

Inflammatory and Immune Response Genes Polymorphisms are Associated with Susceptibility to Chronic Obstructive Pulmonary Disease in Tatars Population from Russia

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Abstract Chronic obstructive pulmonary disease (COPD) is a complex chronic inflammatory disease of the respiratory system affecting primarily distal respiratory pathways and lung parenchyma. This work was designed as a case–control study aimed at investigating the association of COPD with polymorphisms in inflammatory and immune response genes (*JAK1*, *JAK3*, *STAT1*, *STAT3*, *NFKB1*, *IL17A*, *ADIPOQ*, *ADIPOR1*, etc.) in Tatar population from Russia. Ten SNPs (rs310216, rs3212780, rs12693591, rs2293152, rs28362491, rs4711998, rs1974226, rs1501299, rs266729, and rs12733285) were genotyped by the real-time polymerase chain reaction (TaqMan assays) in a case–control study (425 COPD patients and 457 in the control group, from Ufa, Russia). Logistic regression was used to detect the association of SNPs in different models. Linear regression analyses were performed to estimate the relationship between SNPs and lung function parameters and pack-years. In Tatar population, significant associations of *JAK1* (rs310216) ($P = 0.0002$, OR 1.70 in additive model), *JAK3* (rs3212780) ($P = 0.001$, OR 1.61 in dominant model), and *IL17A* (rs1974226) ($P = 0.0037$, OR 2.31 in recessive model) with COPD were revealed. The disease risk was higher in carriers of insertion allele of *NFKB1* (rs28362491) ($P = 0.045$, OR 1.22). We found a significant gene-by-environment interaction of smoking status and *IL17A* (rs1974226) ($P_{\text{interact}} = 0.016$), *JAK3* (rs3212780) ($P_{\text{interact}} = 0.031$), *ADIPOQ* (rs266729) ($P_{\text{interact}} = 0.013$), and *ADIPOR1* (rs12733285) ($P_{\text{interact}} = 0.018$). The relationship between the rs4711998, rs1974226, rs310216, rs3212780, rs28362491, and smoking pack-years was found ($P = 0.045$, $P = 0.004$, $P = 0.0005$, $P = 0.021$, and

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$P = 0.042$). A significant genotype-dependent variation of forced vital capacity was observed for *NFKB1* (rs28362491) ($P = 0.017$), *ADIPOR1* (rs12733285) ($P = 0.043$), and *STAT1* (rs12693591) ($P = 0.048$). The genotypes of *STAT1* (rs12693591) ($P = 0.013$) and *JAK1* (rs310216) ($P = 0.048$) were associated with forced expiratory volume in 1 s.

Keywords Chronic obstructive pulmonary disease · Association · Chronic inflammation · Cytokines · JAK/STAT-signaling · Adiponectin

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the respiratory system primarily affecting the distal respiratory pathways and the lung parenchyma (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2011). COPD is one of the most common chronic diseases; in the absence of adequate management, it can significantly impair the patients' everyday activity and may even lead to a lethal outcome (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2011).

Genome-wide association studies (GWASs) have identified several loci associated with COPD, in particular, in chromosomal regions 15q25.1 near cholinergic receptor, nicotinic, alpha 3/5 (*CHRNA3/5*), and iron-responsive element binding protein 2 (*IREB2*); the chromosome 4q22.1 region near family with sequence similarity 13, member A (*FAM13A*); chromosome 4q31 regions near hedgehog-interacting protein (*HHIP*); and at 4q28.1, 6p21.31, 6q16.1, 10q22.1, and 10q22.3 regions (Pillai et al. 2009, 2010; Caporaso et al. 2009; Cho et al. 2010; Siedlinski et al. 2011). SNPs of these genes were associated with COPD, lung function parameters, and smoking behavior in different populations (Pillai et al. 2009, 2010; Cho et al. 2010; Siedlinski et al. 2011; Caporaso et al. 2009; Ding et al. 2015a, b).

A key phenomenon in the pathogenesis of COPD is inflammation, which may be induced by tobacco smoke, dust particles in the polluted air, or by viruses and bacteria (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2011; Hackett et al. 2008). Cytokines are a family of polypeptide mediators involved in the formation and regulation of defense reactions. Along with adhesion molecules, acute-phase proteins, and antibacterial peptides, cytokines constitute an important pulmonary signaling system that determines the initiation, the progress, and the outcome of the immune response in the lungs (Hackett et al. 2008). Chronic systemic inflammation in COPD is associated with constant productions of IL-1b, TNFA, IL-8, IL-6, fibrinogen, and C-reactive protein by alveolar macrophages and neutrophils, which correlates with disease progression and frequent exacerbations (Hackett et al. 2008; Bianco et al. 2013). The transformation of local inflammation in the lung tissue to chronic systemic inflammation in COPD can be associated with high permeability of pulmonary blood vessels resulting in a release of proinflammatory factors into the general circulation (Bianco et al. 2013). The key system mediating the manifold

effects of cytokines is the JAK/STAT signaling pathway (Janus Kinases–Signal Transducer and Activator of Transcription), which includes cytoplasmic tyrosine kinases of the Janus family (JAK1, JAK2, JAK3, and Tyk2) and cytoplasmic latent transcription factors (in mammals, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6). Cytokines and growth factors act as signaling molecules for the JAK/STAT pathway (Rawlings et al. 2004).

Transcription factor NF- κ B controls the expression of numerous genes that encode proteins involved in immune response reactions, apoptosis, cell cycle, differentiation, and stress response. Impaired NF- κ B signaling can result in developmental abnormalities, inflammation, and a large number of diseases (Karban et al. 2004; Lawrence 2009). The major form of NF- κ B is a heterodimer of the p50 and p65/RelA subunits, which are encoded by the *NFKB1* and *NFKB2* genes, respectively. The *NFKB1* gene located on 4q24 encodes two proteins (p105 and p50) (Karban et al. 2004). The *NFKB1* gene exhibits a high level of polymorphism in different human populations of the world (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). The rs28362491 polymorphism generates a deletion of four nucleotides in the promoter region (−94 ins/del ATTG) causing lowered transcription levels of *NFKB1* and consequently partial depletion of p50. The *NFKB1* promoter containing the insertion allele (rs28362491) has been shown to have higher promoter activity than a promoter containing the deletion allele (Karban et al. 2004). Lai et al. 2015 indicated that *NFKB1* (−94 ins/del ATTG) polymorphism may play a role in coronary artery disease susceptibility in Chinese Uygur population and is functionally associated with IL-6 expression. This functional polymorphism has been associated with malignant tumors (Wang et al. 2014a, b; Wang et al. 2015a, b; Pallavi et al. 2015), myocardial infarction, and congenital heart disease (López-Mejías et al. 2012; Zhang et al. 2013; Yang et al. 2014).

