Genetic Contribution of CFTR Mutations to Chronic Bronchitis in Children: A Case-Control Study

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Abstract

Background: Chronic bronchitis and bronchial asthma are significant respiratory conditions with complex etiologies influenced by genetic and environmental factors. Mutations in the CFTR gene have been implicated in severe respiratory diseases, underscoring the need to explore their association with these conditions. Methods: This study included 150 children with chronic bronchitis and bronchial asthma, alongside a control group of 60 healthy children. Clinical and genealogical analyses were conducted to evaluate hereditary predisposition. Molecular genetic studies focused on eight common CFTR mutations (F508del, W1282X, and N1303K) using RT-PCR with real-time detection. Statistical analyses, including Hardy-Weinberg equilibrium testing and odds ratio calculations, assessed genetic associations. Results: A hereditary predisposition was identified in 32.3% of parents of affected children. Among the patients, heterozygous CFTR mutations were detected, with F508del in 6.25%, W1282X in 2.1%, and N1303K in 2.1%. These findings suggest a strong genetic influence in the studied population. Conclusion: This study reinforces the role of CFTR mutations in chronic bronchitis and bronchial asthma, highlighting the genetic basis of these conditions. Future research should explore additional candidate genes and unidentified CFTR variants to enhance predictive medicine and personalized treatment strategies.

Keywords: CFTR mutations, chronic bronchitis, hereditary predisposition, pediatric respiratory diseases, genetic etiology

Significance | This study determined the CFTR mutations' role in pediatric chronic bronchitis, advancing understanding and paving the way for predictive genetic medicine.

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Introduction

The study of heredity in the development of chronic respiratory diseases has gained significance due to advancements in clinical and diagnostic technologies and the increasing prevalence of bronchopulmonary conditions in children. Understanding the genetic predisposition to these diseases is critical for their early detection, particularly in high-risk groups, through modern, high-tech diagnostic methods (Diab Cáceres & Zamarrón de Lucas, 2023).

Chronic bronchitis, a disease classified under chronic obstructive pulmonary diseases (COPD) alongside emphysema and bronchial asthma, remains poorly understood despite its prevalence. In Uzbekistan, chronic bronchitis constitutes 70–85% of COPD cases, affecting approximately 1,550 per 100,000 individuals (Kesimer et al., 2021). Additionally, chronic bronchitis contributes to 80% of bronchopulmonary disease-related deaths and causes disability in 50% of cases (Diab Cáceres & Zamarrón de Lucas, 2023). Despite this, gaps persist in understanding the etiology, pathogenesis, and effective early diagnostic measures for chronic bronchitis, necessitating further research.

Hereditary lung diseases pose unique diagnostic, pathogenetic, and therapeutic challenges. They are frequently mistaken for non-specific chronic lung diseases, complicating their identification and treatment (Roesch et al., 2018). N. P. Bochkov and colleagues

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highlighted that recurrent and chronic, treatment-resistant respiratory conditions in childhood often involve hereditary factors (Ramananda et al., 2024). Among these conditions, cystic fibrosis (CF), caused by mutations in the CFTR gene, stands out due to its autosomal recessive inheritance and multisystem involvement, primarily affecting the respiratory system (Kesimer et al., 2021).

CF accounts for 14.5% of chronic and recurrent bronchopulmonary conditions in children. Its clinical presentation, characterized by CFTR dysfunction, includes atypical and subtle symptoms, requiring differential diagnoses for conditions such as recurrent pneumonia, chronic bronchitis, and bronchial asthma (Solomon et al., 2016). Most CF cases manifest within the first year of life, although "soft" mutations may delay diagnosis until later childhood, as seen in rare cases (Miravitlles et al., 2024). International guidelines recommend sweat testing in children with asthma or recurrent bronchitis to exclude CF when clinical signs and radiographic changes suggest infection (Barben et al., 2021).

In the context of Uzbekistan, molecular genetic testing has become an integral part of diagnosing chronic bronchopulmonary diseases. Recent studies on children presenting with chronic bronchopulmonary symptoms revealed cases initially misdiagnosed as pulmonary CF or bronchopneumonia. Comprehensive assessments, including sweat testing and imaging, eventually led to revised diagnoses of recurrent or chronic bronchitis (Solomon et al., 2016). These findings underscore the importance of integrating molecular genetic methods for accurate diagnosis, particularly in resource-limited settings. This study aimed to determine the genetic predisposition to chronic bronchitis among school-aged children in Uzbekistan.

