ANALYSIS OF THE POLYMORPHIC VARIANTS OF *ADRB2* GENE ASSOCIATION WITH THE β_2-AGONISTS RESPONSE IN PATIENTS WITH A RARE THERATYPE OF ASTHMA

Mdinaradze DS, Kozlov IB, Pavlova KS ✉, Kofiadi IA, Kurbacheva OM

National Research Center Institute of Immunology of the Federal Medical-Biological Agency, Moscow, Russia

Standard asthma therapy includes prescription of β_2-agonists. Changes in the functional activity of β_2-adrenergic receptor are associated with *ADRB2* gene polymorphism and related to the low therapeutic response to β2-agonists. Identification of carriers of the clinically significant gene variants will help to avoid ineffective treatment and prescribe an alternative therapy. This study aimed to assess clinical significance of the *ADRB2* gene polymorphisms (Arg16Gly and Gln27Glu) associated with the therapeutic response to β_2-agonists in the group of asthma patients. We subjected a small group of adult nonsmoking patients (n = 21) with moderate asthma (III–IV stage of GINA) to clinical and genetic examination. The group included patients with the new theratype, those that poorly respond to β_2-adrenergic drugs but significantly to M-cholinergic agonists. The first group included patients responding well to both salbutamol and ipratropium bromide. The second group was comprised of the patients for whom salbutamol was not effective but who tested positive for response to ipratropium bromide. The analysis of distribution of polymorphic variants of Arg16Gly and Gln27Glu revealed no significant relationship between alleles and genotypes and the efficacy of β_2-agonists (0.52 for the rs1042713 variant, p = 1.0; 1.0 for the rs1042714 variant, p = 0.74, respectively). The genotype of patients that did not respond to salbutamol was either Arg16Gly or Gly16Gly. Further studies are needed that would involve a larger number of patients and an expanded list of the tested polymorphic variants.

Keywords: asthma, asthma control, gene polymorphism, β_2-adrenergic receptors, *ADRB2*, Arg16, Gly16, bronchodilators, short-acting β_2-agonists, SABA, short-acting anticholinergics, SAMA, long-acting anticholinergics, LABA

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Compliance with ethical standards: the study was approved by the ethics committee of the Institute of Immunology of the Federal Medical-Biological Agency (Minutes #13 of October 16, 2017); all patients signed voluntary consent to participate in the study.

✉ **Correspondence should be addressed:** Ksenia S. Pavlova
Kashirskoe shosse, 24, Moscow, 115522; ksenimedical@gmail.com

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АНАЛИЗ АССОЦИАЦИИ ПОЛИМОРФНЫХ ВАРИАНТОВ ГЕНА *ADRB2* С ОТВЕТОМ НА β_2-АГОНИСТЫ У ПАЦИЕНТОВ С РЕДКИМ ТЕРАТИПОМ БРОНХИАЛЬНОЙ АСТМЫ

Д. С. Мдинарадзе, И. Б. Козлов, К. С. Павлова ✉, И. А. Кофиади, О. М. Курбачева

Государственный научный центр «Институт иммунологии» Федерального медико-биологического агентства, Москва, Россия

Стандартная терапия бронхиальной астмы (БА) включает назначение β_2-агонистов. Изменение функциональной активности β_2-адренорецептора ассоциировано с полиморфизмом гена *ADRB2* и связано с низким терапевтическим ответом на β_2-агонисты. Выявление носителей клинически значимых вариантов гена поможет избежать неэффективного лечения и послужит основанием для назначения альтернативной терапии. Целью исследования было оценить клиническую значимость ассоциированных с терапевтическим ответом на β_2-агонисты полиморфных вариантов гена *ADRB2* (Arg16Gly и Gln27Glu) для группы пациентов с БА. Проведено клиническое и генетическое обследование небольшой группы взрослых некурящих пациентов (n = 21) с БА средней степени тяжести (III–IV ступень по GINA), в том числе пациентов нового тератипа, для которых характерны плохой ответ на β_2-адренергические средства, но значимый ответ на М-холинергические средства. В первую группу были определены пациенты с подтвержденной эффективностью применения сальбутамола, которые в то же время имели хороший ответ на ипратропия бромид. Во вторую группу вошли пациенты с низкой эффективностью терапии сальбутамолом и положительным тестом с ипратропия бромидом. Анализ распределения полиморфных вариантов Arg16Gly и Gln27Glu показал отсутствие достоверной связи аллелей и генотипов с эффективностью применения β_2-агонистов (0,52 — для варианта rs1042713, p = 1,0; и 1,0 — для варианта rs1042714, p = 0,74 соответственно). При этом пациенты с отсутствием ответа на сальбутамол имели генотип либо Arg16Gly, либо Gly16Gly. Необходимы дальнейшие исследования с большим числом пациентов и расширением перечня тестируемых полиморфных вариантов.