IL-17 is produced by proinflammatory cells, mainly by type 17 T helpers (Th17). The IL-17 family includes six structurally homologous members: A, B, C, D, E, and F. IL-17A stimulates the syntheses of IL-1, TNFA, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), and other proinflammatory factors (Korn et al. 2009). In the recent years, Th17 cells have been attracting considerable attention as key mediators involved in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis and psoriasis (Korn et al. 2009; Kurimoto et al. 2013). The roles of Th17 and IL-17 in inflammatory diseases of the respiratory and cardiovascular systems are the subjects of extensive research (Kurimoto et al. 2013; Di Stefano et al. 2009; Eustace et al. 2011). Some proinflammatory functions of IL-17 are mediated by activation of matrix metalloproteases, MMP3 and MMP8, and neutrophil recruitment to the inflammation site. Neutrophils, in turn, activate metalloproteases and serine proteases, which lead to tissue damage (Korn et al. 2009). It is this mechanism that is involved in emphysematous lung tissue damage in COPD. Several studies have established IL-17 association with COPD (Eustace et al. 2011). Kurimoto et al. (2013) demonstrated the role of IL-17A in the development of pulmonary inflammation and lung emphysema in mouse models (Kurimoto et al. 2013).

Several studies analyzed the relationship between the adipose tissue and the levels of circulating cytokines (TNFA, IL-6), leptin, and adiponectin, which

contribute significantly to metabolic disorders developing in COPD and to impairment of the respiratory function (Franssen et al. 2008). Cytokines produced by the adipose tissue attract special attention. Adiponectin (ADIPOQ) is a 30-kDa cytokine secreted by adipocytes; it regulates energy homeostasis and has an anti-inflammatory and anti-atherogenic effect (Bianco et al. 2013; Franssen et al. 2008). Its role in inflammation is controversial: adiponectin plasma concentrations are significantly elevated in metabolic syndrome and in type-II diabetes mellitus, but decreased in some inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus (Korn et al. 2009; Pallavi et al. 2015). Some studies showed that the circulating ADIPOQ levels were increased in COPD and were associated with poor prognosis, in particular, with frequent exacerbations (Yuan et al. 2012). Several genome-wide studies showed that ADIPOQ levels were associated with ADIPOQ polymorphisms (Heid et al. 2010). Yuan et al. (2012) first showed that polymorphic *ADIPOQ* loci were associated with COPD (Yuan et al. 2012). It was also found that plasma ADIPOQ levels correlated with the respiratory function (Sato et al. 2014). Adiponectin actions are mediated by specific receptors, ADIPOR1 and ADIPOR2 (Bianco et al. 2013).

The frequency distributions of the *JAK1*, *JAK3*, *STAT1*, *STAT3*, *NFKB1*, *IL17A*, *ADIPOQ*, and *ADIPOR1* polymorphisms and their association with COPD was not yet investigated in the populations of Russia. Association studies of polymorphic markers in such candidate genes effecting development and progression of asthma, cancer, cardiovascular, and autoimmune diseases were published (Karban et al. 2004; McGovern et al. 2009; Sperati et al. 2009; Jiang et al. 2011; Wang et al. 2011; Zhong et al. 2012; Yang et al. 2012; Fantuzzi 2013; Yuan et al. 2014; Wang et al. 2014a, b; Rafiei et al. 2013; Carolanet et al. 2014; Kuruma et al. 2014; Lai et al. 2015; Jin et al. 2015). We hypothesized that inflammatory and immune response genes may be associated also with COPD in our Tatar population. To avoid possible problems arising from population and ethnic stratification, in our study, we analyzed the association of SNP markers with COPD in ethnically homogenous group—ethnic Tatars, historically dispersed over the territory of the Republic of Bashkortostan (Russia). The Republic of Bashkortostan is located in the southern part of the Ural Mountains and adjacent plains, at the border of Europe and Asia. It is a multinational republic, where representatives of more than hundred ethnic groups live, including Russians (39.3 %), Tatars (28.4 %), and Bashkirs (21.9 %).

The purpose of the present study was to investigate the association of COPD with polymorphisms of *JAK1* (rs310216), *JAK3* (rs3212780), *STAT1* (rs12693591), *STAT3* (rs2293152), *NFKB1* (rs28362491), *IL17A* (rs4711998, rs1974226), *ADIPOQ* (rs1501299, rs266729), and *ADIPOR1* (rs12733285) in a population of Tatars from Russia.

Materials and Methods

Prior to implementation, present 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). Written informed consent was obtained from all individuals. All DNA samples used in the study were anonymous.

Patients and Controls

Study design. This work was designed as a case–control study aimed at investigating the association of COPD with *JAK1*, *JAK3*, *STAT1*, *STAT3*, *NFKB1*, *IL17A*, *ADIPOQ*, and *ADIPOR1* polymorphisms in the ethnically homogenous group—Tatar population from Russia. The case–control groups for our candidate gene approach study were accurately selected and collected from 2010 to 2013 years in the pulmonary departments of Ufa City Hospitals: №13, №18, and №21 (Ufa, Russia). The total number of 882 DNA samples of unrelated individuals, representatives of Tatar population, historically dispersed over the territory of the Republic of Bashkortostan have been analyzed in this study. The Republic of Bashkortostan (the capital city is Ufa) is a sovereign state under the jurisdiction of the Russian Federation. We collected COPD and control groups' age-, sex- and ethnically matched data. Ethnic origin (up to the third generation) of all the participants was derived from direct interviews with examined persons. The COPD patients were recruited randomly according to the International Classification of Diseases tenth revision (ICD 10) (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision 2015) 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). The study group consisted in total of 425 unrelated COPD patients, recruited during the period from 2010 to 2013 in the pulmonary departments of Ufa City Hospitals, №13, №18, №21 (Ufa, Russia).

The Inclusion and Exclusion Criteria

For all patients with COPD, the diagnose was detected by the hospital specialists on the basis of the medical histories and the results of general, clinical, and special tests (chest X-ray, spirometry measures, and fibrobronchoscopy), physical examination, and laboratory approaches. Patients were excluded from the study if they had diagnosis of asthma and lung cancer. Subjects performed standardized pre-bronchodilator and post-bronchodilator spirometry in accordance with American Thoracic Society/European Respiratory Society (Miller et al. 2005). The spirometry was done in the in pulmonary departments of Ufa City Hospitals №13, №18, №21 (Ufa, Russia) by the hospital specialists, and the predicted values for FVC, FEV1, and FEV1/FVC ratio were generated using previously defined prediction equations as detailed to the European Coal and Steel Community (ECSC) (Quanjer et al. 1993; Roca et al. 1998). All COPD patients had post-bronchodilator FEV1/FVC values of <70 %.

