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ORIGINAL ARTICLE

Chemokine gene polymorphisms association with increased risk of type 2 diabetes mellitus in Tatar ethnic group, Russia

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Abstract

Recent studies have shown that chemokines play an important role in the development of chronic inflammation in adipose tissue, obesity pathogenesis, glucose intolerance and type 2 diabetes. It has also been revealed that some SNPs in chemokine genes are associated with obesity, insulin resistance, type 2 diabetes and diabetes complications in different ethnic groups. The aim of this study was to determine the associations between SNPs in chemokine genes and type 2 diabetes in participants of Tatar ethnic group, living in Bashkortostan. Case–control and cross-sectional study were included in our study design. Five SNPs were genotyped in 440 type 2 diabetes (160 men and 280 women), 58.8 ± 9.2 years old (mean ± SD), BMI 29.3 ± 3.9 kg/m^2 (mean ± SD) patients of Tatar ethnicity, and a control group of 500 Tatars (180 men and 320 women), 55.2 ± 11.6 years old (mean ± SD), BMI 25.9 ± 4.3 kg/m^2 (mean ± SD). The SNPs rs6749704 in *CCL20* [odds ratio (OR) = 2.77 (95% CI 1.81–4.25), $p = 0.0001$], rs2107538 in *CCL5* [odds ratio (OR) = 1.80 (95% CI 1.46–2.22), $p = 0.0001$] were significantly associated with type 2 diabetes. Regression analysis revealed that rs1696941 in *CCL11* was associated with the onset age and duration of type 2 diabetes as well as with HbA_{1c} level ($p = 0.034$, $p = 0.036$ and $p = 0.0054$, respectively). The SNPs rs223828 in *CCL17* and rs6749704 in *CCL20* were correlated with obesity as estimated by BMI ($p = 0.0004$, $p = 0.029$, respectively). Rs223828 in *CCL17* revealed the association with postprandial glucose level ($p = 0.024$) and HbA_{1c} ($p = 0.008$). These data demonstrate that variants of chemokine genes are associated with type 2 diabetes and obesity of Tatar ethnic group inhabiting Bashkortostan Republic. Novel associations of the polymorphic loci in *CCL20* (rs6749704) and *CCL5* (rs2107538) genes with type 2 diabetes had been identified as a result of the conducted research.

Keywords Tatar population · Single nucleotide polymorphism · Susceptibility genes · Type 2 diabetes · Chemokines

Abbreviations

AIC	Akaike information criterion
T2D	Type 2 diabetes
ICAM	Intercellular adhesion molecule 1
CCL2	Gene of chemokine C–C motif ligand 2
CCL5	Gene of chemokine C–C motif ligand 5
CCL11	Gene of chemokine C–C motif ligand 11
CCL17	Gene of chemokine C–C motif ligand 17
CCL20	Gene of chemokine C–C motif ligand 20
CCL	Chemokine C–C motif ligand
CCR	Chemokine receptor
F	Forward
R	Reverse
RANTES	Regulated on activation, normal T cell expressed and secreted
TLR	Toll-like receptor
VCAM	Vascular cell adhesion molecule

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Introduction

Type 2 diabetes (T2D) is a metabolic disorder mainly arising from insulin resistance in obese people and characterized by chronic hyperglycemia [1]. It is associated with high frequency of complications (cardiovascular diseases, retinopathy, chronic kidney disease, neuropathy, and diabetic foot syndrome), which lead to early disability and death [2–5]. T2D is a health and social problem of modern world [6]. Governments of many countries spend much money to treat diabetes and its complications [7]. Experts of the International Diabetes Federation (IDF) predict that the number of people suffering from diabetes will reach 438 million by 2045, the majority of which will be T2D patients [6]. Numerous recent studies have demonstrated significant role of chronic low-grade inflammatory condition in obesity and T2D development [8].

Recent studies have shown that obesity and consequent adipose tissue inflammation are closely connected with insulin resistance [9–11]. However, a specific correlation between inflammatory and metabolic responses had not been determined yet. That correlation had later been established with the discovery that when compared with lean tissue, obese adipose tissue secretes inflammatory cytokines and that these inflammatory cytokines can inhibit insulin signaling themselves [12].

