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## GLN27GLU polymorphism $\beta_2$ -adrenergic receptor gene and the risk of arterial hypertension in patients with bronchial asthma

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#### Abstract

Arterial hypertension (AH) and bronchial asthma (BA) have common genetic factors, particularly polymorphism in the  $\beta_2$ -adrenergic receptor gene (ADRB<sub>2</sub>). Substitution at the coding element Gln27Glu is best investigated; it can lead to abnormal activity regulation of the receptor. The aim of our research was to study AH in BA patients in Ukrainian population with regard to Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and body mass. Examined patients were divided into 2 groups: group I included 52 patients with BA without AH; group II comprised 143 patients with BA accompanied by AH. Gln27Glu (rs1042714) polymorphism in the ADRB<sub>2</sub> gene was detected using polymerase chain reaction. Statistical analysis was performed using SPSS-21 program. *P*-value <0.05 was considered significant. With no regard to body mass, no correlation was found between AH risk (*p* = 0.69), systolic and diastolic AP (*p*<sub>1</sub> = 0.142 and *p*<sub>2</sub> = 0.073) and Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in BA patients. Still, AH risk evaluation in BA patients with regard to BMI demonstrated that the minor allele homozygotes of Glu27Glu genotype had 2.93 times higher risk of AH development as compared to Gln27Gln genotype carriers. At the same time, obesity was observed in 81.3% of BA patients with AH who were the carriers of Glu27Glu genotype of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene.

**Keywords:** Bronchial asthma, arterial hypertension, obesity,  $\beta_2$ -adrenoceptor, Gln27Glu polymorphism

#### 1. Introduction

Polymorbidity is one of features peculiar to modern clinical picture of internal diseases, while arterial hypertension (AH) and bronchial asthma (BA) remain widespread diseases among adult population of developed countries. According to literature data, about 30% of patients with asthma are diagnosed with concomitant hypertension [8]. Combination of multiple diseases is known to lead to significant changes that worsen patient's condition. Moreover, in many BA patients it is cardiovascular pathology that considerably determines prognosis and capacity for work [2, 4, 5, 7]. Patients with BA and overweight, severe course of disease and/or insufficient control level can form a hypertension risk group. The importance of the genetic component in pathogenesis of BA and AH is indicated by a large number of studies [1, 6, 15, 18, 20, 21, 30]. Apart from that, AH and BA have common genetic factors, which are based on manifold effects of different genes, particularly the  $\beta_2$ -adrenergic receptor gene (ADRB<sub>2</sub>) [5, 9, 10]. ADRB<sub>2</sub> gene is located on chromosome 5q31-32 and consists of 1 exon and 2015 nucleotides. 9 different genetic polymorphisms of ADRB<sub>2</sub> were found. The most well-studied and common polymorphism is Gln27Glu having amino-acid substitution, which is associated with ADRB<sub>2</sub> expression after interaction with  $\beta_2$ -agonists and contributes to bronchial hyperreactivity (BHR) [26, 27].

ADRB<sub>2</sub> take part in a variety of physiological and pathophysiological processes mediated through catecholamines, including the development of cardiovascular diseases and obesity [3, 22, 26]. Excitation of ADRB<sub>2</sub> leads to vasodilatation (of coronary and skeletal muscle vessels) and relaxation of airway smooth muscles [27]. Catecholamines are known to play an important role in energy exchange and lipolysis stimulation due to their binding to ADRB<sub>2</sub>, which results in body mass reduction and realization of anti-inflammatory effects [24, 25]. The general idea is that the substitution of Gln27 (basic amino acid) with Glu (neutral amino acid) affects binding of catecholamines with ADRB<sub>2</sub>, preventing fat splitting. It was established that genetic polymorphisms of ADRB<sub>2</sub> were associated with AH [6, 30], though in some populations the correlation was not proved [1, 15, 16, 17, 18].

In Ukraine there were studies related to association of AH with the gene polymorphisms of angiotensin converting enzyme gene, angiotensinogen, endothelial NO synthase, peroxisome proliferators-activated receptor-g2,  $\beta_1$ , adrenergic receptor [11, 12, 13, 14], but none concerned Gln27Glu polymorphism in the ADRB<sub>2</sub> gene.

Since the results obtained in the world are contradictory, and there were no corresponding studies in Ukraine, the aim of our research was to study AH risk in BA patients with regard to Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and body mass.

**2. Materials and methods.** We examined 195 patients with mild, moderate, and severe persistent BA – 129 women and 66 men – who were undergoing hospital treatment at the pulmonary department at MI of Sumy Regional Council “Sumy Regional Clinical Hospital”. BA was diagnosed in accordance with the Decrees of the Ministry of Health of Ukraine №128 issued on 19-Mar-2007 and № 868 issued on 08-Oct-2013. AH was diagnosed under the Decree of the Ministry of Health of Ukraine №384 issued on 24-May-2012. BMI was assessed according to WHO criteria (1999). The control group consisted of 95 apparently healthy individuals with no allergies and no history of atopic diseases.