The control group is comprised of 457 unrelated age-, sex- and ethnicity matched to the cases healthy residents of Ufa (Russia) with no history of chronic diseases such as respiratory system pathology and allergic diseases in the anamnesis. All the control subjects were collected among those individuals who attended Ufa City

Hospitals №13, 18, 21 (Russia) for regular medical examination. All individuals from control group were unrelated to patients and independent of one another. Control subjects demonstrated normal lung function (FEV1/FVC > 70 %, FEV1 > 80 %). Summary is given in Table 1.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the standard phenol–chloroform extraction procedure (Mathew 1985). We worked with so called candidate genes approach, meaning that we choose for consideration only polymorphisms in genes with known functions and previously shown association with other complex inflammatory diseases. Minor allele frequency (MAF) of $\geq 5\%$ in the Caucasian population, parameters set by the SNP database of the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/projects/SNP/>), were also reviewed. For the current study, ten most widely studied SNPs on *JAK1* (rs310216, c.1649-82C>T, intron variant), *JAK3* (rs3212780, c.3207+75C>T, intron variant), *STAT1* (rs12693591, c.786–557 C>A, intron variant), *STAT3* (rs2293152 c.1233+43C>G, intron variant), *NFKB1* (rs28362491 c.-798_–795delATTG, 2 KB upstream variant), *IL17A* (rs471199, c.–877G>A, 2 KB upstream variant 8; rs1974226, c.*1245C>T, 3 prime UTR variant), *ADIPOQ* (rs1501299, c.214+62G>T, intron variant; rs266729, c.–1124C>G, 2 KB upstream variant), and *ADIPOR1* (rs12733285, c.–95+1329G>A, intron variant) were examined by the real-time polymerase chain reaction (PCR), with the use of TaqMan SNP discrimination assays (Applied Biosystems, Foster City, CA). Accumulation of specific PCR-product by hybridization and cleavage of double-labeled fluorogenic probe during amplification was detected with a BioRad CFX96 instrument (Bio-Rad Laboratories Inc., USA). End-point fluorescence and genotype discrimination were determined according to the BioRad CFX96 protocol, using CFX Manager software. For quality control, 5 per cent dummy duplicates and blank controls were also taken up along with the samples in each experiment. The genotyping was blind to case or control status of the samples. Quality control of genotyping data was assessed by subject and by marker. A priori of the association analysis we run strict quality control on our data to exclude genotyping errors, SNPs and individuals with low call rates and other important quality characteristics. Subject data were excluded after examining missingness, reproducibility, and inbreeding. All subjects with a genotype call rate of <95 % were removed. Subsequently SNPs were filtered according to their proportion of missing, minor allele frequency (MAF) or deviation from Hardy–Weinberg–Equilibrium (HWE).

Statistical Analysis

The sample size was calculated by Quanto software (<http://biostats.usc.edu/software>). We examined eight candidate genes and used the most significant reported SNPs with a high minor allele frequency for each gene. On the basis of our calculations using the Power and Sample Size software program, our sample ($N = 882$) was considered adequate to study the selected SNPs. The sample size

Table 1 Characteristics of groups

	COPD (<i>N</i> = 425)	Controls (<i>N</i> = 457)	<i>P</i> value
Male (%)	369 (86.82)	406 (88.84)	0.51 ^a
Female (%)	56 (13.18)	51 (11.16)	
Age (\pm SD)	63.38 \pm 11.81	58.44 \pm 14.79	0.09 ^b
BMI (\pm SD)	25.81 \pm 5.92	27.06 \pm 3.84	0.06 ^b
Pack-years for smokers (\pm SD)	44.58 \pm 25.92	38.54 \pm 23.12	0.054 ^b
Smoking status			
Current and former smokers (%)	331 (77.88)	322 (70.46)	0.318 ^a
Non-smokers (%)	94 (22.12)	135 (29.54)	
Post-FEV1 % (\pm SD)	41.68 \pm 19.32	102.7 \pm 52.1	0.0001 ^b
Post-FEV1/FVC ratio (\pm SD)	58.66 \pm 13.66	87.94 \pm 10.69	
FVC % (\pm SD)	44.22 \pm 17.88	107.1 \pm 32.05	
GOLD status			
Stage II (%)	149 (29.16)	–	–
Stage III (%)	139 (27.20)		
Stage IV (%)	223 (43.64)		

BMI body mass index, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *Post* post-bronchodilator, *GOLD* global initiative for chronic obstructive lung disease, Pack-years PY (number of cigarettes per day \times number of years smoked)/20

^a Pearson's X^2 test; ^bMann-Whitney *U* test

(*N* = 425 for case group and *N* = 457 for control group) was sufficient to detect the association of examined SNPs and COPD with more than 80 % power (Power: 95.53 %, Disease prevalence, 7 %, error: 5 %).

For the quantitative traits, the mean values and standard deviations ($M \pm SD$) were calculated; the group comparison was performed with a nonparametric Mann–Whitney *U*-test. The frequencies of qualitative traits were compared using the Pearson's X^2 . Statistical analysis was carried out with the Statistica v. 6.0 program (StatSoft Inc., Tulsa, OK, USA). A minor allele frequencies (MAF) and the agreement of the genotype distribution to the Hardy–Weinberg equilibrium (X^2), the association analysis using the basic allele test and the calculation of the odds ratio (OR) for the rare allele of each locus and the significance of intergroup differences in allele and genotype frequencies (X^2 test for sample heterogeneity and the *P* value), and Cochran–Armitage trend test were performed with PLINK v. 1.07 (Purcell et al. 2007). Differences were considered significant if their corresponding *P* values were less than 0.05. To control Type-I error rate, Bonferroni correction for multiple comparison was performed meaning that *P* value was multiplied by the number of SNP loci studied (*n* = 10) to obtained the new P_{cor} value, false discovery rate (FDR) (Benjamini Hochberg) was calculated using the online software program <http://www.sdmproject.com/utilities/?show=FDR>. Logistic regression was used to detect the association of SNPs loci in different models, accounting for quantitative and binary traits (gender, age, pack-years, smoking status, body mass index). The significance of the obtained model accounting for all variables was verified by the

significance of the likelihood ratio test (P_{adj}). The best model was chosen using the Akaike's information criterion (AIC). For each significant locus ($P < 0.05$), the model with the lowest AIC was chosen. Linear regression analyses were performed to estimate the relationship between SNPs and quantitative phenotypes, such as lung function parameters and pack-years. The regression analysis was performed with PLINK v. 1.07 (Purcell et al. 2007) and SNPStats packages (Solé et al. 2006).

Results

Before candidate gene polymorphisms were analyzed for associations with COPD, we checked whether their genotype frequency distributions agreed with the Hardy–Weinberg equilibrium and evaluated minor allele frequencies (MAF) both in the combined group of patients and healthy subjects and in either group individually. For the control group, the following results were obtained: *JAK1* (rs310216) ($P = 0.064$, MAF = 0.128), *JAK3* (rs3212780) ($P = 0.053$, MAF = 0.291), *STAT1* (rs12693591) ($P = 0.38$, MAF = 0.140), *STAT3* (rs2293152) ($P = 0.11$, MAF = 0.306), *NFKB1* (rs28362491) ($P = 0.27$, MAF = 0.378), *IL17A* (rs4711998) ($P = 0.98$, MAF = 0.326) and (rs1974226) ($P = 0.94$, MAF = 0.223), *ADIPOQ* (rs1501299) ($P = 0.17$, MAF = 0.217) and (rs266729) ($P = 0.27$, MAF = 0.298), *ADIPOR1* (rs12733285) ($P = 0.44$, MAF = 0.271).

