Association of leptin receptor gene Gln223Arg polymorphism with insulin resistance and hyperglycemia in patients with metabolic syndrome

Erkin Mirrakhimov[1,2], Erkaiym Bektasheva[1], Jainagul Isakova[3], Olga Lunegova[1],

Alina Kerimkulova[1], Saamay Abilova[1,2], Ksenya Neronova[1], Nazira Alibaeva[1], Yrysbek U. Mamatuulu[1],

Indira Kudaibergenova[1], Maciej Banach[4,5], Aibek Mirrakhimov[6]

[1]Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
[2]National Centre of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan
[3]Institute of Molecular Biology and Medicine, Bishkek, Kyrgyzstan
[4]Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Lodz, Poland
[5]Department of Cardiology and Congenital Diseases of Adults, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[6]Kyrgyz Society of Cardiology

Corresponding author:
Prof. Erkin Mirrakhimov
Kyrgyz State
Medical Academy
National Centre of Cardiology
and Internal Medicine
Bishkek, Kyrgyzstan
E-mail: erkmirr@gmail.com

Abstract

Introduction: Worldwide, there has been an increase in the incidence of metabolic syndrome. The search for genetic markers of this syndrome is ongoing. The leptin receptor has recently received attention. One of the polymorphisms (Gln223Arg) is possibly associated with the development of obesity and insulin resistance. However, the results of studies on this polymorphism remain equivocal. Gln223Arg polymorphism has not been studied previously in the Kyrgyz population. Thus, we aimed to investigate the possible association of the Gln223Arg polymorphism of the leptin receptor gene with metabolic syndrome components in the Kyrgyz population.

Material and methods: 237 Kyrgyz subjects, aged 35–70 years, were studied. For the analysis anthropometric data, glucose, insulin, lipid spectrum, leptin were obtained. The genotype of the Gln223Arg leptin polymorphism was evaluated using TaqMan real-time PCR.

Results: The distribution of genotypes was as follows: Gln223Gln 46.4%, Gln223Arg 40.1%, Arg223Arg 13.5%. In the study no association was found with abdominal obesity, arterial hypertension, hypertriglyceridemia or low-density cholesterol levels. Relationships of Gln223Arg and Arg223Arg genotypes with insulin resistance ($p < 0.03$) were found. Gln223Arg polymorphism was associated with a higher level of glycemia (5.54 vs. 5.39 mmol/l, $p < 0.05$) and insulinemia (8.3 vs. 7.1 µIU/ml, $p < 0.05$). Correlation analysis showed that carriers of the Arg223 allele demonstrated a higher risk of insulin resistance (odds ratio (OR) = 1.83, 95% CI: 1.03–3.24; $p < 0.03$) than carriers of the Gln223 allele.

Conclusions: Gln223Arg polymorphism of the leptin receptor gene may be a marker of predisposition to insulin resistance in the Kyrgyz population. Further studies are necessary to confirm these results in populations from other regions.

Key words: insulin resistance, diabetes mellitus, leptin, leptin receptor, metabolic syndrome, Gln223Arg polymorphism, Kyrgyz ethnicity.

Introduction

The prevalence of metabolic syndrome (MS) is growing [1, 2]. Such a rapid increase in MS can be explained by the tendency to a low physical activity lifestyle and increased consumption of high-calorie food [3]. Obesity, namely its abdominal type (AO), is one of the main components of MS [2]. Genetic predisposition plays a role in the development of AO as a mandatory component of MS, which led to detailed searches for obesity genes and related disorders. Fat cells secrete a number of cytokines into the blood, called adipokines. One of these adipokines is leptin. Leptin concentration is directly proportional to the number of adipocytes [4]. Several polymorphisms of the leptin receptor gene have been described, such as K109R, Gln223Arg, S343S, N567N, K656N, and P1019P. Gln223Arg (rs1137101) has been studied more extensively compared to K109R (rs1137100) in relation to its role in metabolic disorders, in which leptin loses its affinity for the receptor and its regulatory mechanism is disrupted [5–7].