The following reactions inherent in inflammation are observed directly in adipose tissue: infiltration of neutrophils, lymphocytes, macrophages, secretion of chemokines and molecules of adhesion, transformation of monocytes into macrophages [13–15]. Macrophages increase in adipose tissue is a result of their accumulation mediated by the interaction of chemokine/receptors, such as CCR2/CCL2, CCR1/CCL5 and others [16, 17]. Thus, high inflammatory background in adipose tissue and in the whole body remains the same. Chronic inflammation accompanying obesity leads to insulin receptor signaling cascade inhibition and T2D development [18].

Despite certain achievements in studying inflammatory reaction pathogenesis in obesity, initial pathogenetic factors of inflammation development in adipose tissue are not clear. It is possible that lipolysis actively occurs in hypertrophied adipocytes. Fatty acids formed at the same time and interacting with TLR-4, induce chemokines expression leading to macrophages accumulation and activation in adipose tissue [19–21]. Macrophages activated by the production of cellular adhesion molecules (ICAM, VCAM, P- and E-selectin), some chemokines (CCL2, CCL3, CCL5, CCL7, CCL8, CCL11) and their receptors (CCR1, CCR2, CCR3, CCR5) create conditions for monocytes migration and the intensification of local pro-inflammatory activation and oxidative stress system [22, 23]. Transgenic mice with increased CCL2 production in adipocytes have significantly more activated macrophages of adipose tissue [24]. Peripheral and hepatic insulin resistance develops in such animals. A lowered amount of macrophages is observed in adipose tissue of mice with targeted deletion of CCL2 gene or its receptor [24]. A number of authors have established increase in CCL2 level in T2D patients. The role of polymorphic variants of *CCL2* gene in insulin resistance mechanisms is determined, although the obtained results are often contradictory [25, 26].

The intensity of such inflammation has been proved to directly correlate with obesity degree [10, 27]. It has been later demonstrated that a large number of various chemokines (CCL2, CCL3, CCL5, CCL7, CCL8, CCL11) are produced, and CCR1, CCR2, CCR3, CCR5 chemokines receptors are activated in adipose tissue [27]. Thus, chemokines, chemokine receptors and other participants of inflammatory process play an important role in obesity pathogenesis and impaired glucose tolerance formation. They contribute to inflammatory complications of this pathology.

The data on genotypes distribution in polymorphic variants of genes taking part in the pathogenesis of low-grade chronic inflammation is important, as the results studying the role of inflammatory genes in T2D and obesity are often contradictory. It is predominantly caused by ethnic differences among the participants of such study which affect the resulting associations.

Therefore, our research objective was to analyze the contribution of *CCL2* rs1024611, *CCL5* rs2107538, *CCL11* rs16969415, *CCL17* rs223828, and *CCL20* rs6749704 polymorphic variants to the development of T2D in residents of the Republic of Bashkortostan.

Materials and methods

Study design

This is a cross-sectional case–control study.

Participants

We performed an association study of 440 Tatar T2D patients (affected group) and 500 Tatar nondiabetic individuals (unaffected group) living in Bashkortostan. T2D group had the following inclusion criteria: patients of 40 years old and up, T2D diagnosis established according to the WHO criteria (1999–2013), no clinical symptoms of other diabetes types, residents of Bashkortostan Republic since birth, Tatar ethnicity, non-relative to other participants of study, written informed consent. Inclusion criteria for control group were as follows: 40 years old and up, absence of clinical and

laboratory tests proven symptoms of carbohydrate metabolism disturbances and any type of diabetes, absence of diabetes family history, residents of Bashkortostan Republic since birth, Tatar ethnicity, non-relative to other participants of study, written informed consent. Ethnic origin (up to the third generation) of all participants was checked by direct interviews with persons undergoing examination. T2D patients and control group members were matched according to their age and sex. Clinical characteristics are described in Table 1.

