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The role of association of ADRB2 gene polymorphism with therapeutic response to β 2-agonists in children with recurrent bronchial obstruction

Abstract. Background. The study of the effect of drugs at the molecular genetic level in the recurrent course of bronchial obstruction (RBO) in children improved the understanding of the pathogenesis of the disease and made it possible to better characterize the reliability of use in therapy. The aim of the study was to assess the clinical significance of the polymorphism of the Arg16Gly loci of the ADRB2 gene with a therapeutic response to β 2-agonists in children with RBO of Uzbek ethnicity. **Materials and methods.** Tested 88 patients aged 6 to 15 years with recurrent bronchial obstruction and bronchial asthma with the polymorphism of the ADRB2 gene loci and determined the effectiveness of salbutamol in these groups of patients. **Results.** Results of the study of the significance of the polymorphism of the Arg16Gly locus of the ADRB2 gene with a therapeutic response to β 2-agonists in children with RBO showed high efficacy of salbutamol in 72.9 % of children, among whom representatives of the A/G and A/A genotypes were found in the largest number. At the same time, the low efficacy of salbutamol was found in the greatest amount in carriers of the mutational genotype G/G of the Arg16Gly locus of the ADRB2 gene. **Conclusions.** The predictor role of the polymorphic locus rs1042713 (Arg16Gly) was determined in carriers of the unfavorable 46G allele of the G/G genotype of the ADRB2 gene, which was a genetic marker of children's predisposition to RBO and BA in children. Children with the G/G genotype of the Arg16Gly locus of the ADRB2 gene are at risk for severe RBO and BA in children. Children with RBO carriers (Arg16Gly) of the homozygous G/G genotype have a high incidence of RBO recurrence against the background of ARVI and are at risk of developing BA.

Keywords: bronchitis; obstruction; ADRB2 gene; β 2-agonists; children

Introduction

In recent years, the incidence of bronchitis, occurring with the syndrome of bronchial obstruction, among the children's population is growing intensively. Among them, obstructive bronchitis with a recurrent course is observed in 50–70 % of young children and in many cases the cause is bronchial asthma (BA). Numerous studies are devoted to identifying the causes that contribute to the occurrence of recurrent bronchial obstruction (RBO). In the activities of a general practitioner, the differential diagnosis of RBO in children causes its own difficulties and leads to incorrect diagnosis [2, 5]. The high level of bronchopulmonary diseases in children, the complexity of the pathogenesis and the severity of the consequences of recurrent bronchitis necessitate the development of measures for its early diagnosis, prediction of consequences, effective treatment, as well

as the introduction of research results into practical medicine. Further improvement of the child health care system requires the development of a new approach that takes into account, first of all, the needs of groups of people exposed to clinical and genetic risk factors [1]. It is especially important that these preventive measures are carried out before the influence of genetic factors goes beyond the initial preclinical manifestations of disease states [8].

Today, methods for studying the effect of drugs at the molecular genetic level on the treatment of diseases are widely used in pediatric practice. Advances in genomic technology have improved understanding of disease pathogenesis and better characterization of drug toxicity. This provides important information for the personalization of therapy for bronchopulmonary diseases in children and adolescents [3, 6, 7]. Abroad, a large number of scientific works are devoted

to the analysis of the rs1042713 A>G polymorphic variant of the ADRB2 gene and its effect on the development of BA and the effectiveness of β 2-agonist therapy. Of the widely used agonists of β 2-adrenergic receptors are the drugs salbutamol (Ventolin) and fenoterol (Berotek) of prolonged action. They are used as bronchoprotective agents for basic anti-inflammatory therapy in combination with inhaled glucocorticosteroids. The therapeutic effect of β 2-agonists occurs through β 2-adrenergic receptors, which are located in large numbers in the smooth muscle and glandular cells of the bronchi. In the case of long-term use of high doses of β 2-agonists, a decrease in the sensitivity of receptors to them may be observed, which may be the reason for the development of tolerance to the drug.