Ключевые слова: бронхиальная астма, контроль астмы, полиморфизм генов, β_2-адренорецепторы, *ADRB2*, Arg16, Gly16, бронхолитические средства, короткодействующие β_2-агонисты, КДБА, короткодействующие антихолинергические препараты, КДХП, длительно действующие антихолинергические препараты.

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✉ **Для корреспонденции:** Ксения Сергеевна Павлова
Каширское ш., д. 24, г. Москва, 115522; ksenimedical@gmail.com

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Personalized medical assistance employs current molecular genetics technologies (pharmacogenetic testing, identification of genomic and transcriptomic biomarkers) to individualize the choice of the drug [1]. In this context, asthma is of considerable interest, since both the pathology itself and the response to asthma therapy are largely shaped by the genes [2–5]. For example, a change in the functional activity of β_2-adrenergic receptor (ADRB2) associated with polymorphism of its encoding gene can worsen the pharmacological response to β_2-agonists, which asthma therapy mostly relies on [6, 7].

According to the Ensembl database [8], *ADRB2* is a highly polymorphic gene. Its coding part contains over 500 single nucleotide substitutions and insertion-deletion polymorphisms. Of these, 276 are missense mutations causing a shift in the reading frame or appearance of a stop codon. From the point of view of response to anti-asthma therapy, the most interesting are the Argl6Gly (rs1042713), Gln27Glu (rs1042714), and Thrl64Ile (rs1800888) polymorphic variants of the gene. Their association with the efficacy of response to β_2-agonists is clear. However, various studies [9–11] failed to reliably reproduce the associations established for these molecular genetic markers. In this connection, the question of the possibility of clinical application of the results of testing for *ADRB2* gene polymorphisms remains open [12–14].

Some of the reasons behind inability of some researchers to confirm the clinical effect of this or that polymorphic variant of the gene are population heterogeneity, small (insufficient) sample, incomplete description of characteristics of the control groups [15, 16]. Thus, it is necessary to further study the molecular mechanisms of asthma pathogenesis with the involvement of numerous cohorts from different populations. It should be noted that there are practically no efforts pursuing the mentioned purpose in Russia.

Despite the aforesaid, clinicians already have the experience and the necessary tools to use pharmacogenetic testing in practice. It seems interesting to approach the issue of establishing the clinical significance of genetic markers from the other side. We did not aim to establish the association of a marker with a sign; on the contrary, we investigated the applicability of markers with association already established for a limited cohort of patients we have clinically described previously [17]. The confirmation of significance of pharmacogenetic markers for this group would allow actual use of genetic testing results as an additional justification of management decisions made for patients torpid to standard therapy.

Thus, this study aimed to assess the clinical significance of ADRB2 gene polymorphisms associated with therapeutic response to β_2-agonists in a group of patients with a rare asthma theratype which we have described earlier.

METHODS

Patients

The inclusion criteria were: signed informed consent to participate in the study; 18 years of age and older (both genders); severe allergic asthma persisting for two years or more; the ability to adequately assess your symptoms and follow recommendations; confirmed reversibility of the bronchial obstruction (after inhalation of 400 μg of salbutamol FEV1 growth of 12% and 200 ml or more). It was considered acceptable when the patient had reversibility of bronchial obstruction confirmed with a document dated within 12 months before signing of the informed consent.

The exclusion criteria were: acute infectious disease (until recovery), exacerbation of concomitant chronic disease (until stabilization of the condition); any clinically significant, uncontrolled medical condition for which the patient is receiving or not receiving treatment and that would hinder adherence to the study schedule or procedures, efficacy data interpretation, or pose a threat to the safety of the patient; diagnosed malignant neoplasm; development of a serious adverse event during the course of the study.

The study involved non-smoking adult patients (n = 21) of Russian ethnicity of both sexes (8 men and 13 women), the mean age was 53 years (minimum — 47, maximum — 63); they all suffered from moderate asthma (III–IV stage of GINA) for the mean period of 13 years (minimum — 1 year, maximum — 32 years). All patients were prescribed medium to high doses of inhaled corticosteroids as the main therapy in combination with long-acting anticholinergics (LABA). Asthma symptoms were either not controlled or the control was incomplete: the patients needed symptomatic therapy daily; they scored 15–20 points on the ACT scale; the 1 s forced expiration volume (FEV1) before administration of a bronchodilator reached 70.6 ± 5% of the normal values. The patients were divided into two groups. The first (n = 14) included patients who responded well to salbutamol (400 μg of inhaled salbutamol causing the growth of FEV1 of over 12% and 200 ml), with that response confirmed clinically and instrumentally, and, at the same time, exhibited good response to 50 μg of ipratropium bromide (SABA+SAMA+). The second group (n = 7) was comprised of the patients that had poor response to salbutamol (400 μg of inhaled salbutamol causing the growth of FEV1 of less than 12% and 200 ml) and tested positive for response to 50 μg of ipratropium bromide, inhaled (inhalation yielding the growth of FEV1 of over 12% and 200 ml in 30 minutes; SABA–SAMA+).

