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ORIGINAL ARTICLE

The Relationship Between Chemokine and Chemokine Receptor Genes Polymorphisms and Chronic Obstructive Pulmonary Disease Susceptibility in Tatar Population from Russia: A Case Control Study

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease affecting primarily distal respiratory pathways and lung parenchyma. This study aimed to determine possible genetic association of chemokine and chemokine receptor genes polymorphisms with COPD in a Tatar population from Russia. SNPs of *CCL20*, *CCR6*, *CXCL8*, *CXCR1, CXCR2*, *CCL8*, *CCL23*, *CCR2*, and *CX3CL1* genes and their gene–gene interactions were analyzed for association with COPD in cohort of 601 patients and 617 controls. As a result statistically significant associations with COPD in the study group under the biologically plausible assumption of additive genetic model were identified in *CCL20* (rs6749704) ($P = 0.00001$, OR 1.55), *CCR6* (rs3093024) ($P = 0.0003$, OR 0.74), *CCL8* (rs3138035) ($P = 0.0001$, OR 0.67), *CX3CL1* (rs170364) ($P = 0.023$, OR 1.21), *CXCL8* (rs4073) ($P = 0.007$, OR 1.23), *CXCR2* (rs2230054) ($P = 0.0002$, OR 1.32). Following SNPs *CCL20* (rs6749704), *CX3CL1* (rs170364), *CCL8* (rs3138035), *CXCL8* (rs4073), *CXCR2* (rs2230054) showed statistically significant association with COPD only in smokers. The association of *CCR6* (rs3093024) with COPD was confirmed both in smokers and in non-smokers. A relationship between smoking index and *CCL20* (rs6749704) ($P = 0.04$), *CCR6* (rs3093024) ($P = 0.007$), *CCL8 (*rs3138035) ($P = 0.0043$), and *CX3CL1* (rs170364) ($P = 0.04$) was revealed. A significant genotype-dependent variation of Forced Vital Capacity was observed for *CCL23* (rs854655) ($P = 0.04$). Forced Expiratory Volume in 1 s / Forced Vital Capacity ratio was affected by *CCL23* (rs854655) ($P = 0.05$) and *CXCR2* (rs1126579) ($P = 0.02$). Using the APSampler algorithm, we obtained nine gene–gene combinations that remained significantly associated with COPD; loci *CCR2* (rs1799864) and *CCL8* (rs3138035) were involved in the largest number of the combinations. Our results indicate that *CCL20* (rs6749704), *CCR6* (rs3093024), *CCR2* (rs1799864), *CCL8* (rs3138035), *CXCL8* (rs4073), *CXCR1* (rs2234671), *CXCR2* (rs2230054), and *CX3CL1* (rs170364) polymorphisms are strongly associated with COPD in Tatar population from Russia, alone and in combinations. For the first time combination

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of the corresponding SNPs were considered and as a result 8 SNP patterns were associated with increased risk of COPD

Keywords Chronic obstructive pulmonary disease · Inflammation · Chemokines · Chemokines' receptors · Gene–gene interactions · Gene-by-environment interactions

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 (Decramer et al. 2012; Barnes 2016). COPD is the major rising global health problem, which is now the third leading cause of death worldwide and a major cause of morbidity (Decramer et al. 2012; Barnes 2016; Henrot et al. 2019). Complex interactions between environmental (effects of environmental pollutants, tobacco smoke, etc.) and genetic factors are responsible for COPD development (Decramer et al. 2012; Barnes 2016).

Inflammation is a basic physiological process that is aimed to protect the body from various factors and facilitating tissue repair after damage (Medzhitov 2008). A cascade of biochemical and immune processes underlies inflammation, and their regulation involves many humoral mediators, including cytokines (Medzhitov 2008). Inflammation plays a key role in COPD (Barnes 2016). Oxidative stress promotes macrophages and neutrophils activation, and they secrete proinflammatory cytokines and chemokines into blood circulation, where the factors stimulate secretion of acute-phase proteins (Henrot et al. 2019; Beeh et al. 2003). 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 (Eapen et al. 2017). Many studies have shown that chemokines play a crucial role in COPD development and progression (Donnelly and Baenes 2006; Inui et al. 2018; Traves et al. 2002). There is evidence that chemokines and other immune response genes are upregulated in epithelial cells of smokers with COPD, subsequently affecting the disease severity (Shaykhiev and Crystal 2013).

Chemokines are small molecules (8–12 kDa) and belong to the large cytokine family (Zlotnik and Yoshie 2000). Chemokines interact with G protein-coupled receptors (GPCRs) on the cell surface to play their roles in a variety of biological functions, such as chemotaxis, leukocyte degranulation, and hematopoiesis (Zlotnik and Yoshie 2000; Zlotnik et al. 2006). Based on the positions of two cysteine residues at the N end, chemokines are classified into four subfamilies: CXC, CC, (X)C, and CX3C (Zlotnik and Yoshie 2000). Proinflammatory cytokines are produced by macrophages, monocytes, and endothelial cells upon their activation (Zlotnik and Yoshie 2000). CXC chemokines play a key role in attracting neutrophils in early acute inflammation and interact with the receptors CXCR1 and CXCR2 (Zlotnik and Yoshie 2000; Zlotnik et al. 2006). CXCL8 is secreted by alveolar macrophages, neutrophils, and airway epithelial cells (Henrot et al. 2019; Russo et al. 2014). One of

the first identified chemokines implicated in the pathogenesis of COPD was CXCL8 (Barnes 2009). CC chemokines play a key role in the late stages of any inflammatory reaction and chronic inflammation (Zlotnik and Yoshie 2000; Zlotnik et al. 2006). A target cell range of CC chemokines is broader than that of CXC chemokines (Zlotnik et al. 2006). CC chemokines act as chemotactic factors for monocytes, dendritic cells, B cells, memory T cells, and activated T cells (Zlotnik et al. 2006). Apart from their chemotactic effect, CC chemokines stimulate proinflammatory activity of monocytes and macrophages (Zlotnik and Yoshie 2000; Zlotnik et al. 2006). The CCL5, CCL8, and CCL2 are involved in the pathogenesis of COPD, cardiovascular diseases, idiopathic pulmonary fibrosis and cancer (Zlotnik et al. 2006; Lee et al. 2017). The CCL20 is upregulated in the sputum in a number of inflammatory respiratory diseases, including asthma, COPD and cystic fibrosis (Faiz et al. 2018).

In previous study, we demonstrated the association of *SAA1*, *PECAM1*, *ICAM1* and *CCL2* genes polymorphisms with increased COPD risk in the Tatar population from Russia (Korytina et al. 2019a). This work was designed as case–control study aimed at investigating the association of *CCL20*, *CCR6*, *CXCL8*, *CXCR1*, *CXCR2*, *CCL8*, *CCL23*, *CCR2,* and *CX3CL1* polymorphisms with COPD and their gene–gene interactions in the Tatar population from Russia.

Materials and Methods

Study Population

All procedures carried out in a study in humans comply with the ethical standards of the institutional and/or national research ethics committee and the 1964 Helsinki Declaration and its subsequent changes or comparable standards of ethics. 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). All DNA samples used in the study were anonymous. To avoid possible problems arising from population 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 Volga-Ural region of Russia as mentioned previously (Korytina et al. 2019b). The total number of 1218 DNA samples of unrelated individuals from the same region of Russia Federation, representatives of the Tatar population have been analyzed in this study. Ethnic origin (up to the third generation) of all the participants was derived by direct interviews with participants.

