Study of the association of distribution pattern of genotypes of C/A polymorphism of COL1A1_1 collagen gene (RS1107946) with indicators of external breathing in children with bronchial asthma

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A - research concept and design; B - collection and/or assembly of data; C - data analysis and interpretation; D - writing the article; E - critical revision of the article; F - final approval of the article

Purpose. The study of the distribution patterns of allelic genes and genotypes of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) in children with bronchial asthma, taking into account the indicators of external respiration function.

Materials and methods. Molecular-genetic study to determine the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was conducted in 125 children from 6 to 18 years, 100 of them with bronchial asthma who were hospitalized in the Allergic Department of the Municipal Non-Profit Enterprise “City Children Hospital No 5 of Zaporizhzhia City Council” and 25 healthy children (control group). There were no differences in age and sex in the comparison groups (P > 0.05). Genotype determination was performed by polymerase chain reaction method according to the instruction (Applied Biosystems, USA) using the samples of total DNA received from whole venous blood using SNP-Screen reagents (manufactured by “Syntol”) on amplifier CFX96TM Real-Time PCR Detection Systems (“Bio-Rad laboratories, Inc.”, USA). The ventilation function of the lungs was studied by conducting a spirometric study on a computer spirograph “PULMOREM” TU U 33.1-02066769-005-2002 (Kharkiv, Ukraine). To compare the frequencies of alleles and genotypes in different groups, the non-parametric statistical method “2 × 2 Table”, the Chi-square (df = 1) was used. Medians and interquartile intervals were also calculated, the two independent groups were compared by the Mann-Whitney criterion, the χ² criterion. Non-parametric statistics methods for the licensed software package Statistica for Windows 6.1.RU, serial number AXXR712D83214SANS, were used to process the obtained study data.

Results. Molecular-genetic study of distribution patterns of allelic genes of the C/A polymorphism of the COL1A1_1 collagen gene (rs1107946) in patients with bronchial asthma and in practically healthy children, showed that the allele C was registered with a frequency of 69.5 % and 84.0 %, allele A – 30.5 % and 16.0 %; dominant genotype C/C – 58 % and 76 %; heterozygous genotype C/A – 23 % and 16 %; homozygous genotype A/A – 19 % and 8 %, respectively. Children with bronchial asthma with genotype A/A had significantly lower FVC values up to 2.32 (1.55; 3.29), VCmax up to 1.89 (1.40; 2.98), FEV1 up to 1.82 (1.43; 2.98), with genotype C/C – MEF75 up to 2.34 (1.87; 3.14) when compared with patients with heterozygous genotype A/C, and very low rates of FVC were recorded in 68.75 % of children with bronchial asthma with the A/A genotype against 30.77 % of patients with the A/C genotype and 36.17 % with the C/C genotype (P < 0.05).

Conclusion. Homozygous genotype A/A of C/A polymorphism of the COL1A1_1 collagen gene (rs1107946), was associated with more pronounced disorders of ventilatory function of lungs with obstructive breathing type due to impaired collagen formation in the bronchi, which may have prognostic significance both for early diagnosis and prediction of clinical course severity of this disease as well as for prevention and treatment of bronchial obstruction in patients.
Исследование ассоциации распределения генотипов полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) с показателями функции внешнего дыхания у детей с бронхиальной астмой

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Цель работы – исследование закономерности распределения генотипов полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) у детей с бронхиальной астмой, учитывая показатели функции внешнего дыхания.

Материалы и методы. Молекулярно-генетическое исследование для определения полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) проведено у 125 детей в возрасте от 6 до 18 лет, из них 100 детей с бронхиальной астмой, которые находились на стационарном лечении в аллергологическом отделении КНП «Городская детская больница № 5».

Результаты. Гомозиготный генотип А/А полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) ассоциировался с выраженным влиянием поражения вентиляционной функции легких за счет обструктивного типа дыхания у пациентов с гетерозиготным генотипом А/С, а очень низкие показатели ФЖЕЛ зарегистрированы у 68,75 % детей с бронхиальной астмой, которые на обструктивном типе дыхания, что аллергический фактор может быть важным для ранней диагностики и прогнозирования тяжести клинического течения этого заболевания.

