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CONTRIBUTION OF *IL12A*, *IL12B*, *IL13* AND *IL12RB2* GENE POLYMORPHISMS TO THE DEVELOPMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease affecting primarily distal respiratory pathways and lung parenchyma. An abnormal inflammatory response to inhaled harmful particles and tobacco smoke leads to airway remodeling and is thought to be a main mechanism of COPD development.

This study aimed to determine possible genetic association of *IL12A* (rs568408, rs2243115), *IL12B* (rs3212227), *IL13* (rs20541), *IL12RB2* (rs3762317) genes polymorphisms with COPD and studied the relationship between selected candidate genes variants with quantitative lung function parameters and smoking index in a Tatar population from Russia.

SNPs of *IL12A, IL12B, IL13, IL12RB2* genes were analyzed for association with COPD in cohort of 601 patients and 617 controls. SNPs were examined by the real-time polymerase chain reaction (PCR), with the use of TaqMan SNP discrimination assays.

As a result statistically significant associations with COPD in the study group under the biologically plausible assumption of additive genetic model were identified in *IL12A* (rs568408G>A) (P = 0.00001, OR = OR=2.07), *IL12A* (rs2243115T>G) (P = 0.00001, OR = 2.85), *IL13* (rs20541A>G) (P = 0.00001, OR = 1.58). A relationship between smoking index and *IL12A* (rs568408G>A) (P=0.027), *IL12A* (rs2243115T>G) (P=0.0038) was revealed. A significant genotype-dependent variation of Forced Vital Capacity was observed for *IL12A* (rs568408G>A) (P=0.045), *IL12A* (rs2243115T>G) (P=0.013) and *IL13* (rs20541A>G) (P =0.0051). Vital Capacity was affected by *IL12A* (rs2243115T>G) (P =0.0019).

Our data confirm the assumption about the essential role of genes responsible for the synthesis of α- and β-subunits of IL12, structural α-helices of IL13 to increased risk of COPD.

Keywords: chronic obstructive pulmonary disease, inflammation, interleukins 12 and 13.

Introduction. Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory disease that characterized by partly reversible airflow limitation, chronic inflammation, fibrosis of small airways, and destruction of lung parenchyma [15]. Today, the total number of people suffering from this disease is estimated at 251 million people, while COPD is the third most common cause of death in the world, which leads to a high demand for studies of the mechanisms of pathogenesis, new methods of therapy and early diagnosis of the disease [15]. An abnormal inflammatory response to inhaled harmful particles and tobacco smoke leads to airway remodeling and is thought to be a main mechanism of COPD development. In this case, the most important part of the mechanism of its development are inflammatory mediators, chemokines and interleukins, in particular IL12 and IL13 and their receptors [7,15].

IL-12 is a heterodimer consisting of protein α (IL-12p35) and β (IL-12p40)

subunits connected by a covalent disulfide bond [1]. The α-subunit is encoded by the IL-12A gene located in the 3q25.33 locus and consisting of 7185 base pairs [12]. While the β-subunit is encoded by the IL-12B gene located in the 5q33.3 locus and comprising 15708 base pairs [12]. The main function of IL-12 is induction of immune and immune-mediated inflammatory responses to pathogenic microorganisms and intracellular pathogens by activating the differentiation of immature T-lymphocytes into memory T-cells and Th1, Th17 effector cells with their further proliferation. Also IL-12 increases the cytotoxicity of cytotoxic T-cells and natural killer cells, stimulates the synthesis of γ-IFN by the latter [1]. The association of IL-12 secretion and the development of chronic progressive inflammation in COPD has been proven, including due to the activation of T-cell immunity [9].

The IL-12 receptor is a heterodimeric protein complex that includes β1 and β2 subunits (IL-12Rβ1; IL-12Rβ2) [1]. The β1-subunit gene is located in the 19p13.11 region of the 19th chromosome, the β1-subunit gene - in the 1p31.3 region; their size is about 91,000 and 40,000 base pairs, respectively [14].

IL13 is a 13 kDa protein molecule with 4 α-helices in its structure [1]. This protein is encoded by the IL13 gene located at the 5q31.1 locus, which has 4848 base pairs [12]. IL13 is produced by Th2, eosinophils, natural killer cells, T-lymphocytes and is responsible for the development of airway hyperresponsiveness, alternative activation of tissue macrophages with the subsequent development of subepithelial fibrosis of the airways and emphysema, mucus hypersecretion, IgE synthesis, IL13 plays an important role in the development of bronchial asthma, lungs cancer, COPD and pulmonary fibrosis [1, 6, 7].

