UDC 616.248-085:575.117

A.M. Bondarkova, L.N. Prystupa, Yu.O. Kartava, O.V. Teteriuk
Sumy State University, Medical Institute

Level of bronchial asthma control with regard to Gln27Glu polymorphism in the β_2-adrenergic receptor gene

Keywords: *bronchial asthma, Gln27Glu polymorphism, β_2-adrenergic receptor gene, control level, short-acting β_2-agonists.*

Bronchial asthma (BA) is a serious social, epidemiologic and medical problem. BA is a chronic inflammatory disease of the airways, which can greatly affect patients' quality of life and lead to hospitalization and steady performance impairment, if treated inadequately. In recent years, BA control has decreased despite of numerous clinical studies which were to improve therapeutic approach to the treatment of asthma. For example, in Europe in 2006–2010, asthma control reduced by 16 %, and in the Russian Federation for the period from 2010 to 2013 – by 23 % [1, 2, 7].

The goal of modern guidelines for BA control and treatment is to provide full asthma control, to increase patients' quality of life and to insure their complete social adaptation by means of individual treatment adjustment with minimal side effects [10, 17].

There are a number of factors, which prevent a great deal of patients from aquiring asthma control: low compliance with treatment, improper use of inhalers and development of resistance to background therapy with inhaled glucocorticosteroids (IGCs), short and long-acting β2-agonists (SABA and LABA), leukotriene receptor antagonists. These changes can occur due to reduced expression of corresponding receptors on account of a particular genetic polymorphism [11, 12, 14, 16]. According to literature data, the mutations that lead to replacement of one of amino acids in the structure of β2-adrenergic receptors (ADRB2) cause a more severe disease course, reduce therapeutic response and promote the processes of receptor desensitization [8, 18]. The most well-studied and common polymorphism is Gln27Glu having amino-acid substitution; it causes reduction in the number of receptors on bronchial cell surface after interaction with β2-agonists and contributes to bronchial hyperreactivity (BHR). There were no researches conducted in Ukraine as for the association between (rs1042714) Gln27Glu polymorphism in the ADRB2 gene and asthma control level.

Therefore, the aim of our research was to identify asthma control level with regard to Gln27Glu polymorphism in the ADRB2 gene.

We examined 195 patients with BA – 129 men and 66 women – aged 18–70, who were undergoing hospital treatment in pulmonary departments at MI «Sumy Clinical Hospital № 1» and MI «Sumy Regional Clinical Hospital».

Patients with bronchial asthma were divided into 3 groups depending on the genotypes for Gln27Glu polymorphism in the ADRB2 gene. Group I included 102 patients with Gln27Gln (C/C) genotype; group II – 73 individuals with Gln27Glu (C/G) genotype, and group III – 20 patients with Glu27Glu (G/G) genotype. BA was diagnosed in accordance with the GINA guidelines (2011) and the Decree of the Ministry of Health of Ukraine №868 issued on 08 October 2013. Asthma control was assessed with Asthma Control Questionnaire-5 (ACQ-5). Total score was calculated as the mean of 5 answers: < 0.5–0.75 was for adequate control; 0.75–1.5 was for partial control; > 1.5 – for poor control. Respiratory function was studied by means of a diagnostic suite «Кардіоплюс» [Kardioplius] (Ukraine) andthe results were evaluated according to domestic recommendations.

Gln27Glu (rs1042714) polymorphism in the ADRB2 gene was detected using polymerase chain reaction with subsequent analysis of restriction fragment length polymorphism by means of separation with agarose gel electrophoresis.

Statistical analysis was performed using SPSS–21 program.Significance of differences among the

groups was estimated by Pearson's chi-squared test (the value of $p<0.05$ was considered statistically significant). The data were statistically processed using nonparametric statistical techniques. Forced expiratory volume in 1 second (FEV1) and ACQ-5 results were expressed through the median and interquartile range (25-th and 75-th percentiles). Obtained values of FEV1 and results of ACQ-5 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, that is groups did not differ. 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.

