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ABSTRACT

The aim of our work was to analyze the association of polymorphic loci rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu) of the β2-adrenoreceptor (ADRB2) gene in children of the Uzbek population with recurrent bronchial obstruction(RBO). The material for the study was patients with RBO of Uzbek ethnicity aged from 1 to 15 years. The comparison group included children with acute obstructive bronchitis(OOB), bronchial asthma (BA), and practically healthy children of the same age and population. In the molecular genetic study, a diagnostic kit was used to detect polymorphisms in human genes by polymerase chain reaction. In the molecular genetic study, a diagnostic kit was used to detect polymorphisms in human genes by polymerase chain reaction. The results of the obtained studies showed that children who possess polymorphic variants of Gln27Glu of the ADRB2 gene of the G/G mutational genotype are predisposed to the development of recurrent bronchial obstruction in children. Analysis of the prevalence of Gln27Glu polymorphic variants of the ADRB2 gene in patients with RBO showed that the owners of the G/G mutational genotype have a high risk of predisposition to the development of the disease.

Key words: children, bronchitis, polymorphism of the β2-adrenoreceptor gene (ADRß2), alleles Gln27Glu polymorphisms.

INTRODUCTION

Recurrent bronchitis occurring with bronchial obstruction syndrome (BOS) is considered by many scientists and practitioners as a transitional state of bronchial asthma (BA). In this regard, due to the heterogeneity of the BOS, an active search for clinical and genetic predictors of the disease, which allows predicting its further course of transition to a chronic form, is being conducted today. The greatest difficulties for practical pediatricians are the differential diagnosis between relapses of bronchitis with BOS and bronchial asthma (BA), since in most children the development of the disease is provoked by ARVI, which are the main factors of exacerbations of recurrent bronchitis (RB) in children. Therefore, the high incidence of wheezing in children, the phenotypic diversity of BA and the difficulty of analyzing lung function in the first 6 years of life determine late diagnosis and underdiagnosis of the disease, which often leads to incorrect diagnosis [1,2].

To date, recurrent bronchial obstruction (RBO) is considered by practical pediatricians as a diagnosis of BA exclusion in children. Recurrent bronchitis is considered as a multifactorial disease in which genetic and environmental factors of the external environment are involved. The disease is associated with recurrent inflammation of the mucous membrane of the bronchial tree, with a decrease in local defense factors and immunological defense of the body in response to infectious, allergic neurohumoral effects. The level of involvement of these two factors is currently controversial. Many scientists point to the genetic leading role among the factors that increase the risk of developing BA. Internal factors include heredity, in particular the body's gene pool and gender, and external infections, allergens and smoking [3,4].

Studies of the molecular genetic basis of bronchopulmonary diseases have made it possible to establish the important role of polymorphism of many genes, including the β2 adrenergic receptor gene (ADRB2), in the body's susceptibility to the development of the disease. The ADRB2 gene is localized on bronchial smooth muscle cells, neutrophils, eosinophils, and macrophages and plays an important role in bronchial contractility. The ADRB2 gene encodes a beta-2-adrenergic receptor, an ionic protein channel embedded in the cytoplasmic membrane of a cell. In the coding part of the ADRB2 gene located on chromosome 5q31, 9 polymorphisms were identified, 3 of which (Argl6Gly, Gln27Glu, Thrl64Ile) change the functional features of the receptor. The ADRB2 gene encodes a beta-2-adrenergic receptor, an ionic protein channel built into the cytoplasmic membrane of a cell that has a high affinity for adrenaline and provides an increase or decrease in the activity of an innervated tissue or organ. The region of DNA in the protein-coding region of the ADRB2 gene in which guanine (G) is replaced by adenine (A) is called the genetic marker G46A. If a guanine (G) is in this position, this gene variant is designated as the G allele, and if adenine (A), the A allele. As a result of this change in the amino acid sequence of the ADRB2 protein at position 16, arginine is replaced by glycine (Arg16Gly). Possible genotypes: G / G, G / A, A / A [5,6].

Many works of domestic and foreign scientists are devoted to the study of ADRB2 gene polymorphism and the risk of BA in children in various population groups. So, the author Guo X. (2016) conducted a study of the association and meta-analysis of 4 SNPs of the beta-2-adrenergic receptor gene (ADRB2) with the risk of asthma in children. A case-control study was performed to determine the contribution of rs1042713, rs1042714, rs1800888 and rs1042711 to asthma predisposition. In the current case-control study, no significant association was found between the rs1042713, rs1042714, rs1800888, and rs1042711 polymorphisms and asthma. The meta-analysis confirmed that there was no positive association of these SNPs with asthma in children in Asia, South America, Europe and the overall population. Conclusions: None of the four polymorphisms in ADRB2 gene were associated with a risk of asthma in a current. The results of a study in various populations of the relationship between ADRB2 gene polymorphism and the risk of bronchial asthma in different populations were contradictory and inconclusive.

