











# Investigation of *GHRL*, *RETN*, *ADIPOQ*, *NPY* and *MC4R* Gene Polymorphisms in Obese and Non-Obese Patients With Diabetes

Saadet Busra Aksoyer Sezgin<sup>a</sup> , Sermin Durak<sup>b</sup> , Faruk Celik<sup>c, d</sup> , Arezoo Gheybi<sup>e</sup> ,  
Murat Diramali<sup>f</sup> , Ramazan Cakmak<sup>g</sup> , Mustafa Kerem Ozyavuz<sup>e</sup> ,  
Ali Osman Guroh<sup>h</sup> , Ilhan Yaylim<sup>e</sup> , Umit Zeybek<sup>e, i</sup> 

## Abstract

**Background:** Obesity is a major public health issue caused by an abnormal increase in adipose tissue and is linked to increased insulin resistance and type 2 diabetes. Diabetes is a metabolic condition characterized by high glucose levels that is caused by insulin deficiency and alterations in insulin action mechanisms. Many of the genes associated with obesity are expressed in the central nervous system. Ghrelin, the endogenous ligand of the growth hormone secretagogue receptor, has a single-nucleotide polymorphism (SNP), rs4684677, which is associated with insulin resistance and metabolic syndrome. Adipose tissue secretes hormones known as adipokines, which include resistin and adiponectin, encoded by the *ADIPOQ* gene. SNPs in the *RETN* gene (rs1862513) have been linked to obesity and diabetes. Adiponectin is a cytokine generated from adipose tissue, and its polymorphism (rs2241766) increases the incidence of type 2 diabetes. Ghrelin binds to its receptor and promotes the expression of neuropeptide Y (NPY), thereby increasing food intake. *NPY* (rs16147) polymorphism has been

linked to diabetes and obesity. The melanocortin 4 receptor (MC4R) is a regulator of energy balance and appetite. *MC4R* (rs17782313) polymorphism was associated with an increased risk of obesity.

**Methods:** Our study included 99 obese with diabetes and 99 non-obese patients with diabetes. *RETN* (rs1862513), *GHRL* (rs4684677), *MC4R* (rs17782313), *NPY* (rs16147), and *ADIPOQ* (rs2241766) genes were genotyped using real-time polymerase chain reaction.

**Results:** As a result, the *RETN*, *MC4R*, and *NPY* polymorphisms showed statistically significant differences in genotype/allele distributions between groups.

**Conclusions:** In conclusion, by representing data from the Turkish population for the first time, this study offers fresh insights and provides a unique perspective on the impact of the indicated genes on obesity, thereby contributing to the understanding of a hitherto unstudied ethnic group.

**Keywords:** Diabetes; *ADIPOQ*; NPY; MC4R; Resistin; Ghrelin

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<sup>a</sup>Department of Medical Biology and Genetics, Faculty of Medicine, Istanbul Yeni Yuzyil University, Istanbul 34010, Turkey

<sup>b</sup>Department of Medical Microbiology, Faculty of Medicine, Istanbul University Cerrahpasa, Istanbul 34320, Turkey

<sup>c</sup>Department of Medical Genetics, Faculty of Medicine, Alanya Alaaddin Keykubat University, Alanya, Antalya 07425, Turkey

<sup>d</sup>Molecular Medicine Research Center, Alanya Alaaddin Keykubat University, Alanya 07425, Antalya, Turkey

<sup>e</sup>Department of Molecular Medicine, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul 34093, Turkey

<sup>f</sup>Department of Anatomy, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu 14030, Turkey

<sup>g</sup>Department of Internal Disease, Istanbul University, Istanbul 34093, Turkey

<sup>h</sup>Department of Immunology, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul 34093, Turkey

<sup>i</sup>Corresponding Author: Umit Zeybek, Department of Molecular Medicine, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul 34093, Turkey. Email: umz67@yahoo.com

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## Introduction

Obesity is a global health issue because of its association with chronic diseases such as cardiovascular disease, type 2 diabetes mellitus, and cancer. Obesity also promotes the development of proinflammatory molecules that contribute to the pathophysiology of insulin resistance. Many of the genes associated with obesity are expressed in the central nervous system [1]. The leptin-melanocortin pathway is in charge of regulating hunger and energy metabolism. During periods of dietary restriction and low energy stores, the stomach secretes a large amount of ghrelin. Ghrelin, the endogenous ligand of the growth hormone secretagogue receptor, also plays an important role in body weight, insulin, and glucose metabolism. Single-nucleotide polymorphisms (SNPs) in the *GHRL* gene have been linked to obesity and diabetes in the literature, and these variants have been demonstrated to vary between populations [2–4].

