DOI: https://doi.org/10.17816/KMJ678486 EDN: DGXKHK

Unresolved Issues in Chronic Obstructive Pulmonary Disease: Perspectives in Genetic Research

Rustem F. Khamitov, Firyuza I. Sattarova, Emiliya S. Egorova

Kazan State Medical University, Kazan, Russia

ABSTRACT

The global prevalence of chronic obstructive pulmonary disease among individuals aged >40 years is approximately 10%. The disease's progression, often leading to early disability, underscores its significant medical and social impact. Further research of risk factors, particularly genetic underpinnings, of chronic obstructive pulmonary disease is essential for developing effective primary prevention strategies in genetically predisposed individuals. This review aimed to analyze international and Russian scientific sources on genetic polymorphisms associated with chronic obstructive pulmonary disease and their roles in disease pathogenesis and examine the pharmacogenetic aspects of therapy, specifically how genetic variation affects drug efficacy and safety. Full-text articles published between 2000 and 2024 and indexed in *PubMed*, *eLIBRARY.RU*, *Google Scholar*, and *ResearchGate* were analyzed. This review summarizes key genetic studies on chronic obstructive pulmonary disease, including comorbidities and pharmacogenetic characteristics of commonly used drugs. Research on heritable factors confirmed that genetic susceptibility increases the risk of chronic obstructive pulmonary disease. Several variables influence therapeutic response, among which genetic factors are critical for guiding treatment choices. Large-scale genome-wide association studies have identified chronic obstructive pulmonary disease-associated loci that contribute to our understanding of disease pathogenesis. Polygenic risk scores based on multiple single-nucleotide polymorphisms have demonstrated efficacy in predicting disease risk and severity and may be useful in predictive medicine. The investigation of genetic polymorphisms offers promising opportunities for the advancement of personalized approaches to the prediction, prevention, and treatment of chronic obstructive pulmonary disease.

Keywords: review; chronic obstructive pulmonary disease; comorbidity; genetic polymorphisms; genome-wide association studies; pharmacogenetics.

To cite this article:
Khamitov RF, Sattarova FI, Egorova ES. Unresolved issues in chronic obstructive pulmonary disease: perspectives in genetic research. *Kazan Medical Journal.* 2025;106(4):578–589. DOI: 10.17816/KMJ678486 EDN: DGXKHK

Submitted: 12.04.2025 **Accepted**: 02.06.2025 **Published online**: 25.07.2025

DOI: https://doi.org/10.17816/KMJ678486 EDN: DGXKHK

Нерешённые вопросы хронической обструктивной болезни лёгких: перспективы генетических исследований

Р.Ф. Хамитов, Ф.И. Саттарова, Э.С. Егорова

Казанский государственный медицинский университет, г. Казань, Россия

АННОТАЦИЯ

Распространённость хронической обструктивной болезни лёгких в мире среди лиц старше 40 лет составляет около 10%. Наряду с этим неуклонное прогрессирование заболевания, приводящее к ранней инвалидизации, определяет высокую медико-социальную значимость заболевания. Требуется дальнейшее изучение факторов риска, включая генетические особенности хронической обструктивной болезни лёгких, с целью разработки эффективной первичной профилактики среди предрасположенных лиц. Целью нашего исследования явился обзор зарубежной и отечественной научной медицинской литературы, посвящённой генетическим полиморфизмам, ассоциированным с хронической обструктивной болезнью лёгких, и их роли в патогенезе заболевания, а также анализ фармакогенетических аспектов терапии — влияние генетических полиморфизмов на эффективность и безопасность лекарственных препаратов. Проанализированы полнотекстовые публикации за период с 2000 по 2024 год, размещённые в базах данных PubMed, eLibrary.Ru, Google Scholar, ResearchGate. Представлен анализ наиболее важных генетических исследований хронической обструктивной болезни лёгких, включая данные о сочетании заболевания с коморбидными состояниями и особенностях фармакогенетики препаратов. Исследования, посвящённые наследственным факторам, убедительно подтверждают, что генетическая предрасположенность существенно повышает риск развития заболевания. Реакция на лекарственные препараты зависит от множества факторов, среди которых важную роль играют генетические особенности, определяющие выбор терапии. Полногеномные исследования ассоциаций в крупных выборках пациентов позволяют выявить достоверно связанные с заболеванием локусы и играют важную роль в уточнении патогенеза. Шкалы генетического риска, строящиеся на основе объединения эффектов нескольких однонуклеотидных полиморфизмов, показали свою эффективность в прогнозировании риска и тяжести хронической обструктивной болезни лёгких. В дальнейшем такие шкалы могут иметь клиническое значение в рамках предиктивной медицины. Изучение генетических полиморфизмов открывает перспективы для разработки персонализированных медицинских подходов к прогнозированию, профилактике и лечению хронической обструктивной болезни лёгких.

Ключевые слова: обзор; хроническая обструктивная болезнь лёгких; коморбидность; генетические полиморфизмы; полногеномные исследования; фармакогенетика препаратов.

Как цитировать:
Хамитов Р.Ф., Саттарова Ф.И., Егорова Э.С. Нерешённые вопросы хронической обструктивной болезни лёгких: перспективы генетических исследований // Казанский медицинский журнал. 2025. Т. 106, № 4. С. 578–589. DOI: 10.17816/KMJ678486 EDN: DGXKHK

Рукопись получена: 12.04.2025 **Рукопись одобрена:** 02.06.2025 **Опубликована online:** 25.07.2025

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by chronic respiratory symptoms (dyspnea, cough, and sputum production) and exacerbations due to airway (bronchitis and bronchiolitis) and/or alveolar (emphysema) lesions that cause persistent and often progressive airflow limitation. Exacerbations and comorbid conditions are inherent components of COPD and significantly contribute to its clinical presentation [1].

According to studies, the worldwide prevalence of COPD among people aged >40 years is 12.64%, with the highest incidence in the over-60 population. Aging is considered a crucial risk factor for COPD development [2].

In Russia, 2.4 million people are registered as having been diagnosed with COPD [3]. However, these data are inaccurate. According to epidemiological studies of the Russian Respiratory Society, the actual number of patients is approximately 11 million, including undiagnosed cases [3].

COPD is a leading cause of respiratory morbidity and mortality globally [4]. The COPD mortality rate is 42.5 per 100,000 people, ranking third among the causes of death worldwide. Annually, approximately 3.23 million people die from COPD [5, 6].

The high prevalence of COPD is due to environmental degradation, increased prevalence of tobacco smoking and heating systems, and recurrent respiratory infections [5]. Exposure to harmful particles or gases, such as from active or passive smoking, environmental pollution, or the use of biomass for cooking and residential heating, has been found to be an etiological factor of COPD [1].