Выводы. Гомозиготный генотип А/А полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) ассоциировался с более выраженным влиянием поражения функции легких за счет обструктивного типа дыхания у пациентов с генотипом А/А.

Bronchial asthma (BA) remains the most topical issue of modern pediatrics and is a serious chronic disease, affecting millions of children of all ages [1]. Epidemiological, genetic and clinical anamnestic studies have indicated the role of certain environmental factors and genetic composition in the formation of bronchial asthma in children [2,3].

In this regard, medical practitioners and scientists have become interested in understanding the factors that lead to the formation of bronchial asthma, and especially its genetic aspects. The manifestation of this multifactorial disease occurs as a result of the interaction of genetic factors and certain environmental conditions. Allergens, viruses, bacteria, passive smoking, xenobiotics and genetic mechanisms contribute to the onset of bronchial asthma in children and affect the clinical course of the disease. Immune and neurogenic features of pathogenesis, bronchial hyperreactivity in chronic inflammation and other factors contribute to the formation of active forms of oxygen. This leads to the development of hypoxia, oxidative stress, secondary pathological changes in the respiratory tract and lung tissue. At the present stage, the pathogenetic basis for the development of bronchial asthma is a change in the differentiation of activity of T-helpers of type 2, and a genetic determinate imbalance in the functioning of enzymes of oxidative and antioxidant effects. In general, an understanding of the various genetic mechanisms of the development of bronchial asthma makes it possible to re-understand the pathogenesis of this disease [4].

In Ukraine, the studies of genetic factors in the development of asthma have not been fully conducted, reliable
According to the latest data, up to 27 types of collagen were studied. The detection of its heterogeneity allows for the study of collagen strength and elasticity under mechanical loading [11].

Collagen is the main insoluble fibrillar protein that underlies the connective tissue of the body. More than 90% of all collagen accounts for type I collagen, which is a major protein element of the skin, blood vessels, tendons, cartilage, and bones. It is also responsible for the highest strength and elasticity under mechanical loading [11].

An important area of modern genetic study is the identification of variants of genes which allow predicting the individual course of the disease and the response to therapy [6,7].

It is expected that in the near future a personalized BA prognosis will consist of personal environmental risk factors and a set of genes that will cause the development and course of disease [8–10].

This is especially important in children, because the younger the child, the more difficult it is to obtain the necessary information after conducting skin allergy tests or determining indicators of the function of external respiration. The chronic inflammatory processes in the airways in children with bronchial asthma lead to irreversible structural changes in the bronchial wall in the form of thickening of all layers of the bronchial wall, proliferation of collagen fibers in the submucosal layer, hyperplasia and an increase in the number of myofibroblasts that are responsible for the synthesis and accumulation of collagen type I, III, IV in the submucosa layer of bronchus. This leads to a narrowing of the bronchi. In this case, structural disorders of the bronchi can form very early, when there are no clinical symptoms of the disease. Also, there are still no highly informative methods for identifying signs of chronic inflammation in the bronchi and reliable markers for predicting this disease. Today, genetic studies allow both diagnosing and predicting the development of bronchial asthma in a particular child very early in order to timely prevent structural changes in the bronchi that affect the function of external respiration [11].

At the present stage of medical science development, to understand the genesis of the development of bronchial asthma and to assess the individual differences of the phenotype, it is necessary to conduct molecular genetic studies in order to determine the polymorphism of collagen and metabolism genes (COL1A1), which will allow predicting the risk of pathology and to prevent the risk of pathology. Collagen is the main insoluble fibrillar protein that underlies the connective tissue of the body. More than 90% of all collagen accounts for type I collagen, which is a major protein element of the skin, blood vessels, tendons, cartilage, and bones. It is also responsible for the highest strength and elasticity under mechanical loading [11].

The most important achievement of recent years in the study of collagen was the detection of its heterogeneity. According to the latest data, up to 27 types of collagen are distinguished, and each tissue of the body has its own relationship of types [11,12].

The immunological variances of collagen of different types have made it possible in recent years to study the localization of different types of collagen in connective tissue structures by using typo-specific antibodies.

