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Relationship between KCNQ1 gene polymorphisms and type 2 diabetes in the population of northwestern China and a meta-Analysis

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Abstract

Aims The purpose of this study was to explore the correlation between Potassium Voltage-Gated Channel Subfamily Q Member 1 (KCNQ1) gene polymorphisms and the risk of type 2 diabetes mellitus (T2DM) and its clinical indicators in the population of northwestern China, and conducted a meta-analysis on two polymorphic loci that have been studied frequently and controversial. Methods A case control study was conducted, involving 508 patients and 503 healthy individuals in the population of northwest China, and evaluated the associations using the χ2 test, Fisher's exact test, T test, and genetic model analyses. Results We discovered that rs2237895 rs2283228, rs163184, and rs163177 were associated with susceptibility to T2DM. Rs231362 rs231356, rs8181588 were related to the risk of T2DM after stratification. The results of meta-analysis also confirmed that rs2237895 and rs2283228 were strongly correlated with T2DM risk, especially in the East Asian population. Conclusions This study provides evidence for the correlation between KCNQ1 gene polymorphisms and T2DM in the population of northwestern China.

Background

Type 2 diabetes (T2DM), characterized by hyperglycemia characterized by insulin resistance and beta cell dysfunction, has become an obvious global public health problem [1]. In 2017, there were 7.5 billion adults (8.8% of adults aged 20 to 79) with diabetes. It is expected that this rate will rise to 9.9% by 2045, which will affect 9.5 billion adults [2]. The treatment of T2DM imposes enormous social, financial and health system burdens across the world. Therefore, it is urgent to clarify the precise etiology and pathophysiology of T2DM and make the treatment more targeted.

The candidate genes for T2DM have been widely investigated. Numerous single nucleotide polymorphisms (SNPs) have been identified through sequencing, and many of them in critical genes such as *KCNJ11*, *WFS1*, *ABCA 1*, and *ALOX5* were demonstrated to be associated with T2DM susceptibility [3-6]. Among them, *KCNQ1* (Potassium Voltage-Gated Channel Subfamily Q Member 1) is located in a region of chromosome 11p15.5, spanning over 400 kb and containing 676 amino acids. *KCNQ1* encodes a voltage-gated potassium channel required for repolarization phase of the cardiac action potential, and is expressed in the human heart and pancreas and, to a lesser extent, in the placenta, lung, liver and kidney [7]. In two independent GWAS studies (2008), *KCNQ1* was first identified as a T2DM susceptibility gene in East Asian populations [8, 9]. Subsequently, some studies have confirmed that *KCNQ1* was a susceptibility gene of T2DM in Chinese, Singaporean, Indian and some Euro-Caucasian subjects. In addition, the functional studies on *KCNQ1* have shown that it can stimulate insulin secretion by selective blockade of this K + channel [10]. Furthermore, clinical trait association analysis showed that baseline insulin secretion is impaired in KCNQ1 risk allele carriers [8]. It has been found that *KCNQ1* blocker 293B stimulates insulin secretion, and *KCNQ1* inhibitor enhances glucose-stimulated insulin secretion and increases the level of glucagon-like peptide-1 in mice [11]. Similarly, knockdown of *KCNQ1* in mouse models resulted in increased systemic insulin sensitivity and increased insulin-mediated glucose uptake in the liver and muscles [12]. All these studies proved that *KCNQ1* plays an important role in the occurrence of T2DM.

It is well known that different geographic regions can show significant differences in the frequency of certain genetic variations, which lead to differences in susceptibility to disease among populations from different regions. Currently, the correlation of *KCNQ1* variants with T2DM risk has been reported in some regions of China, such as Hong Kong, Singapore and Shanghai, Jiangsu, Wuhan [8, 9, 13-15]. However, the effect of *KCNQ* variation on T2DM risk has not been reported in northwest China. Meanwhile, the relationship between the variants and clinical phenotypes of T2DM has rarely been reported, and it is equally important to find some new variants related to diabetes in *KCNQ1*.

In present study, we selected eight variants (rs117601636, rs231362, rs231356, rs2237895, rs2283228, rs163184, rs163177, rs8181588) of *KCNQ1* gene for genotyping, among which rs8181588 has not been studied. Our aim was to explore the correlation of these eight variants with T2DM risk and some clinical indicators in northwest China. In addition, we also performed a meta-analysis on two polymorphic loci (rs2237895 and rs2283228) that have been extensively studied so far. These studies can enhance our understanding of T2DM development and lead to effective individualized prevention of this disease in different populations.

Methods

Study subjects

Using a case control design, a total of 1011 participants including 508 patients with newly diagnosed T2DM and 503 healthy controls were recruited. All of blood samples of patients were collected from the First Affiliated Hospital of Xi'an Jiaotong University. All subjects were members of Chinese Han population living in the Shaanxi province of China. We diagnosed patients with T2DM according to the World Health Organization (WHO) criteria in 1999: fasting plasma glucose 7.0mmol/l and/or 2 hours postprandial plasma glucose 11.1mmol/L. At the same time, patients with acute diabetes complications, other types of diabetes, type T2DM with lipid-lowering and/or oral hypoglycemic drugs, cardiovascular disease, renal and liver failure, and malignancies were excluded.

The inclusion criteria for unrelated controls were as follows: 1) normal glucose tolerance (fasting plasma glucose < 6.1 mmol/L and 2-h plasma glucose < 7.8 mmol/L), or HbA1c levels < 5.6% with fasting plasma glucose 6.1 mmol/L; 2)No personal or family history of diabetes; 3) no systemic diseases.

SNP selection and genotyping

Eight tag-SNPs (rs117601636, rs231362, rs231356, rs8181588, rs163177, rs163184, rs2283228, rs2237895) in the *KCNQ1* gene were selected from the International HapMap Project (http://www.hapma p.org), dbSNP (http://www.ncbi.nlm.nih.gov/proje cts/ SNP/) and UCSC (http://genom e.ucsc.edu/)

databases for our present study. These SNPs were with minor allele frequencies (MAFs) >5% in Chinese Han population. A multiplexed SNP MassEXTEND assay was designed by Agena MassARRAY Assay Design 3.0 Software (Agena Bioscience, Inc., San Diego, CA, USA). Genotyping of variants was performed by two laboratory personnel in a double-blinded fashion using the Agena MassARRAY system (Agena, San Diego, CA, U.S.A.) [16, 17], and we used Agena Typer 4.0 software for data management and analysis [18, 19]. In order to verify the accuracy of genotyping, marker and sample genotyping efficiency as well as the performance of positive and negative controls were examined. In addition, approximately 10% of the total samples were randomly selected for repeat genotyping with a reproducibility of 100%. The corresponding primers used for SNPs in this study are listed in Table S1.

Data collection

Basic information about the subjects was collected by trained professionals using structured questionnaires. The peripheral blood samples from each participant were contained in tubes coating with ethylene-diaminetetraacetic acid (EDTA) and were stored at − 80°C after centrifugated until analysis. Genomic DNA from whole blood was isolated by the Whole Blood Genomic DNA Extraction Kit (Tiangen Biotech, Beijing, China), and its concentration was measured using the NanoDrop2000 (Thermo Scientific, Waltham, MA, USA).

Data analyses

All the statistical analyses were completed using the Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and the SPSS 18.0 statistical package (SPSS, Chicago, IL, USA). The differences of basic parameters between the cases and controls were examined with the Pearson's χ^2 tests for categorical variables and independent sample Student s t test for continuous variables. For each SNP, Hardy Weinberg equilibrium as well as the differences in allele frequencies and genotype frequencies between cases and controls were examined by χ^2 tests or Fisher s exact test. Beyond that, multiple inheritance model analyses (codominant, dominant, recessive and log-additive) were generated using PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/) to estimate the relationship between SNPs and diabetes risk. Furthermore, we also used multiple genetic models to analyze the correlation between SNPs and diabetes risk in different stratified analyses. Finally, haploview software package (version 4.2) and the SHEsis software (http://analy sis.bio-x.cn/ myAna lysis .php) were used to evaluate the pairwise linkage disequilibrium (LD), haplotype construction, and genetic association of polymorphism loci. The diabetes risk linked with alleles and genotypes was estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis by adjusting covariates such as age. For all tests, a two-sided *p*-value < 0.05 was regarded statistically significant.

Search Strategy and Selection Criteria

We searched for key words such as T2DM, *KCNQ1*, rs2237895 and rs2283228 polymorphism etc. in PUBMED, EMBASE, Cochrane library, HuGNet database and other related publications to determine the literature. We also supplemented the literature by reviewing the reference list of all publications retrieved.

For the meta-analysis, the following inclusion criteria were considered: (1) unrelated case-control studies; (2) sufficient genotypes data were presented to calculate the odds ratios (ORs); (3) The sources of T2DM diagnostic cases and controls should be clearly described; (4) conform to Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: (1) no control population (2) duplication of a previous study, and (3) no available genotype frequency.

Data Extraction

Two investigators extracted data independently and reached a consensus on all of the items. The following information was sought from each article: the first author's name, year of publication, country of origin, ethnicity, representativeness and ascertainment of cases and controls, mean age, male sex percentage in case and control groups, number of cases and controls, genotype frequencies for cases and controls and Hardy-Weinberg equilibrium (HWE) of controls.

