Association Between *KCNQ1* Genetic Variants and Type 2 Diabetes in the Uyghur Population

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Objective: To investigate the association between *KCNQ1* gene polymorphisms and type 2 diabetes (T2D) in an admixed ethnic minority, Uyghur population, living in the Northwest region of China. **Materials and Methods:** We genotyped three tagging single-nucleotide polymorphisms rs2283171, rs11023485, and rs2283208 of the *KCNQ1* gene in 1006 T2D participants and 1004 controls and conducted association analysis. **Results:** The frequencies of the AG and GG genotypes and the G allele of rs2283171 were higher in the control group (51.4%, 22%, and 47.7%, respectively) than in the case group (49%, 17.6%, and 42.1%, respectively). The minor G allele decreased the risk of T2D with a per-allele odds ratio of 0.79 (95% CI: 0.70–0.90) for the additive genetic model in univariate analysis ($p=0.0001$). After adjustment for the covariates of age, gender, smoking, alcohol use, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), triglyceride (TG), and total cholesterol (TC), the diabetic protective effect of the rs2283171-G allele remained. No difference was observed in the frequency distributions of the rs11023485 and rs2283208 genotypes between the two groups. **Conclusion:** We identified a novel association between rs2283171 of *KCNQ1* and T2D in the Uyghur population. Further association and functional studies are required to identify the causal functional variant that is in linkage disequilibrium with this polymorphism.

Introduction

TYPE 2 DIABETES (T2D) is the result of joint action by multiple genes and multiple environmental factors with a high genetic predisposition to the disease. Twin studies have shown that the heritability of glucose levels and diabetes predisposition is as high as 40–70%. Therefore, search genetic variants that contribute to risk of T2D are important for primary prevention and drug target identification. Selection of ideal population may help identify causal variants. The Uyghur population, one of the major ethnic minorities living in the Xinjiang Uyghur Autonomous Region of Northwest China, is a classic admixed population with a genetic background of Caucasian (42.6%) and Asian (57.4%) (Yao *et al.*, 2004; Xu *et al.*, 2008). The increased extent of linkage disequilibrium (LD) between markers on the same chromosome, created by population admixture, may facilitate genome mapping of complex disease genes for the Uyghur population

(Xu *et al.*, 2008). The Uyghur population living in rural areas of Xinjiang is ethnically homogeneous with respect to a variety of factors such as social structure, profession, living environment, and lifestyle (Jiang *et al.*, 2010). In addition, due to their religious beliefs and ethnic psychology, they rarely intermarry with other ethnic groups, thus little migration occurs in the Uyghur population. Therefore, the Uyghur population is an ideal ethnic group to identify genetic contributions of complex traits and polygenetic disease such as T2D.

With the development of genome-wide association studies, a total of 90 genes had been proven to be associated with T2D by the year 2014 (Zeggini *et al.*, 2008; Dupuis *et al.*, 2010; Voight *et al.*, 2010; Yamauchi *et al.*, 2010; Kooner *et al.*, 2011; Cho *et al.*, 2012; Morris *et al.*, 2012; Saxena *et al.*, 2012; Saxena *et al.*, 2013; Tabassum *et al.*, 2013; Li *et al.*, 2013; DIAGRAM *et al.*, 2014; Grarup *et al.*, 2014; Hara *et al.*, 2014; Steinthorsdottir *et al.*, 2014). *KCNQ1* is the

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first T2D susceptibility gene identified in Asian subjects. In 2008, two research teams, led by Unoki and Yasuda, separately found that multiple single-nucleotide polymorphism (SNP) loci (rs2237892, rs2237895, rs2237897, and rs2283228) associated with T2D risk were located in a 40-kb LD region adjacent to intron 15 of *KCNQ1* in a Japanese population (Unoki *et al.*, 2008; Yasuda *et al.*, 2008). The relationship of SNPs in this region with T2D susceptibility has been unanimously verified in Chinese, Singaporean, Pakistani, Danish, German, and Swiss populations (Splawski *et al.*, 1998; Jiang *et al.*, 2003; Hu *et al.*, 2009; Jonsson *et al.*, 2009; Müssig *et al.*, 2009; Rees *et al.*, 2011). Therefore, *KCNQ1* has been shown to be an important candidate gene of T2D and a potential target of diabetic intervention. In this study, we hypothesized that the genetic region other than this 40-kb LD region may also be involved in the pathogenesis of T2D and the association signals might be detected, at least in some ideal populations. To test this hypothesis, we genotyped three tagging SNPs (rs2283171, rs11023485, and rs2283208) in intron 6, 10, and 11 of *KCNQ1* and tested their associations with T2D in the aforementioned admixed Uyghur population.