Association of Candidate Polymorphic Loci with COPD

Data on the allele and genotype frequency distributions for the loci in question, the significance of their differences between the groups, and odd ratio vales calculated for the minor allele, and Cochran–Armitage trend test of each locus are shown in Tables 2 and 3. Significant differences between the groups studied were identified for the following polymorphic loci: *JAK1* (rs310216), *JAK3* (rs3212780), *NFKB1* (rs28362491), *IL17A* (rs1974226). Table 4 presents the characteristics of the detected significant associations with COPD: the regression coefficient (beta), its exponent interpreted as odds ratio (OR) in the logistic model, the corresponding 95 % confidence intervals, and the level of significance, calculated while taking into account the patients' sex, age, smoking status, BMI, and smoking index in different models.

The frequency of the minor *T* allele of *JAK1* (rs310216) was significantly higher in COPD patients than in controls (19.88 vs 12.8 %; $P = 0.0001$, OR 1.69 (95 % CI 1.31–2.18)). The portion of *TT* homozygotes in the group of COPD patients was as high as 5.41 %, in contrast to 0.66 % in healthy subjects ($P = 0.0001$, OR 10.71 (95 % CI 2.48–46.33)) in the recessive model). Significant association with COPD was established in the additive ($P = 0.0002$, OR 1.70 (95 % CI 1.28–2.26)) and in the dominant model ($P = 0.005$, OR 1.58 (95 % CI 1.15–2.19)).

The minor *T* allele of *JAK3* (rs3212780) was shown to be associated with COPD ($P = 0.0001$, OR 1.43 (95 % CI 1.17–1.75)). In the dominant model, *JAK3* (rs3212780) association with COPD was more informative ($P = 0.001$, OR 1.61 (95 % CI 1.21–2.14)), since the portion of homozygous and heterozygous carriers of

Table 2 Allele and genotype frequencies of the *JAK1*, *JAK3*, *STAT1*, *STAT3*, and *NFKB1* polymorphisms in COPD patients and control subjects

Gene refSNP polymorphism location	Chr.	Minor allele	N	Genotypes, alleles	COPD n (%)	Control n (%)	P^a	P^b	OR (95 % CI)
<i>JAK1</i> rs310216 c.1649–82C>T intron variant	1p32.3–p31.3	T	882	TT/TC/CC	23/123/279 (5.41/28.94/65.65)	3/111/343 (0.66/24.29/75.05)	0.0001	0.00017	1.74 (1.32–2.31)
<i>JAK3</i> rs3212780 c.3207+75C>T intron variant	19p13.1	T	882	TT/TC/CC	169/681 (19.88/80.12)	117/797 (12.80/87.20)	0.0001	–	1.69 (1.31–2.18)
<i>STAT1</i> rs12693591 c.786–557C>A intron variant	2q32.2	A	882	AA/AC/CC	62/191/172 (14.59/44.94/40.47)	49/168/240 (10.72/36.76/52.52)	0.001	0.0015	1.41 (1.23–1.67)
<i>STAT3</i> rs2293152 c.1233+43C>G intron variant	17q21.2	C	882	CC/CG/GG	315/535 (37.06/62.94)	266/648 (29.10/70.90)	0.0001	–	1.43 (1.17–1.75)
<i>NFKB1</i> rs28362491 c.–798–795delATTG 2KB upstream variant	4q24	Del	882	Del/Del Del/Ins Ins/Ins	9/110/306 (2.12/25.88/72.00)	12/104/341 (2.63/22.76/74.62)	0.514	0.52	1.10 (0.82–1.46)
					128/722 (15.06/84.94)	128/786 (14.00/86.00)	0.572	–	1.08 (0.83–1.41)
					48/194/183 (11.29/45.65/43.06)	34/212/211 (7.44/46.39/46.17)	0.134	0.13	1.19 (0.95–1.48)
					290/560 (34.12/65.88)	280/634 (30.63/69.37)	0.131	–	1.17 (0.96–1.43)
					59/164/202 (13.88/38.59/47.53)	73/200/184 (15.97/43.76/40.26)	0.094	0.096	0.91 (0.73–1.14)
					282/568 (33.18/66.82)	346/568 (37.86/62.14)	0.045	–	0.81 (0.67–0.99)

Chr.—chromosome location^a χ^2 test for allele or genotypes frequency difference between COPD and control, ^b Cochran–Armitage trend test, OR with 95 % CI for minor allele in basic allele test or Cochran–Armitage trend test

Table 3 Allele and genotype frequencies of the *IL17A*, *ADIPOQ*, and *ADIPOR1* polymorphisms in COPD patients and control subjects

Gene refSNP polymorphism location	Chr.	Minor allele	N	Genotypes, alleles	COPD n (%)	P ^a	Control n (%)	P ^b	OR (95 % CI)
<i>IL17A</i> rs4711998 c.-877G>A 2KB upstream variant	6p12	A	882	AA/AG/GG A/G	51/155/219 (12.00/ 36.47/51.53)	0.087	49/200/208 (10.72/ 43.76/45.51)	0.37	0.90 (0.72–1.13)
<i>IL17A</i> rs1974226 c.*1245C>T 3 prime UTR variant	6p12	T	882	TT/TC/CC T/C	46/133/246 (10.82/ 31.29/57.88)	0.006	23/158/276 (5.03/ 34.57/60.39)	0.067	1.21 (0.73–1.09)
<i>ADIPOQ</i> rs1501299 c.214+62G>T intron variant	3q27	T	882	TT/TG/GG T/G	33/141/251 (7.76/ 33.18/59.06)	0.437	27/145/285 (5.91/ 31.73/62.36)	0.29	1.13 (0.95–1.43)
<i>ADIPOQ</i> rs266729 c.-1124C>G 2KB upstream variant	3q27	G	882	GG/GC/CC G/C	52/171/202 (12.24/ 40.24/47.53)	0.520	46/181/230 (10.07/ 39.61/50.33)	0.33	1.11 (0.90–1.37)
<i>ADIPOR1</i> rs12733285 c.-95+1329G>A intron variant	1q32.1	A	882	AA/AG/GG A/G	31/152/242 (7.29/ 35.76/56.94)	0.642	37/174/246 (8.10/ 38.07/53.83)	0.41	0.91 (0.73–1.14)
					214/636 (25.18/74.82)	0.379	248/666 (27.13/72.87)	–	0.90 (0.73–1.11)

Chr. chromosome location

^a X² test for allele or genotypes frequency difference between COPD and control, ^b Cochran–Armitage trend test, OR with 95 % CI for minor allele in basic allele test or Cochran–Armitage trend test