Results

Analysis of genotypes distribution of Gln27Glu polymorphism in the ADRB2 gene in dependence on asthma control level is presented in Table 1.

As is evident from the Table 1, in our study we established significant difference in the genotype distribution depending on asthma control level by $\chi 2$ Pearson's chi-squared test ($p = 0.0001$). We found out that the patients with controlled asthma predominantly had Gln27Gln genotype, while those with uncontrolled asthma – Glu27Glu genotype. On the other hand, with Gln27Gln genotype, controlled asthma was observed in 61.8 % of carriers, partially controlled asthma – in 29.4 %, and uncontrolled asthma – in 8.8 %; the carriers of Gln27Glu genotype had 4.1 %, 89 % and 6.9 %, respectively; and the carriers of Glu27Glu genotype had 5 %, 10 % та 85 %, respectively. Thus, the major allele homozygotes predominantly had controlled asthma, and the minor allele homozygotes were associated with uncontrolled asthma.

We performed detailed analysis of the dependence between FEV1 and Gln27Glu polymorphism in the ADRB2 gene in BA patients, and the results are presented in Table 2.

The results of FEV1 values analysis in BA patients with regard to Gln27Glu polymorphism in the ADRB2 gene demonstrated a statistically significant difference ($p=0.001$ by Kruskal-Wallis test). Thus, FEV1 was significantly higher in the carriers of Gln27Gln genotype as compared with the carriers of Glu27Glu genotype (by Mann–Whitney, $p1 < 0.001$), and in the carriers of Gln27Glu genotype as compared with those of Glu27Glu genotype ($p2 < 0.001$). That is, the patients with Glu27Glu genotype had statistically lower values of FEV1 than the patients with Gln27Gln and Gln27Glu genotypes.

Analysis of ACQ-5 results with regard to Gln27Glu polymorphism in the ADRB2 gene in BA patients is presented in Table 3.

On performing analysis of BA control with regard to Gln27Glu polymorphism in the ADRB2 gene, a statistically significant difference was observed in ACQ-5 scoring ($p = 0.001$ by Kruskal-Wallis test). Thus, control level was higher (by Mann-Whitney test, $p1 < 0.001$) in the carriers of Gln27Gln genotype as compared with the carriers of Glu27Glu genotype, and in the carriers of Gln27Glu genotype as compared with those of Glu27Glu genotype ($p2 < 0.001$). That is, the patients with Glu27Glu genotype had statistically lower control level according to ACQ-5 than the patients with Gln27Gln and Gln27Glu genotypes for Gln27Glu polymorphism in the ADRB2 gene.

Genotype distribution of Gln27Glu polymorphism in the ADRB2 gene with regard to SABA usage frequency in BA patients is presented in Table 4. Obtained results demonstrate that Glu27Glu genotype carriers used SABA

Table 1

Genotypes distribution of Gln27Glu polymorphism in the β_2 -adrenoceptor gene in dependence on asthma control level

Control level / Genotypes	BA patients					
	Well-controlled		Partially controlled		Uncontrolled	
	n	%	n	%	n	%
Gln27Gln	63	61,8 94,0	30	29,4 30,9	9	8,8 29,0
Gln27Glu	3	4,1 4,4	65	89,0 67,0	5	6,9 16,1
Glu27Glu	1	5,0 1,6	2	10,0 2,1	17	85,0 54,9
	$\chi^2 = 88,4$, $p = 0,0001$					

Table 2

The median (interquartile range) of values of forced expiratory volume in 1 second in patients with bronchial asthma with regard to Gln27Glu polymorphism in the $ADRB_2$ gene

Values / Genotypes	FEV_1 %
Gln27Gln (n = 102)	74,1 (72–76,1)
Gln27Glu (n = 73)	66,2 (64,7–67,7)
Glu27Glu (n = 20)	56,9 (54,3–59,5)

Table 3

The median (interquartile range) of ACQ-5 results in patients with bronchial asthma with regard to Gln27Glu polymorphism in the $ADRB_2$ gene

