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The Significance Of The Arg223gln Lepr Gene Polymorphism In Obesity

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Abstract
Currently, the role of genetic factors in the development of various obesity phenotypes in individuals of different races, ethnicities, and genders is of particular interest. In particular, given the high prevalence of obesity among Uzbek women of childbearing age, studying the characteristics and genetic underpinnings of the various phenotypes of this pathology is of great importance. The action of one of the main obesity hormones, leptin, is controlled by the expression of leptin receptors, which are encoded by the LEPR gene. Mutations in this gene lead to increased leptin levels, decreased expression of the receptors that mediate its action, or altered leptin specificity, leading to the development of leptin resistance. Therefore, studying the allele and genotype frequencies of the ARG223GLN polymorphism of the LEPR gene is of great importance for the early detection and prevention of obesity in this patient population. This article examines and analyzes the prevalence of alleles and genotypes of the ARG223GLN polymorphism in the LEPR gene across various obesity phenotypes.
Key words: women of childbearing age, metabolically healthy obesity, metabolically complicated obesity, gene polymorphism.

Relevance of the study
In recent years, numerous studies have investigated the correlation between genes that cause overweight and obesity and various features of the metabolic syndrome [1,2,3]. Obesity is a heterogeneous disease, both genetic and environmental factors their interaction play an important role in its development [14,10,3].
In obesity, mutations in the genes encoding leptin and its receptors, in particular the LEPR gene, lead to an increase in leptin levels, a decrease in the expression of receptors that exert its effects, or a change in its specificity, leading to the development of leptin resistance [2,3,6,12,13].
Leptin action is regulated by the expression of leptin receptors, which are encoded by the LEPR gene located on chromosome 1 (1p31.3) [2,3,11]. Although it is expressed in the liver, pancreas, and oral cavity, it functions primarily in the hypothalamus [2,3]. Six isoforms of the leptin receptor have been identified, all of which are encoded by the LEPR gene [2,3,5]. Studies have shown that the Gln223Arg polymorphism is associated with leptin resistance, obesity, type 2 diabetes, and their complications [7,9,16-19]. Shi X.H. et al. (2012) and Radhika B. et al. (2020) found that the LEPR Gln223Arg polymorphism is associated with diabetes mellitus and metabolic syndrome [2,3,16,18], while Pena G.G. et al. (2013) found that this polymorphism was positively correlated with elevated serum glucose levels in the Brazilian population [2,3,4,8,15].
The aim of this study was to evaluate the significance of the Arg223Gln polymorphism of the LEPR gene in Uzbek women of childbearing age diagnosed with healthy obesity and metabolically complicated obesity.
Materials and methods. The study included 224 Uzbek women of childbearing age diagnosed with obesity who resided in Tashkent from 2019 to 2022.
Initially, the women's anthropometric parameters (BMI, WC, WHR, W/R) were determined (WHO, 2016). The women were divided into two groups according to the aforementioned studies and the metabolic syndrome criteria (WHO, 2016; International Diabetes Federation, 2009). Group 1 included 133 women diagnosed with MCO, with an average age of 42.0 ± 0.5 years; The second group included 91 women with a mean age of 41.7±0.7 years diagnosed with MS. The control group consisted of 45 healthy volunteers (women, mean age 43.2±0.8 years, BMI <30 kg/m², waist circumference less than 80 cm). In addition to all standard tests to verify the diagnosis of healthy and metabolically complicated obesity, genotyping of Arg223Gln polymorphisms of the LEPR gene was performed in these groups using the molecular genetic method – PCR.

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Results and analysis. The prevalence of the Arg223Gln polymorphism of the LEPR gene was determined in the group of patients with metabolically complicated obesity (MCO), with the ArgArg, ArgGln, and GlnGln genotypes accounting for 33.0, 41.4, and 28.6%, respectively. In the control group, the genotypes of the Arg223Gln polymorphism were 13.3% - ArgArg, 37.8% - ArgGln, and 48.9% - GlnGln. In the MCO group, the Arg allele of the Arg223Gln polymorphism was found in 50.8% of cases, the Gln allele - in 49.2% of cases, while in the control group the Arg allele was found in 32.2% of cases, the Gln allele - in 67.8% of cases (Table 1). Table 1.