The ADRB2 gene is highly related to adrenaline, which, when interacting with bronchial receptors, is involved in bronchodilation and a decrease in CP. In this regard, β 2 receptor agonists are widely used in therapy for the treatment of BO. The use of β 2 receptor agonists makes it possible to use and reduce the dosage of corticosteroids. Based on modern pharmacogenetics, hereditary factors largely determine the severity of the therapeutic response to drugs. In recent years, based on many studies, new pharmacogenetic variants have been identified that are associated with responses to ICS and bronchodilators [3, 4, 9].

The results of studies of polymorphisms of the beta-2-adrenergic receptor gene (ADRB2) by many authors are contradictory in different populations. So, the authors S.K. Liang and others evaluated the relationship between ADRB2 gene polymorphism and the risk of developing BA. The results are inconsistent, with single nucleotide polymorphisms (SNPs) of Arg16Gly, Gln27Glu, Thr164Ile and Arg19Cys identified in 46 case-control studies. The results showed that not all SNPs were associated with BA in the general population [9]. L.A. Livshits and others investigated the association of C79G polymorphism of the ADRB2 gene with the risk of developing BA in children living in different environmental conditions. It was found that the frequency of carriage of the 79G polymorphic variant of the ADRB2 gene was statistically significantly higher ($p < 0.05$) in the group (69.4 %) of children from an environmentally polluted region compared to the control group (55.8 %) [10]. According to N.D. Shah et al. investigated the effect of the Arg16Gly and Gln27Glu polymorphisms of the ADRB2 gene on the development of BA and on the response to salbutamol in South Indian patients. The Arg16Gly and Gln27Glu polymorphisms did not determine the occurrence of BA alone, but the GG-CG haplotype was associated with an increased risk of developing the disease. At the same time, there was no effect of genotypes on the effect of salbutamol [11].

The purpose of the study was to assess the clinical significance of the polymorphism of the Arg16Gly loci of the ADRB2 gene with a therapeutic response to β 2-agonists in children with RBO of Uzbek ethnicity living in Uzbekistan.

Materials and methods

The object of the study was 88 patients aged 6 to 15 years with recurrent bronchial obstruction and bronchial asthma. Diagnosis was made on the basis of clinical and anamnestic data, laboratory and instrumental research methods,

including spirometry with a provocative test. The control group consisted of 72 practically healthy children of the same age and population.

Determining the role of ADRB2 gene loci polymorphism in molecular genetic study, a diagnostic kit was used to detect polymorphisms by real-time polymerase chain reaction (PCR) on the Rotor Gene 6000/Q equipment. The efficacy of salbutamol (Ventolin) was studied in 85 patients with RBO (main group) and 56 children with BA (comparison group) aged 6 to 15 years. Efficacy was determined by conducting a provocative test using salbutamol inhaled with a spacer at a dose of 200 μ g (100 μ g with an interval of 30 seconds) during a spirometric study. The reversibility of bronchial obstruction was determined by changes in FEV1 or FVC. The patients of each group were divided into 2 subgroups: group 1 — children with high salbutamol efficiency and subgroup 2 — with low drug efficiency. The high efficacy of the drug was confirmed in the presence of BO reversibility by 15 % or more after a provocative test. At the same time, the spirogram showed an increase in the forced expiratory volume in 1 s (FEV1). The low efficacy of salbutamol was recorded in the presence of BO reversibility below 12–15 % after a provocative test. The spirogram showed a decrease in forced expiratory volume in 1 s (FEV1). Statistical processing of the obtained results using application programs for mathematical and statistical analysis Microsoft Excel Version 7.0.

Results

In patients with recurrent bronchitis, the first episode of bronchial obstruction (BO) occurred significantly more often in children under 3 years of age compared with the group of children from 3 to 6 years of age (65.2 % vs. 26.8 %; $p < 0.05$). It was noted that among children in At the age of 3 to 6 years, the first episode of SBO occurred less frequently in patients with RBO (26.8 %) compared with the group of children with BA (36.8 %). bronchitis in the development of a recurrent course of obstructive bronchitis Early onset of respiratory infections in the first year of life and a high incidence of ARVI up to 3 years in history had an adverse effect on the formation of RBO in the future. In children with RBO, an association of the A/A genotype of both ADRB2 gene loci with an early onset of ARVI at an early age was revealed. Among children with RBO, the largest percentage was made up of patients aged 3 to 6 years (35.3 ± 3.7 %), while in the group with acute obstructive bronchitis, children from 1 to 3 years (54.2 ± 4.8 %) and BA — from 10 to 15 years (55.2 ± 5.7 %). Among children with RB, male patients were noted significantly more often (64.0 %) than female patients (35.4 %) ($p < 0.05$). The G/G mutation genotype for the Arg16Gly polymorphism was more frequently observed in the group of boys than in the group of girls (27.5 versus 17.6 %; $p < 0.001$).