Inclusion and Exclusion Criteria

Patients with COPD ($N = 601$) were collected from 2010 to 2019 in the pulmonary departments of Ufa City Hospitals No. 21 (Ufa, Russia) according to prespecified inclusion and exclusion criteria. The diagnosis was set 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) (http://goldcopd.org). For withal participants defined as COPD carrier the diagnosis was assigned 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 or lung cancer. Subjects performed standardized bronchodilator spirometry test in accordance with American Thoracic Society/European Respiratory Society (Miller 2005), performed in the Department of Pulmonology of Ufa City Hospitals No. 21 (Ufa, Russia). Inclusion criteria were post-bronchodilator FEV1/FVC values less than 70%.

The control group was comprised 617 unrelated age-, sex- and ethnicity matched to the cases healthy residents of Ufa (Russia) with no history of chronic diseases such as respiratory and allergic diseases in the past. Control group subjects were selected among those individuals who attended Ufa City Hospitals 21 (Russia) for regular medical checkup. All individuals from control group were unrelated to patients and independent of one another. Control subjects

Table 1 Characteristics of the studied cohorts

	COPD ($N=601$)	Controls ($N=617$)	P-value
Male (%)	522 (86.85)	548 (88.88)	0.64[a]
Female (%)	79 (13.15)	69 (11.12)	
Age (±SD)	66.45 ± 10.75	63.33 ± 9.97	0.1[b]
BMI (±SD)	27.55 ± 6.73	26.11 ± 4.33	0.07[b]
Pack-years for smokers (±SD)	46.51 ± 23.63	41.59 ± 21.11	0.07[b]
Smoking status			
Current and former smokers (%) ($N=1001$)	484 (80.53)	517 (83.79)	0.158[a]
Non-smokers (%) ($N=217$)	117 (19.47)	100 (16.21)	
Post-FEV1% (±SD)	40.57 ± 17.45	101.5 ± 42.15	0.0001[b]
Post-FEV1/FVC ratio (±SD)	57.91 ± 15.37	88.05 ± 11.09	
FVC % (±SD)	43.77 ± 18.94	105.2 ± 31.15	
GOLD status			
Stage 2 (%)	175 (29.12)	–	–
Stage 3 (%)	163 (27.12)		
Stage 4 (%)	263 (43.76)		

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

[a]Pearson's χ^2-test

[b]Mann-Whitney U test

demonstrated normal lung function (FEV1/FVC > 70%, FEV1 > 80%). Clinical and demographical data summary is presented in Table 1.

Candidate Genes and SNPs Selection

Study was designed and conducted as a candidate genes approach, which means that only polymorphisms in genes with known functions and /or previously shown association with other complex human diseases were chosen for consideration. Minor allele frequency (MAF) of ≥ 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, 12 most widely studied SNPs of chemokine and chemokine receptor genes: *CCL20* (rs6749704, c.-786 T > C), *CCR6* (rs3093024, c.-98+7291A > G), *CXCL8* (rs4073, c.-352A > T), *CXCR1* (rs2234671, c.827G > C, p.Ser276Thr), *CXCR1* (rs16858811, c.92 T > G, p.Met31Arg), *CXCR2* (rs1126579, c.*127 T > C), *CXCR2* (rs4674258, c.-568 T > C), *CXCR2* (rs2230054, c.786C > T, p.Leu262), *CCL8* (rs3138035, c.-572C > T), *CCL23* (rs854655, c.-289G > T), *CCR2* (rs1799864, c.190G > A, p.Val64Ile), *CX3CL1* (rs170364, c.-65+3384 T > G) were selected. Characteristic of studied SNPs are given in Table 2. The functional significance of SNPs was analyzed by means of RegulomeDB Version 1.1 (https://regulomedb.org), SNPinfo Web Server (https://snpinfo.niehs.nih.gov), and HaploReg v3 (Ward and Kellies 2012). According to RegulomeDB Version 1.1, *CCR6* (rs3093024) had regulatory score 1d, *CXCL8* (rs4073) had regulatory score 2b, and *CCL20* (rs6749704) had regulatory score 3a which confirms the influence of these polymorphisms on gene expression. *CXCR2* (rs1126579) is located in 3 prime UTR which are altered the binding of miR-516a-3p (Ryan et al. 2015) and other miRNAs. *CCL8* (rs3138035, c.-572C > T), *CCL23* (rs854655, c.-289G > T), *CXCR2* (rs4674258, c.-568 T > C) are located in 2 KB upstream region and which are binding sites for several transcriptional factors. *CXCR1* (rs2234671, c.827G > C, p.Ser276Thr), *CXCR1* (rs16858811, c.92 T > G, p.Met31Arg), *CCR2* (rs1799864, c.190G > A, p.Val64Ile) are missense variants; these mutations are predicted to be "benign" according to PolyPhen-2 prediction of functional effects of human nsSNPs (http://genetics.bwh.harvard.edu/pph2/). According to HaploReg v3, *CX3CL1* (rs170364, c.-65+3384 T > G) is located in the region of promoter and enhancer histone marks. *CXCR2* (rs2230054, c.786C > T, p.Leu262) is located in the region of enhancer histone marks and in linkage disequilibrium (LD, D' = 0.99) with functional SNPs of *CXCR2* (rs4674258) and *CXCR2* (rs1126579) genes.

Genotyping

The procedures of genomic DNA isolation and genotyping were carried out as mentioned previously (Korytina et al. 2019b). SNPs 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

Table 2 Characteristic of studied SNPs of the chemokine and chemokine receptor genes and quality control information

No.	Gene	Chr. location	Location	HGVS names	RefSNV	Minor allele	Major allele	MAF (COPD)	MAF (control)	HWE (control) P-value
1	*CCL20*	2q36.3 chr2:227813126	2 KB upstream variant	c.-786 T > C	rs6749704	C	T	0.351	0.269	0.093
2	*CCR6*	6q27 chr6:167119305	Intron variant	c.-98+7291A > G	rs3093024	A	G	0.444	0.525	0.14
3	*CXCL8*	4q12-q13 chr4:73740307	2 KB upstream variant	c.-352A > T	rs4073	A	T	0.380	0.329	0.07
4	*CXCR1*	2q35 chr2:218164385	Missense variant	c.827G > C, p.Ser276Thr	rs2234671	C	G	0.057	0.072	0.1
5	*CXCR1*	2q35 chr2:218165120	Missense variant	c.92 T > G, p.Met31Arg	rs16858811	G	T	0.02	0.0122	0.99
6	*CXCR2*	2q35 chr2:218136011	3 prime UTR variant	c.*127 T > C	rs1126579	C	T	0.478	0.494	0.12
7	*CXCR2*	2q35 chr2:218125863	2 KB upstream variant	c.-568 T > C	rs4674258	T	C	0.458	0.444	0.0047
8	*CXCR2*	2q35 chr2:218135587	Synonymous	c.786C > T, p.Leu262	rs2230054	T	C	0.525	0.457	0.12
9	*CCL8*	17q12 chr17:34318930	2 KB upstream variant	c.-572C > T	rs3138035	T	C	0.317	0.410	0.08
10	*CCL23*	17q12 chr17:36018186	2 KB upstream variant	c.-289G > T	rs854655	G	T	0.169	0.174	0.23
11	*CCR2*	3p21.31 chr3:46357717	Missense variant	c.190G > A, p.Val64Ile	rs1799864	A	G	0.299	0.299	0.06
12	*CX3CL1*	16q21 chr16:57376022	Intron variant	c.-65+3384 T > G	rs170364	T	G	0.308	0.266	0.12

MAF minor allele frequency; *HWE* Hardy–Weinberg equilibrium *P*-value

hybridization and cleavage of double-labeled fluorogenic probe during amplification was detected with BioRad CFX96 instrument (Bio-Rad Laboratories Inc., USA), using CFX Manager software. For quality control, 5% dummy duplicates, blank and positive 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 were assessed by subject and by marker (Korytina et al. 2019b).