COPD is frequently accompanied by other pathologies, including cardiovascular disease (CVD). CVD is common among patients with COPD and significantly contributes to overall morbidity and mortality. COPD is often associated with coronary heart disease (CHD), heart failure (HF), atrial fibrillation, peripheral vascular disease, pulmonary hypertension, and stroke [7, 8].

This relationship is explained by the fact that COPD and CVD have common risk factors, including smoking, poor diet, age, sex, lack of physical activity, and obesity. The key mechanisms linking COPD and CVD are systemic inflammation, oxidative stress, and endothelial dysfunction [9–12]. Additionally, obstructive lung dysfunction is a risk factor of cardiovascular mortality comparable to major cardiovascular risk factors [6].

The Lung Health Study, which included 5887 smokers aged 35–60 years with moderate bronchial obstruction, found that a 10% decrease in forced expiratory volume in the first second (FEV_1) was associated with a 14% increase in total mortality, 28% increase in cardiovascular mortality, and 20% increase in the risk of CHD [13]. Concomitant CVD significantly affects quality of life, increases hospitalization frequency, and worsens survival rates in patients [8, 10].

For an extended period, COPD has been believed to be predominantly caused by external factors [1]. However, studies on heritability have demonstrated that genetic factors significantly increase the risk of developing this disease. COPD heritability estimates range from 20% to 40% for airflow limitation and up to 60% for smoking-related phenotypes [14]. Studies employing twin samples have shown that the heritability of COPD is approximately 60% [15].

The steady progression of COPD, which leads to early disability, and the high prevalence of working-age individuals among patients emphasize the disease's significant medical and social impact [5]. Further study of the risk factors of COPD, including genetic features, is required to develop effective primary prevention strategies for predisposed individuals. Identifying genetic factors may help explain the heterogeneity of COPD, assess individual susceptibility, predict the course of the disease, and develop new, personalized treatment approaches [16].

This review aimed to analyze international and Russian scientific studies on genetic polymorphisms associated with COPD and their roles in disease pathogenesis and examine the pharmacogenetic aspects of therapy, specifically how genetic variation affects drug efficacy.

A data search was performed using PubMed, eLibrary.Ru, Google Scholar, and ResearchGate between 2000 and 2024. Full-text articles on COPD genetics and the pharmacogenetics of drugs used to treat COPD were analyzed. The keywords used in the search were *ХОБЛ* (*COPD*), *генетика* (*genetics*), *генетический полиморфизм* (*genetic polymorphism*), *genotype, inhaled bronchodilators, β2-agonists, muscarinic receptor antagonists, inhaled corticosteroids*, and *comorbidity*.

Initially, studies focused on analyzing a few single-nucleotide polymorphisms (SNPs), which are single-nucleotide substitutions in the deoxyribonucleic acid (DNA) sequence, in or near candidate genes that play a role in COPD pathogenesis. One particularly important SNP is associated with alpha-1-antitrypsin (AAT) deficiency, which may lead to the development of COPD symptoms at a young age. Severe AAT deficiency is the most studied genetic risk factor of COPD and the only genetic COPD subtype for which a specific treatment has been developed. The most common cause of severe AAT deficiency is homozygosity for the *SERPINA1**Z allele, which results from a single-nucleotide substitution in the *SERPINA1* gene's coding sequence. This substitution of one amino acid changes the AAT protein's structure [17]. Consequently, the protein loses its ability to inhibit neutrophil elastase, resulting in the destruction of elastic fibers in the lungs and development of emphysema [18].

As technology has advanced, single-gene studies have been replaced by genome-wide association studies (GWASs), which determine associations between gene polymorphisms and traits or diseases at the genome-wide level. The first GWAS of COPD, which was conducted in 2009, identified a locus near the *CHRNA3/CHRNA5/IREB2* genes and a region near the *HHIP* gene [19]. Subsequent, larger-scale studies identified additional genome regions near the *FAM13A, RIN3, CYP2A6,* and *DSP* genes [20].

DOI: https://doi.org/10.17816/KMJ678486

Hobbs et al. (2017) conducted a study of 15,256 patients with COPD and 47,936 healthy individuals from different ethnic groups and found 22 loci with genome-wide significance, 13 of which were identified for the first time. However, despite the large sample size, there were not enough non-European participants to conduct a complete trans-ethnic genetic analysis. Newly identified loci included *ADGRG6/GPR126, THSD4, ADAM19, TET2, CFDP1, AGER, ARMC2, RARB, EEFSEC, DSP, MTCL1,* and *SFTPD.* These genes influence inflammation, lung remodeling, oxidative stress, and epithelial dysfunction [21]. In previous GWASs, loci have been identified in specific genes: *HHIP, CHRNA5, HTR4, FAM13A, RIN3, TGFB2, GSTCD-NPNT, CYP2A6,* and *IL27—CCDC101*. These genes play a role in lung development and repair and in processes such as proliferation, apoptosis, airway remodeling, inflammatory responses, antioxidant defense, and nicotine dependence. The authors used several independent cohorts to comprehensively analyze genetic susceptibility; however, some sample sizes remained limited. The NETT study included only 389 patients with COPD [19, 22].

New data on the genetic architecture of COPD reveal the significant genetic component of this disease and indicate the need for further research. A 2019 large-scale GWAS including 35,735 patients with COPD and 222,076 healthy individuals identified 82 genetic markers [20].

Chen et al. utilized full-transcriptome association studies—a method that allows for identifying the relationship between inherited traits and changes in predicted gene expression levels—to examine 21,617 patients with COPD and 372,627 controls. They identified a new COPD marker: the *GRK4* gene. This gene is involved in oxidative stress and inflammatory processes. Therefore, it is a potential target for personalized COPD therapy and may form the basis for COPD-targeted therapy [23].

The transient receptor potential (TRP) family is critical in perceiving external stimuli, such as temperature, chemicals, and mechanical effects, and in regulating intracellular calcium. In patients with COPD, increased *TRPA1* expression in the bronchial epithelium is associated with airway hyperresponsiveness and chronic cough. Individuals with the rs11988795 polymorphism of this gene have an increased risk of developing COPD due to an increased oxidative stress response to cigarette smoke. The *TRPV1* gene contributes to neurogenic inflammation and worsens bronchoconstriction [24].

Activation of the *TRPV4* gene causes the breakdown of the alveolar barrier and increased pulmonary edema. The *TRPM8* gene, which is responsible for bronchodilation, is expressed in airway smooth muscle cells. *TRPM8* gene suppression has been observed in individuals with COPD and may contribute to obstruction [25]. The *TRPM2* and *TRPM7* genes activate macrophages and neutrophils, increasing the release of interleukin-8 and tumor necrosis factor alpha. These are key mediators of inflammation in COPD [25].

