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# CLINICAL COURSE OF OBESITY-ASSOCIATED ASTHMA DEPENDING ON THE GLN27GLU POLYMORPHIC VARIANT OF THE β2-ADRENORECEPTOR GENE, TAKING INTO ACCOUNT THE AGE OF ONSET

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**Abstract**. **Introduction.** Studies have shown that bronchial asthma (BA) associated with obesity has a more severe course, lower control, more frequent cases of low efficacy of basic treatment, and exacerbations. Two phenotypes have been distinguished in BA-obesity comorbidity based on age of onset: early atopic and late non-atopic. It is known that genetic factors associated with β2-adrenoceptor (AR) genes are important in the development of both asthma and obesity.

**The purpose of the study** aimed to analyze the association of the Gln27Glu polymorphism of the β2-adrenoceptor gene with the severity of the course of bronchial asthma with obesity, taking into account the age of its onset.

**Research material and methods.** 195 asthma patients with obesity consented for the study participation were examined. The control group consisted of 95 practically healthy people. Patients were divided into two clinical groups depending on the age of onset of BA: the first group included 100 patients with an early onset, the second group - 95 patients with a late onset. The diagnosis and treatment of asthma followed the guidelines of the Global Initiative for Asthma (2016) and its updated versions. The study was approved by the Bioethics Commission of the Educational and Scientific Medical Institute of Sumy State University. Determination of the Gln27Glu polymorphism of the β2-AR gene (rs1042714) was performed using the polymerase chain reaction with the subsequent analysis of restriction fragments. Statistical analysis of the obtained results was carried out using the SPSS-17 program. Pearson's chi-squared test was used to compare genotype distributions between experimental groups. To determine the risk of BA and obesity, odds ratios and 95% confidence intervals were calculated for dominant, recessive, superdominant, and additive models of inheritance. Their relevance was assessed using the Akaike information criterion. All tests were two-sided, and values $p < 0.05$ were considered statistically significant.

**Research results.** The frequency of Gln/Gln, Gln/Glu and Glu/Glu genotypes according to the Gln27Glu polymorphism of the β2-AR gene in patients with early-onset obesity-associated asthma was 70.0; 25.0; 5.0% with a mild course and 55.0; 36.2; 8.8% with severe ($\chi 2 = 1.49$; $p = 0.473$); and with a late debut - 50.0; 43.8; 6.2% with mild and 54.0%; 31.7; 14.3%, respectively, with severe ($\chi 2 = 2.10$; $p = 0.350$). Despite the absence of a probable difference in the distribution of genotypes depending on the severity of the course, it was found that the frequency of homozygotes for the minor allele was 1.8 times higher in patients with a severe course of early BA and 2.3 times higher in late BA compared to that in patients with mild BA course.

The risk of early-onset BA with obesity and a severe course showed no association in all models of inheritance, and in patients with late-onset BA, there was a 1.66-fold increase (95% CI (1.03 – 2.72), $p = 0.04$) in the additive inheritance model ($p = 0.04$).

**Conclusions.** There are no statistically significant differences in the distribution of genotypes according to the Gln27Glu polymorphism of the β2-AR gene depending on the severity of the course of early and late BA with obesity. The risk of developing a severe course of early BA did not depend on the Gln27Glu polymorphism of the β2-AR gene, and late BA increased by 1.66 times in the additive model of inheritance.