Many scientific studies have been dedicated to the study of genes responsible for the formation of atopy, such as IL-4, -6, -13, but collagen plays a special role in the functioning of the bronchopulmonary system.

The special role of collagen in the functioning of the human bronchopulmonary system is also due to the fact that the alveoli are formed precisely by collagen fibers. Defects in the structure of elastin and collagen, caused by endogenous hereditary mechanisms of increasing activity of degradation enzymes, may contribute to the development of configuration abnormalities of the bronchi. The stigmas of dysembyrogenesis by the bronchopulmonary system are manifested in the form of tracheobronchomalacia and tracheobronchomegaly, pulmonary hypertension, polycystic pulmonary disease, detection of apical bulging (during radiographic examination), spontaneous pneumothorax. The weakness of connective tissue structures contributes to the development of tracheobronchomalacia and tracheobronchomegaly – a significant change in the lumen of the trachea and large bronchi during breathing due to expiratory burst of their atonic membrane part [11].

Therefore, the study of gene mutations responsible for the exchange of collagen, which forms connective tissue and contribute to the development of connective tissue dysplasia syndrome, one of the phenotypic manifestations of which is the development of pathology of the bronchopulmonary system in children, is extremely important.

**Purpose**

The study of the distribution patterns of allelic genes and genotypes of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) in children with bronchial asthma, taking into account the indicators of external respiration function.

**Materials and methods**

Molecular-genetic study to determine the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was conducted in 125 children from 6 to 18 years, 100 of them with bronchial asthma who were hospitalized in the Allergic Department of the Municipal Non-Profit Enterprise City Children Hospital No. 5 of Zaporizhzhia City Council and 25 healthy children (control group). There were no differences in age and sex in the comparison groups (P > 0.05).

Genotype determination was performed by polymerase chain reaction method according to the instruction (Applied Biosystems, USA) using the samples of total DNA received from whole venous blood using SNP-Select reagents (manufactured by “Syntol”) on amplifier CFX96TM Real-Time PCR Detection Systems (“Bio-Rad laboratories, Inc.”, USA). The study was carried out in the Department of Molecular and Genetic Studies of the Research Medical-Laboratory Center at the Department of Microbiology, Virology and Immunology of Zaporizhzhia State Medical University.
The ventilation function of the lungs was studied by conducting a spirometric study on a computer spirometer “PULMOREM” TU U 33.1-02066769-005-2002 (Kharkiv, Ukraine). The forced expiratory maneuver has been performed three times, with the following indicators: vital capacity maximal (VCMAX), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1 %F = FEV1/FVC ratio %, maximum expiratory flow at 25 %, 50 %, and 75 % FVLC (MEF25, MEF50, and MEF75).

To compare the frequencies of alleles and genotypes in different groups, the non-parametric statistical method “2 × 2 Table”, the Chi-square (df = 1) was used. Medians and interquartile intervals were also calculated, the two independent groups were compared by the Mann-Whitney criterion, the χ2 criterion. Non-parametric statistics methods for the licensed software package Statistica for Windows 6.1.RU, serial number AXXR712833214SAN5, were used to process the obtained study data.

Results

Molecular and genetic study of C/A polymorphism of collagen gene COL1A1_1 (rs1107946) in children with bronchial asthma has detected that the incidence of allelic gene A was 30.5 %, allele C – 69.5 %, and in healthy children 16 % and 84 %, respectively.

Studies have found that in children with bronchial asthma, the homozygous genotype C/C was most frequently registered and was equal to 58 %. The heterozygous genotype C/A and the homozygous genotype A/A were significantly less frequently reported; the incidence of bridging among children with bronchial asthma was only 23 % and 19 %, respectively (Fig. 1).

In the comparison control group, that is, in healthy children, homozygous C/C genotype (76 %) was also significantly more frequently registered compared with the incidence of homozygous A/A genotype (8 %) and heterozygous C/A genotype (16 %) respectively (Fig. 2).

Depending on the presence or absence of pathology such as bronchial asthma, a comparative analysis of the genotype distribution of C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was also performed. Although in healthy children only a tendency for the prevalence of homozygous genotype C/C and a tendency for a decrease in the incidence of homozygous genotype A/A and heterozygous genotype C/A than in patients with bronchial asthma was observed, there was no significant difference between these parameters.