The study was conducted in accordance with Helsinki Declaration. Study protocol was approved by local Ethics Committee of the Institute of Biochemistry and Genetics of Ufa Scientific Center under Russian Academy of Sciences (IBG USC RAS), Ufa, Russia (Protocol No 17, December 7, 2010). All participants gave their written informed consent to study. The patients and control group members were selected from 2012 to 2017 in endocrinology department of Ufa City Hospital No. 21 and general therapy department No. 1 of Bashkir State Medical University clinic (Ufa, the Republic of Bashkortostan, Russia). The experimental work was carried out in the Genomics Department of IBG USC RAS Ufa, Russia. Blood samples (4 ml) were collected from patients and control group members, in affected and unaffected groups.

Selection of SNPs genotyped in this study

SNPs of five genes involved in chronic adipose tissue inflammation were selected according to the following criteria: (a) their suspected or proved functional significance; (b) association with T2D, diabetes complications, obesity and insulin resistance in previous studies and (c) minor allele frequency (MAF) of more than 5% in the Caucasian population (NCBI).

Particularly, the rs1024611 in *CCL2* and rs2107538 in *CCL5* are promoter SNPs affecting the expression of *CCL2* and *CCL5* genes [28, 29]. Ye et al. concluded that the *CCL17* SNP rs223828 is associated with elevated serum CCL17 concentrations and directly affects *CCL17* promoter activity [30].

The polymorphism rs1024611 (−2518A/G) in *CCL2* has been associated with the development of obesity, T2D and insulin resistance in German, Mexican, Japanese patients [31–35]. Besides, this SNP was found to be associated with one of diabetes microvascular complications, chronic kidney disease, in Koreans, Asian Indians and North-West Indian population of Punjab with T2D [36–38]. Rs1024611 in *CCL2* was also significantly associated with diabetes foot ulcer, atherosclerosis, cardiovascular diseases (arterial hypertension, ischemic heart disease, ischemic stroke), and with other types of diabetes (gestational diabetes mellitus, post-transplant diabetes mellitus) [39–44].

Genetic variations rs2107538 in *CCL5* gene and rs223828 in *CCL17* may still be a useful marker for assessing susceptibility to ischemic heart disease in ethnic Han Chinese population [30, 45]. Recent studies indicate that *CCL11* may be associated with inflammatory-related diseases such as atherosclerosis, myocardial infarction and stroke [46, 47].

The novel aspects in this study are: (1) the analysis of associations with risk of T2D of those chemokine gene polymorphisms which previously associated with diabetes comorbidities; (2) the analysis of associations of rs1024611 in *CCL2* chemokine gene with risk of T2D in Tatar ethnic group, Russia, previously associated with T2D in other populations.

Genotyping SNPs

DNA was sampled from venous blood leukocytes by phenol–chloroform extraction [48]. For the current study, five SNPs in *CCL2* rs1024611 −2518 A/G, *CCL5* rs2107538 −471G/A, *CCL11* rs16969415 −426 C/T, *CCL17* rs223828 −431C/T, *CCL20* rs6749704 −786T/C were examined by real-time PCR, using Taq-Man SNP discrimination assays (Applied Biosystems, Foster City, CA). Specific PCR-product accumulation by hybridization and cleavage of double-labeled fluorogenic probe during amplification was detected using BioRad CFX96 instrument (Bio-Rad Laboratories

Table 1 Clinical characteristics of the studied cohorts

Characteristic	Control group members, n = 500	T2D patients, n = 440
Age, years	55.2 ± 11.6	58.8 ± 9.2
Sex, male/female (*n*)	180/320	160/280
BMI, kg/m^2	25.9 ± 4.3	29.3 ± 3.9
Waist circumference, cm	92.0 ± 11.0	102.0 ± 11.2
T2D duration, years	–	7.5 ± 5.9
Age at T2D onset, years	–	54.9 ± 9.3
HbA_{1c}, % (mmol/mol)	4.8 ± 0.6 (26.0 ± 3.0)	7.5 ± 1.05 (53.0 ± 7.4)
Fasting blood glucose, mmol/l	4.9 ± 0.8	7.4 ± 2.2

The data are n, mean ± SD

Inc., USA). End-point fluorescence and genotype discriminations were determined according to the BioRad CFX96 protocol, using CFX Manager software. For quality control, 5 per cent of dummy samples and blank control samples were also taken 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. Subsequently SNPs were analyzed according to their proportion of missing, MAF (2% threshold) or deviation from Hardy–Weinberg equilibrium (HWE) ($p \geq 0.05$).