The results of studies investigating the relationship of the Gln223Arg polymorphism of the leptin receptor gene with MS components are contradictory. In some studies, relationships with AO [8], hyperglycemia, hyperinsulinemia [9], dyslipidemia [10], and increased blood (BP) pressure [11] have been determined. Other studies have found a link only with insulin resistance (IR) and type 2 diabetes mellitus (DM). The lack of unequivocal results explains the interest in studying the Gln223Arg polymorphism of the leptin receptor gene as a possible predictor of the development of obesity and IR.

The aim of the study was to determine the possible relationship of the Gln223Arg polymorphism of the leptin receptor gene with MS components in the Kyrgyz ethnic population.

Material and methods

Ethical approval was obtained from the Ethical Committee of the Kyrgyz State Medical Academy. The study included: 237 non-consanguineous Kyrgyz ethnic subjects (110 males and 127 females), aged 36–70 years (average age: 51.7 ±8.8 years), who gave written informed consent to participate. We further subdivided the study participants into two groups comparable for age, socio-economic status and eating pattern. The first group consisted of 98 subjects (43 males, 55 females) who had MS and the second group, which was designated as the control group, consisted of 139 subjects (67 males, 72 females) without MS. The study exclusion criteria included: severe heart failure, malignant arterial hypertension, strokes, myocardial infarction, chronic hepatitis, renal and hepatic insufficiency, systemic connective tissue diseases, chronic alcoholism, thyroid dysfunction, cancer, pregnant and lactating women.

Anthropometric measurements

All patients underwent history and physical examination including systolic and diastolic blood pressure measurements as well as anthropometric parameters (weight, height, waist circumference (WC)). Body mass index (BMI) was calculated with the formula: BMI = weight (kg)/height^2 (m)); obesity was diagnosed when BMI $\geq$ 30 kg/m^2.

MS was diagnosed according to the modified criteria of the International Diabetes Federation (2006) [12]. Abdominal obesity was diagnosed at WC $\geq$ 94 cm in men and $\geq$ 88 cm in women for the Kyrgyz population [13].

Biochemical measurements

Blood glucose and blood lipid spectrum (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C)) were determined by the standard method on the Sinchron CX4-DELTA autoanalyzer (Beckman, USA). The cholesterol content of low-density lipoproteins (LDL-C) was calculated using the Friedewald formula [14]. The determination of the insulin level was carried out by the ELISA method at the Hospital Saint Vincent De Paul Laboratory Hormonologie Pediatriqueet Maladies Metaboliques (Paris, France), for which, after blood sampling, the serum was separated and frozen in liquid nitrogen, followed by transportation to the laboratory. The HOMA insulin resistance index was calculated using the formula: HOMA = (serum insulin, mcU/ml x plasma glucose, mmol/l)/22.5. Insulin resistance was diagnosed at a HOMA index $\geq$ 2.77 [15].

Genotyping

DNA was isolated from 5 ml of venous blood by a standard two-stage method of phenol-chloroform extraction. To amplify the polymorphic locus Gln223Arg (rs1137101) of the leptin receptor gene (LEPR), the following primers were used: forward F 5′-ACCCTTTAAGCTGGGTGTCCCAAATAG-3′ and reverse R 5′-AGCTAGCAAATATTTTGTAAGCAATT-3′. After amplification, MspI endonuclease (Promega, USA) was used to cleave PCR products. PCR products were separated by electrophoresis in 3% agarose gel and visualized in ultraviolet light using the gel-documenting system GelDoc IT (UVP, UK).

Statistical analysis

Statistical data processing was carried out using the program Statistica 8.0. Comparisons of

Erkin Mirrakhimov, Erkaiym Bektasheva, Jainagul Isakova, Olga Lunegova, Alina Kerimkulova, Saamay Abilova, Ksenya Neronova, Nazira Alibaeva, Yrysbek U. Mamatuulu, Indira Kudaibergenova, Maciej Banach, Aibek Mirrakhimov

variables with normal distribution were carried out using Student's *t* test. The data are presented as the mean ± standard deviation. Comparisons of variables with nonparametric distributions were carried out using the Mann-Whitney test; the data are presented as the median and interquartile range (25–75%). The relationship between qualitative variables was evaluated by analyzing the contingency tables using the χ^2 test, calculating the odds ratio (OR) and the corresponding 95% confidence interval (95% CI). Spearman correlation analysis was carried out in order to study the relationship between the Gln223Arg polymorphism with the MS components, insulin levels and HOMA index. The criterion of statistical significance was considered to be the value of $p < 0.05$.

