

No Role of rs1137101 Variant of the Leptin Receptor Gene in Manifestation of Obesity

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ABSTRACT

Objective: Obese phenotype can be a consequence of disruption in the physiological integrity of the leptin axis. Leptin acts as a satiety signal and exerts its physiological effects by binding to the leptin receptor; consequently, genetic variants of the leptin receptor may be important in the pathophysiology of human obesity. The current study was therefore carried out to find the association of the leptin receptor rs1137101 variant with obesity and associated anthropometric and metabolic parameters in a sample of the Pakistani population.

Methods: DNA samples from a total of 239 obese and 155 non-obese human subjects with age range of 5–45 years were genotyped for the rs1137101 variant of the leptin receptor gene. Anthropometric measurements of the subjects were taken, and biochemical parameters from the corresponding serum samples were determined. Blood pressure was monitored, and measurements of body weight, height, waist and hip circumference were recorded. Body mass index and waist-to-hip ratio were calculated. Levels of fasting blood glucose, insulin, leptin and leptin receptor were determined, and insulin resistance was calculated.

Results: The statistical analysis of the data showed no significant difference in genotype and allele frequencies of rs1137101 variant between obese and non-obese subjects ($p > 0.05$). Moreover, no significant association of the variant was observed with any of the obesity-related anthropometric and metabolic traits ($p > 0.05$).

Conclusion: The study suggests that rs1137101 variant of the leptin receptor gene may not be involved in conferring obese phenotype in the Pakistani population.

Keywords: Leptin receptor, obesity, Pakistan, rs1137101 variant.

INTRODUCTION

Leptin receptor (LEPR) is a single transmembrane protein that belongs to the class I cytokine receptor family (1). Leptin, an adipokine and central regulator for adiposity-sensing pathways, exerts its physiological effects by binding to LEPR in the hypothalamus. It functions as a satiety signal by downregulating orexiogenic (appetite-stimulating) peptides and upregulating anorexigenic (appetite-decreasing) peptides (2). Leptin receptor is a product of the LEPR gene that is located on human chromosome 1p31 and consists of 20 exons

(3). The expression of the LEPR gene results in at least six isoforms of leptin receptors (LEPRa-f) attributable to alternative mRNA splicing. The isoforms (Ra, Rb, Rc, Rd, and Rf) share the same extracellular and transmembrane domains but differ in the length of the intracellular domain (4).

The secreted isoform Re lacking both transmembrane and intracellular domains can be generated either by alternative splicing (Ob-Re) or by ectodomain shedding. It circulates as a soluble receptor, and may be involved in modulating leptin activity (5, 6). Leptin

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receptors form homodimers, and binding of leptin to the receptors activates Janus-activated kinases (JAK), which in turn activate signal transducers and activators of transcription (STAT). Leptin signalling through the JAKs and activation of transcription system for regulating body fat mass is mainly associated with the longest form (LEPRb) of LEPR that contains both conserved sequence motifs necessary for the binding of the JAKs and STAT family of signal transducing factors required for full leptin signalling function (7). The shorter isoforms lack STAT binding elements, thus having reduced signal transduction capabilities (8). The longest isoform appears to be the most abundant in the hypothalamus, while the shorter isoforms seem to predominate in peripheral tissues (9).

The LEPR gene has been extensively studied in search for several common variants that may be important in the pathophysiology of human obesity (10). One of these variants is non-synonymous Q223R (rs1137101) in exon 6 of the human LEPR gene at codon 223 (11). The LEPR contains two extracellular cytokine receptor homology domains (CRH1 and CRH2). The CRH2 domain is necessary and sufficient for leptin binding, whereas CRH1 is not essential for a high affinity interaction (12). The Q223R variant results from an A to G transversion at nucleotide 668 from the start codon encoding a glutamine (Q) to arginine (R) substitution in the N-terminal CRH1 domain of LEPR (13). Genetic variants, which serve as causal factors for a particular population, may or may not affect another population. In particular, the data on the status of this variant in relation to obesity in the Pakistani population has remained extremely scarce. The current study was therefore undertaken to find the association of Q223R variant of the LEPR gene with obesity and obesity-related anthropometric and metabolic traits in a sample of the Pakistani population.