Biological measurements

Body weight and height were measured in light indoor clothing barefoot. Blood samples were collected after a 12 h overnight fast and 2 h after meal. HbA_1c level was measured by high-performance liquid chromatography. Plasma glucose was measured by glucose oxidase method.

Statistical analysis

Power analysis

The sample size was calculated by Quanto software (http://biostats.usc.edu/software). The sample size (N = 440 for case group and N = 500 for control group) was sufficient to detect the association of examined five candidate chemokine genes and T2D with more than 80% power (power: 95.53%, disease prevalence, 25%, error: 5%, OR, 2.0 and significance level 5 per cent). Based on MAF of five candidate SNPs *CCL2* rs1024611, *CCL5* rs2107538, *CCL11* rs16969415, *CCL17* rs223828, *CCL20* rs6749704 in Caucasians (HapMapCEU), a power calculation was performed for the study [49].

We examined candidate genes and used the most significant reported SNPs with a high MAF 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.

As for the quantitative traits, the mean values and standard deviations were calculated; the group comparison was performed with a non-parametric Mann–Whitney *U* test, our samples had an abnormal distribution. The Mann–Whitney *U* test is a nonparametric test, it does not require the assumption of normal distributions.

Qualitative traits frequencies were compared using Pearson's Chi square analysis. Statistical analysis was carried out with the Statistica v. 6.0 programme (StatSoft Inc., Tulsa, OK, USA). A MAF and genotype distribution agreement to the HWE (χ^2), the association analysis using the basic allele test and the calculation of the OR for the rare allele of each locus and the Cochran–Armitage trend test were performed with PLINK v. 1.07 [50]. Bonferroni correction for multiple testing was performed to control type-I error rate, meaning that *p* value was multiplied by the number of SNP loci studied (n = 5) to obtain new p^{Bf} value; false discovery rate (FDR) (Benjamini Hochberg) was calculated using corresponding online software program https://www.sdmproject.com/utilities/?show=FDR.

Logistic regression was used to detect the association of SNPs in different models (dominant and recessive). The significance of the obtained model accounting for all variables was verified by the significance of the likelihood ratio test (*p*). 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 analysis was performed to estimate the relationship between SNPs and quantitative phenotypes, such as obesity. The regression analysis was performed with PLINK v. 1.07 [50].

Results

Prior to analyzing candidate gene polymorphisms for associations with T2D, we checked whether their genotype frequency distributions agreed with the HWE and the evaluated MAF both in the combined group of patients and control group members and in either group individually. For the control group, the following results were obtained: *CCL2* rs1024611 ($p = 0.087$, MAF = 0.282), *CCL5* rs2107538 ($p = 0.55$, MAF = 0.255), *CCL11* rs16969415 ($p = 0.37$, MAF = 0.047), *CCL17* rs223828 ($p = 0.74$, MAF = 0.125), *CCL20* rs6749704 ($p = 0.10$, MAF = 0.288). None of individuals was discarded.

We have obtained data on the allele and genotype frequency distribution of five SNPs in genes *CCL2* rs1024611, *CCL5* rs2107538, *CCL11* rs16969415, *CCL17* rs223828, *CCL20* rs6749704 in T2D patients and in control group members. Data on alleles and genotypes ratio in the studied polymorphic markers of chemokine genes and significance value (*p*) are presented in Table 2.

The frequency of the minor C allele of *CCL20* rs6749704 was significantly higher in T2D patients than in control group [37.4 vs. 28.8%; $p^{FDR} = 0.0001$, OR 1.47 (95% CI 1.21–1.79)], Table 2. The portion of CC homozygotes in T2D patients was as high as 16.8%, in contrast to 6.8% in control group members [$p^{FDR} = 0.00015$, OR 2.77 (95% CI 1.81–4.25)] in the recessive model, Table 3. Significant association with T2D was also established in the additive model [$p^{FDR} = 0.00015$, OR 1.46 (95% CI 1.21–1.77)], Table 3.