Results

A total of 237 participants (127 females and 110 males) were studied. Among female study participants 74 were in menopause. MS was diagnosed in 98 subjects, with 43 (43.8%) males and 55 (56.1%) females. IR was detected in 72 (30.3%) studied patients: 23 males with MS (53.4%) and 28 females with MS (50.9%). Arterial hypertension was present in 86 (36.2%) patients, among whom 47 (19.8%) were receiving antihypertensive therapy. DM was present in 15 individuals (6.3%) with 8 (3%) receiving treatment. Clinical characteristics of the studied subjects are presented in Table I.

Depending on the presence of IR, the studied individuals were further subdivided into 2 subgroups. The first subgroup without IR included 165 individuals (78 males and 87 females). The second subgroup with IR consisted of 72 patients (32 males and 40 females). The group with IR had higher glucose, insulin, triglyceride and BMI levels irrespective of the gender. In addition, the group with IR had lower concentration of HDL-C. AO was more prevalent in males with IR (Table II).

The prevalence of genotypes and alleles of the Gln223Arg polymorphism of the leptin receptor gene in the examined individuals was in Hardy-Weinberg equilibrium. The frequency of the mutant allele 223Arg was 0.66. The distribution of genotypes was different: Gln223Gln 110 (46.4%), Gln223Arg 95 (40.1%), Arg223Arg 32 (13.5%). We put Arg223Arg and Arg223Gln carrier into one group since the homozygous Arg223Arg carrier group was small and in order to reduce the probability of systematic errors during statistical

Table I. Clinical characteristics of the studied population

Parameters	Total n = 237	Without MS (n = 139)		With MS (n = 98)	
		Men n = 67 (48.2%)	Women n = 72 (51.7%)	Men n = 43 (43.8%)	Women n = 55 (56.1%)
AH, n (%)	86 (36.2)	37 (55)	23 (31.9)	37 (86)	43 (78.1)#
IR, n (%)	72 (30.37)	9 (13.4)	12 (16.6)	23 (53.4)*	28 (50.9)#
Obesity n (%) (BMI ≥ 30 kg/m²)	77 (32.48)	5 (7.4)	14 (19.4)	20 (46.5)*	38 (69)#
Glucose [mmol/l]	5.48 (5.1–5.9)	5.3 (5.11–5.58)	5.25 (5.04–5.54)	5.77 (5.35–6.5)*	5.82 (5.51–6.32)#
AO, n (%)	130 (54.85)	14 (20.8)	18 (25)	43 (100)*	55 (100)#
HTG, n %(%)	72 (30.4)	21 (31.3)	4 (5.5)	26 (60.4)*	21 (38.1)#
Low-HDL-C, n (%)	138 (58.22)	26 (38.8)	34 (47.2)	30 (69.7)*	48 (87.2)#

*p < 0.05 between men in 2 groups, #p < 0.05 between women in 2 groups. AH – arterial hypertension, AO – abdominal obesity, HDL-C – high-density lipoprotein cholesterol, HTG – hypertriglyceridemia.

Table II. Clinical characteristics of patients with insulin resistance

Parameters	Without IR, n = 165 (69.6%)		With IR, n = 72 (30.3%)	
	Men n = 78 (47.2%)	Women n = 87 (52.7%)	Men n = 32 (44.4%)	Women n = 40 (55.5%)
AH, n (%)	49 (62.8)	43 (49.4)	25 (78.0)	23 (57.5)
Glucose [mmol/l]	5.35 (5.12–5.61)	5.38 (5.08–5.71)	6.43 (5.37–7.21)*	5.86 (5.43–6.55)#
Insulin [µIU/ml]	5.6 (3.6–7.41)	6.4 (4.5–8.5)	14.1 (10.7–18.4)*	16 (1.3–19.7)#
BMI [kg/m²]	25.8 ±3.1	27.0 ±4.8	29.0 ±4.3*	30 ±4.6#
AO, n (%)	32 (41.0)	41 (47.1)	25 (78.0)*	32 (80.0)
HTG, n %	27 (34.6)	7 (8.0)	20 (65.2)*	18 (45.0)#
Low HDL-C, n (%)	35 (44.8)	47 (54.0)	21 (65.6)*	35 (87.5)#

