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Association of the G/G Genotype with Insulin Resistance, Dyslipidemia, And Hyperleptinemia

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Abstract

Background. Obesity is a multifactorial disease arising from interactions among environmental, behavioural, metabolic, and genetic factors. The leptin signalling system is a key component of the central regulation of energy balance. The rs1137100 polymorphism of the leptin receptor gene (LEPR) results in the Lys109Arg amino acid substitution and may be associated with variability in leptin sensitivity and the metabolic characteristics of obesity. However, findings vary considerably across populations.

Objective. To evaluate the distribution of alleles and genotypes of the LEPR rs1137100 polymorphism in patients with overweight and obesity and to determine the associations between these genotypes and lipid metabolism, insulin resistance, and circulating leptin levels.

Materials and Methods. The clinical cohort included 171 patients with overweight or obesity. Molecular genetic testing was performed in 74 patients (67 women and 7 men; mean age, 38.5 ± 1.4 years; mean body mass index [BMI], 37.7 ± 0.8 kg/m²). The control group consisted of 70 apparently healthy individuals with normal body weight (mean BMI, 22.6 ± 0.6 kg/m²). Genomic DNA was isolated from peripheral blood leukocytes using the NK-Magnit Base-96 kit. The rs1137100 polymorphism was genotyped using polymerase chain reaction followed by restriction fragment analysis. The A and G alleles and the A/A, A/G, and G/G genotypes were identified. The

metabolic phenotype was assessed based on total cholesterol, low-density lipoprotein cholesterol, triglyceride and leptin concentrations, as well as the homeostatic model assessment of insulin resistance (HOMA-IR). Statistical analyses were performed using STATISTICA version 10.0 and Epi Info version 7.2.2.2.

Results. The G/G genotype was identified in 32.4% of patients and 12.9% of controls (OR = 3.25; 95% CI, 1.42–7.44; p = 0.006, Fisher's exact test). The frequency of the G/G genotype was 30.8% among patients with overweight or class I–II obesity and 36.4% among those with class III obesity; however, direct comparison according to obesity severity revealed no statistically significant differences. Within the patient group, the metabolic parameters progressively worsened across the A/A, A/G, and G/G genotypes. Compared with A/A carriers, G/G carriers had higher levels of low-density lipoprotein cholesterol (3.71 ± 0.05 vs 3.03 ± 0.04 mmol/L), triglycerides (2.23 ± 0.03 vs 1.64 ± 0.03 mmol/L), total cholesterol (5.81 ± 0.06 vs 4.95 ± 0.08 mmol/L), HOMA-IR (4.34 ± 0.04 vs 2.81 ± 0.05), and leptin (29.87 ± 0.80 vs 21.30 ± 0.90 ng/mL).

Conclusion. In the study population, the G/G genotype of the LEPR rs1137100 polymorphism was associated with obesity and a more adverse metabolic phenotype. However, this genotype did not independently differentiate between obesity severity categories. These findings suggest that the G/G genotype may be considered a candidate marker of a metabolically adverse obesity phenotype, although confirmation in larger independent cohorts and multivariable models is required.

Keywords: Obesity; LEPR; rs1137100; K109R; leptin receptor; insulin resistance; dyslipidaemia; hyperleptinaemia.

Introduction

Obesity is a chronic, relapsing disease in which excessive adipose tissue accumulation is associated with an increased risk of type 2 diabetes mellitus, atherosclerotic cardiovascular disease, metabolic dysfunction-associated steatotic liver disease, certain malignancies, and premature mortality [1–3]. The current concept of obesity extends beyond a simple consequence of positive energy balance and recognises it as a biologically heterogeneous condition resulting from complex interactions among environmental, behavioural, neuroendocrine, and polygenic factors [1, 4, 20]. Considerable interindividual variability in body weight and metabolic complications under similar dietary and physical activity conditions further supports the involvement of hereditary mechanisms.

Leptin, secreted predominantly by adipocytes, is one of the principal peripheral signals that informs the central nervous system about the status of the body's energy stores [5–8]. In the hypothalamus, leptin binding to the long signalling isoform of the leptin receptor (LEPR) activates the JAK2–STAT3, PI3K–AKT, and MAPK-dependent pathways, stimulates anorexigenic POMC/CART neurons, and inhibits orexigenic NPY/AgRP neurons [5–7]. Alpha-melanocyte-stimulating hormone (α-MSH), generated through the POMC pathway, activates melanocortin-4 receptors (MC4R), thereby promoting satiety and increasing energy expenditure.

In common obesity, circulating leptin concentrations generally increase in proportion to adipose tissue mass; however, the expected reduction in appetite and body weight does not occur. This condition is referred to as leptin resistance [6–9]. The proposed mechanisms include impaired leptin transport across the blood–brain barrier, reduced receptor expression or sensitivity, activation of the negative regulators SOCS3 and PTP1B, hypothalamic inflammation, and endoplasmic reticulum stress [6–9]. Leptin resistance may sustain hyperphagia while also interacting with impaired insulin signalling, ectopic lipid accumulation, and chronic low-grade inflammation [8–10].