Smoking remains the primary cause of COPD [1, 5]. As smoking is an addictive behavior, genetic polymorphisms associated with this habit are of particular interest. Furthermore, loci associated with nicotine metabolism have been linked to an increased risk of COPD. CHRNA5, CYP2A6, SERPINA1, and MECOM are among these loci that correlate with COPD and behavioral aspects, such as smoking status [26]. These genetic variants underscore the complex interplay between genetic predisposition and environmental influences in disease development. Among the genetic polymorphisms associated with COPD and sensitivity to tobacco smoke exposure, the AA genotype of the *CHRNA5* polymorphic locus is particularly notable. This genotype is associated with an increased risk of COPD, smoking status, and lung cancer [27].

Genetic studies on COPD have been conducted worldwide. Lee et al. (2020) investigated 130 patients with early-stage COPD and 3478 controls (1700 past smokers and 1778 nonsmokers) in a Korean population. They identified two polymorphisms (rs2857210 and rs2621419) in the *HLA-DQB2* gene associated with COPD susceptibility in nonsmokers and examined the association of SNPs with spirometric data [28].

GWASs have increased the understanding on COPD genetics [19]. The genetic markers identified in these studies are used to create genetic risk scales that account for the polygenic contribution to different COPD phenotypes. According to modern concepts, a phenotype is not primarily influenced by single rare variants with large effect sizes, but by the aggregate of many common variants with small effects [29]. The Framingham Heart Study demonstrated that a polygenic risk assessment for COPD enables the more accurate detection of undiagnosed cases of the disease [30]. Consequently, polygenic COPD risk assessment facilitates an earlier diagnosis of COPD and maintains its prognostic value even when known risk factors characteristic of early life are considered [31].

COPD is a disease with sex-based differences in susceptibility and clinical manifestations. Men are known to be affected more frequently [1]. This is primarily due to smoking. However, recently, the number of female smokers has increased, as evidenced by the increasing prevalence of COPD among women. According to research, female patients exhibit a more pronounced clinical presentation of the disease, often accompanied by associated conditions such as anxiety, depression, cachexia, and osteoporosis. In addition, the study revealed sex differences in airway wall structure. In women, the airway lumen was anatomically narrower, and the walls were thicker. These differences may be related to genetic features [32].

Furthermore, Joo and Himes (2022) conducted a sex-disaggregated GWAS that included 12,958 men and 11,311 women with COPD. The control group consisted of 95,631 males and 123,714 females. As in most previous studies, the participants were predominantly from European populations. The researchers identified sex-linked loci, eight of which were specific to males and five to females. The *C5orf56* locus was strongly associated with COPD in men, but not in women. *C5orf56* is a long noncoding gene called *IRF1-AS1*. The neighboring *IRF1* gene encodes interferon regulatory

factor 1, which is responsible for the antiviral response of the airway epithelium. As viruses can exacerbate COPD, this locus may influence susceptibility to the disease by altering the body's response to viral exposure. However, the mechanisms through which the *ARHGEF3, C1orf87*, and *C10orf1* loci influence COPD in men remain unclear. Additional male-specific associations were identified at the *CFDP1, TMEM170A*, and *CHST6* loci, which are linked to CHD and COPD [33]. Furthermore, the study identified COPD risk loci among women in the *ASTN2* and *TRIM32* regions at the 9q33.1 and in the 16q22.1 locus and in several associated genes [33].

Similarly, Hardin et al. identified sex-dependent genetic risk factors of COPD. One such factor is the *CELSR1* gene, which is associated with an increased risk of COPD in women. This finding indicates the importance of considering sex differences in genetic studies and treatment approaches [34].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND PULMONARY FIBROSIS

In addition to increasing susceptibility to COPD, some genetic loci may induce protective effects against other diseases. The genotype of the *FAM13A* polymorphic locus, which is associated with an increased risk of COPD, is also associated with a decreased risk of pulmonary fibrosis. However, some studies have found inverse relationships. Xu et al. (2017) reported that polymorphisms in the *MMP-9* (C-1562T) and *TGF-β1* (T869C) genes are present in patients with COPD accompanied by severe emphysema in the upper lobes of the lungs. Moreover, these polymorphisms are associated with an increased risk of pulmonary fibrosis. These genes play a role in inflammatory processes, alveolar tissue degradation, and airway remodeling. However, this study had two limitations. First, the sample size was small, consisting of only 82 patients with COPD. Second, the study population was limited to the Chinese ethnicity [35]. In a study by Wain et al., (2017) the *ZGPAT* and *RTEL1* genes that play roles in the development of familial pulmonary fibrosis, were identified [36]. These findings underscore the complexity of genetic relationships among different respiratory diseases.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EMPHYSEMA

COPD is commonly accompanied by emphysema. Chest X-ray is used to assess the presence, severity, and distribution of emphysema. Areas with a density below –950 HU correspond to emphysema [37].

In the Multi-Ethnic Study of Atherosclerosis, Manichaikul et al. (2014) found a significant association between the *SNRPF* and *PPT2* loci and the risk of developing emphysema in a sample of 7914 people, reaching genome-wide significance levels [38].

Additionally, Scho et al. (2015) identified five genetic polymorphisms correlating with emphysema severity in over 12,000 patients of European and African–American descent in the COPDGene, ECLIPSE, GenKOLS, and NETT studies. These included two previously identified loci for COPD (polymorphisms of the *HHIP* and *CHRNA3* genes) and three new loci near the *SOWAHB, TRAPPC9*, and *KIAA1462* genes. However, the study included patients with COPD and smokers without COPD, which could obscure specific genetic effects [39].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CARDIOVASCULAR DISEASE

As previously mentioned, COPD is often associated with CVD [7, 8]. In a study involving 12,550 patients with COPD and 46,368 controls, Zhu et al. (2019) found 7 loci significantly associated with COPD and CHD: *CD3EAP, C19orf83, GIPR, FBXO46, AC074212.3, SIX5*, and *DMPK and BCAR1*. These genes influence disease development through systemic inflammation and oxidative stress, leading to airway remodeling and cell apoptosis. Because arterial hypertension is highly prevalent, the study investigated its association with COPD and identified 22 loci. The most significant of these was located near the *ARHGAP42* gene (rs633185). The genetic polymorphism rs7655625, which is associated with heart rate and arterial hypertension, should be emphasized. However, the findings require cautious interpretation owing to several limitations. The study was exclusively conducted on the European population, which complicates the generalizability of the results to other ethnic groups. Additionally, risk factors such as smoking, occupational hazards, and CVD phenotypes were excluded in the analysis [40].

