No Role of rs1137101 Variant of the Leptin Receptor Gene in Manifestation of Obesity
A Shahid¹,2, S Rana¹,3, S Mahmood⁴

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 effect by binding to leptin receptor; consequently, genetic variants of leptin receptor may be important in pathophysiology of human obesity. The current study was, therefore, carried out to find association of leptin receptor rs1137101 variant with obesity and associated anthropometric and metabolic parameters in a sample of Pakistani population.

Methods: DNA samples from a total of 239 obese and 155 non-obese human subjects with age range of 5 to 45 years were genotyped for 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 (BP) was monitored, and measurements of body weight, height, waist and hip circumference were recorded. Body mass index (BMI) and Waist-to-Hip Ratio (WHR) were calculated. Levels of fasting blood glucose (FBG), insulin, leptin and leptin receptor were determined, and insulin resistance (IR) 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 Pakistani population.

Keywords: Leptin receptor, obesity, Pakistan, rs1137101 variant

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INTRODUCTION

Leptin receptor (LEPR) is a single transmembrane protein that belongs to class I cytokine receptor family (1). Leptin, an adipokine and central regulator for adiposity-sensing pathways, exerts its physiological effect by binding to LEPR in the hypothalamus. It functions as a satiety signal by downregulating orexigenic (appetite-stimulating) peptides and upregulating anorexigenic (appetite-decreasing) peptides (2). LEPR is a product of the leptin receptor gene that is located on human chromosome 1p31 and consists of 20 exons (3). The expression of the leptin receptor 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 receptors form homodimers, and binding of the leptin to the receptors activates Janus activated Kinases (JAK), which in turn activate signal transducers and activators of transcription (STAT). Leptin signaling through the JAKs and activation of transcription system for regulating body fat mass is mainly associated with the longest form (LEPRb) of leptin receptor that contains both conserved sequence motifs necessary for the binding of the Janus activated kinases (JAK) and STAT family of signal transducing factors required for full leptin signaling function (7). The shorter isoforms lack STAT binding element, 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).
LEPR gene has been extensively studied in search for several common variants that may be important in pathophysiology of human obesity (10). One of these variants is nonsynonymous Q223R (rs1137101) in exon 6 of the human LEPR gene at codon 223 (11). LEPR contains two extracellular cytokine receptor homology domains (CRH1 and CRH2). CRH2 domain is necessary and sufficient for leptin binding whereas CRH1 is not essential for a high affinity interaction (12). 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 the other population. In particular, the data on the status of this variant in relation to obesity in 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 Pakistani population.

SUBJECTS AND METHODS

The study was performed at University of Health Sciences Lahore 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 BMI ≥ 30 Kg/m² or ≥95th percentile and 155 control subjects with BMI< 25 Kg/m² or 5th-85th percentile. The age range
of the participants was between 5 to 45 years. Simple random sampling was applied for the collection of blood specimens. Subjects with the 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.

**Categorization 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 by BMI ≥30 and normal weight BMI <25 (14). The subjects ≤18 years of age were considered obese by ≥95th percentile and normal weight by 5th–85th percentile by following BMI for age growth charts recommended by Center for Disease Control and Prevention (CDC).

**Demographic information and physical examination**

Full demographic information including name, age, sex, address, education and socioeconomic status was documented on a questionnaire. 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, height, waist (WC) and hip circumference (HC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standard procedures (14). Body height was taken by stadiometer and body weight was measured on digital weighing scale. The body mass index (BMI) of each subject was calculated as weight in kilograms divided by height in meters
squared. WC 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. BP 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 analyzer (Human, Wiesbaden, Germany). Blood insulin, leptin and leptin receptor levels were determined by ELISA (enzyme-linked immunosorbent assay) using commercial kit on an automated EIA analyzer (Bio-Rad Laboratories, Hercules, CA, USA). FBG and fasting insulin concentrations were taken to measure homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR = Fasting insulin (µ IU/ml) × Fasting glucose (mmol/l)/22.5 (15).

**DNA Extraction and Genotyping of rs1137101 Variant**

DNA was extracted from whole blood using genomic DNA purification kit (Fermentas, 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’AGCAAAAGTGAGATAAGCT3’) primer-pair. The PCR was done on Icycler 5 (BioRad, USA). PCR reaction mix was composed of 100 µg DNA, 1X Taq buffer, 2 mM MgCl2, 0.2 mM of each dNTP, 10 pmol of each primer and 0.5 U Taq DNA polymerase in a final volume of 25
μl. PCR conditions involve: initial denaturation at 95°C for 4 min, followed by 35 cycles of
denaturation at 94°C for 30 sec, annealing at 58°C for 30 sec and extension at 72°C for 1 min,
and then a final extension step at 72°C for 10 min. 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 A allele generated a single fragment of 424 bp whereas presence of G allele
revealed two fragments of 285 bp and 139 bp (Fig.1)

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, USA, version 17.0) software
was used for analyzing the data. Quantitative variables were expressed as mean ± standard error
of mean (SEM). Student’s t-test was applied to observe the differences between cases and
controls. The whole data was stratified according to age and sex in sub-categories.

