Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The Role of the ADRB2 rs1042713 Polymorphism in Bronchial Asthma Susceptibility and Its Pharmacogenetic Implications

Ilmira Razikova Sadullayevna

razikovailmiratma@mail.ru

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology UZ

Nargiza Pulatovna Aydarova

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology UZ

Gulmira Rustamovna Razikova

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology UZ

Mexriniso Pardayevna Nosirova

Tashkent State Medical University

Research Article

Keywords: bronchial asthma, ADRB2, rs1042713, Arg16Gly, polymorphism, Hardy-Weinberg equilibrium, odds ratio, pharmacogenetics

Posted Date: November 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11422755/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Introduction. Bronchial asthma (BA) is a multifactorial pathology of the respiratory system, in the development of which the variability of genes regulating the tone of the bronchial smooth muscles plays an important role. One key candidate is the β2-adrenoreceptor gene (ADRB2).

Purpose of the study. To study the distribution features of genotypes and alleles of the rs1042713 (Arg16Gly) polymorphism of the ADRB2 gene in BA patients and control group individuals, as well as to evaluate their association with the risk of disease development.

Materials and methods. 100 BA patients and 100 conditionally healthy individuals (control) were examined. Genotyping of the rs1042713 locus was performed using the PCR method. The compliance of genotype distribution with the HWE equilibrium was evaluated. Statistical analysis included calculations of the χ2 criterion, Fisher's exact criterion, odds ratio (OR), and 95% confidence interval (CI).

Results. The frequency of the Arg/Arg genotype in BA patients was 79.0%, which is significantly higher than in the control group (39.0%) (χ2 = 33.24; p = 6.04 × 10 − 8; (pFisher = 1.79 times 10 − 8). The frequency of the Gly allele in the BA group was significantly lower compared to the control (14.0% vs. 39.0%; χ2 = 30.82; p = 2.83 × 10 − 8). For the Gly allele, OR = 0.255 (95% CI: 0.156–0.416) was calculated. In the patient group, a pronounced deviation from HWE was identified (χ2 = 17.52; p = 2.84 × 10 − 5), while in the control group, the equilibrium was maintained (χ2 = 0.57; p = 0.452).

Conclusion. The homozygous Arg/Arg genotype is associated with a high risk of BA development, which is due to functional changes in β2-adrenoreceptors and their accelerated desensitization. The Gly allele performs a strong protective function. Disruption of HWE in patients indicates a pronounced selective pressure of the disease on genotypic distribution in the population. The obtained results are of great importance for developing systems for the pharmacogenetic prediction of β-agonist efficacy.

Introduction

Bronchial asthma (BA) is a chronic inflammatory disease of the respiratory tract characterized by variable bronchial obstruction and hyperreactivity. In the formation of bronchial asthma, the genetic landscape of the individual is of critical importance, which determines the nature of the immunological and tissue response of the lungs to external triggers.

Among the large number of BA candidate genes, the ADRB2 gene, which encodes the β2-adrenergic receptor, holds a special place. This receptor is expressed in the smooth muscle cells of the respiratory tract and mediates bronchodilation in response to endogenous catecholamines and therapeutic beta-agonists. The single nucleotide polymorphism rs1042713, resulting in the replacement of the amino acid arginine with glycine in position 16 of the polypeptide chain (Arg16Gly), fundamentally alters the regulatory properties of the receptor.

The Arg16 variant is prone to faster desensitization and a decrease in receptor density on the membrane under the influence of ligands, which leads to a weakening of the bronchodilator effect and an increase in bronchial hyperreactivity. In this regard, studying the distribution structure of alleles and genotypes of this locus is of fundamental clinical and pharmacogenetic interest.

The aim of the study is to conduct a molecular-genetic and biostatistical analysis of the association between the rs1042713 (Arg16Gly) polymorphism of the ADRB2 gene and bronchial asthma in the studied population.

Materials and Methods

The clinical and genetic study was conducted on a sample of 200 people divided into two groups:

1. Patient group: 100 patients with a verified diagnosis of BA.
2. Control group: 100 conditionally healthy volunteers without respiratory pathologies.

Genomic DNA extraction was carried out from peripheral blood leukocytes. The determination of allelic variants of the rs1042713 polymorphism of the ADRB2 gene was conducted using the polymerase chain reaction (PCR) method.

Statistical analysis was performed by calculating four-field conjugate tables. The significance of differences was assessed using Pearson's chi-square ($\chi 2$) criterion and Fisher's exact test. Analysis of the compliance of genotype frequencies with the Hardy-Weinberg law (HWE) was conducted separately for each group. The relative risk of the disease was calculated using the odds ratio (OR) indicator with a 95% confidence interval (CI). Critical significance level was recognized ($p < 0.05$).

Results

Analysis of genotypic distribution

When studying the Arg16Gly polymorphism of the ADRB2 gene between the BA patient groups and the control group, deep statistically significant differences were found (Table 1).

