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ABSTRACT

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GLN27GLU POLYMORPHISM IN THE B2-ADRENORECEPTOR GENE IN PATIENTS WITH ASTHMA WITH REGARD TO THE AGE OF ONSET

Aim: The study aimed to assess the frequency of the Gln27Glu polymorphic variant in the β2-AR gene among patients with early and late-onset asthma and assess asthma risks depending on the disease phenotype.

Materials and Methods: Our study included a total of 553 asthma patients who consented to participate in the study. Asthma was diagnosed according to the 2016 GINA recommendations and its later versions. The study was approved by the Bioethics Committee of the Medical Institute of Sumy State University. The analysis for determining genetic polymorphism (designated as rs1042714) was conducted through the use of polymerase chain reaction-restriction fragment length polymorphism. Statistical analysis of obtained results was performed using SPSS–17 program.

Results: It was found that there is a significant difference in the distribution of alleles and genotypes in people with early-onset asthma compared to those with late-onset asthma; the statistical analysis showed a $\chi 2$ value of 41.75 and p-value of 0.001 for early-onset asthma, and a $\chi 2$ value of 44.24 and p-value of 0.001 for late-onset asthma. We did not observe a significant increase in the early-onset asthma risk with an account of different inheritance models connected to the studied polymorphism. Research that took into account the risk of late-onset asthma discovered statistically significant results regarding the dominant ($p = 0.001$), super-dominant ($p = 0.001$), and additive ($p = 0.001$) models of inheritance.

Conclusions: Based on the data collected, it was found that individuals carrying the minor allele (both homozygotes and heterozygotes) were at a greater risk of developing asthma later in life. However, no such correlation was observed in patients with early-onset asthma.

Key words: asthma, onset, β_2-adrenoreceptor gene, the Gln27Glu gene polymorphism.

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РЕЗЮМЕ

GLN27GLU ПОЛІМОРФІЗМ ГЕНА B2-АДРЕНОРЕЦЕПТОРА У ХВОРИХ НА АСТМУ ЗАЛЕЖНО ВІД ВІКУ ДЕБЮТУ

Метою дослідження було оцінити частоту поліморфного варіанту Gln27Glu в гені β2-AR серед пацієнтів з раннім і пізнім початком астми та оцінити ризик виникнення астми залежно від фенотипу захворювання.

Матеріали та методи. У наше дослідження було включено 553 пацієнти з астмою, які погодилися попередньо взяти у ньому участь. Діагноз астми був поставлений відповідно до рекомендацій GINA 2016 року та її пізніших версій. Дослідження схвалено Комісією з біоетики Медичного інституту СумДУ. Визначення генетичного поліморфізму (позначеного як rs1042714) проводили за допомогою полімеразної ланцюгової реакції шляхом аналізу довжини рестрикційних фрагментів. Статистичну обробку отриманих результатів проводили за допомогою програми SPSS–17.

Результати: Було встановлено, що існує достовірна відмінність у розподілі алелів і генотипів за досліджуваним поліморфізмом у людей з раннім початком астми ($\chi2$=41,75, p = 0,001) порівняно з тими, хто має пізній початок астми ($\chi2$ 44,24, p = 0,001). Ми не спостерігали істотного підвищення ризику раннього початку астми з урахуванням різних моделей успадкування, пов'язаних з досліджуваним поліморфізмом. Дослідження, які враховували ризик пізнього початку астми, виявили статистично значущі результати щодо домінантної (p = 0,001), супердомінантної (p = 0,001) та адитивної (p = 0,001) моделей успадкування.

Висновки: на основі отриманих даних було виявлено, що особи, які є носіями мінорного алеля (як гомозиготи, так і гетерозиготи), мають більший ризик розвитку астми в подальшому житті. Однак у пацієнтів із раннім початком астми такого зв'язку не спостерігалося.

Ключові слова: астма, дебют, ген β2-адренорецепторів, поліморфізм гена Gln27Glu.

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INTRODUCTION / ВСТУП

Asthma is a chronic respiratory disorder and affects 1–18% of adult and pediatric populations in various countries. The prevalence of asthma in developed countries is constantly growing. Asthma is a complex heterogeneous disease greatly influenced by genetic factors [1–3]. Identification of genes and molecular mechanisms enrolled in the pathogenesis of asthma is essential for predicting the disease and developing targeted therapeutic approaches.

It is well known that for asthma as a polygenic disease, the age of onset is of great diagnostic and prognostic value [4–6]. Based on current knowledge, there are distinct differences in the causes of asthma between those who develop it early in life and those who develop it later. These differences suggest that there are varying genetic factors at play between these two groups The study conducted by UK Biobank, which involved 447,628 individuals, found specific genetic risk factors that relate to the age at which asthma first occurs [7]. The results showed that early-onset asthma had genetic factors differing from those of late-onset asthma, partly explaining their pathogenesis differences [4–6].