The relationship between COPD and HF is currently being actively studied. Axson et al. conducted a retrospective cohort study involving over 86,000 patients in the British population and proved the negative impact of HF on COPD. However, the study had several limitations, including a short follow-up period after the start of therapy, lacking data on cardiac function parameters (e.g., ejection fraction), and incomplete information on treatment regimen compliance and drug dosages [41]. In a 2014 meta-analysis, Güder and Rutten confirmed an increased prevalence of HF among patients with COPD, emphasizing the critical role of systemic inflammation. The activation of the neurohumoral system along with systemic inflammation in patients with HF worsens COPD progression [42].

The aforementioned studies have prompted a debate on whether there is a causal relationship between COPD and HF. Jiang et al. (2024) conducted a Mendelian randomization study using data from two large genomic databases: the UK Biobank, which included COPD data from 423,796 participants of European descent, and the FinnGen consortium, which comprised 6033 HF cases and 123,000 controls. They demonstrated that COPD significantly increases the risk of developing HF. However, the study did not include data on the increased risk of COPD development in patients with HF [43].

DOI: https://doi.org/10.17816/KMJ678486

The identified loci influence COPD development and progression by affecting the pathogenetic level and causing systemic inflammation and oxidative stress, which lead to airway remodeling.

In the future, detected gene polymorphisms may be useful in calculating the risk of COPD development in persons with CVD and in predicting the probability of heart disease development in those with COPD.

Despite their significant contributions to the study of the genetic architecture of complex diseases, GWASs have several limitations. First, approximately 80% of the studies were conducted in European populations, which limits the extrapolation of findings to other ethnic groups. Second, although the statistical significance threshold ($p < 5 \times 10^{-8}$) is required to control for multiple comparisons, it may result in the omission of weak but biologically significant genetic signals [44].

Interpreting the results is challenging because most of the identified associated SNPs are in noncoding regions of the genome. This indicates that their pathogenic effect may be realized through the regulation of the expression of other genes. The mechanisms of this regulation should be further studied [44]. In addition, repeated studies in independent population cohorts are crucial to confirm and verify the findings. This is particularly important for establishing universal genetic markers of diseases and understanding population-specific genetic effects.

PERSPECTIVES ON MULTI-OMIC RESEARCH OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FROM PATHOGENESIS TO PERSONALIZED THERAPY

Integrating multi-omic data from genomic, epigenomic, proteomic, metabolomic, and microbiomic approaches is crucial for identifying reliable COPD biomarkers. Such approach allows for the investigation of the disease's molecular mechanisms [45]. Epigenetic changes, such as DNA methylation, play a pivotal role in COPD pathogenesis, reflecting the combined effects of environmental factors (e.g., smoking and air pollution) and genetic predisposition [46]. Patients exhibit significant changes in methylation patterns that affect genes associated with inflammation (e.g., *TNF* and *IL-6*), antioxidant defense (e.g., *GSTP1*), and tissue remodeling (e.g., *MMP9*) [47]. These epigenetic modifications contribute to COPD heterogeneity, initiating individual susceptibility to the disease, modulating inflammatory processes, and influencing response to therapy. This provides new opportunities for personalized treatment [48].

Analyzing microRNAs that regulate gene expression in COPD is an important research area. For example, miR-106b-5p in peripheral leukocytes may be a biomarker of disease severity [49]. Proteomic studies have made significant contributions by detecting marker proteins, such as alpha-1-acid glycoprotein, peroxiredoxin-2, and cadherin-5. Evaluating these proteins is superior to traditional methods for the early diagnosis of COPD [50]. Furthermore, respiratory microbiome dysbiosis contributes to chronic inflammation, impaired immunity, and increased susceptibility to infection [51, 52]. Metabolites of microbial origin, such as butyrate, homocysteine, and palmitate, are closely related to host genes associated with COPD [53].

Integrating multi-omic data at all stages of COPD is an effective way to identify new biomarkers and therapeutic targets [45]. Large-scale studies, including the profiling of the disease's early stages, are crucial for improving our understanding of COPD pathogenesis and developing new diagnostic and therapeutic strategies aimed at modifying the course of the disease.

PHARMACOGENETICS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Pharmacogenetics, a subspecialty of medical genetics, is the study of the role of genetic factors in the formation of pharmacological responses of the human body to drugs. The term was first proposed by German scientist F. Vogel in 1958.

Various factors determine the response to medications, including the patient's genetic characteristics. Inhaled bronchodilators are crucial in the treatment of chronic obstructive airway diseases, including bronchial asthma and COPD. However, the efficacy of treatment with these medications varies among patients, largely because of the influence of polymorphic loci on the individual response to bronchodilators [54, 55].

Beta-2 agonists are one of the most widely used drug groups for treating COPD. Individuals may respond differently to this therapy. Its efficacy depends on the initial degree of airway obstruction and the patient's age and smoking status [56]. Changes in the amino acid sequence of beta-2 adrenoreceptors, caused by SNPs, have an equally significant impact on their function. These changes lead to significant conformational and structural rearrangements that directly affect receptor function. Moreover, genetic polymorphisms may cause changes in the expression of genes that regulate beta-2 agonist target receptor function, which further explains variability in response to treatment [54–59].

Although pulmonologists strive to minimize the use of short-acting beta-agonists (SABAs) in favor of long-acting beta-agonists (LABAs), SABAs remain crucial owing to their prevalence in clinical practice. Thus, their pharmacogenetics continues to be studied. *KCNJ2* (rs2367245) and *KCNK1* (rs7552783) polymorphisms have been found to be associated with an effective response to SABAs [54].

The *ADRB2* gene, which encodes the beta-2 adrenergic receptor, is critical in the study of bronchodilator responses. This gene comprises three functional SNPs: Gly16Arg (G46A,

rs1042713), Gln27Glu (C79G, rs1042714), and Thr164Ile (C491T, rs1800888). The presence of the Arg16 allele is associated with decreased response to SABAs in patients with COPD. Individuals homozygous for Arg16 polymorphism exhibit an absence of bronchodilator effect from SABAs five times more frequently than those with the Gly16 allele, and heterozygotes exhibit this absence twice as often [57].

Several studies have found that the Thr164Ile polymorphism of the *ADRB2* gene may increase the risk of exacerbations in patients with bronchial asthma undergoing LABA therapy [58]. These exacerbations may lead to life-threatening conditions, indicating the importance of an individualized treatment approach for this patient population.

In Russian pharmacogenetic studies, COPD patients with the Arg16 and Gln27 alleles of the *ADRB2* gene demonstrated negative spirometry index dynamics, namely, decreased FEV_1 and forced vital capacity, despite formoterol and budesonide therapy. In contrast, positive dynamics in spirometry parameters were observed in individuals with the Gly16 and Glu27 alleles [59].

In a study involving 389 patients with severe COPD, Kim et al. (2009) revealed an association between the response to bronchodilator administration and SNPs in the *EPHX1, SERPINE2*, and *ADRB2* genes among six candidate genes and found that the rs1009668 SNP in the *EPHX1* gene was significantly associated with a poor response to bronchodilators [60].

