DOI 10.11603/mcch.2410-681X.2024.i1.14597
УДК 616-056.52-037:616-008.9:575.174.015.3:577.175.85

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PREDICTING THE PROBABILITY OF DEVELOPING OBESITY DEPENDING ON LEPTIN AND LEPTIN RECEPTOR POLYMORPHISMS

Introduction. *Metabolic syndrome is a heterogeneous pathological condition that combines different stages of obesity, impaired glucose tolerance, atherogenic dyslipidemia and arterial hypertension. Obesity itself is a key element of this syndrome. Hormonal disorders, the central one of which is insulin resistance, trigger a cascade of neuroendocrine changes that lead to the progression of MetS. Monogenic mutations are often detected in patients with severe obesity, as well as with early (up to 10 years) its debut. In recent years, it has been increasingly investigated for a genetically determined breakdown in the mechanism of leptin's influence on the development of obesity.*

The aim of this study *– to evaluate the probability of obesity development in patients with LEP and LEPR polymorphisms in Ukrainian population.*

Research Methods. *53 obesity and 43 non-obesity patients underwent genotyping of the LEP and LEPR genes (K109R (rs1137100), Q223R (rs1137101), K656N (rs1805094), G2548A (rs7799039)) polymorphism was performed using TaqMan™ SNP Genotyping Human Assays (Thermo Fisher Scientific, USA).*

Results and Discussion. *Comparing rs1137101 Allele A, rs1137101 Allele G statistically significant differences were revealed, while comparing rs1805094 Allele C, rs1805094 Allele G, rs7799039 Allele A, rs7799039 Allele G, rs1137100 Allele A, rs1137100 Allele G depending on group indicated no statistically significant differences. SNP (rs1137101) Allele A statistically significant differences depending on obesity degree ($p < 0.001$). Comparing the rest of SNP`s Allele`s (rs1805094 Allele C, rs1805094 Allele G, rs7799039 Allele A, rs7799039 Allele G, rs1137101 Allele G, rs1137100 Allele A, rs1137100 Allele G, rs696217 Allele G) no statistically significant differences was noted. Prediction of the probability of developing obesity depending on the polymorphism of leptin and leptin receptors revealed the dependence of only mutations in LEPR (Q223R (rs1137101)) in the Ukrainian population. According to the results of the ROC analysis sensitivity and specificity of the method were 65.5 % and 67.8 %, respectively.*

Conclusions. *Our analysis showed that LEPR Q223R (rs1137101) polymorphism could be a potential genetic risk factor for obesity in Ukrainian population regardless of the homozygous or heterozygous genotype (genotypes AA, AG, GG). At the same time, allele A was found in 70.83 % of cases of patients with 2nd and 3rd degree obesity. And homozygous AA and GG genotypes in 24.5 % and 28.3 %, respectively. The results obtained can be used in the practice for early diagnosis of different types of obesity and for prognosing of results of bariatric surgery.*

KEY WORDS: **metabolic syndrome; LEP; LEPR genes; allele polymorphism.**

INTRODUCTION. Metabolic syndrome (MetS) is a heterogeneous pathological condition that combines different stages of obesity, impaired glucose tolerance, atherogenic dyslipidemia and arterial hypertension [1]. Obesity itself is a key element of this syndrome [2]. Hormonal disorders, the central one of which is insulin resistance, trigger a cascade of neuroendocrine changes that lead to the progression of MetS [3]. Changes in the environment have undoubtedly led to the rapid increase in the prevalence of MS, and obesity is the result of an interaction between environmental and innate biological factors.

Monogenic mutations are often detected in patients with severe obesity, as well as with early (up to 10 years) its debut. It has also been proven that monogenic obesity is mainly inherited in a recessive type. And therefore blood kinship in certain populations increases the probability of detecting monogenic obesity due to greater chances of detecting homozygous carriers.

Adipose tissue is an active, powerful endocrine organ capable of releasing large amounts of adipokines, which are the pathophysiological basis of the link between obesity and associated metabolic changes [4]. Leptin is normally produced in proportion to the amount of adipose tissue, participates in the regulation of energy homeostasis [5]. The high level of circulating leptin in obese people is the result of the formation of resistance and indicates that its action is weakened by the anorectic reaction.

Its resistance is the result of infections, autoimmune diseases, malnutrition, inflammation. For now, Anjum T. et al. suggests four factors that are responsible for this condition: fewer leptin receptors in the brain, incorrect leptin receptors work, less leptin is crossing the brain-blood barrier, mutation of leptin and leptin receptors genes [6].

In recent years, the works of Mazen I.H. et al., Nunziata A. et al. claimed that the last factor has been increasingly investigated for a genetically determined breakdown in the mechanism of leptin's influence on the development of obesity [7, 8]. Leptin is a protein consisting of 167 amino acids and encoded by the LEP gene located on chromosome 7q31.3. Kleinendorst L. et described several LEPR mutations associated with obesity in humans [9] They showed LEPR deficiency as an autosomal-recessive endocrine disorder causing early-onset severe obesity and wit more prevalence in European population. Yupanqui-Lozno H. et al. reports that genetic variants LEP, LEPR explain up to 30 % of severe obesity from consanguineous populations [10]. Saeed S. et al. indicates that mutations in the genes encoding leptin, LEPR, and MC4R explain 30 % of cases of severe obesity, and defects in a single gene more broadly account for nearly 50 % [11].

