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# CLINICAL FEATURES OF CHRONIC BRONCHITIS AND GENETIC RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ADOLESCENT SMOKERS

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## ABSTRACT

**The aim** is to study the clinical features of the course of CB in adolescent smokers and to study the genetic risk factors for the development of COPD.

**Materials and methods:** There were examined 40 adolescent smokers with CB, 30 never-smokers adolescents with CB and 37 healthy adolescents smokers (control group). The study included the collection of anamnesis, objective examination. calculation of the smoking index and the «pack/year», molecular genetic investigations.

**Results:** It was proved that smoking leads to the development of chronic bronchitis as early as adolescence and affects its course, increasing the frequency and duration of exacerbations. We identified an association of the 2G/2G genotype of MMP1 gene with the development of chronic bronchitis in adolescent smokers. The TT genotype of CYP1A1 gene may be considered as a possible sustainability factor for the development of chronic bronchitis in adolescent smokers.

**Conclusions:** The study of candidate genes for COPD in childhood and adolescence will facilitate the early detection of high-risk groups in the formation of this pathology, which will allow doctors to take the necessary preventive measures.

**KEY WORDS:** chronic bronchitis, COPD, tobacco smoking, adolescents

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## INTRODUCTION

Chronic bronchitis (CB) in children and adolescents is one of the most pressing problems in childhood pulmonology [1-3]. CB is a multifactorial disease with a complex etiological structure, the development of which involves a large number of both internal and external risk factors [4]. One of the main risk factors for the development of CB in adolescence, and COPD in adults is tobacco-smoking [5,6].

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing. COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6 % of all deaths globally [6].

There are several reasons why environmental exposures in childhood are relevant to understanding the pathogenesis of chronic obstructive pulmonary disease (COPD). First, attenuation of lung growth due to air pollution in childhood is a risk factor for adult-onset respiratory disease. Second, there may be common cellular and molecular mechanisms underlying impaired pulmonary innate host defenses in children exposed to air pollution, and the susceptibility to infection in COPD. Third, lung damage initiated in childhood may contribute to an emerging global health issue, namely, COPD due to tobacco smoke exposure [7].

According to the literature, the nature of the development of pathology, clinical manifestations and the course of diseases of the broncho-pulmonary system are determined not only by the duration of the influence of harmful factors, but also on the individual characteristics of the organism [8]. Therefore, an important internal risk factor for the development of CB is the genetic predisposition, with which the features of immunological reactivity, growth and development of the lungs are closely linked [8]. Today, the genetic mechanisms of the formation of COPD in adults have become the object of large-scale research around the world [9,10,11]. But in childhood, the genetic risk factors for chronic respiratory diseases, except for bronchial asthma and cystic fibrosis, have practically not been studied. Thus, the study of the role of tobacco smoking in the development of CB in children and adolescents, analysis of molecular genetic factors can provide additional information on the mechanisms of its formation. It will allow to predict these conditions and develop methods of its prevention.