*p < 0.05 between men in 2 groups, #p < 0.05 between women in 2 groups. AH – arterial hypertension, BMI – body mass index, AO – abdominal obesity, HDL-C – high-density lipoprotein cholesterol, HTG – hypertriglyceridemia.

analysis. General characteristics of the examined individuals are presented in Table III.

The groups were comparable for gender and age. The Arg223Arg + Gln223Arg group had a higher glucose value of 5.54 mmol/l versus Gln223Gln 5.39 mmol/l (p = 0.02), and insulin 8.2 µIU/ml versus 7.1 µIU/ml (p = 0.03). The parameters of the lipid spectrum did not differ significantly between the groups (Table III).

To further investigate the possible relationship between the Gln223Arg polymorphism of the leptin receptor gene, we determined the relationship between the 223Arg mutant allele and IR and MS components (Table IV). A relationship of this allele with IR (χ^2 = 24.41, p < 0.03) OR = 1.83 (95% CI: 1.03–3.24) was detected, while a signif-

icant relationship with the following MS components was not found: AO, AH, hypertriglyceridemia (HTG).

Correlation analysis of the Gln223Arg polymorphism of the leptin receptor gene and the MS components (Table V) demonstrated a positive correlation with insulin, glucose, and the HOMA index.

Discussion

MS represents a major medico-social problem [1, 16]. A lifestyle with reduced physical activity and a diet rich in animal fat and processed carbohydrates contribute to the development of obesity, arterial hypertension, diabetes mellitus, and dyslipidemia. Indeed, environmental factors play

Table III. General characteristics of the examined participants depending on the genotype

Parameter	Genotype		*P*-value
	Gln223Gln (*n* = 110)	Gln223Arg + Argrg223Arg (*n* = 127)	
Men, *n* (%)	56 (50.0)	54 (42.5)	ns
Age [years]	51.1 ±8.5	52.2 ±9.0	ns
AH, *n* (%)	33 (30.0)	53 (41.7)	ns
SBP [mm Hg]	134 ±20	137 ±22	ns
DBP [mm Hg]	85 ±12	86 ±12	ns
Glucose [mmol/l]	5.39 (5.1–5.7)	5.54 (5.2–6.1)	0.022
IR, *n* (%)	26 (23.6)	46 (36.2)	0.036
Insulin [µIU/ml]	7.1 (4.3–10.2)	8.2 (5.9–11.9)	0.032
Diabetes mellitus, *n* (%)	4 (3.63)	11 (11.7)	ns
BMI [kg/m²]	27.1 ±4.7	27.9 ±4.38	ns
WC [cm]	91 ±11.5	92 ±10.7	ns
MS, *n* (%)	44 (40.0)	54 (42.5)	ns
TC [mmol/l]	5.2 ±1.0	5.1 ±1.1	ns
LDL-C [mmol/l]	3.3 ±0.9	3.2 ±1.0	ns
HDL-C [mmol/l]	1.14 ±0.3	1.16 ±0.3	ns
TG [mmol/l]	1.2 (0.95–1.92)	1.2 (0.88 *n* = 1.92)	ns

ns – nonsignificant, AH – arterial hypertension, SBP – systolic blood pressure, DBP – diastolic blood pressure, IR – insulin resistance, BMI – body mass index, WC – waist circumference, MS – metabolic syndrome, TC – total cholesterol, LDL – low-density lipoprotein cholesterol, HDL – high-density lipoprotein cholesterol, TG – triglycerides.

