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ARG16GLY POLYMORPHISM IN THE B2-ADRENOCEPTOR GENE IN PATIENTS WITH BRONCHIAL ASTHMA WITH REGARD TO THE AGE OF ONSET

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The frequency of Arg16Gly polymorphism in the β_2-adrenoceptor gene was studied in 553 patients with bronchial asthma depending on the age of onset: in 282 patients with late onset of asthma and 271 patients with early onset. Also, the study included 95 healthy individuals. In the late-onset asthma group Arg/Arg genotype was present in 35.8 %, Arg/Gly genotype – in 52.5 %, Gly/Gly genotype – in 11.7 % of patients, while in the early-onset asthma group, it was present in 26.6; 38.7 and 34.7 % of patients, respectively (χ^2=41.26; p=0.001). We observed an increased risk of developing early-onset asthma: it was 2.83 times higher (p=0.001) in the recessive model and 1.87 times higher (p=0.001) in the additive model vs. the major allele homozygotes. No association was found with the risk of late-onset asthma. Gly allele carriers, both heterozygotes, and the minor allele homozygotes have an increased risk of developing early-onset bronchial asthma rather than late-onset asthma.

Key words: bronchial asthma, onset, Arg16Gly polymorphism in the β_2 -adrenoceptor gene.

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ARG16GLY ПОЛІМОРФІЗМ ГЕНА В2-АДРЕНОЦЕПТОРА У ХВОРИХ НА БРОНХІАЛЬНУ АСТМУ ЗАЛЕЖНО ВІД ВІКУ ДЕБЮТУ

Вивчено частоту поліморфізму Arg16Gly гена β2-адренорецептора у 553 хворих на бронхіальну астму залежно від віку дебюту: у 282 хворих з пізнім початком і у 271 хворого з раннім початком астми. Також у дослідженні взяли участь 95 здорових осіб. У групі хворих з БА з пізнім початком генотип Arg/Arg було виявлено у 35,8 %, генотип Arg/Gly – у 52,5 %, генотип Gly/Gly – у 11,7 % пацієнтів, тоді як у групі з раннім початком БА – у 26,6; 38,7 та 34,7% пацієнтів відповідно (χ2=41,26; p=0,001). Ми спостерігали підвищений ризик розвитку астми з раннім початком: він був у 2,83 рази вищим (p=0,001) у рецесивній моделі та в 1,87 рази вищим (p=0,001) в адитивній моделі порівняно із гомозиготами за основним алелем. Не було виявлено зв'язку з ризиком розвитку астми з пізнім початком. Носії алеля Gly, як гетерозиготи, так і гомозиготи, мають підвищений ризик розвитку бронхіальної астми з раннім початком.

Ключові слова: бронхіальна астма, початок, поліморфізм Arg16Gly, ген β2-адренорецептора.

The study is a fragment of the research project "Improvement of diagnosis, treatment, and prevention of diseases of internal organs", state registration No. 0121U108891.

Bronchial asthma (BA) remains one of the most common chronic respiratory diseases in children and adults. According to state-of-the-art views, asthma can manifest in a number of phenotypes. Taking into account the phenotypic features of the disease, in particular, the age of asthma onset, will help to perform timely diagnosis and improve treatment effectiveness [2, 5, 9]. The age of disease onset is the leading factor in identifying phenotypes of the disease with early-onset and adult-onset. Perinatal factors, atopy, viral infections of the airways are supposed to play a key role in the development of childhood asthma [7], whereas asthma in adults is associated rather with obesity, smoking, environmental factors, and occupational hazards [8, 12]. Such difference in etiology suggests a distinct difference in genetic factors between early-onset and late-onset asthma. This suggestion was confirmed in the UK Biobank study (n=447,628), which identified 96 genetic risk factors specific to early-onset asthma and three variants strongly representing risk factors for adult-onset asthma [4]. These results demonstrate that early-onset asthma has genetic factors which differ from those of late-onset asthma. It justifies the differences in the pathophysiology between childhood and adult asthma. The literature sources predominantly provide data linking early-onset asthma to the atopic mechanism of the disease and the late-onset asthma phenotype – to the non-atopic mechanism, but this information is controversial. For asthma as a polygenic disease, the age of onset is of diagnostic and prognostic value [2, 9]. It is important to take into account the phenotype of the disease. Each phenotype is characterized by different heterogeneous mechanisms of pathogenesis and different laboratory findings, still clinical symptoms are almost the same for all phenotypes. Thus, the early and late onset of the disease is associated with different mechanisms of pathogenesis and different inflammatory markers, while the clinical course is usually determined by the effectiveness of the response to baseline therapy drugs [1, 2]. Prediction of the development and severity of asthma is based on a number of factors, with an important role being given to genetic determinants. Genetic-based prediction of the age of asthma onset allows the developing of guidelines for planning preventive measures and timely optimal treatment.