**Keywords:** bronchial asthma, risk, onset, obesity, course, Gln27Glu polymorphism, genotypes, β2-adrenoceptor gene.

**Introduction.** Numerous research on the phenotype of bronchial asthma (BA) associated with obesity have shown a more severe course, lower control, more frequent cases of low efficacy of basic treatment and exacerbations [1, 2, 3]. Considering the pathogenetic and clinical heterogeneity of BA-obesity comorbidity, two phenotypes were distinguished depending on the age of onset: early atopic and late without atopy [4]. The results of researches into the etiological features of BA depending on the age of onset made it possible to establish differences in genetic factors and the presence of specific factors for early and late BA. 123 independent associations for early BA and 56 for late BA have been demonstrated, among which only 37 partially coincide [5, 6]. This allows partially explain the differences in the pathophysiology of BA depending on the age of onset. At the same time, it is known that genetic factors associated with the pleiotropic effects of $\beta_2$-adrenoceptor (AR) genes are important in the development of both BA and obesity. Our choice of the Gln27Glu polymorphism of the $\beta_2$-AP gene is due to the fact that a number of researches have proven its role in the development of BA and obesity, bronchial hyperactivity, and the effectiveness of treatment [7], but these results have low reproducibility in different researches, which is due to the heterogeneity of populations, insufficient volume samples, incomplete characteristics of the comparison groups [8, 9]. The identification of clinical phenotypes of BA helped reveal the genetic heterogeneity of the disease, which

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allowed us to think that common genetic factors and, accordingly, common mechanisms of pathogenesis are involved in the formation of certain phenotypes of the disease, in particular, clinical features of the course and its severity. A differentiated approach to the study of genomic associations with the age of onset of the disease can help in the identification of risk variants for a certain BA phenotype, which will generally help to understand the features of the clinical course and help to modify treatment approaches.

**The aim of our research** was to analyze the possible association of the Gln27Glu polymorphism of the $\beta_2$-AP gene with the severity of the course of BA with obesity, taking into account the age of its onset.

**Research material and methods.** 195 patients with bronchial asthma with obesity were examined. The control group consisted of 95 practically healthy people. All the examined previously signed the informed consent to participate in the research. The function of external breathing was studied using the diagnostic complex "Cardioplus" (Ukraine). Patients were divided into two clinical groups depending on the age of onset of BA: 100 patients with an early onset made up the I group, 95 patients - the II group. The research was approved by the Bioethics Commission of the Educational and Scientific Medical Institute of Sumy State University. Determination of the Gln27Glu polymorphism of the $\beta_2$-AP gene (rs1042714) was performed using the polymerase chain reaction followed by the analysis of restriction fragments. Statistical analysis of the obtained results was carried out using the SPSS-17 program. Pearson's $\chi^2$- test was used to compare the distribution of genotypes in the experimental groups. To determine the risk of BA and obesity, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for dominant, recessive, superdominant, and additive models of inheritance. Their relevance was assessed using the Akaike information criterion. All tests were two-sided, values $P < 0.05$ were considered statistically significant.

**Research results.** Taking into account the obtained data on the association of the Gln27Glu polymorphism of the $\beta_2$-AR gene with the severity of the course of the disease, with the formation of therapy-resistant forms of BA [7, 10], we investigated the distribution of genotypes depending on the severity of the course and the age of onset (table 1). Patients with a mild and moderate course were combined into one group with a mild course.

**Table 1**

**The frequency of genotypes according to the Gln27Glu polymorphism of the $\beta_2$-adrenergic receptor gene in patients with bronchial asthma depending on the age of onset and the severity of the course**

| Patients with bronchial asthma associated with obesity, n = 195 | | | | |
|---|---|---|---|---|
| Early onset, n = 100 | | | | |
| Genotypes | Easy course, n = 20 | | Severe course, n = 80 | |
| | n | % | n | % |
| Gln/Gln | 14 | 70.0 | 44 | 55.0 |
| Gln/Glu | 5 | 25.0 | 29 | 36.2 |
| Glu/Glu | 1 | 5.0 | 7 | 8.8 |
| $\chi^2 = 1.49$; p = 0.473 | | | | |
| Late onset, n = 95 | | | | |
| Genotypes | Easy course, n = 32 | | Severe course, n = 63 | |
| | n | % | n | % |
| Gln/Gln | 16 | 50.0 | 34 | 54.0 |
| Gln/Glu | 14 | 43.8 | 20 | 31.7 |
| Glu/Glu | 2 | 6.2 | 9 | 14.3 |
| $\chi^2 = 2,10$; p = 0,350 | | | | |

It was established that there was no significant difference in the distribution of genotypes according to the Gln27Glu polymorphism of the $\beta_2$-AR gene depending on the severity of the course in patients with early ($\chi^2 = 1.49$; p = 0.473) and late ($\chi^2 = 2.10$; p = 0.350) BA associated with obesity. Although, in the process of analysis, it was found that the frequency of homozygotes for the minor allele was 1.8 times higher in patients with severe early BA course and 2.3 times higher in late compared to patients with a mild course.