Prevalence of alleles and genotypes of the Arg223Gln polymorphism of the LEPR gene in the MAS and control groups

Table 1

Allele, genotype	The number of alleles and genotypes encountered				χ^2	P	OR	95% CI
	MCO Group		Control group					
	n=133	%	n=45	%				
Arg	135	50,8	29	32,2	8,6	=0,004	2,2	1,311 -3,585
Gln	131	49,2	61	67,8	9,5	=0,003	0,5	0,279 -0,763
ArgArg	40	30,0	6	13,3	4,1	<0,05	2,8	1,096 -7,128
ArgGln	55	41,4	17	37,8	0,06	=0,8	1,2	0,580 -2,326
GlnGln	38	28,6	22	48,9	5,3	=0,021	0,4	0,209 -0,838

The risk of the Arg allele in the MCO group was 1.031, and the probability of its occurrence in the control group was 0.475, i.e., this allele was found in women in the MCO group 2.2 times more often than in the control group. This result indicates a significant aggressiveness of the Arg allele with respect to the development of MAS (χ^2 = 8.6; OR = 2.2; 95% CI - 1.311 - 3.585; p = 0.004).
The risk of the Gln allele in the MCO group was 0.970, while the probability of its occurrence in the control group was 2.103, i.e. this allele was found 2.2 times more often in the control group than in the MCO group. This result indicates that a high prevalence of the Gln allele in healthy individuals has a reliable protective effect against the development of MCO (χ^2 = 9.5; OR = 0.5; 95% CI - 0.279 - 0.763; p = 0.003).
The Arg/Arg genotype was a risk factor for the development of this disease in the MCO group was of 0.430, while in the control group it was 0.154, i.e., in the MCO group, this genotype was found 2.8 times more often than in healthy individuals. This result indicates a significant aggressive effect of the ArgArg genotype on the development of MCO (χ^2 = 4.1; OR = 2.8; 95% CI - 1.096-7.128; p < 0.05).
The frequency of the ArgGln genotype as a risk factor for developing this disease in the SMA group was 0.705, while in the control group, this figure was 0.607. This means that this genotype was 1.2 times more common in patients with MCO than in healthy individuals. However, this difference was not statistically significant (χ^2 = 0.06; OR = 1.2; 95% CI -0.580-2.326; p = 0.8).
The frequency of the GlnGln genotype as a risk factor for developing this disease in the MCO group was 0.400, while in the control group, its probability was 0.957. This means that this genotype was 2.4 times more common in healthy individuals than in the MCO group. This result suggests that the GlnGln genotype has a significant protective effect against the development of MCO (χ^2=5.3; OR=0.4; CI 95% - 0.209 - 0.838; p=0.021). When determining the frequency of occurrence of the Arg223Gln polymorphism of the

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LEPR gene, the genotypes ArgArg, ArgGln and GlnGln in the group of metabolically healthy individuals with obesity (MHI) were 20.9, 38.4 and 40.7%, respectively.

Table 2

Prevalence of alleles and genotypes of the Arg223Gln polymorphism of the LEPR gene in the MHI and control groups

Allele, genotype	The number of alleles and genotypes encountered				χ^2	P	OR	95% CI
	MHI group		Control group					
	n=91	%	n=45	%				
Arg	73	40,1	29	32,2	1,3	=0,26	1,4	0,827 -2,399
Gln	109	59,9	61	67,8	1,6	=0,20	0,7	0,417 -1,209
ArgArg	19	20,9	6	13,3	2,3	=0,13	1,8	0,835 -3,788
ArgGln	35	38,4	17	37,8	0,02	=0,88	1,0	0,589 -1,850
GlnGln	37	40,7	22	48,9	1,3	=0,26	0,7	0,414 -1,265

In the MHI group, the Arg allele of the Arg223Gln polymorphism of the LEPR gene was detected in 40.1% of women with an odds ratio (OR) of 0.670 in this group and 0.475 in the control group. The OR of this allele in the MHI group was 1.4 times higher than in the control group (χ^2 = 1.3; OR = 1.4; p = 0.26).

The prevalence of the Gln allele in this group was 59.9% with an OR of 1.493, while in the control group this figure was 2.103, i.e., the OR of this allele in healthy individuals was 1.4 times higher than in the MHI group (χ^2 = 1.6; OR = 0.7; p = 0.20).

The ArgArg genotype had an 0.266 for the MHI group and 0.149 for the control group, meaning that the probability of its presence in the MHI group was 1.8 times higher than in the control group (χ^2 = 2.3; OR = 1.8; p = 0.13).

The ArgGln genotype had an 0.613 for the MHI group and 0.587 for the control group, and no differences in their prevalence were found between the groups (χ^2 = 0.02; OR = 1.0; p = 0.88).