2. Materials and methods

To achieve the study's objective, 150 children diagnosed with chronic bronchial diseases, including chronic bronchitis and bronchial asthma, were selected. These children were treated at the pulmonology department of the Republican Specialized Scientific and Practical Center of Pediatrics, Ministry of Health of the Republic of Uzbekistan, and the Bukhara Regional Children's Multidisciplinary Medical Center.

2.1 Genetic and Clinical Investigations

Molecular genetic studies were conducted in the Human Genomics Laboratory at the Institute of Immunology and Genomics, Academy of Sciences of the Republic of Uzbekistan. The primary focus was to examine the polymorphism of the *CFTR* gene in children with chronic bronchitis and bronchial asthma. Genetic analysis targeted the eight most frequent mutations associated with cystic fibrosis (CF).

Among the 150 children, 48 individuals presenting moderate to severe disease severity were selected for genetic analysis. A control group comprising 60 healthy children was included for comparative purposes. Clinical and genealogical research was conducted for all participants. This involved analyzing family pedigrees to determine patterns of disease inheritance, using questionnaires to collect relevant familial and personal medical history. Pedigree analysis identified potential hereditary links and was crucial for establishing the genetic predisposition of chronic bronchitis in the study population.

2.2 Genetic Testing and Analysis

Genotyping was performed using real-time polymerase chain reaction (RT-PCR) with reagent kits from RPA DNA-Technology and Synthol (Moscow, RF). The RT-PCR included:

Amplification of DNA.

Real-time detection of PCR results.

Melting curve analysis.

Endpoint and qualitative analysis.

The genotyping results were statistically analyzed according to Hardy-Weinberg equilibrium principles. The Chi-square (χ^2) test was applied to compare observed and expected genotype frequencies. Pairwise comparisons of genotypes and alleles were conducted using Fisher's exact test. Associations between genetic markers and disease risk were evaluated using the odds ratio (OR), calculated as OR=adbcOR = \frac{ad}{bc}OR=bcad, where:

aaa = Number of patients carrying the marker.

bbb = Number of patients without the marker.

ccc and ddd = Corresponding frequencies in the control group.

Interpretation of OR values was as follows:

OR=1OR = 1OR=1: No association.

OR>1OR > 1OR>1: Positive association (risk factor).

OR<1OR < 1OR<1: Negative association (protective factor).

2.3 Statistical Significance

The statistical analysis was performed using standard methods to ensure reliability. Statistical significance was set at $p<0.05p < 0.05p<0.05$, ensuring robust conclusions about the genetic associations with chronic bronchitis.

2.4 Ethical Considerations

The study was conducted in compliance with ethical standards, including obtaining informed consent from the participants' parents or guardians. Ethical approval was obtained from relevant institutional review boards.

3. Results and Discussion

An analysis of the hereditary burden of bronchopulmonary diseases revealed that 66.7% of parents of children with chronic bronchitis and bronchial asthma did not have a history of bronchopulmonary pathology. However, 32.3% of the parents exhibited a hereditary predisposition to these conditions, as demonstrated through clinical and genealogical research (Figure 1). Among these, chronic

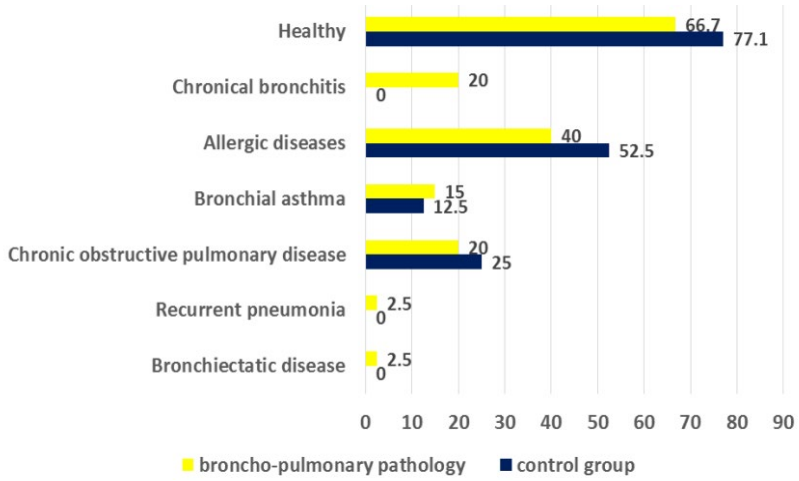

Figure 1. Distribution of hereditary predisposition and allergic diseases in the study population.