Adipose tissue, an endocrine organ, secretes hormones known as adipokines, which include leptin, resistin, and adi-

ponectin. In animals, the resistin protein is important in controlling glucose metabolism. SNPs in the *RETN* gene have been linked to metabolic, inflammatory, and autoimmune illnesses, as well as the development of insulin resistance [5], and some SNP variations have been linked to ethnicity [6, 7].

Adiponectin (*ADIPOQ*), an adipokine produced by adipocytes, has received substantial research for its anti-diabetic, anti-inflammatory, and anti-obesity properties [8–10]. Reduced blood adiponectin levels have been linked to decreased anti-inflammatory and enhanced pro-inflammatory actions, which contribute to the advancement of obesity-related disorders [11]. According to a study published in the literature, the *ADIPOQ* rs1501299 (276 G/T) polymorphism could be a candidate gene regulating obesity risk [12]. Ghrelin binds to the receptor and increases the expression of neuropeptide Y (NPY) and Agouti-related protein (AgRP), thus increasing food intake. Different SNPs in the *NPY* gene have been linked to obesity, glucose, and lipid metabolism from adolescence through young adulthood in the literature [13]. AgRP has been shown to operate as an antagonist to the melanocortin 4 receptor (MC4R), enhance appetite, and decrease energy expenditure [14–16]. MC4R is a major regulator of energy balance and appetite, and *MC4R* gene mutations are the most common monogenic cause of obesity in obese people, with a prevalence of 1.7–3.0% [17]. *MC4R* gene variations (p.N274S, p.S136F, p.V166I, p.R165W, p.I291SfsX10, p.M200del, p.S188L) are relatively prevalent in the Turkish population with childhood obesity, and screening for these variants is critical in children undergoing treatment for childhood obesity [18]. Another study in the literature found that the mutant *MC4R* rs17782313 was strongly related to the risk of obesity [19]. Furthermore, some experimental investigations have revealed that the effect of *MC4R* rs17782313 on obesity is ethnically dependent [20–23].

An examination of the literature revealed that no studies on the *RETN*, *MC4R*, *NPY*, and *ADIPOQ* genes in the Turkish population had been found. This study aimed to investigate the association of the *RETN*, *GHRL*, *ADIPOQ*, *NPY*, and *MC4R* polymorphisms with obesity and diabetes in a Turkish population for the first time, thereby filling a gap in the existing literature.

## Materials and Methods

### Ethical compliance

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Istanbul University Clinical Research Ethics Committee (Decree No. 13.05.2016/09).

### Study design

Our study included 99 diabetic obese people and 99 diabetic

non-obese people. The research was carried out at Istanbul University's Aziz Sancar Experimental Medicine Research Institute, Department of Molecular Medicine. The first group included those who were diagnosed with diabetes using the Turkish Diabetes Association's criteria and also met the criterion for obesity. They were chosen from the Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul University Faculty of Medicine Hospital. The second group, on the other hand, was made up of diabetics who did not have obesity. Individuals with a history of chronic conditions such as cancer were excluded from the study. After describing the goal of the study, all participants signed informed permission forms. All of the participants were of Turkish descent. Individuals' blood samples of 5 mL were collected, and the serums were maintained at –80 °C until the day of analysis after being centrifuged at 3,000 g for 15 min. Urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, and hemoglobin A1c (HbA1c) were all measured in the samples.

### Genomic DNA isolation

Genomic DNA was extracted from 5 mL peripheral blood samples using a robotic system (RINATM M14; Bioeksen/Turkey). This machine separated DNA using magnetic beads, followed by chemical, physical, and enzymatic digestion, and then applied heat treatment with a subsequent washing step.