One of the genes well-studied in asthma pathogenesis and response to bronchodilation therapy is the gene encoding β_2-AR, located on the long arm of chromosome 5 (5q31-q32) [8]. More than 500 single nucleotide substitutions and insertion/deletion polymorphisms were found in the β_2-AR gene. However, the most well-studied are: at the 16th position, glycine has been replaced by arginine– Arg16Gly (rs1042713, + 46A>G) and glutamine for glutamic acid at the 27th position – Gln27Glu (rs1042714, + 79C>G) and threonine for isoleucine at position 164 – Thr164Ile (rs1800888) [9]. According to the previous data, they have an essential impact on receptor functioning [10]. Due to the high polymorphism of the β_2-AR gene, alleles' frequency differs statistically among ethnic groups [9,11–14]. Taking into account the lack of consistent data considering the possible link between rs1042714 polymorphism in the β_2-AR gene and asthma risk, we studied possible associations, including the additional parameters of different disease phenotypes concerning the time of disease onset.

Study objectives. The study aimed to assess the frequency of the Gln27Glu polymorphic variant in the β2-AR gene among patients with early and late-onset asthma and assess asthma risks depending on the disease phenotype.

Materials and methods. The study was conducted during 2016–2019 based on the pulmonology department of the Sumy Regional Clinical Hospital of the Communal Non-Commercial Enterprise, Sumy, Ukraine. Patients were selected from the hospital database and examined during their routine visits to our clinic to verify the diagnosis, excluding/confirming other bronchopulmonary pathology and therapy correction. Our study included a total of 553 asthma patients who consented to participate by signing informed consent forms. 360 women (65.1%) and 193 men (34.9%) were among the examined patients. 42.39±0.71 years was the average age among asthma patients. The average duration of the disease was 16±9,59years. Moreover, 135 (24.4%) patients had a duration of the disease less than 10 years, 272 (49.2%) – from 10 to 20 years, and 146 patients (26.4%) had asthma for more than 20 years. We formed two clinical groups of patients considering the asthma phenotype with its age of onset. There were two groups of patients in the study: Group I, which included 282 patients with late-onset asthma (also known as the late-onset asthma phenotype), and Group II, which consisted of 271 patients with early-onset asthma (also known as the early-onset asthma phenotype). The diagnosis and treatment of asthma followed the guidelines of the "Global Initiative for Asthma" (2016) and its updated versions. The diagnosis was based on the patient's medical history, clinical symptoms, objective examination, and laboratory and instrumental research, such as computer spirography, electrocardiography, and chest X-ray. Detailed characteristics of the examined patients depending on the age of onset are shown in Table 1.

Considering the fact that there are no generally accepted guidelines for the clarification criteria for early and late-onset asthma with age definition, we use measures from previously published studies devoted to the topic of asthma age onset. Hence, we define the onset of asthma as early if it occurs before the age of 12 and late if it occurs after the age of 12 [5]. All of the study participants willingly signed the informed consent form, and the study was carried out in complete adherence to the Declaration of Helsinki. The Bioethics Committee of Sumy State University approved the study. The analysis for determining genetic polymorphism (designated as rs1042714) was conducted through the use of polymerase chain reaction-restriction fragment length polymorphism. To analyze the polymorphism of the first exon of the β2-AR gene, we utilized the following primers: forward – 5`…G C A G C $(N)_8$ …3', reverse – 3'…C G T C G $(N)_{12}$…5'. Thermocycling conditions followed by 37 cycles of 95°C for 3 min, of 95°C for 15s, 62°C for 40s, and 72°C for 20s. The amplification products was incubated at 37°C for 16 h with 3 U *Bse XI* (Bbvl) («Thermoscientific», USA). To separate the restriction fragments, we used horizontal electrophoresis with an electrical field strength of 10 V/cm. After the electrophoresis, we visualized the DNA fragments using ultraviolet transillumination.