Values / Genotypes	ACQ-5, points
Gln27Gln (n = 102)	0,77 (0,69–0,84)
Gln27Glu (n = 73)	1,06 (0,99–1,12)
Glu27Glu (n = 20)	1,85 (1,74–1,97)

Table 4
Genotypes distribution of Gln27Glu polymorphism in the β_2-adrenoceptor gene in dependence on frequency of short-acting β_2-agonists usage

	BA patients					
Usage frequencyя / Genotypes	up to 4 times		4–8 times		more than 8 times	
	n	%	n	%	n	%
Gln27Gln	30	29,4	46	45,1	26	25,5
Gln27Glu	1	1,3	53	72,6	19	26,1
Glu27Glu	2	10	1	5	17	85
	$\chi^2 = 68,4$; p = 0,001					

more often than the carriers of Gln27Gln and Gln27Glu genotypes for Gln27Glu polymorphism in the ADRB2 gene (p = 0.001 according to chi-squared test).

Discussion

Obtaining total control of bronchial asthma is the main goal of treatment by far. Thus, according to GINA, approximately 25 % of patients with BA still have uncontrolled asthma course [10]. Literature sources provide a plenty of reasons for uncontrolled asthma, including Gln27Glu polymorphism in the ADRB2 gene [3–6, 9, 13, 15, 19].

It is known that Gln27Glu polymorphism in the ADRB2 gene is associated with changes in respiratory function parameters, particularly patients-carriers of Glu27Glu genotype had lower FEV1 values as compared with the carriers of Gln27Glu genotype for Gln27Glu polymorphism in the ADRB2 gene [19]. Similar results were obtained in our study. It was also established that the combination of Arg16Gly and Gln27Glu genotypes in the ADRB2 gene, in particular the Gly16Gln27 haplotype, was associated with lower BA morbidity (OR = 0.65, 95 % CI = 0.41 – 1.02, p = 0.049) and with higher values of FEV1, while Arg16Glu27 haplotype was associated with lower values of FEV1 (OR = 0.86, 95 % CI = 0.69 – 1.07, p = 0.163) [4].

Limsuwan T. et al. (2010) stated the association of 27Gln allele for Gln27Glu polymorphism in the ADRB2 gene with higher values of FEV1 and fewer episodes of hospitalization in Thai population[13]. Contopoulos-Ioannidis D. G. et al. (2005) proved that the frequency of respiratory difficulty episodes in bronchial asthma subjects is higher in the carriers of Glu27Glu genotype as compared with those of Gln27Glu genotype for Gln27Glu polymorphism in the ADRB2 gene [6], which is consistent with our findings.

Though, some studies did not reveal any association between BHR, course severity, respiratory function, control level and Gln27Glu polymorphism in the ADRB2 gene [3, 5, 9, 15].

Our data concerning the association between Gln27Glu polymorphism in the ADRB2 gene and bronchial obstruction intensity were confirmed by the frequency of SABA use and the results obtained by means of ACQ-5. Thus, it was stated that Glu27Glu genotype for Gln27Glu polymorphism in the ADRB2 gene was associated with lower level of asthma control and higher frequency of SABA use.

Thus, these results show that respiratory function and asthma control level are associated with Gln27Glu polymorphism in the ADRB2 gene.

Conclusions

Obtained results demonstrate that the carriers of Glu27Glu genotype in the ADRB2 gene more often had uncontrolled asthma and more intensive bronchial obstruction and used SABA more frequently than the carriers of Gln27Gln and Gln27Glu genotypes for Gln27Glu polymorphism in the ADRB2 gene.

Prospects for future research

Taking into account the association between Gln27Glu polymorphism in the ADRB2 gene with asthma control level, it is reasonable to further study the association of this polymorphism with response to treatment in order to achieve optimization.