One of the most well-studied genes-candidates for asthma is the gene encoding β_2-AR. According to the Ensembl database [14], the β_2-AR gene is polymorphic and contains more than 500 single nucleotide substitutions and insertion/deletion polymorphisms in the coding region. The most extensively studied non-synonymous nucleotide substitutions are: arginine for glycine at position 16 (Arg16Gly (rs1042713)) and glutamine for glutamic acid at position 27 (Gln27Glu (rs1042714)), which play an important role in the receptor functioning. The results of numerous studies on the Arg16Gly polymorphism in the β_2-AR gene are contradictory since many studies have shown the role of this single nucleotide polymorphism in the pathogenesis of asthma, while other studies dismissed this association [6, 11]. Although several studies revealed no association between Arg16Gly polymorphism and asthma, the former has been shown to correlate with some disease phenotypes such as severe and nocturnal asthma [13]. Given the discrepant results regarding the role of Arg16Gly polymorphism in the β_2-AR gene in asthma development and the lack of data in our population, the objective of our study was to assess the frequency of this polymorphism in the β_2-AR gene and the risk of development of early and late BA phenotypes concerning Arg16Gly polymorphism in the β_2-AR gene. This will help to improve prognosis and promote the elaboration of preventive measures and personalized treatment.

The purpose of our study was to assess the frequency of this polymorphism in the β_2-AR gene and the risk of development of early and late BA phenotypes concerning Arg16Gly polymorphism in the β_2-AR gene.

Materials and methods. We examined 553 patients with BA (the experimental group) and 95 apparently healthy individuals who had no personal or family history of allergy and atopy symptoms, who were non-smokers and had no history of smoking, no acute or chronic somatic diseases in the acute stage within 3 months prior to the enrollment, or chronic infectious diseases of the upper airways, or autoimmune and oncological diseases (the control group). Among the studied patients with BA, there were 360 women (65.1 %) and 193 men (34.9 %), and the control group consisted of 45 men (47.4 %) and 50 women (52.6 %). The patients were divided into 2 clinical groups depending on the age of BA onset. Group I included 282 patients with late-onset asthma (late-onset asthma phenotype) and group II included 271 patients with early-onset asthma (early-onset asthma phenotype). There was no significant difference in gender, age, severity, or control level between the groups ($p>0.05$). BA diagnosis, severity, and control level were determined according to the GINA recommendations-2016 and its later versions.

The study has been approved by the Bioethics Committee of the Medical Institute of Sumy State University. Arg16Gly polymorphism in the β_2-AR gene (rs1042713) was determined using polymerase chain reaction-restriction fragment length polymorphism analysis. Statistical analysis of obtained results was performed using SPSS–17 program. Comparison of the distribution of genotypes in the experimental and control groups and verification of the correspondence of this distribution to the Hardy-Weinberg equilibrium was performed using Pearson's chi-squared test. In order to determine BA risk, the odds ratio (OR) and 95 % confidence interval (CI) for dominant, recessive, superdominant, and additive inheritance models were calculated. The relevance of the obtained results was assessed with Akaike's information criterion. All tests were two-sided, and the p-value <0.05 was considered statistically significant.