An analysis of the obstetric and somatic anamnesis of mothers of patients with RBO showed that mostly children were born from 2–3 pregnancies, while in 62.2 % of women the period of pregnancy proceeded against the background of anemia, in 44.5 % of toxicosis, with previous abortions 8.5 %, taking medications during pregnancy in 34.1 %, cases of ARVI in mothers were often recorded (51.8 %). The re-

sults of studies of the premorbid background in the examined groups of children showed: the course of RBO against the background of anemia ($78.0 \pm 3.2\%$), PEI grades 1–2 ($26.2 \pm 3.4\%$); constitutional anomalies ($23.8 \pm 3.3\%$). Food allergy was more often observed in the group of children with BA, compared with the group of children with RBO ($60.5 \pm 5.6\%$ versus $47.4 \pm 5.7\%$; $p < 0.05$). Chronic foci of ENT organs were more often observed in the group of children with RBO compared with the control group ($31.7 \pm 3.6\%$ versus $18.0 \pm 5.4\%$; $p < 0.05$). Therefore, the severity of the premorbid background, the presence of allergic concomitant diseases is an unfavorable factor for the formation of a recurrent course of SBO. The influence of exogenous factors was observed most often in the group of children with RB and BA, compared with the group of children with AOB and control: cases of early transition to artificial feeding ($51.2 \pm 3.9\%$ and $67.1 \pm 5.4\%$), frequent respiratory infections in family members ($39.0 \pm 3.8\%$ and $31.6 \pm 5.3\%$), passive smoking ($35.40 \pm 3.73\%$ and $32.90 \pm 3.84\%$) and other factors.

When studying the rs1042713 (Arg16Gly) locus in the main group, the Arg(A) allele frequency is dominant and occurs significantly higher compared to the G allele (61.4 versus 38.6% , respectively; $\chi^2 = 8.23$; $p = 0.001$) (Table 1). At the same time, among the main group, the carriage of the Gly (G) allele was detected with a higher frequency than in the control group (38.6 vs. 23.6% , $\chi^2 = 8.23$; $p = 0.001$). The calculated relative chance of the presence of this allele in patients compared with controls was $OR = 2.04$ at 95% $CI = 1.25–3.31$.

When studying the polymorphism of the Arg16Gly locus of the ADRB2 gene, the results of a study of children in the main group showed that the frequency of occurrence of the G/G genotype (13.6%) was significantly lower than that of the A/A (36.4%) and A/G (50.0%) genotypes. The same trend is noted in the groups of children with RBO and BA. The G/G genotype of the Arg16Gly locus in patients of the main group was significantly higher compared to the control group (13.6 versus 6.9% , $\chi^2 = 1.87$; $P = 0.01$; $RR = 1.9$; $OR = 2.1$; 95% $CI = 0.72–6.20$). At the same time, the A/A genotype in the main group was found to be significantly lower than in the control group (59.7 versus 36.4% ; $\chi^2 = 8.6$; $P = 0.01$; $OR = 0.39$; 95% $CI = 0.21–0.73$). Replacing adenine with guanine A46G, the calculated relative chance of having this allele in patients of the examined groups was $OR = 1.0$; 95% $CI = 1.75–3.61$. The frequency of occurrence of the heterozygous A/G genotype of the Arg16Gly ADRB2 gene locus in the main group is higher compared to

the control group (50.0 versus 33.3% ; $\chi^2 = 4.5$; $P = 0.04$; $RR = 1.5$; $OR = 2.0$; 95% $CI = 1.05–3.79$).