Список літератури

1. Архипов, В.В. Контроль над бронхиальной астмой в России: результаты многоцентрового наблюдательного исследования НИКА [Текст] / В.В. Архипов // Пульмонология. – 2011. – № 6.– С. 87–93.
2. Исследования ГфК-Русь 2012–2013 // http://www.evrika.ru [Электронный ресурс] / show / 6625 / company_feed.
3. Куренкеева, К.А. Гиперреактивность бронхов и ее связь с полиморфизмом гена β_2-адренорецепторов у больных бронхиальной астмой кыргызской национальности [Текст] / К.А. Куренкеева // Пульмонология. – 2006. –№ 1. – С. 76–80.
4. Association of haplotypes of beta2-adrenoceptor polymorphisms with lung function and airway responsiveness in a pediatric cohort [Text] / G. Zhan [et al.] // Pediatr. Pulmonol. J. – 2006. – Vol. 41 (12). – P. 1233–1241.
5. Cichy, M. The functional relevance of Arg16Gly and Gln27Glu beta2-adrenoreceptor polymorphism in patients with asthma and allergic rhinitis [Text] / M. Cichy, T. Adamek-Guzik, D. Uracz // Folia. Med. Cracov. Folia. Med. – 2005. –Vol. 46 (1–2). – P. 33–51.

References

1. Arkhipov VV. Kontrol' nad bronkhial'noy astmoy v Rossii: rezul'taty mnogotsentrovogo nablyudatel'nogo issledovaniya NIKA (Control of asthma in Russia: results of a multicenter observational study NIKA). Pul'monologiya. 2011;6:87–93.
2. Issledovaniya GfK-Rus' 2012–2013 (Research GfK-Rus 2012–2013). Available from: http://www.evrika.ru/show/6625/company_feed.
3. Kurenkeeva KA. Giperreaktivnost' bronkhov i ee svyaz' s polimorfizmom gena β2-adrenoretseptorov u bol'nykh bronkhial'noy astmoy kyrgyzskoy natsional'nosti (Bronchial hyperreactivity and its connection with the polymorphism of the gene β2-adrenergic receptors in Kyrgyz patients with bronchial asthma). Pul'monologiya. 2006;1:76–80.
4. Zhan G, et al. Association of haplotypes of beta2-adrenoceptor polymorphisms with lung function and airway responsiveness in a pediatric cohort. Pediatr. Pulmonol. J. 2006;41(12):1233–1241.
5. Cichy M, Adamek-Guzik T, Uracz D. The functional relevance of Arg16Gly and Gln27Glu beta2-adrenoreceptor polymorphism

6. Contopoulos-Ioannidis, D.G. Meta-analysis of the association of beta2-adrenergic receptor polymorphisms with asthma phenotypes [Text] / D.G. Contopoulos-Ioannidis, E.N. Manoli, J.P Ioannidis // J Allergy. Clin. Immunol. – 2005. – Vol. 115 (5). – P. 963–972.

7. Demoly, P. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years [Text] / P. Demoly // Eur. Respir. J. – 2012. – Vol. 21, № 123. – P. 66–74.

8. Europen respiratory society statement: asthma control and exacerbations, standardizing endpoints for clinical asthma trials and clinical practice. Part 2 [Text] / D.R. Taylor [et al.] // J. Pulmonology. – 2007. – Vol. 55. – P. 762–765.

9. Genetic basis for personalized medicine in asthma [Text] / M. Portelly [et al.] // Expert Rev. Respir. Med. – 2012. – Vol. 6, № 2. – P. 223–236.

10. GINA 2014 [Електронний ресурс] // www.ginasthma.org

11. Israel, E. Use of regularly scheduled albuterol treatment in asthma: genotypestratified, randomized, placebo-controlled cross-over trial Lancet 2004 [Text] / E. Israel // Lancet. – 2004. – Vol. 364. – P. 1505–1512.

12. Johnson, R. Acute Lung Injury: Epidemiology, Pathogenesis, and Treatment [Text] / R. Johnson, A. Michael, M.D. Matthay // J. Aerosol. Med. Pulm. Drug Deliv. – 2010. – Vol. 23. – № 5.– P. 243–252.

13. Limsuwan, T. Possible protective effects of the Glu27 allele of beta2-adrenergic receptor polymorphism in Thai asthmatic patients [Text] / T. Limsuwan // Asian. Pac. J. Allergy. Immunol. – 2010. – Vol. 28, № 2–3. – P. 107–114.