Statistical Meta-Analysis

Stata software was used for all statistical analyses (version 11.0;StataCorp LP, College Station, TX), using bilateral *p* values. $p < 0.05$ was considered statistically significant in all analyses except for the heterogeneity test. Heterogeneity was assessed using a chi-square based Q test. If the *p* value is greater than 0.100 of the q-test, indicating a lack of heterogeneity between studies, the summary OR estimate for each study is calculated using the fixed effects model (the Mantel–Haenszel method/ the inverse variance method). Instead, perform the random effects model (the DerSimonian-Laird method with the estimate of heterogeneity being taken from the Mantel-Haenszel model/the inverse-variance fixed-effect model). Heterogeneity was also assessed using I^2 statistics, with values between 0% and 100%. A higher value indicates a greater degree of heterogeneity (I^2 = 0 - 25%: no heterogeneity; I^2 = 25 - 50%: moderate heterogeneity; I^2 = 50 - 75%: large heterogeneity; I2 = 75 - 100%: extreme heterogeneity). Use the Z test to determine the significance of the merged OR. Funnel plots, Begg's test and Egger's test were used to check for potential publication bias.

Results

Characteristics of patients and controls

The basic characteristics of cases and controls are summarized in Table 1. In this case-control study, a total of 508 patients (277 males and 231 females; age at diagnosis: 59.34 ± 7.62 years) and 503 healthy individuals (279 males and 224 females; age at diagnosis: 59.21 ± 11.90 years) were enrolled. There were no statistically significant differences (p = 0.248) in the distributions of gender and age between the cases and controls groups.

Hardy-Weinberg equilibrium and SNPs alleles

Table 2 presented the basic information of the eight SNPs of *KCNQ1* in terms of gene, SNP ID, chromosomal position, role, minor allele frequency (MAF) of cases and controls, Hardy-Weinberg equilibrium (HWE) test results and call rate. The call rate for all SNPs was above 99.5% in case and controls, which was considered high enough to perform association analyses. For all of the *KCNQ1* polymorphisms, the genotype distribution in controls subjects were no deviation from the HWE (p > 0.05). We used χ^2 tests to compare the difference in allele frequency between cases and controls, and evaluate the association with the risk of diabetes by ORs. Finally, we found that three significant SNPs in *KCNQ1* were associated with the risk of T2DM. Rs163177 and rs2237895 were associated with a higher T2DM risk in the allele genetic model (rs163177, T vs. C: OR = 1.21, 95% CI = 1.01 - 1.44, p = 0.036; rs2237895, C vs. A: OR = 1.20, 95% CI = 1.00 - 1.44, p = 0.046). Conversely, rs2237895 was associated with a reduced risk of T2DM in the allele genetic model (C vs A: OR = 0.78, 95% CI = 0.65 - 0.93, p = 0.007).

Association between *KCNQ1*and the risk of diabetes

Furthermore, we analyzed the association between the SNPs and the risk of T2DM under multiple inheritance models (codominant, dominant, recessive, additive models) (Table 3). The results showed that rs163177 significantly increased the risk of T2DM under the codominant, dominant and log-additive model (TC vs. TT: OR = 1.52, 95% CI = 1.12 - 2.05, p = 0.007; CC vs. TT: OR = 1.48, 95% CI = 1.03 - 2.13, p = 0.035; C/C - TC vs. TT: OR = 1.51, 95% CI = 1.13 - 2.01, p = 0.006; C vs. T: OR = 1.22, 95% CI = 1.02 - 1.47, p = 0.030). The SNP site rs2237895 was significantly correlated with increased risk of T2DM under the codominant and log-additive model (A/A vs. CC: OR = 1.53, 95% CI = 1.02 - 2.30, p = 0.039; A vs. C: OR = 1.21, 95% CI = 1.01 - 1.46, p = 0.044). The SNP site rs163184 only increased the risk of T2DM in dominant model (T/G-G/G vs. TT: OR = 1.30, 95% CI = 1.00 - 1.74, p = 0.049). However, rs2283228 polymorphism had a significantly reduced the risk of T2DM based on codominant, dominant and log-additive model (AA vs. CC: OR = 0.60, 95% CI = 0.39 - 0.91, p = 0.016; A/C-A/A vs. CC: OR = 0.74, 95% CI = 0.57 - 0.94, p = 0.016; A vs. C: OR = 0.77, 95% CI = 0.64 - 0.93, p = 0.007).

Stratification analysis by age and gender

We performed a subgroup analysis to evaluate the effect of the SNPs on T2DM stratified by age adjusted for age and gender. As shown in Table 4, the results indicated that rs163177 was associated with an increased T2DM risk at age ≤ 50 years in codominant model, dominant model ((TC vs. TT, OR = 1.74, 95% CI = 1.13 - 2.69, p = 0.012; C/C - T/C vs. TT, OR = 0.1.65, 95% CI = 1.08 - 2.54, p = 0.022). Rs818158 polymorphism was observed to be associated with the reduced the susceptibility of T2DM at age 50 years under allele model (C vs. T, OR = 0.78, 95% CI = 0.60 - 1.00, p = 0.046). Meanwhile, rs2283228 also showed a negative effect on T2DM at age 50 years under both the log-additive (A vs. C, OR = 0.76, 95% CI: 0.58 - 0.99, p = 0.041) and the allele model (A vs. C, OR= 0.74, 95% CI: 0.58 - 0.96, p = 0.024).

Stratified analysis by gender adjusted for age also revealed significant associations between three SNPs and the risk of T2DM as presented in Table 4. Rs163177 polymorphism was significantly associated with increasing the T2DM risk among the female subgroup under the co-dominant model (CC vs. TT, OR = 1.81, 95% CI = 1.05–3.13, p = 0.033), dominant model (C/C-T/C vs. TT, OR = 1.55, 95% CI: 1.01 - 2.38, p = 0.045), log-additive model (C vs. T, OR=1.35, 95% CI: 1.03 - 1.77, p = 0.030) and allele model (C vs. T, OR=1.32, 95% CI:1.02 - 1.71, p = 0.038). Rs2237895 polymorphism also exhibited an increased T2DM risk among female in the co-dominant model (AA vs. CC, OR = 2.04, 95% CI = 1.11 - 3.76, p = 0.023), recessive model (A/A vs. C/C-A/C, OR = 1.81, 95% CI: 1.04 - 1.81, p = 0.026), log-additive model (A vs. C, OR = 1.37, 95% CI: 1.04 - 1.81, p = 0.026) and allele model (A vs. C, OR = 1.36, 95% CI: 1.03 - 1.78, p = 0.028). Conversely, rs2283228 polymorphism was associated with reduced susceptibility of diabetes in females under co-dominant (AC vs. CC, OR = 0.67, 95% CI = 0.45 - 0.99, p = 0.045) and dominant model (A/C-A/A vs. CC, OR = 0.67, 95% CI = 0.46 - 0.97, p = 0.033,). However, there was no relationship existed between the selected SNPs and diabetes risk in males.

Stratification analysis by smoking and alcohol drinking

We further explored the potential interactions between the selected SNPs and the development of T2DM based on smoking and drinking stratification, and found the results in Table 5. According to the stratification of smoking status, it was found that rs231362 can increase the susceptibility of non-smokers to T2DM under the co-dominant (TC vs. TT: OR = 1.76, 95% CI = 1.05 - 2.98, p = 0.034), dominance model (C/C-T/C vs. TT: OR = 1.81, 95% CI = 1.08 - 3.04, p = 0.023), log-additive model (C vs. T, OR=1.77, 95% CI: 1.09 - 2.87, p = 0.021). For rs2283228, nonsmokers' susceptibility to T2DM in the allele model was reduced (A vs. C, OR=0.74, 95% CI: 0.55 - 0.99, p = 0.043).

When stratified by drinking status, rs231362 was observed to decrease the susceptibility to T2DM among individuals without drinking history based on co-dominant (TC vs. TT: OR = 2.01, 95% CI = 1.20 - 3.35, p = 0.008), dominance model (C/C-T/C vs. TT: OR = 2.06, 95% CI = 1.25 - 3.42, p = 0.005), log-additive model (C vs. T, OR = 1.99, 95% CI: 1.24 - 3.20, p = 0.005) and allele model (C vs. T, OR = 1.53, 95% CI: 1.04 - 2.25, p = 0.032). Both rs231362 and rs231356 were associated with a reduced risk of T2DM under codominant, dominance, and regression models among drinkers (rs231362: CC vs. TT: OR = 0.31, 95% CI = 0.12 - 0.83, p = 0.005; C/C-T/C vs. TT: OR = 0.33, 95% CI = 0.13 - 0.83, p = 0.019; C vs. T, OR= 0.40, 95% CI: 0.18 - 0.93, p = 0.033; rs231356: TA vs. TT: OR = 0.39, 95% CI = 0.17 - 0.89, p = 0. 024; A/A-T/A vs. TT: OR = 0.39, 95% CI = 0.18 - 0.85, p = 0.018; A vs. T, OR= 0.48, 95% CI: 0.25 - 0.93, p = 0.030).