### Real-time polymerase chain reaction (PCR)

*RETN* rs1862513, *GHRL* rs4684677, *MC4R* rs17782313, *NPY* rs16147, and *ADIPOQ* rs2241766 genes were genotyped using real-time PCR. Two forward and one reverse primer were designed for each SNP. Table 1 lists the primers used to amplify the relevant SNP. All reactions were carried out using a Bio-Rad CFX96 instrument (Bio-Rad, Hercules, CA) and analyzed with the CFX Maestro Manager Software (Bio-Rad, Hercules, CA). The genotype distribution and allele frequencies of four gene polymorphisms in diabetic obese and non-obese diabetic groups were studied. The qPCR reactions contained 3 µL of oligo primer with Sybr Green, 5 µL of qPCR Master Mix (Bioeksen/Turkey), and 2 µL of template DNA. The total reaction volume was set for 10 µL for each primer. The qPCR protocol was followed: 3 min at 95 °C, and then by 40 cycles at 95 °C for 10 s, 60 °C for 30 s.

### Statistical analysis

We used post-amplification fluorescence melting curve analysis to determine the allelic types of the SNP. Cq values obtained from standard curves and PCR were determined using CFX Manager Software version 3.1 (Bio-Rad Laboratories). SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) was used to compare the demographic data of the groups. Statistical sig-

**Table 1.** Primer Sequences for PCR Amplification of *RETN* rs1862513, *GHRL* rs4684677, *MC4R* rs17782313, *NPY* rs16147 and *ADIPOQ* rs2241766 Genes

SNP	Forward primer (5'-3')	Forward/reverse primer (5'-3')	Reverse primer (5'-3')
rs1862513	GGGCATTGGGTATGAATGTG	TTCCAACAGGGCCTCCG	TTCCAACAGGGCCTCCA
rs4684677	TGGCTGTGCTGCTGGTACT	TGGCTGTGCTGCTGGTACC	AGATGGTGAGTGGGAAGGTG
rs17782313	GCTTTTCTGTCAATTCATCA	GCTTTTCTGTCAATTCATCT	TAACAAACAGCCCCAAGTC
rs16147	TCAGCAAAGTGGGGGAATAG	CCTGCCAACAGGACTACAA	CCTGCCAACAGGACTACCAT
rs2241766	GCTATTAGCTCTGCCCGGT	GCTATTAGCTCTGCCCGGG	TGAGGGTGAAGATGGGAAAG

PCR: polymerase chain reaction; SNP: single-nucleotide polymorphism.

nificance was defined as a P value less than 0.05.

The conformity of continuous data (Table 2) to normal distribution was assessed using the Shapiro-Wilk test. Data conforming to a normal distribution were presented as mean  $\pm$  standard error (SE). The distribution of variances was examined using the Levene test. Differences between groups were assessed using the Student's *t*-test or the Welch test. Categorical data (Table 3) were presented as frequencies and percentages. Differences between groups were assessed using the Chi-square test.

## Results

### Results obtained from biochemical parameters

Our study is a case-control study with diabetic obese (n = 99, 50%) and non-obese diabetic (n = 99, 50%) patients. When

**Table 2.** Demographic and Clinical Data of Obese and Non-Obese Diabetic Groups

	Non-obese diabetic	Obese diabetic	P value
Age	50.86 $\pm$ 1.51	55.89 $\pm$ 1.02	0.006*
Urea	31.37 $\pm$ 0.98	35.79 $\pm$ 1.82	0.034*
Creatinine	0.78 $\pm$ 0.02	0.85 $\pm$ 0.04	0.08
ALT	19.60 $\pm$ 1.01	23.27 $\pm$ 1.25	0.024*
AST	18.10 $\pm$ 0.66	20.03 $\pm$ 0.84	0.075
TC	200.50 $\pm$ 5.63	211.35 $\pm$ 8.26	0.281
TG	139.64 $\pm$ 8.53	189.82 $\pm$ 13.42	0.002*
HDL-c	50.89 $\pm$ 1.76	46.29 $\pm$ 1.02	0.025*
LDL-c	122.01 $\pm$ 4.58	121.87 $\pm$ 3.33	0.968
Glucose	163.98 $\pm$ 6.81	181.78 $\pm$ 6.71	0.064
HbA1c	8.14 $\pm$ 0.22	8.33 $\pm$ 0.19	0.514
BMI	24.80 $\pm$ 0.31	36.00 $\pm$ 0.45	< 0.0001*