Differences in the frequency of occurrence of allelic and genotypic variants of the Arg16Gly polymorphism in the ADRB2 gene showed that the G/G genotype was significantly more common in the group of RBO children compared to the control group (12.5 vs. 6.9% , respectively, $\chi^2 = 0.7$; $P = 0.41$; $RR = 1.8$; $OR = 1.9$; 95% $CI = 0.43–8.51$). At the same time, the same trend is observed in relation to carriers of the heterozygous A/G genotype of the Arg16Gly locus with a slight difference, in particular in the group of children with RBO, than in the control (45.8 versus 33.3% , respectively, $\chi^2 = 1.2$; $P = 0.28$; $OR = 1.7$, 95% $CI = 0.66–4.31$). A comparative analysis of the distribution of Arg16Gly alleles and genotypes in the ADRB2 gene between BA and control groups showed that the frequency of the Arg(A) allele was significantly higher in the group of healthy children (76.4%) than in the group with BA (60.7%); the frequency of the Arg G allele is more frequent in the group of children with AD (39.3 versus 23.6% , $\chi^2 = 6.3$; $p = 0.01$; $RR = 1.3$; $OR = 2.1$; 95% $CI = 1.17–3.72$); a high frequency of the A/G genotype was found compared to the control group (54.8 versus 33.3% , respectively, $\chi^2 = 5.03$; $P = 0.03$; $RR = 1.6$; $OR = 2.4$; 95% $CI = 1.12–5.24$); in genotype carriers an analysis of the distribution of the Arg16Gly ADRB2 gene polymorphism depending on the severity of RBO in children showed that the homozygous genotype A/A was most observed in the group of children with mild course ($64.3 \pm 12.8\%$), while the heterozygous genotype A/G ($45.83 \pm 10.2\%$) — with a moderate course; a severe course was found in carriers of the G/G mutation genotype ($44.7 \pm 7.3\%$). A/A showed an opposite trend.

Discussion

The results of the study of the clinical significance of polymorphic variants Arg16Gly of the ADRB2 gene with a therapeutic response to β_2 -agonists in children with RBO ($n = 85$) showed (Figure 1): high efficiency of salbutamol in $72.9 \pm 4.8\%$ and low efficiency in $27.1 \pm 4.8\%$ ($p < 0.05$); among children with high efficiency of salbutamol, carriers of Arg16Gly heterozygous genotype A/G ($48.4 \pm 6.4\%$) and homozygous A/A ($43.5 \pm 6.3\%$) were found in the largest number; low efficacy of salbutamol was found more often in carriers of the G/G mutation genotype ($56.5 \pm 10.3\%$) compared to the A/A ($26.1 \pm 9.1\%$) and AG ($17.4 \pm 7.9\%$) genotypes ($p < 0.05$).

In the group of children with RBO carriers of the Gln27Glu locus of the ADRB2 gene, low efficacy of

Table 1. The distribution frequency of allelic and genotypic variants of the rs1042713 (Arg16Gly) polymorphism of the ADRB2 gene among the examined groups of children

Group	Allele frequency		Frequency of genotype distribution		
	A, %	G, %	A/A, %	A/G, %	G/G, %
Main group (n = 88)	61.36	38.64*	36.36*	50.0*	13.64*
RBO	64.58	35.42*	41.67	45.83	12.5*
BA	60.71	39.29*	33.33*	54.76*	11.9*
Control group (n = 72)	76.39	23.61	59.72	33.33	6.94

Note: * — significant difference compared to the control group.

salbutamol was found in carriers of the G/G mutation genotype (45.0 ± 11.1 %) and heterozygous A/G genotype (35.0 ± 10.6 %) in relation to the A/A genotype (20.0 ± 8.9 %) ($p < 0.05$). Comparative analysis of the Arg16Gly locus of the ADRB2 gene showed high drug efficacy more often in patients with RBO carriers of the A/G genotype, compared with the group of children with AD carriers of the A/G genotype (48.4 vs. 23.7 %; $p < 0.05$). The low efficacy of salbutamol was found more often in carriers of the G/G genotype in patients with RBO (56.5 %) compared with carriers of other genotypes. At the same time, in carriers of the G/G genotype of the Arg16Gly locus, low drug efficacy is observed more often in patients

with BA, compared with the group of children with RBO (72.3 vs. 56.5 %; $p < 0.001$). Among the patients with low drug efficacy were children with severe respiratory impairment in the Gln27Glu G/G ADRB2 gene variant, of which children with RBO (45.0 %) and BA (47.5 %). Thus, the identification of carriers of negative polymorphisms of the ADRB2 gene variants in children with BO will help to avoid ineffective treatment and will serve as the basis for prescribing alternative therapy.