The LEPR gene is located on chromosome 1p31.3 and encodes a transmembrane receptor belonging to the class I cytokine receptor family [7, 11]. The rs1137100 single-nucleotide variant is an A>G substitution that results in the replacement of lysine with arginine at amino acid position 109 (K109R, Lys109Arg) within the extracellular domain of the receptor. Theoretically, this substitution may affect the three-dimensional organisation of the protein, ligand binding, or signal transduction efficiency. However, the functional effect of this common variant is not comparable to that of rare pathogenic LEPR mutations causing severe early-onset obesity. Therefore, the clinical effect of rs1137100 should be regarded as probabilistic and population-dependent [11–13].

Recent studies of common LEPR variants have produced heterogeneous results. In certain populations, rs1137100 has been associated with BMI, obesity, or metabolic characteristics [12–14, 17, 19], whereas other studies have not confirmed an independent association between K109R and obesity [18]. These inconsistencies may be attributable to ethnic differences in allele frequencies, small sample sizes, sexual dimorphism in the leptin system, variations in study design, and linkage disequilibrium between rs1137100 and other LEPR variants [12–19].

Most published studies have assessed rs1137100 primarily in relation to BMI or the categorical presence of obesity. Considerably less evidence is available regarding whether this variant is associated with a distinct metabolic profile among individuals with obesity. The simultaneous assessment of lipid parameters, HOMA-IR, and circulating leptin levels enables the analysis to extend beyond a simple genetic association towards a more clinically meaningful characterisation of the genotype-associated phenotype [9, 10, 14].

The aim of the present study was to evaluate the distribution of alleles and genotypes of the LEPR rs1137100 polymorphism in patients with overweight and obesity and to determine the associations of the A/A, A/G, and G/G genotypes with lipid metabolism, insulin resistance, and circulating leptin levels.

Methods

Study Design and Participants

This observational comparative study included a clinical cohort of 171 patients with overweight or obesity, comprising 136 women and 35 men, with a mean age of 43.18 ± 1.15 years. Molecular genetic testing was performed in a subgroup of 74 patients, including 67 women and 7 men. Their mean age was 38.5 ± 1.4 years, and their mean body mass index (BMI) was 37.7 ± 0.8 kg/m². The control group consisted of 70 apparently healthy individuals with normal body weight and a mean BMI of 22.6 ± 0.6 kg/m².

According to BMI categories, 7 patients were overweight, 21 had class I obesity, 24 had class II obesity, and 22 had class III obesity. For the analysis according to obesity severity, the patients were divided into two groups. Group I included 52 patients with overweight or class I–II obesity (mean BMI, 34.07 ± 0.50 kg/m²), whereas Group II comprised 22 patients with class III obesity (mean BMI, 46.3 ± 1.4 kg/m²). BMI categories were defined according to the standard criteria for adults.

Table 1. Distribution of Patients in the Study Group According to BMI Categories

Category	BMI, kg/m²	n	%
Overweight	25,0–29,9	7	9,5
Class I obesity	30,0–34,9	21	28,4
Class II obesity	35,0–39,9	24	32,4
Class III obesity	≥40,0	22	29,7
Total	-	74	100,0

Table 1 shows that the genetic subgroup encompassed the full range of elevated BMI categories, although most participants had clinically established obesity. Patients with class II–III obesity accounted for 62.1% of the subgroup, while 29.7% had class III obesity. Thus, the sample was suitable not only for comparison with individuals of normal body weight but also for evaluating whether the genetic association became more pronounced with increasing obesity severity. Moreover, the relatively similar numbers of patients with class I, II, and III obesity reduced the likelihood that the findings were driven by a single predominant BMI category.

A more detailed examination of Table 1 shows that only 7 of the 74 participants (9.5%) were overweight without meeting the criteria for obesity. Consequently, 90.5% of the genetic subgroup had obesity. Class II obesity represented the largest individual category, comprising 24 patients (32.4%), followed closely by class III obesity, which was identified in 22 patients (29.7%). Class I obesity was recorded in 21 patients (28.4%). This distribution indicates that the study population was predominantly characterised by marked adiposity, consistent with the mean BMI of 37.7 ± 0.8 kg/m².

Combining patients with overweight and class I–II obesity into Group I provided an adequate sample size for comparison with the control group; however, it also resulted in substantial within-group heterogeneity in BMI. In contrast, Group II was more clinically homogeneous but had a smaller sample size. Therefore, the absence of statistically significant differences between the two patient groups should be interpreted in the context of potentially insufficient statistical power rather than as conclusive evidence that the genotype has no effect on obesity severity.