The minor T allele of *CCL5* rs2107538 was shown to be associated with T2D [$p^{FDR} = 0.00025$, OR 1.73 (95% CI 1.42–2.11)], Table 2. In the dominant model, *CCL5* rs2107538 association with T2D was informative [$p^{FDR} = 0.00015$, OR 2.08 (95% CI 1.60–2.70)], since the

Table 2 Genotypes and alleles frequency distribution by variable chemokine gene loci in T2D patients and control group members

Gene SNP	Genotypes alleles	T2D (N = 440) N/%	Controls (N = 500) N/%	p^a	p^b	OR (95% CI)
CCL2 g.2493A>G	AA/AG/GG	243/180/17 55.2/40.9/3.9	250/218/32 50.0/43.6/6.4	0.11	0.045	0.80 (0.65–1.00)
	A/G	666/214 75.7/24.3	718/282 71.8/28.2	0.06	–	
CCL11 rs16969415 c.−426C>T	CC/TC/TT	392/44/4 89.1/10.0/0.9	455/43/2 91.0/8.6/0.4	0.46	0.04	1.50 (1.02–2.22)
	C/T	828/52 94.1/5.9	953/47 95.3/4.7	0.29	–	
CCL17 rs223828 c.26−369T>C	CC/CT/TT	333/103/4 75.7/23.4/0.9	382/111/7 76.4/22.2/1.4	0.723	0.84	1.03 (0.77–1.37)
	C/T	769/111 87.4/12.6	875/125 87.5/12.5	0.996	–	
CCL20 rs6749704 c.−786T>C	TT/CT/CC	185/181/74 42.1/41.1/16.8	246/220/34 49.2/44.0/6.8	0.0001	0.0001	1.46 (1.20–1.78)
	T/C	551/329 62.6/37.4	712/288 71.2/28.8	0.0001	–	
CCL5 rs2107538 c.−471G>A	CC/CT/TT	163/226/51 37.0/51.4/11.6	275/195/30 55.0/39.0/6.0	0.0001	0.0001	1.78 (1.46–2.18)
	C/T	552/328 62.7/37.3	745/255 74.5/25.5	0.0001	–	

[a] χ^2 test for genotype frequency difference between T2D and control group

[b] Cochran–Armitage trend test, OR with 95% CI for minor allele in basic allele test

Table 3 Analysis of the chemokine genes polymorphisms association with T2D

Gene SNP	Test/model	T2D N (%)	Contro N (%)	OR (95% CI)	*p* Value	AIC	P^{Bf}	P^{FDR}
CCL20 rs6749704	TT CT–CC dominant model	185 (42.0%) 255 (58.0%)	246 (49.2%) 254 (50.8%)	1.00 1.33 (1.03–1.73)	0.028	1298.5	0.14	0.028
	TT–CT CC recessive model	366 (83.2%) 74 (16.8%)	466 (93.2%) 34 (6.8%)	1.00 2.77 (1.81–4.25)	0.0001	1279.9	0.0005	0.00015
	Log-additive	–	–	1.46 (1.21–1.77)	0.0001	1288.1	0.0005	0.00015
CCL5 rs2107538	CC CT–TT dominant model	163 (37.0%) 277 (63.0%)	275 (55.0%) 225 (45.0%)	1.00 2.08 (1.60–2.70)	0.0001	1272.8	0.0005	0.00015
	CC–CT TT recessive model	389 (88.4%) 51 (11.6%)	470 (94.0%) 30 (6.0%)	1.00 2.05 (1.28–3.29)	0.0023	1294	0.0115	0.00276
	Log-additive	–	–	1.80 (1.46–2.22)	0.0001	1271.2	0.0005	0.00015

P^{Bf}, significance after the Bonferroni correction for multiple testing

P^{FDR}, significance after FDR correction

portion of homozygous and heterozygous carriers of T allele was 63.0% in T2D patients in comparison to 45.0% in healthy controls (Table 3).