Table 1 – Characteristics of examined patients bronchial asthma depending on the age of onset

	Early-onset, n = 271	**Late-onset, n = 282**	**p**	**F / χ^2**
BMI, kg/m^2	28,0±0,35	27,9±0,32	0,90	0,015
Age, years	36,4±0,88	48,1±1,01	0,001	77,7
Sex, n/% Female Male	 190/70,1% 81/29,9%	 170/60,3% 112/39,7%	0,015	χ^2 5,87
Age of asthma onset	9,8±0,21	33,9±0,87	0,001	687,5
Asthma duration, years	26,6±0,92	14,2±0,54	0,001	136,7
Genetic anamnesis, n/%	118/43,5%	87/30,9%	0,002	χ^2 9,54
FEV1, % of predicted value	66,06±0,95	67,85±0,95	0,18	1,77
FVC, % of predicted value	82,25±0,86	83,52±0,84	0,29	1,12
FEV1:FVC, %	85,10±4,92	86,13±4,78	0,88	0,02
Reverersibility, %	15,75±0,21	14,91±0,23	0,007	7,35

Statistical Analysis

The results were analyzed using Statistical Package for Social Science software (SPSS, version 17.0, Chicago, IL, USA). To check for deviation from Hardy–Weinberg equilibrium, we consulted the Online Encyclopedia for Genetic Epidemiology Studies which led us to examine the studied polymorphism. Using Pearson's chi-squared test, we compared the allele and genotype distributions of rs1042714 SNPs between the case and control groups. In order to determine asthma risk, the odds ratio (OR) and 95% confidence interval (CI) for the four models of inheritance, logistic regression was used: dominant (where major homozygous genotype was used as a reference), recessive (genotypes with major allele were used as a reference), superdominant (major and minor homozygous genotypes were used as a reference), and additive (heterozygous genotype and minor homozygous genotype with major homozygous genotype were used as a reference), the models (each of four) was one-variable. To determine the significance of the results, we used Akaike's information criterion (AIC). Our tests were based on a two-tailed probability and we considered a p-value of less than 0.05 to be statistically significant.

Results. Given the fact that early-onset and late-onset asthma has their phenotypic differences, we analyzed the frequency of alleles and genotypes for the Gln27Glu polymorphism in the β_2-AR gene depending on the disease onset age in order to check for the association between the studied polymorphic variant and different phenotypes (Table 2).

Table 2 – Genotype frequency for the Gln27Glu polymorphism in the β_2-adrenoceptor gene in patients with asthma with regard to the age of onset

rs 1042714	**Late-onset, n = 282**		**Early-onset, n = 271**	
Genotype	n	%	n	%
Gln/Gln	110	39.0	182	67.2
Gln/Glu	136	48.2	73	26.9
Glu/Glu	36	12.8	16	5.9
χ^2 = 44.24; p = 0.001				
Gln allele	63.1		80.6	
Glu allele	36.9		19.4	
χ^2 = 41.75; p = 0.001				

We found that there is a significant difference in the distribution of alleles and genotypes in people with early-onset asthma compared to those with late-onset asthma; the statistical analysis showed a $\chi 2$ value of 41.75 and p-value of 0.001 for early-onset asthma, and a $\chi 2$ value of 44.24 and p-value of 0.001 for late-onset asthma. As can be seen from the table above, the frequency of Gln/Gln genotype (67.2%) was higher in the patients with early-onset asthma vs. late-onset asthma (39.0%), while Gln/Glu (48.2%) and Glu/Glu (48.2%) genotypes were more frequent in late-onset asthma vs. early-onset asthma (26.9% and 5.9%). The frequency of the Gln allele was higher in the subjects with early-onset asthma (80.6%) compared to late-onset asthma (63.1%), and the Glu allele was more frequent in patients with the late-onset disease (36.9%) vs. early-onset disease (19.4%). Given the significant difference in the distribution of alleles and genotypes for the Gln27Glu polymorphism in the β_2-adrenergic receptor gene depending on the age of onset, we performed a statistical analysis to identify a possible association between genetic markers and the risk of early-onset and late-onset asthma developing. We did not observe a significant increase in the early-onset asthma risk with an account of different inheritance models connected to the studied polymorphism. (Table 3). Research that took into account the risk of late-onset asthma discovered statistically significant results regarding the dominant (p = 0.001), super-dominant (p = 0.001), and additive (p = 0.001) models of inheritance (Table 3).

Table 3 – The risk of asthma with regard to the Gln27Glu polymorphism in the β_2-adrenergic receptor gene

Model	P_{obs}	OR_{obs} (95% CI)	AIC
Late-onset			
Dominant	0.001	3.4 (2.08–5.6)	17.93
Recessive	0.09	2.2 (0.95–5.88)	39.62
Super-dominant	0.001	2.8 (1.66–4.7)	26.93
Additive	0.001	2.5 (1.68–3.81)	20.96
Early-onset			
Dominant	0.82	1.06 (0.65– 1.77)	17.85
Recessive	0.88	0.93 (0,37– 2,66)	17.88
Super-dominant	0.75	1.09 (0.65– 1.89)	17.8
Additive	0.9	1.02 (0.7– 1.53)	17.89

After analyzing all inheritance models, we chose the dominant model with the lowest AIC (17.93). The risk of developing asthma in the minor allele carriers (Glu/Glu+Gln/Glu) was 3.4 times higher than that in the major allele homozygotes (95% CI 2.08–5.6; p <0.001). Our results suggested that the minor allele carriers (minor homozygotes and heterozygotes) are at a higher risk of late-onset asthma.