Table 4 Association between *JAK1*, *JAK3*, and *IL17A* polymorphisms and COPD

Gene, SNP	Minor allele	N	Genotype/model	COPD aB.C. (%)	Control aB.C. (%)	OR _{adj} (CI 95 %)	P ^a _{adj}	P ^b _{cor-Bf}	P ^c _{cor-FDR}	
<i>JAK1</i> rs310216 c.1649–82C>T	T	882	CC	279 (65.6)	343 (75.1)	1.00	0.005	0.05	0.007	
			TC + TT	146 (34.4)	114 (24.9)	1.58 (1.15–2.19)				
			dominant							
			CC + TC	402 (94.6)	454 (99.3)	1.00	0.0001	0.001	0.0009	
<i>JAK3</i> rs3212780 c.3207+75C>T	T	882	TT	23 (5.4)	3 (0.7)	10.71 (2.48–46.33)				
			recessive							
			Log-additive							
			CC	172 (40.5)	240 (52.5)	1.00	0.0002	0.002	0.0009	
<i>IL17A</i> rs1974226 c.*1245C>T	T	882	CT + TT	253 (59.5)	217 (47.5)	1.61 (1.21–2.14)				
			dominant							
			CC + CT	363 (85.4)	408 (89.3)	1.00	0.13	–	–	
			TT	62 (14.6)	49 (10.7)	1.39 (0.91–2.13)				
<i>IL17A</i> rs1974226 c.*1245C>T	T	882	recessive							
			Log-additive							
			CC	246 (57.9)	276 (60.4)	1.00	0.0019	0.019	0.004	
			CT + TT	179 (42.1)	181 (39.6)	1.11 (0.82–1.50)				
<i>IL17A</i> rs1974226 c.*1245C>T	T	882	dominant							
			CC + CT	379 (89.2)	434 (95.0)	1.00	0.0037	0.037	0.006	
			TT	46 (10.8)	38 (5.0)	2.31 (1.28–4.16)				
			recessive							
<i>IL17A</i> rs1974226 c.*1245C>T	T	882	Log-additive							

^a P_{adj}, significance in the likelihood ratio test for the regression model adjusted for age, sex, BMI, smoking status and pack-years; OR_{adj}, adjusted odds ratio and CI, 95 % confidence interval; ^b P_{cor-Bf}, significance after the Bonferroni correction for multiple testing; ^c P_{cor-FDR}, significance after the FDR correction

the *T* allele was 59.5 % in COPD patients in comparison to 47.5 % in healthy controls.

The frequency of the *Del* allele of the *NFKB1* insertion/deletion polymorphism rs28362491 was lower in COPD patients than in controls (33.18 vs 37.86 %; $P = 0.045$, OR 0.81 (95 % CI 0.67–0.99)). The more frequent *Ins* allele was the marker associated with the disease (OR 1.22 (95 % CI 1.05–1.49)). However, regression analysis failed to detect a significant association between *NFKB1* (rs28362491) and COPD.

The minor allele of *IL17A* (rs1974226) was also shown to be associated with COPD ($P = 0.048$, OR 1.25 (95 % CI 1.01–1.56)); its frequency was 26.47 % in the group of patients, in contrast to 22.32 % in healthy controls. A regression analysis established *IL17A*'s (rs1974226) association with COPD in the recessive model ($P = 0.0037$, OR 2.31 (95 % CI 1.28–4.16)). The observed association was because the portion of homozygous and heterozygous carriers of the minor *T* allele was higher in COPD patients.

Analysis of Genotype-by-Environment Interactions in COPD

Significant interactions with the smoking status were observed for the loci *IL17A* (rs1974226) ($P_{\text{interact}} = 0.016$), *JAK3* (rs3212780) ($P_{\text{interact}} = 0.031$), *ADIPOQ* (rs266729) ($P_{\text{interact}} = 0.013$), and *ADIPOR1* (rs12733285) ($P_{\text{interact}} = 0.018$). We analyzed the contribution of candidate gene genotypes to the variation of the quantitative trait characterizing smoking intensity (smoking index, packs/year) and found that the smoking index was affected by the genotypes by *IL17A* (rs4711998, rs1974226), *JAK1* (rs310216), *JAK3* (rs3212780), and *NFKB1* (rs28362491) (Table 5).

In particular, the smoking index was significantly higher in carriers of *IL17* genotypes *AA* (rs4711998) and *TT* (rs1974226) ($P = 0.045$ and $P = 0.004$, respectively). In *TT* homozygotes by the minor allele of *JAK1* (rs310216), the smoking index was as high as 43.48 packs/years, in contrast to 23.31 packs/year in heterozygotes and *CC* homozygotes ($P = 0.0005$). The *CC* genotype by *JAK3* (rs3212780) was associated with lower smoking index values ($P = 0.021$), whereas the homozygous insertion variant (*Ins/Ins*) of *NFKB1* (rs28362491) was associated with an elevated smoking index ($P = 0.042$).

Genotype-by-environment interactions were also analyzed by comparing odds ratio values calculated for the candidate genes in subgroups formed according to the presence or absence of the environmental factor ((Table 6). We found that the polymorphisms *IL17A* (rs1974226), *JAK1* (rs310216), and *NFKB1* (rs28362491) were significantly associated with COPD only in the group of smokers. *IL17A* (rs1974226) was associated with COPD in smokers ($P = 0.017$, OR 1.39 (95 % CI 1.06–1.83) in the additive model). In the subgroup of smokers, the risk of COPD was associated with *JAK1* (rs310216) ($P = 0.0001$, OR 1.94 (95 % CI 1.37–2.74)) in the additive model, while *NFKB1* (rs28362491) was associated with COPD in smokers in the dominant model ($P = 0.032$, OR 0.66 (95 % CI 0.45–0.97)).

In nonsmokers, significant associations were established for *JAK3* (rs3212780) ($P = 0.0016$, OR 2.63 (95 % CI 1.43–4.84) in the dominant model), *STAT3*

Table 5 The relationship between the inflammation and immune response genes polymorphisms and quantitative phenotypes (lung function parameters and pack-years)

Gene, SNP	Model/genotypes	M ± SE	P ^a	Beta (CI 95 %)
Forced vital capacity (FVC)				
<i>NFKB1</i> , rs28362491 c.-798_-795delATTG	(Ins/Ins + Ins/Del)	48.88 (1.27)	0.015	0
	Del/Del	57.4 (3.78)		8.52 (1.59–15.45)
<i>ADIPOR1</i> , rs12733285 c.-95+1329G>A	(GG + AA)	48.28 (1.47)	0.039	0
	GA	53.21 (2.06)		4.93 (0.01–9.85)
Forced expiratory volume in 1 s (FEV1)				
<i>JAK1</i> , rs310216 c.1649–82C>T	(CC + CT)	41.93 (1.1)	0.011	0
	TT	30.44 (3.29)		–11.49 (–20.5 to –2.47)
<i>STAT1</i> , rs12693591 c.786-557 C>A	(CC + AC)	40.27 (1.01)	0.043	0
	AA	27.75 (2.81)		–12.52 (–24.9 to –0.13)
Pack-years				
<i>IL17A</i> , rs4711998 c.-877G>A	(GG + AG)	24.98 (1.15)	0.038	0
	AA	31.96 (3.74)		6.98 (0.16–13.8)
<i>IL17A</i> , rs1974226 c.*1245C>T	(CC + CT)	24.23 (1.04)	0.0031	0
	TT	35.26 (4.95)		11.03 (3.57–18.50)
<i>JAK1</i> , rs310216 c.1649- 82C>T	(CC + CT)	23.31 (0.97)	0.00043	0
	TT	43.48 (7.98)		20.16 (8.87–31.46)
<i>JAK3</i> , rs3212780 C>T	CC	22.58 (1.33)	0.017	0
	(TC + TT)	27.1 (1.41)		4.52 (0.69–8.35)
<i>NFKB1</i> , rs28362491 c.-798_-795delATTG	Ins/Ins	28.23 (1.66)	0.038	0
	(Ins/Del + Del/Del)	23.82 (1.41)		–4.42 (–8.66 to –0.17)

Data presented are beta, mean and standard error with two-sided *P* values.

