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GLN27GLU polymorphism in the β_2-adrenergic receptor gene in patients with bronchial asthma

V. V. Kachkovska*

Sumy State University, Ukraine

The aim of the study was to analyze the frequency of the polymorphism in the β_2-adrenoceptor (Gln27Glu) gene in patients with bronchial asthma (BA) and to assess the association of the polymorphism with disease risks.

Materials and methods. A total of 553 patients with BA and 95 apparently healthy individuals were examined. The Gln27Glu polymorphism in the β_2-AR gene (rs1042714) was determined using polymerase chain reaction-restriction fragment length polymorphism analysis. Statistical analysis of the results was performed using SPSS-17 program.

Results. The allele and genotype distribution of the Gln27Glu polymorphism in the β_2-AR gene in apparently healthy individuals and BA patients was consistent with Hardy–Weinberg equilibrium (P > 0.05). The analysis revealed that heterozygotes for the Gln27Glu polymorphic variant in the β_2-AR gene were more frequent among BA patients vs. apparently healthy individuals (P = 0.018). The minor allele homozygotes (Glu/Glu) were 1.5 times more frequent among BA patients vs. the controls only in terms of trends without statistical significance. There was no statistically significant difference in the genotype distribution of the studied polymorphic variant between men and women in the control group and BA patient group (P = 0.55; P = 0.47). The analysis of BA risk showed a statistically significant association within the dominant (P = 0.01), super-dominant (P = 0.02), and additive (P = 0.01) models. The minor allele carriers Glu (predominantly heterozygotes) had 1.9 times higher risk of BA in the dominant model and 1.6 times higher risk of BA in the additive model vs. the major allele homozygotes.

Conclusions. The statistically significant difference in the distribution of the homozygous and heterozygous genotypes of the β_2-AR gene (Gln27Glu) polymorphism was found between asthma patients and apparently healthy individuals regardless of sex. The minor allele carriers (Gln/Glu genotypes) had the higher risk of BA vs. the major allele homozygotes.

Key words: bronchial asthma, Gln27Glu polymorphism in the β_2-adrenoceptor gene, polymorphism genetic.

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***E-mail:** vlady_dytko@ukr.net

GLN27GLU поліморфізм гена β_2-адренорецептора у хворих на бронхіальну астму

В. В. Качковська

Мета роботи – вивчення частоти поліморфізму гена β_2-адренорецептора (Gln27Glu) у хворих на бронхіальну астму (БА) та взаємозв'язку визначених генотипів із ризиком розвитку захворювання.

Матеріали та методи. Обстежили 553 хворих на БА та 95 практично здорових пацієнтів. Визначення Gln27Glu поліморфізму гена β_2-АР (rs1042714) здійснили за допомогою полімеразно-ланцюгової реакції з наступним аналізом рестрикційних фрагментів. Статистичний аналіз виконали за допомогою програми SPSS-17.

Результати. Розподіл алелів і генотипів за Gln27Glu поліморфізмом гена β_2-АР у практично здорових осіб і хворих на БА відповідав теоретично очікуваній рівновазі Харді–Вайнберга (p > 0,05). Результати аналізу частоти Gln27Glu поліморфного варіанта гена β_2-АР у хворих на БА та у практично здорових осіб показали, що гетерозиготи частіше виявляли у хворих на БА порівняно з практично здоровими особами (p = 0,018). Носіїв гомозигот за мінорним алелем Glu/Glu виявляли в 1,5 раза частіше серед хворих на БА порівняно з контролем (тільки на рівні тенденції), але вірогідні відмінності не реєстрували. Розподіл генотипів за цим поліморфним варіантом в жінок і чоловіків групи контролю та хворих на БА статистично значущо не відрізнявся (p = 0,55; p = 0,47). Аналіз ризику розвитку БА показав статистично значущий зв'язок у рамках домінантної (p = 0,01), наддомінантної (p = 0,02) та адитивної (p = 0,01) моделей успадкування. Ризик розвитку БА в носіїв мінорного алеля (переважно через гетерозиготи) зростав у 1,9 раза в домінантній, в 1,6 раза – в адитивній моделі успадкування порівняно з гомозиготами за основним алелем.