The values expressed as X  $\pm$  SE in the table were analyzed using independent samples *t*-tests (X: mean; SE: standard error). P represents the significance of value between the groups. \*P < 0.05. ALT: alanine aminotransferase; AST: aspartate aminotransferase; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; BMI: body mass index.

we compared the groups in terms of biochemical and anthropological parameters, we discovered that the diabetic obese group had significantly higher age, urea, ALT, body mass index (BMI) and TG parameters (P < 0.05) (Table 2), while the non-obese diabetic group had significantly higher HDL parameters (P < 0.05) (Fig. 1). Other metrics showed no significant difference between groups (P > 0.05) (Table 2).

### Results obtained from genotype and allele frequencies

The genotype and allele distributions of the *RETN*, *MC4R*, *NPY*, *GHRL*, and *ADIPOQ* polymorphisms were compared between groups in our study. The genotype distribution of *RETN* polymorphism was shown to be statistically significant between groups (P = 0.005). The diabetic obese group had a considerably greater C allele of the *RETN* polymorphism compared to the non-obese group (69.7% vs. 60.1%; P = 0.002). Furthermore, diabetic patients with the C allele of the *RETN* polymorphism had a nearly fourfold increased risk of obesity (odds ratio (OR) = 3.98; 95% confidence interval (CI) = 1.619–9.773).

The genotype distribution of the *MC4R* polymorphism was likewise shown to be statistically significant between groups (P = 0.008). The diabetic obese group had a higher and statistically significant C allele of the *MC4R* polymorphism (51% vs. 47%; P = 0.007). Diabetes patients with the C allele of the *MC4R* polymorphism had a nearly threefold increased incidence of obesity (OR = 3.33; 95% CI = 1.337–8.282).

The genotype distribution of the *NPY* polymorphism was statistically significant between groups (P < 0.0001). The diabetic obese group had a substantially greater T allele of the *NPY* polymorphism (62.1% vs. 45%; P < 0.0001), whereas the non-obese diabetic group had a higher and significantly different C allele (55% vs. 37.9%; P = 0.006). Furthermore, diabetic patients with the T allele of the *NPY* polymorphism had a 13-fold greater risk of obesity (OR = 13.058; 95% CI = 2.970–57.403). There was no significant difference in genotype and allele distribution between the groups for the *GHRL* and *ADIPOQ* polymorphisms (P > 0.05) (Table 3).

### Biochemical parameters and findings from genotypes

Individuals having the C allele of the *RETN* polymorphism showed higher TC levels in the non-obese diabetic group (mean  $\pm$  SE = 207.47  $\pm$  6.5, P = 0.018). Individuals with the

**Table 3.** Genotype and Allele Frequencies of *RETN* rs1862513, *GHRL* rs4684677, *MC4R* rs17782313, *NPY* rs16147 and *ADIPOQ* rs2241766 Polymorphisms in the Study Groups