Table 1. Frequency of CFTR gene mutations in children with chronic bronchitis.

Diagnosed mutations in the CFTR gene	Cases (48)	Control (60)	χ2	value
CFTR F508de1	0.045	0	3.06	0.04
CFTR G542X	0	0	0	1
CFTR W1282X	0.015	0	1.02	0.11
CFTR N1303K	0.015	0	1.02	0.11
CFTR 2143de1T	0	0	0	1
CFTR 2184insA	0	0	0	1
CFTR 3849+10kbC> T	0	0	0	1
CFTR dele 21kb	0	0	0	1

bronchitis was identified in 20% of the cases, while allergic diseases were noted in 40% of the main group and 62.5% of the control group (Figure 1). This highlights a notable familial link to bronchopulmonary diseases.

Genotyping conducted on the cohort of children with chronic bronchitis identified heterozygous mutations in the *CFTR* gene, specifically *F508del* (6.25%, 3 children), *W1282X* (2.1%, 1 child), and *N1303K* (2.1%, 1 child). These findings underline the genetic variability among affected individuals (Table 1).

The results indicate a significant hereditary predisposition to bronchopulmonary diseases, emphasizing the role of genetic factors in the etiology of chronic bronchitis and bronchial asthma. A history of chronic bronchitis in parents, coupled with the high prevalence of allergic conditions, further supports the genetic linkage. This aligns with prior research indicating that hereditary factors significantly contribute to the pathogenesis of respiratory diseases (Raju et al., 2016)ion of heterozygous *CFTR* mutations (*F508del*, *W1282X*, and *N1303K*) among children with chronic bronchitis underscores the relevance of *CFTR* gene variants in bronchopulmonary pathology. The *F508del* mutation, detected in 6.25% of the cases, has been frequently associated with severe respiratory diseases (Solomon et al., 2016) . These findings highlighting the increased occurrence of heterozygous *CFTR* mutations in non-cystic fibrosis conditions such as chronic bronchitis (Kesimer et al., 2021) .

Additionally, allergic diseasesnt in both the study and control groups, suggest potential environmental or non-genetic contributions. This reinforces the multifactorial nature of bronchopulmonary disorders, where genetic predisposition interacts with external factors (Diab Cáceres & Zamarrón de Lucas, 2023).

The obse*CFTR* mutations with chronic bronchitis necessitates further investigation to elucidate the functional consequences of these variants. Expanding the analysis to include a broader array of candidate genes could enhance the understanding of genetic contributions to respiratory diseases (Ramananda et al., 2024) . Moreover, as unidentified *CFTR* mutations may exist, whole-genome seould provide comprehensive insights, paving the way for predictive medicine and tailored therapeutic strategies.

4. Conclusion

This study determined the significant hereditary predisposition to chronic bronchitis and bronchial asthma, as observed in 32.3% of parents of affected children. Through genotyping, key mutations in the CFTR gene, including F508del, W1282X, and N1303K, were identified in children with chronic bronchitis,

reinforcing the strong genetic component in the disease's etiology. The association of these mutations aligns with prior research, emphasizing the role of CFTR dysfunction in severe respiratory conditions. Despite this progress, the study underscores the necessity to expand investigations to include additional candidate genes and unidentified CFTR mutations, which may further elucidate the genetic architecture of chronic bronchitis. Moving forward, the integration of comprehensive genetic profiling with predictive medicine can enable earlier diagnosis, personalized treatment, and better management strategies. These findings provide a valuable foundation for advancing our understanding of chronic bronchitis and its genetic underpinnings, facilitating improved outcomes for affected children.

Author contributions

M.M.S. contributed to the conceptualization, methodology, data analysis, manuscript drafting, and supervision of the study. G.S.X. was responsible for investigation, data collection, statistical analysis, and manuscript editing. D.A.K. conducted the literature review, validation, and visualization of findings. N.R.A. handled experimental design, project administration, and final approval of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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