American Journal of Medicine and Medical Sciences 2022, 12(6): 668-672
DOI: 10.5923/j.ajmms.20221206.12

The Importance of Polymorphic Variants of the B2-Adrenoreceptor Gene in the Formation of Bronchopulmonary Diseases in Children

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Abstract The association of polymorphism of rs1042714 (Gln27Glu) loci of the ADRB2 gene in children with bronchopulmonary pathology was analyzed. A molecular genetic study was conducted in children with bronchopulmonary pathology (BPP) aged 1 to 15 years of Uzbek ethnicity, which included patients with acute obstructive bronchitis (AOB), recurrent bronchial obstruction (RBO) and bronchial asthma (BA). The predictor role of the polymorphic locus rs1042714 (Gln27Glu) of the 79G allele of the A/G and G/G genotypes of the ADRB2 gene was established, which were a genetic marker of the morbidity of children with RBD and a factor in the formation of BA in children. Children with amino acid substitution C/G and genotype G/G of the Gln27Glu locus of the ADRB2 gene are at risk with severe RBO in children. The allele with the Gly16/Glu27 locus polymorphism of the ADRB2 gene in carriers of the homozygous A/A genotype provided protection against the development of BA and were associated with a milder course of RBO and BA in children.

Keywords Children, Acute obstructive bronchitis, Recurrent bronchial obstruction, Bronchial asthma, Gly16/Glu27 locus polymorphism

1. Introduction

To date, timely clinical and genetic diagnosis and prognosis of bronchial asthma (BA) in children with recurrent bronchial obstruction (RBO) makes it possible to avoid burdensome, unnecessary diagnostic and expensive therapeutic measures and to interest parents in the recovery process. Undertreatment, the presence of an incomplete rehabilitation stage in the process of remission of the disease is one of the reasons for the transformation of acute forms of bronchitis into a recurrent course and chronic pathology. Therefore, identification of candidate genes in the development of RBO and BA for early diagnosis, personalization of therapy and timely preventive measures is relevant and timely [1,2]. The prevalence of RBD among the child population is a modern problem of a social and economic nature, and belongs to one of the most frequent pathologies, especially in children, and account for 50 to 70% of all inflammatory diseases of the bronchi. According to many authors, the high frequency of RBO and the ineffectiveness of the treatment is associated with the prevalence and changes in the evolution of bacterial and viral infections, an increase in immunodeficiency in children, environmental problems [3,4,5,6].

Currently, a number of studies are being conducted worldwide aimed at identifying clinical and genetic aspects and improving the effectiveness of diagnosis and treatment of chronic respiratory and atopic diseases in children. In this regard, it is necessary to establish the association of gene polymorphisms with the peculiarities of the course of bronchial asthma and recurrent bronchitis, to determine the presence of hereditary predisposition in children, to determine genetic markers in the diagnosis of the disease; to identify candidate genes causing recurrent bronchial obstruction.

The obtained research results of many scientists are mainly devoted to BA and are contradictory: in some works, the significance of the influence of polymorphic alleles of the ADRB2 gene in the pathogenesis of BA, as well as in the formation of patients' response to therapy with β2-agonists has been determined, and in other works it has been shown that these polymorphic variants of the ADRB2 gene are not associated with BA. In foreign and domestic literature, great importance is attached to the role of polymorphic variants rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu) of the β2-adrenoreceptor ADRB2 gene in the pathogenesis of asthma, bronchopulmonary dysplasia and chronic obstructive pulmonary disease (COPD). There are no studies

Received: May 25, 2022; Accepted: Jun. 12, 2022; Published: Jun. 18, 2022
Published online at http://journal.sapub.org/ajmms

studying the association of polymorphic variants Arg16Gly and Gln27Glu of the ADRB2 gene in recurrent bronchial obstruction in children. The authors Ponomareva M. S., Furman E. G., Khuzina A.M. (2015) in children with BA from Perm found that the mutation in the ADRB2 gene in children with BA occurs 2 times more often in the Arg16Gly polymorphism and 3 times in Gln27Glu, compared with practically healthy children.