^a Linear regression analysis adjusting for age, gender, BMI, and smoking status

(rs2293152) (*P* = 0.0046, OR 1.93 (95 % CI 1.22–3.06) in the additive model), *ADIPOQ* (rs266729) (*P* = 0.019, OR 1.64 (95 % CI 1.08–2.48) in the additive model), and *ADIPOR1* (rs12733285) (*P* = 0.017, OR 0.46 (95 % CI 0.24–0.89) for the GA genotype) (Table 6).

Contribution of Candidate Gene Polymorphisms to the Variation of Quantitative Characteristics of the Respiratory Function

We also analyzed whether quantitative characteristics of the respiratory function: vital capacity (VC), forced vital capacity (FVC), and forced expiration volume in

Table 6 Association analysis of the inflammation and immune response genes polymorphisms with COPD in smokers and non-smokers

Gene, SNP	Minor allele	N	Test/model	COPD n (%)	Control n (%)	P_{adj}^a	P_{cor-BF}^b	$P_{cor-FDR}^c$	OR _{adj}	CI95 (%)
Smokers										
<i>IL17A</i> , rs1974226 C>T	T	653	CC	186 (56.1)	209 (64.9)	0.043	0.43	0.043	1.00	
			CT + TT (dominant)	145 (43.9)	113 (35.1)				1.45 (1.01–2.08)	
			CC(0) CT(1) TT(2) Log-additive	–	–	0.017	0.17	0.023	1.39 (1.06–1.83)	
<i>JAK1</i> , rs310216 C>T	T	653	CC	218 (66.0)	252 (78.2)	0.0019	0.019	0.006	1.00	
			CT + TT (dominant)	113 (34.0)	70 (21.8)				1.85 (1.25–2.74)	
			CC(0) CT(1) TT(2) Log-additive	–	–	0.0001	0.001	0.001	1.94 (1.37–2.74)	
<i>NFKB1</i> , rs28362491	del	653	Ins/Ins	163 (49.2)	126 (39.1)	0.032	0.32	0.035	1.00	
			Ins/Del + Del/Del (dominant)	168 (50.8)	196 (60.9)				0.66 (0.45–0.97)	
			Log-additive	–	–					
Non-smokers										
<i>JAK3</i> , rs3212780 C>T	T	229	CC	34 (36.2)	80 (59.3)	0.0016	0.016	0.006	1.00	
			CT + TT (dominant)	60 (63.8)	55 (40.7)				2.63 (1.43–4.84)	
			CC(0) CT(1) TT(2) Log-additive	–	–	0.0063	0.063	0.012	1.78 (1.17–2.69)	
<i>STAT3</i> , rs2293152 C>G	C	229	CG + GG	74 (78.7)	126 (93.0)	0.0064	0.064	0.012	1.00	
			CC (recessive)	20 (21.3)	9 (7.0)				3.55 (1.44–8.76)	
			GG(0) GC(1) CC(2) Log-additive	–	–	0.0046	0.046	0.011	1.93 (1.22–3.06)	
<i>ADIPOQ</i> , rs266729 C > G	G	229	CC(0) CG (1) GG (2) Log-additive	–	–	0.019	0.19	0.023	1.64 (1.08–2.48)	

Table 6 continued

Gene, SNP	Minor allele	N	Test/model	COPD n (%)	Control n (%)	$P_{\text{adj}}^{\text{a}}$	$P_{\text{cor-BF}}^{\text{b}}$	$P_{\text{cor-FDR}}^{\text{c}}$	OR _{adj}	OR _{adj} (CI95 %)
<i>ADIPOR1</i> , rs12733285	G>A	A	229	GA vs (GG + AA)	72 (76.5)	81 (60.0)	0.017	0.17	0.023	0.46 (0.24–0.89)
					22 (23.5)	54 (40.0)				

^a P_{adj} , significance in the likelihood ratio test for the regression model adjusted for age, sex, and pack-year (only in smokers), BMI; OR_{adj}, adjusted odds ratio and CI, 95 % confidence interval; ^b $P_{\text{cor-BF}}$, significance after the Bonferroni correction for multiple testing; ^c $P_{\text{cor-FDR}}$, significance after the FDR correction

1 s (FEV1), depended on the genotypes at the loci studied in COPD patients. Polymorphisms of *JAK3* (rs3212780), *STAT3* (rs2293152), *IL17A* (rs4711998, rs1974226), and *ADIPOQ* (rs1501299, rs266729) were not significantly associated with quantitative characteristics of the respiratory function.

Carriers of the *NFKB1* (rs28362491) genotype *Del/Del* exhibited higher FVC values ($P = 0.017$) (Table 5), which further confirmed that this locus was associated with COPD. Patients heterozygous at the *ADIPOR1* (rs12733285) also had higher FVC ($P = 0.043$). FEV1 was found to depend on *JAK1* (rs310216) and *STAT1* (rs12693591) genotypes. Patients homozygous for the *T* allele of *JAK1* (rs310216) had lower FEV1 than those with *CC* and *CT* genotypes ($P = 0.013$). In *AA* homozygotes by *STAT1* (rs12693591), FVC values were significantly decreased ($P = 0.048$).

Discussion

The objective of this study was to evaluate the contribution of *JAK1* (rs310216), *JAK3* (rs3212780), *STAT1* (rs12693591), *STAT3* (rs2293152), *NFKB1* (rs28362491), *IL17A* (rs4711998, rs1974226), *ADIPOQ* (rs1501299, rs266729), and *ADIPOR1* (rs12733285) polymorphisms to susceptibility to COPD in a Tatar population from Russia. We also investigated the associations of these candidate gene loci with quantitative parameters characterizing COPD progression and analyzed interactions between genetic and environmental factors.

Several *STAT1*, *STAT3*, *JAK1*, and *JAK3* SNPs were reported to be significantly associated with cervical cancer (Wang et al. 2011), nonsmall cell lung cancer (Jiang et al. 2011), leukemia (Zhong et al. 2012), gastric cancer (Yuan et al. 2014), Crohn's disease (Wang et al. 2014a, b), and cardiovascular diseases (Sperati et al. 2009). Based on previous studies, our case-control study detected the effect of *JAK1* (rs310216, c.1649-82C>T), *JAK3* (rs3212780, c.3207+75C>T), *STAT1* (rs12693591, c.786-557G>T), *STAT3* (rs2293152, c.1233+43C>G) gene polymorphisms on COPD in Tatar population from Russia. The most significant associations have been established for the polymorphisms of *JAK1* and *JAK3*. Minor alleles of *JAK1* (rs310216) and *JAK3* (rs3212780) were associated with COPD in general. *JAK1* (rs310216) was also associated with variation in respiratory function characteristics reflecting the severity of airway obstruction. In particular, homozygous carrier of the minor *T* allele exhibited lower FEV1 values. *JAK3* (rs3212780) showed a significant interaction with the smoking status. *JAK3* (rs3212780) association with COPD was confirmed only in nonsmokers, whereas *JAK1* (rs310216) was associated with COPD in smokers. It should be noted that *TT* homozygotes by the minor allele of *JAK1* (rs310216) had a significantly higher smoking index. At the same time, homozygous carriers of the frequent *C* allele of *JAK3* (rs3212780) exhibited lower smoking index values. *JAK1* and *JAK3* encode cytoplasmic tyrosine kinases of the Janus family whose function is to mediate interferon- and cytokine-induced signaling. The distinctive feature of Janus kinases differing them from other mammalian tyrosine kinases is the presence of a tandem of a kinase (JH1) and pseudokinase (JH2) domains (Rawlings et al. 2004).