Anthropometric assessment included measurements of body weight, height, and waist circumference. Body weight was measured in the morning using electronic scales, and height was measured using a stadiometer. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Body mass index was calculated using the Quetelet formula: BMI = body weight (kg)/height² (m²). Obesity severity was classified according to the World Health Organization criteria.

The inclusion criterion for the patient group was a BMI ≥25.0 kg/m², whereas individuals included in the control group were required to have a BMI of 18.5–24.9 kg/m². The exclusion criteria were overt untreated hypothyroidism; endogenous hypercortisolism or other established endocrine disorders associated with secondary obesity; severe renal, hepatic, or cardiovascular diseases accompanied by oedema or marked fluid retention; pregnancy; current use of medications known to have a substantial effect on body weight; and confirmed syndromic or monogenic forms of obesity, including Prader–Willi and Bardet–Biedl syndromes.

The study was conducted at the Multidisciplinary Clinic of Tashkent State Medical University between 2020 and 2025. Written informed consent was obtained from all participants before enrolment.

Laboratory and Molecular Genetic Methods

All participants underwent standard clinical and laboratory assessments, including evaluation of carbohydrate and lipid metabolism and measurement of serum leptin concentrations. The lipid profile was assessed using biochemical enzymatic methods on an automated VITROS analytical system. The measured parameters included total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C).

Total cholesterol was measured using VITROS CHOL reagent systems on VITROS 250/350/5.1 FS/4600/XT 3400 analysers and VITROS 5600/XT 7600 integrated systems. The assay is based on an enzymatic reaction according to the Allain method, using a multilayer analytical element followed by photometric detection of the reaction product.

Triglyceride concentrations were measured using VITROS TRIG reagents on the aforementioned analytical systems. The assay is based on a sequence of enzymatic reactions involving triglyceride hydrolysis, hydrogen peroxide formation, and subsequent reflectance spectrophotometry. The intensity of the resulting colour is directly proportional to the triglyceride concentration in the sample. Serum LDL-C concentrations were measured using the automated VITROS system and the appropriate diagnostic reagents in accordance with the manufacturer's instructions. Serum leptin concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) with FineTest kits (Wuhan Fine Biotech Co., Ltd., China).

Fasting serum glucose concentrations were measured using a glucose oxidase enzymatic method with VITROS GLU reagents on an automated VITROS analytical system (Ortho Clinical Diagnostics, USA). Fasting insulin concentrations were determined by ELISA using the Human Insulin ELISA Kit (Wuhan Fine Biotech Co., Ltd., China) according to the manufacturer's instructions. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance according to the following formula: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5.

Molecular genetic testing was performed in 74 patients selected from the overall clinical cohort. Genomic DNA was extracted from peripheral blood leukocytes using the NK-Magnit Base-96 reagent kit (NPF LITTECH, Russia). The LEPR rs1137100 polymorphism was determined by polymerase chain reaction using specific oligonucleotide primers. Amplification was performed using a DTlite 5S1 thermal cycler (DNA-Technology LLC, Russia) and diagnostic test systems manufactured by NPF LITTECH (Russia).

Allelic variants were identified by restriction fragment analysis of the PCR amplification products. The resulting DNA fragments were separated by electrophoresis, and the A/A, A/G, and G/G genotypes were identified according to their restriction fragment patterns. The frequencies of the A and G alleles and the corresponding genotypes were calculated in the patient and control groups.

Statistical Analysis

Clinical and laboratory data were analysed using STATISTICA version 10.0, whereas molecular genetic data were processed using Epi Info version 7.2.2.2. Continuous variables are presented as the arithmetic mean and standard error of the mean (mean ± SEM), whereas categorical variables are reported as absolute numbers and percentages. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. The strength of associations was estimated using odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Continuous variables were compared across the three genotype groups, followed by pairwise comparisons. Compliance

of the genotype distribution with Hardy–Weinberg equilibrium was assessed using Pearson's chi-square test. Observed and expected heterozygosity were also calculated. The predictive performance of the genetic markers was evaluated using receiver operating characteristic (ROC) curve analysis, including calculation of the area under the ROC curve (AUC), sensitivity, and specificity. Differences were considered statistically significant at $p < 0.05$.

Results

Distribution of the LEPR rs1137100 Polymorphism

The frequency of the G allele was 47.3% in the patient group and 35.0% in the control group, whereas the frequency of the A allele was 52.7% and 65.0%, respectively. The most pronounced difference was observed for the homozygous G/G genotype, which was identified in 32.4% of patients compared with 12.9% of controls. Carriage of the G/G genotype was associated with a 3.25-fold increase in the odds of belonging to the patient group (OR = 3.25; 95% CI, 1.42–7.44; p = 0.006, Fisher's exact test). No statistically significant associations were observed for the A/A or A/G genotypes.

The frequency of the G/G genotype was 30.8% in Group I and 36.4% in Group II. Direct comparison between Groups I and II revealed no statistically significant differences in allele or genotype distributions. Therefore, the observed association appears to reflect susceptibility to obesity rather than its severity.