Stratification analysis by BMI

Finally, when stratified analysis according to BMI, we found that four SNPs sites were significantly correlated with T2DM risk, as listed in Table 6. Rs231362 polymorphism was associated with a higher T2DM risk in allele genetic models at BMI ≤ 24 (A vs. C: OR = 1.67, 95% CI = 1.02 - 2.72, *p* = 0.039). Rs163177 and rs163184 polymorphisms also increased the risk of T2DM in co-dominant, dominant, log-additive model, allele model at BMI ≤ 24 (rs163177: CC vs. TT, OR = 2.27, 95% CI = 1.05 - 4.90, *p* = 0.037; C/C-T/C vs. TT, OR = 1.95, 95% CI: 1.02 - 3.73, *p* = 0.043; C vs. T, OR = 1.49, 95% CI: 1.01 - 2.18, *p* = 0.042; C vs. T, OR=1.43, 95% CI: 1.04 - 1.98, *p* = 0.029; rs163184: G/T vs. T/T, OR = 1.92, 95% CI: 1.02 - 3.65, *p* = 0.045; GG vs. T/T, OR = 2.07, 95% CI: 1.00 - 4.27, *p* = 0.049; G vs. T: OR = 1.44, 95% CI =1.00 - 2.07, *p* = 0.049; G vs. T: OR = 1.39, 95% CI =1.01 - 1.93, *p* = 0.045). Rs2283228 polymorphism was associated with decreased risk of T2DM under both log-additive model and allele model at BMI ≤ 24 (log-additive model: A vs. C: OR = 0.67, 95% CI = 0.45 - 0.98, *p* = 0.041; allele model: A vs. C: OR = 0.67, 95% CI = 0.48 - 0.95, *p* = 0.025).

Relationship between the genotype of RETN SNPs and clinical indicators in patients with T2DM

We also analyzed the relationship between eight SNPs in *KCNQ1* gene and the clinical parameters of T2DM, including fasting glucose, glycosylated hemoglobin, total cholesterol, triglyceride, LDL, HDL and urea, etc., and the positive results were listed in Table 7. We found that “GA”, “AG” and “AA” genotypes of rs117601636 were significantly associated with total cholesterol and LDL levels. The genotypes “AA” of rs231362 carriers have higher UCRP and TJCTNT levels than “AG” and “AA” genotype carriers. For locus rs8181588, “CC” carriers were observed to have higher total cholesterol, LDL and ALBP levels than “CA” and “AA” carriers. The “TT”, “GT” and “GG” genotypes of rs163177 were significantly correlated with total cholesterol and INS content. The “CC”, “CA” and “AA” genotypes of rs2237895 were significantly related to LDL content. There also was a significant correlation between the three genotypes of rs2237895 and LDL content. Compared with those with “CC” and “AA” genotypes in rs2237895, the LDL levels of “CA” genotype carriers were higher.

Association of *KCNQ1* haplotypes with the risk of diabetes

Finally, the relationship between *KCNQ1* haplotype and the risk of T2DM under different stratification was evaluated. Supplementary Figure S1 - Figure S6 listed the linkage disequilibrium (LD) blocks of SNPs in the *KCNQ1* gene. The frequencies distribution of haplotypes in case and control group is presented in Supplementary Table S2. The haplotype “TC” constructed by rs163184 | rs2283228 was associated with a reduced risk of T2DM at age 50 years (OR = 1.33; 95% CI = 1.02 - 1.74; *p* = 0.035). The haplotype “TT” constructed by rs163177|rs163184 has a protective effect on the risk of T2DM in female (OR = 0.74; 95% CI = 0.56 - 0.97; *p* = 0.027). The haplotype“AA” constructed by rs231362|rs231356 was associated with an increased risk of T2DM among non-smokers (OR = 1.73; 95% CI = 1.06 - 2.81; *p* = 0.027). The haplotypes “AA” and “GT” constructed by rs231362|rs231356 were associated with an increased risk of T2DM in drinkers (AA: OR = 2.33, 95% CI = 1.02 - 5.33, *p* = 0.045; GT: OR = 2.19, 95% CI = 1.12-4.27, *p* = 0.022). The haplotype “AA” constructed by rs231362|rs231356 can increase the susceptibility to T2DM among individuals without drinking history (OR = 1.93; 95% CI = 1.20 - 3.11; *p* = 0.007). The haplotype “CG” constructed by rs163177|rs163184 was associated with an increased risk of T2DM at BMI ≤ 24 (OR = 1.45; 95% CI = 1.00 - 2.08; *p* = 0.049), while haplotype “CG” can reduced the risk of T2DM at BMI ≤ 24 (OR = 0.68; 95% CI = 0.46 - 0.99; *p* = 0.044).

Characteristics of eligible studies

For the polymorphic locus rs2237895, a total of 18 articles were included with 25,620 patients and 10,352 controls. Site rs2283228 was eventually included in 7 articles. It was found that these two polymorphisms occurred at a frequency consistent with HWE in the control populations of the vast majority of the published studies. The detailed characteristics of rs2237895 and rs2283228 loci included in this meta-analysis are shown in Supplementary Table S3 - Table S4.

Meta-analysis of the relationship between rs2237895 and T2D susceptibility

The associations between rs2237895 gene polymorphism and T2DM risk, as well as heterogeneity tests, were shown in Table 8. The forest diagrams of rs2237895 in different gene models were shown in Figure 1 and Supplementary Figure S11 –Figure S14. The overall results showed that rs2237895 polymorphism was significantly associated with an increased T2DM risk in different genetic models. (OR = 1.25, 95% CI =1.07 - 1.47, *p* = 0.001 for allele model A vs. C; OR = 1.23, 95% CI = 1.06 - 1.42, *p* = 0.006 for Homozygote comparison model AA vs. CC; OR = 1.24, 95% CI = 1.05 - 1.32, *p* = 0.012 for heterozygote comparison model AC vs CC). When the study was stratified by region, rs2237895 polymorphism was associated with an increased risk of T2DM under the allelic model (A vs. C: OR = 1.26, 95% CI = 1.03 - 1.53, *p* = 0.009), the homozygous comparison model (AA vs. CC; OR = 1.23, 95% CI = 1.02 - 1.47, *p* = 0.028), the heterozygous model (AA vs. CC; OR = 1.26, 95% CI = 1.02 - 1.55, *p* = 0.035) in the East Asian population. However, no significant association was found for South Asian, Caucasian and other ethnic populations.

Meta-analysis of the relationship between rs2283228 and T2D susceptibility

We presented the detailed results of association between rs2283228 polymorphism and T2DM risk in Table 9. The forest diagrams of rs2283228 in different gene models were shown in Figure 5 and Supplementary Figure S15 –Figure S18. Overall, we detected significant association between rs2283228 polymorphism and T2DM risk among all genetic models (OR = 0.83, 95% CI = 0.77 - 0.89, *p* = 0.000 for allele model A vs. C; OR = 0.81, 95% CI = 0.73 - 0.90, *p* = 0.000 for dominant model AA/AC vs. CC; OR = 0.74, 95% CI = 0.67 - 0.81, *p* = 0.000 for recessive model AA vs. AC/CC; OR = 0.66, 95% CI = 0.60 - 0.74, *p* = 0.000 for Homozygote comparison model AA vs. CC; OR = 0.85, 95% CI = 0.76 - 0.95, *p* = 0.006 for heterozygote comparison model AC vs CC).

Further subgroup analysis by region, a significantly decreased T2DM risk was observed in East Asian population under all genetic models (OR = 0.82, 95% CI = 0.78 - 0.86, *p* = 0.000 for allele model A vs. C; OR = 0.79, 95% CI = 0.74 - 0.86, *p* = 0.000 for dominant model AA/AC vs. CC; OR = 0.73, 95% CI =

0.66 - 0.81, p = 0.000 for recessive model AA vs. AC/CC; OR = 0.67, 95% CI = 0.60 - 0.75, p = 0.000 for Homozygote comparison model AA vs. CC; OR = 0.84, 95% CI = 0.76 - 0.91, p = 0.000 for heterozygote comparison model AC vs CC), but not Caucasians and North Africa population.

Publication bias and sensitivity test

In this study, we first used Q test and I^2 statistics to test the heterogeneity between studies, and all models showed significant heterogeneity. Therefore, the random effect model was used to generate wider CIs. There was no significant evidence of publication bias for any association investigated based on visual examination of funnel plots (Supplement Figure S7 - Figure S10). As to the sensitivity analysis, there was no significant change in the overall results after the omission of each study, reflecting the stability and reliability of these results.

Discussion

In this case control study, the allele, genotype and haplotype frequencies of eight SNPs in *KCNQ1* gene between T2DM patients and healthy control group were compared and stratification analyses by age or gender etc. Our study found that four of eight SNPs (rs2237895 rs2283228, rs163184, rs163177) were correlated with susceptibility to T2DM. Three polymorphism loci (rs231362 rs231356, rs8181588) are associated with the risk of T2DM after stratification. Meanwhile, the results of large-scale meta-analysis also confirmed that rs2237895 and rs2283228 were strongly correlated with T2DM risk, especially in the East Asian population. To our knowledge, this is the first study to evaluate the relationship between *KCNQ1* gene variation and the risk of developing T2DM in the population of northwestern China.