Results of the study and their discussion. Given the clinical heterogeneity of patients with asthma, which is, among other things, accounted for by different ages of onset, we analyzed the frequency of alleles and genotypes for the studied polymorphism depending on the age of disease onset (Table 1).

Table 1

Distribution of genotypes and alleles for Arg16Gly polymorphism in the β_2-adrenergic receptor gene in patients with bronchial asthma with regard to the age of onset

Late-onset	Late onset, n=282		Early onset, n=271	
Genotype	N	%	n	%
Arg/Arg	101	35.8	72	26.6
Arg/Gly	148	52.5	105	38.7
Gly/Gly	33	11.7	94	34.7
χ^2=41.26; p=0.001				
Arg allele	62.1		45.9	
Gly allele	37.9		54.1	

A significant difference was found in the distribution of genotypes between patients with early-onset and late-onset asthma (χ^2=41.26; p=0.001). As can be seen from the table above, the frequency of the Arg/Arg genotype (35.8 %) in the patients with late-onset asthma was higher than in those with early-onset asthma (26.6 %), and Gly/Gly genotype frequency (34.7 %) was higher in early-onset asthma vs. late-onset asthma (11.7 %).

Given the significant difference in the distribution of genotypes for Arg16Gly polymorphism in the β_2-adrenergic receptor gene depending on the age of onset, we performed a statistical analysis based on different inheritance models to identify a possible association between genetic markers and relative risk of early-onset and late-onset asthma (Table 2).

Table 2

The risk of BA with regard to Arg16Gly polymorphism in the β_2-adrenergic receptor gene

Early onset			
Model	P_{obs}	OR_{obs} (95 % CI)	AIC
Dominant	0.001	2.19 (1.34–3.56)	25.03
Recessive	0.001	2.83 (1.58–5.36)	21.81
Super-dominant	0.83	0.95 (0.59–1.54)	34.83
Additive	0.001	1.87 (1.37–2.58)	19.15
Late-onset			
Dominant	0.15	1.42 (0.88–2.28)	21.08
Recessive	0.3	0.71 (0.37–1.4)	22.16
Super-dominant	0.04	1.66 (1.04–2.67)	18.73
Additive	0.59	1.1 (0.78–1.57)	22.88

Notes: P_{obs} – observed p-value (not adjusted for covariates); OR_{obs} – observed odds ratio; CI – confidence interval; AIC – Akaike's information criterion.

As we can see, a statistically significant correlation was found for dominant (P_{obs}=0.001), additive (P_{obs}=0.001), and recessive (P_{obs}=0.001) models in patients with early-onset asthma. The risk of developing asthma in minor allele carriers (Arg/Gly and Gly/Gly genotypes) was 2.19 times higher than in the major allele homozygotes (Arg/Arg) (according to the dominant model). The calculation of the relative risk in the additive model showed that the Gly16 allele carriers (heterozygotes and the minor allele homozygotes) have a 1.87 times higher risk of developing early-onset asthma (p=0.001) vs. the major allele homozygotes. The highest relative risk for BA development was found in the recessive model (Gly16 allele carriers – the minor allele homozygotes), which presented 2.83 times higher risk (p=0.001) vs. the major allele homozygotes. Thus, Gly allele carriers, both heterozygotes, and homozygotes have a significantly higher relative risk of developing early-onset bronchial asthma.

A statistical analysis of the possible association between Arg16Gly polymorphism in the β_2-adrenoceptor gene and the relative risk of late-onset BA did not reveal any increased risk in the dominant, recessive, or additive models of inheritance as compared with early-onset asthma. Only a 1.66-fold increase in the risk of late-onset asthma was found in heterozygotes for Arg16Gly polymorphism in the β_2-AR gene (p=0.04) in the superdominant model.

