Original Research Article: full paper

(2022), «EUREKA: Life Sciences»
Number 2

GENETIC TESTING OF ALLELIC VARIANTS OF PIZ (GLU342LYS, RS28929474) AND PIS (GLU264VAL, RS17580) OF *SERPINA1* GENE IN CHILDREN WITH BRONCHIAL ASTHMA

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Abstract

According to world publications, mutations in the *SERPINA1* gene may be a genetic risk factor for severe chronic obstructive pulmonary disease and, consequently, rapid progression of respiratory dysfunction. This disease leads to a decrease in the level of alpha-1-antitrypsin protein. It is inherited by autosomal recessive type, but there are registered cases of codominance. In the absence of treatment, diseases of the respiratory system become chronic and lead to disability in adulthood.

Early diagnosis of AAT deficiency is important to prevent complications and reduce mortality among people with this pathology. Due to these factors, genetic testing of *SERPINA1* gene mutations in children with chronic lung diseases is appropriate to detect and prevent severe complications, associated with AATD.

The aim of this work is to improve the effectiveness of early diagnosis of AAT deficiency in children with bronchial asthma and recurrent obstructive bronchitis by identifying different genotypes and phenotypes of A1AT deficiency, studying their relationship with the clinical course of respiratory diseases in children.

Keywords *SERPINA1* gene, Alpha1-antitrypsin, bronchial asthma, codominance, heterozygous, liver, lungs, genotype, phenotype, recessive.

DOI: 10.21303/2504-5695.2022.002415

1. Introduction

Respiratory diseases are the most common pathology in the structure of childhood morbidity and have a significant impact on the overall infant mortality rate in the world. In Ukraine, there is a steady trend of increasing rates of respiratory diseases in children. In addition, diseases of the respiratory system that develop in childhood, further lead to disability of patients in adulthood. Among chronic lung diseases in children, the leading positions are occupied by bronchial asthma (40 %) and recurrent bronchitis (40 %) [1, 2].

According to world publications, mutations in the *SERPINA1* gene may be a genetic risk factor for severe chronic obstructive pulmonary disease and, consequently, rapid progression of respiratory dysfunction [3, 4]. In the presence of pathogenic mutations in the gene, an autosomal recessive genetic disorder occurs, in which there is a decrease in the level and functional activity of the alpha-1-antitrypsin protein (AAT). AAT is a protease inhibitor (Pi), an enzyme that is produced mainly in the

liver. AAT is continuously produced and transported in the bloodstream and can be detected in high concentrations in the lungs. AATD (alpha-1-antitrypsin deficiency) underlies the pathogenesis of pulmonary emphysema, liver damage and other disorders in this disease (OMIM 613490).

The most important function of alpha1-antitrypsin is the inactivation of proteolytic enzymes in the lungs. Such enzymes are released during the immune response when the lungs are exposed to long-term pathogens. Although these proteolytic enzymes are key to killing pathogens if left unchecked, they can destroy the lung tissue [1].

With a deficiency of AAT the excess of proteolytic enzymes, in particular neutrophil elastase, components of the pulmonary matrix, alveolar structures and blood vessels, is gradually destroyed. Clinically, this is accompanied by liver damage, chronic obstructive pulmonary disease, bronchiectasis, pulmonary emphysema, idiopathic fibrosis and the development of lung cancer [5]. Typical complaints of respiratory damage due to AAT deficiency are cough, shortness of breath, the presence of wheezing in the lungs. This clinical picture is not specific and similar to bronchial asthma or chronic obstructive pulmonary disease, which complicates the differential diagnosis [6, 7].

Usually the persistence of bright clinical signs of defeat of the respiratory system at AATD in children is not observed as it is characteristic of adult population. Children with AATD are diagnosed and mainly associated with the development of liver disease [8, 9]. However, recurrent respiratory manifestations in a child with AATD may be a trigger for disease progression. [10, 11]

The period of diagnosis is on average from 5 to 7 years from the first visit to the doctor. Insufficiency of AAT for a long time cannot be shown clinically, even at very low levels of protein.