Materials and Methods

Subjects

In this hospital-based case-control study, 2010 Chinese Uyghur participants were recruited from the Department of Cadre Healthcare of the First Affiliated Hospital of Xinjiang Medical University; this group of participants consisted of 1006 unrelated individuals with T2D (628 men and 378 women; aged 51.13 ± 9.64 years) and 1004 age- and gender-matched controls (630 men and 374 women; aged 50.41 ± 9.65 years). The diagnosis of T2D was established according to WHO criteria or based on the history of T2D. Exclusion criteria included patients with other type of diabetes such as type I diabetes, MODY, gestational diabetes, stress hyperglycemia, malignant tumor, chronic infection, nervous-mental system disease, autoimmune disease, heart disease, and hepatic disease.

The control subjects were individually matched with case subjects according to the following criteria: ethnicity, gender, age (± 2 years), residence area, presence of impaired fasting glucose or not, and presence of glucose intolerance or not.

Subjects with a history of any type of diabetes, severe hepatic and renal dysfunction, autoimmune disease, severe organic disease, chronic infection, and nervous-mental system disease were not included.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data collection

All participants received a physical examination after overnight fasting. Blood samples were drawn for biochemical measurements, including fasting plasma glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), and total cholesterol (TC) levels. A standardized interview was conducted by trained personnel, and detailed information was collected concerning subject medical history and lifestyle characteristics, such as smoking and alcohol consumption. A standardized mercury sphygmomanometer was used to measure SBP and DBP, and these measurements were performed by two cardiologists. Body weight and height were measured with subjects wearing only light indoor clothing and without shoes. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Data are shown as medians (25–75% range) or mean $\pm$ SD (Table 1).

Single-nucleotide polymorphism selection and genotyping

Tag SNPs of *KCNQ1* were selected on the International HapMap Project Website (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap24_B36/). According to HapMap CHB databank (public data release 21 a/phase II, Jan. 2007), there are 352 common SNPs with a minor allele frequency (MAF) $>5\%$. Eligible SNPs (MAF $<5\%$ was excluded) were entered into Haploview 4.0 software to identify common haplotype tagging SNPs with an LD measure r^2 threshold at 0.8. We obtained three tagging SNPs (rs2283171, rs11023485, and rs2283208), which tagged five common SNPs span from intron 2 to intron 6 of the *KCNQ1*. Genomic DNA was isolated from peripheral blood leukocytes using a Wizard[®] Genomic DNA

TABLE 1. CLINICAL CHARACTERISTICS OF PARTICIPANTS

Characteristics	T2D	Control	p
Number of subjects	1006	1004	
Male/female (%)	628/378 (62.4/37.6)	630/374 (62.7/37.3)	0.881
Age (years, mean $\pm$ SD)	51.13 ± 9.64	50.41 ± 9.65	0.097
Smoking (%)	384 (38.2)	352 (35.1)	0.148
Alcohol drinking (%)	158 (15.7)	124 (12.4)	0.030
BMI (kg/m^2 , mean $\pm$ SD)	27.90 ± 6.16	26.77 ± 6.08	0.000
SBP (mm Hg, mean $\pm$ SD)	130.69 ± 24.22	126.24 ± 28.56	0.000
DBP (mm Hg, mean $\pm$ SD)	82.56 ± 16.44	79.94 ± 20.07	0.001
LDL (mM, mean $\pm$ SD)	2.89 ± 1.45	2.99 ± 0.84	0.090
HDL (mM, mean $\pm$ SD)	1.04 ± 0.37	1.18 ± 0.34	0.000
TG (mM, mean $\pm$ SD)	2.19 ± 2.0	2.63 ± 2.23	0.000
TC (mM, mean $\pm$ SD)	4.73 ± 1.32	4.27 ± 1.69	0.000

BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride.