Висновки. Встановили статистично значущу відмінність у розподілі гомозиготних і гетерозиготних генотипів за поліморфізмом гена β_2-АР (Gln27Glu) у хворих на БА та практично здорових осіб незалежно від статі. Носійство мінорного алеля у складі гетерозиготного генотипу (Gln/Glu) підвищує ризик розвитку БА порівняно з гомозиготами за основним алелем.

Ключові слова: бронхіальна астма, Gln27Glu поліморфізм гена β_2-адренорецептора, поліморфізм генетичний.

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Bronchial asthma is known to have a multifactorial nature and to develop due to the interaction of environmental factors, epigenetic changes, and hereditary predisposition. The study on molecular and genetic grounds of asthma revealed the important role of polymorphisms in many genes, in particular, in the β_2-adrenergic receptor (β_2-AR) gene, which plays a key role in airway contractility and is a target for β_2-agonists. The most extensively studied and common polymorphic variants of the β_2-AR gene are Gln27Glu, Arg16Glu, and Thr164Ile, which determine the functional features of the receptor associated with asthma phenotypes and the effectiveness of β_2-agonist treatment [1–3].

At present, the β_2-AR gene polymorphisms are associated with individual predisposition to airway hyperreactivity and asthma, variability in response to β_2-agonists, and the development of resistance to their bronchodilator effect. The link between the Gln27Glu polymorphism in the β_2-AR gene and the risk of asthma, which was proven in numerous studies, still relates to contradictory and sometimes opposite results in other studies [4–6].

Some papers, especially concerning pediatric asthma, also demonstrated that the Gln27Glu polymorphism in the β_2-AR gene was not associated with a higher risk of asthma in different ethnic groups within general population

[4,6,7]. Given the ambiguous and sometimes discordant results as for the role of the Gln27Glu polymorphism in the β_2-AR gene in asthma occurrence and the effectiveness of its treatment and considering that only isolated studies involving small populations were conducted in Ukraine, this problem needs further study.

Aim

The aim of the work was to study the frequency of Gln27Glu polymorphism in the β_2-adrenoceptor gene in patients with bronchial asthma (BA) and to assess the association of the polymorphism with BA risk.

Materials and methods

A total of 553 patients with BA were examined. All of them had previously signed an informed consent form. A control group consisted of 95 apparently healthy individuals. Among the BA patients, there were 360 (65.1 %) women and 193 (34.9 %) men; the control group consisted of 45 (47.4 %) men and 50 (52.6 %) women. The mean age of BA patients was 42.3 ± 0.71 years, and the mean age of the controls was 44.1 ± 1.53 years.

The study was approved by the Bioethics Committee of Medical Institute of Sumy State University. Gln27Glu 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.

Results

The analysis of the allele and genotype frequency of the Gln27Glu polymorphism in the β_2-AR gene in apparently healthy individuals (from the Sumy region) was consistent with the data of European authors [1,8,9]. The distribution of alleles and genotypes of the studied polymorphism in apparently healthy individuals and BA patients corresponded to Hardy-Weinberg equilibrium (P > 0.05). The analysis of the Gln27Glu polymorphic variant frequency in the β_2-AR gene (rs 1042714) in apparently healthy individuals and BA patients is presented in *Tables 1, 2*.

The frequency of the Glu allele was significantly higher among BA patients, at the same time, we found 1.69 times (P = 0.007) increased asthma risk among minor allele carriers.

The heterozygotes and minor allele homozygotes were found to be more frequent among BA patients than those among apparently healthy individuals (P = 0.018). Also, a significantly 1.8 times increased risk of BA was revealed among heterozygous patients.

The analysis of the Gln27Glu genetic polymorphism distribution in the β_2-AR gene in the control group and in BA patients stratified by sex is given in *Table 3*.

There was no statistically significant difference in the distribution of the major allele homozygotes, heterozygotes, and minor allele homozygotes for the studied polymorphic variant between men and women in the control group and BA patients (P = 0.55; P = 0.47). Thus, we identified no sex-related differences in the allele and genotype distribution of the Gln27Glu polymorphism in the β_2-AR gene between the control group and BA patients.