This work was designed as case-control study aimed at investigating the association of *IL12A* (rs568408, rs2243115), *IL12B* (rs3212227), *IL13* (rs20541), and *IL12RB2* (rs3762317) polymorphisms with COPD in the Tatar population from Russia.

Materials and methods. We used DNA samples from unrelated individuals, Tatars by ethnicity, living in the Republic of Bashkortostan. The COPD patients were selected and collected from 2010 to 2019 years in the pulmonary department of Ufa City Hospitals №21 (Ufa, Russia). The COPD patients were recruited randomly according to the International Classification of Diseases tenth revision (ICD 10) (http://www.who.int/classifications/icd/en/) and following the recommendations of the Global Initiative for Chronic Obstructive Lung Disease (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2011-2019). The group of patients included 601 individuals (522 men (86.85%) and 79 women (13.15%)), the average age was 63.38 ± 11.81 years. Among patients with COPD, the number of smokers and former smokers was 484 people (80.53%), non-smokers - 117 (19.47%). The smoking index for current and former smokers was 44.58 ± 25.92 pack-years. Subjects performed standardized pre-bronchodilator and post-bronchodilator spirometry. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and the ratio of this volume to lung vital capacity (FEV1/VC) were evaluated as well. In the group of patients, the indices (in % of the norm) were FEV1 = 41.68 ± 19.32, FVC = 44.22 ± 17.88, VC = 49.02 ± 15.54, and FEV1/FVC = 58.66 ± 13.66. The control group included 617 individuals (548 men (88.88%) and 69 women (11.12%)), the average age was 58.44 ± 14.79. The number of smokers and former smokers was 517 (83.79%) and non-smokers - 100 (16.21%)); the smoking index in smokers was 38.54 ± 23.12 pack-years. Inclusion and exclusion criteria in the COPD group and control are described earlier in our previous works [13]. Informed voluntary consent was obtained from each of the participants in the study. Study was approved by the Local Ethical Committee of Institute of Biochemistry and Genetics of Ufa Scientific Center of Russian Academy of Sciences (IBG USC RAS), Ufa, Russia (Ufa, Protocol No 17, December 7, 2010).

DNA was isolated from peripheral blood leukocytes using phenol-chloroform extraction. For our study were selected the following polymorphic loci: *IL12A* (rs568408, c.* 121G> A; rs2243115, c.-564T> G), *IL12B* (rs3212227, c. *159A> C), *IL13* (rs20541, c.236A> G, p.Gln79Arg), *IL12RB2* (rs3762317, c.-1105A> G). SNPs were examined by the real-time polymerase chain reaction (PCR), with the use of TaqMan SNP discrimination assays (https://www.oligos.ru, OOO DNA-Sintez, Russia). Accumulation of specific PCR-product by hybridization and cleavage of double-labelled fluorogenic probe during amplification was detected with BioRad CFX96 instrument (Bio-Rad Laboratories Inc., USA), using CFX Manager software. The methods of analysis were described in detail by us earlier [13]. Statistical data processing was carried out using the Statistica v. 6.0 (StatSoft Inc., USA) and PLINK v. 1.07. A detailed description of the methods of statistical analysis are described earlier in our previous works [13].

Results. Systematic quality control procedures were performed to guarantee a high quality of the data. Subsequently, SNPs were filtered according to their proportion of missing data, MAF or deviation from Hardy–Weinberg equilibrium within the controls. For the control group, the following results were obtained: *IL12A* (rs568408) (P^{X-B}=0.24), *IL12A* (rs2243115) (P^{X-B}=0.81), *IL12B* (rs3212227) (P^{X-B}=0.07), *IL13* (rs20541) (P^{X-B}=0.43), *IL12RB2* (rs3762317) (P^{X-B}=0.14).

Statistically significant differences in the genotypes and alleles frequencies distribution of the *IL12A* (rs568408G> A) gene were revealed between the COPD and controls group (P = 0.001 and P = 0.00001) (Table 1). The frequency of the rare allele A of *IL12A* (rs568408G> A) was significantly higher in the COPD group (OR = 1.38 95% CI 1.16-1.64).

Association between COPD and *IL12A* (rs568408 G>A) in the dominant (P=0.00001, $P_{cor-FDR}$=0.00002, OR=2.31 95%CI 1.62-3.28), recessive (P=0.0014, $P_{cor-FDR}$=0.0022, OR=2.87 95%CI 1.49-5.5) and additive (P=0.00001, $P_{cor-FDR}$=0.00002, OR=2.07 95%CI 1.56-2.75) models was revealed.

