)	151 (87.8)/21 (12.2)	-	-
Leptin (+19) AG			
AA	19 (11.4)	18 (12.4)	-
GG	83 (49.7)	71 (49.0)	-
AG	65 (38.9)	56 (38.6)	-
Total	167 (100)	145 (100)	-
Leptin (2548)			
AA	33 (24.6)	32 (22.9)	-
GA	59 (44.0)	58 (41.4)	-
GG	42 (31.4)	50 (35.7)	-
Total	134 (100)	140 (100)	-
LepR Gln223Arg			
AA	68 (46.6)	55 (36.7)	-
GG	24 (16.4)	18 (12.0)	-
AG	54 (37.0)	77 (51.3)	-
Total	146 (100)	150 (100)	-

Values are presented as mean±standard deviation or frequency (%).
BMI: body mass index, TG: triglyceride, HOMA-IR: homeostasis model assessment of insulin resistance, HDL-C: high-density lipoprotein cholesterol.
Biochemical test results are given for the obese group, as samples were taken only for gene analysis in the control group (those who were not obese or overweight).

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Table 2. Leptin (+19) gene and allele distribution of gene polymorphic regions in patient and control groups

Leptin (+19) AG	Group		*p*-value	OR (95% CI)
	Obese	Control		
Genotype				
AA	19 (11.4)	18 (12.4)	0.96	1 (Ref)
GG	83 (49.7)	71 (49.0)		0.903 (0.440–1.852)
AG	65 (38.9)	56 (38.6)		0.909 (0.435–1.900)
Total	167 (100)	145 (100)		
Allele				
A	103 (30.8)	92 (31.7)	0.44	1 (Ref)
G	231 (69.2)	198 (68.3)		0.960 (0.684–1.347)
Total	334 (100)	290 (100)		

Values are presented as number (%).
OR: odds ratio, CI: confidence interval.

Table 3. Leptin (2548) gene and allele distribution of gene polymorphic regions in patient and control groups

Leptin (2548) GA	Group		*p*-value	OR (95% CI)
	Obese	Control		
Genotype				
AA	33 (24.6)	32 (22.9)	0.74	1 (Ref)
GA	59 (44.0)	58 (41.4)		1.014 (0.553–1.859)
GG	42 (31.4)	50 (35.7)		1.228 (0.650–2.319)
Total	134 (100)	140 (100)		
Allele				
A	125 (46.6)	122 (43.6)	0.26	1 (Ref)
G	143 (53.4)	158 (56.4)		1.132 (0.808–1.585)
Total	268 (100)	280 (100)		

Values are presented as number (%).
OR: odds ratio, CI: confidence interval.

Table 4. Leptin receptor Gln223 genotype and allele distribution of polymorphic region of Arg gene in patient and control groups

LepR Gln223Arg	Group		*p*-value	OR (95% CI)
	Obese	Control		
Genotype				
AA	68 (46.6)	55 (36.7)	0.04*	1 (Ref)
GG	24 (16.4)	18 (12.0)		0.927 (0.457–1.880)*
AG	54 (37.0)	77 (51.3)		1.763 (1.072–2.899)
Total	146 (100)	150 (100)		
Allele				
A	190 (65.1)	187 (62.3)	0.27	1 (Ref)
G	102 (34.9)	113 (37.7)		1.126 (0.805–1.574)
Total	292 (100)	300 (100)		

Values are presented as number (%).
OR: odds ratio, CI: confidence interval.
*There was a significant relation between leptin receptor Gln223Arg and group (p=0.04). The risk of disease is affected by 0.927 times. GG was found to play a protective role against obesity.

DISCUSSION

In this study, we investigated the relationship between obesity and leptin (+19) AG, leptin (2548) GA, and LEPR Gln223Arg polymorphisms in Turkish children. No association was found between leptin (+19) AG and leptin (2548) GA polymorphisms and obesity, but a relationship between the leptin receptor Gln223Arg polymorphism and obesity was detected. GG has been found to play a protective role against obesity. Furthermore, no association between leptin (+19) AG, (2548) GA, Gln223Arg polymorphisms, and MS could be evidenced.

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Table 5. Of leptin (+19) AG, leptin (2548) GA, and leptin receptor Gln223Arg gene and allele distribution by metabolic syndrome, triglyceride, HOMA-IR, glucose, blood pressure, and HDL-C