## THE AIM

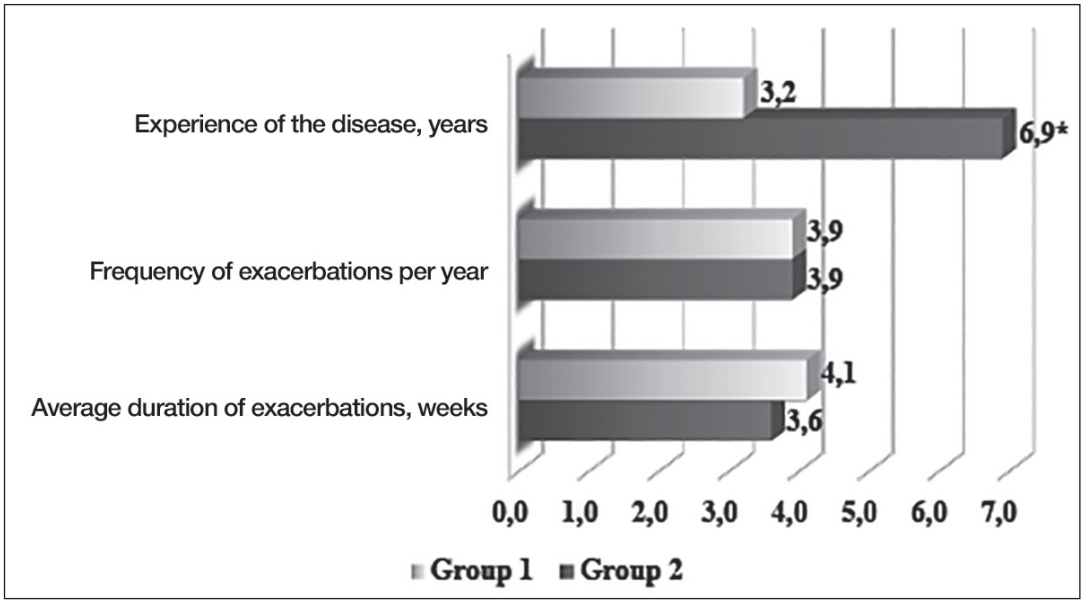
The aim of the investigation is to study the clinical features of the course of CB in adolescent smokers and to study the genetic risk factors for the development of COPD.

## MATERIALS AND METHODS

We examined 107 adolescents. All patients were divided into three groups. The Group 1 consisted of 40 adolescent smok-

**Table 1.** Indicators of the tobacco smoking status in adolescent smokers, Me (Q25; Q75)

| Indicator | Group 1 (n=40) | Control group (n=37) | p |
|---|---|---|---|
| Age of the beginning of smoking, years | 14,0 (12,0; 14,0) | 14,0 (13,0; 15,0) | p>0,05 |
| Experience of active tobacco smoking, years | 4,0 (3,0; 5,5) | 2,0 (1,0; 2,0) | p<0,05 |
| Number of smoked cigarettes per day, pieces | 10,0 (10,0; 13,5) | 7,0 (5,0; 10,0) | p<0,05 |
| Smoking index | 120,0 (120,0; 162,0) | 84,0 (60,0; 120,0) | p<0,05 |
| «Pack/year» | 2,0 (1,5; 3,25) | 0,5 (0,25; 1,0) | p<0,05 |




*: significance of differences (p<0,05)

**Figure 1.** Clinical and anamnestic features of the course of chronic bronchitis in the examined adolescents

ers with chronic bronchitis (mean age – 17.5±0.2 years). The Group 2 consisted of 30 never-smokers adolescents with chronic bronchitis (mean age – 16.0±0.4 years). The Group 3 (control group) consisted of 37 healthy adolescents-smokers (average age – 16.3±0.3 years). Verification of the diagnosis was carried out and based on standard criteria (a laboratory-clinical and instrumental examination).

The study included the collection of anamnesis and objective examination. The status of smoking among adolescent smokers has been examined as a risk factor for the development of the disease with the calculation of the smoking index (SI was defined as number of cigarettes smoked per day multiplied by years smoked) and the indicator «pack/year» ((number of cigarettes smoked per day/20) × number of years smoked).