However, with the monogenic theory of obesity inheritance, the influence of mutations in the leptin gene and its receptor is less noticeable. Although single-nucleotide (SNP) mutations of these genes can determine the prerequisites for some metabolic disorders and, therefore, disease in the future.

The aim of this study was to asses LEP (rs7799039), LEPR (rs 1137100, rs 1137101, rs 1805094) genes polymorphism in Ukrainian population and their role in obesity genesis.

MATERIALS AND METHODS . The study was conducted in January–November 2022 at the Department of Surgery of Postgraduate Faculty at the I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine and consisted of 96 subjects, which were devided into two groups – 53 obesity and 43 non-obesity (controls), as 42 males and 54 females, aged 24–45 years. There were no significant age and sex differences found between the individual in both groups.

Heights, body weight, body mass index (BMI) were analyzed and according to these patients with <30 kg/m^2 were confirmed as inclusion criteria for control group and with >30 kg/m^2 as obesity group. All patients with obesity were subdivided into categories: 1st degree (BMI of 30 to <35), 2nd degree (BMI of 35 to <40), 3^{d} degree (BMI of 40 or higher). Class 3 obesity was categorized as "severe" obesity.

Genotyping of the LEP and LEPR genes polymorphism (rs7799039, rs1137100, rs1137101, rs1805094).

Venous blood from patients was collected in a sterile Vacutainer and stabilized with K2EDTA. Total DNA was isolated from peripheral blood using the GeneJET Whole Blood Genomic DNA Purification Mini Kit (K0781, Thermo Fisher Scientific, USA), following the manufacturer's instructions.

Pre-designed TaqMan™ SNP Genotyping Assays, Human, (Thermo Fisher Scientific, USA) were used for next SNPs: K109R (rs1137100), Q223R (rs1137101), K656N (rs1805094), G2548A (rs7799039). All specimens were genotyped applying TaqMan probes and TaqMan Genotyping Master Mix (4371355) on CFX96™ Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., USA). Polymerase chain reaction (PCR) for TaqMan genotyping was conducted, adhering to the requirements enclosed in the kit (Applied Biosystems, USA). TaqMan Genotyping Master Mix contains DNA polymerase AmpliTaq Gold®, dNTPs, reference dye ROX™, and the composition of buffers. TaqMan probes are target-specific oligonucleotides with reporter dyes labeled at the 5' end of each probe: (VIC® dye at the 5' end of the Allele 1 probe and 6 FAM™ dye at the 5' end of the Allele 2 probe), and a non-fluorescent quencher (NFQ) labeled at the 3' end of the probe. Genomic DNA was intensified in a 10 µL reaction mix comprising genomic DNA, forward and reverse primers, fluorescent probes, and TaqMan Genotyping Master Mix. Genotyping of the specimens was conducted on the CFX-Maestro™ software applying the technique of allele discrimination based on the magnitude of relative fluorescence units (RFU).

Statistics. Open-source statistical package "R" was used for for results processing. Comparison of frequencies was performed using Pearson's chi-square test. Nagelkerke R^2 was used as a measure of the model performance. In the linear regression model, the coefficient of determination, R^2, summarizes the proportion of variance in the dependent variable associated with the predictor (independent) variables, with larger R^2 values indicating that more of the variation is explained by the model, to a maximum of 1.

Logistic regression was used for development of a prognostic model for the probability of a binary outcome. To assess the diagnostic performance of quantitative variables in predicting a categorical outcome ROC analysis was used. The optimal cut-off value of the quantitative variable at was estimated using the Youden's J statistic. Statistical differences between comparison groups were considered probable at $p<0.05$.

Ethical details. Adherence to bioethical norms, such as the Helsinki Declaration and the World Medical Association's "Ethical Principles for Medical Research Involving Human Subjects", was ensured [12]. Every patient singed a consent form to enroll in this study. Ethics Committee of I. Horbachevsky Ternopil National Medical University approved this study (protocol No. 82 from 04.10.2023).

RESULTS. According to analysis of the obesity group, statistically significant differences were found (p<0.001) (Fig. 1). Thus, 34 % of patients were diagnosed with second-degree obesity, and 56 % had third-degree obesity.

Allele conditioning analysis on group presented in Table 1. According to that data comparing rs1137101 Allele A, rs1137101 Allele G statistically significant differences were found (p=0.009, p=0.013 respectively). When comparing of rs1805094 Allele C, rs1805094 Allele G, rs7799039 Allele A, rs7799039 Allele G, rs1137100 Allele A, rs1137100 Allele G depending on group there were no statistically significant differences (p=0.658, p=0.727, p=0.257, p=0.322, p=0.460, p=0.290 respectively).

Genotypes analysis of rs1137101 was performed in two groups (Table 2). Statistically significant differences were found depending on group (p=0.008). Comparing genotypes rs 1805094, rs7799039, rs1137100 depending on group no statistically significant differences were found (p=0.877, p=0.429, p=0.442 respectively).