Therefore, we further analyzed the association of genotype distribution of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) with indicators of external respiratory function in children with bronchial asthma. In the study of ventilatory function of the lungs, obstructive breathing with a decrease in external respiration, at the time of examination, was recorded in 76 children with bronchial asthma. All 25 practically healthy children and 24 children with controlled bronchial asthma during sustained remission had all indicators of external respiration within the age range.

Indicators of external respiratory function in children with bronchial asthma, depending on their genotypes of C/A polymorphism of COL1A1_1 collagen gene (rs1107946) are presented in Table 1.

Concurrently children with bronchial asthma and homozygous A/A genotype, when compared with patients with heterozygous A/C genotype, had significantly lower rates of forced vital lung capacity (2.32 (1.55; 3.29) versus 3.20 (2.51; 3.77)), P < 0.05; vital lung capacity (1.69 (1.40; 2.98) vs. 2.37 (1.97; 2.88)), P < 0.05; forced expiratory volume in the first second (1.82 (1.43; 2.98) vs. 2.40 (1.89; 3.08)), P < 0.05. At the same time, in children with bronchial asthma and homozygous C/C genotype, the maximum exhalation volume rate at 75 % of FLVC was significantly lower than in children with A/C genotype (2.34 (1.87; 3.14) vs. 2.46 (1.95; 3.24)), P < 0.05.

The distribution of genotypes of the C/A polymorphism of COL1A1_1 collagen gene (rs1107946) in children with bronchial asthma and with impaired ventilatory function of the lung, characterized by very low rates of external respiration during spirometry, are presented in Table 2.

Concurrently 68.75 % of children with bronchial asthma with A/A genotype were significantly more likely to have very low rates of forced vital lung capacity, compared to 30.77 % of patients with A/C genotype and 36.17 % with C/C genotype.

According to our hypothesis, these data can be explained by the fact that in children with bronchial asthma with the A/A genotype of C/A polymorphism of the collagen gene COL1A1_1 (rs1107946) the violation of collagen formation in the bronchi is observed, which causes more pronounced disorders of lung ventilatory function with obstruction respiratory type and children with genotypes C/A and C/C have bronchial obstruction due to the well-known heterogeneous chronic inflammation of the respiratory tract.
Table 1. Indicators of external respiratory function, depending on their genotypes of C/A polymorphism of COL1A1_1 collagen gene (rs1107946) in children with bronchial asthma (Me (Q25; Q75))

| Indicators | FVC | VC_{max} | FEV_{1} | FEV_{1} %F | MEF_{25} | MEF_{50} | MEF_{75} |
|------------|-----|----------|---------|------------|----------|---------|----------|
| Genotype A/A (n = 16) | 2.32 (1.51; 3.29) | 1.69 (1.40; 2.98) | 1.82 (1.43; 2.98) | 0.62 (0.72; 0.90) | 4.46 (3.59; 5.12) | 3.41 (2.27; 3.93) | 1.87 (1.20; 2.29) |
| Genotype A/C (n = 13) | 3.20 (2.51; 3.77) | 2.37 (1.97; 2.88) | 2.40 (1.99; 3.08) | 0.83 (0.92; 0.90) | 5.23 (4.76; 5.57) | 3.79 (2.64; 4.43) | 2.46 (1.95; 3.24) |

Discussion

Other scientific works that we analyzed in the course of our study are dedicated as well to the identification of genotypic and associated with it phenotypic features of bronchial asthma.

Thus, three subgroups of patients participated in the study of the association of the rs10432 polymorphism of the ATG5 gene with indicators of forced expiratory volume in the first second (FEV1). The first subgroup included 18 patients (18.37 %) with the major (homozygous) genotype, the second – 51 children (52.04 %) with the heterozygous genotype, the third – 29 persons (29.59 %) with minor (homozygous) genotype. At the same time, no statistically significant differences between the average values of FEV1 in patients with major and heterozygous genotype, heterozygous and minor genotype were found (P > 0.05). However, average FEV1 values in patients with a minor genotype were significantly lower than with the major genotype (P < 0.05). Thus, the rs10432 polymorphism of ATG5 gene is also considered to be a predictor of decreased respiratory function in children, allowing individually prescription of prophylactic measures and / or treatment to prevent the development or exacerbation of bronchial asthma [13–15].