Discussion. Our study aimed to provide supplementary state-of-the-art data about genetic aspects of asthma considering the age of asthma onset, taking into account rs1042714 polymorphism. The analysis was performed by estimating the genotypes frequency for the studied polymorphism and assessing the risk of developing early and late onset asthma phenotypes. Taking into account the time of asthma onset and its features, we determine the distribution of genotypes for the studied polymorphism: The Gln/Gln genotype was revealed 1.7 times more often among asthma patients with early onset. Moreover, the results showed that the Glu/Glu genotype was 2.2 times more frequent among patients with late disease start.

This substantial difference in the genotypes distribution for the Gln27Glu polymorphism concerning the age of disease onset provided the basis for a differentiated analysis of risks of early and late-onset asthma phenotypes. The results we obtained in the previous study involving the smaller population of examined asthma patients (195) showed that the Glu27Glu genotype carriers have twice a risk of asthma developing (OR = 1.99; 95% CI = 1.14–3.47; p = 0.03) as the carriers of the Gln27Gln genotype [15]. The risk estimation (n = 553), regardless of the phenotypes and with regard

to the studied polymorphism, showed a significant association related to the following models of inheritance: dominant (p = 0.01), super-dominant (p = 0.01), and additive (p = 0.02). Asthma patients with minor alleles genotypes were prone to 1.9 times higher risk of asthma in the dominant model and 1.6 – in the additive model compared to major homozygotes. Our resulta demonstrates higher asthma risk among the minor allele carriers (homozygotes and heterozygotes)**.** Differentiated analysis of the possible connection between the studied polymorphism in the β_2-AR gene and different asthma phenotypes demonstrated that the patients with early-onset asthma had no statistically significant increase in asthma risk, while the patients with late-onset asthma presented with increased asthma risk related to the dominant (p = 0.001), super-dominant (p = 0.001), and additive (p = 0.001) models. The odds of developing asthma in the minor allele carriers (Glu/Glu+Gln/Glu) was 3.4 times higher than that in the major allele homozygotes (95% CI 2.08–5.6; p <0.001). Based on the results received, it appears that individuals who are homozygous or heterozygous for the minor allele are more susceptible to developing asthma later in life. These findings may be used to predict the occurrence of this phenotype of the disease.

Numerous studies have shown no connection between the Gln27Glu polymorphism and the likelihood of developing asthma, asthma severity, pulmonary function test results, as well as demographic and clinical information [12,16–20]. Despite this, certain studies have indicated that there may be a correlation between polymorphic variants in the β2-AR gene and a reduced risk of asthma in both children and adults [21–23]. The data discrepancies may be explained by studied group heterogeneity of this disease considering pathogenetic, clinical, demographic, and phenotypical data. This suggestion was confirmed in our study. Given the heterogeneity of asthma, an in-depth study of pathogenesis mechanisms and genetic factors that cause the disease in adults and children will help to develop new strategies for the prevention and treatment of asthma.

Study limitations. Our study was conducted among representatives of the Northern part of Ukraine; therefore, to complete our understanding of the above-mentioned single nucleotide polymorphisms in the Ukrainian population, we need to analyze them among patients from different regions. Also, considering that asthma is a complex disorder with multiple gene involvement, it will be necessary to study other genes to fulfill our understanding of the possible genes involved in the formation of a particular asthma phenotype.

CONCLUSIONS / ВИСНОВКИ

There was a notable contrast in the distribution of alleles and genotypes among patients with asthma onset at different stages (p = 0.001). Patients with early-onset asthma had a 1.7 times higher frequency of the Gln/Gln genotype compared to those with late-onset asthma. On the other hand, patients with late-onset asthma had a 2.2 times higher frequency of the Glu/Glu genotype than those with early-onset asthma.

The odds of developing late-onset asthma in the minor allele carriers (Glu/Glu+Gln/Glu) was 3.4 times higher than that in the major allele homozygotes (95% CI 2.08–5.6; p <0.001). Based on the data collected, it was found that individuals carrying the minor allele (both homozygotes and heterozygotes) were at a greater risk of developing asthma later in life. However, no such correlation was observed in patients with early-onset asthma.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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