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Original Article

Association of polymorphisms rs290487, rs864745, rs4430796 and rs23136 with type 2 diabetes in the Uyghur population in China

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Abstract: Studies have showed a number of susceptibility genes variants such as transcription factor 7-like 2 (*TCF7L2*), potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*), juxtaposed with another zinc finger protein 1 (*JAZF1*) and HNF1 homeobox B (*HNF1B*) been strongly associated with type 2 diabetes (T2D) in various ethnic groups. However, few studies have conducted in Uyghur, a Chinese minority ethnic group as an admixture population of Caucasians and East Asians. This study was performed to evaluate the association of genetic polymorphism with T2D susceptibility in the Uyghur population. The genomic samples from the blood of unrelated 284 T2D patients and 258 healthy controls were genotyped and analyzed using denaturing high performance liquid chromatography (DHPLC) assay. We found that four SNPs (rs290487, rs864745, rs4430796 and rs23136) in *TCF7L2*, *JAZF1, HNF1B* and *KCNQ1* genetic regions show unique association with T2D in Uyghur population with an OR of 6.67295% (CI 1.06-1.48, *P*=0.002), an OR of 0.302 (CI 1.21-1.53, *P*=0.005) and an OR of 0.223 (CI 0.98-1.17, *P*=0.001), respectively. Subjects with mutant CC genotype of rs290487 were at high increased risk of T2D in Uyghur especially for the male subjects with an OR=11.782 (CI 1.12-1.53, *P*=0.001). Further metabolic evaluation confirmed that subject with rs290487 genotype have higher waste-hip circumference ratio (*P*<0.05), diastolic blood pressure (*P*<0.05), fasting blood glucose (*P*<0.05) and hemoglobin A1c levels (*P*<0.05). While mutant AA genotype for rs23136 (OR=0.223, CI 1.03-1.44, *P*=0.002) respectively were a protective factor in the Uyghur population. The rs231362 have also found been associated with fasting blood glucose and high-density lipoprotein respectively (*P*<0.05). However, none of the genotypes showed the significant association with T2D in local Han Chinese population. Taken together, we confirmed the rs290487, rs231362 and rs4430796 transcription variants may act as genetic risk factors for the development of T2D in the Uyghur population in China and these results might provide supporting evidences for T2D diagnosis for Uyghur people in the future.

Keywords: Uyghur population, type 2 diabetes, polymorphisms, transcription factor 7-like 2 (TCF7L2), potassium voltage-gated channel subfamily Q member 1 (KCNQ1), juxtaposed with another zinc finger protein 1 (JAZF1), HNF1 homeobox B (HNF1B)

Introduction

Type 2 diabetes (T2D) is a global epidemic with chronic metabolic disorder characterized by abnormal hyperglycemia due to impaired insulin secretion and/or peripheral insulin resistance [1]. Asian populations tend to develop diabetes at younger ages and lower BMI levels than Caucasians and the prevalence of diabetes in China has increased substantially over recent decades, with more than 100 million people estimated to be affected by the disease presently [2]. With a rapidly rising prevalence, it now accounts for the major social and economic burden broadly in China. The burden of T2D is much higher for minorities in China since previous surveys demonstrated that the prevalence of diabetes was much higher in ethnic minority Uyghur population (10.47%) than in the Han population (7.36%) in urban area of Xinjiang Uyghur Autonomous Region from northwestern China [3]. The Uyghur population is a minority group in the Xinjiang Uyghur Autonomous Region, northwestern frontier area of China,

with a typical admixture of Eastern and Western anthropometric traits [4]. However, still little is known about the genetic susceptibility and risk factors in Uyghur population possibly associated with T2D, which hampers the further molecular diagnosis and risk assessment in early detection and prevention of diabetes for Uyghur patients.