Table IV. Relationship of Gln223Arg polymorphism of leptin receptor gene with IR, MS, and MS components

Parameter	Gln223Gln *n* = 110	Gln223Arg + Arg223Arg *n* = 127	χ^2	*P*-value	OR (95% CI)
IR, *n* = 72	26 (33.4%)	46 (38.5%)	4.41	< 0.03	1.83 (1.03–3.24)
AO, *n* = 130	56 (60.3%)	74 (69.6%)	1.28	ns	0.73 (0.44–1.24)
AH, *n* = 140	63 (64.9%)	77 (75%)	0.27	ns	0.87 (0.51–1.46)
HTG, *n* = 72	31 (33.4%)	41 (38.5%)	0.46	ns	0.82 (0.47–1.43)
Low HDL, *n* = 138	66 (64%)	72 (73.9%)	0.26	ns	1.46 (0.68–1.92)
MS, *n* = 98	44 (40%	54 (42.5%)	0.12	ns	1.11 (0.66–1.86)

ns – nonsignificant, IR – insulin resistance, AO – abdominal obesity, AH – arterial hypertension, HTG – hypertriglyceridemia, HDL-C – high-density lipoprotein cholesterol, MS – metabolic syndrome.

Erkin Mirrakhimov, Erkaiym Bektasheva, Jainagul Isakova, Olga Lunegova, Alina Kerimkulova, Saamay Abilova, Ksenya Neronova, Nazira Alibaeva, Yrysbek U. Mamatuulu, Indira Kudaibergenova, Maciej Banach, Aibek Mirrakhimov

Table V. Correlation analysis with the Gln223Arg polymorphism of the leptin receptor gene with components of metabolic syndrome

Parameter	*R*	*P*-value
AO	0.073	0.25
SBP	0.083	0.20
DBP	0.030	0.64
HDL-C	0.037	0.56
TC	−0.041	0.52
Glucose	0.148	0.021
Insulin	0.139	0.032
HOMA Index	0.177	0.006

AO – abdominal obesity, SBP – systolic blood pressure, DBP – diastolic blood pressure, HDL-C – high-density lipoprotein cholesterol, TC – total cholesterol.

a significant role in patients with genetic susceptibility to cardiometabolic disease.

Genetic studies help better understand the physiological and pathologic traits in humans. Identification of genetic predictors of cardiometabolic risk factors allows the detection of high-risk patients at an early stage, which will aid in primary prevention in a high-risk group and hopefully reduce cardiovascular mortality.

In our study, we assessed the relationship of the polymorphism of the Gln223Arg gene of the leptin receptor with anthropometric, biochemical changes and the formation of MS components in subjects of Kyrgyz ethnicity. We identified all three genotypes Gln223Gln, Gln223Arg, Arg223Arg, and compared the prevalence of the 223Arg allele

with other populations. In the Kyrgyz population, the frequency of the 223Arg allele was quite high at 0.66; similar results were observed in Britons (0.61), Europeans (0.53) and Americans (0.56) according to data registered on the basis of the National Center for Biotechnology Information [17]. However, among East Asians, particularly Chinese and Japanese, the 223Arg allele frequency was low, 0.13 and 0.15. The heterogeneous frequency of this allele may be related to multiple environmental, nutritional, and genetic factors, depending on the place of residence [17].

In our study, carriers of the Gln223Arg genotype showed an association with hyperinsulinemia; similar results were obtained by others, who had an increased risk of type 2 DM [18–21]. However, in a study by Fang *et al.*, the increased risk of type 2 DM was associated with the Gln223 allele [22]. Such heterogeneous polymorphism data are likely related to the characteristics of the ethnic groups included in the study.

The mechanism of IR in Gln223Arg polymorphism of the leptin receptor gene is attributed to a decrease in the sensitivity of leptin receptors. [23]. A single nucleotide polymorphism with the substitution of adenine for guanine at the 668 position leads to the replacement of glutamine with arginine at the 223 position of the protein product (Gln223Arg) [24]. This mutation is located in exon 6 and disrupts signal transmission by leptin receptors. Normally, leptin binds to leptin receptors located in β cells in the pancreas, as a result of which insulin secretion is suppressed [25]. So, after eating, in response to changes in glucose

Table VI. Studies of associations between Gln223Arg polymorphism of the leptin receptor gene and MS components