A change in the functional activity of the β 2-adrenergic receptor is associated with polymorphism of the ADRB2 gene and is associated with a low therapeutic response to β 2-agonists. We carried out a comparative analysis of the clinical

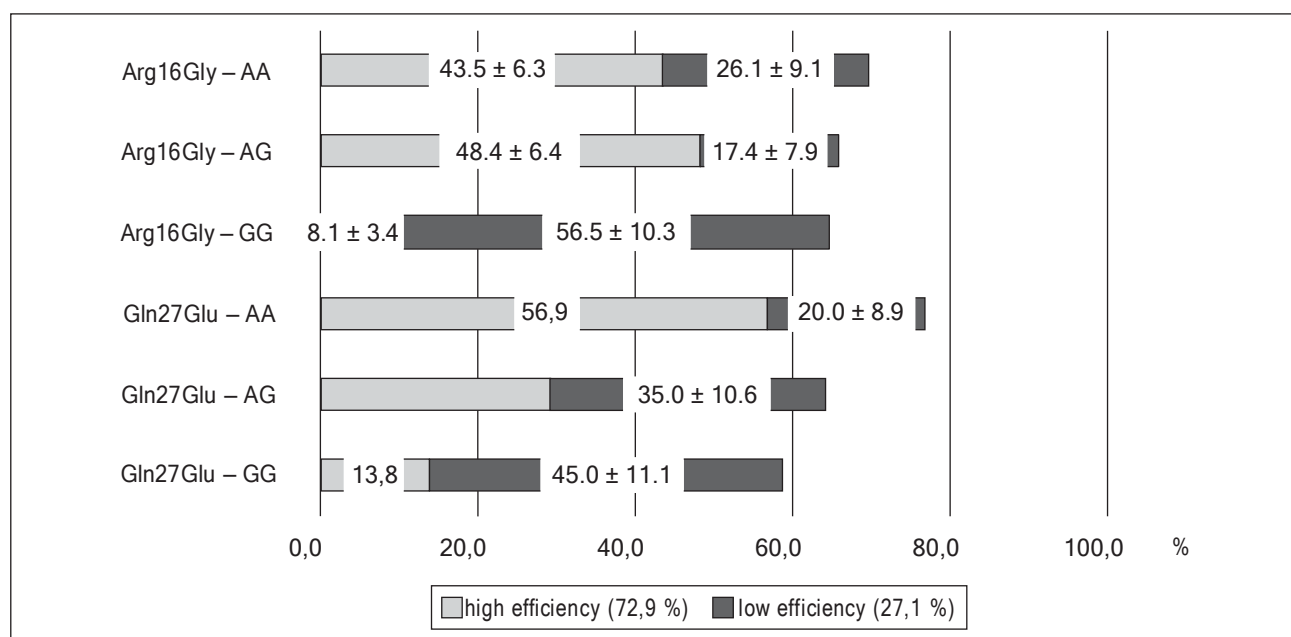


Figure 1. Polymorphism of Arg16Gly and Gln27Glu of the ADRB2 gene with a therapeutic response to β 2-agonists in children with RB