According to the data obtained in Table 3 when comparing of rs1137101 Allele A statistically significant differences were found depending on obesity degree (p<0.001). Comparing the rest of SNP's Allele's (rs1805094 Allele C, rs1805094 Allele G, rs7799039 Allele A, rs7799039 Allele G,

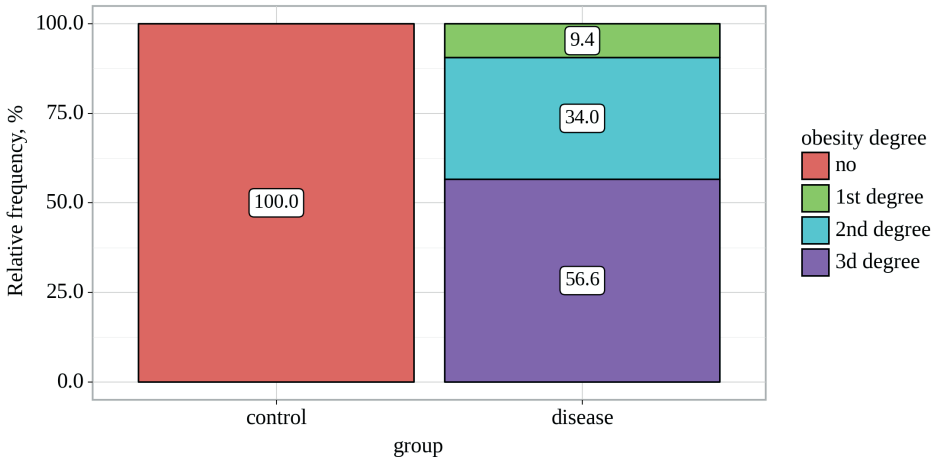

Figure 1. Analysis of obesity degree depending on group.
Source: compiled by the authors.

Table 1 – **Analysis of Allele in both groups**

SNPs Alleles	Categories, yes/no	group		p
		control	disease	
rs1805094	no	31 (72.1)	36 (67.9)	0.658
Allele C	yes	12 (27.9)	17 (32.1)	
rs1805094	no	3 (7.0)	5 (9.4)	0.727
Allele G	yes	40 (93.0)	48 (90.6)	
rs7799039	no	16 (37.2)	14 (26.4)	0.257
Allele A	yes	27 (62.8)	39 (73.6)	
rs7799039	no	7 (16.3)	13 (24.5)	0.322
Allele G	yes	36 (83.7)	40 (75.5)	
rs1137101	no	3 (7.0)	15 (28.3)	0.009*
Allele A	yes	40 (93.0)	38 (71.7)	
rs1137101	no	21 (48.8)	13 (24.5)	0.013*
Allele G	yes	22 (51.2)	40 (75.5)	
rs1137100	no	5 (11.6)	3 (5.7)	0.460
Allele A	yes	38 (88.4)	50 (94.3)	
rs1137100	no	23 (53.5)	34 (64.2)	0.290
Allele G	yes	20 (46.5)	19 (35.8)	

Notes: * – differences are statistically significant (p<0.05).
Source: compiled by the authors.

Table 2 – **Analysis of Genotype in both groups**

SNP	Genotypes	Group		p
		control	disease	
rs1805094	CC	3 (7.0)	5 (9.4)	0.877
	CG	9 (20.9)	12 (22.6)	
	GG	31 (72.1)	36 (67.9)	
rs7799039	AA	7 (16.3)	13 (24.5)	0.429
	AG	20 (46.5)	26 (49.1)	
	GG	16 (37.2)	14 (26.4)	
rs1137101	AA	21 (48.8)	13 (24.5)	0.008*
	AG	19 (44.2)	25 (47.2)	
	GG	3 (7.0)	15 (28.3)	
rs1137100	AA	23 (53.5)	34 (64.2)	0.442
	AG	15 (34.9)	16 (30.2)	
	GG	5 (11.6)	3 (5.7)	

Notes : * – differences are statistically significant (p<0.05).
Source: compiled by the authors.

Table 3 – **Allele's analysis in both groups**

SNPs Alleles	Categories, yes/no	Obesity degree				p
		no	1st degree	2nd degree	3d degree	
rs1805094 Allele C	no	31 (72.1)	3 (60.0)	9 (50.0)	24 (80.0)	0.160
	yes	12 (27.9)	2 (40.0)	9 (50.0)	6 (20.0)	
rs1805094 Allele G	no	3 (7.0)	0 (0.0)	2 (11.1)	3 (10.0)	0.838
	yes	40 (93.0)	5 (100.0)	16 (88.9)	27 (90.0)	
rs7799039 Allele A	no	16 (37.2)	0 (0.0)	6 (33.3)	8 (26.7)	0.346
	yes	27 (62.8)	5 (100.0)	12 (66.7)	22 (73.3)	
rs7799039 Allele G	no	7 (16.3)	2 (40.0)	3 (16.7)	8 (26.7)	0.482
	yes	36 (83.7)	3 (60.0)	15 (83.3)	22 (73.3)	
rs1137101 Allele A	no	3 (7.0)	1 (20.0)	1 (5.6)	13 (43.3)	<0.001* $p_{no-3d\ degree}$ =0.001 $p_{2nd\ degree-3d\ degree}$ =0.027
	yes	40 (93.0)	4 (80.0)	17 (94.4)	17 (56.7)	
rs1137101 Allele G	no	21 (48.8)	2 (40.0)	5 (27.8)	6 (20.0)	0.072
	yes	22 (51.2)	3 (60.0)	13 (72.2)	24 (80.0)	
rs1137100 Allele A	no	5 (11.6)	1 (20.0)	0 (0.0)	2 (6.7)	0.355
	yes	38 (88.4)	4 (80.0)	18 (100.0)	28 (93.3)	
rs1137100 Allele G	no	23 (53.5)	3 (60.0)	14 (77.8)	17 (56.7)	0.357
	yes	20 (46.5)	2 (40.0)	4 (22.2)	13 (43.3)	