Authors	Population/Association
Yang Y, *et al.* [6]	Meta-analysis/Association with T2DM
Fan SH, *et al.* [7]	Malaysian/Association with plasma leptin levels and obesity
Adiga U, *et al.* [9]	Indian/Association with IR
Gu P, *et al.* [11]	Chinese/Association with essential hypertension
Ying J, *et al.* [19]	Chinese/Association with T2DM
Li YY, *et al.* [20]	Meta-analysis/Association with T2DM
Boumaiza I, *et al.* [21]	Tunisian/Association with obesity and MS
Dieguez-Campa CE, *et al.* [28]	Mexican/Association with obesity
Endo K, *et al.* [30]	Japanese/No association with obesity
Ashraf R, *et al.* [34]	Kashmir/Association with T2DM
Al-Harithy, *et al.* [35]	Saudi females/Association with T2DM and obesity
Daghestani MH, *et al.* [36]	Saudi females/Association with metabolic profile
Ali EMM, *et al.* [37]	Egyptian/Association with obesity
Wu H, *et al.* [38]	Meta-analysis/No association with T2DM
Komşu-Ornek Z, *et al.* [39]	Turkish children/No association with obesity and MS
Murugesan D, *et al.* [40]	Indian/Association with leptin, insulin, and BMI

IR – insulin resistance, T2DM – type 2 diabetes mellitus, MS – metabolic syndrome, BMI – body mass index.

levels, insulin begins to be produced, which stimulates the production of leptin in fat cells. Leptin, in turn, should reduce the production of insulin through leptin receptors [26]. In the absence of signal transmission by leptin receptors, suppression of insulin production does not occur, which in turn can lead to hyperinsulinemia and subsequent development of IR [27]. According to our data, people of Kyrgyz ethnicity have an increased risk of developing type 2 DM in the future. Further prospective follow-up of patients is necessary to clarify this hypothesis.

Studies on the association of Gln223Arg polymorphism and obesity have shown heterogeneous results (Table VI). Diéguez-Campa *et al.* demonstrated a link between this polymorphism and obesity in young Mexicans [28] and Ben Ali *et al.* found an association with an increase in BMI in Tunisian patients [29]. Endo *et al.* did not find an association of Gln223Arg polymorphism with obesity in Japanese school children [30]. In our study, the Gln223Arg+Arg223Arg group had higher values of BMI and AO, but we did not find a significant relationship. Overweight people have an increased level of leptin, which indicates possible leptin resistance [31–33]. A mutation in the leptin receptor gene leads to uncontrolled leptin production and impaired appetite regulation in the brain. Normally, leptin receptors are expressed in the hypothalamus, where, acting on neuropeptide Y, they suppress appetite and promote a feeling of satiety, which is not observed with mutations in the leptin receptor gene.

Our study did not reveal an association of Gln223Arg polymorphism with hypertension, obesity and dyslipidemia. Perhaps the contradictory results are related to the different genetic background in the study population and probably due to the limited study sample.

Limitations of the study. Only patients of Kyrgyz ethnicity were included in the study. In our study, there were fewer participants with the homozygous Arg223Arg genotype than patients with the other genotypes. Therefore, we had to combine patients with Arg223Arg and Arg223Gln genotypes into one group. Therefore, we could not fully assess the effect of each genotype on the incidence of each individual MS component, which may have influenced our results. Also, the absence of prospective observational studies limits the risk assessment of MS components in the Kyrgyz ethnic group. A larger sample size, inclusion of other ethnic groups living in Kyrgyzstan and a prospective study type are needed to better understand the association of leptin gene polymorphism and MS components.

In conclusion, the Gln223Arg polymorphism of the leptin receptor gene has not been previously studied in the Kyrgyz population. This study sheds light on the nature of the Gln223Arg polymorphism of the leptin receptor gene in the Kyrgyz ethnic population. In our study, there was no association with all components of MS. However, the study demonstrated an association with hyperinsulinemia and IR in carriers of Gln223Arg, indicating a possible role of leptin receptor gene polymorphism in the pathogenesis of DM development.

Conflict of interest

The authors declare no conflict of interest.