Statistical Analysis

The sample size was calculated by Quanto software version 1.2.4 (Gauderman 2002). On the basis of our calculations using the Power and Sample Size software program, our sample ($N=1218$) was considered adequate to study the selected SNPs. The sample size ($N=601$ for case group and $N=617$ for control group) was sufficient to detect the association of examined SNPs and COPD with more than 80% power (power: 95.57%, disease prevalence, 10%, error: 5%). Statistical analysis methods that we used in our current work are described earlier in our previous works (Korytina et al. 2019b). For the quantitative traits, the mean values and standard deviations (Mean ± SD) were calculated; the normality was checked by the Shapiro Wilk test, the group comparison was performed with a nonparametric Mann–Whitney *U* test. The frequencies of qualitative traits were compared using the Pearson's Chi-square (χ^2) test. The Statistica v. 6.0 software was used for all analysis. A minor allele frequencies (MAF) and the agreement of the genotype distribution to the Hardy–Weinberg equilibrium (χ^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 (χ^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). Logistic regression was used to detect the association of SNPs in different models (dominant, recessive, log-additive), accounting for quantitative and binary traits (gender, age, pack-years, smoking status, body mass index); 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 in different models (Korytina et al. 2019b). The significance of the obtained model accounting for all variables was verified by the significance of the likelihood ratio test (P_{adj}) (Korytina et al. 2019b). We used a logistic regression approach implemented in the software package PLINK v. 1.07 (Purcell et al. 2007) to assess the effects of genotype × smoking interactions. Linear regression analyses were performed to estimate the relationship between SNPs and quantitative phenotypes, such as lung function parameters and pack-years (Korytina et al. 2019b). The regression analysis was 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 false discovery rate (FDR) (Benjamini Hochberg) was calculated using the online software program http://www.sdmproject.com/utilities/?show=FDR. Association between gene–gene combinations and risk of COPD was tested using APSampler 3.6.0, the program and its

description are available at http://apsampler.sourceforge.net/, common algorithm has been described elsewhere (Favorov et al. 2005). Correction for multiple testing was performed using the false discovery rate (FDR) method.

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: *CCL20* (rs6749704) ($P = 0.093$), *CCR6* (rs3093024) ($P = 0.14$), *CXCL8* (rs4073) ($P = 0.07$), *CXCR1* (rs2234671) ($P = 0.1$), *CXCR1* (rs16858811) ($P = 0.99$), *CXCR2* (rs1126579) ($P = 0.12$), *CXCR2* (rs4674258) ($P = 0.0047$), *CXCR2* (rs2230054) ($P = 0.12$), *CCL8* (rs3138035) ($P = 0.08$), *CCL23* (rs854655) ($P = 0.23$), *CCR2* (rs1799864) ($P = 0.06$), *CX3CL1* (rs170364) ($P = 0.12$) (Table 2). The SNP *CXCR2* (rs4674258), with a genotype distribution that differs significantly from the Hardy–Weinberg equilibrium in the control group was excluded from the analysis.

Genetic Association Between Chemokine and Chemokine Receptor Genes Variants and COPD Susceptibility

Data on the allele and genotype frequency distributions for the loci in question, the significance of their differences between the groups, and odd ratio values calculated for the minor allele, and Cochran–Armitage trend test of each locus are shown in Table 3. Significant differences between the groups studied were identified for the following polymorphic loci: *CCL20* (rs6749704) ($P = 0.00001$, OR 1.46 for allele test and $P = 0.0001$, OR 1.55 for Cochran-Armitage test), *CCR6* (rs3093024) ($P = 0.0001$, OR 0.72 for allele test and $P = 0.0001$, OR 0.74 for Cochran-Armitage test), *CCL8* (rs3138035) ($P = 0.00001$, OR 0.66 for allele test and $P = 0.00001$, OR 0.67 for Cochran-Armitage test), *CCR2* (rs1799864) ($P = 0.032$ for genotype test), *CX3CL1* (rs170364) ($P = 0.025$, OR 1.22 for allele test), *CXCL8* (rs4073) ($P = 0.009$, OR 1.25 for allele test and $P = 0.017$, OR 1.23 for Cochran-Armitage test), *CXCR2* (rs2230054) ($P = 0.0001$, OR 1.31 for allele test and $P = 0.00027$, OR 1.32 for Cochran-Armitage test). Further association analysis and calculation of OR and significance levels in different models was performed only for this set of candidate loci.

By this approach, *CCL20* (rs6749704) showed association with COPD in the log-additive ($P_{adj} = 0.00001$, $P_{cor\text{-}FDR} = 0.00012$, OR 1.55) and dominant ($P_{adj} = 0.00001$, $P_{cor\text{-}FDR} = 0.00012$, OR 1.73) models (Table 4). A regression analysis established *CCR6* (rs3093024) association with COPD in the log-additive ($P_{adj} = 0.0003$, $P_{cor\text{-}FDR} = 0.001$, OR 0.74), dominant ($P_{adj} = 0.0007$, $P_{cor\text{-}FDR} = 0.0021$, OR 0.63) and recessive ($P_{adj} = 0.0095$, $P_{cor\text{-}FDR} = 0.016$, OR 0.70) models (Table 4). The frequency of the minor T allele of *CCL8* (rs3138035) appeared to decrease in COPD patients

Table 3 Allele and genotype frequencies distribution of chemokine and chemokine receptor genes polymorphisms in COPD patients and control subjects

Gene polymorphism	Minor allele	Chr. location	Genotypes. alleles	COPD n (%) (*N* = 601)	Control n (%)(*N* = 617)	P[a]	P[b]	OR (95% CI)
CCL20 rs6749704 c.-786 T > C	C	2q36.3	TT/TC/CC	232/316/53 (38.60/52.58/8.82)	321/260/36 (52.03/42.14/5.83)	0.0001	0.0001	1.55 (1.26–1.90)
			T/C	780/422 (64.89/35.11)	902/332 (73.10/26.90)	0.00001	–	1.46 (1.24–1.75)
CCR6 rs3093024 c.-98+7291A > G	A	6q27	GG/GA/AA	201/266/134 (33.44/44.26/22.30)	149/288/180 (24.15/46.68/29.17)	0.0001	0.0001	0.74 (0.63–0.87)
			G/A	668/534 (55.57/44.43)	586/648 (47.49/52.51)	0.0001	–	0.72 (0.61–0.84)
CCL8 rs3138035 c.-572C > T	T	17q12	CC/CT/TT	279/263/59 (46.42/43.76/9.82)	229/270/118 (37.12/43.76/19.12)	0.00001	0.00001	0.67 (0.55–0.82)
			C/T	821/381 (68.30/31.70)	728/506 (59.00/41.00)	0.00001	–	0.66 (0.56–0.78)
CCL23 rs854655 c.-289G > T	G	17q12	TT/TG/GG	410/178/13 (68.22/29.62/2.16)	416/187/14 (67.42/30.31/2.27)	0.955	0.756	0.96 (0.76–1.22)
			T/G	998/204 (83.03/16.97)	1 019/ 215 (82.58/17.42)	0.809	–	0.96 (0.78–1.19)
CCR2 rs1799864 c.190G > A, p.Val64Ile	A	3p21.31	GG/AG/AA	288/266/47 (47.92/44.26/7.82)	315/234/68 (51.05/37.93/11.02)	0.032	0.09	1.30 (0.99–1.71)
			G/A	842/360 (70.05/29.95)	864/370 (70.02/29.98)	0.979	–	0.99 (0.83–1.80)
CX3CL1 rs170364 c.-65+3384 T > G	T	16q21	GG/GT/TT	297/238/66 (49.42/39.60/10.98)	342/222/53 (55.43/35.98/8.59)	0.085	0.068	1.21 (0.99–1.48)
			G/T	832/370 (69.22/30.78)	906/328 (73.42/26.58)	0.025	–	1.22 (1.03–1.46)