We also analyzed whether quantitative clinical-demographic characteristics of T2D depended on the genotypes in the loci studied in T2D patients (Table 4). *CCL2* rs1024611 and *CCL5* rs2107538 polymorphisms were not significantly associated with quantitative characteristics of diabetes.

The variable rs16969415 locus of the *CCL11* gene was shown to be associated with the age of T2D onset. T2D

Table 4 Association between *CCL2, CCL5, CCL11, CCL17* and *CCL20* genes and clinical-demographic characteristics of T2D patients

Characteristics	*CCL2* rs1024611		*p*	*CCL11* rs16969415		*p*	*CCL17* rs223828		*p*	*CCL20* rs6749704		*p*	*CCL5* rs2107538		*p*
	AA–AG	*GG*		*CC–TC*	*TT*		*CC–CT*	*TT*		*TT–CT*	*CC*		*CC–CT*	*TT*	
Age, years	61.39 (0.47)	62.8 (2.43)	0.570	61.57 (0.45)	57 (6.75)	0.340	61.29 (0.47)	72.33 (3.76)	**0.044**	61.36 (0.49)	61.83 (1.11)	0.690	61.54 (0.48)	60.9 (1.25)	0.650
Age at T2D onset, years	54.88 (0.48)	56.27 (2.32)	0.580	54.88 (0.46)	44.5 (2.1)	**0.034**	54.67 (0.47)	64.33 (4.18)	0.078	54.53 (0.49)	55.51 (1.2)	0.410	54.71 (0.49)	54.62 (1.33)	0.950
T2D duration, years	6.41 (0.28)	6.6 (0.99)	0.900	6.55 (0.28)	12.75 (5.84)	**0.036**	6.59 (0.29)	8 (2.52)	0.670	6.79 (0.3)	6 (0.62)	0.270	6.72 (0.3)	6.35 (0.67)	0.680
BMI, kg/m^2	30.74 (0.26)	31.57 (1.06)	0.540	30.6 (0.24)	35.77 (5.93)	0.044	30.59 (0.26)	28.7 (0.93)	0.530	30.63 (0.27)	30.62 (0.51)	0.980	30.53 (0.26)	31.1 (0.78)	0.470
FBG, mmol/l	7.42 (0.11)	6.34 (0.32)	0.065	7.37 (0.11)	8.82 (1.51)	0.200	7.39 (0.12)	8.9 (2.28)	0.250	7.45 (0.12)	7.07 (0.24)	0.180	7.31 (0.12)	7.89 (0.33)	0.110
PPG, mmol/l	10.01 (0.12)	8.9 (0.47)	0.070	9.94 (0.12)	11.22 (1.54)	0.280	9.93 (0.12)	12.93 (2.58)	**0.024**	9.98 (0.13)	9.8 (0.28)	0.540	9.96 (0.12)	10.21 (0.35)	0.500
$HbA1_c$, %	7.49 (0.05)	7.25 (0.11)	0.340	7.45 (0.05)	8.8 (0.84)	**0.005**	7.49 (0.05)	9.03 (1.59)	**0.008**	7.44 (0.05)	7.61 (0.14)	0.170	7.48 (0.06)	7.38 (0.08)	0.520
C-Peptide, ng/dl	2.24 (0.07)	2.62 (0.29)	0.300	2.26 (0.07)	2 (0.43)	0.710	2.23 (0.07)	1.5 (0.32)	0.360	2.22 (0.08)	2.38 (0.15)	0.360	2.24 (0.07)	2.2 (0.15)	0.850
TC, mmol/l	5.55 (0.06)	5.07 (0.28)	0.120	5.5 (0.06)	6.2 (0.76)	0.240	5.57 (0.06)	5.73 (0.13)	0.820	5.56 (0.06)	5.48 (0.12)	0.620	5.54 (0.06)	5.65 (0.21)	0.540
TG, mmol/l	1.78 (0.07)	1.36 (0.21)	0.230	1.74 (0.06)	2.63 (1.23)	0.180	1.77 (0.07)	1.3 (0.29)	0.550	1.81 (0.07)	1.54 (0.13)	0.099	1.72 (0.06)	1.99 (0.28)	0.200
LDL, mmol/l	3.15 (0.09)	3.2 (0.11)	0.730	1.22 (0.02)	1.52 (0.23)	0.240	1.21 (0.03)	1.25 (0.36)	0.890	1.23 (0.03)	1.19 (0.06)	0.590	1.22 (0.03)	1.27 (0.07)	0.520
HDL, mmol/l	1.23 (0.03)	1.1 (0.11)	0.320	3.15 (0.07)	4.19 (0.64)	0.150	3.21 (0.07)	2.91 (1.18)	0.720	3.18 (0.08)	3.08 (0.15)	0.560	3.16 (0.08)	3.4 (0.23)	0.300
Obesity, n (%) yes	345 (96.1)	14 (3.9)	0.280	372 (99.2)	3 (0.8)	0.680	248 (73.2)	91 (26.8)	**0.000**	146 (38.8)	230 (61.2)	**0.029**	321 (88.7)	41 (11.3)	0.740
Obesity, n (%) no	66 (98.5)	1 (1.5%)		75 (98.7)	1 (1.3)		64 (91.4)	6 (8.6)		38 (52.8)	34 (47.2)		63 (90)	7 (10)	