KCNQ1 is closely related to the occurrence of T2DM. The evidence to date demonstrated that common variants of *KCNQ1* could mediate the susceptibility of people of different ethnic backgrounds to T2DM by altering insulin secretion [20, 21]. For example, the rs2237895 allele was related to b-cell dysfunction in the Danish population [13]. The rs2283228 risk allele was associated with elevated fasting glucose and impaired b-cell function in Asians [22]. In the present study, we selected eight common variants in *KCNQ1* to explore their correlation with T2DM risk. Currently, rs2283228 and rs2237895 have been widely reported in different populations, but their correlations with the risk of T2DM in different populations were inconsistent. Previous studies have shown that rs2237895 variant was associated with T2DM risk in Asians (Japanese, Chinese and Koreans), and in Europeans (Danish and Scandinavian) [5, 9, 13, 20, 23, 24]. In contrast, rs2237895 were not associated with the incidence of T2DM in Punjabi and Asian Indian populations [25][20], Singaporean (Chinese and Malays, Asian Indians) and Malaysian Chinese the subjects, Spanish Renastur cohort or Tunisians [22, 26-28]. Similarly, rs2283228 variants have also been shown to be associated with T2DM in Europe (Denmark), Singapore (Chinese, Malays, and Asian Indians), Japan, and South Korea, but not associated with T2DM in Singapore (China) and Tunisia Arabs [8, 9, 22, 26]. In our current study, we observed that rs2237895 and rs2283228 were significantly correlated with T2DM risk in the population of northwestern China, and the meta analysis also observed that these two sites were significantly related to T2DM susceptibility in the overall population and the population of East Asia.

In addition, the association between rs163184 polymorphism to the earlier onset of T2DM has not been observed in the Slovakian population [29]. Our study found that rs163184 was associated with an increased risk of T2DM in the dominant model, which was inconsistent with the reports in the Slovakian population. Regarding the rs163177 locus, a study to identify SNPs associated with the risk of T2DM in Korean adults found a prospective association between rs163177 (*KCNQ1*) and T2DM [30]. We also found that this site could increase the risk of T2DM in the population of northwestern China, which was consistent with the results in the Korean population. The above studies in different population have both consistent and inconsistent places, which may be attributed to ethnic difference, environmental factor, or inappropriate sample size. At the same time, more sample studies are needed to confirm our results.

Tobacco smoking, an established modifier of DNA methylation,is associated with an increased risk of T2DM diabetes [31]. In a Dutch population-based cohort study, the allele of rs231356 was observed to be associated with hyomethylation of *KCNQ1* and a higher risk of diabetes [32]. In our study, we found that rs231356 was not associated with the risk of T2DM in smokers or non-smokers, which may be due to the small sample size or ethnic differences, requiring more samples for further study.

The most common feature of classic T2DM patients is obesity, but recent studies have shown that lean patients with T2DM exhibit more rapid, early loss of b-cell function while still having low levels of insulin resistance in contrast to obese patients with T2DM [33]. The study of Kong et al. found that T2DM-related risk alleles showed a stronger predisposition to lean T2DM than to obese T2DM in Chinese Han population [34]. In our study, we found that four polymorphisms (s231362 rs2283228, rs163184 and rs163177) were associated with an increased risk of diabetes at BMI $\leq$ 24, which further prove that lean T2DM patients was higher than that for obese T2DM patients.

Some limitations in our study must be noted. First, the sample size was relatively small after stratification by sex, which might convert the positive findings into negative results. Second, a relatively small sample size in stratified analysis may translate a positive result into a negative one. In addition, the contribution of gene environment interactions to the pathogenesis of T2DM should not be overlooked, as it will directly impact on the association of possible (susceptibility) loci with the risk of T2DM. A larger case control study is required to reduce errors. Despite these limitations, our current findings provide scientific evidence for future in-depth studies of polymorphisms and T2D risk.

Conclusion

In conclusion, our present study provided the first evidence that *KCNQ1* was associated with T2DM susceptibility in the population of northwestern China. Our latest meta-analysis also confirmed that two polymorphic loci (rs2237895, rs2283228) in *KCNQ1* were significantly correlated with the risk of T2DM. Nevertheless, we believe that further efforts are needed to re-sequence *KCNQ1* in depth to identify causal variants and reveal the molecular mechanisms underlying this association.

Abbreviation List

abbreviations	English full name
KCNQ1	Potassium Voltage-Gated Channel Subfamily Q Member 1
T2DM	type 2 diabetes mellitus
SNP	Single nucleotide polymorphism
HWE	Hardy–Weinberg equilibrium
OR	Odds ratio
95%CI	95% confidence intervals
LD	Linkage disequilibrium
MAF	Minor allele frequency

Declarations

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and in compliance with the Declaration of Helsinki. The purpose of this study was well informed to the all participants and written informed consents were obtained from all participants prior to biological material collection in this study. All subsequent study analyses were conducted in accordance with the approved guidelines and regulations.

Consent for publication

Written informed consent was obtained from the patient for publication of this report.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest

The authors declare that they have no conflict of interests.

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Author Contributions

BYS and WC: conceived and designed the experiments;

JX, WZ and WS: performed the experiments;

JX and JQC: analyzed the data;

YNT, HC and PH: contributed reagents/materials/analysis tools;

SJY and LW: prepared the figures and/or tables;

XH and LW: drafted the work or revised it critically for important content.

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Tables

Table 1 Demographic characteristics of cases and controls in this study

Characteristics	Case	Control	*p* value
Number	508	503	
Age			> 0.05 [a]
≤ 59	245(48%)	238(47%)	
> 59	263(52%)	265(53%)	
Age (mean ± SD)	59.34 ± 7.62	59.21 ± 11.90	
Gender			> 0.05 [b]
Male	277(55%)	279(55%)	
Female	231(45%)	224(45%)	
Smoking			
Yes	135(27%)	115(23%)	
No	230(45%)	188(37%)	
Drinking			
Yes	68(13%)	106(21%)	
No	277(55%)	182(36%)	
BMI index			
≤ 24	130(26%)	173(34%)	
> 24	187(37%)	185(37%)	

[a] Two-side Chi-squared test;

[b] Independent samples *t* test;

$p < 0.05$ indicates statistical significance.

Table 2 Basic information and allele frequencies about *KCNQ1* candidate SNPs in this study

SNP	Chr	Position	Gene(s)	Role	Alleles	Frequency (MAF)		Call rate (%)	*p*-H WE HWE	OR	*p* value
					A/B	Cases	Controls				
rs117601636	11	2620807	*KCNQ1*	ncRNA exonic	A/G	0.085	0.093	100.00%	0.790	0.90(0.67-1.23)	0.520
rs231362	11	2670241	*KCNQ1*	ncRNA exonic	C/T	0.135	0.126	100.00%	0.685	1.08(0.84-1.40)	0.546
rs231356	11	2684113	*KCNQ1*	ncRNA exonic	A/T	0.216	0.224	99.90%	0.307	0.96(0.78-1.18)	0.682
rs8181588	11	2810311	*KCNQ1*	intronic	C/T	0.349	0.390	99.80%	0.851	0.84(0.70-1.01)	0.061
rs163177	11	2817183	*KCNQ1*	intronic	C/T	0.510	0.463	99.70%	0.788	1.21(1.01-1.44)	0.036*
rs163184	11	2825839	*KCNQ1*	intronic	G/T	0.493	0.453	99.50%	0.527	1.18(0.99-1.40)	0.071
rs2283228	11	2828300	*KCNQ1*	intronic	A/C	0.311	0.368	99.60%	0.632	0.78(0.65-0.93)	0.007*
rs2237895	11	2835964	*KCNQ1*	intronic	A/C	0.381	0.338	99.60%	0.319	1.20(1.00-1.44)	0.046*

SNP, single nucleotide polymorphism; Alleles A/B, Minor/Major alleles; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium;

p values were calculated with Pearson's χ 2 tests;

* $p \leq 0.05$ indicates statistical significance.