T2D is regarded as a complex disease resulted from both the interaction of genetic and environmental factors. The *TCF7L2* (transcription factor 7-like 2) gene, a Wnt signaling pathway effector, encodes a transcription factor that involves in the modulation of glucose homeostasis in multiple tissues and blood sugar level through transcription activation of a large number of glucagon metabolism related genes such as glucagon, glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) [5]. The non-coding genetic variation in *TCF7L2* locus is one of the most strongest genetic determinant of T2D risk in humans associated with the impaired insulin secretion, glucose production, and glucose tolerance in multiple ethnic groups around the globe including Han Chinese [6-16]. In this study, other genetic factors which have been proved to be associated with the T2D including *JAZF1*, *KCNQ1* and *HNF1B* were also taken into consideration and further performed analyses [17-22].

Up to date, although several reports have been published on association of genetics makers with T2D in Uyghur, there was no report conducted a detailed study on the *TCF7L2* genetic susceptibility with T2D in Uyghur population so far [23, 24]. Here in the present study, we investigated and evaluated the association between the susceptible SNPs in *TCF7L2* gene and T2D, as well as the metabolic effects of the SNP on the risk of T2D in the Uyghur population.

Subjects and methods

Subject recruitment and selection

We recruited 542 unrelated Uyghur subjects belonging to the same demographic, including 284 T2D and 258 healthy control cases from the First Affiliated Hospital of Xinjiang Medical University. Meanwhile, a total of 286 Han Chinese T2D cases were also used as ethnic control. The normal control participants were included based on the following criteria: no known family history of diabetes based on a question naire, and the normal glucose tolerance as assessed by a standard 75 g oral glucose tolerance test (OGTT) (fasting plasma glucose <5.6 mM), or HbA1c <5.6%. The diagnose procedure were operated according to the standard recommendation offered by WHO (World Health Organization) in 1999 (fasting glucose level ≥126 mg/dL or >7.0 mmol/L). Those cases with acute infection, drug abuse, cancer, stress-induced hyperglycemia, extreme weakness, severe diseases in heart, brain and liver or other types of diabetes, were excluded from further study. Body mass index (BMI) was calculated according to an index of the weight in kg divided by the square of the height. Study protocols were approved by ethics committee of Xinjiang Medical University. Informed consent has been given to all study participants involved in this study.

Blood sample collection

The peripheral venous blood samples (0.5 mL) anticoagulated by EDTA were obtained from each participant. The genomic DNA from each sample was extracted using isolation kit containing proteinase K (Qiagen, USA). The purity of genomic DNA samples was qualified by measuring the ratio of optical density (OD) at 260/280 nm (1.6-1.8) under an ultraviolet spectrophotometer. The samples were stored in -80°C refrigerator till use.

Genotyping for polymorphisms and Tag SNP selection

The sequences spanning *TCF7L2, KCNQ1, JAZF1* and *HFN1B* genomic regions were amplified under polymerase chain reaction (PCR) using primers designed by Primer Premier 5.0 (California, USA). The PCR products were directly analyzed by polyacrylamide gel electrophoresis and visualized after silver staining. Denaturing high performance liquid chromatography (DHPLC) analysis and subsequent DNA sequencing method were applied to evaluate the genotyping of *TCF7L2.* The HPLC peak profiles were obtained and DNA samples with different HPLC peak patterns were randomly selected for PCR amplification and subsequently DNA sequencing. Four SNP were selected after consideration of minor allele frequencies (MAF) less than 0.1 and r^2 more than 0.5 more than 0.05 in both HapMap CHB data (http://hapmap.ncbi.nlm.nih.gov/).