Fedortsev O. Y. also studied the function of external respiration in children with bronchial asthma; but according to his conclusions, the changes in spirometric parameters in patients are informative only during the attacks allowing distinguishing the types of disorders of the function of external respiration – mixed with obstruction predominance and purely obstructive. During exacerbation of bronchial asthma, priority indicators are violated that are dependent on the exhalation phase (mid-expiratory flow (MEF_{25%;75%}), maximum expiratory flow at 25 %, 50 % and 75 % FVLC (MEF_{25;50;75} and MEF_{35})). But in our study the most diagnostically informative indicators turned out to be FVC, VC_{max}, FEV_{1}, [16].

In studying clinical and spirometric features of phenotypic features of bronchial asthma of physical tension in school-age children, divided into two groups of comparisons, O. G. Grigola established the following data. Thus, in children with the asthma phenotype of physical exertion, unlike the peers in the comparison group, there was more severe clinical course of the disease, accompanied by the risk of loss of control with odds ratio of 3.45 and relative risk of 1.47. Patients with asthma phenotype of physical exertion were distinguished by higher rates of non-specific hypersensitivity of the bronchi to direct and indirect bronchoprovocation stimuli and more pronounced skin hypersensitivity of immediate type to standard household allergens, which is due to a greater degree of burden of family allergic anamnesis [17].

Banadya N. V. has put forward an assumption that the polymorphism of the rs1042713 Arg16Gly of the ADRB2 gene in children with bronchial asthma is represented by the predominance of the Arg16Gly variant in all phenotypes, as well as in the case of early debut disease. Late manifestation of the disease is associated with the homozygous variant Gly16GlyADRB2 [18]. It has also been shown that among patients with bronchial asthma with a difficult hereditary history of atopy, the Arg16Gly genotype of ADRB2 gene prevails. At that time, in families with no cases of allergic pathology, the Gly16Gly genotype registered with a frequency of 53.33 %, occupies a leading place [19].

According to the results of genotyping, Ivanova L. A. states that the genotype T1delM1 + is registered in eosinophilic bronchial asthma in 15.5 % of cases, that is more often than in the neutrophilic type of airway inflammation (11.6 %). The T1 + M1del genotype was more frequently reported in children with a non-eosinophilic disease phenotype of disease (32.6 %) than in their peers with eosinophilic bronchial asthma (28.9 %). Severe form of disease was detected in 4 of 5 carriers of the T1delM1del genotype (80 %) in patients with eosinophilic asthma and in 2 of 5 carriers (40 %) with neutrophilic type of respiratory passages inflammation. At the same time, carriers of the T1 + M1 + genotype were diagnosed with severe form of disease in 12 of 21 (57.1 %) patients with eosinophilic asthma and in 8 of 19 (42.1 %) with non-eosinophilic type of respiratory passages inflammation. Thus, in patients with an eosinophilic phenotype of bronchial asthma who have the T1delM1del genotype, the disease more often passed
in the severe forms. In general, it should be noted that in patients with eosinophilic asthma, which are carriers of defective alleles of GSTT1 and M1 genes in the homozygous state, there was a tendency to increased bronchial lability due to a more pronounced bronchospasm, and the index of hyper-reactivity of the bronchi was significantly higher than in children with functionally complete alleles of these genes. Therefore, genetically caused lack of activity of individual enzymes of the biotransformation system of xenobiotics, in particular GSTT1 and M1, may be a cause of higher lability of the bronchi [20].

In recent years, children with chronic somatic pathology have been increasingly diagnosed with signs of undifferentiated connective tissue dysplasia [21]. It is known that the development of both bronchial asthma and undifferentiated connective tissue dysplasia is caused by the interaction of genetic and external factors, which, in turn, leads to changes in the functional activity of the hereditary apparatus of somatic cells [22,23].

Changes from the side of the bronchopulmonary system occupy a significant place among patients with undifferentiated connective tissue dysplasia, complicating the course of the underlying disease [24].