Table 3 (continued)

Gene polymorphism	Minor allele	Chr. location	Genotypes. alleles	COPD n (%) (*N* = 601)	Control n (%)(*N* = 617)	P[a]	P[b]	OR (95% CI)
CXCL8 rs4073 c.-352A > T	A	4q12-q13	TT/TA/AA	234/277/90 (38.94/46.09/14.98)	288/252/77 (46.68/40.84/12.48)	0.023	0.017	1.23 (1.04–1.46)
			T/A	745/457 (61.98/38.02)	828/406 (67.10/32.90)	0.009	–	1.25 (1.06–1.47)
CXCR1 rs16858811 c.92 T > G, p.Met31Arg	G	2q35	TT/TG/GG	577/24/0 (96.01/3.99/0)	602/15/0 (97.57/2.43/0)	0.166	0.18	1.65 (0.79–3.43)
			T/G	1178/24 (98.00/2.00)	1219/15 (98.78/1.22)	0.169	–	1.65 (0.86–3.17)
CXCR1 rs2234671 c.827G > C, p.Ser276Thr	C	2q35	GG/GC/CC	532/69/0 (88.52/11.48)	528/89/0 (85.58/14.42/0)	0.149	0.15	0.77 (0.54–1.10)
			G/C	1 133/69 (94.26/5.74)	1 145/89 (92.79/7.21)	0.164	–	0.78 (0.56–1.08)
CXCR2 rs2230054 c.786C > T, p.Leu262	T	2q35	CC/CT/TT	136/299/166 (22.63/49.75/27.62)	171/328/118 (27.71/53.16/19.12)	0.001	0.00027	1.32 (1.10–1.58)
			C/T	571/631 (47.50/52.50)	670/564 (54.29/45.71)	0.0001	–	1.31 (1.11–1.54)
CXCR2 rs4674258 c.-568 T > C	T	2q35	CC/CT/TT	197/257/147 (32.78/42.76/24.46)	213/260/144 (34.52/42.14/23.34)	0.793	0.51	1.06 (0.89–1.26)
			C/T	651/551 (54.16/45.84)	686/548 (55.59/44.41)	0.503	–	1.06 (0.90–1.24)
CXCR2 rs1126579 c. *127 T > C	C	2q35	TT/TC/CC	169/289/143 (28.12/48.09/23.79)	168/288/ 161 (27.23/46.68/26.09)	0.650	0.48	0.94 (0.79–1.11)
			T/C	627/575 (52.16/47.84)	624/610 (50.57/49.43)	0.455	–	0.93 (0.80–1.09)

Chr. Chromosome location

[a]X^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

than in controls (31.7% vs 41.0%) (Table 3), and association of *CCL8* (rs3138035) with COPD was found under the log-additive ($P_{adj}=0.0001$, $P_{cor\text{-}FDR}=0.00048$, OR 0.67), dominant ($P_{adj}=0.001$, $P_{cor\text{-}FDR}=0.002$, OR 0.68) and recessive ($P_{adj}=0.0001$, $P_{cor\text{-}FDR}=0.00048$, OR 0.46) models (Table 4). The COPD risk was higher in homozygous and heterozygous carriers of the rare T allele of *CX3CL1* (rs170364) ($P_{adj}=0.023$, $P_{cor\text{-}FDR}=0.036$, OR 1.23 for log-additive model). Significant association of *CXCL8* (rs4073) with COPD was detected using the log-additive ($P_{adj}=0.007$, $P_{cor\text{-}FDR}=0.014$, OR 1.23) and dominant ($P_{adj}=0.008$, $P_{cor\text{-}FDR}=0.014$, OR 1.37) models (Table 4). In the COPD group, the frequency of TT genotype of *CXCR2* (rs2230054) more than 1.5-fold increase (27.62% vs. 19.12% in control, $P_{adj}=0.0001$, $P_{cor\text{-}FDR}=0.00048$, OR 1.61 for recessive model). The association of *CXCR2* (rs2230054) was obtained for log-additive model with corresponding $P_{adj}=0.0002$ ($P_{cor\text{-}FDR}=0.0008$, OR 1.32) (Table 4). Regression analysis failed to detect a significant association between *CCR2* (rs1799864) and COPD (Table 4).

Analysis of Gene-by-environment Interactions in COPD

A significant gene-by-environment interaction of the *CX3CL1* (rs170364) polymorphism and smoking status was detected in the log-regression analysis ($P_{interact}=0.006$, OR 1.74 CI 95% 1.02–2.96 under the assumption of recessive model, and $P_{interact}=0.022$, OR 1.91 CI 95% 1.10–3.30 under the assumption of log-additive model). We did not observe significant gene-by-environment interactions in the log-regression analysis of *CCL20* (rs6749704), *CCR6* (rs3093024), *CXCL8* (rs4073), *CXCR1* (rs2234671), *CXCR1* (rs16858811), *CXCR2* (rs1126579), *CXCR2* (rs2230054), *CCL8* (rs3138035), *CCL23* (rs854655), and *CCR2* (rs1799864) polymorphisms with smoking status.

Gene-by-environment interactions were also analyzed by comparing odds ratio values calculated for the candidate genes in subgroups stratified by smoking status. The significant associations of the candidate polymorphisms with COPD observed in the subgroups stratified by smoking status are shown in Table 5. The COPD in smokers was associated with *CCR6* (rs3093024) ($P_{adj}=0.002$, $P_{cor\text{-}FDR}=0.008$, OR 0.75 for log-additive model), *CCL20* (rs6749704) ($P_{adj}=0.0001$, $P_{cor\text{-}FDR}=0.0005$, OR 1.81 for dominant model), *CX3CL1* (rs170364) ($P_{adj}=0.003$, $P_{cor\text{-}FDR}=0.016$, OR 1.34 for log-additive model), *CCL8* (rs3138035) ($P_{adj}=0.0001$, $P_{cor\text{-}FDR}=0.0005$, OR 0.69 for log-additive model), *CXCR2* (rs2230054) ($P_{adj}=0.0046$, $P_{cor\text{-}FDR}=0.012$, OR 1.53 for recessive model). *CXCL8* (rs4073) ($P_{adj}=0.028$, $P_{cor\text{-}FDR}=0.039$, OR 1.21 for dominant model). In nonsmokers, associations were established only for *CCR6* (rs309302) in the log-additive ($P_{adj}=0.005$, $P_{cor\text{-}FDR}=0.012$, OR 0.57) and dominant ($P_{adj}=0.007$, $P_{cor\text{-}FDR}=0.013$, OR 0.42) models.