The most common genetic variants, found in AATD, are the PIZ (Glu342Lys, rs28929474) and PIS (Glu264Val, rs17580) alleles of the SERPINA1 gene [12].

Early diagnosis of AAT deficiency is important to prevent complications and reduce mortality among people with this pathology. Due to these factors, genetic testing of SERPINA1 gene mutations in children with chronic lung disease is appropriate to detect and prevent severe complications, associated with AATD.

The aim of this work is to study the frequency of pathogenic variants of PIZ (Glu342Lys, rs28929474) and PIS (Glu264Val, rs17580) of the *SERPINA1* gene in children with bronchial asthma for early diagnosis of alpha-1-antitrypsin deficiency and its share in this cohort of children.

2. Materials and methods

The study included 57 children (48 boys and 9 girls) with a mean age of 10.82±3.88 years, who met the criteria for inclusion and did not meet the criteria for exclusion. The prospective study was conducted on the basis of the pulmonology and allergology department of the MNPE LRC LRCCH "OKHMATDIT" and the allergology department of the City Children's Clinical Hospital of Lviv in 2021–2022.

The research was approved by the Commission on Ethics of Research, Experimental Developments and Scientific Works of Danylo Halytsky Lviv National Medical University No. 7 dated 20.01.2020 and the Ethics Commission at the Municipal Non-Profit Enterprise "Children's Clinical Hospital of Lviv" No. 1 dated 19.11.2020. The members of the commission noted that the submitted documents provide for measures to comply with moral and ethical standards in accordance with the principles of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, ICHGCP and current regulations of Ukraine. The collection of material for the study was carried out after the parents signed an informed consent for the study. A scan of the minutes of the meeting on bioethics will be sent soon. We will send a sample of informed consent.

Criteria for inclusion of patients in the study:

– age of patients over 3 years and under 18 years;

– the presence of clinical signs of bronchial asthma;

– informed consent of children and parents to participate in the study.

Exclusion criteria:

– children with congenital malformations of the bronchi and lungs;

– refusal to participate in the study at any stage.

Surveys of children and parents were conducted in order to determine in detail the course of pregnancy, childbirth, early neonatal period in the patient, the presence of chronic jaundice in children of the study group, bad habits of parents, chronic diseases in parents and close relatives, allergic diseases in the family. The questionnaire was conducted by our questionnaire cards.

The examination of patients was conducted in accordance with the Unified Clinical Protocol of primary, secondary (specialized) medical care for children with bronchial asthma from 8.10.2013 No. 868.

The examination includes: general blood test to determine the level of eosinophils, biochemical blood test to determine the level of general and specific Ig E, pulse oximetry, spirometry (after 5 years), chest radiography (according to clinical indications). The studies of the hepatobiliary system were performed by determining the level of total bilirubin, transaminases, alkaline phosphatase and ultrasound of the abdominal cavity. The collection of material for genetic research was performed after the parents signed an informed consent.

Statistical data are given as $M \pm m$ (arithmetic mean±standard arithmetic mean error).

For taking a sample of DNA, there were used leukocytes of peripheral blood, washed in 2–5 ml of venous blood by the method of enzymatic disintegration with K proteinase and further salting out [13]. The analysis of *SERPINA1* gene mutations was carried out by PCR RFLP and real Time PCR methods. There were used two pairs of primers: PI*S allele: F5`-AAGGTGCCTATGATGAAGCGTTT, R 5` ATGATATCGTGGGTGAGTTCATGT, PI*Z allele – F5` CATAAGGCTGTGCTGACCATCCTC, R 5` TTCCCATGAAGAGGGGAGACTTGG [14]. The following pairs of primers were used for detection of PI*S mutation in Real-time F5`-AAGGTGCCTATGATGAAGCGTTT, R 5` TCAGTCCCAACATGGCTAAGAG, Probe S mutant 5` FAM-ATATCGTGGGTGAGTTCATTTACCA-HBQ1, Probe S wild type 5` ROX-TGGGTGAGTTCATTTTCCAGGT-HBQ2. The following pairs of primers were used for detection of PI*Z mutation in Real-time: F5` GCTTCCTGGGAGGTGTCCACG, R5` TTCCCATGAAGAGGGGAGACTTGG, Probe Z wild type ROX-CCAGCAGCTTCAGTCCCTTTCTCGTC-HBQ2, Probe Z mutant FAM-CCAGCAGCTTCAGTCCCTTTCTTGTC-HBQ1. The amplification was performed automatically using the BioRad CFX96 amplifier.