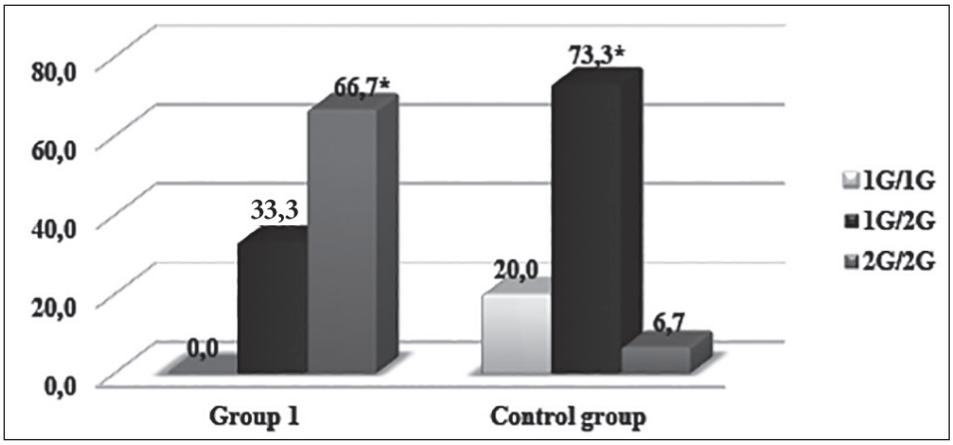
To achieve the aim, the MMP1 gene -1607 1G/2G (rs1799750) polymorphism, CYP1A1 gene T3801C polymorphism have been studied. Molecular genetic investigations were performed at the Institute of Hereditary Pathology, Academy of Medical Sciences of Ukraine.

All statistical calculations were performed by means of Statistica v 10.0. The results were defined as means ± standard deviation (SD) and Me (Q25; Q75). Each of the SNPs in the five genes was analyzed for Hardy-Weinberg equilibrium (HWE) using a computer program for analyzing genetic data «GeneExpert» (http://gen-exp.ru/calculator_or.php). To determine the SNPs associated with the risk of CB, the frequencies of the genotypes of the three study groups were compared, and the odds ratio (OR) was calculated with a 95% CI. Statistical significance was defined as p<0.05.

## RESULTS AND DISCUSSION

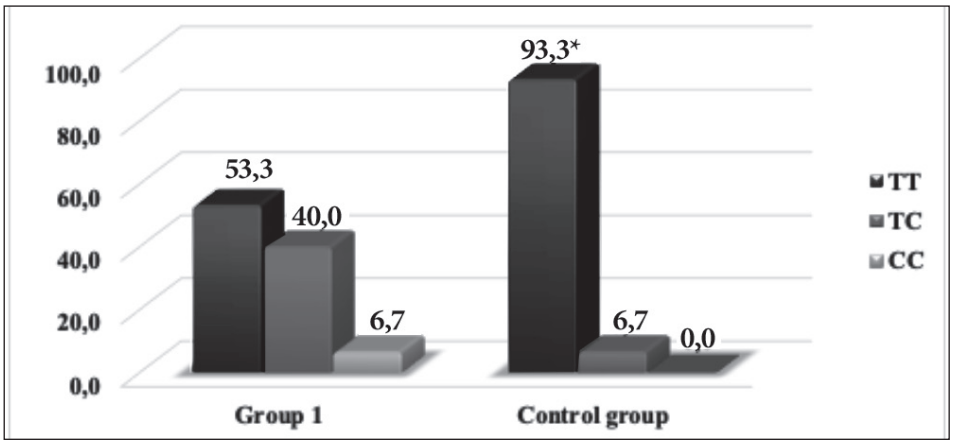
The analysis of the tobacco smoking status showed that patients of the Group 1 compared to control were 2,0 times more likely to experience tobacco smoking (p<0,05), table 1.

In addition, they smoked significantly more cigarettes per day than control (in 1,4 times respectively; p<0,05), had significantly higher values of SI (in 1,4 times respectively;




*: significance of differences (p<0,05)

**Figure 2.** Genotype frequencies of MMP1 gene -1607 1G/2G (rs1799750) polymorphism in the studied groups




*: significance of differences (p<0,05)

**Figure 3.** Genotype frequencies of CYP1A1 gene T3801C polymorphism in the studied groups

p<0,05) and the indicator "Pack/year" (4,0 times; p<0,05).

Comparison of clinical features of the course of bronchitis has shown that in patients of Group 2 the average length of the disease was significantly superior to those in Group 1 and was (6.9 ± 0.8) years vs (3.2 ± 0.2) respectively (p<0,05), figure.1.