Notes: * – differences are statistically significant (p<0.05).
Source: compiled by the authors.

rs1137101 Allele G, rs1137100 Allele A, rs1137100 Allele G, rs696217 Allele G) no statistically significant differences were found (p=0.160, p=0.838, p=0.346, p=0.482, p=0.072, p=0.355, p=0.357, p=0.742 respectively).

Based on the obtained data a predictive model was built to estimate the probability of group conditioning on rs1137101 Allele A, rs1137100 Allele G. The observed association can be described by the following equation:

$$P = 1 / (1 + e^{-z}) \times 100\ \%$$
$$z = 2.373 - 2.108X_{yes} - 0.974X_{yes}$$

where P – probability of disease, X_{yes} – rs1137101 Allele A (0 – no, 1 – yes), X_{yes} – rs1137100 Allele G (0 – no, 1 – yes)

The regression model was statistically significant (p=0.002). And based on the value of Nagelkerke R^2, the model explains 15.8 % of the observed group variance. Presence of yes was associated with 8.233 times decrease of disease Odds. Presence of yes is associated with 2.650 times decrease of disease odds (Fig. 2, Table 4).

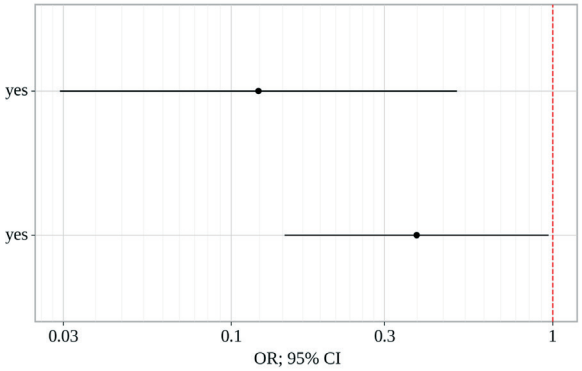

Figure 2. Odds ratios estimates with corresponding 95 % CI's for predictors included to the model group.
Source: compiled by the authors.

Table 4 – **Characteristics of the association of predictors with the probability**

Predictors	Unadjusted		Adjusted	
	COR; 95 % CI	p	AOR; 95 % CI	p
rs1137101 Allele A : yes	0.190; 0.051 – 0.709	0.013*	0.121; 0.029 – 0.504	0.004*
rs1137101 Allele G: yes	0.643; 0.283 – 1.461	0.291	0.377; 0.147 – 0.972	0.044*

Notes: * – association of the outcome value with the predictor value is statistically significant (p<0.05), COR – correlation coefficient, CI – confidence interval.

Source: compiled by the authors.

Evaluation the dependence of the probability of disease on the Value of logistic function P was obtained in the following curve (Fig. 3).

The area under the curve comprised (0.686±0.054) with 95 % CI: 0.581–0.791. So the resulting model was statistically significant (p<0.001) (Fig. 4).

Prediction of the probability of developing obesity depending on the polymorphism of leptin and leptin receptors revealed the dependence of only mutations in LEPR (Q223R (rs1137101)) in the Ukrainian population. According to the results of the ROC analysis sensitivity and specificity of the method were 65.5 % and 67.8 %, respectively.

DISCUSSION. Polygenic obesity and severe monogenic obesity with early onset are often considered as separate diseases. Studies of candidate genes for both of these forms of obesity show that they have common genetic and biological bases.

The role of leptin in the regulation of energy homeostasis has been demonstrated by observing leptin-deficient patients who develop hyperphagia and obesity. However, most obese people are not deficient in the leptin gene, and blood leptin levels are elevated compared to non-obese individuals. Leptin receptors are coded by the gene (db gene), its long and short isoforms have been identified and are located in the arcuate nucleus and ventromedial hypothalamus, where the centers of hunger, satiety and thermoregulation are located. It is with a violation of leptin transport through the blood-brain barrier and a violation of the sensitivity of its receptors on peripheral target organs as a result of "genetic damage" that severe leptin resistance occurs, which leads to severe obesity.

It is known that LEPR gene mutations, in contrast to leptin gene polymorphisms, lead to more pronounced leptin resistance with the phenomena of constant hyperphagia, which causes severe obesity. In addition, the anorexigenic effect of leptin is impaired in patients with sporadic obesity [13]. However, low prevalence of monogenic obesity, as a result of LEPR mutation in the population, causes difficulties in establishing criteria and threshold values of leptin resistance [14].

Nevertheless, several studies have been conducted to assess the impact of leptin and leptin receptors genes polymorphisms on the likelihood of developing obesity among different ethnic groups of people [15–17].