Abroad, a large number of scientific papers are devoted to the analysis of the polymorphic variant rs1042713 A>G of the ADRB2 gene and its influence on the development of BA and the effectiveness of therapy with β2-agonists (Figueiredo R. G., Costa R. S. va boskalar, 2021, California) [8]. Bleeker Yu., Dirkier S. (2012) studied the polymorphism of the ADRB2 gene for long-term therapy with β2-agonists in combination with inhaled glucocorticosteroids. At the same time, it was noted that the polymorphic variant of the rs1042714 allele of the G/G genotype is not associated with a response to therapy with β2-agonists in patients with BA [7]. In individuals from the USA of European origin, there was no association of the polymorphic variant rs1042713Gln27Glu A/G of the ADRB2 gene with the frequency of exacerbations and indicators of respiratory function (E. Israel et al., 2010). Scientists from the Assiut Medical University of Egypt found that carriers of the allele of the heterozygous Arg16Gly group were good responders to therapy with β2-agonists, and carriers of the G/G mutational genotype were bad responders (Heba S. E. and others, 2018). Scientists Srinivas B., Joti A. and others (2015) analyzed a variant of the ADRB2 gene (Arg16Gly) with a pharmacogenetic response and severity of the disease in asthmatics of South India. It was found that the polymorphism Arg16Gly G is greater than A-Gly16Arg in the gene encoding ADRB2, which was associated with receptor insensitivity after exposure to β2-agonist.

The purpose. Analyze the association of polymorphism of the rs1042714 (Gln27Glu) loci of the ADRB2 gene in children with bronchopulmonary pathology of Uzbek ethnicity.

2. Materials and Methods

A molecular genetic study was conducted in 89 children with bronchopulmonary pathology (BLP) aged 1 to 15 years of Uzbek ethnicity, which included patients with acute obstructive bronchitis AOB (n=25), recurrent bronchial obstruction RBO (n=22) and bronchial asthma BA (n=42). The control group included 72 children of the same age and population. Polymorphism of variants of the β2-adrenergic receptor (ADRB2) gene of rs1042714 (Gln27Glu) loci was determined by real-time PCR using a set of reagents "SNP-express-SHOT" on modern equipment "Rotor Gene 6000/Q" (Real-time CFX96 C1000 Touch) Bio-Rad (Germany). Diagnoses were made on the basis of clinical and anamnestic data, laboratory and instrumental research methods, including spirography with a provocative test. The study was conducted using general clinical, molecular genetics, functional and statistical research methods.

3. Result

Studies have shown that among children with RBO, the largest percentage were patients aged 3 to 6 years (35.3±3.7%), while in the group with AOB-children from 1 to 3 years (54.2±4.8%) and BA - from 10 to 15 years (55.2±5.7%). At the age of 1 to 3 years, the largest number belonged to carriers Arg16Gly (A/A)-45.5% and Gln27Glu (A/G)-50.0%, whereas in the older age group carriers Arg16Gly (A/A) and Gln27Glu (G/G) in children with RBO. Among children with RB, male patients were significantly more frequent (64.0%) than female patients (35.4%) ($p<0.05$). The G/G mutational genotype according to the Arg16Gly polymorphism was more often observed in the boys' group compared to the girls' group (27.5% vs. 17.6%; $p<0.001$). The heterozygous genotype of the Gln27Glu (A/G) locus was significantly less frequent in the boys' group compared to the girls' group (43.1% vs. 61.8%; $p<0.001$). Thus, male children carriers of Arg16Gly (G/G) and the Gln27Glu (A/A) ADRB2 locus were more predisposed to RBO.

We investigated the frequency of distribution of alleles and genotypes of Gln27Glu polymorphism in the ADRB2 gene in the main group of patients and controls. The frequency of the Gln(C) allele was dominant compared to the prevalence of Glu (G) (61.8% vs. 38.2%; $p<0.01$). Among the Gln27Glu genotypes in the ADRB2 gene, the largest number belongs to the carrier of the heterozygous A/G genotype (51.7%), while the mutated G/G genotype was found much less frequently (12.4%) ($p<0.05$) (table 1).