No significant associations were observed between *CXCR1* (rs2234671), *CXCR1* (rs16858811), *CXCR2* (rs1126579), *CCL23* (rs854655), *CCR2* (rs1799864) gene polymorphisms and COPD in the subgroups stratified by smoking status.

We investigated the relationship between the candidate gene polymorphisms and smoking index (in pack-years) in smoking subjects (Table 6 and Suppl. Table 1).

Table 4 Association of chemokine and chemokine receptor genes polymorphisms with COPD

Gene, SNP	Minor allele	genotype/ model	COPD n (%) (N = 601)	Control n (%) (N = 617)	OR_{adj} (CI 95%)	P_{adj}	$P_{cor\text{-}FDR}$
CCL20 rs6749704	C	TT TC+CC Dominant	232 (38.60) 369 (61.40)	321 (52.03) 296 (47.97)	1.00 1.73 (1.35–2.23)	0.00001	0.00012
		TT+TC CC Recessive	548 (91.18) 53 (8.82)	581 (94.17) 36 (5.83)	1.00 1.58 (1.01–2.42)	0.059	0.078
		Log-additive	–	–	1.55 (1.26–1.90)	0.00001	0.00012
CCR6 rs309302	A	GG GA+AA Dominant	201 (33.44) 400 (66.56)	149 (24.15) 468 (75.85)	1.00 0.63 (0.49–0.83)	0.0007	0.0021
		GG+GA AA Recessive	467 (77.70) 134 (22.30)	437 (70.83) 180 (29.17)	1.00 0.70 (0.53–0.92)	0.0095	0.016
		Log-additive	–	–	0.74 (0.63–0.87)	0.0003	0.001
CCL8 rs3138035	T	CC CT+TT Dominant	279 (46.42) 322 (53.58)	229 (37.12) 388 (62.88)	1.00 0.68 (0.51–0.89)	0.001	0.002
		CC+CT TT Recessive	542 (90.18) 59 (9.82)	499 (80.88) 118 (19.12)	1.00 0.46 (0.31–0.68)	0.0001	0.00048
		Log-additive	–	–	0.67 (0.55–0.82)	0.0001	0.00048
CCR2 rs1799864	A	GG GA+AA Dominant	288 (47.92) 313 (52.08)	315 (51.05) 302 (48.95)	1.00 1.13 (0.91–1.42)	0.592	0.61
		GG+GA AA Recessive	554 (92.18) 47 (7.82)	549 (88.98) 68 (11.02)	1.00 0.68 (0.46–1.01)	0.07	0.084
		Log-additive			0.99 (0.81–1.23)	0.99	0.99
CX3CL1 rs170364	T	GG GT+TT Dominant	297 (49.42) 304 (50.58)	342 (55.43) 275 (44.57)	1.00 1.27 (1.02–1.49)	0.041	0.0615
		GG+GT TT Recessive	535 (89.02) 66 (10.98)	564 (91.41) 53 (8.59)	1.00 1.31 (0.83–2.07)	0.25	0.285
		Log-additive	–	–	1.21 (1.05–1.48)	0.023	0.036

Table 4 (continued)

Gene, SNP	Minor allele	genotype/ model	COPD n (%) (N = 601)	Control n (%) (N = 617)	OR $_{adj}$ (CI 95%)	P_{adj}	$P_{cor\text{-}FDR}$
CXCL8 rs4073	A	TT TA+AA Dominant	234 (38.94) 367 (61.06)	288 (46.68) 329 (53.32)	1.00 1.37 (1.08–1.73)	0.008	0.014
		TT+TA AA Recessive	511 (85.02) 90 (14.98)	540 (87.52) 77 (12.48)	1.00 1.21 (0.86–1.70)	0.27	0.294
		Log-additive	–	–	1.23 (1.04–1.46)	0.007	0.014
CXCR2 rs2230054	T	CC CT+TT Dominant	136 (22.63) 465 (77.37)	171 (27.71) 446 (72.29)	1.00 1.31 (1.01–1.70)	0.048	0.067
		CC+CT TT Recessive	435 (72.38) 166 (27.62)	499 (80.88) 118 (19.12)	1.00 1.61 (1.23–2.11)	0.0001	0.00048
		Log-additive	–	–	1.32 (1.23–1.58)	0.0002	0.0008

[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; $P_{cor\text{-}FDR}$, significance after the FDR correction

The smoking index was affected by the genotypes of *CCL20* (rs6749704), *CCR6* (rs3093024), *CCL8* (rs3138035), *CX3CL1* (rs170364). In specific, the smoking index was significantly higher in carriers of the C allele of *CCL20* (rs6749704) ($P = 0.04$). In carriers of the GT genotype of *CX3CL1* (rs170364) ($P = 0.04$), TT genotype of *CCL8* (rs3138035) ($P = 0.0043$), and AA genotype of *CCR6* (rs309302) ($P = 0.007$) smoking index value was significantly lower.

Association Analysis of Chemokine and Chemokine Receptor Genes Variants with Lung Function Parameters

We investigated the relationship between the chemokine and chemokine receptor 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 6 and Suppl. Table 2). As shown in Table 6, the TT genotype of *CCL23* (rs854655) was associated with a decrease in FVC ($P = 0.04$) and FEV1/FVC ($P = 0.05$) values. Carriers of the *CXCR2* (rs1126579) TT genotype exhibited higher FEV1/FVC value ($P = 0.02$). *CX3CL1* (rs170364), *CCL8* (rs3138035), *CCR6* (rs3093024), *CCR2* (rs1799864), *CXCR1* (rs16858811), *CXCR1* (rs2234671), *CXCR2* (rs2230054) were not significantly associated with lung function parameters.

Analysis of Gene–gene Interactions

Using the APSampler algorithm, we obtained 2823 genotype / allele combinations of the studied polymorphic variants associated with COPD. Combinations that remained significantly associated with COPD after the FDR test was applied (with OR ≤ 2 for combinations associated with increased risk of COPD, and OR ≤ 0.5 for those associated with decreased risk of COPD) are presented in Table 7. A total of nine gene–gene combinations fulfilled with the above-mentioned criteria. Eight patterns were associated with increased risk of COPD. Loci *CCR2* (rs1799864) and *CCL8* (rs3138035) contributed to the most significant combinations associated with COPD risk (see Table 7). The *CXCL8* rs4073*A, *CCL20* rs6749704*C, *CXCR1* rs2234671*G, *CXCR2* rs2230054*T/T, and *CCR6* rs3093024*G were frequent featured as well. One gene–gene combination conferred a protective effect and included *CXCR2* rs2230054*C and *CCL20* rs6749704*T/T.

Discussion

A long-term inflammatory process underlies the pathogenesis of COPD and involves all lung tissue structures (bronchi, bronchioles, alveoli, and lung vessels) (Eapen et al. 2017; Barnes 2009), and the classic local inflammation often becomes systemic (Hackett et al. 2008). In this work, *CCL20*, *CCR6*, *CXCL8*, *CXCR1*, *CXCR2*, *CCL8*, *CCL23*, *CCR2*, *CX3CL1* genes polymorphisms were tested for association with COPD in the Tatar population from Russia. We evaluated gene–gene and gene-by-environmental interactions and studied the relationship between selected candidate genes variants with quantitative lung function parameters and smoking index.