In Indonesia population, was detected connection of polymorphisms of rs1137100 (K109R) and rs1137101 (Q223R) LEPR genes with severe obesity. Foucan et al. [18] in recent genotypic analysis of LEPR (K109R, Q223R, K656N) mutations in Afro-Caribbean's, has single out subjects carrying four variants alleles of the all studied SNPs with a higher risk of obesity comparing to subjects without variant allele. In Maroccan population, El Fessikh et al. identified LEPR (Lys656Asn) polymorphism association with obesity [19]. Ali E.M. et al., among Egyptian subjects confirmed LEPR rs1137101 (Q223R) mutation in obese patients comparing with non-obese controls [20]. The same

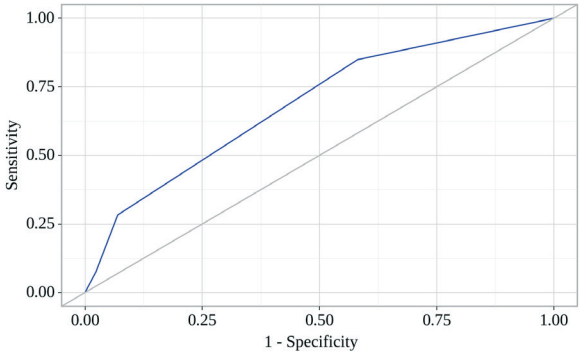

Figure 3. ROC-curve characterizing the dependence of the probability group on Value of logistic function P.

Source: compiled by the authors.

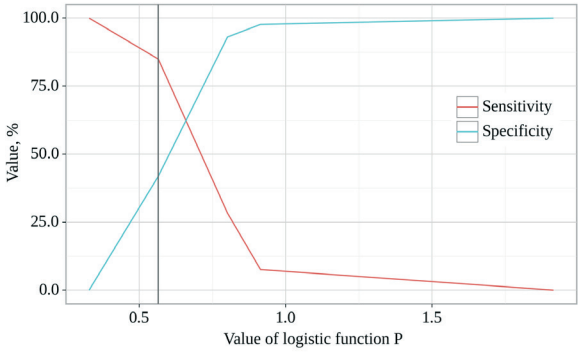

Figure 4. Sensitivity and specificity of group depending on Value of logistic function P.

Source: compiled by the authors.

results reported in study of Ortega, F. L. et al. who provided strong evidence of a significant association of LEPR (Q223R) polymorphism in Indian patients with increased risk of metabolic syndrome development [21].

On the other hand results of Constantin, A. et al. showed no LEP G-2548A and LEPR Q223R SNPs association with a genetic risk factors for obesity in Romanian population. However, LEPR 223R allele's might predispose subjects without obesity to develop some metabolic disturbances [22].

Of corse, conducted research work has several limitations, such as a small sample compared to larger studies in laboratories with routine genetic testing. In addition, the genetic panel used in this study is certainly not complete enough to cover all common and rare genetic variants of obesity caused by mutations in leptin or its receptor genes. The mutations in the genes that has been evaluated in this study maybe not sufficient to cause obesity, but the established changes in the genotype Q223R indicates its potential partial role in the pathogenesis of obesity.

CONCLUSIONS. Our analysis showed that LEPR Q223R (rs1137101) polymorphism could be a potential genetic risk factor for obesity in Ukrainian population regardless of the homozygous or heterozygous genotype (genotypes AA, AG, GG). At the same time, allele A was found in 70.83 % of cases of patients with 2nd and 3rd degree of obesity. And homozygous AA and GG genotypes in 24.5 % and 28.3 %, respectively.

The results obtained can be used in the practice for early diagnosis of different types of obesity and for prognosing of results of bariatric surgery. However, further additional clinical studies with larger sample size are needed to confirm or to disprove the link between polymorphism of leptin genes and its receptors in the genesis of metabolic syndrome.

This work was supported by the state budget of Ukraine as part of the scientific work on the topic "Newest methods of surgical treatment of metabolic syndrome" No. 0123U100300.

LITERATURE

1. Lonardo A. The heterogeneity of metabolic syndrome presentation and challenges this causes in its pharmacological management: a narrative review focusing on principal risk modifiers / A. Lonardo // Expert Review of Clinical Pharmacology. – 2023. – **16** (10). – P. 891–911. DOI: 10.1080/17512433.2023.2259306

2. Metabolic syndrome: updates on pathophysiology and management in 2021 / G. Fahed, L. Aoun, M. Bou Zerdan [et al.] // International Journal of Molecular Sciences. – 2022. – **23** (2). – P. 786. DOI: 10.3390/ijms23020786

3. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited / A. A. da Silva, J. M. do Carmo, X. Li [et al.] // Canadian Journal of Cardiology. – 2020. – **36** (5). – P. 671–682. DOI: 10.1016/j.cjca.2020.02.066

4. Scheja L. The endocrine function of adipose tissues in health and cardiometabolic disease / L. Scheja, J. Heeren // Nature Reviews Endocrinology. – 2019. – **15** (9). – P. 507–524. DOI: 10.1038/s41574-019-0230-6

5. Leptin, obesity, and leptin resistance: where are we 25 years later? / A. G. Izquierdo, A. B. Crujeiras, F. F. Casanueva, M. C. Carreira // Nutrients. – 2019. – **11** (11). – P. 2704. DOI: 10.3390/nu11112704