The electrophoresis of restriction fragment for detection of rs28929474 and rs17580 was carried out in 3 % agarose gel. The presence of a fragment of 167 pairs of bases testifies to the absence of PI*S mutation. The presence of a fragment of 143 pair of bases testifies to the presence of PI*S mutation in the homozygous condition. Two fragments of 167 and 143 pairs of bases testify to the mutation in the heterozygous condition [15]. The presence of a fragment of 137 pairs of bases testifies to the absence of PI*S mutation. The presence of a fragment of 160 pair of bases testifies to the presence of PI*S mutation in the homozygous condition. Two fragments of 137 and 160 pairs of bases testify to the mutation in the heterozygous condition [15].

3. Results

Complaints at the time of admission were: asthma – in 55 children (96.49 %), wheezing – 49 (85.96 %). Shortness of breath with little exercise was observed in 28 (72.44 %) patients. Dry cough bothered 49 (85.96 %) children. In contrast, whooping cough was significantly less common in 7 (14.04 %) patients. Bronchospasm, which was poorly treated in an outpatient setting, was observed in 32 (56.14 %) subjects. 38 (66.67 %) patients complained of nasal breathing difficulties.

According to the collected anamnesis, the duration of the disease was more than 1 year – in 54 (94.74 %) cases, and 51 (89.47 %) children had more than 2 exacerbations per year, requiring hospitalization. According to the results of the survey, the seasonality of the disease was observed, and it was more common in the autumn – 33 children (57.89±6.54 %). According to life history, we found that chronic jaundice was observed in 25 patients (43.86 %). Auscultatory, all children had dry wheezing on both sides on the background of hard breathing.

Changes in laboratory parameters were found in some children. Thus, in 19 (33.33 %) children the number of eosinophils in the total blood test was above 5 %. The level of ALT in 11

(19.3 %) children was elevated and was 33.1±8, the level of ACT exceeded the norm in 22 (38.6 %) patients and averaged 36.3±6.2. CRP was increased in 9 (22.81 %) surveyed children.

After obtaining written consent from parents, the genotyping of PI*S and PI*Z mutations of the *SERPINA1* gene was performed. The presence of a 167 bp fragment on the electrophoregram corresponds to the genotype of the wild-type *SERPINA1* gene. The presence of the PI*S mutation creates a recognition site for the RsaI restriction endonuclease, resulting in a 143 bp fragment on the electrophoregram. The electrophoregram detection of the PI*S mutation is shown in **Fig. 1**.

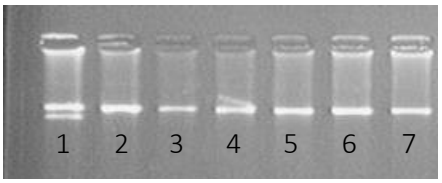


Fig. 1. Electrophoregram detection of the PI*S mutation of the *SERPINA1* gene. 1– mutation in the heterozygous state. 2–7 – wild type.