Examined patients were divided into 2 groups: group I included 52 patients with BA without AH; group II comprised 143 patients with BA accompanied by AH.

Gln27Glu (rs1042714) polymorphism in the ADRB<sub>2</sub> gene was detected using polymerase chain reaction with subsequent analysis of restriction fragment length polymorphism by means of separation with agarose gel electrophoresis.

Significance of differences among the groups was estimated by Pearson's chi-squared test. The data were statistically processed using nonparametric statistical techniques, because Gaussian distribution of systolic (SAP) and diastolic (DAP) arterial pressure was far from normal. SAP and DAP values were analyzed by the median and interquartile range (25-th and 75-th percentiles). Obtained values of SAP and DAP were compared by means of rank analysis of variance (ANOVA) by Kruskal-Wallis. With this method we checked the null hypothesis of no difference among groups. With  $p > 0.05$ , the null hypothesis of no difference in median values of groups was confirmed. With  $p < 0.05$ , the null hypothesis was not confirmed and, respectively, the alternative hypothesis was accepted stating that there were differences in median values of groups. In this case, we performed pair-wise comparison of groups using Mann-Whitney nonparametric test. To evaluate the influence of polymorphism genotypes on AH risk in BA patients, the odds ratio (OR) and 95% confidence interval (CI) were calculated.

**3. Results**

Genotype distribution of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene with regard to AH status in BA patients is presented in Table 1.

**Table 1:** Genotypes distribution of Gln27Glu polymorphism in the  $\beta_2$ -adrenoceptor gene in dependence on arterial hypertension status

AH	BA patients					
	Gln27Gln		Gln27Glu		Glu27Glu	
	n	%	n	%	n	%
No	22	42.0	26	50.0	4	8.0
Present	80	55.9	47	32.8	16	11.3
$\chi^2 = 0.08; p = 0.69$						

Obtained results demonstrate that distribution of Gln27Gln, Gln27Glu and Glu27Glu genotypes of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in BA patients with regard to AH status did not differ ( $p = 0.69$  by chi-squared test).

Analysis of AH risk in BA patients using Glu allele as a reference allele did not demonstrate any statistical significance (OR = 1.05, CI – 95% 0.67–1.62,  $p = 0.84$ ) (Table 2).

**Table 2:** Allele distribution of Gln27Glu polymorphism in the  $\beta_2$ -adrenoceptor gene in dependence on arterial hypertension status

Allele	AH present	No AH	$\chi^2$	P	OR	
	n=102	n=93			value	95% CI
C (Gln)	0.706	0.715	0.04	0.84	0.96	0.62 – 1.48
G (Glu)	0.294	0.285			1.05	0.67 – 1.62

Table 3 shows the results of analysis of association between SAP and DAP and Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in BA patients

**Table 3:** The median (interquartile range) of arterial pressure values in patients with bronchial asthma with regard to Gln27Glu polymorphism in the ADRB<sub>2</sub> gene

Genotype	Blood pressure	Systolic, mm Hg	Diastolic, mm Hg
Gln27Gln (n=102)		138 (120 – 150)	84 (70 – 98)
Gln27Glu (n=73)		141 (120 – 152)	82 (70 – 100)
Glu27Glu (n=20)		146 (142 – 172)	95 (90 – 101)
p (Kruskal-Wallis).		p = 0.142	p = 0.073

The results of analysis demonstrated no statistically significant difference in SAP and DAP values with regard to the genotypes of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene ( $p = 0.142$  and  $p = 0.073$  by Kruskal-Wallis). Pair-wise comparison of SAP and DAP values by means of Mann-Whitney test in the patients with Gln27Gln and Gln27Glu genotypes ( $p_1 = 0.832$  and  $p_2 = 0.987$ ) vs. Gln27Glu and Glu27Glu genotypes ( $p_1 = 0.241$  and  $p_2 = 0.498$ ) vs. Gln27Gln and Glu27Glu genotypes also revealed no statistically significant difference ( $p_1 = 0.546$  and  $p_2 = 0.783$ ).

Thus, as a result of the study no association was found between AH risk, SAP and DAP values in patients with asthma and Gln27Glu polymorphism in the ADRB<sub>2</sub> gene.

Taking into account the importance of obesity in AH development, we analyzed the distribution of genotypes of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in non-AH BA patients in dependence on BMI (Table 4).