The aims of this study were to analyse the potential correlations between the risk of developing recurrent wheezing and the presence of specific polymorphisms of some genes regulating immune system function, and to study the relative importance of the associations of different viruses and genetic polymorphisms in causing recurrent episodes. Results IL8-rs4073AT, VEGFA-rs833058CT, MBL2-rs1800450CT and IKBKB-rs3747811AT were associated with a significantly increased risk of developing wheezing ($p = 0.02$, $p = 0.03$, $p = 0.05$ and $p = 0.0018$), whereas CTLA4-rs3087243AG and NFKBIB-rs3136641TT were associated with a significantly reduced risk ($p = 0.05$

and p = 0.04). IL8-rs4073AT, VEGFA-rs2146323AA and NFKBIA-rs2233419AG were associated with a significantly increased risk of developing recurrent wheezing (p = 0.04, p = 0.04 and p = 0.03), whereas TLR3-rs3775291TC was associated with a significantly reduced risk (p = 0.03. This study shows a clear relationship between the risk of wheezing and polymorphisms of some genes involved in the immune response. Although further studies are needed to confirm the results, these findings may be useful for the early identification of children at the highest risk of developing recurrent episodes and possibly subsequent asthma. [7].

The aim of our work was to analyze the association of polymorphic loci rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu) of the β2-adrenergic receptor ADRB2 gene in children of the Uzbek population with recurrent bronchial obstruction.

The material for the study was 85 patients with recurrent obstructive bronchitis (RBO) of Uzbek ethnicity at the age from 1 to 15 years. The comparison group included children with AOB, BA and practically healthy children of the same age and population. In the molecular genetic study, a diagnostic kit was used to detect polymorphisms in human genes by the method of polymerase chain reaction (PCR) in real time on the equipment "Rotor Gene 6000 / Q" (Real-time CFX96 C1000 Touch), Bio-Rad. The object of the study was blood samples on filter paper.

The results of a molecular genetic study of the Arg16Gly nucleotide of the ADRB2 gene in children with RB occurring with SBO showed: a homozygous variant with the A/A genotype was found in 52.9 %, a heterozygous variant with the A/G genotype was found in 32.9% and 14.1% – the G\G genotype was detected, which corresponds to a gene mutation. Compared with the control group, the G\G mutational genotype was significantly more common in the group of children with RBO (14.1%) than in the control group (6.7%). This suggests that the mutational genotype G\G of the Arg16Gly nucleotide of the ADRB2 gene is a prognostic factor for the development of RBO in children (Figure 1).

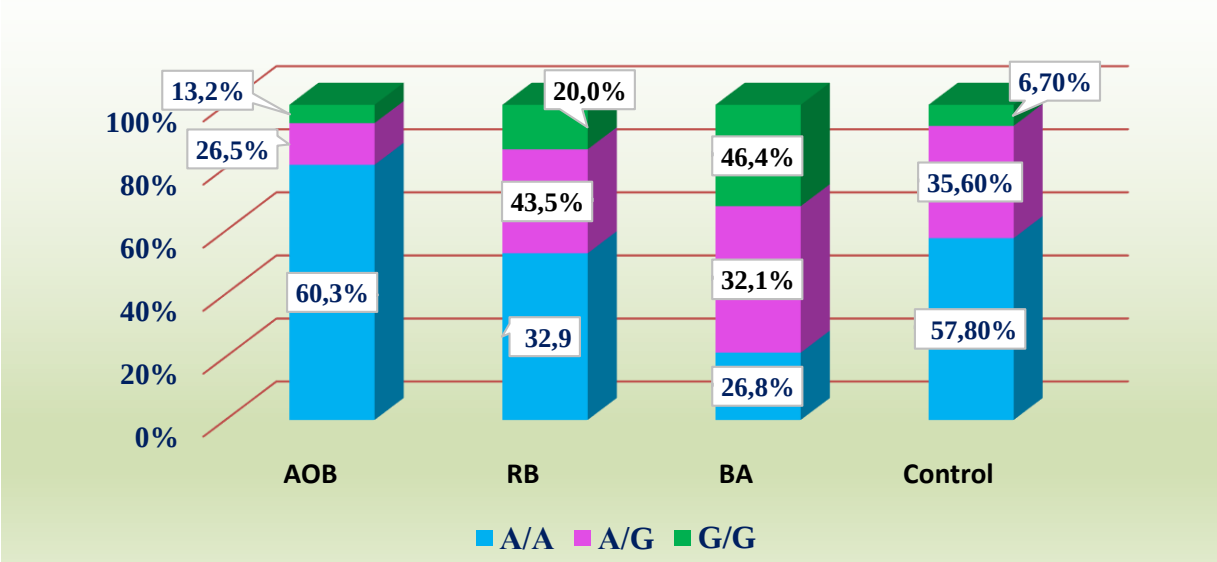

Figure 1. Aggregation of the Arg16Gly genotype of the ADRB2 gene in children with RBO