Data obtained in our study confirmed the association of *CCL20* (rs6749704) and *CCR6* (rs3093024) with COPD. The minor allele C of *CCL20* (rs6749704) was associated with higher risk of COPD. The association with COPD was established using the dominant and log-additive models. Our study showed that *CCL20* (rs6749704) was associated with COPD only in smokers. The analysis performed in a group of smokers showed a higher smoking index for carriers of the TC and CC genotypes of *CCL20* (rs6749704). When gene–gene combinations were analyzed, the C allele of *CCL20* (rs6749704) was found in several informative combinations associated with higher risk of COPD, while the T and T/T genotype of *CCL20* (rs6749704) occurred in combinations associated with lower risk of COPD. CCL20 is a CC chemokine with selective chemotactic activity for lymphocytes and dendritic cells (Ranasinghe and Eri 2008). CCL20 is produced by activated cells, including monocytes, T cells, epithelial cells, and fibroblasts, and is expressed in the liver, the lung, and certain lymphoid tissues (Ranasinghe and Eri 2008). CCL20 plays an important role in regulating dendritic cell migration and T-cell recruitment and activation (Schutyser et al. 2003; Homey et al. 2000). Various cytokines induce *CCL20* expression, the set including TNFA, IL-1β, CD40 ligand, IFN-γ, and IL-17 (Ranasinghe and Eri 2008). The *CCL20* is located on chromosome 2q36.3 (https://www.ncbi.nlm.nih.gov/gene/6364). The contribution to COPD has not been studied for the *CCL20* allelic variants before. However, there are sufficient data about the

Table 5 Association of chemokine and chemokine receptor genes polymorphisms with COPD in smokers and non-smokers

Gene, SNP	Minor allele	Test/model	COPD n (%)	Control n (%)	OR_{adj} (CI 95%)	P_{adj}	$P_{cor\text{-}FDR}$
Smokers			(N = 484)	(N = 517)			
CXCL8 rs4073	A	TT TA+AA Dominant	194 (40.08) 290 (59.92)	244 (47.20) 273 (52.8)	1.00 1.34 (1.03–1.73)	0.028	0.039
		TT+TA AA Recessive	414 (85.54) 70 (14.46)	451 (87.23) 66 (12.77)	1.00 1.15 (0.79–1.68)	0.46	0.46
		Log-additive	–	–	1.21 (1.01–1.46)	0.043	0.053
CCL20 rs6749704	C	TT TC+CC Dominant	182 (37.60) 302 (62.4)	270 (52.22) 247 (47.78)	1.00 1.81 (1.41–2.33)	0.0001	0.0005
		TT+TC CC Recessive	438 (90.50) 46 (9.50)	486 (94.00) 31 (6.00)	1.00 1.64 (0.99–2.74)	0.057	0.07
		Log-additive	–	–	1.60 (1.29–2.00)	0.0001	0.0005
CX3CL1 rs170364	C	GG GT+TT Dominant	234 (48.35) 250 (51.6)	286 (55.32) 231 (44.68)	1.00 1.32 (1.03–1.70)	0.032	0.042
		GG+GT TT Recessive	424 (87.6) 60 (12.40)	480 (92.84) 37 (7.16)	1.00 1.84 (1.19–2.82)	0.007	0.013
		Log-additive	–	–	1.34 (1.11–1.64)	0.003	0.0105
CCL8 rs3138035	T	CC CT+TT Dominant	232 (47.93) 252 (52.07)	200 (38.68) 317 (61.32)	1.00 0.68 (0.53–0.88)	0.004	0.012
		CC+CT TT Recessive	437 (90.29) 47 (9.71)	421 (81.43) 96 (18.57)	1.00 0.47 (0.32–0.68)	0.0001	0.0005
		Log-additive	–	–	0.69 (0.55–0.85)	0.0001	0.0005
CCR6 rs3093024	A	GG GA+AA Dominant	155 (32.02) 329 (67.98)	127 (24.56) 390 (75.44)	1.00 0.69 (0.52–0.91)	0.011	0.019
		GG+GA AA Recessive	376 (77.69) 108 (22.31)	369 (71.37) 148 (28.63)	1.00 0.72 (0.53–0.97)	0.027	0.039
		Log-additive	–	–	0.75 (0.63–0.90)	0.002	0.008

Table 5 (continued)

Gene, SNP	Minor allele	Test/model	COPD n (%)	Control n (%)	OR $_{adj}$ (CI 95%)	P_{adj}	$P_{cor\text{-}FDR}$
CXCR2 rs2230054	T	CC CT+TT Dominant	113 (23.35) 371 (76.65)	142 (27.47) 375 (72.53)	1.00 1.24 (0.90–1.69)	0.19	0.199
		CC+CT TT Recessive	349 (72.1) 135 (27.9)	416 (80.46) 101(19.54)	1.00 1.53 (1.18–2.14)	0.0046	0.012
		Log-additive	–	–	1.28 (1.05–1.56)	0.012	0.019
Non-smokers			($N=117$)	($N=100$)			
CCR6 rs3093024	A	GG GA+AA Dominant	47 (40.17) 70 (59.83)	22 (22.00) 78 (78.00)	1.00 0.42 (0.23–0.76)	0.007	0.013
		GG+GA AA Recessive	91 (77.78) 26 (22.22)	68 (68.00) 32 (32.00)	1.00 0.60 (0.30–1.20)	0.14	0.15
		Log-additive	–	–	0.57 (0.39–0.83)	0.005	0.012

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; $P_{cor\text{-}FDR}$, significance after the FDR correction

association of *CCL20* polymorphic variants with various diseases (Schutyser et al. 2003; Valverde-Villegas et al. 2017). For example, the rs6749704 polymorphism has been associated with multiple sclerosis (Jafarzadeh et al. 2014) and type 2 diabetes mellitus (Kochetova et al. 2019).

According to our data, statistically significant association was observed between *CCR6* (rs3093024) polymorphism and COPD. We found that *CCR6* (rs3093024) was significantly associated with COPD susceptibility both in smokers and non-smoking after stratifying for smoking status. Risk of COPD was lower for minor A allele carriers and the proportion GG genotype was significantly higher in the patient group. Moreover, *CCR6* (rs3093024) was associated with smoking index, which was significantly higher in carriers of the G allele of *CCR6* (rs3093024). In our study, the G allele of *CCR6* (rs3093024) was observed in several gene–gene combinations associated with higher risk of COPD, including those with the C allele of *CCL20* (rs6749704). CCR6 chemokine receptor has been identified as a functional receptor for CCL20 (Ranasinghe and Eri 2008). The receptor is expressed on memory T, B, and dendritic cells; CCR6 expression on the cell surface confers responsiveness to CCL20 (Schutyser et al. 2003). The *CCR6* gene is located on chromosome 6q27 (https://www.ncbi.nlm.nih.gov/gene/1235). The *CCR6* (rs3093024) polymorphism have been associated with thyroid autoimmune disorders, rheumatoid arthritis, and Crohn disease (Kunisato et al. 2018; Kochi et al. 2010; Teng et al. 2012). Bracke et al. (2006) have shown that in mouse models of COPD the interaction of CCR6 with its ligand CCL20 is pathogenetically related to tobacco smoke-induced

Table 6 The relationship between chemokine and chemokine receptor genes polymorphisms and quantitative phenotypes (lung function parameters and pack-years)

Gene, SNP	model / genotypes	M ± S.E	*P* [a]	Beta (CI 95%)
Forced vital capacity (FVC)				
CCL23	TT+GG	51.83 (1.28)	0.029	0.00
rs854655	TG	57.23 (2.25)		5.40 (0.57–10.23)
FEV1/FVC ratio (%)				
CCL23	TT+GG	56.21 (1.16)	0.05	0.00
rs854655	TG	59.46 (1.68)		3.25 (1.11–7.17)
CXCR2	TT	61.26 (1.8)	0.02	0.00
rs1126579	CT+CC	56.41(1.12)		−4.84 (−9.11 to −0.58)
Pack-years				
CCL20	TT	27.87 (1.18)	0.04	0.00
rs6749704	TC+CC	31.31 (1.2)		3.44 (0.13–6.75)
CX3CL1	GG+TT	36.95 (1.37)	0.04	0.00
rs170364	GT	32.69 (1.43)		−4.26 (−8.31 to −0.21)
CCL8	CC+CT	36.48 (1.09)	0.0043	0.00
rs3138035	TT	28.18 (2.21)		−8.30 (−13.98 to −2.61)
CCR6	GG+GA	31.96 (0.96)	0.007	0.00
rs309302	AA	26.96 (1.48)		−5.00 (−8.63 to −1.37)

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 (for lung function parameters)

pulmonary tissue inflammation and emphysema (Bracke et al. 2006). Sun et al. (2016) have verified the findings in rat COPD models (Sun et al. 2016).