Table 2. Distribution of Alleles and Genotypes of the LEPR rs1137100 Polymorphism in the Patient and Control Groups

Study groups	Allele and Genotype Frequencies									
	A		G		A/A		A/G		G /G	
	n	%	n	%	n	%	n	%	n	%
Patient group (n = 74)	78	52,7	70	47,3	28	37,84	22	29,73	24	32,43
Group I: overweight and class I–II obesity (n = 52)	55	52,88	49	47,12	19	36,54	17	32,69	16	30,77
Group II: class III obesity (n = 22)	23	52,27	21	47,73	9	40,91	5	22,73	8	36,36
Control group (n = 70)	91	65	49	35	30	42,86	31	44,29	9	12,86

The combined presentation of allele and genotype frequencies in Table 2 revealed an important pattern. The allele distribution was nearly identical between Groups I and II, with the frequency of the G allele differing by only 0.6 percentage points. In contrast, both patient groups differed from the control group, showing higher frequencies of the G allele and, particularly, the G/G genotype. Thus, the transition from less severe to class III obesity was not accompanied by a proportional increase in the G allele frequency, despite a modest rise in the proportion of the G/G genotype to 36.4%. These findings do not support the interpretation of rs1137100 as a genetic marker of obesity severity.

At the same time, the patient group showed a lower proportion of the A/G genotype accompanied by increased proportions of both homozygous genotypes. This distribution requires cautious interpretation. The observed heterozygote deficiency may reflect selection characteristics of the study sample, population stratification, technical aspects of genotyping, or a true biological effect. Until genotyping quality has been independently verified and Hardy–Weinberg equilibrium has been appropriately assessed, this finding should not be interpreted as an independent mechanism underlying obesity.

In absolute terms, the difference in the G allele frequency between the overall patient group and the control group was 12.3 percentage points, whereas the corresponding difference in the G/G genotype frequency reached 19.5 percentage points. Compared with the control group, the G/G genotype was approximately 2.5 times more frequent among patients. In contrast, the A/A genotype frequency differed by only 5.1 percentage points, suggesting the absence of a pronounced independent protective effect of this genotype. The frequency of the A/G genotype was 14.6 percentage points lower among patients; however, this reduction should be interpreted in

conjunction with the overall heterozygote deficiency identified in the Hardy–Weinberg equilibrium analysis.

Stratification by obesity severity showed that the frequency of the G allele remained almost unchanged: 47.1% in? Wait. 47.. correct given user: 47: 47.1 Group I and and 47.7 Group II.? Need be exact.

Table 3. Association of the LEPR rs1137100 G/G Genotype with the Presence and Severity of Obesity

Comparison|	G/G in the study group|	G/G in the comparison group|	OR (95% CI)	p*
All patients vs control	24/74 (32.4%)	9/70 (12.9%)	3.25 (1.42–7.44)	0.006|
Group I vs control	16/52 (30.8%)	9/70 (12.9%)	3.01 (1.23–7.35)	0.023
Group II vs control	8/22 (36.4%)	9/70 (12.9%)	3.87 (1.33–11.30)	0.024
Group I vs Group II	16/52 (30.8%)	8/22 (36.4%)	0.78 (0.28–2.20)	0.786

Note: p values were calculated consistently using the two-sided Fisher's exact test based on absolute frequencies. Group I included patients with overweight or class I–II obesity; Group II included patients with class III obesity.

Table 3 confirms that the direction of the association with the G/G genotype remained consistent regardless of how the patients were grouped. In the overall sample, carriers of the G/G genotype had approximately 3.25-fold higher odds of being overweight or obese. Similar estimates were obtained separately for Groups I and II, although the wide confidence intervals reflect the limited sample sizes of these subgroups.

A direct comparison between the two patient groups yielded an OR below 1, with a confidence interval that included 1 and a p value of 0.786. Thus, the findings support an association between the G/G genotype and the presence of overweight or obesity but do not demonstrate a consistent association with progression to class III obesity.

When all patients were compared with the control group, the lower limit of the 95% CI was 1.42; therefore, the entire confidence interval was above 1.0. The same pattern was observed separately in Groups I and II, with ORs of 3.01 and 3.87 and lower confidence limits of 1.23 and 1.33, respectively. These findings confirm that the direction of the association was consistent across both obesity categories.

However, the higher OR observed in Group II should not automatically be interpreted as evidence of a stronger effect because the confidence intervals overlapped substantially.

The wide confidence interval for class III obesity, ranging from 1.33 to 11.30, clearly demonstrates the uncertainty of the point estimate of OR = 3.87. The true magnitude of the association may therefore range from moderate to very strong. Accordingly, it is scientifically more appropriate to describe the G/G genotype as being more frequent among patients with class III obesity rather than to claim an almost fourfold increase in an individual's risk of class III obesity.