A meta-analysis by Hardin et al. (2015) of 5789 COPD patients showed associations between responses to bronchodilators and SNPs in the *KCNJ2, CDH13*, and *GOLGA8B* genes. However, the results did not reach full genomic significance.

These findings emphasize the complex genetic landscape that affects response to bronchodilators in patients with COPD.

No other loci responsible for the expression of genes that regulate beta-2 agonist receptor function have been identified in ongoing pharmacogenetic studies of COPD.

Kehinde et al. (2023) described the role of *CYP2D6* gene polymorphisms in drug metabolism, including that of drugs used to treat COPD. Beta-2 agonists are partially metabolized by the CYP2D6 enzyme, which may affect their degradation rate and consequently decrease the efficacy of therapy. Decreased metabolism may lead to drug accumulation in the blood, increasing the risk of side effects. Although theophylline is poorly metabolized by CYP2D6, its toxicity depend on enzyme activity. Consequently, standard doses of theophylline may not be optimal for individuals with rare *CYP2D6* gene variants. It may be critical to adjust the dosage to minimize toxicity [61].

Contrary to initial assumptions, the results of candidate gene studies have been inconsistent and have not been confirmed by subsequent GWASs.

Anticholinergic drugs play a key role among bronchodilators used to treat COPD. The muscarinic acetylcholine receptor M3, encoded by the *CHRM3* gene (rs6688537), is of particular interest. This receptor is a well-studied drug target, and many approved drugs have been developed for its use in treating asthma and COPD [36].

Inhaled glucocorticoids (IGCs) are often prescribed for COPD; however, their efficacy and the risk of adverse effects may vary depending on genetic factors. The 2019 Lung Health Study found that rs111720447 polymorphism was associated with changes in the rate of decrease in FEV_1 in patients receiving IGCs. Patients who were carriers of allele C of this genetic polymorphism and received IGCs showed an increase in FEV_1 of 56.4 mL per year. However, in the placebo group, patients with the same allele showed a 27.6 mL decrease in FEV_1 per year. Patients with allele A of polymorphism rs111720447 who received IGCs experienced a greater decrease in FEV_1 than those who received a placebo. ENCODE data revealed that the rs111720447 variant is located near the glucocorticoid receptor-binding sites in A549 alveolar cells. Although this variant does not affect gene expression, its position indicates a potential structural impact on the glucocorticoid receptor complex [62].

Additionally, an association was found between the rs4713916 polymorphism of the *FKBP5* gene and various indices of response to IGCs in patients with COPD. Specifically, GA genotype carriers demonstrated improvements in the 6-min walk test and lung function indices following IGC therapy [63]. This group exhibited higher cognitive function and quality of life indices throughout the study. Furthermore, a low predisposition to depression and anxiety was observed [64].

Notably, some gene polymorphisms cause drug insensitivity. One example is the *FKBP5* gene, which encodes the FK506-binding protein 5. The expression of this gene is regulated by rs2766545 polymorphism. This polymorphic locus is associated with glucocorticoid resistance. However, this study's sample size was small (71 patients with COPD), there was no control group, and the drug's efficacy was evaluated only after 3 weeks of therapy [63].

Moreover, Lei et al. (2017) conducted a study of a Chinese population, which included 204 patients with COPD. They examined the association between the *GLCCI1* gene rs37973 polymorphism and the response to ICSs (the patients received combined fluticasone propionate and salmeterol at a dose of 500/50 μg twice daily for 24 weeks). In vitro, neutrophils isolated from patient tissues were incubated with different concentrations of dexamethasone, with or without cigarette smoke extract. Subsequently, apoptosis was assessed. After 24 weeks of treatment, patients with the GG genotype exhibited a significantly smaller improvement in FEV_1 (15.3 ± 33.2 mL increase) than those with the AA (92.7 ± 29.6 mL; $p < 0.001$) or AG (59.4 ± 26.9 mL; $p < 0.001$) genotypes. In vitro, dexamethasone had a weaker inhibitory effect on the apoptosis of neutrophils with the GG genotype, further confirming that the presence of the G allele may negatively affect glucocorticoid sensitivity, regardless of smoking status. Therefore, the GG genotype of the rs37973 polymorphism may be associated with decreased IGC efficacy in Chinese patients with COPD [65].

According to the clinical guidelines for COPD, theophylline may be used as adjunctive therapy for patients with severe COPD. Xiong and Li (2018) identified variants of the *CYP1A2* gene that may alter enzyme activity and directly affect theophylline metabolism in 120 Chinese patients with bronchial asthma or COPD. In a study that focused on *CYP1A2* gene polymorphisms, patients with bronchial asthma or COPD who carried specific alleles demonstrated significantly decreased theophylline clearance [66].

The use of genetically engineered biological therapy in patients with COPD is being actively studied [67]. In recent years, T2 inflammation, which is associated with bronchial asthma and detected in a significant proportion of COPD patients, has gained attention in the study of disease pathogenesis [68]. Furthermore, eosinophilia is observed in patients with COPD and is associated with a more severe disease course and increased risk of exacerbations [68]. However, some studies showed no difference in COPD progression [67].

Rabe et al. (2024) conducted a study on the effects of itepekimab in patients with COPD and found no genetic associations responsible for the response to treatment [69].

Research shows that patients respond differently to drug treatment. Therefore, it is crucial to consider each patient's mental and physical characteristics and the possible genetic reasons for these differences.

CONCLUSION

Genetic studies of COPD show promise. An important factor is the use of GWASs on a large sample of patients, considering only the loci that are associated with COPD. Active searches in this area are ongoing.

Genetic risk scales that combine the effects of several SNPs effectively predict COPD risk and severity. In the future, these scales may be clinically relevant in predictive medicine, initiating a preventive approach to COPD. Along with ethnic and sex differences in genetic polymorphisms, these scales provide the prospect of personalized medical approaches to predicting, preventing, and treating COPD.

ADDITIONAL INFORMATION

Author contributions: Kh.R.F.: conceptualization, methodology, supervision, writing—review & editing; S.F.I.: writing—original draft, visualization, methodology; E.E.S.: writing—original draft, visualization, methodology. All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: Not applicable.

Funding sources: No funding.

Disclosure of interests: The authors have no relationships, activities, or interests for the last three years related to for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

Statement of originality: No previously published material (text, images, or data) was used in this work.

Data availability statement: The editorial policy regarding data sharing does not apply to this work, as no new data was collected or created.

Generative AI: No generative artificial intelligence technologies were used to prepare this article.