We failed to obtain significant association of *CCR2* (rs1799864) with COPD. On the other hand, the *CCR2* (rs1799864) polymorphism was associated with COPD in the gene–gene combinations analysis of all studied genes. The G allele of *CCR2* (rs1799864) occurred in the majority of significant combinations associated with higher risk of COPD, often together with the C allele of *CCL8* (rs3138035). The *CCR2* gene codes for receptor for the CCL2 and is located on chromosome 3p21.31 (https://www.ncbi.nlm.nih.gov/gene/729230). CCL2 (monocyte chemoattractant protein 1, MCP-1) plays a key role in the initiation and development of predominantly monocyte associated inflammatory processes (Deshmane et al. 2009). CCL2 acts to promote migration of circulating lymphocytes from the blood stream into tissues and inflammation foci and simultaneously activation (Zlotnik and Yoshie 2000; Zlotnik et al. 2006; Deshmane et al. 2009). CCL2 interacts with the CCR2 receptor, which is expressed mostly on monocytes and T cells (Deshmane et al. 2009). Our previous study associated *CCL2* (rs1024611, -2518A > G) polymorphism with COPD in the same population (Korytina et al. 2019a). *CCL2* (rs1024611) and *CCR2* (rs1799864) have been associated with COPD in the Chinese population (Bai et al.

Table 7 Gene–gene combinations of chemokine and chemokine receptor genes polymorphisms most significantly associated with COPD

Combination				COPD (%)	Control (%)	P-$_{value}$	P_{FDR}	OR	CI (95%)
Risk									
CCR2 rs1799864*G	*CCL8* rs3138035*C	*CXCR1* rs2234671*G	*CCL23* rs854655*T	86.03	65.59	$1.02*10^{-9}$	$2.88*10^{-6}$	3.23	2.19–4.76
CCR2 rs1799864*G	*CCL8* rs3138035*C	*CXCR1* rs2234671*G	*CXCL8* rs4073*A	53.25	30.85	$5.21*10^{-9}$	$3.67*10^{-6}$	2.55	1.84–3.52
CCR2 rs1799864*G	*CCL8* rs3138035*C	*CXCL8* rs4073*A	*CCL20* rs6749704*C	31.79	13.39	$8.84*10^{-9}$	$4.99*10^{-6}$	3.01	2.03–4.46
CCR2 rs1799864*G	*CCL8* rs3138035*C	*CCR6* rs3093024*G		68.01	47.84	$1.02*10^{-8}$	$4.21*10^{-6}$	2.31	1.73–3.11
CCR2 rs1799864*G	*CCL8* rs3138035*C	*CXCR1* rs2234671*G	*CXCR1* rs216858811*T	85.39	67.09	$1.61*10^{-8}$	$5.69*10^{-6}$	2.86	1.96–4.18
CCL20 rs6749704*C	*CCL8* rs3138035*C	*CCR6* rs3093024*G		41.64	22.71	$3.21*10^{-8}$	$6.04*10^{-6}$	2.42	1.75–3.35
CCR2 rs1799864*G	*CXCR2* rs2230054*T/T			25.79	14.11	$7.91*10^{-5}$	0.0008	2.12	1.44–3.12
CCR6 rs3093024*G	*CXCR2* rs1126579*T	*CXCL8* rs4073*A	*CX3CL1* rs170364*T	23.46	12.37	0.00014	0.001	2.17	1.42–3.30
Protective									
CCL20 rs6749704*T/T	*CXCR2* rs2230054*C			27.50	43.79	$9.41*10^{-7}$	$4.74*10^{-5}$	0.49	0.36–0.65

P-$_{value}$ – significance level estimated using Fisher's exact test, P_{FDR}—significance level corrected for multiple testing using FDR approach, OR -odds ratio and CI—95% confidence interval

2012), but the associations have not been confirmed in the Taiwan population (Liu et al. 2010). Associations with the polymorphic loci *CCL2* (rs1024611) and *CCR2* (rs1799864) have been studied in detail in cardiovascular disorders (Cai et al. 2015).

CCL8 (monocyte chemoattractant protein 2, MCP-2) is structurally similar to CCL2 and CCL7 and is expressed in fibroblasts and endothelial cells upon their activation with IL-1B and IFN-γ (Zlotnik and Yoshie 2000; Zlotnik et al. 2006; Proost and Wuyts. 1996). CCL8 acts through the receptors CCR1, CCR2, CCR3, and CCR5 to recruit monocytes, granulocytes, and effector T cells (Zlotnik and Yoshie 2000; Zlotnik et al. 2006; Proost and Wuyts 1996; Struyf et al. 2009). High CCL8 concentrations are produced in viral and bacterial infections to facilitate the intense recruitment of monocytes, lymphocytes, natural killers, dendritic cells, eosinophils, and basophils to inflammation foci (Struyf et al. 2009). The *CCL8* gene is located on chromosome 17q12 (https://www.ncbi.nlm.nih.gov/gene/6355). In our work, the *CCL8* (rs3138035) polymorphism has been shown for the first time to be associated with COPD; this association was further confirmed in the subgroup of smokers. Higher risk of COPD was associated with the major allele C, while the minor allele T exerted a protective effect. A significantly higher smoking index was observed in carriers of the risk C allele of *CCL8* (rs3138035). In addition, the C allele of *CCL8* (rs3138035) was detected in the most significant gene–gene combinations associated with COPD in our sample. Ma et al. have associated the CC genotype of *CCL8* (rs3138035) with higher risk of death from non-small cell lung cancer (Ma et al. 2011). On the other hand, an association with arterial hypertension has not been detected for *CCL8* (rs3138035) (Timasheva et al. 2018).

CCL23 (myeloid progenitor inhibitory factor 1 (MPIF-1), or macrophage inflammatory protein 3 (MIP-3)) is expressed in activated monocytes and dendritic cells (Zlotnik and Yoshie 2000; Zlotnik et al. 2006; Poposki et al. 2011). CCL23 is found in the serum at high concentrations and induces chemotaxis of immune cells and chemotactic migration of endothelial cells by activating the receptor CCR1 (Zlotnik and Yoshie 2000; Hwang et al. 2005; Nardelli et al. 1999). The *CCL23* gene is located on chromosome 17q12 (https://www.ncbi.nlm.nih.gov/gene/6368). The polymorphism rs854655, which was investigated in the present study, is located in the promoter region of gene. We did not observe an association of the *CCL23* (rs854655) polymorphism with COPD, but the T allele of *CCL23* (rs854655) was detected in gene–gene combination to be associated with higher risk of COPD. In homozygous carriers of the major allele T of *CCL23* (rs854655) the lung function parameters FVC and FEV1/ FVC were significantly downregulated. SNPs of *CCL23* gene has not been evaluated for COPD before. CCL23 has been shown to play a pathogenetic role in the development and progression of several inflammatory diseases, such as atherosclerosis (Kim et al. 2011) and ischemic stroke (Bonaventura and Montecucco 2018).