Metabolic Parameters According to Genotype

A consistent gradient from A/A through A/G to G/G was observed for all five metabolic parameters. Compared with A/A carriers, participants with the G/G genotype had 22.4% higher LDL-C, 36.0% higher triglycerides, 17.4% higher total cholesterol, 54.4% higher HOMA-IR, and 40.2% higher leptin levels. The largest relative difference was observed for HOMA-IR, indicating a close association between the G/G genotype and an insulin-resistant phenotype in the study population.

The heterozygous A/G genotype occupied an intermediate position. Compared with A/A carriers, individuals with the A/G genotype had higher triglyceride, total cholesterol, HOMA-IR, and leptin levels.

Carriers of the G/G genotype additionally demonstrated significant deterioration in LDL-C, triglycerides, HOMA-IR, and leptin compared with A/G carriers. This allele-count-related gradient supports the hypothesis that an increasing number of G alleles may be associated with more pronounced metabolic abnormalities. However, it does not establish a causal or allele-dose effect in the absence of a formal trend test and multivariable adjustment.

The absolute increase in LDL-C between the A/A and G/G genotypes was 0.68 mmol/L. The transition from A/A to A/G was accompanied by a relatively small increase of 0.16 mmol/L, whereas the difference between A/G and G/G reached 0.52 mmol/L and was statistically significant. This finding

suggests that the most pronounced deterioration in LDL-C may be associated specifically with homozygosity for the G allele rather than with the presence of a single copy of this allele.

A more consistent stepwise pattern was observed for triglycerides, with concentrations of 1.64, 1.82, and 2.23 mmol/L in the A/A, A/G, and G/G groups, respectively. The difference between the two homozygous genotypes was 0.59 mmol/L. Triglyceride levels were already significantly higher in A/G carriers than in A/A carriers and increased further in G/G carriers compared with A/G carriers. Among the lipid parameters examined, this pattern was the most consistent with a potential allele-dose association.

Total cholesterol increased by 0.79 mmol/L from the A/A to the A/G genotype, whereas the additional increase from A/G to G/G was only 0.07 mmol/L and was not statistically significant. Thus, the presence of at least one G allele may account for most of the observed difference in total cholesterol, while G homozygosity was not associated with a substantial further increase. This pattern distinguishes total cholesterol from LDL-C, triglycerides, HOMA-IR, and leptin.

HOMA-IR increased from 2.81 in A/A carriers to 3.57 in A/G carriers and 4.34 in G/G carriers. The absolute difference between the two homozygous genotypes was 1.53 units, corresponding to a relative increase of 54.4%. The nearly identical increases at each successive step—0.76 and 0.77 units—represented the most consistent quantitative gradient among the parameters examined. This finding supports an association between the G allele and increasing insulin resistance; however, adjustment for BMI is required to determine whether this effect is independent of adiposity.

Leptin levels increased by 3.4 ng/mL between the A/A and A/G genotypes and by a further 5.17 ng/mL between the A/G and G/G genotypes. Overall, the difference between G/G and A/A carriers reached 8.57 ng/mL, corresponding to a 40.2% increase. The highest leptin concentration and the strongest statistical significance observed in G/G carriers suggest that hyperleptinaemia is a central feature of the identified metabolic phenotype.

Thus, Table 4 demonstrates a coordinated cluster of metabolic abnormalities rather than an isolated change in a single parameter: hyperleptinaemia was accompanied by insulin resistance and atherogenic dyslipidaemia. Differences in the shape of the genotype-related gradients were also informative. HOMA-IR and triglycerides demonstrated an approximately stepwise increase; LDL-C and leptin showed a more pronounced increase in G/G carriers; and most of the increase in total cholesterol was already evident in A/G carriers. These patterns may indicate that individual components of the metabolic phenotype differ in their sensitivity to the LEPR rs1137100 genotype

Table 4 Lipid Parameters, HOMA-IR, and Leptin Levels According to the LEPR rs1137100 Genotype in Patients with Obesity

Parameter	A/A n=28	A/G n=22	G/G n=24
LDL-C, mmol/L	3,03±0,04	3,19±0,07	3,71±0,05*†
Triglycerides, mmol/L	1,64±0,03	1,82±0,04*	2,23±0,03*†
Total cholesterol, mmol/L	4,95±0,08	5,74±0,04*	5,81±0,06*
HOMA-IR	2,81±0,05	3,57±0,05*	4,34±0,04*†
Leptin, ng/mL	21,3±0,9	24,7±0,96*	29,87±0,8**††

Note: $p < 0.05$ and $p < 0.001$ versus the A/A genotype; †$p < 0.05$ and ††$p < 0.001$ versus the A/G genotype.

Predictive Characteristics of the G/G Genotype

To assess the potential clinical utility of the G/G genotype, it was evaluated as a binary marker across different between-group comparisons. In all comparisons between patients and controls, specificity was 0.87, indicating that the absence of the G/G genotype was characteristic observed in most individuals with normal body weight. However, sensitivity remained low, ranging from 0.31 to 0.36, because the genotype was present in only approximately one-third of patients. Therefore, the G/G genotype may provide supportive evidence in the comprehensive assessment of genetic susceptibility but is unsuitable as a stand-alone screening marker for obesity.