The objective of our study was to provide supplementary state-of-the-art knowledge about genetic aspects of BA concerning the age of onset, taking into account Arg16Gly polymorphism in the β_2-AR gene. When analyzing the frequency of Arg16Gly polymorphism in the β_2-AR gene, we found out that the distribution of Arg/Arg, Arg/Gly, and Gly/Gly genotypes for Arg16Gly polymorphism were 44.2 %, 40.0 %, 15.8 % in the control group vs. 31.3 %; 45.7 % and 23.0 among BA patients, respectively (χ^2=6.59; p=0.037). When adjusted for the age of BA onset, the analysis revealed some features of genotype distribution: in the patients with late-onset asthma, Arg/Arg genotype was present in 35.8 %, Arg/Gly genotype – in 52.5 %, Gly/Gly genotype – in 11.7 % of subjects, while in the patients with early-onset asthma, the values were 26.6; 38.7 and 34.7 % of patients, respectively. The obtained results show that the frequency of the Gly/Gly genotype was 2.2 times higher in patients with early-onset disease vs. control group and almost 3 times higher vs. the late-onset bronchial asthma group. We observed a higher frequency of Gly/Gly genotype in the patients with early-onset BA and an increased risk of developing early-onset asthma, which was 2.83 times higher (p=0.001) in the recessive model (Gly16 allele carriers – the minor allele homozygotes), 1.87 times higher (p=0.001) in the additive model (heterozygotes and the minor allele homozygotes) and 2.19 times higher (p=0.001) in the dominant model vs. the major allele homozygotes. Thus, Gly allele carriers, both heterozygotes, and homozygotes have a significantly higher relative risk of developing early-onset bronchial asthma vs. late-onset bronchial asthma.

Most previous studies on the association between the Arg16Gly polymorphism in the β_2-AR gene and asthma demonstrated that this polymorphism was not associated with a predisposition to asthma and BHR in different ethnic groups [6, 10, 11]. However, the association with severe and nocturnal asthma phenotypes was proven [13]. The association of the 16Gly allele with nocturnal asthma was also found in Mexicans, Taiwanese, and Caucasians living in the United States, and with severe BA – in Caucasians from New Zealand [3, 15]. The results obtained in our study also demonstrate an increased risk of asthma with early onset.

The heterogeneity and even discordance of data concerning the role of the Arg16Gly polymorphism in the β_2-AR gene in the occurrence of asthma can be partly accounted for by the phenotypic features.

The Gly allele carriers, both heterozygotes, and homozygotes, have a significantly higher relative risk of developing early-onset bronchial asthma vs. late-onset bronchial asthma. A UK Biobank study found that SNPs that influence molecular mechanisms underlying allergies can account for the higher risk of early-onset asthma as compared to late-onset asthma [4].

Asthma is known to be a heterogeneous disease with many phenotypes, and the age of onset is the key factor in phenotype formation. Therefore, 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.

Conclusion

The frequency of Arg/Arg, Arg/Gly, and Gly/Gly genotypes for Gly16Arg polymorphism in the β_2-AR gene was 35.8 %, 52.5 %, 11.7 % in the late-onset asthma group vs. 26.6 %; 38.7 %, and 34.7 in the early-onset asthma group; the frequency of Arg16 allele was 62.1 % and 5.9 %, respectively; the frequency of Gly allele was 54.1 % and 37.9 %, respectively (χ^2=41.26; p=0.001). The frequency of the Gly/Gly genotype was 3 times higher in patients with early-onset disease vs. late-onset bronchial asthma group.

We observed an increased risk of developing early-onset asthma: it was 2.83 times higher (p=0.001) in the recessive model, 1.87 times higher (p=0.001) in the additive model, and 2.19 times higher (p=0.001) in the dominant model vs. the major allele homozygotes. The study did not confirm the association of Arg16Gly polymorphism in the β_2-adrenoceptor gene with the relative risk of late-onset bronchial asthma in the dominant, recessive, and additive models of inheritance as compared with early-onset asthma. Gly16 allele carriers had a higher risk of developing early-onset asthma vs. the major allele homozygotes. This finding can be used to predict BA development.

Given the clinical heterogeneity of asthma, further research is recommended to determine the role of genetic factors in the development of this disease, taking into account the age of BA onset.

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