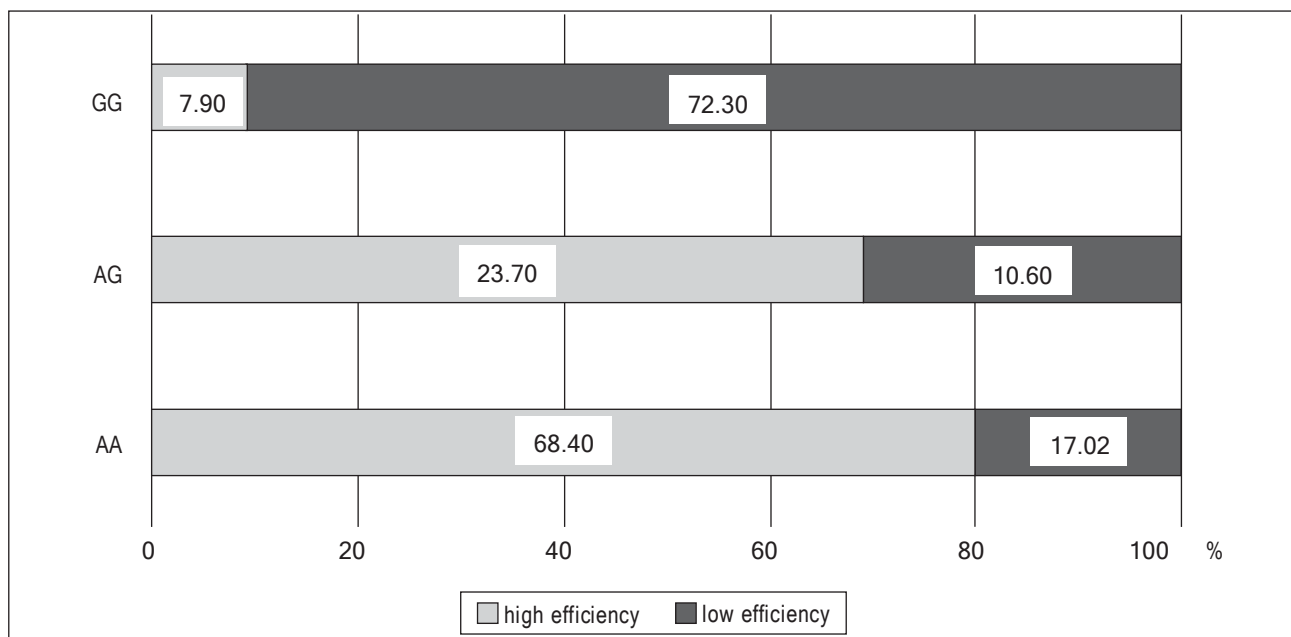


Figure 2. Arg16Gly polymorphism of the ADRB2 gene with a therapeutic response to β 2-agonists in children with BA

significance of ADRB2 gene loci polymorphism with therapeutic response to β 2-agonists in children with BA (Figure 2).

In carriers of the Arg16Gly locus of the ADRB2 gene, spirometry and a provocative test in the group of children with AD revealed the effectiveness of salbutamol in 47 (55.3 %) children, while in 38 (44.7 %) children, the effectiveness was low. Among children with high efficiency of salbutamol, representatives of the heterozygous genotype A/G (72.3 %) of the Arg16Gly locus of the ADRB2 gene were found in the greatest number, which is significantly lower compared to other genotypes A/A (17.0 %) and G/G (10.6 %) ($p < 0.05$).

The high reversibility of BO, therefore, the high efficiency of salbutamol in the group of BA patients was found in the largest number in carriers of the homozygous A/A genotype (68.4 %) of the Arg16Gly locus. The mutation genotype was found significantly less frequently in this group of children compared to representatives of other genotypes, in particular G/G (7.9 %) ($p < 0.05$). Therefore, in children with AD, carriers of the homozygous A/A genotype of the Arg16Gly locus of the ADRB2 gene have a high efficiency of therapy, and representatives of the G/G genotype (72.3 %) have a low efficiency of using salbutamol in therapy. A large number of scientific studies are devoted to the study of the rs1042713A>G polymorphic variant of the ADRB2 gene and its significance in the development of BA. For example, the results of studies in children of Russian ethnicity of the allele rs1042713 genotype G/G of the ADRB2 gene were associated with a low effect of therapy with short-acting β 2-agonists. Our data are consistent with the results of studies by scientists in whom the rs1042713*G/G allele genotype of the ADRB2 gene led to the development of a severe course of BA. In patients from USA ADRB2*rs1042713 allele of the A/A genotype was found to be associated with low respiratory function compared with patients who were carriers of the homozygous rs1042713*G allele of the ADRB2 gene.