Table 5. Predictive Performance of the LEPR rs1137100 G/G Genotype

Comparison	Sensitivity	Specificity	AUC	OR (95% CI)
All patients vs control	0.32	0.87	0.60	3.25 (1.42–7.43)
Group I vs control	0.31	0.87	0.59	3.01 (1.23–7.34)
Group II vs control	0.36	0.87	0.62	3.87 (1.33–11.29)
Group I vs Group II	0.31	0.64	0.48	0.78 (0.28–2.20)

Note: An AUC of 0.50 corresponds to random classification. Group I included patients with overweight or class I–II obesity; Group II included patients with class III obesity.

The highest AUC value was obtained when patients with class III obesity were compared with the control group (AUC = 0.62). However, even this value indicates only limited discriminatory performance. When Groups I and II were compared, the AUC was 0.48, demonstrating that the genotype was essentially unable to distinguish between less severe and class III obesity. Together with the OR estimates, these findings illustrate an important distinction between association and prediction: increased odds of disease do not necessarily translate into sufficient accuracy for individual classification.

A specificity of 0.87 indicates that 87% of individuals in the control group did not carry the G/G genotype. However, a sensitivity of 0.32 in the overall patient group indicates that approximately two-thirds of patients were also not G/G carriers. Therefore, detection of the genotype increases the likelihood of belonging to the obesity group, whereas its absence provides little evidence for excluding the condition. This low sensitivity limits the applicability of the marker in population-based screening.

The consistently high specificity across all comparisons with the control group can be explained by the unchanged frequency of the G/G genotype in the same control population. The modest increase in sensitivity from 0.31 in Group I to 0.36 in Group II reflects the increase in the frequency of the G/G genotype from 30.8% to 36.4%; however, this difference was insufficient to produce a clinically meaningful improvement in AUC. Therefore, the diagnostic performance measures support the findings of the frequency analysis: the G/G genotype is associated with obesity but does not provide reliable individual prediction of obesity severity.

Hardy–Weinberg Equilibrium and Heterozygosity

The observed genotype distribution was additionally compared with that expected under Hardy–Weinberg equilibrium. In the overall patient group, the observed frequency of the A/G genotype was substantially lower than expected (0.297 vs 0.499), whereas the frequencies of both homozygous genotypes exceeded their expected values. A similar pattern was observed in both clinical subgroups and was most pronounced among patients with class III obesity. In the control group, the observed and expected genotype frequencies were nearly identical.

Table 6. Observed and Expected Genotype Frequencies of the LEPR rs1137100 Polymorphism Under Hardy–Weinberg Equilibrium

Group	Allele A	Allele G	Genotype	Observed frequency	Expected frequency	χ^2	p	df
Overall patient group	0,53	0,47	A/A	0,378	0,278			
	0,53	0,47	A/G	0,297	0,499			
	0,53	0,47	G/G	0,324	0,224	12,058	0,054	1
Group I: overweight and class I–II obesity	0,53	0,47	A/A	0,365	0,28			
	0,53	0,47	A/G	0,327	0,498			
	0,53	0,47	G/G	0,308	0,222	6,152	0,015	1

Group II: class III obesity	0,52	0,48	A/A	0,409	0,273			
	0,52	0,48	A/G	0,227	0,499			
	0,52	0,48	G/G	0,364	0,228	6,523	0,011	1
Control group	0,65	0,35	A/A	0,429	0,423			
	0,65	0,35	A/G	0,443	0,455			
	0,65	0,35	G/G	0,129	0,123	0,05	0,788	1

Deviation from Hardy–Weinberg equilibrium in the patient group does not, by itself, confirm a biological effect of rs1137100. Such deviation may arise from an association between the locus and the disease but may also result from population stratification, relatedness among participants, genotyping errors, or non-random patient selection. Therefore, the observed deficiency of the A/G genotype highlights the need for laboratory quality control and repeat genotyping of a subset of samples.

Compliance with Hardy–Weinberg equilibrium in the control group is reassuring but does13?? it does not eliminate the need to verify genotyping quality in the patient group.

In the overall patient group, the observed frequency of the A/G genotype was 0.202 lower than expected, whereas the observed frequencies of both A/A and G/G exceeded the expected values by 0.100. The A/G deficiency was 0.171 in Group I and reached 0.272 in Group II. Thus, the deviation observed in class III obesity was attributable not only to an excess of the G/G genotype but also to a simultaneous excess of the A/A genotype.