The COPD group significantly differed from the control group by the genotypes and alleles frequencies distribution of the *IL12A* (rs2243115 T>G) (P = 0.00001 and P = 0.00001). The frequency of the rare G allele of *IL12A* (rs2243115 T> G) was significantly higher in the group of COPD (21.31% vs 9.97% in the control, OR = 2.45 95% CI 1.94-3.08). The *IL12A* rs2243115 T> G) was associated with COPD in the dominant (P=0.00001, $P_{cor-FDR}$=0.00002, OR=2.93 95%CI 2.00-4.30), recessive (P=0.00001, $P_{cor-FDR}$=0.00002, OR=16.3 95%CI 5.09-52.17) and the additive (P = 0.00001, $P_{cor-FDR}$ = 0.00002, OR = 2.85 95% CI 2.05-3.95) models. This was due to an increase in the proportion of heterozygotes and homozygotes for the rare G allele in the group of patients.

Significant differences in the frequency distribution of genotypes and alleles of the *IL13* (rs20541 A> G) were revealed between the studied groups (P = 0.002 and P = 0.002). Considerable associations between the COPD development and *IL13* (rs20541 A> G) were obtained in the dominant (P = 0.012, $P_{cor-FDR}$ = 0.0152, OR = 1.56 95% CI 1.10-2.20), recessive (P = 0.00001, $P_{cor-FDR}$ = 0.00002, OR = 2.54 95% CI 1.60-4.03) and the

additive (P = 0.00001, $P_{cor-FDR}$ = 0.00002, OR = 1.58 95% CI 1.24-2.01) models, which was due to an increase in the frequency of the AA genotype in the group of patients.

No significant associations were observed between *IL12B* (rs3212227), *IL-12RB2* (rs3762317) gene polymorphisms and COPD.

We investigated the relationship between the candidate gene polymorphisms and smoking index (in pack-years) in smoking subjects (Table 2). The smoking index was affected by the genotypes of *IL12A* (rs568408 G>A and rs2243115 T>G). In specific, the smoking index was significantly higher in carriers of the GG genotypes of *IL12A* (rs568408 G>A) and *IL12A* (rs2243115 T> G) (P = 0.27 and P = 0.0038).

We investigated the relationship between the studied genes polymorphisms and lung function parameters: Forced Vital Capacity (FVC), Forced Expiration Volume in 1 s (FEV1), and FEV1/FVC ratio in COPD patients (Table 2).

As shown in Table 2, the allele A carriers of the *IL12A* (rs568408 G>A) (P = 0.045), the GG genotype of the *IL12A* (rs2243115 T>G) (P = 0.013), and the AA genotype of the *IL13* (rs20541 A>G) (P = 0.0051) were associated with a decrease in FVC values. Carriers of the

Table 1

Frequency distribution of genotypes and polymorphic loci alleles of candidate genes in COPD and control groups and association of candidate genes polymorphic loci with the development of COPD (log regression analysis)