We observed that *CXCL8* (rs4073) was significantly associated with COPD in Tatar population from Russia. The minor allele A was identified as a marker of higher risk of COPD; this association was also confirmed in the subgroup of smokers. The allele A of *CXCL8* (rs4073) was detected in the majority of gene–gene combinations associated with higher COPD risk. CXCL8 is a proinflammatory CXC family chemokine (Zlotnik et al. 2006). Various cells have been shown to release

CXCL8 in response to activation by proinflammatory cytokines (IL-1B and TNFA); the cell set includes monocytes, macrophages, endothelial cells, T cells, fibroblasts, epithelial cells, hepatocytes, and keratinocytes (Henrot et al. 2019; Zlotnik et al. 2006; Russo et al. 2014). The main function of CXCL8 is inducing neutrophils to exit the blood circulation and to migrate into inflammation targeted loci (Russo et al. 2014). The *CXCL8* gene is located on chromosome 4q12-21 (https://www.ncbi.nlm.nih.gov/gene/3576). Published meta-analyses indicate that the *CXCL8* gene polymorphisms are associated with coronary artery disease (Zhang et al. 2019). The SNP rs4073 is located in the promoter region of *CXCL8* and affects the *CXCL8* expression level; the allele A is associated with a higher expression level and an increase in CXCL8 (Hull et al. 2001). The receptors CXCR1 and CXCR2 recognize CXCL8 and are expressed on neutrophils and are distinguished by their different selectivity for CXCL8 (Henrot et al. 2019; Zlotnik and Yoshie 2000; Ha et al. 2017). The human *CXCR1* and *CXCR2* genes have been mapped on chromosome 2q35 (http://www.ncbi.nlm.nih.gov/projects/SNP). Our results detected that the minor allele T of the *CXCR2* (rs2230054) polymorphism was associated with COPD in our studied population. Association was confirmed only in smokers after stratifying for smoking status. The TT genotype of *CXCR2* (rs2230054) was detected in gene–gene combination significantly associated with higher risk of COPD, while the C allele of *CXCR2* (rs2230054) was detected in the protective gene–gene combination. The FEV1/FVC ratio was significantly lower in carriers of the minor allele C of the *CXCR2* (rs1126579) polymorphism. The G allele of *CXCR2* (rs1126579) was found in several significant gene–gene combinations associated with higher risk of COPD. Previously, Matheson et al. (2006) studied association of several *CXCL8*, *CXCR1* and *CXCR2* polymorphisms, lung function and respiratory symptoms in subjects from Melbourne (Australia) and did not reveal any significant associations of *CXCL8* (rs4073) with COPD-related phenotypes, but their results suggest that *CXCR2* (rs2230054) may be important modulators of inflammatory response in the airways (Matheson et al. 2006). The allele A of *CXCL8* (rs4073) has been identified as a risk factor of bronchiolitis due to viral infection in children (Hull et al. 2001), increases the risk of idiopathic pulmonary fibrosis (Ahn et al. 2011) and coronary heart disease (Zhang et al. 2019). Córdoba-Lanús et al. (2015) have not observed significant associations of *CXCL8*, *CXCR1,* and *CXCR2* polymorphic variants with COPD in the Spanish population, but have associated *CXCL8* (rs4073) with disease progression (Córdoba-Lanús et al. 2015). The *CXCL8* (rs4073) associated with asthma severity in Tunisian children (Charrad et al. 2017). Furlan et al. (2016) identified the *CXCL8* (rs4073, rs2227306, rs2227307) polymorphism as potentiating factors for the degree of variability in the severity of cystic fibrosis (Furlan et al. 2016). The results of our study are in agreement with the previously published data and indicate that *CXCL8* (rs4073) may constitute an important risk factor for diseases associated with chronic systemic inflammation, such as COPD.

CX3CL1 (fractalkine) is a unique chemokine and the only member of the CX3C family in humans (Liu et al. 2016). CX3CL1 is synthesized in endothelial cells and is associated with their membrane. CX3CL1 is functionally similar to CC chemokines and acts as a chemoattractant, causing adhesion, migration, and proliferation of activated inflammatory cells (Zlotnik et al. 2006; Liu et al. 2016). Previous studies by

McComb et al. (2008) showed that CX3CL1 expression is upregulated in mouse and rat lungs exposed to tobacco smoke, indicating that CX3CL1 activation plays an important role in the pathogenesis of COPD and emphysema (McComb et al. 2008). The *CX3CL1* gene is located on chromosome 16q21 (https://www.ncbi.nlm.nih.gov/gene/6376). In our study the *CX3CL1* (rs170364) polymorphism was associated with COPD, the minor allele T, providing a risk marker. The association remained significant only in the smokers after smoking status stratification. Characteristically, *CX3CL1* (rs170364) exhibited a significant gene-by environment interaction with the smoking status ($P_{\text{interact}} = 0.006$). Moreover, the smoking index was significantly lower in carriers of the heterozygous GT genotype of *CX3CL1* (rs170364). Previously, an association has been observed between rs170364 and coronary heart disease (Zhang et al. 2015). Ample evidence supports the important role that CX3CL1 play in atherosclerosis, cardiovascular disorders due to chronic inflammation (Liu et al. 2016; Apostolakis and Spandidos 2013), interstitial lung disease (Hoffmann-Vold et al. 2018), and allergic asthma (Lee et al. 2018). Hao et al. (2019) have shown that CX3CL1 may provide a convenient biomarker of frequent exacerbations and emphysema severity in COPD patients because the serum CX3CL1 level correlates with emphysema severity (Hao et al. 2019). Our data were consistent with the previously published results concerning association of *CX3CL1* gene with other diseases related to chronic inflammation and confirm that CX3CL1 is involved in the pathogenesis of COPD.

Our study also had some potential limitations. Present study was only restricted to a population of Tatars from Russia (the Volga-Ural region of Russia). Further large sample size studies with more diverse ethnic populations are required to replicate our results. The strengths of the study include population homogeneity and well-defined clinical phenotype. Importantly, we identified both single locus associations and gene–gene combinations associated with COPD risk.

In summary, we analyzed the associations of the chemokine and their receptor genes polymorphisms with COPD in Tatar population from Russia. Our study has associated a number of polymorphic variants of studied genes with COPD, both individually and in combination. The data obtained indicate the contribution of *CCL20*, *CCR6*, *CCL8,* and *CX3CL1* polymorphisms to this disease. The association of *CXCL8, CXCR2,* and *CCR2* polymorphisms with COPD was confirmed in a Tatar population from Russia. For the first time combination of the corresponding SNPs were considered and as a result eight SNP patterns were associated with increased risk of COPD.

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Availability of Data and Materials The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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

Ethical Approval The study was approved by the Ethics 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).

Consent to Participate All procedures carried out in a study with the participation of people comply with the ethical standards of the institutional and/or national research ethics committee and the 1964 Helsinki Declaration and its subsequent changes or comparable standards of ethics. Informed voluntary consent was obtained from each of the participants in the study.

Consent for Publication Written informed consent for the publication of any associated data were obtained from each of the participants in the study.

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