Genetic markers

The *ADRB2* gene is located on the long arm of chromosome 5q32, next to a cluster of genes encoding cytokines and the glucocorticoid receptor. *ADRB2* belongs to the genes of receptor molecules that control bronchial lability [18].

The Arg16Gly polymorphism (international polymorphism code: rs1042713) is a single nucleotide substitution in the coding region of the *ADRB2* gene, where guanine nucleotide (G) is replaced with adenine nucleotide (A) (genetic marker G46A). This substitution changes the amino acid sequence of the ADRB2 protein at position 16: arginine is replaced by glycine (Arg16Gly). Thus, the following variants are possible: Arg16Arg, Arg16Gly, Gly16Gly. In vitro studies have shown a change in the functional activity of *ADRB2* [19]. Some researchers report that the patients homozygous for these gene variants quickly lose sensitivity to short-acting β_2-agonists (SABA) and need to corticosteroids prescribing [14].

The Glu27Gln polymorphism (international polymorphism code: rs1042714) is a single nucleotide substitution of cytosine for guanine (genetic marker C79G). As a result of this substitution, the amino acid sequence of the ADRB2 protein has glutamine replaced by glutamic acid (Glu27Gln) at position 27. Martinez et al have reported that Glu27 allele is associated with decreased sensitivity of asthma patients airways to methacholine [20].

DNA purification and typing

Genomic DNA was isolated from peripheral blood lymphocytes through phenol-chloroform extraction. The obtained samples were immediately used for genotyping or stored at –20 °C. The DNA concentration was determined with the help of

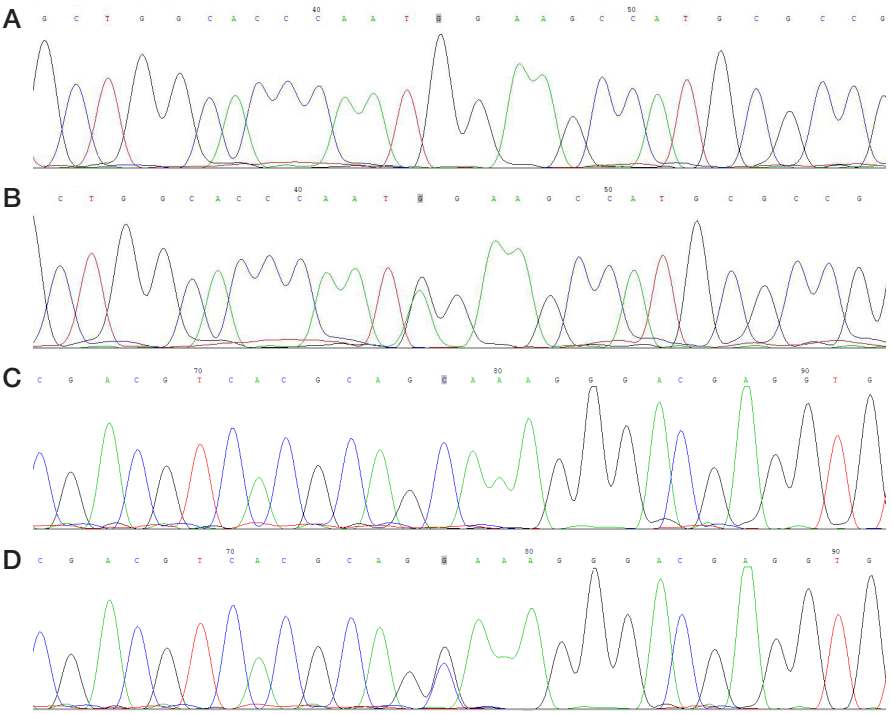

Fig. 1. The results of sequencing of homozygous and heterozygous samples. The varying nucleotides are shown in gray. Peculiar to the homozygotes is a single peak in the chromatogram at the position of the rs1042713 and 1042714 polymorphisms (**A** and **B**, respectively). Heterozygotes are characterized by a double peak at the position of the rs1042713 and 1042714 polymorphisms (**B** and **D**, respectively)