To detect the PI*Z mutation of the *SERPINA1* PCR gene, the product was treated with TaqI restriction endonuclease (65 °C). The presence of a fragment of 137 bp on the electrophoregram indicates the absence of mutations. The presence of a pathogenic variant disrupts the recognition site for TaqI restriction endonuclease, thus a 160 bp fragment is visualized on the electrophoregram. The electrophoregram detection of the PI * Z mutation of the *SERPINA1* gene is shown in **Fig. 2.**

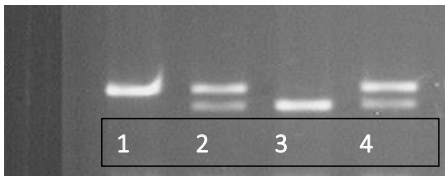


Fig. 2. Electrophoregram detection of the PI*Z mutation of the *SERPINA1* gene. 1 – PCR product without restriction, 2,4 – PI*Z mutation in the heterozygous state. 3 – wild type

The detection of PI*Z and PI*S mutations of the *SERPINA1* gene was performed in parallel by real-time PCR. The curvature amplifications are shown in **Fig. 3** and **Fig. 4.**

The study of DNA samples for the presence of mutations in the *SERPINA1* gene was performed using both methods: restriction fragment length analysis and real-time PCR. The coincidence of the results of the genetic testing by different methods is shown. These techniques show the specificity and sensitivity of detecting mutations in the *SERPINA1* gene.

The results of the genotyping are shown in **Table 1.**

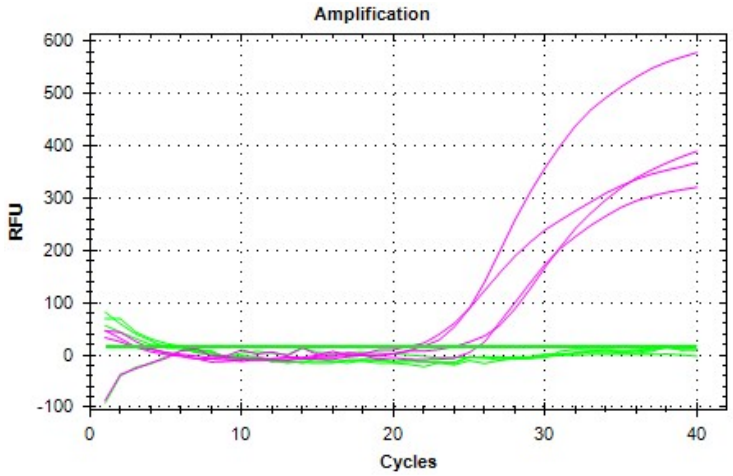
Table 1

Frequency of mutations in the *SERPINA1* gene in children with bronchial asthma

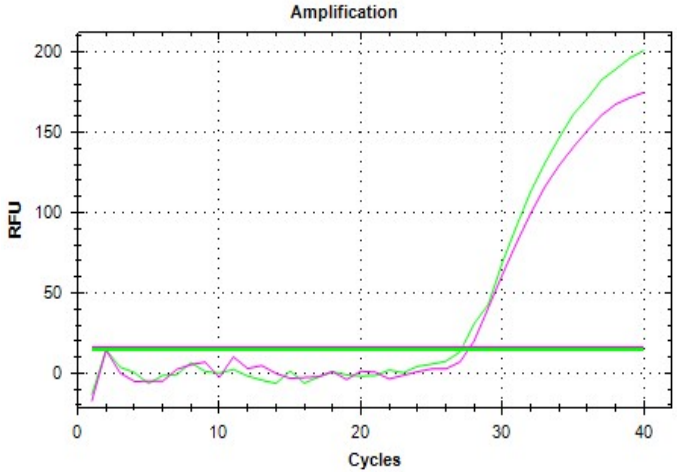
Number of examined	Number and frequency of detected pathogenic manifestations	
	PI*Z (Glu342Lys, rs28929474), N (%)	PI*S (Glu264Val, rs17580), N (%)
cases, n57	4 (7.0 %)	4 (7.0 %)
alleles, n114	4 (3.5 %)	4 (3.5 %)

As can be seen from the data in **Table 1, 4** cases of heterozygous PIZ mutation carriers and 4 cases of heterozygous PIS mutation carriers were found in the study sample. No mutations

were found in homozygous or compound heterozygous states. In total, 8 of the 57 children with bronchial asthma were carriers of one pathogenic variant of the *SERPINA1* gene. The frequency of the mutant PIZ allele in this sample is 3.5 %, the frequency of the mutant PIS allele is the same – 3.5 %.