Table 3 Relationship between *KCNQ1* gene polymorphisms and risk of T2DM under multiple models of inheritance

SNP	Model	Genotype	control	case	Without adjustment		With adjustment	
					OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
rs163177	Codominant	T/T	143(28.4%)	106(20.9%)	1.00		1.00	
		T/C	254(50.5%)	285(56.2%)	1.51(1.12-2.05)	0.007*	1.52(1.12-2.05)	0.007*
		C/C	106(21.1%)	116(22.9%)	1.48(1.03-2.12)	0.036*	1.48(1.03-2.13)	0.035*
	Dominant	T/T	143(28.4%)	106(20.9%)	1.00	0.006*	1.00	0.006*
		C/C-T/C	360(71.6%)	401(79.1%)	1.5(1.13-2.01)		1.51(1.13-2.01)	
	Recessive	T/C-T/T	397(78.9%)	391(77.1%)	1.00	0.488	1.00	0.488
		C/C	106(21.1%)	116(22.9%)	1.11(0.82-1.5)		1.11(0.82-1.50)	
	Log-additive	---	---	---	1.22(1.02-1.47)	0.030*	1.22(1.02-1.47)	0.030*
rs163184	Co-dominant	T/T	153(30.7%)	128(25.1%)	1.00		1.00	
		G/T	240(48.1%)	260(51.1%)	1.3(0.97-1.74)	0.084	1.3(0.97-1.74)	0.082
		G/G	106(21.2%)	121(23.8%)	1.36(0.96-1.94)	0.083	1.37(0.96-1.95)	0.079
	Dominant	T/T	153(30.7%)	128(25.1%)	1.00	0.051	1.00	0.049*
		T/G-G/G	346(69.3%)	381(74.9%0	1.32(1.00-1.74)		1.32(1.00-1.74)	
	Recessive	T/T-T/G	393(78.8%)	388(76.2%)	1.00	0.337	1.00	0.329
		G/G	106(21.2%)	121(23.8%)	1.16(0.86-1.56)		1.16(0.86-1.56)	
	Log-additive	---	---	---	1.18(0.99-1.4)	0.072	1.18(0.99-1.40)	0.068
rs2283228	Co-dominant	C/C	197(39.4%)	239(47.0%)	1.00		1.00	
		A/C	238(47.6%)	223(43.8%)	0.77(0.59-1.00)	0.054	0.77(0.59-1.01)	0.055
		A/A	65(13.0%)	47(9.2%)	0.60(0.39-0.91)	0.016*	0.60(0.39-0.91)	0.016*
	Dominant	C/C	197(39.4%)	239(47.0%)	1.00	0.016*	1.00	0.016*
		A/C-A/A	303(60.6%)	270(53.0%)	0.73(0.57-0.94)		0.74(0.57-0.94)	
	Recessive	C/C-A/C	435(87.0%)	462(90.8%)	1.00	0.058	1.00	0.058
		A/A	65(13.0%)	47(9.2%)	0.68(0.46-1.01)		0.68(0.46-1.01)	
	Log-additive	---	---	---	0.77(0.64-0.93)	0.007*	0.77(0.64-0.93)	0.007*
rs2237895	Co-dominant	C/C	214(42.7%)	193(38.0%)	1.00		1.00	
		A/C	235(46.9%	243(47.8%)	1.15(0.88-1.49)	0.311	1.15(0.88-1.50)	0.309
		A/A	52(10.2%)	72(34.6%)	1.54(1.02-2.31)	0.039*	1.53(1.02-2.30)	0.039*
	Dominant	C/C	214(42.7%)	193(38.0%)	1.00	0.127	1.00	0.126
		A/C-A/A	287(57.3%)	315(62.0%)	1.22(0.95-1.57)		1.22(0.95-1.57)	
	Recessive	C/C-A/C	449(89.8%)	436(65.4%)	1.00	0.067	1.00	0.068
		A/A	52(10.2%)	72(34.6%)	1.43(0.97-2.09)		1.42(0.97-2.08)	
	Log-additive	---	---	---	1.21(1.01-1.46)	0.044*	1.21(1.01-1.46)	0.044*

ORs, odds ratios; 95% CI, 95% confidence interval;

p values were calculated with Pearson's χ 2 tests;

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 4 Relationship of *KCNQ1* gene polymorphisms and risk of T2DM stratified by gender and age (adjusted by sex, age)

SNP	Model	Genotype	Age (years)				Gender			
			Age (years) ≤ 59		Age (years) > 59		Male		Female	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs8181588	Co-dominant	T/T	1.00		1.00		1.00		1.00	
		T/C	0.83(0.57-1.22)	0.344	0.9(0.61-1.32)	0.573	0.95(0.66-1.35)	0.759	0.74(0.50-1.10)	0.133
		C/C	0.91(0.51-1.64)	0.762	0.6(0.34-1.04)	0.067	0.68(0.41-1.15)	0.150	0.72(0.40-1.32)	0.292
	Dominant	T/T	1.00	0.49	1.00	0.268	1.00	0.446	1.00	0.111
		C/C-T/C	0.87(0.60-1.28)		0.81(0.57-1.17)		0.88(0.62-1.23)		0.74(0.50-1.07)	
	Recessive	T/C-T/T	1.00	0.865	1.00	0.081	1.00	0.154	1.00	0.59
		C/C	0.95(0.54-1.69)		0.63(0.38-1.06)		0.70(0.43-1.14)		0.86(0.49-1.50)	
	Log-additive	---	0.92(0.69-1.22)	0.554	0.8(0.62-1.04)	0.093	0.86(0.67-1.09)	0.206	0.82(0.62-1.08)	0.153
	Allele	T	1.00	0.532	1.00	0.046*	1.00	0.203	1.00	0.160
		C	0.92(0.71-1.20)		0.78(0.60-1.00)		0.85(0.67-1.09)		0.82(0.63-1.08)	
rs163177	Codominant	T/T	1.00		1.00		1.00		1.00	
		T/C	1.74(1.13-2.69)	0.012*	1.26(0.81-1.96)	0.297	1.56(1.03-2.35)	0.035	1.46(0.93-2.28)	0.101
		C/C	1.63(0.96-2.74)	0.068	1.23(0.72-2.08)	0.446	1.25(0.76-2.04)	0.381	1.81(1.05-3.13)	0.033*
	Dominant	T/T	1.00	0.022*	1.00	0.292		0.06		0.045*
		C/C-T/C	1.65(1.08-2.54)		1.25(0.82-1.90)		1.46(0.98-2.16)		1.55(1.01-2.38)	
	Recessive	T/C-T/T	1.00	0.740	1.00	0.846	1.00	0.679	1.00	0.140
		C/C	1.08(0.69-1.69)		1.04(0.68-1.60)		0.92(0.62-1.37)		1.41(0.89-2.21)	
	Log-additive	---	1.26(0.96-1.65)	0.098	1.11(0.85-1.45)	0.434	1.12(0.88-1.44)	0.350	1.35(1.03-1.77)	0.030*
	Allele	T	1.00	0.059	1.00	0.296	1.00	0.370	1.00	0.038*
		C	1.28(0.99-1.64)		1.14(0.89-1.45)		1.11(0.88-1.41)		1.32(1.02-1.71)	
rs2283228	Co-dominant	C/C	1.00		1.00		1.00		1.00	
		A/C	0.75(0.52-1.10)	0.141	0.77(0.53-1.12)	0.174	0.87(0.61-1.23)	0.423	0.67(0.45-0.99)	0.045*
		A/A	0.7(0.37-1.31)	0.259	0.57(0.32-1.02)	0.059	0.56(0.31-0.98)	0.044*	0.66(0.35-1.23)	0.187
	Dominant	C/C	1.00	0.149	1.00	0.073	1.00	0.185	1.00	0.033*
		A/C-A/A	0.76(0.52-1.11)		0.72(0.5-1.03)		0.8(0.57-1.12)		0.67(0.46-0.97)	
	Recessive	C/C-A/C	1.00	0.381	1.00	0.127	1.00	0.064	1.00	0.468
		A/A	0.76(0.40-1.42)		0.65(0.37-1.13)		0.6(0.35-1.03)		0.8(0.45-1.45)	
	Log-additive	---	0.8(0.60-1.07)	0.131	0.76(0.58-0.99)	0.041*	0.78(0.61-1.01)	0.060	0.76(0.58-1.01)	0.054
	Allele	C	1.00	0.133	1.00	0.024*	1.00	0.064	1.00	0.054
		A	0.81(0.62-1.07)		0.74(0.58-0.96)		0.79(0.62-1.01)		0.76(0.58-1.01)	
rs2237895	Co-dominant	C/C	1.00							
		A/C	1.19(0.81-1.74)	0.378	1.07(0.73-1.57)	0.731	1.24(0.72-2.15)	0.441	1.25(0.84-1.86)	0.270
		A/A	1.46(0.81-2.63)	0.209	1.61(0.9-2.86)	0.109	1.07(0.75-1.53)	0.695	2.04(1.11-3.76)	0.023*
	Dominant	C/C	1.00	0.501	1.00	0.413	1.00	0.564	1.00	0.091
		A/C-A/A	1.14(0.78-1.66)		1.16(0.81-1.67)		1.11(0.79-1.55)		1.38(0.95-2.02)	
	Recessive	C/C-A/C	1.00	0.486	1.00	0.113	1.00	0.500	1.00	0.043*
		A/A	1.23(0.69-2.19)		1.55(0.90-2.65)		1.19(0.71-1.99)		1.81(1.02-3.21)	
	Log-additive	---	1.13(0.85-1.49)	0.404	1.21(0.93-1.57)	0.166	1.10(0.86-1.42)	0.45	1.37(1.04-1.81)	0.026*
	Allele	C	1.00	0.183	1.00	0.129	1.00	0.464	1.00	0.028*
		A	1.2(0.92-1.56)		1.22(0.95-1.56)		1.1(0.86-1.40)		1.36(1.03-1.78)	

ORs, odds ratios; 95% CI, 95% confidence interval;

p values were calculated by unconditional logistic regression analysis with adjustments for age;

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 5 Relationship of *KCNQ1* gene polymorphisms and risk of T2DM stratified by smoking and drinking (adjusted by sex, age)