Gene, polymorphic locus	rare allele	Genotypes, alleles	COPD n (%) (N=601)	Control n (%) (N=617)	P / P_{adj}	OR (95% CI)
IL12A rs568408 G>A	A	GG/GA/AA	280/273/57 (45.90/44.75/9.34)	339/245/33 (54.94/39.71/5.35)	0.001	-
		G/A	833/387 (68.28/31.72)	923/311 (74.80/25.20)	0.00001	1.38 (1.16-1.64)
		GG GA+AA dominant	280 (45.90) 330 (54.1)	339 (54.94) 278 (45.06)	0.00001	1.00 2.31 (1.62-3.28)
		GG+GA AA recessive	544 (90.66) 57 (9.34)	584 (94.5) 33 (5.35)	0.0014	1.00 2.87 (1.49-5.5)
		additive	-	-	0.00001	2.07 (1.56-2.75)
IL12A rs2243115 T>G	G	TT/TG/GG	406/148/56 (66.56/24.26/9.18)	499/113/5 (80.88/18.31/0.81)	0.00001	-
		T/G	960/260 (78.69/21.31)	1 111/123 (90.03/9.97)	0.00001	2.45 (1.94-3.08)
		TT TG+GG dominant	406 (66.56) 154 (33.44)	499 (80.88) 118 (21.12)	0.00001	1.00 2.93 (2.00-4.30)
		TT+TG GG recessive	554 (90.82) 56 (9.18)	612 (99.19) 5 (0.81)	0.00001	1.00 16.3 (5.09-52.17)
		additive	-	-	0.00001	2.85 (2.05-3.95)
IL12B rs3212227 A>C	C	AA/AC/CC	459/129/22 (75.25/21.15/3.61)	436/156/25 (70.66/25.28/4.05)	0.192	-
		A/C	1 047/173 (85.82/14.18)	1 028/ 206 (83.31/16.69)	0.096	0.82 (0.66-1.03)
IL13 rs20541 A>G	A	GG/GA/AA	235/254/121 (38.52/41.64/19.84)	270/269/78 (43.76/43.60/12.64)	0.002	-
		G/A	724/496 (59.34/40.66)	809/425 (65.56/34.44)	0.002	1.30 (1.11-1.54)
		GG GA+AA dominant	235 (38.52) 375 (61.48)	270 (43.76) 347 (56.24)	0.012	1.00 1.56 (1.10-2.20)
		GG+GA AA recessive	489 (80.16) 121 (19.84)	539 (87.36) 78 (12.64)	0.00001	1.00 2.54 (1.60-4.03)
		additive	-	-	0.00001	1.58 (1.24-2.01)
IL12RB2 rs3762317 A>G	G	AA/AG/GG	419/155/36 (68.69/25.41/5.90)	400/186/31 (64.83/30.15/5.02)	0.166	-
		A/G	993/227 (81.39/18.61)	986/248 (79.90/20.10)	0.377	0.91 (0.74-1.11)

Note: P- is the significance for X2 test for allele or genotypes frequency difference between COPD and control). OR - odds ratio for a rare allele (basic allelic test) or regression model; CI95% - 95% confidence interval for OR; Padj, significance in the likelihood ratio test for the regression model adjusted for age, sex, BMI, smoking status and pack-years.

Table 2

The relationship between chemokine and chemokine receptor genes polymorphisms and quantitative phenotypes (lung function parameters and pack-years)

Gene, polymorphic locus	Genotype	M± S.E	P	beta (CI 95%)
Smoking index (pack-years) in the total smokers group (N=1001)				
IL12A rs568408 G>A	GG GA+AA	32.87 (1.34) 28.87 (1.12)	0.027	0.00 -3.90 (-7.35 – (-0.44)
	GG+AA AG	32.39 (1.23) 28.73 (1.2)	0.042	0.00 -3.66 (-7.18 – (-0.14)
IL12A rs2243115 T>G	TT+TG GG	31.08 (0.87) 43.97 (5.39)	0.0038	0.00 12.93 (4.19-21.68)
FVC (Forced Vital Capacity) (N=601)				
IL12A rs568408 G>A	GG GA+AA	57.02 (1.74) 52.41 (1.51)	0.045	0.00 -4.61 (-9.11 – (-0.11)
IL12A rs2243115 T>G	TT TG+GG	57.04 (1.44) 47.8 (2.65)	0.0001	0.00 -9.24 (-13.78- (-4.7)
	TT+TG GG	54.81 (1.21) 45.84 (2.65)	0.013	0.00 -8.97 (-16.04- (-1.9)
IL13 rs20541 A>G	GG+GA AA	55.29(1.33) 47.16 (2.14)	0.0051	0.00 -8.13 (-13.78- (-2.48)
VC (Vital Capacity) (N=601)				
IL12A rs2243115 T>G	TT+GG TG	56.62 (1.33) 48.41 (1.84)	0.0012	0.00 -8.20 (-13.11- (-3.29)

Note: M ± S.E - mean values and standard error of the mean, P - significance level for the regression equation, beta (CI 95%) - regression coefficient and 95% confidence interval for coefficient.

IL12A (rs2243115T>G) TG genotype are characterized by lower VC values (P = 0.0019).

Discussion. In this work, *IL12A*, *IL12B, IL13, IL12RB2* genes polymorphisms were tested for association with COPD in the Tatar population from Russia. We studied the relationship between selected candidate genes variants with quantitative lung function parameters and smoking index.

The risk of COPD developing in our study was associated with the A allele of the *IL12A (rs568408)*. Further analysis showed that rare A allele carriers had a reduced Forced Vital Capacity. On the other hand, the rare A allele carriers have a lower smoking index, which may indicate that the development of the disease in these individuals is not associated with prolonged exposure to cigarette smoke. A number of studies have shown that the A allele of the *IL12A (rs568408)* is associated with the development of bronchial asthma, its severity [3, 4] and lung cancer [8, 10, 11] in the populations of China, Taiwan, Italy, Tunisia, Great Britain, USA.