References

1. Dobrowolski P, Prejbisz A, Kuryłowicz A, et al. A Metabolic syndrome – a new definition and management guidelines A joint position paper by the Polish Society of Hypertension, Polish Society for the Treatment of Obesity, Polish Lipid Association, Polish Association for Study of Liver, Polish Society of Family Medicine, Polish Society of Lifestyle Medicine, Division of Prevention and Epidemiology Polish Cardiac Society, "Club 30" Polish Cardiac Society, and Division of Metabolic and Bariatric Surgery Society of Polish Surgeons. Arch Med Sci 2022; 18: 1133-56.
2. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute scientific statement. Curr Opin Cardiol 2006; 21: 1-6.
3. Tirandi A, Carbone F, Montecucco F, Liberale L. The role of metabolic syndrome in sudden cardiac death risk: recent evidence and future directions. Eur J Clin Invest 2022; 52: e13693.
4. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-32.
5. Wasim M, Awan FR, Najam SS, et al. Role of leptin deficiency, inefficiency, and leptin receptors in obesity. Biochem Genet 2016; 54: 565-72.
6. Yang Y, Niu T. A meta-analysis of associations of LEPR Q223R and K109R polymorphisms with type 2 diabetes risk. PLoS One 2018; 13: e0189366.
7. Fan SH, Say YH. Leptin and leptin receptor gene polymorphisms and their association with plasma leptin levels and obesity in a multi-ethnic Malaysian suburban population. J Physiol Anthropol 2014; 33: 15.
8. Yang MM, Wang J, Fan JJ, et al. Variations in the obesity gen" "LE"R" contribute to risk of type 2 diabetes mellitus: evidence from a meta-analysis. J Diabetes Res 2016; 11: 5412084.
9. Adiga U, Banawalikar N, Mayur S, et al. Association of insulin resistance and leptin receptor gene polymorphism in type 2 diabetes mellitus. J Chin Med Assoc 2021; 84: 383-8.
10. Okada T, Ohzeki T, Nakagawa Y, Sugihara S. Impact of leptin and leptin receptor gene polymorphisms on lipid levels in the serum of Japanese obese children. Acta Paediatr 2010; 99: 1213-7.
11. Gu P, Jiang W, Chen M, et al. Association of leptin receptor gene polymorphisms and essential hypertension in a Chinese population. J Endocrinol Invest 2012; 35: 859-65.
12. https://www.idf.org/e-library/consensus-statements. 2006

Erkin Mirrakhimov, Erkaiym Bektasheva, Jainagul Isakova, Olga Lunegova, Alina Kerimkulova, Saamay Abilova, Ksenya Neronova, Nazira Alibaeva, Yrysbek U. Mamatuulu, Indira Kudaibergenova, Maciej Banach, Aibek Mirrakhimov

13. Mirrakhimov AE, Lunegova OS, Kerimkulova AS, et al. Cut off values for abdominal obesity as a criterion of metabolic syndrome in an ethnic Kyrgyz population (Central Asian region). Cardiovasc Diabetol 2012; 11: 16.

14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.

15. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998; 47: 1643-9.

16. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep 2018; 26: 12.

17. https://www.ncbi.nlm.nih.gov/snp/rs1137101

18. Chiu KC, Chu A, Chuang LM, Saad MF. Association of leptin receptor polymorphism with insulin resistance. Eur J Endocrinol 2004; 150: 725-9.

19. Ying J, Shi NS, Pan RW, et al. Association between Gln223Arg and type 2 diabetes in Zhejing. Chin Gerontol 2009; 29: 858-60.

20. Li YY, Wang H, Yang XX, et al. LEPR gene Gln223Arg polymorphism and type 2 diabetes mellitus: a meta-analysis of 3,367 subjects. Oncotarget 2017; 8: 61927-34.

21. Boumaiza I, Omezzine A, Rejeb J, et al. Relationship between leptin G2548A and leptin receptor Q223R gene polymorphisms and obesity and metabolic syndrome risk in Tunisian volunteers. Genet Test Mol Biomarkers 2012; 16: 726-33.