SNP	Model	Genotype	smokers		nondrinkers		drinkers		without drinking history	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs231362	Co-dominant	T/T	1.00		1.00		1.00		1.00	
		T/C	0.73(0.33-1.57)	0.416	1.76(1.05-2.98)	0.034*	0.52(0.04-6.03)	0.599	2.01(1.20-3.35)	0.008*
		C/C	0.89(0.11-7.33)	0.912	3.20(0.35-29.56)	0.305	0.31(0.12-0.83)	0.020*	3.63(0.40-32.74)	0.251
	Dominant	T/T	1.00	0.427	1.00	0.023*	1.00	0.019*	1.00	0.005*
		C/C-T/C	0.74(0.35-1.56)		1.81(1.08-3.04)		0.33(0.13-0.83)		2.06(1.25-3.42)	
	Recessive	T/C-T/T	1.00	0.969	1.00	0.367	1.00	0.734	1	0.314
		C/C	0.96(0.12-7.87)		2.79(0.30-25.93)		0.65(0.06-7.57)		3.11(0.34-28.20)	
	Log-additive	---	0.79(0.41-1.52)	0.481	1.77(1.09-2.87)	0.021*	0.40(0.18-0.93)	0.033*	1.99(1.24-3.20)	0.005*
	Allele	T	1.00	0.719	1.00	0.081	1.00	0.084	1.00	0.032*
		C	1.10(0.65-1.85)		1.42(0.96-2.11)		0.55(0.28-1.09)		1.53(1.04-2.25)	
rs231356	Co-dominant	T/T	1.00		1.00		1.00		1.00	
		T/A	0.91(0.45-1.86)	0.795	1.05(0.67-1.63)	0.849	0.39(0.17-0.89)	0.024*	1.27(0.82-1.97)	0.279
		A/A	0.92(0.21-3.99)	0.913	2.35(0.72-7.63)	0.157	0.40(0.07-2.27)	0.301	2.79(0.87-8.93)	0.084
	Dominant	T/T	1.00	0.789	1.00	0.572	1.00	0.018*	1.00	0.136
		A/A-T/A	0.91(0.46-1.8)		1.13(0.73-1.75)		0.39(0.18-0.85)		1.38(0.90-2.11)	
	Recessive	T/A-T/T	1.00	0.950	1.00	0.161	1.00	0.503	1.00	0.110
		A/A	0.95(0.23-4.04)		2.31(0.72-7.43)		0.56(0.10-3.08)		2.56(0.81-8.12)	
	Log-additive	---	0.93(0.54-1.63)	0.809	1.21(0.83-1.74)	0.324	0.48(0.25-0.93)	0.030*	1.41(0.98-2.02)	0.066
	Allele	T	1.00	0.588	1.00	0.753	1.00	0.068	1.00	0.297
		A	1.12(0.74-1.72)		1.05(0.76-1.46)		0.61(0.36-1.04)		1.19(0.86-1.63)	
rs2283228	Co-dominant	C/C	1		1.00		1.00		1.00	
		A/C	0.60(0.3-1.23)	0.162	0.83(0.54-1.30)	0.418	0.65(0.31-1.36)	0.25	0.79(0.51-1.22)	0.289
		A/A	1.03(0.31-3.4)	0.963	0.58(0.27-1.22)	0.150	0.44(0.08-2.51)	0.359	0.72(0.36-1.42)	0.340
	Dominant	C/C	1.00	0.233	1.00	0.244	1.00	0.201	1.00	0.224
		A/C-A/A	0.66(0.33-1.31)		0.78(0.51-1.18)		0.62(0.30-1.29)		0.78(0.51-1.17)	
	Recessive	C/C-A/C	1.00	0.602	1.00	0.204	1.00	0.494	1.00	0.505
		A/A	1.35(0.44-4.16)		0.63(0.31-1.29)		0.55(0.10-3.01)		0.80(0.42-1.54)	
	Log-additive	---	0.84(0.50-1.40)	0.506	0.79(0.57-1.09)	0.145	0.65(0.35-1.22)	0.182	0.83(0.61-1.12)	0.223
	Allele	C	1.00	0.868	1.00	0.043*	1.00	0.260	1.00	0.157
		A	0.97(0.67-1.40)		0.74(0.55-0.99)		0.77(0.48-1.22)		0.82(0.61-1.08)	

ORs, odds ratios; 95% CI, 95% confidence interval;

p values were calculated by unconditional logistic regression analysis with adjustments for age;

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 6 Relationship of *KCNQ1* gene polymorphisms and risk of T2DM stratified by BIM (adjusted by sex, age)

SNP	Model	Genotype	BMI < 24				BMI ≥ 24			
			control	case	OR (95% CI)	*p-value*	control	case	OR (95% CI)	*p-value*
rs231362	Co-dominant	T/T	142(82.1%)	92(70.8%)	1.00		137(74.1%)	136(72.7%)	1.00	
		T/C	28(16.2%)	36(27.7%)	1.82(0.97-3.43)	0.063	44(23.8%)	47(25.2%)	0.91(0.51-1.61)	0.747
		C/C	3(1.7%)	2(1.5%)	1.36(0.19-10)	0.760	4(2.2%)	4(2.1%)	2.84(0.28-28.71)	0.377
	Dominant	T/T	142(82.1%)	92(70.8%)	1.00	0.064	137(74.1%)	136(72.7%)	1.00	0.904
		C/C-T/C	31(17.9%)	38(29.2%)	1.79(0.97-3.29)		48(25.9%)	51(27.3%)	0.97(0.55-1.69)	
	Recessive	T/C-T/T	170(98.3%)	128(98.5%)	1.00	0.857	181(97.8%)	183(97.9%0	1.00	0.891
		C/C	3(1.7%)	2(1.5%)	1.2(0.16-8.76)		4(2.2%)	4(2.1%)	1.04(0.62-1.73)	
	Log-additive	---	---	---	1.62(0.93-2.82)	0.087	---	---	2.91(0.29-29.28)	0.364
	Allele	T	148(86.0%)	148(86.0%)	1.00	0.039*	318(85.6%)	319(85.3%0	1.00	0.800
		C	24(14.0%)	24(14.0%)	1.67(1.02-2.72)		52(14.1%)	55(14.7%)	1.05(0.7-1.59)	
rs163177	Codominant	T/T	47(27.2%0	20(15.4%)	1.00		51(27.6%)	47(25.3%)	1.00	
		T/C	86(49.7%)	72(655.4%)	1.81(0.92-3.57)	0.087	94(20.8%)	99(53.8%)	0.75(0.40-1.39)	0.358
		C/C	40(23.1%)	38(29.2%)	2.27(1.05-4.90)	0.037*	40(21.6%)	40(21.5%)	0.85(0.40-1.82)	0.682
	Dominant	T/T	47(27.2%0	20(15.4%)	1.00	0.043*	51(27.6%)	47(25.3%)	1.00	0.403
		C/C-T/C	126(72.8%)	110(84.6%0	1.95(1.02-3.73)		145	146	0.78(0.43-1.41)	
	Recessive	T/C-T/T	133(76.9%)	92(70.8%)	1.00	0.194	145(48.4%)	146(79.1%)	1.00	0.877
		C/C	40(23.1%)	38(29.2%)	1.48(0.82-2.65)		40(21.6%)	40(21.5%)	1.05(0.57-1.94)	
	Log-additive	---	---	---	1.49(1.01-2.18)	0.042*	---	---	0.92(0.63-1.34)	0.662
	Allele	T	180(52.0%)	112(43.1)	1	0.029*	196(53.0%)	193(51.9%)	1.00	0.766
		C	166(48.0%0	148(56.9%)	1.43(1.04-1.98)		174(47.0%)	179(48.1%)	1.05(0.78-1.39)	
rs163184	Co-dominant	T/T	54(31.8%)	26(20.0%)	1.00		51(27.7%)	51(27.3%)	1.00	
		G/T	77(45.3%)	68(52.3%)	1.92(1.02-3.65)	0.045*	92(50.0%)	96(51.3%)	0.76(0.41-1.41)	0.378
		G/G	39(22.9%)	36(27.7%)	2.07(1.00-4.27)	0.049*	41(22.3%)	40(21.4%)	0.81(0.39-1.71)	0.584
	Dominant	T/T	54(31.8%)	26(20.0%)	1.00	0.026*	51(27.7%)	51(27.3%)	1.00	0.392
		T/G-G/G	116(68.2%)	104(80.0%)	1.97(1.09-3.59)		133(72.3%)	136(72.7%)	0.77(0.43-1.40)	
	Recessive	T/T-T/G	131(12.9%)	94(72.3%)	1.00	0.313	143(77.7%0	147(78.6%)	1.00	0.961
		G/G	39(22.9%)	36(27.7%)	1.36(0.75-2.45)		41(22.3%)	40(21.4%)	0.98(0.54-1.81)	
	Log-additive	---	---	---	1.44(1.00-2.07)	0.049*	---	---	0.9(0.62-1.30)	0.567
	Allele	T	185(54.4%)	120(46.2%0		0.045*	194(52.7%)	198(52.9%)		0.951
		G	155(45.6%0	140(53.8%)	1.39(1.01-1.93)		174(47.3%)	176(47.1%)	0.99(0.74-1.32)	
rs2283228	Co-dominant	C/C	66(38.4%)	66(51.2)	1.00		81(44.0%)	92(49.2%)	1.00	
		A/C	82(47.6%)	51(39.5%)	0.69(0.40-1.21)	0.194	84(45.7%)	77(41.2%0	0.83(0.49-1.38)	0.467
		A/A	24(14.0%)	12(9.3%)	0.43(0.18-1.02)	0.056	19(10.3%)	18(9.6%)	1.31(0.47-3.68)	0.609
	Dominant	C/C	66(38.4%)	66(51.2)	1.00	0.080	81(44.0%)	92(49.2%)	1.00	0.614
		A/C-A/A	106(61.6%)	63(48.8%)	0.63(0.37-1.06)		103(56%)	95(50.8%)	0.88(0.54-1.45)	
	Recessive	C/C-A/C	148(86.0%)	117(90.7%)	1.00	0.112	165(89.7%)	169(90.4%)	1.00	0.483
		A/A	24(14.0%)	12(9.3%)	0.51(0.22-1.17)		19(10.3%)	18(9.6%)	1.43(0.53-3.91)	
	Log-additive	---	---	---	0.67(0.45-0.98)	0.041*	---	---	0.98(0.66-1.45)	0.913
	Allele	C	214(62.2%)	183(70.9%)	1.00	0.025*	246(66.8%)	261(69.8%)	1.00	0.390
		A	130(37.8%)	75(29.1%0	0.67(0.48-0.95)		122(33.2%)	113(30.2%)	0.87(0.64-1.19)	