Table 1
Distribution of ADRB2 gene rs1042713 polymorphism genotypes in the study groups

Group	n	Arg/Arg, n (%)	Arg/Gly, n (%)	Gly/Gly, n (%)	Sum of hetero- and mutant genotypes (Arg/Gly + Gly/Gly), n (%)
Patients	100	79 (79.0%)	14 (14.0%)	7 (7.0%)	21 (21.0%)
Control	100	39 (39.0%)	44 (44.0%)	17 (17.0%)	61 (61.0%)
Frequency difference	-	+ 40.0%	-30.0%	-10.0%	-40.0%

In BA patients, a colossal dominance of the homozygous Arg/Arg genotype was recorded, reaching a frequency of 79.0%, which is 40.0% higher than the control (39.0%). Conversely, healthy individuals were characterized by a high frequency of Arg/Gly heterozygotes (44.0% versus 14.0% in patients). The total proportion of Gly allele carriers (Arg/Gly + Gly/Gly) in healthy individuals was 61.0%, exceeding the similar pool in patients by 2.9 times. Assessment of the correlation tables confirmed the high reliability of intergroup differences: ($\chi 2 = 33.24$); ($p = 6.04$ times $10 - 8$); (pFisher = 1.79 times $10 - 8$) ($p < 0.05$).

Allele analysis and risk assessment

Frequency analysis of alleles showed a similar pattern of polarization (Table 2).

Table 2
Allele frequencies of the rs1042713 polymorphism of the ADRB2 gene

Group	Total alleles	Allele Arg, n (%)	Gly allele, n (%)	Gly Allele Difference
Patients	200	172 (86,0%)	28 (14,0%)	-25,0%
Control	200	122 (61,0%)	78 (39,0%)	-

The frequency of the risk allele Arg in patients was 86.0% (pArg = 0.86), decreasing to 61.0% (pArg = 0.61) in the control group. Accordingly, the protective Gly allele in healthy individuals was found almost 3 times more frequently than in patients (39.0% vs. 14.0%; the difference was 25.0%). Mathematical analysis revealed a strong statistical relationship between the distribution of alleles and pathology: ($\chi 2 = 30.82$); ($p = 2.83$ times $10 - 8$). The calculation of the odds ratio demonstrated a pronounced protective effect of the Gly allele: **OR = 0.255** with a narrow and statistically significant **95% CI = 0.156–0.416** confidence interval.

Hardy-Weinberg equilibrium test

An important result of the study was the discovery of genetic imbalance in individuals with bronchial asthma (Table 3).

Table 3
Results of the Hardy-Weinberg equilibrium analysis (HWE)

Group	Observed genotypes (Arg/Arg / Arg/Gly / Gly/Gly)	Expected genotypes (Arg/Arg / Arg/Gly / Gly/Gly)	(χ^2)	p-value	HWE Eligibility
Patients	79 / 14 / 7	73,96 / 24,08 / 1,96	17,52	0,000	**No!**
Control	39 / 44 / 17	37,21 / 47,58 / 15,21	0,57	0,452	**Yes.**

In the control group, the distribution of observed genotypes almost fully coincided with theoretically expected ($\chi 2 = 0.57$); ($p = 0.452$), indicating the representativeness of the sample and the absence of random genetic shifts. However, in the BA patient group, a catastrophic deviation from the Hardy-Weinberg equilibrium was identified: ($\chi 2 = 17.52$); ($p = 2.84$ times $10 - 5$) ($p < 0.001$).

A sharp deficit of heterozygotes (14 against the expected 24.08) and an excess of homozygotes for both alleles is observed, which directly reflects the influence of the disease factor (genotype selection).

Table 4
Summary statistics of rs1042713 polymorphism analysis

Analysis type	(χ^2)	p (χ^2)	p (Fisher)	OR (Gly)	95% CI	Association
Genotypic	33,24	0,000	0,000	-	-	Yes.
Allele	30,82	0,000	0,000	0,255	0,156 -0,416	Yes.

Discussion

The identified critical accumulation of the homozygous Arg/Arg genotype (79.0% versus 39.0% in the control) at a high level of significance ($\chi 2 = 33.24$); ($p = 0.001$) clearly proves the key pathogenetic role of this locus in the destabilization of respiratory tract tone.

From a biological perspective, this is explained by the phenomenon of ligand-induced desensitization. β2-adrenoreceptors carrying arginine (Arg16) in position 16 undergo accelerated endocytosis and intracellular proteolysis upon binding with agonists. In conditions of constant contact between respiratory epithelium and pollutants or allergens, this leads to functional blockade of beta reception, causing persistent bronchospasm and lung hyperexcitability.