Provenance and peer review: This paper was submitted unsolicited and reviewed following the standard procedure. The review process involved three external reviewers, a member of the editorial board, and the in-house scientific editor.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Х.Р.Ф. — разработка концепции и методологии, научное руководство, написание рукописи — рецензирование и редактирование; С.Ф.И. — написание черновика рукописи, визуализация, разработка методологии; Е.Э.С. — написание черновика рукописи, визуализация, разработка методологии. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

Этическая экспертиза. Неприменимо

Источники финансирования. Отсутствуют.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали три внешних рецензента, член редакционной коллегии и научный редактор издания.

REFERENCES

1. Agusti A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Eur Respir J*. 2023;61(4):2300239. doi: 10.1183/13993003.00239-2023 EDN: INNNID

2. Al Wachami N, Guennouni M, Iderdar Y, et al. Estimating the global prevalence of chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMC Public Health*. 2024;24(1):297. doi: 10.1186/s12889-024-17686-9 EDN: ZCCRJA

3. Avdeev SN, Leshchenko IV, Aisanov ZR. Chronic obstructive pulmonary disease (COPD 2024). Clinical guidelines (short version). *Journal of Respiratory Medicine*. 2025;1(2):5–16. doi: 10.17116/respmed202510215

4. Bhatt SP, Casaburi R, Agustí À, et al. Chronic obstructive pulmonary disease: hiding in plain sight, a Statement from the COPD Foundation Medical and Scientific Advisory Committee. *Lancet Respir Med*. 2023;11(12):1041–1043. doi: 10.1016/s2213-2600(23)00436-8

5. Celli BR, Fabbri LM, Aaron SD, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am J Respir Crit Care Med*. 2021;204(11):1251–1258. doi: 10.1164/rccm.202108-1819PP EDN: GPOTVG
6. Abdullaeva NM, Fesenko OV, Belousov AS, et al. Epidemiology and Pathogenesis of Pathology Associated with Chronic Obstructive Pulmonary Disease. *Effective pharmacotherapy*. 2024;20(16):63–67. doi: 10.33978/2307-3586-2024-20-16-63-67 EDN: LSGWAI
7. Chen H, Luo X, Du Y, et al. Association between chronic obstructive pulmonary disease and cardiovascular disease in adults aged 40 years and above: data from NHANES 2013–2018. *BMC pulmonary medicine*. 2023; 23(1):318. doi: 10.1186/s12890-023-02606-1 EDN: MZRCIY
8. Voulgaris A, Archontogeorgis K, Steiropoulos P, Papanas N. Cardiovascular Disease in Patients with Chronic Obstructive Pulmonary Disease, Obstructive Sleep Apnoea Syndrome and Overlap Syndrome. *Current vascular pharmacology*. 2021;19(3):285–300. doi: 10.2174/1570161118666200318103553 EDN: JBZGZI
9. Rogliani P, Ritondo BL, Laitano R, et al. Advances in understanding of mechanisms related to increased cardiovascular risk in COPD. *Exp Rev Respirat Med*. 2021;15(1):59–70. doi: 10.1080/17476348.2021.1840982 EDN: KXGKVF
10. Balbirsingh V, Mohammed AS, Turner AM, Newnham M. Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review. *Thorax*. 2022:thoraxjnl-2021-218333. doi: 10.1136/thoraxjnl-2021-218333 EDN: UFARUB
11. Papaporfyriou A, Bartziokas K, Gompelmann D, et al. Cardiovascular Diseases in COPD: From Diagnosis and Prevalence to Therapy. *Life*. 2023;13(6):1299. doi: 10.3390/life13061299 EDN: OSSIDA
12. Martinez-Garcia MÁ, Faner R, Oscullo G, et al. Chronic bronchial infection and incident cardiovascular events in chronic obstructive pulmonary disease patients: A long-term observational study. *Respirology*. 2021;26(8):776–785. doi: 10.1111/resp.14086 EDN: CYVWUL
13. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respirat Crit Care Med*. 2002;166(3):333–339. doi: 10.1164/rccm.2110093
14. Zhou JJ, Cho MH, Castaldi PJ, et al. Heritability of chronic obstructive pulmonary disease and related phenotypes in smokers. *Am J Respirat Crit Care Med*. 2013;188(8):941–947. doi: 10.1164/rccm.201302-0263OC
15. Silverman EK. Genetics of COPD. *Annual review of physiology*. 2020;82:413–431. doi: 10.1146/annurev-physiol-021317-121224 EDN: XGTMZD
16. Cho MH, Hobbs BD, Silverman EK. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. *Lancet Respir Med*. 2022;10(5):485–496. doi: 10.1016/S2213-2600(21)00510-5 EDN: YCQOON
17. Dasí F. Alpha-1 antitrypsin deficiency. *Medicina clinica*. 2024;162(7):336–342. doi: 10.1016/j.medcli.2023.10.014 EDN: KQXTKH
18. Larshina EA, Milovanova NV, Kamenets EA. Alpha-1-antitrypsin deficiency: diagnosis and treatment (literature review). *Medical genetics*. 2021;20(1):12–24. doi: 10.25557/2073-7998.2021.01.12-24 EDN: UIUUUF
19. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genetics*. 2009;5(3):e1000421. doi: 10.1371/journal.pgen.1000421 EDN: MNEZBJ
20. Sakornsakolpat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Gen*. 2019;51(3):494–505. doi: 10.1038/s41588-018-0342-2 EDN: WQQNCY
21. Hobbs BD, de Jong K, Lamontagne M, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. *Nat Gen*. 2017;49(3):426–432. doi: 10.1038/ng.3752 EDN: YXPCKP
22. Hobbs BD, Parker MM, Chen H, et al. Exome Array Analysis Identifies a Common Variant in IL27 Associated with Chronic Obstructive Pulmonary Disease. *Am J Respirat Crit Care Med*. 2016;194(1):48–57. doi: 10.1164/rccm.201510-2053OC EDN: XTSQQH
23. Chen G, Jin Y, Chu C, et al. A cross-tissue transcriptome-wide association study reveals GRK4 as a novel susceptibility gene for COPD. *Sci Rep*. 2024;14(1):28438. doi: 10.1038/s41598-024-80122-w EDN: QALGSM
24. Wang M, Zhang Y, Xu M, et al. Roles of TRPA1 and TRPV1 in cigarette smoke -induced airway epithelial cell injury model. *Free Radic Biol Med*. 2019;134:229–238. doi: 10.1016/j.freeradbiomed.2019.01.004 EDN: RTSZTE
25. Kuvaeva EE, Mertsalov IB, Simonova OB. Transient receptor potential (TRP) family of channel proteins. *Russian Journal of Developmental Biology*. 2022;53(5):309–320. doi: 10.31857/S0475145022050044 EDN: XFJJUC
26. Kim W, Prokopenko D, Sakornsakolpat P, et al. Genome-Wide Gene-by-Smoking Interaction Study of Chronic Obstructive Pulmonary Disease. *Am J Epidemiol*. 2021;190(5):875–885. doi: 10.1093/aje/kwaa227 EDN: NNPEEQ
27. Hopkins RJ, Duan F, Gamble GD, et al. Chr15q25 genetic variant (rs16969968) independently confers risk of lung cancer, COPD and smoking intensity in a prospective study of high-risk smokers. *Thorax*. 2021; 76(3):272–280. doi: 10.1136/thoraxjnl-2020-214839 EDN: MDMMOF
28. Lee YJ, Choi S, Kwon SY, et al. A Genome-Wide Association Study in Early COPD: Identification of One Major Susceptibility Loci. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2967–2975. doi: 10.2147/COPD.S269263
29. Cho MH, Hobbs BD, Silverman EK. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. *Lancet Respir Med*. 2022;10(5):485–496. doi: 10.1016/S2213-2600(21)00510-5 EDN: YCQOON
30. Zhang J, Hobbs BD, Silverman EK, et al. Polygenic Risk Score Added to Conventional Case Finding to Identify Undiagnosed Chronic Obstructive Pulmonary Disease. *JAMA*. 2025;333(9):784–792. doi: 10.1001/jama.2024.24212 EDN: ZUELIQ
31. Zhang J, Xu H, Qiao D, et al. A polygenic risk score and age of diagnosis of COPD. *Eur Respir J*. 2022;60(3):2101954. doi: 10.1183/13993003.01954-2021 EDN: PIQEUW
32. Li N, Li X, Liu M, et al. Sex differences in comorbidities and mortality risk among patients with chronic obstructive pulmonary disease: a study based on NHANES data. *BMC Pulmon Med*. 2023;23(1):481. doi: 10.1186/s12890-023-02771-3 EDN: UJXYCZ
33. Joo J, Himes B. Gene-Based Analysis Reveals Sex-Specific Genetic Risk Factors of COPD. AMIA Annual Symposium proceedings. *AMIA Annu Symp Proc*. 2022;2021:601–610. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8861659/
34. Hardin M, Cho MH, Sharma S, et al. Sex-Based Genetic Association Study Identifies CELSR1 as a Possible Chronic Obstructive Pulmonary Disease Risk Locus among Women. *Am J Respir Cell Mol Biol*. 2017;56(3):332–341. doi: 10.1165/rcmb.2016-0172OC EDN: YXPBTR
35. Xu L, Bian W, Gu XH, Shen C. Genetic polymorphism in matrix metalloproteinase-9 and transforming growth factor-β1 and susceptibility to combined pulmonary fibrosis and emphysema in a Chinese population. *Kaohsiung J Med Sci*. 2017;33(3):124–129. doi: 10.1016/j.kjms.2016.12.004
36. Wain LV, Shrine N, Artigas MS, et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. *Nat Gen*. 2017;49(3):416–425. doi: 10.1038/ng.3787 EDN: YXQWLD
37. Vegas-Sánchez-Ferrero G, José Estépar RS. Statistical Framework for the Definition of Emphysema in CT Scans: Beyond Density Mask. *Med Image Comput Comput Assist Interv*. 2018;11071:821–829. doi: 10.1007/978-3-030-00934-2_91
38. Manichaikul A, Hoffman EA, Smolonska J, et al. Genome-wide study of percent emphysema on computed tomography in the general population. The Multi-Ethnic Study of Atherosclerosis Lung/SNP Health Association Resource Study. *Am J Respir Crit Care Med*. 2014;189(4):408–418. doi: 10.1164/rccm.201306-1061OC EDN: SRIKUL
39. Cho MH, Castaldi PJ, Hersh CP, et al. A Genome-Wide Association Study of Emphysema and Airway Quantitative Imaging Phenotypes. *Am J Respir Crit Care Med*. 2015;192(5):559–569. doi: 10.1164/rccm.201501-0148OC
40. Zhu Z, Wang X, Li X, et al. Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: a large-scale genome-wide cross-trait analysis. *Respir Res*. 2019;20(1):64. doi: 10.1186/s12931-019-1036-8 EDN: QTQKVO