Table 1. Clinical characteristics of study subject

Population demographics			
Characteristic	T2DM cases (293)	Control (258)	*P* value
Age (years)	58.37±11.98	54.21±9.87	0.453
Sex (M/F)	164/129	139/119	0.385
BMI (kg/m^2)	26.97±3.59	23.29±1.23	0.028
Waist-hip ratio	0.978±0.027	0.952±0.015	0.031
Systolic blood pressure (mmHg)	123.91±13.63	121.83±11.58	0.042
Diastolic blood pressure (mmHg)	76.31±10.01	75.38±9.58	0.031
Fasting glucose tolerance (mmol/l)	13.91±5.63 (3.87-29.3)	4.59±1.31 (3.21-5.92)	0.016
HDL-c (mmol/l)	0.93±0.23 (0.51-1.92)	0.87±0.19 (0.51-1.31)	0.001
LDL-c (mmol/l)	2.27±0.74 (1.2-3.83)	1.98±0.39 (1.34-1.87)	0.028
Total triglyceride (mmol/l)	2.32±0.70 (0.87-3.95)	1.16±0.32 (0.89-1.32)	0.128
Total cholesterol (mmol/l)	4.79±1.08 (2.08-6.53)	4.41±0.97 (3.05-4.98)	0.054
Urea nitrogen	340±98.10 (117.60-540.31)	279±21.35 (120.56-360.21)	0.153
Uric acid	5.94±1.96 (2.60-9.51)	3.96±1.21 (2.01-6.61)	0.531
Blood creatinine	81.62±27.73 (47.5-160.53)	80.22±12.56 (40.9-120.37)	0.429

Demographic, ethnic groups, clinical, and biochemical characteristics of T2DM patients and healthy subjects in the studied population.

Table 2. The genotype distribution of rs290487, rs4430796, rs864745 and rs231362 of *TCF7L2* gene polymorphisms in T2DM and control group

	Genotype Frequency distribution			
	Cases (284)	*P value*	Controls (101)	*P value*
rs290487				
TT	94 (33.1%)	0.808	68 (68.6%)	1.000
TC	141 (49.6%)		28 (28.2%)	
CC	49 (17.3%)		3 (3.2%)	
rs4430796				
AA	104 (36.6%)	0.902	25 (25.5%)	0.108
AG	135 (47.5%)		58 (59.1%)	
GG	45 (15.8%)		18 (18.4%)	
rs864745				
TT	128 (45.1%)	0.340	50 (50.0%)	1.000
TC	131 (46.1%)		25 (25.0%)	
CC	25 (8.8%)		25 (25.0%)	
rs231362				
GG	160 (56.3%)	1.000	26 (26.2%)	0.550
GA	107 (37.7%)		53 (53.5%)	
AA	17 (6.0%)		22 (22.2%)	

Metabolic characteristics analysis

The metabolic characteristics of all the subjects enrolled in were recorded including gender, age, height, weight, blood pressure (systolic blood pressure/diastolic blood pressure) as well as the duration of hypertension, smoking history and BMI. The OGTT, insulin and C-peptide release test, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) tests were subsequently carried. The total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) from the subjects blood. The uric acid (UA), blood urea nitrogen (BUN), creatinine (Cr) concentration was also measured. The insulin resistance index (HOMA-IR) was calculated according to the formula: FPG * FIns/22.5. The functional index of islet β cell (HOMA-β) was calculated according to the formula FIns * 20/(FPG-3.5).

Statistical analysis

All data were expressed as mean ± SD (continuous variables) or as a percentage of the total (categorical variables). We used the Chi-square to test the Hardy-Weinberg equilibrium for genotype frequencies. Continuous variables between T2D and control group were compared by Student's *t*-test. The differences in the frequencies of various alleles and genotypes between T2D patients and controls were performed by Chi-square test, and Fisher's exact test was applied to the loci with a small number of alleles or genotypes (equal to or less than 5). Associations between SNPs and T2D risks were assessed using odds ratios (ORs) with 95% confidence intervals (95% CIs) and *P* value

Table 3. Genotype distribution analysis of *TCF7L2* polymorphisms

	TCF7L2 polymorphisms			
	rs290487	rs4430796	rs864745	rs231362
Genotype (number of T2D)	TT (49)	AA (104)	TT (128)	GA (160)
	TC (141)	AG (135)	TC (131)	AA (107)
	CC (94)	GG (45)	CC (25)	GG (17)
OR (95%CI)	0.392 (0.260-0.590)	0.788 (0.555-1.119)	0.521 (0.368-0.737)	0.394 (0.270-0.573)
	0.196 (0.120-0.320)	0.420 (0.241-0.734)	0.484 (0.251-0.932)	0.165 (0.055-0.500)
P-value	0.000	0.008	0.000	0.000

CI: confidence interval; OR: odd ratio.