The results of a statistical analysis to determine the relative risk of developing severe early- and late-onset BA depending on the Gln/Glu polymorphism of the $\beta_2$-AR gene, taking into account different inheritance models, are presented in the (table 2).

Calculation of the relative risk of developing early-onset BA with obesity and severe course showed no association in all models of inheritance, and in patients with late-onset BA - a 1.66-fold increase in the additive model of inheritance (p = 0.04).

**Discussion of research results.** Taking into account the results of researches on the differences in the factors of origin and mechanisms of pathogenesis in the formation of BA phenotypes, in particular, the clinical features of the course and its severity [4, 11], the aim of our research was to analyze the possible association of the Gln27Glu polymorphism of the $\beta_2$-AR gene with the severity of the course of BA with obesity and taking into account the phenotype of early and late BA.

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**Table 2**

**The risk of developing a severe course of bronchial asthma depending on the Gln27Glu polymorphism of the β2-adrenergic receptor gene**

| Bronchial asthma patients with obesity,n = 195 | | | |
|---|---|---|---|
| Model | $P_{observation}$ | Odds ratio(95 % OR)Confidence interval CI | Information Akaiake Criteria |
| Early onset, n = 100 | | | |
| Dominant | 0.07 | 1.77 (0.96 – 3.3) | 16.58 |
| Recessive | 0.54 | 1.42 (0.45 – 4.6) | 19.54 |
| Overdominant | 0.12 | 1.68 (0.88 – 3.24) | 17.44 |
| Additive | 0.1 | 1.49 (0.93 – 2.43) | 17.16 |
| Late onset, n = 95 | | | |
| Dominant | 0.07 | 1.85 (0.96 – 3.58) | 17.29 |
| Recessive | 0.1 | 2.47 (0.84 – 7.74) | 17.92 |
| Overdominant | 0.37 | 1.38 (0.68 – 2.78) | 19.87 |
| Additive | 0.04 | 1.66 (1.03 – 2.72) | 16.36 |

The obtained results did not show a significant difference in the distribution of genotypes by Gln27Glu polymorphism of the β2-AP gene depending on the severity of the course (all p more than 0.05), however, it was found that the frequency of homozygotes for the minor allele was 1.8 times higher in patients with a severe course in early BA and 2.3 times in late compared to that in patients with a mild course.A 1.66-fold increase in the risk of developing only severe late-onset BA with obesity was statistically proven in the additive model of inheritance. Thus, carrying the Glu27 allele is associated with an increased risk of late-onset severe BA as opposed to early BA. The obtained results are consistent with previous data on the prevalence of the Gln27Gln genotype in patients with mild and controlled disease and the Glu27Glu genotype in patients with severe and uncontrolled disease [10]. The obtained results by us are comparable to the results of Alghobashy A.A., who also established the association of the Glu/Glu genotype with a severe course and low treatment efficiency in patients with BA [12].

The lack of association between the Gln27Glu polymorphism of the β2-AR gene and the risk of developing early BA [13] was supplemented by the absence of associations with the severity of its course. On the other hand, the existing connection of this polymorphism with the risk of developing late-onset BA is supplemented by the connection with its severe course. This proves the difference in the role of genetic factors not only in relation to the occurrence of BA, but also in relation to the severity of its course.

Our results regarding the lack of association with early-onset BA and severity of its course are consistent with the data of Songlin Zhao (2019) and Yan-Qin Zhang (2019) obtained in meta-analyses, which showed no association between increased risk of developing BA in children and Gln27Glu polymorphism of the β2-AR gene [14, 15]. Therefore, an in-depth study of the mechanisms of pathogenesis and genetic factors that cause the disease in adults and children, and their relationship with the severity of the course, will help to develop new strategies for predicting the onset of BA, the severity of its course, timely treatment and prevention.