Leptin gene and allel distribution	Metabolic syndrome		Triglyceride		HOMA-IR		Glucose		Blood pressure		HDL-C	
	Negative (n=130)	Positive (n=130)	Normal	High	Normal	High	Normal	High	Normal	High	Normal	Low
Leptin (+19) AG												
AA	14 (11.1)	5 (13.5)	14 (13.2)	5 (9.0)	4 (6.0)	13 (14.3)	18 (12)	1 (6.7)	10 (11.2)	6 (11.3)	16 (11.1)	3 (14.3)
AG	52 (38.9)	13 (35.1)	39 (36.8)	25 (45.5)	28 (41.8)	37 (40.7)	59 (40.0)	6 (40.0)	34 (38.2)	21 (39.6)	59 (41.7)	6 (28.6)
GG	64 (50.0)	19 (51.4)	53 (50.0)	25 (45.5)	35 (52.2)	41 (45.0)	72 (48.0)	8 (53.3)	45 (50.6)	26 (49.1)	68 (47.2)	12 (57.1)
χ^2	0.258		1.358		2.906		0.417		0.033		1.318	
p	0.879		0.507		0.234		0.812		0.984		0.517	
Allele frequency												
A	77 (30.6)	23 (31.1)	67 (31.6)	35 (31.8)	36 (26.9)	63 (34.6)	96 (32.0)	8 (26.7)	54 (30.3)	33 (31.1)	92 (31.9)	12 (28.6)
G	175 (69.4)	51 (68.9)	145 (68.4)	75 (68.2)	98 (73.1)	119 (65.4)	204 (68.0)	22 (73.3)	124 (69.7)	73 (68.9)	196 (68.1)	30 (71.4)
χ^2	0.003		0.002		2.154		0.359		0.020		0.193	
p	0.954		0.969		0.142		0.549		0.888		0.660	
Leptin (2548) GA												
AA	26 (23.8)	7 (24.1)	23 (29.5)	9 (19.1)	12 (24.5)	19 (25.7)	31 (26.3)	2 (18.2)	18 (25.0)	11 (26.8)	29 (26.2)	4 (22.2)
GA	47 (44.8)	12 (41.4)	30 (38.4)	25 (53.2)	22 (44.9)	32 (43.2)	52 (44.1)	5 (45.4)	34 (47.2)	15 (36.6)	50 (45.0)	7 (38.9)
GG	32 (31.4)	10 (34.5)	25 (32.1)	13 (27.7)	15 (30.6)	23 (31.1)	35 (29.6)	4 (36.4)	20 (27.8)	15 (36.6)	32 (28.8)	7 (38.9)
χ^2	0.126		2.857		0.037		0.411		1.370		0.744	
p	0.939		0.240		0.982		0.814		0.504		0.689	
Allele frequency												
A	97 (46.2)	28 (46.7)	76 (48.7)	43 (45.7)	46 (46.9)	70 (47.3)	114 (48.3)	9 (40.9)	70 (48.6)	37 (45.1)	108 (48.6)	15 (41.7)
G	113 (53.8)	32 (53.3)	80 (51.3)	51 (54.3)	52 (53.1)	78 (52.7)	122 (51.7)	13 (59.1)	74 (51.4)	45 (54.9)	114 (51.4)	21 (58.3)
χ^2	0.004		0.208		0.003		0.441		0.255		0.605	
p	0.948		0.648		0.956		0.507		0.613		0.437	
LepR Gln223Arg												
AA	54 (47.7)	14 (42.4)	47 (52.8)	20 (40.8)	27 (47.4)	36 (45.6)	60 (46.5)	7 (50.0)	33 (44.0)	22 (45.8)	59 (47.2)	9 (50.0)
AG	39 (33.9)	15 (45.5)	30 (33.7)	20 (40.8)	19 (33.3)	32 (40.5)	47 (36.4)	6 (42.9)	28 (37.3)	19 (39.6)	44 (35.2)	8 (44.4)
GG	20 (18.4)	4 (12.1)	12 (13.5)	9 (18.4)	11 (19.3)	11 (13.9)	22 (17.1)	1 (7.1)	14 (18.7)	7 (14.6)	22 (17.6)	1 (5.6)
χ^2	1.650		1.872		1.069		0.945		0.347		1.815	
p	0.438		0.392		0.586		0.624		0.841		0.404	
Allele frequency												
A	141 (64.7)	43 (65.2)	124 (69.7)	60 (61.2)	57 (46.7)	82 (45.1)	167 (64.7)	20 (71.4)	94 (62.7)	63 (65.6)	162 (64.8)	26 (72.2)
G	77 (35.3)	23 (34.8)	54 (30.3)	38 (38.8)	65 (53.3)	100 (54.9)	91 (35.3)	8 (28.6)	56 (37.3)	33 (34.4)	88 (35.2)	10 (27.8)
χ^2	0.006		2.025		0.082		0.501		0.222		0.770	
p	0.939		0.155		0.775		0.479		0.638		0.380	

Values are presented as number (%).
HOMA-IR: homeostasis model assessment of insulin resistance, HDL-C: high-density lipoprotein cholesterol.

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Gln22Arg, also known as the Q223R polymorphism, was first reported in 1997 by Thompson et al. [20]. Scientists continue to investigate the etiology of obesity because it threatens health and decreases the quality of life. Furusawa et al. [21] conducted the first study that reported the presence of LEP and LEPR Q223R polymorphisms in a wide range of the Pacific Islander population. Furthermore, this is the first study to report the relationship between LEPR Q223R polymorphisms and body weight, BMI, and obesity. The results of this study are consistent with those of other ethnic groups. In another study from Pakistan conducted by Shabana and Hasnain [22] reporting the association of LEPR Gln223Arg polymorphism with obesity in the Pakistani population for the first time, they also found an association with total cholesterol and TGs, and reported a new association of this polymorphism with low-density lipoprotein cholesterol (LDL-C) and HDL-C levels.