6. Leptin: Mechanisms involved in signaling and resistance / T. Anjum, Z. Arif, M. Dar [et al.] // Journal of Pharmaceutical Research & Reports. – 2021. – **4** (2). – P. 2–5. DOI: 10.47363/JPRSR/2021

7. Congenital leptin and leptin receptor deficiencies in nine new families: identification of six novel variants and review of literature / I. H. Mazen, M. A. El-Gammal, A. A. Elaidy [et al.] // Molecular Genetics and Genomics. – 2023. – P. 1–11. DOI: 10.1007/s00438-023-02025-1

8. Functional and phenotypic characteristics of human leptin receptor mutations / A. Nunziata, J. B. Funkke, G. Borck [et al.] // Journal of the Endocrine Society. – 2019. – **3** (1). – P. 27–41. DOI: 10.1210/js.2018-00123

9. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics / L. Kleinendorst, O. Abawi, H. J. van der Kamp [et al.] // European Journal of Edocrinology. – 2020. – **182** (1). – P. 47–56. DOI: 10.1530/EJE-19-0678

10. Congenital leptin deficiency and leptin gene missense mutation found in two colombian sisters with severe obesity / H. Yupanqui-Lozno, R. A. Bastarrachea, M. E. Yupanqui-Velazco [et al.] // Genes. – 2019. – **10** (5). – P. 342. DOI: 10.3390/genes10050342

11. Genetic variants in LEP, LEPR, and MC4R explain 30 % of severe obesity in children from a consanguineous population / S. Saeed, A. Bonnefond, J. Manzoor [et al.] // Obesity. – 2015. – **23** (8). – P. 1687–1695. DOI: 10.1002/oby.21142

12.The World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects [Internet]. Available from: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

13. Role of leptin deficiency, inefficiency, and leptin receptors in obesity / M. Wasim, F. R. Awan, S. S. Najam [et al.] // Biochemical Genetics. – 2016. – **54**. – P. 565–572. DOI: 10.1007/s10528-016-9751-z

14. Updates on monogenic obesity in a multifactorial disease / J. Baxter, P. R. Armijo, L. Flores [et al.] // Obesity Surgery. – 2019. – **29**. – P. 4077–4083. DOI: 10.1007/s11695-019-04200-z

15. Hastuti P. Polymorphism in leptin receptor gene was associated with obesity in Yogyakarta, Indonesia /

P. Hastuti, I. Zukhrufia, M. H. Padwaswari [et al.] // Egyptian Journal of Medical Human Genetics. – 2016. – **17** (3). – P. 271–276. DOI: 10.1016/j.ejmhg.2015.12.011

16. Association of the leptin receptor Q223R (rs1137101) polymorphism with obesity measures in Sri Lankans / Y. A. Illangasekera, P. V. R. Kumarasiri, D. J. Fernando, C. F. Dalton // BMC Research Notes. – 2020. – **13** (1). – P. 1–4. DOI: 10.1186/s13104-020-4898-4

17. Association between Adiponectin and Leptin Receptor Genetic Polymorphisms and Clinical Manifestations of Metabolic Syndrome // I. I. Shramko, E. S. Ageeva, K. D. Maliy [et al.] // Journal of Diabetes Research. – 2022. – P. 23–29. DOI: 10.1155/2022/9881422

18. Influence of K656N polymorphism of the leptin receptor gene on obesity-related traits in nondiabetic Afro-Caribbean individuals // L. Foucan, V. Bassien-Capsa, C. Rambhojan [et al.] // Metabolic Syndrome and Related Disorders. – 2019. – **17** (4). – P. 197–203. DOI: 10.1089/met.2018.0133

19. Association study of leptin receptor polymorphisms in women with obesity and their impact on protein domains: a case-control study and in silico analyses / M. El Fessikh, Z. Elkarhat, D. Flatters [et al.] // Journal of Biomolecular Structure and Dynamics. – 2023. – **41** (14). – P. 6546–6558. DOI: 10.1080/07391102.2022.2109755

20. Fat mass and obesity-associated (FTO) and leptin receptor (LEPR) gene polymorphisms in Egyptian obese subjects / E. M. Ali, T. Diab, A. Elsaid [et al.] // Archives of Physiology and Biochemistry. – 2021. – **127** (1). – P. 28–36. DOI: 10.1080/13813455.2019.1573841

21. LEP (G2548A-G19A) and ADIPOQ (T45G-G276T) gene polymorphisms are associated with markers for metabolic syndrome / F. L. Ortega, A. M. Camberos, M. I. Arredondo [et al.] // Diabetology & Metabolic Syndrome. – 2023. – **15** (1). – P. 237. DOI: 10.1186/s13098-023-01215-6

22. Leptin G-2548A and leptin receptor Q223R gene polymorphisms are not associated with obesity in Romanian subjects / A. Constantin, G. Costache, A. V. Sima [et al.] // Biochemical and biophysical research communications. – 2010. – **391** (1). – P. 282–286. DOI: 10.1016/j.bbrc.2009.11.050