There are morphological changes of the respiratory tract of inflammatory nature. These is thickening of the sub-mucosal layer, infiltration of the respiratory passages walls by eosinophils and lymphocytes with damage to the epithelium, smooth muscle hypertrophy, redistribution of interstitial collagen as a mechanism of respiratory passages remodeling. These changes occur with the participation of the same cytokines as in classical bronchial asthma – histamine, prostaglandins, leukotrienes [25].

Scientific articles have also highlighted studies aimed at studying the collagen gene COL1A1_1, phenotypic and clinical manifestations of other diseases in children [26–29].

Peigen Xie, Bin Liu, Liang Ming Zhang suggested that type I collagen is the most common protein and is a component of the bone matrix. The collagen COL1A1_1 gene is considered to be a strong candidate gene, which may be important for the regulation and function of connective tissue, therefore, potential associations between polymorphism within collagen 1 alpha 1 (COL-1A1) in the examined patients lead to abnormalities in bone matrix structure and connective tissues [30].

Victor A. Mc Kusick’s article discusses that COL3A1 gene mutations are life-threatening for a person, and leads to enlargement, rupture of the arteries, and risk of damage to internal organs such as the lungs [31].

Malachkova N. V. studied the value of the rs1107946 polymorphism of the COL1A1 gene in children and states that the average population frequency of the A SNP rs1107946 variant allele in the world is 0.26–0.27, and the average genotype distribution indicators according to various data are: C/C – 55.5–66.0 %, A/C – 27.0–37.5 %, A/A – 5–7 %. However, there is considerable geographical variability in the frequency of allelic variants of the SNP rs1107946 of the COL1A1 gene in different populations of the world. It should be noted that the population of Europe is characterized by a very low incidence of homozygous AA SNP rs1107946 carriers – in average 0.8 %, which coincides with the data obtained in our studies and explains the absence of homozygous with variant alleles in the sample of persons who participated in genotyping by this polymorphism. A more detailed analysis of the above studies conducted in Ukraine allows the assumption that the most probable cause of such significant differences in the frequency of allelic variants of the SNP rs1107946 of the COL1A1 gene may be the differences in the size of the sampling at genotyping. Thus, the studies which showed the high frequency of the SNPsrs1107946 variant allele, the number of persons in the control groups was 20 and 30, respectively. Thus, the results of genotyping SNPsrs1107946 of the COL1A1 gene among children obtained in our study do not differ from the European average population data and coincide with the data of prevalence of allelic variants in Ukraine obtained in large samplings [32].

Conclusions

1. Molecular-genetic study of distribution patterns of allelic genes of the C/A polymorphism of the COL1A1_1 collagen gene (rs1107946) in patients with bronchial asthma and in practically healthy children showed, that the allele C was registered with a frequency of 69.5 % and 84.0 %, allele A – 30.5 % and 16.0 %; dominant genotype C/C – 58 % and 76 %; heterozygous genotype C/A – 23 % and 16 %; homozygous genotype A/A – 19 % and 8 %, respectively.

2. Children with bronchial asthma with genotype A/A had significantly lower FVC values up to 2.32 (1.55; 3.29), VCmax up to 1.69 (1.40; 2.98), FEV1 up to 1.82 (1.43; 2.98), with genotype C/C – MEF75 up to 2.34 (1.87; 3.14) when compared with patients with heterozygous genotype A/C, and very low rates of FVC were recorded in 68.75 % of children with bronchial asthma with the A/A genotype against 30.77 % of patients with the A/C genotype and 36.17 % with the C/C genotype (P < 0.05).

3. Homozygous genotype A/A of C/A polymorphism of the COL1A1_1 collagen gene (rs1107946), was associated with more pronounced disorders of ventilatory function of lungs with obstructive breathing type due to impaired collagen formation in the bronchi, which may have prognostic significance both for early diagnosis and prediction of clinical course severity of this disease as well as for prevention and treatment of bronchial obstruction in patients.

Prospects for further studies. In the future, we are planning to study the occurrence frequency of the presented genotypes depending on the clinical and laboratory data in children with bronchial asthma.

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