14. Noncompliance and treatment failure in children with asthma [Text] / H. Milgrom [et al.] // J. Allergy Clin. Immunol.– 1996. – № 98. – P. 1051–1057.

15. Pharmacogenomics of pediatric asthma / S. Gupta [et al.] // Indian. J. Hum. Genet. – 2010. – Vol. 16 (3). – P. 111–118.

16. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study [Text] / N.W. Wainwright [et al.] // J. Allergy. – 2007. – Vol. 62 (5). – P. 554–560.

17. Rees, J. Asфthma control in adults [Text] / J. Rees // BMJ. – 2006. – Vol. 332. – P. 767–771.

18. Wechsler, M.E. β-adrenergic receptor polymorphism and response to salmeterol [Text] / M.E. Wechsler // Am. J. Respir. Crit. Care. Med. – 2006. – Vol. 173. – P. 519–526.

19. Zhang, J.Q. Relationship between polymorphisms in the 5' leader cistron, positions 16 and 27 of the adrenergic β_2-receptor gene and asthma in a Han population from southwest China [Text] / J.Q. Zhang, L. Wang, J.K. Shu // J. Respirology. – 2011. – Vol. 16 (8). – P. 1221–1227.

in patients with asthma and allergic rhinitis. Folia. Med. Cracov. Folia. Med. 2005;46(1–2):33–51.

6. Contopoulos-Ioannidis DG, Manoli EN, Ioannidis JP. Meta-analysis of the association of beta2-adrenergic receptor polymorphisms with asthma phenotypes. J Allergy. Clin. Immunol. 2005;115(5):963–972.

7. Demoly P. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. Eur. Respir. J. 2012;21(123):66–74.

8. Taylor DR, et al. Europen respiratory society statement: asthma control and exacerbations, standardizing endpoints for clinical asthma trials and clinical practice. Part 2. J. Pulmonology. 2007;55:762–765.

9. Portelly M, et al. Genetic basis for personalized medicine in asthma. Expert Rev. Respir. Med. 2012;6(2):223–236.

10. GINA 2014. Available from: www.ginasthma.org

11. Israel E. Use of regularly scheduled albuterol treatment in asthma: genotypestratified, randomized, placebo-controlled cross-over trial Lancet 2004. Lancet. 2004;364:1505–1512.

12. Johnson R, Michael A, Matthay MD. Acute Lung Injury: Epidemiology, Pathogenesis, and Treatment. J. Aerosol. Med. Pulm. Drug Deliv. 2010;23(5):243–252.

13. Limsuwan T. Possible protective effects of the Glu27 allele of beta2-adrenergic receptor polymorphism in Thai asthmatic patients. Asian. Pac. J. Allergy. Immunol. 2010;28(2–3):107–114.

14. Milgrom H, et al. Noncompliance and treatment failure in children with asthma. J. Allergy Clin. Immunol. 1996;98:1051–1057.

15. Gupta S, et al. Pharmacogenomics of pediatric asthma. Indian. J. Hum. Genet. 2010;16(3):111–118.

16. Wainwright NW, et al. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. J. Allergy. 2007;62(5):554–560.

17. Rees J. Asthma control in adults. BMJ. 2006;332:767–771.

18. Wechsler ME. β-adrenergic receptor polymorphism and response to salmeterol. Am. J. Respir. Crit. Care. Med. 2006;173:519–526.

19. Zhang JQ, Wang L, Shu JK. Relationship between polymorphisms in the 5' leader cistron, positions 16 and 27 of the adrenergic β2-receptor gene and asthma in a Han population from southwest China. J. Respirology. 2011;16(8):1221–1227.

Theoretical and practical J. «Asthma and Allergy», 2017, 1

A.N. Bondarkova, assistant, postgraduate student of internal medicine department of postgraduate education,
Medical institute of Sumy state university
str. Troitskaya, 48, Sumy, Ukraine, 40022;
tel.: +38 (050) 208-18-53; e-mail: BAN241088@mail.ru