REFERENCES

1. Lonardo, A. (2023). The heterogeneity of metabolic syndrome presentation and challenges this causes in its pharmacological management: a narrative review focusing on principal risk modifiers. *Expert Review of Clinical Pharmacology,* 16 (10), 891-911. DOI: 10.1080/17512433.2023.2259306

2. Fahed, G., Aoun, L., Bou Zerdan, M., Allam, S., Bou Zerdan, M., Bouferraa, Y., & Assi, H.I. (2022). Metabolic syndrome: updates on pathophysiology and management in 2021. *International Journal of Molecular Sciences,* 23(2), 786. DOI: 10.3390/ijms23020786

3. da Silva, A.A., do Carmo, J.M., Li, X., Wang, Z., Mouton, A.J., & Hall, J.E. (2020). Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited. *Canadian Journal of Cardiology,* 36(5), 671-682. DOI: 10.1016/j.cjca.2020.02.066

4. Scheja, L., & Heeren, J. (2019). The endocrine function of adipose tissues in health and cardiometabolic disease. *Nature Reviews Endocrinology,* 15(9), 507-524. DOI: 10.1038/s41574-019-0230-6

5. Izquierdo, A.G., Crujeiras, A.B., Casanueva, F.F., & Carreira, M.C. (2019). Leptin, obesity, and leptin resistance: where are we 25 years later? *Nutrients,* 11(11), 2704. DOI: 10.3390/nu11112704

6. Anjum, T., Arif, Z., Dar, M., Raza, A., & Bibi, Z. (2021). Leptin: Mechanisms Involved In Signaling and Resistance. *Journal of Pharmaceutical Research & Reports,* (2)4, 2-5. DOI: 10.47363/JPRSR/2021

7. Mazen, I.H., El-Gammal, M.A., Elaidy, A.A., Anwar, G.M., Ashaat, E.A., Abdel-Ghafar, S.F., & Abdel-Hamid, M.S. (2023). Congenital leptin and leptin receptor deficiencies in nine new families: identification of six novel variants and review of literature. *Molecular Genetics and Genomics,* 1-11. DOI: 10.1007/s00438-023-02025-1

8. Nunziata, A., Funcke, J.B., Borck, G., von Schnurbein, J., Brandt, S., Lennerz, B., ... & Wabitsch, M. (2019). Functional and phenotypic characteristics of human leptin receptor mutations. *Journal of the Endocrine Society,* 3(1), 27-41. DOI: 10.1210/js.2018-00123

9. Kleinendorst, L., Abawi, O., van der Kamp, H.J., Alders, M., Meijers-Heijboer, H.E., van Rossum, E.F., ... & van Haelst, M.M. (2020). Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. *European Journal of Endocrinology,* 182 (1), 47-56. DOI: 10.1530/EJE-19-0678

10. Yupanqui-Lozno, H., Bastarrachea, R.A., Yupanqui-Velazco, M.E., Alvarez-Jaramillo, M., Medina-Méndez, E., Giraldo-Peña, A.P., ... & Celis-Regalado, L.G. (2019). Congenital leptin deficiency and leptin gene missense mutation found in two colombian sisters with severe obesity. *Genes,* 10(5), 342. DOI: 10.3390/genes10050342

11. Saeed, S., Bonnefond, A., Manzoor, J., Shabir, F., Ayesha, H., Philippe, J., ... & Froguel, P. (2015). Genetic variants in LEP, LEPR, and MC4R explain 30% of severe obesity in children from a consanguineous population. *Obesity,* 23(8), 1687-1695. DOI: 10.1002/oby.21142

12. The World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects [Internet]. Available from: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

13. Wasim, M., Awan, F.R., Najam, S.S., Khan, A.R., & Khan, H.N. (2016). Role of leptin deficiency, inefficiency, and leptin receptors in obesity. *Biochemical Genetics,* 54, 565-572. DOI: 10.1007/s10528-016-9751-z

14. Baxter, J., Armijo, P.R., Flores, L., Krause, C., Samreen, S., & Tanner, T. (2019). Updates on monogenic obesity in a multifactorial disease. *Obesity Surgery,* 29, 4077-4083. DOI: 10.1007/s11695-019-04200-z

15. Hastuti, P., Zukhrufia, I., Padwaswari, M.H., Nuraini, A., & Sadewa, A.H. (2016). Polymorphism in leptin receptor gene was associated with obesity in Yogyakarta, Indonesia. *Egyptian Journal of Medical Human Genetics,* 17(3), 271-276. DOI: 10.1016/j.ejmhg.2015.12.011

16. Illangasekera, Y.A., Kumarasiri, P.V.R., Fernando, D.J., & Dalton, C.F. (2020). Association of the leptin

receptor Q223R (rs1137101) polymorphism with obesity measures in Sri Lankans. *BMC Research Notes,* 13(1), 1-4. DOI: 10.1186/s13104-020-4898-4

17. Shramko, I.I., Ageeva, E.S., Maliy, K.D., Repinskaya, I.N., Tarimov, C.O., Fomochkina, I.I., ... & Shekhar, S. (2022). Association between Adiponectin and Leptin Receptor Genetic Polymorphisms and Clinical Manifestations of Metabolic Syndrome. *Journal of Diabetes Research,* 2022. DOI: 10.1155/2022/9881422