The number of exacerbations per year in patients of Group 1 and Group 2 practically did not differ and was (3.9±0.1) vs (3.9±0.3) (p>0.05). However, in patients of Group 1, the duration of exacerbations was significantly higher than in patients of the Group 2 (4.1 ± 0.1 weeks versus 3.6 ± 0.1 weeks) (p <0.05). (p<0,05).

It was found that in adolescent smokers of Group 1, the duration of exacerbations significantly differed, and the frequency of exacerbations correlated with the number of smoked cigarettes per day (r=+0,56; p<0,05), SI (r=+0,56; p<0,05) and the "Pack-year" (r=+0,59; p<0,05).

The analysis of clinical data showed that the course of CB in adolescent smokers in the period of clinical remission was characterized by complaints of permanent (65.0 % vs 12.5 %; p<0,05) low-productive cough (95.0 % vs 18.7 %; p<0,001) predominantly in the morning (90.0 % vs 25.0 %; p<0,001). Periods of exacerbation in patients of Group 1 compared to Group 2, according to primary medical documentation, were characterized by the absence of seasonality (90.0 % vs 25.0 %; p<0,001), complaints of low-productive cough (80.0 % vs 31.2 %; p<0,01) with predominantly mucosal sputum (85.0 % vs 25.0 %; p<0,001), dyspnea during exercise (60.0 % vs 25.0 %; p<0,05) and prevalence during auscultation of dry wheezing (70.0 % vs 6.3 %; p<0,05). In patients of Group 2 were more likely to hear moist rales (56.2 % versus 20.0 %; p<0.05) and mixed rales (37.5 % vs 10.0 %; p<0,05) at auscultation.

The results of the molecular genetic study revealed a statistically significant difference between Group 1 and control, figure 2.

When comparing the frequencies of the genotypes of the MMP1 gene -1607 1G/2G (rs1799750) polymorphism in patients of Group 1 compared with control, the frequency of the homozygous genotype 2G/2G was significantly higher (66.7 % vs 6.7 %; OR=28.00; 95 % CI (2.82-277.97)). In the control group, the heterozygous genotype 1G / 2G is more common (73.3 % vs 33.3 %; OR=0.18; 95 % CI (0.04-0.87)).

The analysis of the frequency distribution of genotypes of the CYP1A1 gene showed a significant increase in the proportion of homozygous TT carriers in the control group compared to Group 1 (93.3 % vs 53.3 %, $\chi 2$=6.21, p<0.05), figure 3.

Thus, the molecular genetic study revealed the association of the 2G/2G genotype of MMP1 gene -1607 1G/2G (rs1799750) polymorphism (OR=28.00; 95 % CI (2.82-277.97)) with the development of chronic bronchitis in adolescent smokers. The TT genotype of CYP1A1 gene T3801C polymorphism (OR=0.08; 95 % CI (0.01-0.79)) may be considered as a possible sustainability factor for the development of chronic bronchitis in adolescent smokers.

## CONCLUSIONS

1. Tobacco smoking leads to the development of chronic bronchitis as early as adolescence and affects its course, increasing the frequency and duration of exacerbations.
2. The 2G/2G genotype of MMP1 gene -1607 1G/2G (rs1799750) polymorphism can be considered as a risk factor for the development of chronic bronchitis in Ukrainian adolescent smokers and chronic obstructive pulmonary disease in the future.
3. The presence of TT genotype of CYP1A1 gene T3801C polymorphism in adolescent smokers can be considered as a possible marker of resistance to chronic diseases of the respiratory system.
4. The study of the genes for chronic obstructive pulmonary disease in childhood and adolescence will contribute to the early detection of high-risk patients for the formation of this pathology, which will make it possible to carry out the necessary preventive measures and to maximize postponement of the disease.

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**Conflicts of interest:**

*Authors declare no conflict of interest.*


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