Table 1. Frequency of distribution of alleles and genotypes of Gln27Glu polymorphism in the ADRB2 gene in patient and control groups

N	Group	Frequency of alleles				Frequency of genotype distribution					
		C		G		A/A		A/G		G/G	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n=89)	110	61,8	68	38,2**	32	36,0	46	51,7	11	12,4**
2	AOB (n=25)	32	64,0	18	36,0	11	44,0	10	40,0	4	16,0**
3	BA (n = 42)	51	60,7	33	39,3	14	33,3	23	54,8	5	11,9**
4	RBO (n =22)	27	61,4	17	38,6	7	31,8	13	59,1	2	9,09**
5	Control group (n=72)	117	81,3*	27	18,8*	48	66,7*	21	29,2*	3	4,17*

Note: * - a significant difference compared to the control group, ** - a significant difference in the frequencies of alleles and genotypes within the group of patients

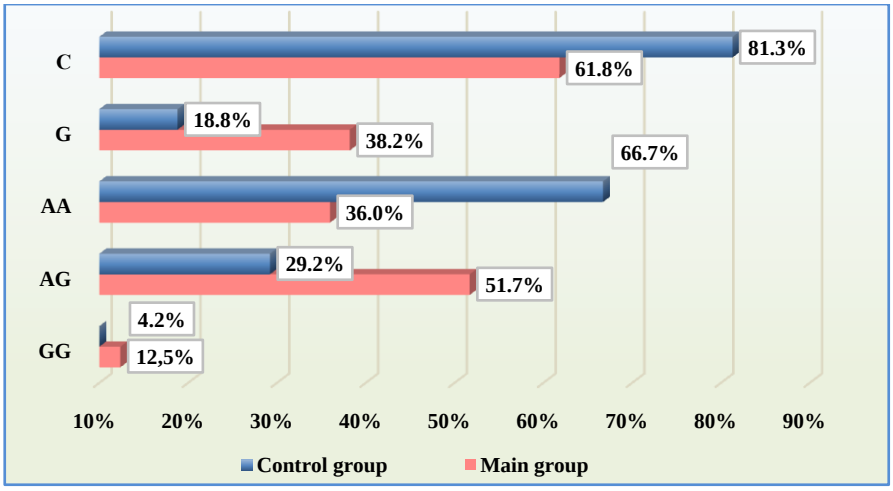

Figure 1. Differences in the frequency of allelic and genotypic variants of Gln27Glu polymorphism in the ADRB2 gene of the main group of examined patients

At the same time, the frequency of the A/A genotype of the Gln27Glu locus was 2 times higher in the control group compared to the main group of patients (66.7% vs. 36.0%, respectively $\chi2$=15.02; P=0.01; OR=0.28; 95% CI=0.148-0.534) (Fig. 1). Among the genotypes of the locus The largest number of Gln27Glu belongs to the carrier of the heterozygous A/G genotype (51.7%), while the mutated G/G genotype was found much less frequently (12.4%). At the same time, the mutated genotype G/G of the Gln27Glu locus of the ADRB2 gene was observed significantly more often in the main group of patients than in healthy ones (12.4% vs. 4.2%, respectively $\chi2$=3.4; P=0.07; RR =2.97; OR=3.24; 95% CI=0.92-11.4). It follows that carriers of the mutational genotype G/G of the Gln27Glu polymorphism in the ADRB2 gene are predictors of the development of the disease.

A comparative analysis of the frequency of genotype distribution between groups showed a significantly high frequency of representatives of the G/G genotype of the Gln27Glu locus in the group of patients with RBO compared with the control (16.0 vs. 4.2%, respectively $\chi2$=3.9; P=0.05; RR=3.8; OR=4.4; 95% CI=1.01-19.05).