Table 4 presents the analysis results of the association between genetic Gln27Glu polymorphism in the β_2-AR gene and BA risk using binary logistic regression in four models of inheritance.

The relative risk estimation showed a statistically significant association within the dominant (P = 0.01), super-dominant (P = 0.02), and additive (P = 0.01) models. The minor allele carriers (Gln/Glu and Glu/Glu genotypes) had 1.9 times higher risk of BA in the dominant model and 1.6 times higher risk of BA in the additive model vs. the major allele homozygotes. The obtained data indicated that the minor allele carriers (homozygotes and heterozygotes) had the higher risk of BA.

Discussion

Sufficient data were obtained indicating that a plenty of genes are involved in the pathogenesis of asthma, and each of them individually makes a certain contribution to the realization of this mechanism. This confirms that asthma development involves a genetic mechanism. Along with genetic factors, which determine the Th2-type of inflammation and directly define predisposition to atopy, the most significant role in the development of asthma belongs to the genes that control the degree of bronchial reactivity. The key place regarding bronchial contractility is dominated by the β_2-AR, which determines the contractile capacity of the bronchi and is a target for the most widely used bronchodilators – β_2-agonists [10,11]. Numerous studies have demonstrated that the risk of asthma, clinical course of the disease, variability of the response to β_2-agonist depend on polymorphisms in the β_2-AR gene [3,12]. Therefore, our study was aimed to identify the allele and genotype distribution of the Gln27Glu polymorphism in the β_2-AR gene in BA patients and apparently healthy individuals, as well as to analyze possible association between this polymorphic variant and BA risk.

Our study has revealed the statistically significant difference in the distribution of Gln27Glu genetic polymorphism in the β_2-AR gene between the BA patients and apparently healthy individuals (χ^2 = 7.99; P = 0.018). The major allele homozygotes (Gln/Gln) were observed more frequently among apparently healthy individuals, while the minor allele homozygotes (Glu/Glu) were 1.5 times more frequent among BA patients (9.4 %) vs. the controls (6.3 %). The findings were consistent with our previous data obtained for a small population of BA patients (n = 195) [9] and with the data of M. S. Ponomariova et al., who found a 3 times higher frequency of the Glu/Glu genotype of the Gln27Glu polymorphism in the β_2-AR gene in the BA patients in Russia vs. apparently healthy subjects. Apart from higher frequency of the minor allele carriers and Glu/Glu homozygotes among BA patients vs. the controls, we have found that the minor allele carriers (Gln/Glu and Glu/Glu genotypes) had 1.9 times higher risk of BA in the dominant model and 1.6 times higher risk of BA in the additive model vs. the major allele homozygotes. Trofimov et al. reported that there was an association between this polymorphic variant in the β_2-AR gene and a severe resistance to BA therapy. Thus, the Glu-27Glu genotype carriage was associated with a higher risk

Table 1. The allele frequency among apparently healthy individuals and BA patients

Allele	BA patients, n = 553	Apparently healthy subjects, n = 95	P	χ^2	OR	
					OR_{obs}	95 % CI
Gln	71.7 %	81.1 %	0.007	7.21	0.59	0.40–0.87
Glu	28.3 %	18.9 %			1.69	1.15–2.48

Table 2. The Gln27Glu polymorphism in the β_2-adrenergic receptor gene in apparently healthy individuals and BA patients

rs 1042714	BA patients, n = 553		Apparently healthy subjects, n = 95		P	χ^2	OR	
Genotype	n	%	n	%			OR_{obs}	95 % CI
Gln/Gln	292	52.8	65	68.4	0.018	7.99	0.52	0.32–0.82
Gln/Glu	209	37.8	24	25.3			1.80	1.10–2.94
Glu/Glu	52	9.4	6	6.3			1.54	0.64–3.69