41. Axson EL, Bottle A, Cowie MR, Quint JK. Relationship between heart failure and the risk of acute exacerbation of COPD. *Thorax*. 2021;76(8):807–814. doi: 10.1136/thoraxjnl-2020-216390 EDN: XLCFEC
42. Güder G, Rutten FH. Comorbidity of heart failure and chronic obstructive pulmonary disease: more than coincidence. *Curr Heart Fail Rep*. 2014;11(3):337–346. doi: 10.1007/s11897-014-0212-x EDN: QQQNRH
43. Jiang R, Sun C, Yang Y, et al. Causal relationship between chronic obstructive pulmonary disease and heart failure: A Mendelian randomization study. *Heart Lung*. 2024;67:12–18. doi: 10.1016/j.hrtlng.2024.04.007 EDN: YRXATG
44. Uffelmann E, Huang QQ, Munung NS, et al. Genome-wide association studies. *Nature reviews methods primers*. 2021;1:1–21. doi: 10.1038/s43586-021-00056-9
45. Kim S, Oesterreich S, Kim S, et al. Integrative clustering of multi-level omics data for disease subtype discovery using sequential double regularization. *Biostatistics*. 2017;18(1):165–179. doi: 10.1093/biostatistics/kxw039
46. Barnes PJ. Oxidative stress-based therapeutics in COPD. *Redox biology*. 2020;33:101544. doi: 10.1016/j.redox.2020.101544 EDN: LYMAMX
47. Morrow JD, Qiu W, Chhabra D, et al. Identifying a gene expression signature of frequent COPD exacerbations in peripheral blood using network methods. *BMC Med Genomics*. 2015;8:1. doi: 10.1186/s12920-014-0072-y EDN: ZYNEQB
48. Aggarwal T, Wadhwa R, Thapliyal N, et al. Oxidative, inflammatory, genetic, and epigenetic biomarkers associated with chronic obstructive pulmonary disorder. *J Cell Physiol*. 2019;234(3):2067–2082. doi: 10.1002/jcp.27181
49. Wang R, Xu J, Liu H, Zhao Z. Peripheral leukocyte microRNAs as novel biomarkers for COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1101–1112. doi: 10.2147/COPD.S130416
50. Zhang Z, Wang J, Li Y, et al. Proteomics and metabolomics profiling reveal panels of circulating diagnostic biomarkers and molecular subtypes in stable COPD. *Respir Res*. 2023;24(1):73. doi: 10.1186/s12931-023-02349-x EDN: DTAEKJ
51. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. *Lancet*. 2014;384(9944):691–702. doi: 10.1016/S0140-6736(14)61136-3
52. Budden KF, Shukla SD, Rehman SF, et al. Functional effects of the microbiota in chronic respiratory disease. The Lancet. *Respir Med*. 2019;7(10):907–920. doi: 10.1016/S2213-2600(18)30510-1 EDN: YULISS
53. Wang Z, Yang Y, Yan Z, et al. Multi-omic meta-analysis identifies functional signatures of airway microbiome in chronic obstructive pulmonary disease. *ISME J*. 2020;14(11):2748–2765. doi: EDN: PGUJKC
54. Hardin M, Cho MH, McDonald ML, et al. A genome-wide analysis of the response to inhaled β2-agonists in chronic obstructive pulmonary disease. *The Pharmacogenomics Journal*. 2016;16(4):326–335. doi: 10.1038/tpj.2015.65
55. Matera MG, Rogliani P, Novelli G, Cazzola M. The impact of genomic variants on patient response to inhaled bronchodilators: a comprehensive update. *Expert Opin Drug Metab Toxicol*. 2023;19(5):285–295. doi: 10.1080/17425255.2023.2221848 EDN: UXJPBO
56. Celli BR, Christenson S, Rabe KF, et al. Current Smoker: A Clinical COPD Phenotype Affecting Disease Progression and Response to Therapy. *Am J Respir Crit Care Med*. 2025;211(5):729–736. doi: 10.1164/rccm.202407-1379CI
57. Taylor DR, Drazen JM, Herbison GP, et al. Asthma exacerbations during long term beta agonist use: influence of beta (2) adrenoceptor polymorphism. *Thorax*. 2000;55(9):762–767. doi: 10.1136/thorax.55.9.762
58. Lima JJ. Do genetic polymorphisms alter patient response to inhaled bronchodilators? *Exp Opin Drug Metabol Toxicol*. 2014;10(9):1231–1240. doi: 10.1517/17425255.2014.939956
59. Mustafina MKh, Tsvetkova OA. Pharmacogenetic effect of ADRB2 gene polymorphism on therapeutic response in chronic obstructive pulmonary disease. *Pulmonologiya*. 2013;(3):21–24. doi: 10.18093/0869-0189-2013-0-3-21-24 EDN: RBJUHP
60. Kim WJ, Hersh CP, DeMeo DL, et al. Genetic association analysis of COPD candidate genes with bronchodilator responsiveness. *Respirat Med*. 2009;103(4):552–557. doi: 10.1016/j.rmed.2008.10.025
61. Kehinde O, Ramsey LB, Gaedigk A, Oni-Orisan A. Advancing CYP2D6 Pharmacogenetics through a Pharmacoequity Lens. *Clin Pharmacol Therap*. 2023;114(1):69–76. doi: 10.1002/cpt.2890 EDN: EARWIK
62. Obeidat M, Faiz A, Li X, et al. The pharmacogenomics of inhaled corticosteroids and lung function decline in COPD. *Eur Respirat J*. 2019;54(6):1900521. doi: 10.1183/13993003.00521-2019
63. Russo P, Tomino C, Santoro A, et al. FKBP5 rs4713916: A Potential Genetic Predictor of Interindividual Different Response to Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease in a Real-Life Setting. *Int J Mol Sci*. 2019;20(8):2024. doi: 10.3390/ijms20082024
64. Marcolongo F, Scarlata S, Tomino C, et al. Psycho-cognitive assessment and quality of life in older adults with chronic obstructive pulmonary disease-carrying the rs4713916 gene polymorphism (G/A) of gene FKBP5 and response to pulmonary rehabilitation: a proof of concept study. *Psychiatr genet*. 2022;32(3):116–124. doi: 10.1097/YPG.0000000000000308 EDN: JVANWC
65. Lei Y, Gao Y, Chen J, et al. GLCCI1 rs37973: a potential genetic predictor of therapeutic response to inhaled corticosteroids in Chinese chronic obstructive pulmonary disease patients. *Sci Rep*. 2017;7:42552. doi: 10.1038/srep42552 EDN: YXHFPZ
66. Xiong S, Li L. The effect of CYP1A2 gene polymorphism on the metabolism of theophylline. *Exp Ther Med*. 2018;15(1):109–114. doi: 10.3892/etm.2017.5396 EDN: YKLWQJ
67. Trushenko NV, Lavginova BB, Belkina OS, Avdeev SN. Targeted therapy as a new perspective in the treatment of COPD. *Meditsinskiy Sovet*. 2024;18(20):10–16. doi: 10.21518/ms2024-519 EDN: EKLCZI
68. Singh D, Higham A, Beech A. The relevance of eosinophils in chronic obstructive pulmonary disease: inflammation, microbiome and clinical outcomes. *J Leukoc Biol*. 2024;116(5):927–946. doi: 10.1093/jleuko/qiae153 EDN: DYQQDW
69. Rabe KF, Martinez FJ, Bhatt SP, et al. AERIFY-1/2: two phase 3, randomised, controlled trials of itepekimab in former smokers with moderate-to-severe COPD. *ERJ Open Research*. 2024;10(5):00718–2023. doi: 10.1183/23120541.00718-2023