The frequency of the GlnGln genotype as a risk factor for obesity in the MHI group was 0.695, while in the control group this figure was 0.961, i.e., the frequency of this genotype in the control group was 1.4 times higher than in the MHI group. This result indicates a protective effect of the GlnGln genotype on the development of obesity (χ^2=1.3; OR=0.7; p=0.26).

Thus, although no significant difference in the frequency of alleles and genotypes of the Arg223Gln polymorphism of the LEPR gene was detected between the MHI and control groups, it was established that the frequency of the Arg allele and the ArgArg genotype of this polymorphism was higher in the MHI group than in the control group, while the probability of occurrence of the Gln allele and the GlnGln genotype was higher in the control group. This result indicates the aggressiveness of the former allele and genotype in increasing BMI, while the latter allele and genotype are protective.

Based on the data obtained, the following conclusions **were made:**

1. It was established that the Arg allele of the Arg223Gln polymorphism of the LEPR gene occurs 2.2 times more often in the MCO group than in the control group, which indicates its reliable aggressive feature in terms of the development of MCO;
2. The risk of the Gln allele of this polymorphism in the MCO group was significantly lower (2.2 times) than in the control group, which suggests that the Gln allele, which is more common in healthy individuals, has a reliable protective effect against the development of MCO.

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3. The Arg223Gln polymorphism of the LEPR gene, Arg/Arg genotype, was found 2.8 times more frequently in the MCO group than in the control group, indicating that this genotype has a significant aggressive feature for the development of MCO.
4. The GlnGln genotype of the Arg223Gln polymorphism of the LEPR gene was 2.4 times more common in the control group than in the MCO group. This result indicates a significant protective effect of the GlnGln genotype against the development of MCO.

References

1. Belyayeva O.D., Bazhenova Ye.A., Berezina A.V. ya doktor. Uroven' leptina i polimorfizm gena Q223R retseptora leptina u pasitinov s abdominal'nym ozhirinom // Problemy zhenskogo zdorov'ya. - 2010. - T. 5. № 2. - S. 28 - 34. Belyaeva O.D., Bazhenova E.A., Berezina A.V. I am a doctor. Leptin level and polymorphism of the leptin receptor gene Q223R in pacitins with abdominal obesity // Problems of Women's Health. - 2010. - V. 5. No. 2. - P. 28-34.
2. Dadabayeva R.K. Funktsional'noye sostoyaniye pochek i geneticheskaya predraspolozhennost' k tubulointerstitsial'nym izmeneniyam u zdorovykh i stradayushchikh ozhireniyem lyudey s metabolicheskim sindromom // 14.00.05 - avtoreferat dissertatsii doktora meditsinskikh nauk. - Tashkent, - 2024. - 63 s. Dadabaeva R.K. Functional state of the kidneys and genetic predisposition to tubulointerstitial changes in healthy and obese people with metabolic syndrome // 14.00.05 - abstract of the dissertation of Doctor of Medical Sciences. - Tashkent, - 2024. - 63 p.
3. Dadabayeva R.K., Gadayev A.G., Kurbanov A.K. Rol' biologicheski aktivnykh veshchestv v razvitii i kontrole ozhireniya (obzor literatury) // Zhurnal teoreticheskoy i klinicheskoy meditsiny. 2023. № 1. S. 35-42. http://elibrary.ru/item.asp?id=53737648. Dadabaeva R.K., Gadaev A.G., Kurbanov A.K. The role of biologically active substances in the development and control of obesity (literature review) // Journal of Theoretical and Clinical Medicine. 2023. No. 1. P. 35-42. http://elibrary.ru/item.asp?id=53737648
4. Sharafetdinov KH.KH., Yudochkin A.V., Plotnikova O.A. Rol' geneticheskikh faktorov v razvitii metabolicheskogo sindroma // Voprosy diyetologii. - 2016. - T.6. - № 4. - S. 29 – 35. Sharafetdinov Kh.Kh., Yudochkin A.V., Plotnikova O.A. The role of genetic factors in the development of metabolic syndrome // Issues of dietology. - 2016. - T.6. - No. 4. - P. 29 - 35.
5. Yagoda A. V., Geyvandova T. V., Rogova S. SH., Geyvandova N. I. Polimofizm gena retseptora leptina i leptinorezistentnost' pri nealkogol'noy zhirovoy bolezni pecheni, assotsiirovannoy s ozhireniem // Effektivnaya farmakoterapiya. - 2019. - T.15. №18. - S. 82 - 87. DOI 10. 33978 / 2307-3586-2019-15-18-82-87.. Yagoda A. V., Geyvandova T. V., Rogova S. Sh., Geyvandova N. I. Leptin receptor gene polymorphism and leptin resistance in non-alcoholic fatty liver disease associated with obesity // Effective pharmacotherapy. - 2019. - Vol. 15. No. 18. - P. 82-87. DOI 10. 33978 / 2307-3586-2019-15-18-82-87.
6. Aboelros S.A., Nassar A.M., Elshabrawy M.M. et al. Association of Leptin Gene G2548A Polymorphism and Leptin Resistance with Insulin Resistance and Obesity among Egyptians // Suez Canal University Medical Journal. – 2017. - Vol. 20 (2). – P. 142 – 152.
7. Bender N., Allemann N., Marek D., Vollenweider P., Waeber G., Mooser V., Egger M., Bochud M. Association between LEPR and Obesity Association between variants of the Leptin Receptor Gene (LEPR) and overweight: a systematic review and an analysis of the CoLaus study // Plos One. – 2011. –Vol.6(10). - e26157.
8. Gottlieb M.G., Bodanese L.C., Leite L.E. et al. Association between the Gln223Arg polymorphism of the leptin receptor and metabolic syndrome in free-living community elderly // Metab. Syndr. Relat. Disord. - 2009. - Vol.7.,№ 4. - P. 341 - 348.
9. Domínguez - Reyes T., Astudillo -López C.C., Salgado-Goytia L. Muñoz-Valle J.F., Salgado-Bernabé1 A.B., Guzmán-Guzmán I.P., Castro-Alarcón N., Moreno-Godínez M.E., Parra-Rojas I. Interaction of dietary fat intake with APOA2, APOA5 and LEPR polymorphisms and its relationship with obesity and dyslipidemia in young subjects // Lipids in Health and Disease. – 2015. – Vol. 14 (106). http:// creativecommons.org/licenses/by/4.0/.