a

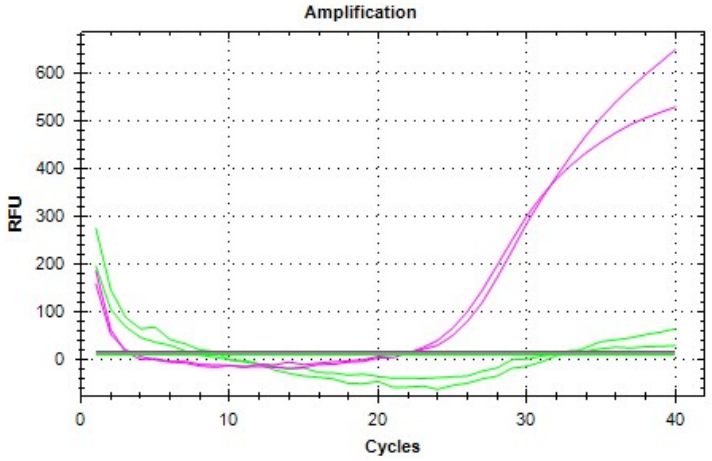


b

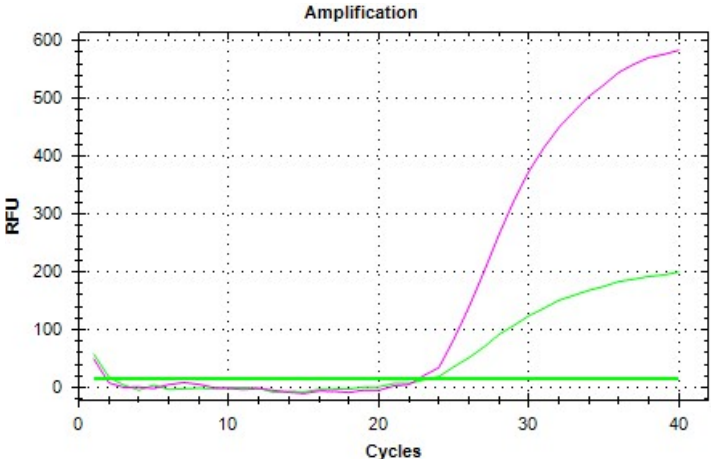
Fig. 3. Real-time image detection of the PI*S mutation of the *SERPINA1* gene allele: *a* – the presence of an amplification curve on one ROX channel indicates the absence of mutations among the studied samples; *b* – the presence of two-channel amplification curves (ROX and FAM) indicates the presence of the mutation in the heterozygous state

AATD is classically considered an autosomal recessive disorder, i.e. pathogenic variants in both alleles of the *SERPINA1* gene must be detected for clinical manifestation. However, according to reports [16], a codominant type of manifestation is possible and clinical manifestations of AAT insufficiency are also found in heterozygous carriers [17]. In the cases of heterozygous mutations of the *SERPINA1* gene in children with bronchial asthma, we can assume the presence of AAT insufficiency, which is manifested by lung lesions and clinical manifestations similar to bronchial asthma. However, this assumption needs further observation. Data on clinical manifestations in carriers of different allelic variants of the *SERPINA1* gene are conflicting. Thus, it is believed, that heterozygous carriers of the S allele (PiMS genotype) do not show a decrease in lung function [18], information on the preservation of lung

function in heterozygous carriers of the Z allele (PiMZ genotype) is insufficient even in light of meta-analysis [15]. Several population-based studies have not shown adverse health effects, but they have differed in the phenotype studied and the inclusion of interactions between genes and the environment [19, 20, 21]. It has been suggested, that the intrapulmonary antiproteolytic capacity in people with mild or moderate AAT deficiency may be insufficient to counteract the excess of inflammatory triggers, directed to the respiratory system.