AUTHORS INFO

*** Firyuza I. Sattarova**, Assistant Lecturer, Depart. of Internal Diseases;
address: 49 Butlerov st, Kazan, Russia, 420012;
ORCID: 0009-0002-1157-0984;
eLibrary SPIN: 8579-1605;
e-mail: fifuza@mail.ru

Rustem F. Khamitov, MD, Dr. Sci. (Medicine), Professor, Head, Depart. of Internal Diseases;
ORCID: 0000-0001-8821-0421;
eLibrary SPIN: 5362-0356;
e-mail: rhamitov@mail.ru

Emiliya S. Egorova, Junior Research Associate, Lab. of Genetics of Aging and Longevity, Central Research Laboratory;
ORCID: 0000-0002-6210-4660;
eLibrary SPIN: 8706-8630;
e-mail: jastspring@yandex.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Саттарова Фирюза Ильдаровна**, ассистент, каф. внутренних болезней;
адрес: Россия, 420012, Казань, ул. Бутлерова, д. 49;
ORCID: 0009-0002-1157-0984;
eLibrary SPIN: 8579-1605;
e-mail: fifuza@mail.ru

Хамитов Рустэм Фидагиевич, д-р мед. наук, профессор, заведующий, каф. внутренних болезней;
ORCID: 0000-0001-8821-0421;
eLibrary SPIN: 5362-0356;
e-mail: rhamitov@mail.ru

Егорова Эмилия Сергеевна, младший научный сотрудник; лаб. генетики старения и долголетия Центральной научно-исследовательской лаборатории;
ORCID: 0000-0002-6210-4660;
eLibrary SPIN: 8706-8630;
e-mail: jastspring@yandex.ru