The results of a molecular genetic study of the Gln27Glu allele polymorphism of the β2-adrenergic receptor ADRB2 gene in children with recurrent bronchitis occurring with BOS showed an association of this gene with the disease. At the same time, the homozygous genotype (AA) of the Gln27Glu allele of the ADRB2 gene was observed significantly less frequently in children with RBO (28.2%) than in the group of

practically healthy children (51.1%) (p <0.001) (Figure 1). Carriers of the heterozygous genotype (AG) of the ADRB2 gene in children in the compared groups were observed almost the same. The mutational genotype (GG) of the Gln27Glu allele of the ADRB2 gene was found significantly more often in children with RBO (23.5%) than in the group of healthy children (6.6%) (p <0.05).

Earlier, we studied the polymorphism of the Arg16Gly nucleotide of the ADRB2 gene in children with RBO. It should be noted that the homozygous Gln27Glu variant with the A / A genotype was noted in 28.2% of cases, while in RB with the Arg16Gly nucleotide 52, 9% (p <0.05), the heterozygous variant with the A / G genotype was observed in 48, 2% and in group c with Arg16Gly RB -32.9% of cases. Gln27Glu with the G \ G genotype was detected in 23.5% of children with RB, whereas in the group of children with the Arg16Gly nucleotide, this genotype was observed in 14.1% of cases (p <0.05) (Table 4.3.1). The results of the studies showed that patients with RBO who are the owner of the Gln27Glu polymorphic variants of the ADRB2 gene of the G / G mutation genotype are predisposed to the development of the disease.

A comparative analysis of the associations of polymorphic loci rs1042714 (Gln27Glu) of the β2-adrenergic receptor ADRB2 gene in the group of children with AHD showed that the homozygous variant with the A /A genotype of the Arg16Gly nucleotide was found in the greatest amount (80.9%) than the A / A genotype of the Gln27Glu (47.0%) (Table 1). At the same time, the A / A genotype of the Gln27Glu nucleotide was observed less frequently in the group of children with RB (23.5% versus 47.0%; p <0.05) than in the group of children with AR. The heterozygous A / G genotype of the Gln27Glu nucleotide was observed in all the examined groups with almost the same frequency.

Table 1.

Aggregation of genotypes of Gln27Glu polymorphic variants of the ADRB2 gene in the examined children,%.

	Control (n=45)	**AOB (n=68)**	**RB (n=85)**	**BA (n=56)**
Gln27Glu	M±m	M±m	M±m	M±m
AA (гомозигота)	29 64,44±7,14	32 47,06±6,05	20 23,53±4,60*	9 16,07±4,91*
AG (гетерозигота)	12 26,67±6,59	24 35,29±5,80	43 50,59±5,42*	27 48,21±6,68*
GG (мутация)	4 8,89±4,24	12 17,65±4,62	22 25,88±4,75*	20 35,71±6,40*

N o t e : * p <0.001 - p <0.01 significant differences between the groups of AHB, RB; ** between RB and BA; *** between groups of OOB, RB, BA and control.

It should be noted that cases of the mutational gene G \ G of the nucleotide Gln27Glu were observed significantly more often than in the group of children with AHO (25.8% versus 8.8%; p <0.001). In the group of children with BA, the mutational G \ G gene of the Gln27Glu nucleotide was observed significantly more often than the homozygous A / A genotype (35.7% versus 17.6%; p <0.001). At the same time, the mutation gene G \ G of the Gln27Glu nucleotide was noted less frequently in the group of children with RB than in the group of children with AD (25.8% versus 35.7%).

A comparative analysis of the associations of polymorphic loci rs1042713 (Arg16Gly) of the ADRB2 gene showed that the homozygous variant with the A/A

genotype was found in the greatest number (80.9%) in children with OOB. The homozygous phenotype of the Arg16Gly A / A nucleotide of the ADRB2 gene was significantly more frequent in the group of children with RBO than in the group of children with BA (52.9% vs. 21.4%; p< 0.05). In the group of children with AD, the mutational genotype (G\G) is significantly more frequent than in the group of children with OOB and RBO and practically healthy children(p<0.05) (Figure 1).Thus, children with RBO who are the owner of the mutational genotype GG of the Arg16Gly nucleotide of the ADRB2 gene are candidates for predisposition to the development of BA.

The results of the studies showed that children who are the owner of the Gln27Glu polymorphic variants of the ADRB2 gene of the G / G mutation genotype are predisposed to the development of recurrent bronchial obstruction in children. Analysis of the prevalence of the Gln27Glu polymorphic variants of the ADRB2 gene in patients with RBO showed that those with the G / G mutational genotype have a high risk of predisposition to the development of the disease. A comparative study of the aggregation of Gln27Glu variants of the ADRB2 gene in the examined groups confirmed that children with the Gln27Glu G \ G mutational gene are at risk of AD morbidity.

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