22. Fang MZ. Association between LEPR gene variation and bone metabolism in II diabetes mellitus. Kumings: Kunming Medical University 2001; 31.

23. Stratigopoulos G, LeDuc CA, Matsuoka N, et al. Functional consequences of the human leptin receptor (LEPR) Q223R transversion. Obesity (Silver Spring) 2009; 17: 126-35.

24. Thompson DB, Ravussin E, Bennett PH, Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. Hum Mol Genet 1997; 6: 675-9.

25. Kieffer TJ, Heller RS, Habener JF. Leptin receptors expressed on pancreatic β-cell. Biochem Biophys Res Commun 1996; 224: 522-7.

26. German JP, Thaler JP, Wisse BE, et al. Leptin activates a novel CNS mechanism for insulin-independent normalization of severe diabetic hyperglycemia. Endocrinology 2011; 152: 394-404.

27. Levi J, Gray SL, Speck M, et al. Acute disruption of leptin signaling in vivo leads to increased insulin levels and insulin resistance. Endocrinology 2011; 152: 3385-95.

28. Diéguez-Campa CE, Angel-Chávez LI, Reyes-Ruvalcaba D, et al. Leptin levels and Q223R leptin receptor gene polymorphism in obese Mexican young adults. EJIFCC 2020; 31: 197-207.

29. Ben Ali S, Kallel A, Sediri Y, et al. LEPR p.Q223R Polymorphism influences plasma leptin levels and body mass index in Tunisian obese patients. Arch Med Res 2009; 40: 186-90.

30. Endo K, Yanagi H, Hirano C, et al. Association of Trp64Arg polymorphism of the beta3-adrenergic receptor gene and no association of Gln223Arg polymorphism of the leptin receptor gene in Japanese school children with obesity. Int J Obes Relat Metab Disord 2000; 24: 443-9.

31. Korac A, Srdic-Galic B, Kalezic A, et al. Adipokine signatures of subcutaneous and visceral abdominal fat in normal-weight and obese women with different metabolic profiles. Arch Med Sci 2021; 17: 323-36.

32. Mazidi M, Shekoohi N, Katsiki N, Rakowski M, Mikhailidis DP, Banach M. Serum anti-inflammatory and in-flammatory markers have no causal impact on telomere length: a Mendelian randomization study. Arch Med Sci 2021; 17: 739-51.

33. Banach M, Burchardt P, Chlebus K, et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci 2021; 17: 1447-547.

34. Ashraf R, Khan MS, Lone SS, et al. Implication of leptin and leptin receptor gene variations in type 2 diabetes mellitus: a case-control study. J Endocrinol Metab 2022; 12: 19-31.

35. Al-Harithy R, Al-Zahrani N. Leptin receptor RS1137101 variant is risk factor for obesity and Type II diabetes in Saudi adult women. Intern J Med Sci Health Care 2013; 1: 7.

36. Daghestani MH, Daghestani MH, Daghistani MH, et al. The influence of the rs1137101 genotypes of leptin receptor gene on the demographic and metabolic profile of normal Saudi females and those suffering from polycystic ovarian syndrome. BMC Womens Health 2019; 19: 10.

37. Ali EMM, Diab T, Elsaid A, et al. Fat mass and obesity-associated (FTO) and leptin receptor (LEPR) gene polymorphisms in Egyptian obese subjects. Arch Physiol Biochem 2021; 127: 28-36.

38. Wu H, Tang W, Liu C, Xue Y, Hou J. The association of LEPR rs1137101 G>A polymorphism with the risk of type 2 diabetes mellitus: from a case-control study to a meta-analysis. Int J Clin Exp Med 2019; 12: 3798-809.

39. Komşu-Ornek Z, Demirel F, Dursun A, et al. Leptin receptor gene Gln223Arg polymorphism is not associated with obesity and metabolic syndrome in Turkish children. Turk J Pediatr 2012; 54: 20-4.

40. Murugesan D, Arunachalam T, Ramamurthy V, Subramanian S. Association of polymorphisms in leptin receptor gene with obesity and type 2 diabetes in the local population of Coimbatore. Indian J Hum Genet 2010; 16: 72-7.