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10. de Mutsert R., den Heijer M., Rabelink T. J. et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection // European Journal of Epidemiology. – 2013. - Vol.28 (6). – P. 513 - 523.
11. Li Y.Y., Wang H., Yang X.X., Wu J.J., Geng H.Y., Kim H.J., Yang Z.J. et al. LEPR gene Gln223Arg polymorphism and type 2 diabetes mellitus: a meta-analysis of 3,367 subjects // Oncotarget. - 2017. - Vol. 8(37). - P. 61927 - 61934.
12. Myers M.G., Cowley M.A., Münzberg H. "Mechanisms of leptin action and leptin resistance // Annu Rev Physiol. – 2010. – Vol. 70. – P. 537 - 56.
13. Munzberg H., Bjornholm M., Bates S.H., Myers M.G. Leptin receptor action and mechanisms of leptin resistance // Cell Mol Life Sci. – 2005. – Vol. 62(6). – P. 642–52.
14. Nirmala A., Reddy B. M., Reddy. Genetics of human obesity: an overview // International Journal of Human Genetics. – 2008. - Vol. 8 (1-2). – P. 217 - 226.
15. Pena G.G., Guimaraes A.L.S., Veloso R.R.., Reis T.C., Neto J.R., Velasquez-Melendez G. et al. No association of leptin receptor gene Gln223Arg polymorphism with capillary glucose levels: a preliminary population base cross-sectional study // ISRN Genetics. – 2013. Vol. 2013. – P. 1 - 7.
16. Radhika B., Sriprajna M., Usha A., Sudheendrs R. Single nucleotide polymorphism of leptin receptor gene in type 2 diabetes mellitus: a cross-sectional study // Research J. Pharm. and Tech. – 2020. – Vol.13(2). – P. 560 - 564.
17. Sahin S. Rustemoglu A., Tekcan A. et al. Investigation of Associations between Obesity and LEP G2548A and LEPR 668A/G Polymorphisms in a Turkish Population // Disease Markers. - 2013. - Vol. 35 (6). - P. 673 - 677. doi. org /10.11 55/2013/216279.
18. Shi X.H., Sun L., Wang L., Jin F., Zhu X.Q., Tang L., Yang Z. Association between Q223R gene polymorphism and type2 diabetes mellitus in Chinese north population // Med Res J. – 2012. – Vol. 41. – P. 23 - 26.
19. Ying J., Shi N.S., Pan R.W., Li P.Z., Zhang H.Q. Association between Gln223Arg and type 2 diabetes in Zhejing // Chin Gerontol. – 2009. – Vol. 29. – P. 858 - 860.