ORs, odds ratios; 95% CI, 95% confidence interval; BMI, body mass index;

p values were calculated by unconditional logistic regression analysis with adjustments for age;

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 7 The relationship between *KCNQ1* genotype and clinical indicators of T2DM

SNP	Genotype	Total cholesterol	Triglycerides	LDL	HDL	ALBP	INS	UCRP	TJCTNT
rs117601636	AA	4.57±1.34	2.6±2.37	2.65±1.05	1.67±8.42	41.24±132.36	19.29±19.75	0.58±1.37	0.01±0.01
	GA	4.27±0.97	2.01±1.63	2.42±0.82	1.18±0.35	14.41±19.65	16.53±11.09	0.36±0.66	0.01±0
	GG	5.79±3.05	2.28±1.84	3.61±2.33	1.34±0.51	5.32±2.27	13.78±13.38	0.48±0.63	0.01±0
	p	0.036*	0.224	0.043*	0.895	0.432	0.585	0.527	0.271
rs231362	GG	4.56±1.35	2.6±2.38	2.62±1.04	1.19±0.58	43.26±140.4	19.28±19.35	0.58±1.39	0.01±0.01
	AG	4.46±1.24	2.25±1.99	2.65±1.08	2.64±14.68	17.99±28.82	18.03±17.19	0.35±0.6	0.01±0
	AA	4.54±1.26	2.14±1.31	2.52±0.94	1.2±0.32	35.99±59.34	10.83±3.62	1.84±2.79	0.02±0.03
	p	0.813	0.438	0.53	0.249	0.37	0.558	0.015*	0.001*
rs231356	TT	4.57±1.37	2.74±2.55	2.61±1.01	1.2±0.65	47.4±151.48	19.59±20.18	0.52±1.13	0.01±0.01
	AT	4.48±1.28	2.2±1.81	2.65±1.14	2.3±12.98	19.02±29.39	18.93±16.7	0.54±1.41	0.01±0.01
	AA	4.38±0.93	1.75±0.87	2.5±0.7	1.25±0.3	20.87±37.59	9.49±5.92	0.82±1.82	0.01±0.02
	p	0.685	0.052	0.802	0.406	0.206	0.116	0.664	0.472
rs8181588	TT	4.45±1.26	2.32±2.16	2.55±0.9	1.24±0.59	23.53±53.5	18.02±20.72	0.51±1.41	0.01±0.01
	CT	4.55±1.3	2.41±1.89	2.67±1.14	1.16±0.44	39.25±96.25	18.49±15.72	0.6±1.23	0.01±0
	CC	4.83±1.61	3.76±3.64	2.68±1.16	4.81±23.44	89.42±305.03	23.76±20.58	0.44±0.67	0.01±0.01
	p	0.226	0.006*	0.547	0.015*	0.040*	0.317	0.746	0.871
rs163177	TT	4.53±1.32	2.91±2.59	2.54±0.81	1.27±0.77	39.49±70.33	23.77±24.17	0.75±1.36	0.01±0
	CT	4.54±1.36	2.6±2.35	2.65±1.18	1.84±10.21	45.72±159.06	16.65±12.19	0.5±1.34	0.01±0.01
	CC	4.55±1.21	1.96±1.65	2.61±0.85	1.25±0.36	14.82±16.42	19.32±23.74	0.47±1.06	0.01±0.01
	p	0.993	0.038*	0.692	0.756	0.261	0.039*	0.384	0.411
rs163184	TT	4.51±1.38	2.88±2.7	2.47±0.85	2.82±15.42	41.16±68.58	21.56±22.5	0.77±1.51	0.01±0
	GT	4.52±1.34	2.57±2.28	2.68±1.19	1.15±0.58	45.57±161.67	16.81±12.79	0.47±1.25	0.01±0.01
	GG	4.59±1.22	1.99±1.65	2.63±0.85	1.26±0.36	13.63±14.09	20.25±23.98	0.47±1.06	0.01±0.01
	p	0.897	0.051	0.264	0.188	0.233	0.165	0.243	0.185
rs2283228	CC	4.67±1.29	3.17±2.9	2.61±0.69	5.79±26.86	27.66±35.16	25.41±20.86	0.54±0.73	0.01±0.01
	CA	4.53±1.4	2.59±2.39	2.62±1.2	1.19±0.63	54.34±179.24	17.51±15.08	0.59±1.28	0.01±0
	AA	4.51±1.24	2.32±2.04	2.6±0.92	1.23±0.56	24.71±54.92	18.82±20.72	0.51±1.35	0.01±0.01
	p	0.811	0.198	0.987	0.005*	0.169	0.169	0.89	0.784
rs2237895	CC	4.51±1.36	2.23±2.09	2.53±0.84	1.23±0.41	16.24±17.57	21.84±28.94	0.51±0.96	0.01±0.01
	CA	4.63±1.32	2.58±2.41	2.75±1.21	1.99±11.12	46.35±171.08	18.23±14.55	0.47±1.38	0.01±0.01
	AA	4.4±1.28	2.51±2.15	2.47±0.83	1.21±0.61	34.99±64.33	18.56±18.2	0.65±1.26	0.01±0.01
	p	0.296	0.662	0.038*	0.6	0.405	0.539	0.542	0.848

HDL-C, high-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; ALBP, Adipocyte Lipid-binding Protein;

Data are presented as means SD or percentages;

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 8 Meta-analysis of the rs2237895 polymorphism and T2DM risk

Model	Genotype	Subgroup	Total	East Asian	South Asian	Caucasian	Other
Allele model	A vs. C	OR(95% CI)	1.25(1.07-1.47)	1.26(1.03-1.53)	1.76(0.97-3.22)	0.97(0.74-1.26)	1.06(0.90-1.26)
		p [a]	0.000	0.000	0.000	0.025	0.636
		p	0.001*	0.009*	0.058	0.773	0.832
		Effect model	Random	Random	Random	Random	Random
Dominant model	AA/AC vs. CC	OR(95% CI)	0.92(0.81-1.06)	0.94(0.79-1.12)	0.6(0.34-1.05)	1.05(0.63-1.77)	1.18(0.86-1.61)
		p [a]	0.000	0.000	0.000	0.120	0.796
		p	0.005*	0.025*	0.064	0.811	0.476
		Effect model	Random	Random	Random	Random	Random
Recessive model	AA vs. AC/CC	OR(95% CI)	1.08(0.95-1.24)	1.06(0.89-1.26)	1.68(0.95-2.97)	0.95(0.56-1.60)	0.91(0.72-1.24)
		p [a]	0.000	0.000	0.007	0.031	0.51
		p	0.247	0.483	0.074	0.850	0.422
		Effect model	Random	Random	Random	Random	Random
Homozygote	AA vs. CC	OR(95% CI)	1.23(1.06-1.42)	1.23(1.02-1.47)	2.12(1.00-4.47)	0.91(0.49-1.69)	0.96(0.74-1.23)
		p [a]	0.000	0.000	0.001	0.020	0.522
		p	0.006*	0.028*	0.050	0.773	0.724
		Effect model	Random	Random	Random	Random	Random
Heterogeneity	AC vs. CC	OR(95% CI)	1.24(1.05-1.32)	1.26(1.02-1.55)	1.52(0.96-2.39)	1.01(0.92-1.10)	1.10(0.92-1.32)
		p [a]	0.000	0.000	0.015	0.382	0.927
		p	0.012*	0.035*	0.072	0.879	0.299
		Effect model	Random	Random	Random	Random	Random

p[a] values obtained from chi-square tests for heterogeneity

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Table 9 Meta-analysis of the rs2283228 polymorphism and T2DM risk