The data are n, mean (SD)

$p < 0.05$ in bold is statistically significant

FBG fasting blood glucose, *PPG* postprandial blood glucose, *TC* total cholesterol, *TG* triglyceride

manifested earlier in TT genotype carriers (44.5 years old) than in patients with CC and CT genotypes (54.9 years old, $p=0.034$). T2D duration was longer in TT genotype carriers (12.8 years) compared with 6.6 years in CC and CT genotype carriers ($p=0.036$). Patients homozygous for T allele of *CCL11* rs16969415 had higher HbA_{1c} level (8.8%) when compared with CC and CT genotype carriers (7.45%, $p=0.0054$). Patients with TT genotype had higher postprandial glycaemia 12.9 mmol/l vs. 9.9 mmol/l in patients with CC and CT genotypes ($p=0.024$).

Variable loci of genes *CCL17* rs223828 and *CCL20* rs6749704 were associated with obesity. Carriers of *CCL17* (rs223828) genotype CT and TT were more frequent among obese T2D patients than in those of normal weight (26.8% vs. 8.6%, $p=0.0004$, OR = 3.91, 95% CI 1.64–9.35). The carrier status of *CCL20* rs6749704*T allele was significantly associated with obesity ($p=0.029$, OR = 1.76, 95% CI 1.06–2.92). Carriers of *CCL17* rs223828*TT genotype had higher HbA_{1c} level (9.03%) compared with patients with CC and CT genotypes (7.45%, $p=0.008$).

Discussion

Having genotyped SNPs in five chemokine genes in a group of patients with T2D and non-diabetic control group, we have found a significant association between *CCL20* rs6749704 and *CCL5* rs2107538 polymorphisms and T2D in Tatars. Genetic markers *CCL2* rs1024611, *CCL5* rs2107538, *CCL11* rs16969415, *CCL17* rs223828 and *CCL20* rs6749704 have been tested for the association with a number of traits, including T2D onset age and duration, obesity and BMI, parameters of glycemic control, serum lipid profile, C-peptides. Novel associations of the polymorphic loci in *CCL20* (rs6749704) and *CCL5* (rs2107538) genes with T2D had been identified as a result of the conducted research.

We have established association of rare allele C of *CCL20* rs6749704 locus both with the risk of T2D development in general and with obesity. The association of *CCL20* rs6749704 polymorphism with T2D has not been investigated yet, at the same time it is known that CCL20 is an adipochemokine the expression of which is modulated by an anatomic arrangement of adipose tissue and by obesity degree [51]. The increased *CCL5* and *CCL20* gene expression in adipocytes was revealed, and its expression in visceral fat was higher than in subcutaneous. Mature adipocytes in obese people excrete higher amount of CCL20, than in lean ones [51]. The researches have shown that CCL20 plays an important role in T-lymphocytes accumulation in adipose tissue. It has also been shown that lymphocytes of adipose tissue are regulators of insulin-mediated lipogenesis [51].