Qubit fluorimeter (Invitrogen; USA); it averaged at 50–100 μg/ml. *ADRB2* gene's polymorphisms rs1042713 and rs1042714 were PCR-analyzed (real-time PCR) in the DTprime amplifier (DNA-Technology LLC; Russia) with primers ADRB2-f: 5'-AGTGCGCTCACCTGCCAGACTG-3' and ADRB2': 5'-CCAAACACGATGGCCAGGACGA-3'. The primers were synthesized on a solid support using inverted (5') phosphoramidites and photodegradable linkers. The latter were used to take primers off the solid support, the process relying on the ultraviolet radiation.

To determine the genotypes, we resorted the modified adjacent probes method [21]. This approach compares favorably with the majority of molecular genetic methods enabling determination of single nucleotide polymorphisms, including those relying on the TaqMan technology. The genotype is determined twice, independently, using two fluorescence channels, which significantly increases the reliability of genotyping. No other approach allows this level of accuracy. For amplification, we used 35 μL of reaction mixture, which contained 2.5 μL of 10 — Taq buffer (67 mM Tris-HCl (pH 8.8), 16.6 mM (NH4) 2SO4, 2.5 mM MgCl2, 0.01% Tween-20), 0.1 μg of genomic DNA, dNTP mixture (dATP, dGTP, dCTP, dTTP, 200 μM each), 1 unit of DNA polymerases (DNA-Technology LLC; Russia) and 5–10 pM of locus-specific oligonucleotide primers and probes. The amplification temperature regime was as follows: 94 °C for 10 s, 64 °C for 30 s, for 50 cycles. When the amplification was complete, the reaction mixture was cooled to 25 °C at the rate of 2 °C/s. The melting curves were obtained as follows: the temperature of the reaction mixture was increased from 25 to 75 °C in 1 °C increments, with the fluorescence level measured at each increment.

MS Excel 2013 (Microsoft; USA) enabled statistical processing of the data, which employed Fisher's exact test to check the equivalence of the observed distribution of genotype frequencies [24, 25]. The differences between groups were considered significant at $p < 0.05$. The following formula was used to establish frequency of the alleles:

$$f = {}^{n}/_{2N} * 100\%,$$

where n is the occurrence of the allele.

RESULTS

The study focused on the rs1042713 and rs1042714 polymorphisms (rs1800888 was not included because of its low occurrence [24, 25]). To accomplish the objective declared, we designed a new test system to analyze the *ADRB2* gene polymorphisms using real-time PCR, and confirmed its efficacy by direct sequencing of homozygous and heterozygous samples (Fig. 1).

In the course of the study, we formed control groups from patients at the Institute of Immunology of the FMBA of Russia. These patients had asthma of different theratypes; we genotyped them and analyzed the differences in the occurrence of alleles and genotypes. Table shows the results of genotyping.

DISCUSSION

We subjected moderate BA patients (III–IV stage of GINA) with variable pharmacological response to β_2-agonists to clinical and genetic examination; SABA+SAMA+ are the patients with clinically and instrumentally confirmed positive response to salbutamol, and SABA–SAMA+ are patients that responded poorly to salbutamol but well to ipratropium bromide. In the previous paper, we provided detailed clinical characteristics of these groups of patients [17]. Alleles and genotypes of patients were determined for rs1042713 (Arg16Gly) and rs1042714 (Glu27Gln), polymorphisms of the *ADRB2* β_2-adrenergic receptor gene.

Arg16Gly polymorphism (rs1042713)

Among the SABA+SAMA+/SABA–SAMA+ patients, those that exhibited poor response to salbutamol had the frequency of

Table. Distribution of the allele and genotype frequencies of *ADRB2* gene's rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu) polymorphisms in asthma patients with various theratypes (SABA+SAMA+ — patients with clinically and instrumentally confirmed positive response to salbutamol)

Patient group, *n* (%)	Arg16Gly						
	Alleles			Genotypes			
	Arg	Gly	*p*-value	Arg16Arg	Arg16Gly	Gly16Gly	*p*-value
SABA+SAMA+ (*n* = 14)	10 (36%)	18 (64%)	1	2 (14%)	6 (43%)	6 (43%)	0.52
SABA+SAMA+ (*n* = 7)	5 (36%)	9 (64%)		0	5 (71%)	2 (29%)	
All patients (*n* = 21)				2 (10%)	11 (52%)	8 (38%)	
	Gln27Glu						
	Alleles			Genotypes			
	Glu	Gln	*p*-value	Glu27Glu	Gln27Glu	Gln27Gln	*p*-value
SABA+SAMA+ (*n* = 14)	17 (61%)	9 (39%)	0.74	4 (29%)	9 (64%)	1 (7%)	1
SABA+SAMA+ (*n* = 7)	8 (57%)	6 (43%)		2 (29%)	4 (57%)	1 (14%)	
All patients (*n* = 21)				6 (28%)	13 (62%)	2 (10%)	

heterozygotes 1.5 greater than those that responded well to the drug. Both groups had the Arg16 and Gly16 alleles detected with the same frequency (see Table).