a



b

Fig. 4. Real-time image detection of the PI*Z mutation of the *SERPINA1* gene allele: *a* – the presence of an amplification curve on one ROX channel indicates the absence of mutations among the studied samples; *b* – the presence of two-channel amplification curves (ROX and FAM) indicates the presence of the mutation in the heterozygous state

We do not rule out that the cases we have identified are healthy heterozygous carriers of mutations in the *SERPINA1* gene. Data on the distribution of PIZ (Glu342Lys, rs28929474) and PIS (Glu264Val, rs17580) alleles in the general population of Ukraine are unknown. The obtained data are twice as high as the prevalence of these pathogens among healthy people in European countries, in particular for the population of Poland the prevalence of these pathogens is 2.1 % for PIS and 2.1 % for PIZ allele of the *SERPINA1* gene [22], and for others European countries, this figure is in the range of 1.5–4 % [23]. We consider it expedient to further study the frequency of PIZ mutations and PIS mutations in the general population sample

of Ukrainians to determine the difference in their frequency among children with bronchial asthma. We believe that these indicators will be able to help in the further interpretation of the obtained data. According to numerous epidemiological studies, it has been established, that AATD is widespread in different geographical regions and is not a rare disease. In the countries of northern and western Europe, the PIZ allele is more common, among the countries of southern Europe, PIS is more common [24]. The PIZ allele is found in 0.1 % of the world's population. 41 % of these cases occur in Eastern, Northern and Central Europe, and 24 % – in North America. The PISZ genotype is diagnosed in 0.7 % of the world's population, of which 48 % in northern and central Europe, 20 % in North and Central America and 16 % in South America. Blanco I. and co-authors (2017) in their publications note that 23.2 per 1,000 people in the United States have PIS deficiency alleles, 10.5 have PIZ deficiency alleles, and 1 in 9,000 has the homozygous PIZZ genotype [25].

It will be useful to further monitor the identified cases of mutant alleles of the *SERPINA1* gene in children with bronchial asthma, including liver damage. In addition to the lungs, abnormal AAT protein can accumulate in the liver and cause liver damage, especially in people with the PIZZ genotype. The more common heterozygous genotypes PiMS and PiMZ (wild-type M allele) only slightly reduce the level of AAT in the blood [4] and are therefore considered mild (for PiMS) and intermediate (for PiMZ) AAT deficiencies. Patients with identified pathogenic variants of the *SERPINA1* gene are recommended to periodically determine the level of AAT protein to determine the expedience of an appropriate therapy. In the case of diagnosis of AATD you should exclude the influence of external risk factors, the main of which is smoking, as well as the possible appointment of treatment with alpha one antitrypsin [26].

It should be noted, that this test does not exclude the presence of other mutations in the *SERPINA1* gene, so it is advisable to determine the level of alpha 1 protein antitrypsin in patients with mutations, detected in the heterozygous state.

4. Conclusions

Both methods of genetic testing: restriction fragment length analysis and real-time PCR reveal the specificity and sensitivity of detection of *SERPINA1* gene mutations. The coincidence of the results of genetic testing by different methods is shown.

Pathogenic variants of the PIZ or PIS gene of the *SERPINA1* gene have been identified in 14 % of children with bronchial asthma, which may indicate the etiology of bronchopulmonary disorders in these patients.

We consider it appropriate to perform genetic testing of the *SERPINA1* gene in patients with asthma, as early diagnosis is important to prevent complications in individuals with alpha 1 antitrypsin deficiency.

Conflict of interest

The authors state that there is no conflict of interest and own financial interest in the preparation of this article.

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Received date 07.02.2022
Accepted date 16.03.2022
Published date 31.03.2022

How to cite: *Shymanska, I., Trutiak, O., Lychkovska, O., Makukh, H., Akopyan, H. (2022). Genetic testing of allelic variants of PIZ (GLU342Lys, RS28929474) and PIS (GLU264Val, RS17580) of SERPINA1 gene in children with bronchial asthma. EUREKA: Life Sciences, 2, 36–44. doi: https://doi.org/10.21303/2504-5695.2022.002415*