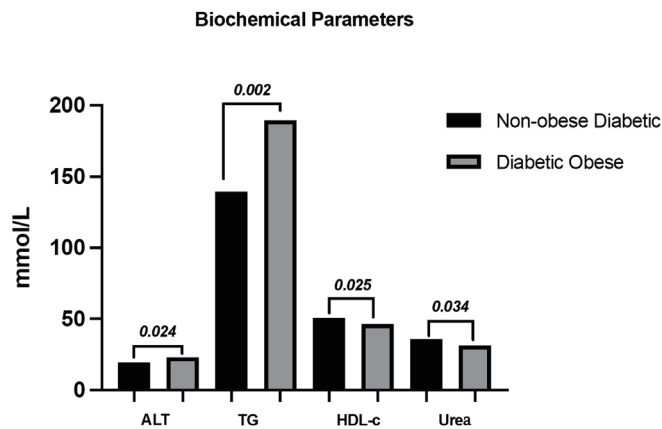
Genotypes/alleles	Obese diabetic, n (%)	Non-obese diabetic, n (%)	P value
<i>RETN</i> rs1862513			
CC	46 (46.5%)	43 (43.4%)	0.005*
CG	46 (46.5%)	33 (33.3%)	
GG	7 (7.1%)	23 (23.2%)	
C allele	138 (69.7%)	119 (60.1%)	0.002*
G allele	60 (30.3%)	79 (39.9%)	0.67
<i>GHRL</i> rs4684677			
TT	0 (0%)	2 (2%)	0.36
TA	5 (5.1%)	5 (5.1%)	
AA	94 (94.9%)	92 (92.9%)	
T allele	5 (2.5%)	9 (4.5%)	0.551
A allele	193 (97.5%)	189 (95.5%)	0.155
<i>MC4R</i> rs17782313			
TT	7 (7.1%)	20 (20.2%)	0.008*
TC	83 (83.8%)	65 (65.7%)	
CC	9 (9.1%)	14 (14.1%)	
T allele	97 (49%)	105 (53 %)	0.267
C allele	101 (51%)	93 (47%)	0.007*
<i>NPY</i> rs16147			
TT	26 (26.3%)	11 (11.1%)	< 0.0001*
TC	71 (71.7%)	67 (67.7%)	
CC	2 (2%)	21 (21.2%)	
T allele	123 (62.1%)	89 (45%)	< 0.0001*
C allele	75 (37.9%)	109 (55%)	0.006*
<i>ADIPOQ</i> rs2241766			
TT	76 (76.8%)	78 (78.8%)	0.1
TG	10 (10.1%)	3 (3%)	
GG	13 (13.1)	18 (18.2%)	
T allele	162 (81.8%)	159 (80.3%)	0.328
G allele	36 (18.2%)	39 (19.7%)	0.732

P represents the significance of value between the groups. \*P < 0.05.

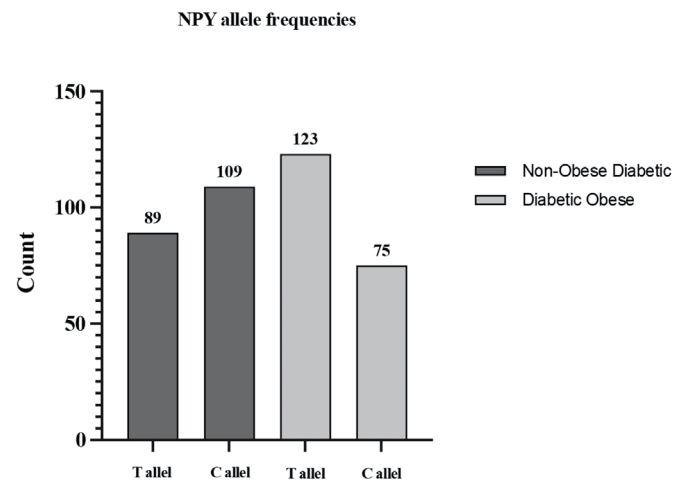
*GHRL* polymorphism's A allele had statistically substantially higher TC levels (mean SE = 201.79 ± 5.5, P = 0.033), while those with the C allele had a higher age parameter (mean SE = 51.34 ± 1.5, P = 0.025). Individuals with the TT genotype of the *MC4R* polymorphism showed a substantial rise in TG levels in the non-obese diabetic group (mean SE = 179 ± 29.2, P = 0.017). Individuals with the G allele of the *ADIPOQ* polymorphism had significantly lower HbA1c levels (mean SD = 7.41 ± 0.36, P = 0.044).

There was no significant relationship between genotype and allele frequencies of the *NPY* polymorphism and metabolic markers in the non-obese diabetic group (Fig. 2).