At the same time, the same trend was observed with respect to the heterozygous A/G genotype (40.0% vs. 29.2%; $\chi2$=1.0; P=0.32; RR=1.4; OR=1.6; 95%CI=0.63-4.16). At the same time, the opposite trend is observed with respect to the homozygous A/A genotype (44.0% vs. 66.7% of the control group, respectively, $\chi2$=4.0; P=0.05; OR=0.4; 95% CI=0.16-0.98). It follows that children with Gln27Glu polymorphism in the ADRB2 gene with the dominant Gln(C) allele and carriers of the A/G and G/G genotypes are candidates for the development of RBO.

A comparative analysis of the frequency distribution of allelic and genotypic variants of Gln27Glu polymorphism in the ADRB2 gene in groups of patients with BA and control showed a high frequency of the Gln(C) allele (60.7%) compared with the Glu(G) allele (39.3%) of the Gln27Glu locus in the ADRB2 gene. Gln(C) alleles (60.7%) in patients with BA were significantly less frequent compared with the control group (60.7% vs. 81.3%), whereas in the case of the Glu(G) allele, the opposite trend was observed (39.3% vs. 18.8%, respectively $\chi2$=11.5; P=0.05; OR=2.8; 95% CI=1.54-5.08). In relation to mutational genotypes of the G/G locus, Gln27Glu was detected 2 times more often in the group of children with AD than in the control group (11.9% vs. 4.2%, $\chi2$=2.4; P=0.13; RR=2.9; OR=3.0; 95% CI=0.75-12.91).

At the same time, the A/G genotypes of the Gln27Glu locus were also significantly more frequent than in the control group (54.8% vs. 29.2%; $\chi2$=7.3; P=0.01; RR=1.8; OR=2.9; 95% CI=1.35-6.42).

Figure 2 presents a comparative analysis of the frequency of allelic and genotypic variants of Gln27Glu polymorphism in the ADRB2 gene in children with OB and control. In the group of children with AOB, the Glu(G) allele of the Gln27Glu locus was significantly more frequent compared to the control group (38.6% vs. 18.8; $\chi2$=7.4; P=0.01; RR=1.3; OR=2.7; 95% CI=0.08-0.62). In children with AOB, homozygous genotype A/A was observed less frequently than in the control group (66.7 vs. 31.8%; $\chi2$=8.4; P=0.01; OR=0.23; 95% CI=0.08-0.62). At the same time, the heterozygous A/G genotype was detected significantly more often than in the control group (59.1% vs. 29.2%; $\chi2$=6.5; P=0.01; RR=2.0; OR=3.5; 95%CI=1.34-9.18). The mutational genotype G/G of the Gln27Glu locus in the ADRB2 gene in children with OB as well as in groups of children with RB and BA was significantly higher compared to healthy children (9.1% vs. 4.2%; $\chi2$=0.8; P=0.39; RR=2.2; OR=2.3; 95%CI= 0.37-14.09).

Differences in the frequency of allelic and genotypic variants of Gln27Glu polymorphism in the ADRB2 gene among children with RB and BA showed some differences between the groups. Thus, the A/G genotype was observed more often in the group of children with BA, compared with the group of children with RBD (54.8% vs. 40.0%; $\chi2$=1.37; RR=0.73; P=0.25; OR=1.9; 95% CI=0.20-1.49). At the same time, the reverse trend was observed with respect to the homozygous genotype A/A (44.0% vs. 33.3%; $\chi2$=0.76; RR=1.32; P=0.4; OR=1.6; 95% CI=0.57-4.33).