**Conclusions.**

1. No probable differences were found in the distribution of genotypes according to the Gln27Glu polymorphism of the β2-AP gene depending on the severity of the course of early and late BA with obesity.

2. The relative risk of developing a severe course of early BA did not depend on the Gln27Glu polymorphism of the β2-AR gene, and late BA increased by 1.66 times in the additive model of inheritance.

**Prospects for further research.** Identification of clinical phenotypes of bronchial asthma through in-depth study of genetic and laboratory markers will allow us to develop personalized targeted strategies for the treatment of bronchial asthma, moreover, it will enable early diagnosis of this disease.

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## КЛІНІЧНИЙ ПЕРЕБІГ БРОНХІАЛЬНОЇ АСТМИ, АСОЦІЙОВАНОЇ З ОЖИРІННЯМ, ЗАЛЕЖНО ВІД GLN27GLU ПОЛІМОРФНОГО ВАРІАНТУ ГЕНА $\beta_2$-АДРЕНОРЕЦЕПТОРА З УРАХУВАННЯМ ВІКУ ДЕБЮТУ

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**Резюме. Мета дослідження:** аналіз асоціації Gln27Glu поліморфізму гена $\beta_2$-адренорецептора (АР) з тяжкістю перебігу бронхіальної астми (БА) з ожирінням з урахуванням віку її початку.

**Матеріал та методи дослідження.** Обстежено 195 хворих на БА з ожирінням. Контрольну групу склали 95 практично здорових осіб. Пацієнтів розподілено на дві клінічні групи залежно від віку дебюту БА: 100 хворих із раннім дебютом склали I групу, 95 хворих – II. Дослідження було схвалено Комісією з питань біоетики навчально-наукового медичного інституту Сумського державного університету. Визначення Gln27Glu поліморфізму гена $\beta_2$-АР (rs1042714) проводили за допомогою полімеразно-ланцюгової реакції з наступним аналізом рестрикційних фрагментів. Статистичний аналіз отриманих результатів проводили за допомогою SPSS-17 програми.

**Результати дослідження.** Частота Gln/Gln, Gln/Glu та Glu/Glu генотипів за Gln27Glu поліморфізмом гена $\beta_2$-АР у хворих на БА, асоційовану з ожирінням, із раннім дебютом становила 70,0; 25,0; 5,0 % при нетяжкому перебігові та 55,0; 36,2; 8,8 % при тяжкому ($\chi^2$ = 1,49; p = 0,473); а при пізньому дебюті – 50,0; 43,8; 6,2 % при нетяжкому та 54,0; 31,7; 14,3 %, відповідно, при тяжкому ($\chi^2$ = 2,10; p = 0,350). Незважаючи на відсутність вірогідної відмінності в розподілі генотипів залежно від тяжкості перебігу виявлено, що частота гомозигот за мінорним алелем була вищою в 1,8 разів у пацієнтів із тяжким перебігом ранньої БА та в 2,3 рази при пізній порівняно із такою у пацієнтів із нетяжким перебігом.

Ризик розвитку ранньої БА з ожирінням і тяжким перебігом показав відсутність зв'язку в усіх моделях успадкування, а у хворих на БА з пізнім дебютом – зростання в 1,66 разів (95 % ДІ (1,03 – 2,72), p = 0,04) в адитивній моделі успадкування (p = 0,04).

**Висновки.** Відсутні вірогідні відмінності в розподілі генотипів за Gln27Glu поліморфізмом гена $\beta_2$-АР залежно від тяжкості перебігу ранньої та пізньої БА з ожирінням. Ризик розвитку тяжкого перебігу ранньої БА не залежав від Gln27Glu поліморфізму гена $\beta_2$-АР, а пізньої БА – зростав в 1,66 разів в адитивній моделі успадкування.

**Ключові слова:** бронхіальна астма, ризик розвитку, дебют, ожиріння, перебіг, Gln27Glu поліморфізм, генотипи, ген $\beta_2$-адренорецептора.

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