We have found out that the minor T allele of *CCL5* rs2107538 is associated with increased risk of T2D. There are no mentions concerning *CCL5* rs2107538 and T2D patients association studies in available literature. It is known that SNP G(-403)A in the promotor region of *CCL5* gene is associated with the enhanced RANTES transcription [52]. Jeong et al. have shown that allele T of *CCL5* rs2107538 is associated with the development of post-transplantational diabetes mellitus in Koreans that to some extent corresponds with our results [53]. Smeoni et al. also have shown that carriers of allele rs2107538*T have an increased risk of coronary heart disease development [54]. It is shown that a couple of a ligand—CCR5 receptor—CCL5 participates in the regulation (activation) of insulin signal transfer into the hypothalamus and influences glucose metabolism in hepatocytes, increasing body weight of *Ccl5* knockout animals. It is shown that CCL5, CCL11 chemokines contribute to the development of insulin resistance [55].

Eotaxin CCL11 is produced by many types of human cells, including vascular, smooth muscle cells. Its receptor CCR3 is expressed in atherosclerotic plaques and participates not only in attraction of eosinophils, but also basophiles, neutrophils and monocytes, regulating inflammatory process in T2D and obesity. A number of authors have revealed eotaxin level increase in plasma of patients with obesity [56]. Moreover, the increased expression of eotaxin in adipose tissue was found. The association of *CCL11* rs16969415 polymorphic locus with the HbA_{1c} level, the disease onset age and duration were detected for the first time in our research. There are no investigations concerning eotaxin impact in T2D, however, a number of researchers emphasize *CCL11* association with obesity [57]. It is considered that eotaxin is the key regulator of immune processes. CCL11 blockade may lead to the suppression of age-associated cellular dysfunction [58]. Increased CCL11 level is observed in elderly people. Age association regularity is reflected in our research.

CCL17 is Th2-associated chemokine taking part in inflammation processes; it is involved in the pathogenesis of asthma and allergy. It is activated by cytokines such as TNF, IL-4 and IL-13 and contacts with chemokine C–C of receptor 4 (CCR4). CCL17 performs a number of functions, including Th2- and regulatory T-cells migration, TLR2 and TLR4 receptors inhibition [59]. General impact of the aforesaid gene in allergic diseases is shown. The polymorphic locus rs223828 of *CCL17* gene impacts the linking of transcription factors with *CCL17* promotor and promotor activity. According to Ye et al., minor allele T is associated with hyperactivity of the gene whereas the allele C is associated with the decreased gene activity [30]. We have obtained data on T allele association with the increased level of HbA_{1c} and postprandial blood glucose level. According to scientific literature data, this allele is also associated with the risk of

atherosclerotic plaques development, the increased concentration of CCL17 and a number of allergic diseases (atopic dermatitis etc.), coronary aneurysm, multiple sclerosis, ischemic heart disease [30, 60]. *CCL17* gene polymorphic variants association with the risk of T2D development was not studied yet. At the same time, the increased expression of CCL17 in patients with obesity and in T2D patients has been observed. CCL17 is chemoattractant for TH2 lymphocytes, basophiles and macrophages. It is known that adipose tissue in T2D patients has a chemoattractant profile [61].

We have not observed any *CCL2* rs1024611 associations with T2D or clinical disease parameters. Whereas previous studies of SNPs in *CCL2* gene have revealed T2D development risk association with insulin resistance in Caucasians, Japanese, Mexicans [33–35]. This discrepancy may be largely attributed to the differences of ethnic and genetic parameters of participants [62].

It is obvious that chemokines and cytokines are important participants of the processes resulting in insulin resistance, T2D and related complications. Identification of new biomarkers participating in pathogenesis of chronic adipose tissue inflammation and T2D development will contribute to diabetes prevention or treatment.

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Author contributions TVM: conceptualization; DSA: data curation; OEM: formal analysis; TVM: funding acquisition; OVK and DSA: investigation; OVK: methodology; OEM: project administration; TVM: supervision; OEM: validation; OVK: writing—original draft; DSA: writing—review and editing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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