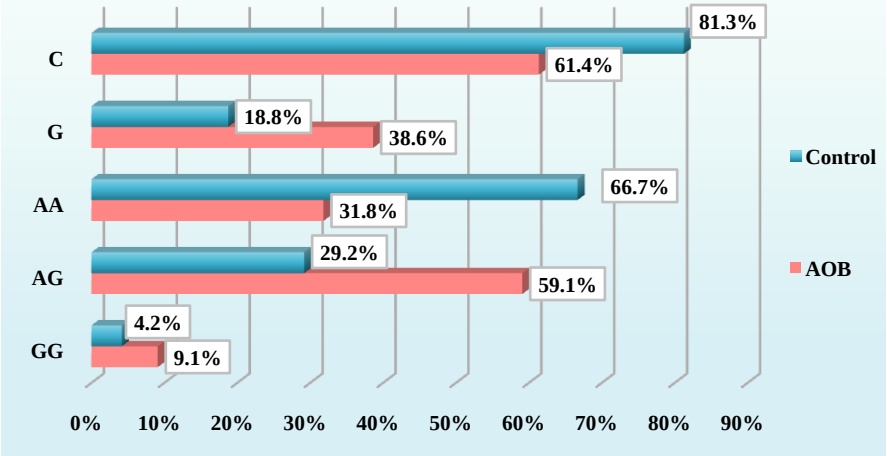

Figure 2. Comparative analysis of the frequency of allelic and genotypic variants of Gln27Glu polymorphism in the ADRB2 gene in children with AOB and control

In children with AOB, the mutational genotype G/G of the Gln27Glu locus was observed less frequently compared to the group of children with RBO (16.0% vs. 9.1%; $\chi 2$=0.5; RR=1.8; P=0.49; OR=1.9; 95% CI=0.32-11.32). In the main group, there was a correspondence between the expected and observed frequencies of the distribution of genotypes of the Arg16Gly locus in the ADRB2 gene according to the Hardy-Weinberg equilibrium law. In the combined group of patients of the main group, the observed and expected frequencies of A/A, A/G and G/G genotypes of the Arg16Glu locus and were 0.36/0.38, 0.5/0.47 and 0.14/0.15, respectively. In the control group, the frequency of these genotypes remained - 0.6/0.58, 0.33/0.36 and 0.07/0.06. In the case of the Gln27Glu variant in the ADRB2 gene, the observed and expected frequencies of A/A, A/G and G/G genotypes were 0.36/0.38, 0.52/0.47 and 0.12/0.15, which indicates their correspondence.

Thus, the Gln27Glu polymorphism of the ADRB2 gene in children with RBO showed that Gln(C) served as the dominant allele, with the genotype A/G (40.0% vs. 29.2%, respectively $\chi 2$=1.0; P=0.32; OR=1.62; 95% CI=0.63-4.159) and genotype G/G (16.0% vs. 4.2%, respectively $\chi 2$=3.8; P=0.05; OR=4.4; 95% CI=1.01 - 19.05) were found in greater quantities compared to the control group. It follows that children with a variant of the polymorphism of the Gln27Glu locus in the ADRB2 gene with cytosine replacement by guanine C79G and carriers of the A/G and G/G genotypes are candidates for the development of RBO and are at relative risk of BA formation.

4. Discussion

The results of our research have shown that human β2-adrenoreceptors, which play an important role in bronchial dilatation, belong to the pathogenetic causes of bronchial diseases. We have identified differences in the distribution of variants of the polymorphism of the ADRB2 gene, while our data are consistent with the results of some studies of children of the Russian population. When analyzing the association of polymorphism of rs1042714 (Gln27Glu) loci of the ADRB2 gene of the examined groups of children, it was found that the frequency of the Gln(C) allele dominates compared to the prevalence of Glu(G). Among the Gln27Glu genotypes in the ADRB2 gene, the largest number belongs to the carrier of the heterozygous A/G genotype (51.7%), while the mutated G/G genotype was found much less frequently (12.4%). At the same time, the frequency of the A/A genotype was 2 times higher in the control group compared with the main group of patients (66.7% vs. 36.0%, respectively, $\chi 2$=15.02; P=0.01; OR=0.28; 95% CI=0.148-0.534). The reverse trend is observed with respect to the heterozygous genotype A/G and G/G in relation to the control group. At the same time, the mutated genotype G/G of the Gln27Glu polymorphism in the ADRB2 gene was significantly more frequent than in the control group (12.4% vs. 4.2%, respectively $\chi 2$=3.4; P=0.05; OR=3.24; 95% CI=0.92-11.4). The heterozygous A/G genotype was also detected significantly more often compared to the control group (51.7% vs. 29.2%, respectively $\chi 2$=8.3; P=0.01; OR=2.6; 95% CI= 1.35 - 4.97). Verification of the Hardy-Weinberg ratio for the polymorphic marker Gln27Glu of the ADRB2 gene showed genetic equilibrium in the population.