Mutations of the JH2 domain can inhibit or stimulate the catalytic activity of Janus kinases depending on their particular location (Rawlings et al. 2004). Another function of the pseudokinase domain is to provide binding sites for STAT proteins. JAK1 is expressed in different tissues and can be activated by many cytokines, while JAK3 expression is specific to certain tissues. It is constitutively expressed in natural killer cells and thymocytes, and can be induced in T and B cells, as well as in myeloid cells (Rawlings et al. 2004). *JAK3* (rs3212780) was associated with cardiovascular complications in patients on dialysis (Sperati et al. 2009). *JAK1* polymorphisms were significantly associated with Vogt–Koyanagi–Harada disease and with Behcet’s disease in a Chinese Han population (Hu et al. 2013; Hou et al. 2013). Previously, *JAK1* polymorphisms were associated with bronchial asthma (Hsieh et al. 2011), and hepatocellular carcinoma (Xie et al. 2009).

For signal transduction and activation of transcription, protein 1 (STAT1) is a transcription factor mediating constitutive transcription of numerous genes (Ramana et al. 2000). It is also involved in signal transduction from a variety of different ligands, including interferons (type 1, IFNA and IFNB; and type 2, IFNG), cytokines (IL-6, IL-22, TNF, and IL-10), MAP kinases, peptide hormones, and lipopolysaccharides. The STAT1-encoding gene is located on 2q32.2 and comprises 25 exons. The promoter region of *STAT1* contains binding sites for transcription factors STAT5B, Max1, AP-1, IRF-1, S8, COMP1, FOXO1a, RSRFC4, and c-Myc. *STAT1* polymorphisms have been associated with an increased risk of hepatocellular carcinoma (Zhu et al. 2010) and with atopic sensitization (Pinto et al. 2007). STAT3 is the main signal transducer for gp130-like receptors. It is activated by phosphorylation induced by cytokines of the IL-6 and IL-10 families, and leptin. This transcription factor is involved in the signaling pathways induced by cytokines and chemokines, nerve growth factor, and leptin, as well as in Notch signaling, and the Th17 differentiation pathway (Geraghty et al. 2013). Through mediating the effects of different cell stimuli on the expressions of numerous genes, STAT3 plays an important role in a variety of cell processes. In particular, STAT3 regulates all key processes involved in airway damage and lung tissue destruction in COPD: inflammation, apoptosis, and protease expression (Geraghty et al. 2013). It was shown in a mouse model that exposure to tobacco smoke caused STAT3 activation (Geraghty et al. 2013). Expression of the *STAT3* gene located on chromosome 17q21.2 gives rise to two STAT3 isoforms by alternative splicing. *STAT3* polymorphisms have been associated with Crohn’s disease (Wang et al. 2014a, b), gastric cancer (Yuan et al. 2014), autoimmune thyroiditis (Xiao et al. 2013), and multiple sclerosis (Lill et al. 2012). In the present work, *STAT3* (rs2293152) exhibited an association with COPD in nonsmokers. The genotype by *STAT1* (rs12693591) affected the FVC parameter corresponding to COPD severity: it was significantly decreased in homozygous carriers of the minor allele.

In our study, the insertion allele of the *NFKB1* (rs28362491, c.-798_-795delATTG) was associated both with COPD in general and with decreased lung function parameters characterizing the severity of the disease. The rs28362491 genotype was found to affect the smoking index: it was significantly higher in homozygous carriers of the *Ins* allele. The rs28362491 (−94 insertion/deletion ATTG) functional *NFKB1* polymorphism is located between two putative key

promoter regulatory elements. The study of *in vitro* promoter expression indicated that the ATTG insertion allele may increase the mRNA expression of the *NFKB1*, resulting in the production of p50/p105 NF- κ B protein (Karban et al. 2004). The *NFKB1* (rs28362491, -94 insertion/deletion ATTG) polymorphism may influence the susceptibility to inflammatory diseases by inducing imbalance in the pro-inflammatory and anti-inflammatory responses (Karban et al. 2004; Lai et al. 2015). The deletion allele of *NFKB1* (rs28362491) is a marker of an increased risk of malignant tumors and dilated cardiomyopathy, but a decreased risk of myocardial infarction, pathogenesis of which also involves an inflammatory component (Yang et al. 2014; Zhou et al. 2009). The role of inflammation in the pathogenesis of COPD is well known (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease 2011; Hackett et al. 2008), and *NFKB1* is therefore a reliable candidate gene for COPD. Moreover, *NFKB1* (rs28362491) is located in 4q24, and it is possible that this polymorphism is in linkage with other polymorphisms that are associated with COPD. Recent GWASs and replication studies have identified several SNPs in chromosomal region 4q22.1 (*FAM13A*), 4q31 region (*HHIP*), and at 4q28.1 region, which were associated with COPD, lung function parameters, and smoking behaviors in different populations (Pillai et al. 2009, 2010; Cho et al. 2010; Siedlinski et al. 2011; Caporaso et al. 2009; Ding et al. 2015a,b). Caporaso et al. (2009) observed association between rs10489113 located on 4q28.1 near *NFKB1* and smoking behavior. Ding et al. 2015a studied rs950063 on 4q28.1 in case-control study of COPD in Hainan region, and did not find any significant association between the rs950063 and risk of COPD, but detected that SNPs from *FAM13A* (rs7671167) on 4q22.1 are associated with COPD in Chinese Li minority population (Ding et al. 2015b).