18. Foucan, L., Bassien-Capsa, V., Rambhojan, C., Lacorte, J.M., & Larifla, L. (2019). Influence of K656N polymorphism of the leptin receptor gene on obesity-related traits in nondiabetic Afro-Caribbean individuals. *Metabolic Syndrome and Related Disorders,* 17(4), 197-203. DOI: 10.1089/met.2018.0133

19. El Fessikh, M., Elkarhat, Z., Flatters, D., Camproux, A.C., Belghiti, H., Guerinech, H., ... & El Baghdadi, J. (2023). Association study of leptin receptor polymorphisms in women with obesity and their impact on protein domains: a case-control study and in silico analyses. *Journal of Biomolecular Structure and Dynamics,* 41(14), 6546-6558. DOI: 10.1080/07391102.2022.2109755

20. Ali, E.M., Diab, T., Elsaid, A., Abd El Daim, H.A., Elshazli, R.M., & Settin, A. (2021). Fat mass and obesity-associated (FTO) and leptin receptor (LEPR) gene polymorphisms in Egyptian obese subjects. *Archives of Physiology and Biochemistry,* 127(1), 28-36. DOI: 10.1080/13813455.2019.1573841

21. Ortega, F.L., Camberos, A.M., Arredondo, M.I., Magallanes, N.G., & Meraz, E.A. (2023). LEP (G2548A-G19A) and ADIPOQ (T45G-G276T) gene polymorphisms are associated with markers for metabolic syndrome. *Diabetology & Metabolic Syndrome,* 15(1), 237. DOI: 10.1186/s13098-023-01215-6

22. Constantin, A., Costache, G., Sima, A.V., Glavce, C.S., Vladica, M., & Popov, D.L. (2010). Leptin G-2548A and leptin receptor Q223R gene polymorphisms are not associated with obesity in Romanian subjects. *Biochemical and Biophysical Research Communications,* 391(1), 282-286. DOI: 10.1016/j.bbrc.2009.11.050

Received 18.01.2024

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ

ПРОГНОЗУВАННЯ ЙМОВІРНОСТІ РОЗВИТКУ ОЖИРІННЯ ЗАЛЕЖНО ВІД ПОЛІМОРФІЗМУ ГЕНІВ ЛЕПТИНУ ТА РЕЦЕПТОРІВ ЛЕПТИНУ

Резюме

Вступ. *Метаболічний синдром – гетерогенний патологічний стан, який поєднує в собі різні стадії ожиріння, порушення толерантності до глюкози, атерогенну дисліпідемію та артеріальну гіпертензію. Саме ожиріння є ключовим елементом цього синдрому. Гормональні порушення, центральним з яких є інсулінорезистентність, запускають каскад нейроендокринних змін, що призводять до прогресування метаболічного синдрому. Моногенні мутації часто виявляють у хворих з вираженим ожирінням, а також з раннім (до 10 років) його дебютом. В останні роки все частіше досліджують генетично зумовлений збій у механізмі впливу лептину на розвиток ожиріння.*

Мета дослідження *– оцінити ймовірність розвитку ожиріння у хворих з поліморфізмом генів LEP та LEPR в українській популяції.*

Методи дослідження. *Генотипування генів LEP і LEPR (K109R (rs1137100), Q223R (rs1137101), K656N (rs1805094), G2548A (rs7799039)) за допомогою TaqMan™ SNP Genotyping Human Assays (Thermo Fisher Scientific, США) пройшли 53 пацієнти з ожирінням і 43 пацієнти без ожиріння.*

Результати й обговорення. *При порівнянні rs1137101 алель A, rs1137101 алель G виявлено статистично значущі відмінності. При порівнянні rs1805094 алель C, rs1805094 алель G, rs7799039 алель A, rs7799039 алель G, rs1137100 алель A, rs1137100 алель G залежно від групи статистично значущих відмінностей не спостерігали. При порівнянні rs1137101 алель A відзначено статистично значущі відмінності залежно від ступеня ожиріння (p<0,001). При порівнянні решти алелів SNP (rs1805094 алель C, rs1805094 алель G, rs7799039 алель A, rs7799039 алель G, rs1137101 алель G, rs1137100 алель A, rs1137100 алель G, rs696217 алель G) статистично значущих відмінностей не відмічено. Прогнозування ймовірності розвитку ожиріння залежно від поліморфізму лептину та лептинових рецепторів виявило залежність лише мутацій у LEPR Q223R (rs1137101) в українській популяції. За результатами ROC-аналізу, чутливість і специфічність методу становили 65,5 та 67,8 % відповідно.*

Висновки. *Наш аналіз показав, що поліморфізм LEPR Q223R (rs1137101) може бути потенційним генетичним фактором ризику розвитку ожиріння в українській популяції незалежно від гомозиготного чи гетерозиготного генотипу (генотипи AA, AG, GG). При цьому алель A виявлено в 70,83 % пацієнтів з ожирінням 2-го і 3-го ступенів, гомозиготні генотипи AA та GG – у 24,5 і 28,3 % відповідно. Отримані результати можна використати в практиці для ранньої діагностики ожиріння різних типів та прогнозування результатів баріатричної хірургії.*

КЛЮЧОВІ СЛОВА: **метаболічний синдром; гени LEP та LEPR; алельний поліморфізм.**