Table 3. Genotype and allele distribution of the Gln27Glu polymorphism in the β2-adrenergic receptor gene depending on sex

rs 1042714	Apparently healthy subjects, n = 95				BA patients, n = 553			
	Men, n = 45		Women, n = 50		Men, n = 193		Women, n = 360	
Genotype	n	%	n	%	n	%	n	%
Gln/Gln	31	68.9	34	68.0	95	49.2	197	54.7
Gln/Glu	10	22.2	14	28.0	78	40.4	131	36.4
Glu/Glu	4	8.9	2	4.0	20	10.4	32	8.9
Allele	χ^2 = 1.21; P = 0.55				χ^2 = 1.4; P = 0.47			
Gln	80.0		82.0		69.4		72.9	
Glu	20.0		18.0		30.6		27.1	

Table 4. Association between the Gln27Glu polymorphism in the β_2-adrenergic receptor gene and BA risk

Model	Genotypes	BA patients, n = 553	Apparently healthy subjects, n = 95	OR_{obs}	(95 % CI)	P_{obs}	AIC
Dominant	Gln/Gln	292	65	1.9	(1.23–3.11)	0.01	18.28
	Gln/Glu+Glu/Glu	261	30				
Recessive	Gln/Gln+ Gln/Glu	501	89	1.5	(0.69–4.1)	0.33	25.45
	Glu/Glu	52	6				
Super-dominant	Gln/Gln+ Glu/Glu	344	71	1.8	(1.11–3.0)	0.02	20.7
	Gln/Glu	209	24				
Additive	Gln/Gln	292	65-	1.6	(1.13–2.4)	0.01	19.38
	2Glu/Glu+ Gln/Glu	–	–				

of therapy-resistant BA vs. therapy-responsive BA (OR 3.35; 95 % CI 1.16–9.66) Gln27Gln + Gln27Glu vs. Glu27 allele (Glu27Glu + Gln27Glu vs. Gln27Gln) – with a 7.2 times higher risk (OR 7.2; 95 % CI 1.19–43.48). These results have confirmed the role of the Glu27 allele as a marker associated with severe and therapy-resistant BA, which could be related to impaired β_2-AR function.

In contrast to previous findings, there are a number of studies that found no association between the studied polymorphism and the occurrence of asthma, disease severity, spirometric parameters, demographic and clinical variables, baseline respiratory function, number of exacerbations and hospitalizations, exercise tolerance, serum IgE, or the quality of patients' life [2,6,13]. Nevertheless, there was a study suggesting an association between polymorphic variants in the β_2-AR gene and a lower BA risk in children and adults [4,14]. The inconsistency of findings on the role of the Gln27Glu polymorphism in the β_2-AR gene in the asthma development and course can be explained by the clinical heterogeneity of this disease, different age of onset, and pathogenetic differences between different phenotypes of the disease. Identification of clinical phenotypes of asthma in recent studies demonstrated the genetic heterogeneity of the disease, seeing as their pathogenesis involves different genetic factors and, accordingly, different pathogenetic mechanisms that determine a particular disease phenotype [8,15]. Therefore, it is important to study gene polymorphisms in combination with clinical parameters specifying the disease phenotype.

Conclusions

1. The statistically significant difference in the distribution of the homozygous and heterozygous genotypes of the β2-AR gene (Gln27Glu) polymorphism was found between asthma patients and apparently healthy individuals, whereas no sex-related statistically significant difference was observed. The minor allele homozygotes (Glu/Glu) were 1.5 times more frequent among BA patients vs. apparently healthy individuals.

2. The minor allele carriers (Gln/Glu and Glu/Glu genotypes) had 1.9 times higher risk of BA in the dominant model and 1.6 times higher risk of BA in the additive model vs. the major allele homozygotes.

Prospects for future research. The study of β_2-AR polymorphisms considering the disease phenotypes will allow developing phenotype-specific criteria for predicting the occurrence of asthma.

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Information about author:
Kachkovska V. V., MD, PhD, Assistant of the Department of Internal Medicine with the Center of Respiratory Medicine, Sumy State University, Ukraine.
ORCID ID: 0000-0002-9563-5425

Відомості про автора:
Качковська В. В., канд. мед. наук, асистентка каф. внутрішньої медицини з центром респіраторної медицини, Сумський державний університет, Україна.

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