IL-17 is a proinflammatory cytokine encoded by *IL17A*, which is located on chromosome 6p12. The human *IL17A* gene is composed of three exons and two introns covering 4, 252 bases of genomic DNA (Nakada et al. 2011). IL-17 stimulates the expression of IL-6 and cyclooxygenase 2 (COX₂) (Dariusz et al. 2014). It was recently demonstrated that, apart from Th17 lymphocytes, IL-17 is produced by other types of cells, including macrophages, neutrophils, and mast cells (Korn et al. 2009). By stimulating macrophages, IL-17 promotes the production of proinflammatory cytokines and matrix metalloproteases and thus can be involved in the pathogenesis of not only autoimmune, but also other inflammatory diseases, including COPD. Our case-control study detected the effect of the *IL17A* (rs4711998, c.-877A>G) the 2 KB upstream variant, and the *IL17A* (rs1974226, c.*1245C>T) the 3 prime UTR variant on COPD in Tatar population from Russia. The variant *IL17A* (rs4711998, c.-877A>G) located within 5'UTR region possibly was associated with a change in transcriptional activity of *IL17A* (Nakada et al. 2011). A study by McGovern et al. (2009) confirmed the contribution of *IL17* and *IL23* polymorphisms to Crohn's disease, a classical autoimmune condition (McGovern et al. 2009). At the same time, a polymorphism in the *IL17A* promoter was shown to be significantly associated with gastric cancer in an Iranian population (Rafiei et al. 2013) and with postmenopausal osteoporosis in a Polish population (Dariusz et al. 2014). A number of *IL17A* polymorphisms were analyzed for association with brucellosis (Rasouli et al. 2013). Jin et al. (2015) in systematic

review showed that *IL17A* (rs4711998) may be potential risk factors for asthma susceptibility (Jin et al. 2015). The transcript of *IL17A* (1859 bp) has a relatively long 3'UTR region (1345 bp), where the *IL17A* (rs1974226, c.*1245C>T) polymorphism is located (Nakada et al. 2011). The potential mechanism of the rs1974226 effect is alteration of gene regulation (Nakada et al. 2011). Chen et al. (2006) in their review have provided evidence for the role of the 3' UTR region in regulation of gene expression, such as mRNA stability and/or degradation as well as translation efficiency (Chen et al. 2006). In our work, rs1974226, (c.*1245C>T) polymorphism of *IL17A* has for the first time been shown to be associated with COPD; this association was further confirmed in the subgroup of smokers. Characteristically, rs1974226 exhibited a significant gene-by-environment interaction with the smoking status ($P_{\text{interact}} = 0.016$), and the smoking index (describing the number of cigarettes smoked) depended on the *IL17A* polymorphisms, rs1974226 and rs4711998. In study by Chang et al. (2014) was demonstrated that IL-17A plays important roles in the initial inflammatory response to cigarette smoke exposure and on alveolar epithelial cell damage. These findings support an important role for IL-17 in the pathogenesis of COPD (Chang et al. 2014). The data by Roos et al. suggest IL-17A involvement in COPD progression and in the formation of secondary lymph nodes in the lung tissue of patients with very severe COPD (Roos et al. 2015). The role of cytokines IL-9, IL-17, IL-22, IL-25, and IL-33 in airway inflammation in bronchial asthma is discussed in (Farahani et al. 2014). The fact that the associations of *IL17A* loci, rs1974226 and rs4711998, with COPD were confirmed only in smokers, along with the detected relationship between *IL17A* polymorphisms and smoking index and smoking status, seems to support the notion that IL-17 acts by activating matrix metalloproteases and serine proteases and destroys the lung tissue similarly to cartilage degradation in rheumatoid arthritis. It is known that smoking is the principal factor that triggers the chronic inflammation cascade in COPD and leads to emphysematous degradation of lung tissue. It is not unlikely that autoimmune mechanisms are also involved in this processes (Eustace et al. 2011).

Adiponectin (ADIPOQ) is a cytokine that is secreted by adipocytes and regulates energy homeostasis (Bianco et al. 2013; Franssen et al. 2008). Circulating ADIPOQ levels are significantly decreased in obesity (Franssen et al. 2008). Increased systemic ADIPOQ levels were observed in patients with inflammatory and autoimmune diseases (Fantuzzi 2013). Peripheral blood biomarkers can serve as accurate indicators predicting COPD phenotypes and other systemic manifestations of the disease. One of such biomarkers is ADIPOQ, whose level clearly correlates with COPD severity and emphysematous changes in the lungs, it may play an important role in the pathogenesis of smoking-induced pulmonary diseases (Carolan et al. 2014). It was also found that significant amounts of ADIPOQ are expressed in bronchoalveolar lavage and in epithelial cells of the respiratory pathways of patients with COPD and lung emphysema, but not in controls (Miller et al. 2009). Some polymorphisms have been found at the *ADIPOQ* gene (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). We chose genotypes, rs266729 and rs1501299, because these SNP are the most common SNPs and have been studied extensively by others as to their functionality and in relation to other complex inflammatory diseases (Yuan

et al. 2012; Yang et al. 2012; Sato et al. 2014; Leu et al. 2011; Laumen et al. 2009; de Faria et al. 2015). Among them, intron variant rs1501299 (c.214+62G>T) is the one most extensively studied. *ADIPOQ* (rs1501299, c.214+62G>T), situated in the intron 2 region, has opposite effects on up-regulating adiponectin levels (Zhang et al. 2009; de Faria et al. 2015). The *T* allele of the rs1501299 is associated with high adiponectin levels in plasma (Woo et al. 2006; Vasseur et al. 2002). It is possible that this intron variant (rs1501299) is in linkage with other functional polymorphisms. The rs1501299 locus was associated with pancreatic cancer in a Japanese population (Kuruma et al. 2014), and with reduced prevalence of depression (Wang et al. 2015).

The *ADIPOQ* (rs266729, c.-1124C>G), located in the promoter region and has been associated with down-regulation of *ADIPOQ* (Zhang et al. 2009). The presence of the G allele of the rs266729 polymorphism results in loss of transcriptional stimulatory protein (SP1) binding site and consequently affects *ADIPOQ* regulation and expression (Zhang et al. 2009; Laumen et al. 2009). In a study by Yuan et al. (2012), *ADIPOQ* polymorphisms were for the first time shown to be associated with COPD (Yuan et al. 2012). In the present work, the rs266729 (c.-1124C>G) polymorphism of *ADIPOQ* was found to be associated with COPD in nonsmoking subjects; at the same time, no association with COPD was observed for rs1501299 in the population studied. Carriers of the heterozygous *ADIPOR1* (rs12733285, c.-95+1329G>A) genotype had higher FVC values, i.e., this genotype acts as protective against COPD in nonsmokers. The loci *ADIPOQ* (rs266729) and *ADIPOR1* (rs12733285) exhibited significant gene-by-environment interactions with smoking status in COPD.

The present study also had some potential limitations. Our study was only restricted to a population of Tatars from Russia. Further large sample size studies with more diverse ethnic populations are required to replicate our results. Second, although our study suggested that *JAK1* (rs310216), *JAK3* (rs3212780), *NFKB1* (rs28362491), and *IL17A* (rs1974226) were associated with the risk of COPD, more biological background data and functional studies are needed to explain the results.

In summary, our analysis of COPD association with polymorphisms of candidate genes involved in systemic inflammatory response in a population of Tatars from Russia has for the first time shown that polymorphisms of *JAK1* (rs310216), *JAK3* (rs3212780), *NFKB1* (rs28362491), and *IL17A* (rs1974226) are implicated in this disease in our population. Association of *ADIPOQ* (rs1501299 and rs266729) polymorphisms with COPD has also been confirmed in a Tatar population. Further research aimed at elucidating the mechanisms underlying the development of systemic inflammatory reaction in COPD will contribute to the understanding of the hereditary factors predisposing to the disease and will help specify new targets for its therapy.

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Compliance with Ethical Standards

Conflict of interest None of the authors has conflicts of interest to report with regard to this manuscript.

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