Analysis of the distribution of polymorphisms of the ADRB2 gene depending on the severity of the course of RBO in children showed in severe cases the majority of carriers of Gln27Glu genotype A /G, compared with genotype A /A (51.06±7.3% vs. 14.89±5.2%) ($p<0.05$). This suggests that carriers of the G/G mutational genotype of both loci and representatives of Gln27Glu with the A/G genotype are at risk with severe RBD. Many authors explain that polymorphic variants of ADRB2 are associated with a violation of the regulatory signal in b-adrenoreceptors, which leads to a severe course of RBO and BA [2,7]. It is possible that in patients with RBO, the carriage of allelic variants of Gln27Glu of the ADRB2 gene is associated with varying degrees of insufficiency of the b-adrenergic system, therefore, it can lead to different course of RBO and BA in children.

5. Conclusions

The predictor role of the polymorphic locus rs1042714 (Gln27Glu) of the 79G allele of the A/G and G/G genotypes of the ADRB2 gene was established, which were a genetic marker of the morbidity of children with RBD and a factor in the formation of BA in children. Children with amino acid substitution C/G and genotype G/G of the Gln27Glu locus of the ADRB2 gene are at risk with severe RBO in children. The allele with the Gly16/Glu27 locus polymorphism of the ADRB2 gene in carriers of the homozygous A/A genotype provided protection against the development of BA and were associated with a milder course of RBO and BA in children. The practical significance of the study is the early detection of children with RBD with a high risk of BA formation by determining the alleles of the ADRB2 gene in the blood.

REFERENCES

[1] Baranov S., Baranova E.V. Human genome, epigenetics of multifactorial diseases and personalized medicine. // Interdisciplinary scientific and applied journal "Biosphere. - 2012. - Vol. 4. No. 1. - pp. 76-85.

[2] Voropaev E.V., Ruzanov D.Yu., Osipkina O.V. et all. Association of polymorphism of the MDR1, ADRB2 and IL-13 genes with the development of resistant bronchial asthma. // Health and environmental issues. -2018. -No.2 -p. 50.

[3] Dmitrievna S.N., Dzhumagaziev A.A., Bezrukova D.A. Recurrent bronchitis in children: the state of the problem. // Astrakhan Medical Journal. 2014. - p. 29-37.

[4] Zakirova U.I. Forecasting the risk of developing bronchial asthma in children of the Uzbek population. // Problems of biology and medicine. / Samarkand – 2021. -No.1. -pp. 104-107.

[5] Yusupova G.A., Karimdzhanov I.A. Recurrent bronchitis in children: pathogenetic aspects, features of the course and treatment. // Monograph. -Tashkent. -2020. Pp. 82-86.

[6] Yusupova G.A., Zakirova U.I. Kinesohydrotherapy in the activities of a family doctor for the prevention of bronchopulmonary diseases. // Problems of biology and medicine. - Samarkand – 2021. -№6 (131). - Pp. 45-49.

[7] Bleeker Yu., Dirkye Yu. et al. Ecological epigenetic study of ADRB2 5'-UTR methylation and severity of childhood asthma. A. Fu [et al.] // Clinical and experimental allergy: Journal of the British Society of Allergy and Clinical Immunology. 2012. - Vol.42. - pp. 1575-1581.

[8] Figueiredo R.G. Genetic determinants of poor response to treatment in severe asthma // Int J Mol Sci. – 2021 -No. 22 (8). p. 4251.