TABLE 2. CHARACTERISTICS OF CANDIDATE SINGLE-NUCLEOTIDE POLYMORPHISMS OF *KCNQ1* IN PARTICIPANTS

SNPs	Gene region	Group	Allele frequency (%)				Genotype frequency (%)		
			A	G	OR (95% CI) ^a	p-value ^b	AA	AG	GG
rs2283171	Intron6	Case	1147 (0.58)	833 (0.42)	0.80	3.97×10^{-4}	331 (0.33)	485 (0.49)	174 (0.18)
		Control	1034 (0.52)	942 (0.48)	(0.70–0.90)		263 (0.27)	508 (0.51)	217 (0.22)
rs11023485	Intron10	Case	889 (0.47)	1023 (0.54)	1.13	0.065	216 (0.23)	457 (0.48)	283 (0.30)
		Control	834 (0.44)	1082 (0.57)	(0.99–1.28)		179 (0.19)	476 (0.50)	303 (0.32)
rs2283208	Intron1	Case	697 (0.36)	1269 (0.65)	0.93	0.279	134 (0.14)	429 (0.44)	420 (0.43)
		Control	723 (0.37)	1225 (0.63)	(0.82–1.06)		136 (0.14)	451 (0.46)	387 (0.40)

^aMinor allele OR (95% CI).^bMinor allele *p*-value.

CI, confidence intervals; OR, odds ratio; SNP, single-nucleotide polymorphism.

Purification Kit (Promega Corp., Madison, WI) according to the manufacturer's protocol. The SNPs were genotyped using the Sequenom MassARRAY system (San Diego, CA) according to the iPLEX Gold Application Guide.

Statistical analysis

The Statistical Package for Social Sciences version 16.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis, and SHEsis was used for haplotype LD estimation. Student's *t*-test was used to assess significant differences in clinical characteristics between case and control subjects. The chi-squared test was applied to evaluate the significance of each locus. Logistic regression analysis was performed to estimate the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), adjusting for the covariates of age, gender, smoking, drinking, and SBP, DBP, BMI, TG, and TC values, under the assumption of different genetic models (dominant, additive, and recessive).

Results

The clinical characteristics of T2D patients (*n*=1007) and control (*n*=1004) subjects are summarized in Table 1. The alcohol use and BMI, SBP, DBP, HDL, TG, and TC values were significantly different between the two groups (*p*<0.05), whereas sex, age, smoking, and LDL levels were not significantly different between these two groups (*p*>0.05).

The genotyping success rates of rs2283171, rs11023485, and rs2283208 were 98.4%, 95.2%, and 97.3%, respectively.

All SNPs were in the Hardy–Weinberg equilibrium in both the case and control groups.

Genotype and allele frequencies of rs2283171, rs11023485, and rs2283208 are presented in Table 2. Rs2283171 was significantly associated with prevalence of T2D in the Uyghur population. The frequencies of the AG, GG genotype, and G allele of rs2283171 were higher in the control group (51%, 22%, and 48%, respectively) than in the case group (49%, 18%, and 42%, respectively). No difference was observed in the frequency distribution of the rs11023485 and rs2283208 genotypes between the two groups.

The minor G allele was associated with a decreased risk of T2D, with a per-allele OR of 0.79 (95% CI: 0.70–0.90, *p*= 3.97×10^{-4}). Under a dominant genetic model for the G allele, GG carriers had a 0.72-fold decreased risk of T2D (Table 3). After adjustment for the covariates of age, gender, smoking, alcohol use, SBP, DBP, BMI, TG, and TC, the diabetic protected effect of G allele remained (Table 3).

The overall LD of three SNPs of the *KCNQ1* gene is weak in the Uyghur population. Therefore, we did not conduct haplotype-based association analysis.

Discussion

In the present study, we observed an SNP rs2283171, other than the unanimously verified 40-kb LD region adjacent to intron 15 of *KCNQ1*, to be associated with T2D in Uyghur subjects. To the best of our knowledge, we are the first to explore the association between this polymorphism and the risk of T2D.