Table 7. Observed and Expected Heterozygosity of the LEPR rs1137100 Polymorphism

Group	**Ho**	**He**	**D***
Overall patient group	0,30	0,50	-0,40
Group I: overweight and class I–II obesity	0,33	0,50	-0,34
Group II: class III obesity	0,23	0,50	-0,54
Control group	0,44	0,46	-0,03

The D coefficient represents the relative deviation of observed heterozygosity from its expected value. In the control group, D was close to zero (−0.03), whereas it was −0.40 in the overall patient group. The greatest heterozygote deficiency was observed in Group II (D = −0.54), in which the observed frequency of the A/G genotype was less than half its expected frequency. However, the greater heterozygote deficiency among patients with class III obesity cannot be interpreted as evidence of a progressively increasing genetic effect because the direct comparison of the G/G genotype between the two patient groups was not statistically significant, and the small size of Group II increased the uncertainty of the estimates.

The absolute difference between observed heterozygosity (Ho) and expected heterozygosity (He) was 0.20 in the overall patient group, 0.17 in Group I, and 0.27 in Group II, compared with only 0..02 in the control group. The progressive decrease in D from −0.34 in Group I to −0.54 in Group II formally indicates a greater heterozygote deficiency with increasing obesity severity. Nevertheless, D is a descriptive population-genetic measure and does not replace a formal association test. It should not be interpreted as an individual risk coefficient or as evidence that the A/G genotype protects against obesity.

Joint consideration of Tables 6 and 7 shows that the reduction in heterozygosity represents the same underlying

pattern as the deficiency of the A/G genotype identified in the Hardy–Weinberg equilibrium analysis, expressed using a different metric. Therefore, these findings should not be regarded as two independent lines of evidence. Their value lies in providing a clear quantitative description of the genetic structure of the study sample and highlighting the need to verify genotyping quality and population homogeneity before drawing definitive conclusions regarding the association.

Discussion

The principal finding of this study was the combination of two complementary observations. First, the G/G genotype of the LEPR rs1137100 polymorphism was more frequent among patients with overweight or obesity than among individuals with normal body weight. Second, within the patient group, G/G carriers had higher levels of atherogenic lipids, HOMA-IR, and leptin. Thus, the observed association was not limited to the categorical presence of obesity but was accompanied by a distinct clinical and metabolic phenotype.

Elevated circulating leptin levels in obesity generally reflect increased adipose tissue mass and reduced sensitivity to the anorexigenic effects of leptin [6–9]. The higher leptin levels observed in G/G carriers may indicate more pronounced leptin resistance. However, the cross-sectional design does not allow us to determine whether hyperleptinaemia results from greater adiposity, a genotype-associated alteration in LEPR signalling, or a combination of both mechanisms. Distinguishing among these possibilities requires adjustment for BMI, waist circumference, sex, and age because sex and the degree of adiposity can substantially modify circulating leptin levels [8, 18, 19].

The association between the G/G genotype and H-IR is biologically plausible. The leptin system interacts with insulin signalling at both central and peripheral levels and influences appetite, energy expenditure, fatty acid oxidation, and lipid distribution [8–10]. In the presence of leptin resistance, excess adipose tissue, chronic low-grade inflammation, ectopic lipid accumulation, and disturbances in the adipokine profile may contribute to reduced insulin sensitivity [9, 10].

Previous studies investigating the relationships of LEPR variants with insulin resistance and type 2 diabetes have produced inconsistent findings. Some studies have reported genotype-associated differences, whereas others have linked rs1137100 primarily to BMI but not to diabetes [12, 14, 16]. Nevertheless, HOMA-IR is a surrogate rather than a direct measure of insulin resistance.

The adverse lipid profile observed in G/G carriers—characterised by elevated LDL-C, triglycerides, and total cholesterol—is consistent with a metabolically unfavourable obesity phenotype and the established contribution of adipokine imbalance to cardiometabolic risk [9, 10]. The particularly pronounced increase in triglyceride levels may reflect an increased flux of free fatty acids to the liver, enhanced synthesis of very-low-density lipoproteins, and insulin resistance. Similar combinations of genetic and biochemical abnormalities have been described for other polymorphisms of the leptin signalling system, although the direction and magnitude of their effects have varied across populations [14–16, 18]. The absence of data on HDL-C, non-HDL cholesterol, apolipoprotein B, and liver function limits a comprehensive assessment of atherogenic risk.

Studies of rs1137100 across different ethnic groups have produced inconsistent findings. Kochetova et al. reported an association between this locus and BMI but not with the presence of type 2 diabetes mellitus [12]. Studies conducted in Middle Eastern and Asian populations have reported both positive associations of rs1137100 with obesity and metabolic abnormalities and an absence of such associations [13, 14, 17, 18]. A study of Moroccan women did not confirm an independent association between Lys109Arg and obesity, although it demonstrated the potential structural relevance of individual LEPR variants [18]. Recent evidence regarding interactions between LEPR genotype and the gut microbiota further suggests that phenotypic effects may be expressed in the context of environmental and biological modifiers rather than through the isolated action of a single nucleotide polymorphism [16].