Table 4. Interaction of the metabolic parameters with different SNP polymorphisms

	TCF7L2 polymorphisms			
	rs290487	rs4430796	rs864745	rs231362
BMI (kg/m^2)	0.798 (0.451)	0.349 (0.706)	1.766 (0.172)	0.180 (0.173)
Waist-hip ratio	0.598 (0.001)	2.525 (0.421)	0.880 (0.005)	1.644 (0.218)
SBP (mmHg)	1.366 (0.256)	1.919 (0.706)	1.325 (0.172)	0.365 (0.835)
DBP (mmHg)	3.334 (0.036)	1.236 (0.291)	0.324 (0.732)	0.280 (0.756)
FGT (mmol/l)	5.118(0.024)	4.784(0.029)	0.266 (0.606)	7.602 (0.006)
HDL-c (mmol/l)	0.984 (0.374)	1.546 (0.214)	0.642 (0.572)	3.335 (0.036)
LDL-c (mmol/l)	1.317 (0.269)	0.494 (0.610)	0.269 (0.746)	3.011 (0.043)
Total triglyceride (mmol/l)	0.404 (0.668)	0.394 (0.675)	0.719 (0.488)	2.152 (0.117)
Total cholesterol (mmol/l)	0.396 (0.673)	0.047 (0.954)	0.45 (0.684)	0.509 (0.601)
Urea nitrogen	0.471 (0.624)	2.091(0.125)	0.835 (0.434)	1.543 (0.215)
Uric acid	0.443 (0.643)	1.851 (0.158)	1.961 (0.142)	0.673 (0.510)
HbAc1 (%)	4.517 (0.034)	2.906 (0.089)	0.622 (0.431)	0.014 (0.907)

Data represented by mean (*P*-values).

derived from logistic regression adjusted for age and BMI.

Results

Population and biochemical characteristics

A total of 551 subjects including 258 health controls and 293 T2D patients were recruited from The First Affiliated Hospital of Xinjiang Medical University in our study. The demographic and clinical characteristics of the studysubjects were illustrated in **Table 1** with the detailed clinical features of the validation cohorts. Age, sex, blood pressures, BMI and blood biochemical features were comparable between the two groups. The age and sex of the subjects have no significant difference (P= 0.453 and 0.385 respectively) between the patients and controls. Meanwhile, significant differences were noted in BMI (P<0.05), presence of hypertension (P<0.05), and HDL (P< 0.05), total cholesterol (P<0.05), and triglyceride (P<0.05) levels between patients and controls (**Table 1**).

Tag SNP selection for association study

Tagging SNP sets were selected from our result based on the resources from both the HapMap project (Phase II) and Ensembl database at a threshold of minor allele frequency (MAF)>0.1 and $r^2 \geq 0.5$ using Haploview 4.2 software. We also used the Chinese Han population (CHB) in the HapMap project was used as a control. The result confirmed that four variants (rs290487, rs4430796, rs864745 and rs231362) in *TCF7L2* genewere selected as Tagging SNP sets. As shown in **Table 2**, the distribution of genotypes and allele frequencies of the rs290487, rs4430796, rs864745 and rs23-1362 (TC) polymorphism in T2D patients and healthy controls were in accordance with the Hardy-Weinberg equilibrium (P>0.05). The frequencies of TT genotype of rs290487 were significantly higher in controls than the T2D cases

(33.1% versus 68.6%, *P*=0.001), while TC and CC were higher in controls than the T2D cases (49.6% versus 28.2% *P*=0.001, 17.3% versus 3.2% *P*=0.002). The GA and AA genotype frequencies were 37.7 and 6.0%, respectively, in T2DM group and 53.5 and 22.2%, respectively, in controls regardless of obesity status (**Table 2**).