TABLE 3. ASSOCIATION OF THREE SINGLE-NUCLEOTIDE POLYMORPHISMS WITH TYPE 2 DIABETES IN THE CASE AND CONTROL SUBJECTS

		Additive		Dominant		Recessive	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
rs2283171	Model 1	0.79 (0.70–0.90)	3.7×10^{-4a}	0.72 (0.60–0.88)	0.001 ^a	0.76 (0.61–0.95)	0.014 ^a
	Model 2	0.77 (0.66–0.89)	4.07×10^{-4a}	0.68 (0.55–0.85)	0.001 ^a	0.73 (0.57–0.95)	0.021
rs11023485	Model 1	1.13 (0.99–1.28)	0.067	1.10 (0.91–1.34)	0.336	1.27 (1.02–1.59)	0.035
	Model 2	1.13 (0.97–1.31)	0.107	1.12 (0.90–1.40)	0.316	1.25 (0.96–1.62)	0.092
rs2283208	Model 1	0.93 (0.82–1.06)	0.286	0.88 (0.74–1.06)	0.179	0.97 (0.75–1.26)	0.832
	Model 2	0.96 (0.82–1.11)	0.538	0.92 (0.75–1.13)	0.422	0.99 (0.74–1.32)	0.925

Model-1: unadjusted model.

Model-2: adjusted for age, gender, smoking, drinking, and SBP, DBP, BMI, TG, and TC values.

^aIndicates that the *p*-value remained statistically significant after Bonferroni correction (*p*=0.05/3=0.017).

As a voltage-dependent potassium channel family member, *KCNQ1* is located at 11p15.5. KvLQT1, which is encoded by *KCNQ1*, plays a critical role in the depolarization of the cardiac action potential and water and salt metabolism in epithelial tissue (Jiang *et al.*, 2003). Warth *et al.* (2002) found that *KCNQ1/KCNE1* is highly expressed in the mouse pancreas to form membrane potential potassium channels and slow-activated potassium current, which indirectly regulates the intracellular calcium ion concentration and reduces the electrical conductivity of calcium-activated chloride channels in response to acetylcholine, thereby regulating pancreatic secretion.

KCNQ1 is extremely large, which spans approximately 40 kb. *KCNQ1* may harbor different causal variants in different LD regions that predispose to risk of diabetes, which need to be identified and whose function is yet to be clarified. Several T2D-associated variants (i.e., rs2237892, rs2237895, rs2237897, rs2283228, and rs163184) located at the 40-kb LD region of the 15th intron (Unoki *et al.*, 2008; Yasuda *et al.*, 2008; Morris, 2014) were identified in the past years, which were in different degrees of LDs (moderate to high) and which show different allelic frequencies (i.e., the frequencies of rs2237892, rs2237897, and rs2074196 is 30–40% in Asians and only 10% in Europeans) (Unoki *et al.*, 2008; Yasuda *et al.*, 2008). These SNPs may point to a same causal variant that needs to be identified. Later, another region of this gene, intron 11, was also found to have genetic variants (i.e., rs231361 resides in the *KCNQ1-OT1* transcript that controls regional imprinting) conferring to risk of T2D, which may point to another causal variants (Tsai *et al.*, 2010; Morris *et al.*, 2012; Morris, 2014).

The SNP rs2283171 we detected had significant association with T2D in the present study and may also have the possibility to suggest causal variants. Located in the intron 6 of the *KCNQ1* gene, rs2283171 tagged two SNPs (rs6578273 and rs10832305, located in intron 2 and intron 6, respectively) based on the data of the International HapMap Database. Like the T2D-associated variants of intron15 and intron 11, rs2283171 may also be a genetic marker for T2D linked with an unknown functional variant (i.e., predicted regulatory elements) residing somewhere. Intronic variants are particularly important in the etiology of complex diseases. It may be a genetic marker in LD with a functional causal variant somewhere from intron 2 to intron 6, which needs to be identified. This region may harbor elements that regulate transcription such as a transcription enhancer and silence (Rohrer *et al.*, 1998; Lio *et al.*, 2002; Tokuhiro *et al.*, 2003; Wan *et al.*, 2011), which may be affected by the functional causal variant.

There are a few advantages and limitations of the present study. The major strength of this study is that the studied Uyghurs are an admixed homogeneous population with respect to a variety of environment factors, which increased the possibilities of genetic discovery. However, the study sample size is relatively small, which decreased the power of genetic associations; thus, chance findings cannot be fully excluded. In addition, we only selected three tagging single-nucleotide polymorphisms representing a portion of common genetic variants. Therefore, we may have missed the effects of other common and rare alleles of the *KCNQ1* gene.

In conclusion, we detected a new genetic variant of the *KCNQ1* gene (rs2283171) that confers a predisposition to the risk of T2D in the Uyghur population. The functional sig-

nificance of the causal allele in LD with the minor G allele of the rs2283171 also calls for future exploration.

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Author Disclosure Statement

No competing financial interests exist.

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