Individuals with the T allele of the *MC4R* polymorphism had substantially higher levels of glucose (mean SE = 185.75 ± 7.2; P < 0.001) and HbA1c (mean SE = 8.4 ± 0.2; P = 0.022) in the diabetes obese group. Diabetic obese people with the C allele of the *NPY* polymorphism had a significant rise in BMI (mean SE = 37.1 ± 0.5; P < 0.001). Furthermore, diabetic obese people with the T allele of the *ADIPOQ* polymorphism had a significant rise in BMI (mean SE = 36.4 ± 0.4; P < 0.001). There was no statistically significant connection between genotypes and allelic distributions of *RETN*, *GHRL*, and *ADIPOQ* polymorphisms and biochemical markers in the diabetic obese group (P > 0.005).



**Figure 1.** Biochemical parameters measured in the study groups. ALT: alanine aminotransferase; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol.



**Figure 2.** *NPY* allele distribution in study groups.

## Discussion

Obesity is a major public health issue that is becoming more prevalent around the world. It is caused by an abnormal increase in adipose tissue and is linked to increased insulin resistance, type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. Diabetes, on the other hand, is a metabolic condition characterized by high blood glucose levels that are caused by insulin deficiency and alterations in insulin action mechanisms [24].

Ghrelin, a 28-amino acid gastrointestinal peptide, and its receptor are found in many peripheral organs, intestines, pancreatic islets, and brain regions. Gln90Leu rs4684677 is one of the SNPs associated with insulin resistance and metabolic syndrome. A study in the Spanish population discovered a link between the Ghrelin rs4684677 polymorphism and metabolic syndrome. However, no correlation was identified between genotype haplotypes and BMI [25].

The *GHRL* rs4684677 polymorphism has been reported to affect insulin sensitivity and eating behavior in different population studies in the literature [26, 27], but no association with gestational diabetes or type 2 diabetes [28]. Similarly, no significant differences were observed between the genotype and allele distributions of *GHRL* rs4684688 and biochemical parameters in the study groups and the diabetic obese group ( $P > 0.05$ ). These findings in our study with diabetic obese and non-obese diabetic individuals are consistent with the results of relevant publications in literature.

Resistin is an adipokine produced by adipose tissue and is a member of the cysteine-rich secretory protein family. Obesity, insulin resistance, and type 2 diabetes have all been linked to SNPs in the *RETN* gene and elevated resistin concentrations in serum [29, 30]. The GG genotype of rs1862513 was indicated to be an indication of lower homeostasis model assessment of insulin resistance (HOMA-IR), insulin, and LDL cholesterol in a study conducted by De Luis et al in non-diabetic obese patients [30].

However, in different studies conducted in different populations, the rs182513 polymorphism was found to have no ef-

fect on metabolic syndrome susceptibility in individuals with obesity and diabetes, and no significant relationship was found between the allelic frequencies of rs1862513 and the genotypic distributions with metabolic syndrome [31, 32].

Contrary to the literature, the genotype distribution of the *RETN* rs1862513 SNP was shown to be significant in our investigation, and it was reported that carrying the C allele enhanced the risk of obesity in diabetic patients by four times. These findings show that people with the C allele are more likely to develop metabolic syndrome. Individuals having the C allele had significantly higher TC levels ( $P < 0.05$ ) in the non-obese diabetic group; however, no significance was observed when assessing genotype and allele distributions in terms of biochemical markers in the diabetic obese group. These data show that having high TC among non-obese diabetics with the C allele may raise the risk of cardiovascular disease; however, further studies are needed to confirm this finding.

Adiponectin is a cytokine generated from adipose tissue that influences diabetes. *ADIPOQ* rs2241766 polymorphism increases the incidence of type 2 diabetes [33] and is highly related to diabetes [34–39]. Studies in diverse populations have also found that the *ADIPOQ* rs2241766 polymorphism is linked to the risk of obesity [40] and the development of type 2 diabetes [10, 38, 41, 42].

In contrast to these findings, there are studies in the literature that show no link between the *ADIPOQ* rs2241766 polymorphism and type 2 diabetes [43] or obesity risk [44].