**Table 4:** Genotypes distribution of Gln27Glu polymorphism in the  $\beta_2$ -adrenoceptor gene in dependence on body mass index in patients with bronchial asthma

Body mass index	BA patients without AH					
	Gln27Gln		Gln27Glu		Glu27Glu	
	n	%	n	%	n	%
Normal body mass	9	40.9	5	19.2	1	25.0
Overweight	2	9.1	4	15.4	1	25.0
Obesity	11	50.0	17	65.4	2	50.0
$\chi^2 = 1.09 p > 0.05$						

Obtained results demonstrate that BMI-specific distribution of genotypes of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in non-AH BA patients did not significantly differ ( $p > 0.05$  by chi-squared test).

Analyzing the BMI-specific genotype distribution of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in BA patients with AH, it was found that obesity was more often observed in the carriers of Glu27Glu genotype, while normal body mass was more characteristic of the carriers of Gln27Gln genotype of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene ( $p = 0.001$  by Pearson's chi-squared test) (Table 5).

**Table 5:** Genotypes distribution of Gln27Glu polymorphism in the  $\beta_2$ -adrenoceptor gene in dependence on body mass index in patients with bronchial asthma

BMI	BA patients with AH					
	Gln27Gln		Gln27Glu		Glu27Glu	
	n	%	n	%	n	%
Normal body mass	67	83.7	27	57.4	1	6.2
Overweight	7	8.7	10	21.3	2	12.5
Obesity	6	7.6	10	21.3	13	81.3
$\chi^2 = 20.34$ $p > 0.05$						

Frequency of Glu27Glu genotype was higher in the group of BA patients with AH and obesity as compared to non-obese BA patients with AH (44.8% and 1.1%) and increased AH risk by 2.93 times (OR = 2.93, CI – 95% 1.81–8.41,  $p < 0.001$ ). Gln27Gln genotype was observed more frequently in the group of non-obese BA patients with AH as compared to BA patients with AH and obesity (70.5% and 20.7%). Gln27Gln genotype decreased AH risk (OR = 0.12, CI – 95% 0.04–0.30,  $p < 0.001$ ), which can be indicative of its protective role as concerns AH development in obese BA patients.

#### 4. Discussion

Association of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene with bronchial asthma occurrence and effectiveness of treatment is best investigated, though results of the studies are controversial. Some researchers could not manage to find an association of the locus with BA; nevertheless, they reported correlation with the severity of the disease [19, 20, 21]. A number of studies related to the role of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in AH development were also controversial. Thus, an association of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene with AH was documented in Malaysian population [6]. In Northern Europe it was found that Glu27Glu genotype in the ADRB<sub>2</sub> gene was more often observed in the children, whose parents suffered from AH; in Sweden Arg16Gly/Gln27Gln haplotype was associated with high SAP [18, 30]. The results of a study conducted in Bashkortostan demonstrated that polymorphism in the ADRB<sub>2</sub> gene was associated with AH risk, and intensity of this effect increased along with BMI [23]. However, other studies show no association between Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and AH. Thus, in African, European and Asian populations there was no significant correlation between Glu27Glu polymorphism in the ADRB<sub>2</sub> gene and AH in BA patients [15, 18]. Yan Z. T. (2010) and Huang J. (2005) also found no associations between Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and AH development in a Chinese population (OR = 0.64, CI – 95% 0.41–1.00,  $p > 0.05$ ) [16, 17]. Our results are consistent with these data, because analysis of AH risk in patients with asthma revealed no statistically significant difference ( $p = 0.84$ ) in Ukrainian population. In a huge racially homogeneous population of African males with high prevalence of obesity and AH, no significant association was shown between Arg16Gly and Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and obesity and AH

development [28]. A case-control study (7808 white subjects of middle age) also recorded no association between Gln27Glu polymorphism in the ADRB<sub>2</sub> gene and obesity, AH and type 2 diabetes [27].

A study among the population of the Pacific Islands documented a statistically insignificant association between Glu27Glu genotype and obesity [29]. In our study the carriers of Glu27Glu genotype of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene had 2.93 times higher risk of AH among obese BA patients ( $p < 0.001$ ).

Because the results of genetic studies depend on the size and homogeneity of population, polymorphism-dependent diseases can be reported in one geographic area and absent in another, as is shown in our study.

#### 5. Conclusions

With no regard to body mass, no correlation was found between AH risk, systolic and diastolic AP and Gln27Glu polymorphism in the ADRB<sub>2</sub> gene in BA patients.

AH risk evaluation in BA patients with regard to BMI demonstrated that the minor allele homozygotes of Glu27Glu genotype had 2.93 times higher risk of AH.

Obesity was observed in 81.3% of BA patients with AH who were carriers of Glu27Glu genotype of Gln27Glu polymorphism in the ADRB<sub>2</sub> gene.

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