In our sample, an association with COPD was established for the *IL12A* (rs2243115). The risk of disease development was associated with a rare G allele. Our results confirm the data on the association of the *IL12A* (rs2243115) with COPD in the Chinese population, where the risk was also associated with rare G allele [16]. We have shown that in rare G allele carriers Forced Vital Capacity and Vital Capacity are significantly decreased, and in GG homozygotes the smoking index is increased, which indicates a possible interaction of the environmental factor (smoking) and the *IL12A* (rs2243115) during the development of COPD.

The rare A allele of the *IL13* (rs20541) was identified as a risk marker of COPD development; the highest risk was found for AA homozygotes. Moreover, homozygotes for the rare A allele have significantly decreased of Forced Vital Capacity, which indicates the role of this SNP in the progression of airway obstruction in patients with COPD. Our results are consistent with the data obtained in other studies, as the A allele of the *IL13* (rs20541) was associated with the development of bronchial asthma and COPD in the Asian and Caucasians populations [2, 5].

In conclusion, our data confirm the assumption about the essential role of genes responsible for the synthesis of α- and β-subunits of IL12, structural α-helices of IL13 to COPD development and progression. The data obtained indicate the contribution of genes *IL12A* (rs568408, rs2243115) and *IL13* (rs20541) polymorphisms to this disease.

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SEARCH FOR ASSOCIATION OF DELETION POLYMORPHISMS OF GLUTATHIONE-S-TRANSFERASE *GSTM1* AND *GSTT1* GENES WITH RISK OF LUNG CANCER IN THE YAKUT POPULATION

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In the structure of oncological morbidity, lung cancer occupies one of the leading positions. According to scientific sources, lung cancer is a multifactorial disease in which both external and internal factors are involved. The aim of this work is to search for an association of deletion polymorphisms of the enzyme glutathione-S-transferase *GSTM1* and *GSTT1* with the risk of lung cancer in the Yakut population. Analysis of polymorphic variants of specific loci of genes *GSTM1*, *GSTT1* was carried out in a sample of patients with lung cancer (n = 112) and control (n = 65). In our study, in the Yakut population, we did not find a significant association between the null genotypes *GSTT1* and *GSTM1* and their combinations. We found that the genotype *GSTM1* * + / *GSTT1* * 0 in the group of patients with non-small cell lung cancer occurred 3.7 times less frequently than in the control group (OR 0.226 (CI 95%: 0.0609-0.841); $\chi 2 = 5.621$, $p = 0.0177$).

Keywords: glutathione-S-transferase, genes for biotransformation of xenobiotics, xenobiotic detoxification enzymes, lung cancer, isozymes, deletion.

Introduction. Lung cancer occupies a leading position in the structure of cancer morbidity in Yakutia. In the Sakha Republic (population: 982.1 thousand) lung cancer affects approximately 400 people yearly [1]. The severity of the problem is due not only to the high prevalence of the disease, but also to late diagnosis, unsatisfactory treatment results and, as a result, high mortality.

According to our sources, the development of lung cancer can be promoted by external background factors, such as: asbestos [15], radon [27], arsenic [28] polycyclic aromatic hydrocarbons [19], etc. According to many researchers, one of the most important causes of lung cancer worldwide is smoking [7,9,24], but lung cancer does not develop in all smokers, only in 5-10% [22]. Tobacco smoke contains about 4,000 known chemical substances. It has been established that 60 of them cause oncological diseases [29]. These carcinogenic substances are neutralized by enzymes of the xenobiotic detoxification system. An important role in this process is played by enzymes of the glutathione-S-transferase family [16; 26].

Glutathione-S-transferases (GST; EC 2.5.1.18) are enzymes of the second phase of xenobiotic biotransformation that catalyze the conjugation reaction of glutathione with a wide range of nonpolar compounds of endogenous and exogenous origin containing electrophilic carbon, sulfur, nitrogen and phosphorus atoms [20]. In humans, GST enzymes are represented mainly by the cytosolic GST family, while there are eight classes of dimeric enzymes, which are classified based on the basis of their amino acid sequence and substrate specificity of α (A), (K), μ (M), π (P), θ (T), σ (S), ω (O), ζ (Z) [25]. The spectrum of substrates of these isoenzymes partially overlaps. For example, for all GST isoenzymes, the substrate is the substance 1-chloro-2,4-dinitrobenzene, the only exception is the isoenzyme GSTT1 [23]. But despite this, GST isoforms show their specificity, as

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