Bender et al. [23] conducted a meta-analysis of LepR Q223R in overweight individuals. The study reported that there was no significant relationship between being overweight and LepR Q223R. The results of this study were in concordance with those of the meta-analysis by Bender et al. [23]. No relationship was found between the Gln223Arg polymorphism and obesity or obesity-related metabolic disorders, including insulin resistance, hyperlipidemia, and hyperleptinemia [24].

Obesity is a topic of interest and much research has been done to investigate every aspect of it. Several studies have reported several important relationships between being overweight/obese and LepR Q223R [23]. The Tunisian researchers Zayani et al. [10] found a significant association between 2548 G/A and 223 Q/R polymorphisms and obesity, but no such association was observed with leptin concentration.

Very few studies have been conducted in children that assess leptin receptor Gln223Arg gene polymorphism. In Japan, Endo et al. [25] investigated the relationship between leptin receptor Gln223Arg gene polymorphism and obesity in schoolchildren. The study reported that obesity did not appear to be associated with leptin receptor Gln223Arg polymorphism in children, contrary to the results of Becer et al. [26], which showed an association between this leptin variant (leptin receptor Gln223Arg) and increased waist and hip circumference.

Many studies have examined the same gene polymorphism, and a relationship between high TG levels and polymorphisms was detected. However, a relationship between the leptin receptor Gln223Arg and high total cholesterol was observed only in a single study in Japan [27]. Shabana et al. [22] reported high LDL-C and low HDL-C levels. These results were similar to those of other studies [22,26].

The etiology and treatment are currently under investigation. According to our study, leptin receptor Gln233Arg gene polymorphism was found to be associated with obesity but not with MS. According to our results, GG affected the risk of obesity by 0.927 times (played a protective role). There was no association of this gene polymorphism with hyperglycemia, hypertriglyceridemia, hypertension, HOMA-IR, and low HDL.

Mammés et al. [28] were the first to identify leptin (2548) GA gene polymorphism. Furthermore, leptin (2548) GA polymorphism has been found to be associated with high BMI in overweight women, as well as with being overweight in Europeans and Tunisian people and with obesity in Taiwanese and Aborigines.

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In a study conducted in the Turkish population, there was no significant relationship between leptin (2548) GA polymorphism and BMI [29]. Becer et al. [29] found no association between leptin (2548) GA gene polymorphism and BMI in Turkish children. Hassanzadeh et al. [30] also investigated leptin (2548) GA polymorphism and concluded that the frequency of LEP G-2548A polymorphism in MS (MetS) and in healthy subjects were not significantly different, and more studies with a larger sample size are needed.

New studies on leptin (2548) GA polymorphism showed an increased frequency of the G allele in obese patients, but revealed no significant differences in anthropometric indices, glucose, HDL-C, TG, HOMA-IR, and BP among children with this polymorphism [29-31]. According to our study, there was no difference in the frequency of G or A allele among obese children, and no difference was observed in the frequency of the three genotypes of the leptin (2548) GA gene between simple uncomplicated obese patients and obese patients with MS. Other factors such as ethnicity, lifestyle, and nutrition have been suggested to affect energy homeostasis [29-31].

Le Stunff et al. [32] investigated leptin (2548) GA gene polymorphism and demonstrated that there was no significant difference in genotype distribution between patients with MS and control groups, and controversial data between this polymorphism, BMI, fat mass, and obesity should be discussed. It was thought that these different results may be due to interactions between the polymorphism and leptin, leptin receptor, or other parts of the genes [32,33].

Skibola et al. [34] conducted a study in the Tunisian obese and normal-weight groups. The study concluded that there was no association between leptin (2548) GA polymorphism and obesity. In addition, there was no statistically significant difference between leptin (2548) GA genotypes and BMI, glucose, insulin, and plasma lipid levels in both obese and normal individuals [34]. In our study, there was no relationship between leptin (2548) GA polymorphism and obesity or MS, and there was no association of this gene with hypertriglyceridemia, hyperglycemia, low HDL HOMA-IR, and hypertension.

Since the discovery of leptin in 1994, several studies have been conducted on whether leptin affects obesity as it is known that the most important factor in determining leptin level is total fat mass. In a study conducted in Italy, there was no difference in the frequency of leptin (+19) A and G allele distribution in the obese and control groups. Apart from the polymorphism of leptin (+19) AG, there were no differences in leptin, glucose, TG, HDL-C, and BP levels in obese individuals [35]. In our study, there was no correlation between leptin (+19) GA polymorphism and obesity or MS. Furthermore, no significant difference was observed between these three genotypes and hyperglycemia, hypertriglyceridemia, low HDL-C, HOMA-IR, and hypertension.

There was no association between leptin (+19) AG and leptin (2548) GA polymorphisms, and obesity. However, a relationship between leptin receptor Gln223Arg polymorphism and obesity was seen. In addition, leptin (+19) AG, leptin (2548) GA, leptin receptor Gln223Arg polymorphisms were not associated with MS. The genetic etiologies of obesity should be further investigated, and genetic and molecular treatments could soon provide a solution for obesity.

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