Conversely, the low representation of the Gly allele among patients (14.0% versus 39.0% in the control group) and the OR = 0.255 value indicate a strong protective function of this variant. Gly16 receptors are more resistant to long-term ligand effects and maintain the functional stability of the membrane pool, inhibiting the development of the inflammatory cascade.

The fact that the Hardy-Weinberg law was violated exclusively in the patient group ($\chi 2 = 17.52$); $p < 0.001$) indicates that the studied polymorphism is involved in the structure of selective selection induced by the disease. The accumulation of Arg/Arg homozygotes among patients reflects the direct determination of the clinical phenotype of BA by this genetic construction.

Our results are fully consistent with the data from major international consortia. Thus, in the fundamental works of Thompson and co-authors, as well as Bleecker et al. [11], it has been convincingly proven that carriers of the homozygous Arg16 genotype have a minimal response to therapy with β2-agonists and have a high risk of severe exacerbations of BA. The protective effect of the Gly16 allele, recorded at 30–40% in Asian populations, is also attributed to its pharmacodynamic superiority.

The scientific and practical value of the work lies in the formation of new prognostic criteria for personalized medicine. The implementation of rs1042713 locus genotyping will allow clinicians to pre-evaluate the therapeutic response to β2-agonists, modify dosage regimens, and optimize BA treatment protocols while avoiding ineffective therapeutic cycles.

Conclusion

1. The rs1042713 polymorphism of the ADRB2 gene is a strong genetic predictor of bronchial asthma. The homozygous Arg/Arg genotype is associated with a high risk of disease development ($\chi 2 = 33.24$); ($p = 6.04$ times $10 - 8$).
2. The Gly allele has a pronounced protective effect (OR = 0.255; 95% CI: 0.156–0.416), reducing the likelihood of bronchial asthma manifestation by maintaining the stability of respiratory receptor response.
3. Identified Hardy-Weinberg imbalance in the patient group ($\chi 2 = 17.52$); ($p = 2.84$ times $10 - 5$) mathematically confirms the strong association of the Arg/Arg genotype with the clinical phenotype of BA and substantiates the feasibility of using this marker in personalized pharmacogenetic strategies.

Declarations

Ethics Approval

The study was conducted in accordance with the applicable ethical principles and guidelines for research involving human participants. Ethical approval was granted by the Ethics Committee of the Republican Specialized Scientific and Practical Medical Center of Allergology and Clinical Immunology (Approval No. 1/2024, dated January 5, 2024; Protocol No. 9, dated September 29, 2026).

Consent to Participate

Written informed consent to participate in the study was obtained from all participants before their inclusion in the study.

Consent to Publish

Consent to publish was obtained from all participants in accordance with the applicable ethical requirements and the journal's policies.

Author Contribution

Author Contributions StatementI.S.R. conceptualized the study and contributed to the development of the research methodology. N.P.A. contributed to data collection and clinical interpretation. G.R.R. contributed to the analysis and interpretation of the findings. M.P.N. contributed to the literature review and manuscript revision. All authors reviewed and approved the final version of the manuscript.I.S.R. — Ilmira Sadullayevna RazikovaN.P.A. — Nargiza Pulatovna AydarovaG.R.R. — Gulmira Rustamovna RazikovaM.P.N. — Mexriniso Pardayevna Nosirova

Data Availability Statement

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Martinez FD, Vercelli D. Asthma. N Engl J Med. 2013;368(8):743–53.
2. Global Initiative for Asthma. (2023) *Global Strategy for Asthma Management and Prevention*. https://ginasthma.org.
3. Liggett SB. (2000) The pharmacogenetics of beta2-adrenergic receptors on airway smooth muscle. *Am J Respir Crit Care Med* 161(3 Pt 2)–S201.
4. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry. 1994;33(32):9414–9. https://doi.org/10.1021/bi00198a006.
5. Contopoulos-Ioannidis DG, Manoli EN, Ioannidis JP. Meta-analysis of the association of beta2-adrenergic receptor polymorphisms with susceptibility to asthma and responsiveness to beta2-agonists. Am J Respir Crit Care Med. 2005;171(11):1186–98.
6. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011;242(1):10–30.
7. Erle DJ, Sheppard D. The cell biology of asthma. J Cell Biol. 2014;205(5):621–31.
8. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010;363(13):1211–21. https://doi.org/10.1056/NEJMoa0906312.
9. Wittke-Thompson JK, Pluzhnikov A, Cox NJ. Rational inferences for Hardy-Weinberg equilibrium deviations in genetic association studies. Am J Hum Genet. 2005;76(6):967–86.

10. Thompson MD, et al. Pharmacogenomics of beta2-adrenergic receptor gene (ADRB2) polymorphisms in asthma management. J Asthma Allergy. 2019;12:315–28.
11. Bleecker ER, Postma DS, Lawrance RM, et al. Effect of ADRB2 polymorphisms on response to long-acting beta2-agonist therapy. Lancet. 2007;370(9605):2118–25.
12. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215.