Thus, the predictor role of the rs1042713 (Arg16Gly) polymorphic locus was determined in carriers of the unfavorable 46G allele of the G/G genotype of the ADRB2 gene, which was a genetic marker of children's predisposition to RBO and AD in children. Children with the G/G genotype of the Arg16Gly locus of the ADRB2 gene are at risk for severe RBO and AD in children. Children with RBO carriers (Arg16Gly) of the homozygous G/G genotype have a high frequency of relapses of RBO against the background of ARVI and are at risk of developing BA. Significant risk factors for the formation of RBO in children are: age from 3 to 6 years, male sex, frequent ARVI in history, early episode of primary BO, concomitant allergic pathology; anemia and ARVI in mothers in the antenatal period, birth asphyxia; early transition to artificial feeding; diseases of the ENT organs. Carriers of the Arg16Gly locus of the G/G mutation genotype in males and carriers of the Gln27Glu locus of the heterozygous A/G genotype in females are more likely to develop RBO.

Conclusions

Our studies have shown that in the group of children with RBO carriers of the Arg16Gly locus, high efficacy (72.9 %) of salbutamol was found in the greatest amount in carriers

of the A/G and A/A genotypes, while low efficacy (27.1 %) was found in carriers of the G/G genotype (56.5 %) of the ADRB2 gene. The same trend was noted among patients with AD, while low efficiency was noted more often among carriers of the Arg16Gly locus with G/G genotype. At the same time, SNP substitutions of A46G and C79G nucleotides affected the synthesis of partner proteins, and amino acid substitution in proteins was localized near binding to ligands and reduced the effectiveness of salbutamol to the corresponding mutant receptor.

Thus, the contradictory results of studies in different populations prove the relevance of studying the association of ADRB2 gene polymorphism in children of Uzbek ethnicity. Evaluation of the clinical significance of the ADRB2 gene polymorphism with a therapeutic response to β 2-agonists in children with recurrent bronchial obstruction should be carried out for personalization and alternative therapy.

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Karimdzhanov I.A., Zakirova U.I., Yusupova G.A., Karimova U.N.

Ташкентська медична академія, м. Ташкент, Республіка Узбекистан

Роль асоціації поліморфізму гена ADRB2 з терапевтичною відповіддю на β 2-агоністи в дітей із повторною бронхіальною обструкцією

Резюме. Актуальність. Вивчення впливу препаратів на молекулярно-генетичному рівні при рецидивуючому перебігу бронхіальної обструкції (РБО) у дітей покращило розуміння патогенезу захворювання та дало змогу краще охарактеризувати надійність використання в терапії. **Метою дослідження** була оцінка клінічної значущості поліморфізму локусів Arg16Gly гена ADRB2 з терапевтичною відповіддю на β 2-агоністи у дітей з РБО узбецької національності. **Матеріали та методи.** Обстежені 88 пацієнтів віком від 6 до 15 років із рецидивуючою бронхіальною обструкцією та бронхіальною астмою (БА) з поліморфізмом локусів гена ADRB2 та визначена ефективність сальбутамолу в цих групах пацієнтів. **Результати.** Результати дослідження значущості поліморфізму локусу Arg16Gly гена ADRB2 з терапевтичною відповіддю на β 2-агоністи у дітей з РБО показали високу

ефективність сальбутамолу у 72,9 % дітей, серед яких у найбільшій кількості виявлені генотипи представників A/G та A/A. При цьому низька ефективність сальбутамолу виявлена в найбільшій кількості у носіїв мутаційного генотипу G/G локусу Arg16Gly гена ADRB2. **Висновки.** Визначена предикторна роль поліморфного локусу rs1042713 (Arg16Gly) у носіїв несприятливої алелі 46G генотипу G/G гена ADRB2, який був генетичним маркером схильності дітей до РБО та БА. Діти з генотипом G/G локусу Arg16Gly гена ADRB2 знаходяться в групі ризику тяжких РБО та БА. Діти, які є носіями Arg16Gly гомозиготного генотипу G/G, мають високу частоту рецидивів РБО на фоні ГРВІ та мають ризик розвитку БА.

Ключові слова: бронхіт; обструкція; ген ADRB2; β 2-агоністи; діти