We have shown that the Arg16Gly polymorphism is associated with desensitization of the *ADRB2* receptor. A receptor with Gly16Gly is more susceptible to desensitization by endogenous catecholamines than a receptor with Arg16Arg or Arg16Gly in its structure [26]. As described in the published papers, a variability in response to β_2-agonists was revealed [27]. Our data partially agree with the data stating lack of therapeutic response to β_2-agonist inhalation therapy in moderate asthma patients that have the Gly allele (Arg16Gly and Gly16Gly genotypes) dominating [28]. In our study, the genotype of all patients showing no response to salbutamol was Arg16Gly or Gly16Gly. However, we could not confirm the association when assessing the effect the Gly allele has on poor response to β_2-agonists (odds ratio [OR], 1.00; 95% CI 0.26–3.81). The most pronounced response to a single administration of a β_2-adrenergic agonist was registered in the group of patients homozygous for Arg at position 16 (Arg16Arg) compared with homozygous for Gly at this position (genotype Gly16Gly) [20]. Another study also confirms that the Arg16Arg genotype is associated with mild asthma and a better response to salbutamol [29]. According to our data, 14% of patients that responded well to salbutamol in the SABA+SAMA+ group had the Arg16Arg genotype. No patient in the poor response group has this genotype.

Unfortunately, we only managed to recruit a small number of SABA–SAMA+ asthma patients, since this theratype is rare. Probably, further identification of such patients and a study on a larger sample will yield significant differences.

Glu27Gln polymorphism (rs1042714)

The distribution of genotypes and alleles for the 27th position among SABA+SAMA+/SABA–SAMA+ patients was almost identical. The two groups did not differ significantly in this regard (see Table). However, in the SABA+SAMA+ group we revealed a number of Gln27Glu heterozygotes (64%) that is relatively larger than the frequency of 45.7% previously established for the Russian population [30], but this observation requires confirmation on a larger sample.

The studies focusing on the Gln27Glu polymorphism and variability of response to β_2-agonists are limited, and these results are inconsistent, which prevents us from correlating our data with those reported in the literature. The key subject for research was the distribution of genotype frequencies with asthma of various severity in the background. It was shown that the prevailing genotype in the cohort of severe asthma patients is Glu27Glu (55 and 75%, respectively) [31, 32]. Another study reported the following distribution of genotypes for the 27th position in asthma patients: Glu27Glu — 9.2%, Gln27Glu — 27.8%, Gln27Gln — 63%; there were no differences found in patients with different severity and response to β_2-agonists [29]. Thus, the data we obtained are consistent with the data reported in [29] that reports lack of relationship between the response to β_2-agonists and the rs1042714 (Gln27Glu) polymorphism.

In this study, we did not evaluate other polymorphisms of the *ADRB2* gene that could influence the response to β_2-agonists. It is possible that other, nongenetic reasons for desensitization of the ADRB2 gene underlie the poor response to salbutamol in patients with the rare SABA–SAMA+ theratype.

CONCLUSION

The analysis of distribution of rs1042713 (Arg16Gly), *ADRB2* gene polymorphisms, showed that the genotype of all patients with no response to β_2-agonists (salbutamol) was either Arg16Gly or Gly16Gly, however, we could not confirm the association when assessing the effect the Gly allele has on poor response to β_2-agonists, with small sample size being the possible reason therefor. We established no differences in the distribution of rs1042714 (Gln27Glu) allele and genotype frequencies when comparing groups of patients with different clinical responses to β_2-agonists. A further study that would include a larger sample of asthma patients with the rare SABA–SAMA+ theratype may reveal statistically significant differences in the distribution of polymorphic rs1042713 (Arg16Gly) variants. In this study, we did not evaluate other polymorphisms of the *ADRB2* gene for their possible effect on the response to β_2-agonists. It is advisable to include in further research rare functional variants identified as a result of resequencing of polyethnic cohorts. In addition, other, nongenetic reasons for desensitization of the *ADRB2* gene may be associated with a poor response to salbutamol in patients with the rare SABA–SAMA+ theratype.

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