In our investigation, similar to the findings of Lu et al [44], no significant differences in the genotype and allele distributions of the *ADIPOQ* rs2241766 polymorphism were detected in diabetic obese and non-obese diabetic groups. In terms of biochemical parameters, however, individuals carrying the G allele in the non-obese diabetic group had decreased and significant HbA1c levels, whereas there was no significant difference in terms of genotype and allele in the diabetic obese group.

*NPY* is a 36-amino acid peptide neurotransmitter produced by chromaffin cells and noradrenergic neurons. The

*NPY* rs16147 SNP has been linked to type 2 diabetes and obesity risk [45], and it has been proposed that this is due to enhanced *NPY* signaling caused by elevated *NPY* expression in the hypothalamus [46]. BMI, fat mass, waist circumference, leptin, and insulin levels were considerably lower in males bearing the A allele in a study on *NPY* rs16147 polymorphism in obese patients [47]. The rs16139 SNP has been found to be strongly associated with obesity measures such as BMI and waist circumference, and the T allele is associated with an increased risk of obesity [48, 49]. This points to a consistent link between rs16147 and obesity risk in Caucasians and Asians.

Similarly, the *NPY* rs16147 genotype distribution was shown to be significant in our study, and the C allele is high and significant in the non-obese diabetes group, whereas the T allele is high and significant in the diabetic obese group. Furthermore, those with the T allele had a 13-fold increased risk of obesity. The correlation of the *NPY* SNP with obesity is extremely consistent in the populations analyzed in the literature, and our population's homogeneity also suggests a genetically connected link. In terms of biochemical markers, no significance was found in the genotype and allele distributions in the non-obese diabetic group; however, it was established that BMI was greater and significant in persons carrying the C allele in the diabetic obese group. Although the mechanism behind the link between the *NPY* variation and increased BMI is thought to be increased food consumption, there is limited evidence from epidemiological research to support this idea. More research is needed to understand the molecular mechanisms behind the observed relationships.

*MC4R* mutations are the most prevalent monogenic cause of obesity, accounting for 1.7–3.0% of obese people [17]. The most commonly researched *MC4R* gene variant, rs17782313, has been linked to obesity [50, 51], and has substantial associations with calorie consumption [52], increased snacking, and hunger [53]. Several studies in diverse populations have found that the *MC4R* rs17782313 polymorphism is related to an increased risk of obesity and diabetes [19, 54, 55, 56]. Another study in overweight and obese adults discovered that different *MC4R* rs17782313 genotypes were related to energy consumption and the C allele [57]. Similarly, we discovered that the genotype distribution and C allele of *MC4R* rs17782313 were considerably greater in diabetic obese individuals in our study. As a result, diabetes patients having the C allele have a threefold increased risk of obesity. When we looked at the biochemical markers, we found that patients with the TT genotype had considerably higher TG levels in the non-obese diabetic group, while individuals with the T allele had higher and significant levels of glucose and HbA1c in the diabetic obese group. This suggests that non-obese diabetics are more likely to acquire cardiovascular disease. Our work is the first to look at the combined effects of *RETN*, *GHRL*, *MC4R*, *NPY*, and *ADIPOQ* polymorphisms in diabetic patients with and without obesity. The findings of this study add significantly to the existing body of knowledge regarding the phenotypic impact of these disorders. Furthermore, to our knowledge, this is the first scientific study conducted in Turkey to examine all of these genes within a different ethnic group.

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## Conflict of Interest

The authors declare no competing interests.

## Informed Consent

Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

## Author Contributions

All authors contributed to the study conception and design. Study concept and design: Saadet Busra Aksoyer Sezgin and Umit Zeybek; acquisition of data: Saadet Busra Aksoyer Sezgin, Sermin Durak, Ramazan Cakmak, Mustafa Kerem Ozyavuz; analysis and interpretation of data: Saadet Busra Aksoyer Sezgin, Umit Zeybek, Sermin Durak, Faruk Celik and Arezoo Gheybi; drafting of the manuscript: Saadet Busra Aksoyer Sezgin, Sermin Durak and Faruk Celik; critical revision of the manuscript: Umit Zeybek, Ali Osman Gurol and Ilhan Yaylim; statistical analysis: Murat Diramali; study supervision: Umit Zeybek.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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