Hardy Weinberg equilibrium test (HWE) was applied to determine the variation in distribution of
alleles and genotypes. Allelic frequencies were calculated by gene counting. Chi-square (χ²) test
was used to determine the significant differences of 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 interval (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 General Linear Model (GLM) 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 (ANOVA), 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 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 (AN) 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 heights (HT) of obese and control subjects. Waist, hip circumference and 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 leptin receptor levels were significantly lower as compared to that of control subjects. This above comparison of various parameters between obese and control subjects clearly indicate 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 gender 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 sub-categories 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 gender.

Lepr rs1137101 variant and obesity

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

**Lepr rs1137101 variant and various obesity grades**

The whole study population was stratified with respect to 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 also super obese (≥ 50) groups. No significant association (p>0.05) of any genotype (AA, AG or GG) with any grade of obesity was observed (Table 2).

LEPR rs1137101 Variant and, Anthropometric and Metabolic Traits

GLM multivariate analysis revealed no significant association (p>0.05) of 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 leptin receptor 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 leptin receptor rs1137101 variant with obesity and associated anthropometric and metabolic parameters in obese and non-obese subjects of Pakistani population. Both obese male and female subjects of 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). 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 hyperinsulinemia 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 the previous reports (19, 20). Moreover, a positive correlation of leptin with BMI, waist and hip circumference, IR and SBP in the obese subjects of the current study suggests that it is a possible risk factor for predisposition to hypertension (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 the of LEPR gene and obesity in our study indicates that 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. (2009) observed no difference in adiposity between wild-type and Q223R isogenic mice fed a high fat diet. Recently, Verkerke et al. (2014) 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 younger group (≤18 years). Likewise, no significant difference was observed in anthropometric parameters such as BMI, waist and hip circumference 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 on 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 ten 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 population (Japan and Korea) showed relatively higher frequency (0.85) of G allele than other populations. In contrast, our study reported low (0.35) allelic frequency of G allele. Yiannakouris et al. (30) observed increase risk of obesity in G allele carriers whereas Portolés et al. (31) found inverse association of rs1137101 variant with obesity, which described that carriers of G allele had low BMI in Mediterranean Spanish population; later on similar results were reported by Furusawa et al. (32) in 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 leptin receptor levels across genotypes of rs1137101 variant. Lack of association of rs1137101 variant with leptin levels in the current study is in line with the previous report (29). Guízar-Mendoza et al. (34) reported high body fat percentage and plasma leptin levels in carriers of A allele and low in G allele carriers of Mexican adolescent population. However, another study reported high plasma leptin levels in G allele carriers in Greek subjects
There was no association of plasma leptin receptor levels with rs1137101 variant in our study that is similar to the observation of Ogawa et al. in 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 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 body mass index, systolic and diastolic blood pressure, 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 more similar studies with same exclusion and inclusion criteria and by considering a bigger sample size.
ACKNOWLEDGMENTS

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AUTHORS’ NOTE

Authors declare that they have no conflict of interest.
REFERENCES


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

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| Alleles | 0.001/   | 0.01/ | 0.02/ | 0.03/ | 0.04/ |

A=Wild, G=polymorphic
Table 2: Genotype frequencies of LEPR rs1137101 variant across different obesity grades

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<td>Non-obese</td>
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<td>Grade I obese (BMI ≥ 30)</td>
<td>GG 22%</td>
<td>GA 42%</td>
<td>AA 36%</td>
<td>2.07/0.355</td>
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<td>Grade II obese (BMI ≥35)</td>
<td>13%</td>
<td>43%</td>
<td>44%</td>
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<td>Grade III obese (BMI ≥ 40)</td>
<td>15%</td>
<td>32%</td>
<td>53%</td>
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Chi Square analysis of genotypes
Table 3: Differences of anthropometric and metabolic traits across genotypes of LEPR variant (mean ±SEM)

Data is presented as mean ± SEM and was compared by ANOVA followed by Tukey post hoc test. P < 0.05 was considered statistically significant

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<th>AA</th>
<th>AG</th>
<th>GG</th>
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<td>Body Weight (Kg)</td>
<td>82.42±2.55</td>
<td>77.41±3.47</td>
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<td>Height (m)</td>
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<td>BMI(Kg/m²)</td>
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<td>Waist(cm)</td>
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<td>Hip (cm)</td>
<td>111.8±1.88</td>
<td>104±2.18</td>
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<td>WHR</td>
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<td>Insulin (µIU/ml)</td>
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<td>HOMA</td>
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<td>Leptin (ng/ml)</td>
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<tr>
<td>Leptin receptor (ng/ml)</td>
<td>15.53±0.93</td>
<td>18.67±1.65</td>
<td>17.3±0.79</td>
<td>0.956</td>
</tr>
</tbody>
</table>
Figure. Restriction Fragment Length Polymorphism (RFLP) analysis of rs1137101 variant in the LEPR gene.