SUBJECTS AND METHODS

The study was performed at the University of Health Sciences Lahore, Pakistan, after the approval from the Institutional Review Board of the University. All procedures involving collection of blood samples and anthropometric measurements were carried out with the adequate understanding and written informed consent of the subjects.

Study population

The participants of the study involved 239 obese individuals with body mass index (BMI) ≥ 30 kg/m² or $> 95^{\text{th}}$ percentile and 155 control subjects with BMI < 25 kg/m²

or 5^{th} – 85^{th} percentile. The age range of the participants was between 5 and 45 years. Simple random sampling was applied for the collection of blood specimens. Subjects with a history of any endocrine disorder were not included in the study. Similarly, subjects who were taking antidepressants, anticonvulsants and steroids were not included in the study.

Categorisation of study population

Subjects were further classified into two categories: category 1 involving individuals ≤ 18 years of age and category 2 involving individuals > 18 years of age. The subjects > 18 years of age were considered obese with a BMI ≥ 30 and normal weight with a BMI < 25 (14). The subjects ≤ 18 years of age were considered obese if their BMI was $> 95^{\text{th}}$ percentile and normal weight if their BMI fell within the 5^{th} – 85^{th} percentile by following BMI for age growth charts recommended by the Centers for Disease Control and Prevention.

Demographic information and physical examination

Full demographic information including name, age, sex, address, education and socio-economic status was documented on a questionnaire. A complete general physical examination was carried out. A blood volume of 5 ml was collected from each subject aseptically.

Anthropometric and blood pressure measurements

Body weight (BW), height, waist circumference (WC) and hip circumference (HC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standard procedures (14). Body height was measured using a stadiometer and BW was measured on digital weighing scale. The BMI of each subject was calculated as weight in kilograms divided by height in metres squared. Waist circumference was taken just above the belly button in the middle of the lower border of the costal margin and uppermost border of the iliac crest to the nearest 0.1 cm. Hip circumference was measured as the maximal circumference over the buttocks. Waist-to-hip ratio was calculated from the values of waist and hip circumference. Blood pressure was taken two times in a sitting position from the right arm of the subject by a standard mercury sphygmomanometer.

Biochemical measurements

Blood samples were collected after an overnight fast of 8–12 hours. Fasting blood glucose (FBG) levels were determined by the glucose oxidase method on Huma Star 180 chemistry analyser (Human, Wiesbaden, Germany).

Blood insulin, leptin and LEPR levels were determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits on an automated EIA analyser (Bio-Rad Laboratories, Hercules, CA, USA). Fasting blood glucose and fasting insulin concentrations were taken to measure homeostasis model assessment of insulin resistance (HOMA-IR). $\text{HOMA-IR} = \text{Fasting insulin } (\mu\text{ IU/ml}) \times \text{Fasting glucose (mmol/L)} / 22.5$ (15).

DNA extraction and genotyping of rs1137101 variant

DNA was extracted from whole blood using a genomic DNA purification kit (Fermentas, Waltham, MA, USA). Genotyping of rs1137101 variant was carried out by PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism assay). A DNA fragment containing rs1137101 variant site was amplified using a specific forward (5'TAAGCTGGGTGTCCCAAATA3') and reverse (5'AGCAAAGTGAGATAAGCT3') primer-pair. The PCR was done on Icyler 5 (Bio-Rad). The PCR reaction mix was composed of 100 μg DNA, 1X Taq buffer, 2 mM MgCl_2 , 0.2 mM of each dNTP, 10 μmol of each primer and 0.5 U Taq DNA polymerase in a final volume of 25 μl . The PCR conditions involve initial denaturation at 95°C for 4 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 58°C for 30 seconds and extension at 72°C for 1 minute, and then a final extension step at 72°C for 10 minutes. MspI restriction enzyme (Favorgen, Taiwan) was used to digest amplified products of 424 bp in order to examine rs1137101 variant by RFLP assay. Presence of the A allele generated a single fragment of 424 bp, whereas presence of the G allele revealed two fragments of 285 and 139 bp (Figure)