This heterogeneity may be attributable to population differences in allele frequencies, linkage disequilibrium with other LEPR variants, small sample sizes, differences in sex and age distributions, and inconsistent adjustment for dietary intake and physical activity [15, 17–19]. Therefore, the present findings should be interpreted as specific to the population examined rather than as evidence of a universal effect of the K109R variant. A strength of our analysis is that the genetic association was accompanied by a consistent direction of change across five metabolic parameters. However, the independence of this phenotype can only be established using a regression model that incorporates relevant clinical covariates.

The absence of statistically significant differences between Groups I and II, together with the similar frequency of the G allele, indicates that rs1137100 should not be regarded as a marker of class III obesity. A more appropriate interpretation is that the G/G genotype may be associated with susceptibility to obesity and a metabolically adverse obesity phenotype. The

independent diagnostic value of this variant is limited: despite the elevated OR, the genotype has low sensitivity. Therefore, genetic testing cannot be used as a stand-alone tool for obesity screening or diagnosis outside a comprehensive predictive model.

The clinical relevance of these findings does not lie in recommending an isolated genetic test for all patients but in improving our understanding of the biological heterogeneity of obesity. If this association is confirmed, G/G carriers may represent a subgroup warranting particularly careful assessment of glucose metabolism, lipid profile, and overall cardiometabolic risk. Until external validation is obtained, however, this approach should be considered investigational and should not replace standard clinical assessment based on established risk factors.

Comparison of Tables 2–5 provides a coherent framework for interpreting the findings. The G allele was moderately more frequent among patients; however, most of the observed effect was concentrated in the homozygous G/G state. This genotype showed a similar direction of association in both Groups I and II but did not discriminate between these groups. Therefore, the findings are more consistent with a threshold or recessive model of susceptibility to obesity itself than with a linear effect of the G allele on increasing BMI. Nevertheless, the underlying inheritance model can only be formally established by comparing additive, dominant, and recessive regression models.

The metabolic data provide qualitatively different information that complements the genotype-frequency analysis. Whereas the distribution of G/G indicates the groups in which the genotype occurs more frequently, HOMA-IR, leptin, and lipid measurements characterise the metabolic phenotype of its carriers. The progressive increase in all five parameters from A/A to G/G forms a consistent pattern that is unlikely to be explained by a random change in a single laboratory measurement. Of particular importance are the parallel increases of 54.4% in HOMA-IR and 40.2% in leptin levels, suggesting the coexistence of insulin and leptin resistance, which may contribute to metabolic deterioration in obesity [8–10].

The lipid abnormalities should be considered part of the same phenotypic cluster. The 36.0% increase in triglyceride levels in G/G carriers compared with A/A carriers was more pronounced than the corresponding increases in total cholesterol and LDL-C. This pattern may be consistent with insulin resistance-related dyslipidaemia, in which increased delivery of free fatty acids to the liver promotes the production of triglyceride-rich lipoproteins. At the same time, the 22.4% increase in LDL-C indicates that the potential risk is not limited to hypertriglyceridaemia. However, without measurements of HDL-C, apolipoprotein B, and non-HDL cholesterol, the number and atherogenicity of circulating lipoprotein particles cannot be fully characterised.

The findings presented in Tables 6 and 7 require particular methodological consideration. The heterozygote deficiency in the patient groups was consistent with the increased frequency of the G/G genotype; however, the observed frequency of the A/AA genotype also exceeded its expected value. Therefore, the deviation cannot be attributed solely to an accumulation of the presumed risk genotype. It may reflect population stratification or characteristics of patient recruitment. Before publication, the absence of missing or misclassified genotypes should be confirmed, the genotyping call rate should be reported, and Hardy–Weinberg equilibrium should be reassessed using absolute genotype counts and a consistent statistical method.

Thus, the most compelling evidence lies not in any single parameter but in the consistency of the overall findings: a higher frequency of the G/G genotype compared with controls, similar ORs across the clinical subgroups, and an adverse biochemical profile among G/G carriers. However, the modest AUC values, low sensitivity, and absence of differences between obesity severity categories limit the individual predictive value of this variant. This combination of a strong group-level association and weak discriminatory performance is typical of common polygenic variants and highlights the need to incorporate rs1137100 into a multivariable model alongside age, sex, BMI, waist circumference, family history, and other genetic markers [4, 12, 19].

Conclusion

In the study population, the G/G genotype of the LEPR rs1137100 polymorphism was more frequent among patients with overweight or obesity than among controls and was associated with increased odds of obesity. Within the patient group, this genotype was associated with higher LDL-C, triglyceride, total cholesterol, HOMA-IR, and leptin levels. However, the frequency of the G/G genotype did not differ significantly between patients with less severe and class III obesity.

Therefore, the G/G genotype should be regarded not as a marker of obesity severity but as a candidate marker of susceptibility to obesity and a metabolically adverse phenotype. Larger multicentre studies, multivariable analyses, and external validation are required to confirm its independent predictive value.

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