Genotype distribution analysis

We subsequently analyze the association of the genotypes of each SNPs with T2D risk. The occurrence of CC mutant genotype is a risk factor for Uyghur population and especially for the male population with an OR=6.672, 95% CI 2.031-21.925 and OR=11.782, CI 1.556-89.221 respectively. The occurrence of TT wild type genotype of rs290487 was a protective factor for T2DM of Uygur (female), and the occurrence of rs290487 mutant genotype was the risk factor of T2DM in Uygur (whole, male) OR=0.189. The occurrence of CC mutant genotype of rs864745 was the protective factor of T2DM in Uygur population (OR=0.302, OR=0.351, OR=0.256). (OR=0.223, OR=0.307, OR =0.158). The rs231362 gene mutation is a protective factor for T2DM in Uygur population (OR=0.223, OR=0.307, OR=0.158) shown in **Table 3**. The occurrence of these genotype distributions of rs290487, rs864745 and rs231362 was significantly different between T2D group and the healthy control group in an Uygur population of Xinjiang China.

Association of TGF7L2 variants with metabolic parameters

Subsequently, we studied the effects of *TCF7L2* polymorphisms on the different clinical parameters in the Uyghur population. The distribution of these variables in relation to the various genotypes was analyzed. The subjects with rs290487 locus of *TCF7L2* gene exhibited a significant with waist-hip ratio, DBP (mmHg), FPG (mmol/L) and HbA1C (%) of diabetic patients, with *P* values of 0.001, 0.036, 0.024, and 0.034 respectively. The subjects with the rs4430796 genotype showeda higher FPG (mmol/L) among the diabetic patients (*P*= 0.029). Meanwhile, the subject with rs864745 genotype showed a higher waist-hip ratio (*P*=0.005) and the subjects with rs231362 genotype with HDL-C (mmol/L) with *P* value of 0.036, among diabetic patients (**Table 4**).

Discussion

T2D is one of the most common long term metabolic disorders in modern countries and represents a health problem and a major epidemic during the past decades. We observed a positive association between the polymorphisms of *TCF7L2, JAZF1, HNF1B, KCNQ1* and T2D in the Uyghur population. We found that the genotype occurrence of rs290487, rs4430796, rs864745, rs231362 gene were significantly different between T2D group and the healthy control group in the Uyghur population. Previous study showed that *TCF7L2* rs290487 (C/T) polymorphisms was associated with the T2D and affect therapeutic efficacy in various ethnic groups with type 2 diabetes especially eastern Asian people such as Han Chinese population [10, 15, 25]. We also confirmed that the CC genotype of TCF7L2 gene rs290487 was a risk factor of T2D in a Uygur population, with a strong association of metabolic parameters such asthe 2 waist-hip ratio, DBP, FPG and HbA1C. Human gene *HNF1B* encodes a liver-specific expressed transcription factor and its dysfunctional genetic mutations are considered as the cause of the Maturity-Onset of Diabetes, Type 5 (MODY5) [26]. Studies found that the rs4430796 in *HNF1B* region was associated with T2D in Han Chinese populations, indicating its association with T2D [27, 28]. In our result, we also found that subjects with rs4430796 mutant have a higher FGT level compared to the control groups. In addition, we also found the CC mutant genotype of rs864745 in *JAZF1* genetic region was protective factors for T2D in Uygur populations. Previous studies also found that variants in KCNQ1 increase T2D susceptibility in various of ethnic groups including Han Chinese, African Americans and American Indians [29-31]. In our results, we provided that evidence that occurrence of mutant AA genotype of rs231362 in *KCNQ1* locus was the protective factor of T2DM of the Uygur population, whichwas associated with concentration of HDL-C in T2D patients. In conclusion, our result provided novel insight and a solid evidence for the specific genetic variations and their association with T2D in the Uyghur population in China and we believe that these research would facilitate the early T2D clinical diagnose specific for Uyghur population in the future.

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Disclosure of conflict of interest

None.

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