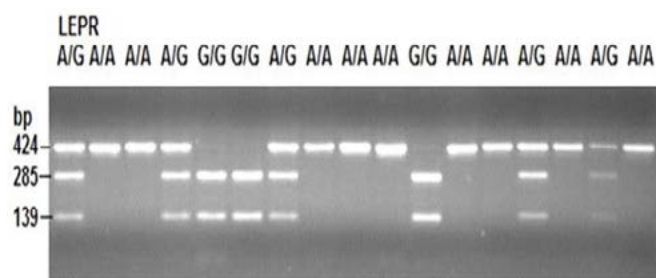


Figure: Restriction fragment length polymorphism (RFLP) analysis of rs1137101 variant in the LEPR gene.

Statistical analysis

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) software was used for analysing the data. Quantitative variables were expressed as mean $\pm$ standard error of mean (SEM).

Student's *t*-test was applied to observe the differences between cases and controls. The whole data were stratified according to age and sex into subcategories.

Hardy-Weinberg equilibrium test was applied to determine the variation in distribution of alleles and genotypes. Allelic frequencies were calculated by gene counting. Chi-square test was used to determine the significant differences in genotype and allelic frequencies between study and control groups. Association of rs1137101 variant (A>G transition) with obesity was determined by Pearson Chi-square using co-dominant, dominant and recessive models. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to determine the risk of obesity associated with the risk allele. The association of rs1137101 variant with anthropometric and metabolic traits was determined using a general linear model assuming co-dominant, dominant and recessive genetic models. The genotypes were coded as (0, 1 and 2) in co-dominant model, (0 and 1) in dominant model and (1, 0) in recessive model corresponding to the number of copies of risk allele. Analysis of variance, Tukey post hoc analysis and *t*-test were applied to test the differences of obesity-related anthropometric and metabolic traits across genotypes of rs1137101 variant adjusted for age and sex. Bonferroni adjustment was carried out for multiple comparisons. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

Obese subjects and high-risk factors for cardiometabolic disorders

In our study, family history of obesity (FHO) was found in 77% of the obese subjects (one or both parents) as compared to FHO in 31% of the control subjects. Hypertension (HTN) was found in 18% of the obese subjects, whereas no control subject was found to be hypertensive. Similarly, among obese subjects, 7% were found to have type 2 diabetes (T2D) and 33.4% had impaired fasting glucose (IFG) in comparison to 2% of the control subjects were diabetic and 3% had IFG. Acanthosis nigricans was observed in 43% of the obese subjects as compared to 3.2% of the controls. Cardiovascular disease (CVD) was observed in 4.2% of the obese subjects, whereas no control subject had CVD. There was no significant difference found between body height (HT) of obese and control subjects. Waist and hip circumference and waist-to-hip-ratio (WHR) of obese subjects were found significantly greater than that of control subjects ($p < 0.05$). Obese subjects were found to have significantly higher SBP and DBP ($p < 0.05$) as

compared to the control subjects. Insulin levels and HOMA-IR values of obese subjects were found significantly ($p < 0.05$) higher as compared to that of control subjects. Leptin levels of the obese subjects were higher and LEPR levels were significantly lower as compared to that of control subjects. This above comparison of various parameters between obese and control subjects clearly indicates that obese individuals are more prone to develop various cardiometabolic disorders.

Genotypic frequencies of rs1137101 variant in obese and control subjects

The genotypes of rs1137101 variant were in Hardy–Weinberg equilibrium ($p > 0.05$) in both obese and control individuals. There was no significant difference ($p > 0.05$) in the genotype and allele frequencies of LEPR rs1137101 variant between obese and control subjects (Table 1). Analysis of whole data after stratification by sex revealed no significant difference in the genotype and allele frequencies ($p > 0.05$) between obese and non-obese males and similarly obese and non-obese females (Table 1). When all obese and control subjects were further stratified according to age in two categories ≤ 18 years and > 18 years, no significant difference was found in the genotype and allele frequencies between obese and control subjects > 18 years and ≤ 18 years ($p > 0.05$) (Table 1). Similarly, stratification of obese and control subjects > 18 years and ≤ 18 years into male and female subcategories revealed no significant difference in genotype and allele frequencies between > 18 years obese and control females, > 18 years obese and control males, ≤ 18 years obese and control females, and ≤ 18 years obese and control males (Table 1). Overall, these results revealed no significant difference in the frequencies of genotypes and alleles between obese and control subjects with and without stratification of the data according to age and sex.

Table 1: Genotype and allele distribution of LEPR rs1137101 variant in obese and non-obese subjects

	All subjects				Females		Males		> 18 years				Females > 18 years				Males > 18 years				≤ 18 years				Females ≤ 18 years				Males ≤ 18 years			
	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR	Obese	Non-obese	n	OR				
Co-dominant model																																
GG	34 (14%)	18 (14%)	52	0.78	16 (14.5%)	6 (11%)	22	0.78	11 (17%)	6 (13%)	17	0.83	6 (17%)	12 (14%)	27 (17%)	0.91	16 (17%)	16 (15%)	32	0.81	11 (17%)	6 (13%)	17	0.83	7 (9%)	7 (16%)	14	0.77	2 (6%)	7 (21%)	5 (11%)	0
AG	98 (41%)	56 (43%)	154	0.964	42 (38%)	28 (49%)	70	0.93	27 (42%)	22 (48%)	49	0.83	43 (44%)	39 (45%)	82	0.81	43 (44%)	43 (41%)	86	0.81	27 (42%)	22 (48%)	49	0.83	28 (36%)	19 (43%)	47	0.28	13 (42%)	13 (39%)	15 (33%)	6 (55%)
AA	105 (44%)	57 (43%)	162	0.964	52 (47%)	23 (40%)	75	0.78	36 (39%)	36 (41%)	72	0.78	37 (39%)	36 (41%)	73	0.78	37 (39%)	37 (44%)	74	0.78	26 (40%)	18 (39%)	44	0.77	42 (55%)	18 (41%)	60	0.28	16 (52%)	13 (39%)	26 (56%)	5 (45%)
Dominant model																																
GG+AG	132 (55%)	74 (56%)	206	0.92	58 (53%)	34 (60%)	92	0.92	38 (59%)	28 (61%)	66	0.92	59 (61%)	51 (59%)	110	0.92	59 (61%)	53 (56%)	112	0.92	38 (59%)	28 (61%)	66	0.92	35 (45%)	26 (59%)	61	0.28	15 (48%)	20 (61%)	20 (43%)	6 (55%)
AA	105 (44%)	57 (43%)	162	0.964	52 (47%)	23 (40%)	75	0.78	36 (39%)	36 (41%)	72	0.78	37 (39%)	36 (41%)	73	0.78	37 (39%)	37 (44%)	74	0.78	26 (40%)	18 (39%)	44	0.77	42 (55%)	18 (41%)	60	0.28	16 (52%)	13 (39%)	26 (56%)	5 (45%)
Recessive model																																
GG	34 (14%)	18 (14%)	52	0.78	16 (14.5%)	6 (11%)	22	0.78	11 (17%)	6 (13%)	17	0.83	6 (17%)	12 (14%)	27 (17%)	0.91	16 (17%)	16 (15%)	32	0.81	11 (17%)	6 (13%)	17	0.83	7 (9%)	7 (16%)	14	0.77	2 (6%)	7 (21%)	5 (11%)	0
AG	203 (85%)	113 (86%)	316	0.86	94 (85.4%)	51 (89%)	145	0.86	63 (83%)	63 (83%)	126	0.86	80 (83%)	75 (86%)	155	0.86	80 (83%)	80 (85%)	160	0.86	53 (83%)	40 (87%)	93	0.85	70 (90%)	37 (84%)	107	0.25	29 (94%)	26 (79%)	41 (89%)	11 (100%)
AA	105 (44%)	57 (43%)	162	0.964	52 (47%)	23 (40%)	75	0.78	36 (39%)	36 (41%)	72	0.78	37 (39%)	36 (41%)	73	0.78	37 (39%)	37 (44%)	74	0.78	26 (40%)	18 (39%)	44	0.77	42 (55%)	18 (41%)	60	0.28	16 (52%)	13 (39%)	26 (56%)	5 (45%)
Alleles																																
G	166 (35%)	92 (35%)	258	0.97	74 (33.6%)	40 (35%)	114	0.97	49 (38%)	34 (37%)	83	0.97	75 (39%)	63 (36%)	138	0.97	75 (39%)	75 (39%)	150	0.97	49 (38%)	34 (37%)	83	0.97	42 (27%)	33 (38%)	75	1.27	17 (27%)	27 (41%)	25 (27%)	6 (27%)
A	308 (65%)	170 (65%)	478	0.99	146 (66.3%)	74 (65%)	220	0.99	79 (62%)	58 (63%)	137	0.99	117 (61%)	111 (64%)	228	0.99	117 (61%)	117 (61%)	234	0.99	79 (62%)	58 (63%)	137	0.99	112 (73%)	55 (62%)	167	0.09	45 (72%)	39 (59%)	67 (73%)	16 (73%)

A = wild; G = polymorphic

LEPR rs1137101 variant and obesity

No significant association of any genotype or allele of the LEPR rs1137101 was observed with obesity ($p > 0.05$) in any of the genetic models (co-dominant, dominant or recessive models) used in the current study (Table 1). When the entire data were stratified according to age and sex, no significant association of any LEPR rs1137101 genotype or allele with obesity was found in any of the subcategories ($p > 0.05$). Thus, no age and sex-specific association of LEPR rs1137101 variant with obesity was observed in our study (Table 1).

LEPR rs1137101 variant and various obesity grades

The entire study population was stratified with respect to the WHO criteria of BMI into overweight (BMI 25.00–29.99), obese grade I (BMI 30.00–34.99), obese grade II (BMI 35.00–39.99), obese grade III (BMI ≥ 40.00), and super obese (BMI ≥ 50) groups. No significant association ($p > 0.05$) of any genotype (AA, AG or GG) with any grade of obesity was observed (Table 2).

Table 2: Genotype frequencies of LEPR rs1137101 variant across different obesity grades

Obesity status							
	Obese			Non-obese			χ^2/p
Grades of obesity	GG	GA	AA	GG	GA	AA	
Grade I obese (BMI ≥ 30)	22%	42%	36%				2.07/0.355
Grade II obese (BMI ≥ 35)	13%	43%	44%	13%	46%	41%	0.17/0.91
Grade III obese (BMI ≥ 40)	15%	32%	53%				1.85/0.39

Chi-square analysis of genotypes.

BMI = body mass index.

LEPR rs1137101 variant, and anthropometric and metabolic traits

General linear model multivariate analysis revealed no significant association ($p > 0.05$) of the LEPR rs1137101 variant with any of the anthropometric and metabolic traits, including BW, HT, BMI, WC, HC, WHR, SBP, DBP, FBG, insulin levels, HOMA-IR, and leptin and LEPR levels (Table 3). There were no significant differences ($p > 0.05$) in anthropometric and metabolic parameters observed between carriers of AA, AG, and GG genotypes (Table 3).

DISCUSSION

The current study examined the association of the LEPR rs1137101 variant with obesity and associated anthropometric and metabolic parameters in obese and non-obese

Table 3: Differences of anthropometric and metabolic traits across genotypes of LEPR variant (mean $\pm$ SEM)

	AA n = 162	AG n = 156	GG n = 54	p-value
Body weight (kg)	82.42 $\pm$ 2.55	77.41 $\pm$ 3.47	73.4 $\pm$ 2	0.262
Height (m)	1.54 $\pm$ 0.016	1.59 $\pm$ 0.01	1.57 $\pm$ 0.01	0.217
BMI (kg/m ²)	33.69 $\pm$ 0.68	30 $\pm$ 1.06	29.38 $\pm$ 2	0.603
Waist(cm)	102.3 $\pm$ 1.71	92.3 $\pm$ 2.5	91.19 $\pm$ 1.77	0.622
Hip (cm)	111.8 $\pm$ 1.88	104 $\pm$ 2.18	102 $\pm$ 1.77	0.485
WHR	0.91 $\pm$ 0.007	0.87 $\pm$ 0.01	0.88 $\pm$ 0.006	0.925
SBP (mmHg)	121.45 $\pm$ 1.80	116 $\pm$ 1.8	115 $\pm$ 1.4	0.613
DBP (mmHg)	82 $\pm$ 1.18	78 $\pm$ 1.3	77.8 $\pm$ 0.95	0.436
FBS (mg/dL)	103.32 $\pm$ 3.98	93.1 $\pm$ 2	97.3 $\pm$ 2.64	0.536
Insulin (μ IU/ml)	22.50 $\pm$ 1.93	15.7 $\pm$ 2.9	16.6 $\pm$ 1.37	0.841
HOMA	5.12 $\pm$ 0.51	3.5 $\pm$ 0.71	3.84 $\pm$ 0.36	0.887
Leptin (ng/ml)	28.78 $\pm$ 3.8	22.08 $\pm$ 1.838	24.28 $\pm$ 1.81	0.504
Leptin receptor (ng/ml)	15.53 $\pm$ 0.93	18.67 $\pm$ 1.65	17.3 $\pm$ 0.79	0.956

Data are presented as mean $\pm$ SEM and was compared by analysis of variance followed by Tukey Post hoc test. $p < 0.05$ was considered statistically significant.

BMI = body mass index; WHR = waist-to- hip ratio; SBP= systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar; HOMA = homeostasis model assessment.

subjects of the Pakistani population. Both obese male and female subjects in the current study showed higher WHR than normal values, but male subjects with obesity had significantly higher WHR than female subjects with obesity, and therefore, they were predisposed to high risk of developing CVD (16). A WHR > 0.9 in males and > 0.85 in females is considered as a parameter for the diagnosis of CVD (17).

In the current study, obese subjects had significantly higher leptin levels as compared to control subjects; hyperleptinemia and leptin resistance might be involved in the development of hyperinsulinaemia and insulin resistance as shown by high HOMA-IR in the obese subjects of our study, a risk for development of T2D in later life (18). High FBG and high insulin levels found in obese subjects of our study might serve as a biomarker of disturbed carbohydrate metabolism and a future risk for T2D in these subjects. A significant correlation of plasma leptin levels with BMI in obese subjects was also seen in the current study. This observation is in agreement with previous reports (19, 20). Moreover, a positive correlation of leptin with BMI, WC, HC, HOMA-IR, and SBP in the obese subjects of the current study suggests that it is a possible risk factor for predisposition to HTN, CVD and T2D. A high leptin level induces endothelial damage and inflammatory reaction in blood vessels; these alterations may contribute to the pathogenesis of HTN (21).

Lack of association between rs1137101 variant of the LEPR gene and obesity in our study indicates that the amino acid change as a result of this polymorphism might not affect the phenotype of the subject in our population. This variant occurs in the CRH1 domain, which is not essential for high-affinity leptin binding (12). Stratigopoulos *et al.* observed no difference in adiposity between wild-type and Q223R isogenic mice fed a high fat diet (13). Recently, Verkerke *et al.* also reported that the rs1137101 variant in the LEPR extracellular CRH1 domain does not affect the rates at which leptin binds to and dissociates from its receptor (22).

Regarding the role of rs1137101 variant in obesity, the results of different association studies are controversial. The present study showed no association of this variant with obesity in adults or in the younger group (≤ 18 years). Likewise, no significant difference was observed in anthropometric parameters such as BMI, WC, HC, and WHR across genotypes of this variant. These findings are consistent with initial studies that also failed to identify any association of this variant with the risk of obesity (23–27). Later, the pooled and meta-analysis of genetic data by Heo *et al.* (10, 28) revealed conflicting results regarding the association of this polymorphism with BMI. Another meta-analysis by Paracchini *et al.* (29) involving 10 studies carried out in Asians, Caucasians, Pima Indians and Brazilians also reported no association of this variant with obesity. Large variation in the allelic frequency across different ethnicities and countries has been reported. Asian populations (Japan and Korea) showed relatively higher frequencies (0.85) of G allele than other populations. In contrast, our study reported a lower (0.35) allelic frequency of G allele. Yiannakouris *et al.* (30) observed an increased risk of obesity in G allele carriers, whereas Portolés *et al.* (31) found an inverse association of rs1137101 variant with obesity, which described that carriers of G allele had low BMI in the Mediterranean Spanish population; later on similar results were reported by Furusawa *et al.* (32) in a Pacific Island population demonstrating that carriers of A allele had high BW and BMI. Lack of association of rs1137101 genetic variant with obesity in the present study is in agreement with a recent study on Turkish children (33).

The present study also reported no difference in the metabolic parameters such as FBG, insulin, HOMA-IR, leptin and LEPR levels across genotypes of rs1137101 variant. Lack of association of rs1137101 variant with

leptin levels in the current study is in line with a previous report (29). Guízar-Mendoza *et al.* (34) reported high body fat percentage and plasma leptin levels in carriers of A allele and low levels in G allele carriers in the Mexican adolescent population. However, another study reported high plasma leptin levels in G allele carriers in Greek subjects (30). There was no association of plasma LEPR levels with rs1137101 variant in our study that is similar to the observation of Ogawa *et al.* in the Japanese population (35).

The current study showed no association of rs1137101 variant with obesity in both males and females, whereas Masuo *et al.* reported gender-specific effect with association of this variant with obesity in Caucasian males (36). Another study in Caucasians reported an association of higher BMI with G allele carrier girls but not in boys (37). A recent meta-analysis revealed no association of rs1137101 variant with overweight and obesity including no gender-specific effect and hence supports the results of the current study (38). The lack of association of rs1137101 variant with obesity and obesity-related anthropometric and biochemical parameters seen in the current study is also in agreement with many previous reports (23–27, 29, 33, 37, 38). However, a recent study from Pakistan reported the association of rs1137101 variant with BMI, SBP, DBP and weight in obese subjects (39). This disagreement with our study may be attributable to the differences in the inclusion and exclusion criteria of the two studies.

In a nutshell, lack of association of rs1137101 variant of the LEPR gene with obesity and obesity-related anthropometric and metabolic traits in our study implies that this variant appears to have no role in causing susceptibility of our population to obesity and associated cardiometabolic disorders. The findings of the current study can be further validated by conducting similar studies with the same exclusion and inclusion criteria and by considering a bigger sample size.

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AUTHORS’ NOTE

The authors declare that they have no conflicts of interest.

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