Model	Model	Subgroup	Total	East Asian	South Asian	North Africa
Allele model	A vs. C	OR(95% CI)	0.83(0.77-0.89)	0.82(0.78-0.86)	1.19(0.29-4.86)	0.88(0.62-1.24)
		p [a]	0.000	0.101	0.000	.
		p	0.000*	0.000*	0.810	0.469
		Effect model	Random	Random	Random	Random
Dominant model	AA/AC vs. CC	OR(95% CI)	0.81(0.73-0.9)	0.79(0.74-0.86)	1.10(0.2-6.12)	0.9(0.63-1.29)
		p [a]	0.000	0.048	0.000	.
		p	0.000*	0.000*	0.915	0.573
		Effect model	Random	Random	Random	Random
Recessive model	AA vs. AC/CC	OR(95% CI)	0.74(0.67-0.81)	0.73(0.66-0.81)	0.88(0.41-1.9)	0.43(0.07-2.58)
		p [a]	0.271	0.177	0.276	.
		p	0.000*	0.000*	0.747	0.355
		Effect model	Random	Random	Random	Random
Homozygote	AA vs. CC	OR(95% CI)	0.66(0.6-0.74)	0.67(0.6-0.75)	0.87(0.22-3.45)	0.43(0.07-2.56)
		p [a]	0.194	0.156	0.115	.
		p	0.000*	0.000*	0.841	0.351
		Effect model	Random	Random	Random	Random
Heterogeneity	AC vs. CC	OR(95% CI)	0.85(0.76-0.95)	0.84(0.76-0.91)	1.09(0.19-6.38)	0.93(0.64-1.34)
		p [a]	0.000	0.011	0.000	.
		p	0.006*	0.000*	0.923	0.692
		Effect model	Random	Random	Random	Random

p^a values obtained from chi-square tests for heterogeneity

*p value < 0.05 indicates statistical significance ($p < 0.05$).

Figures

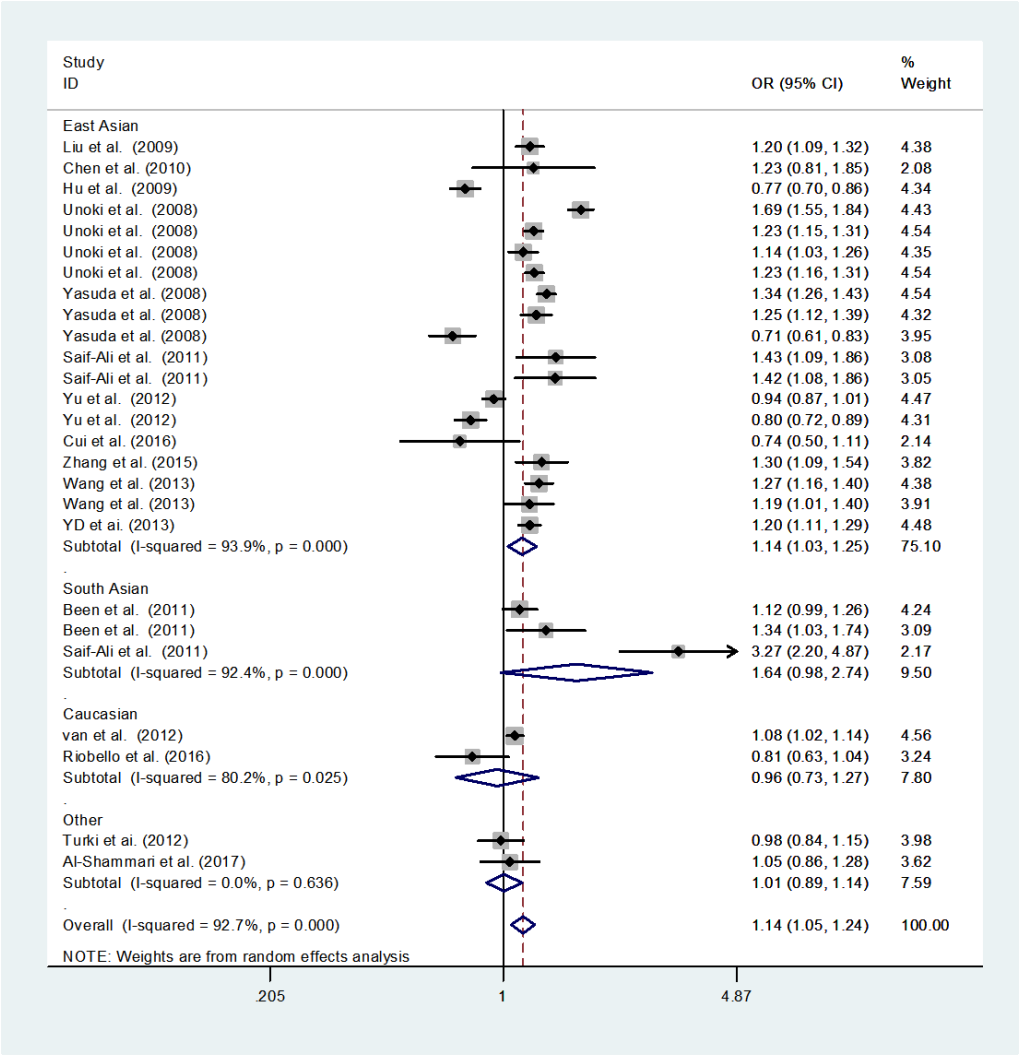

Figure 1

Forest plot of rs2237895 polymorphism and the risk of T2DM under the allele model (a vs c).

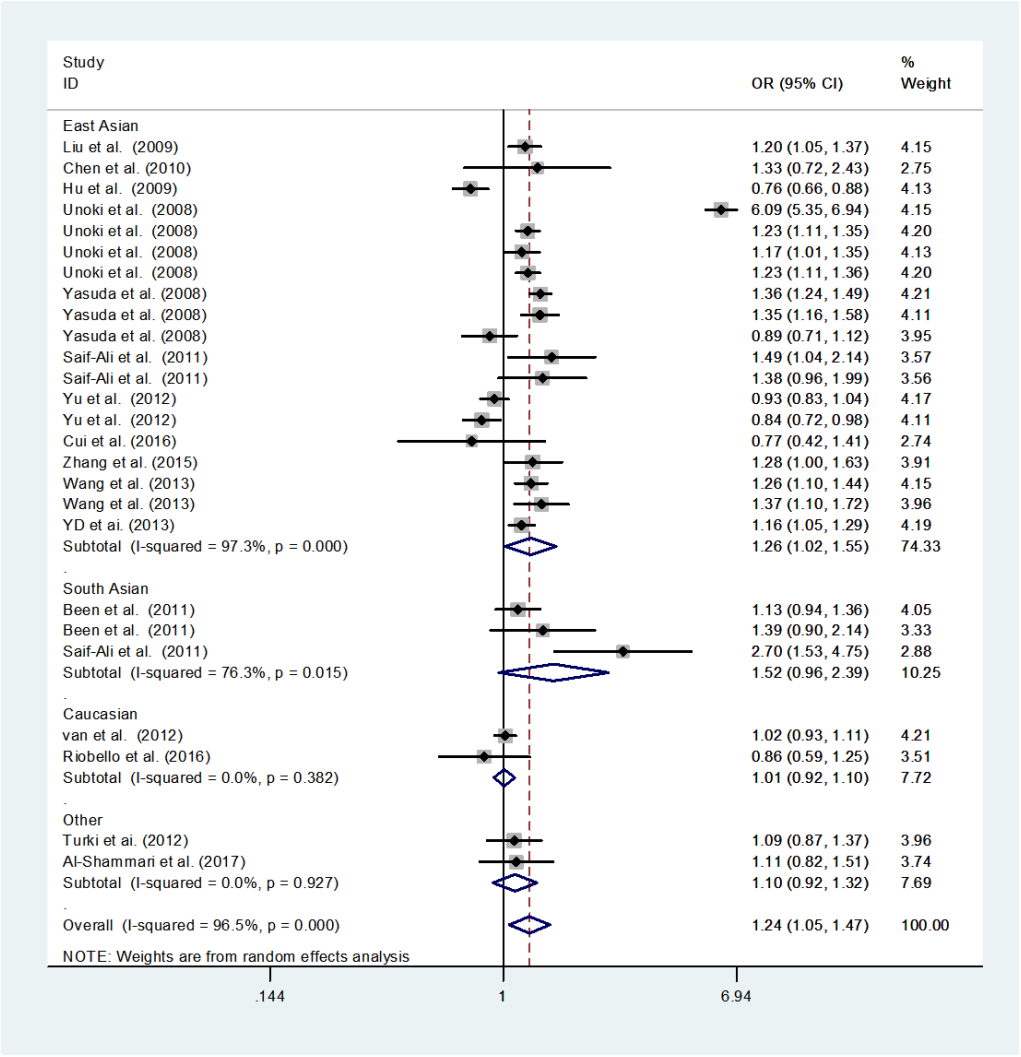

Figure 2

Forest plot of rs2283228 polymorphism and the risk of T2DM under the allele model (a vs c).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx