



Association of the rs11196218 polymorphism in *TCF7L2* with type 2 diabetes mellitus in Asian population



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ABSTRACT

Objective: To clarify the association of rs11196218 polymorphism in transcription factor 7-like 2 (*TCF7L2*) and type 2 diabetes mellitus (T2DM) in Asian population by a case–control study and meta-analysis.

Methods: In the case–control study, 1842 patients with T2DM and 7777 normal glucose-tolerant controls in the Henan province of China were genotyped for rs11196218 in *TCF7L2* by PCR–ligase detection reaction. We used allele, co-dominant, dominant and recessive models to evaluate the risk association and performed a meta-analysis of the results of different genetic models in previous studies and the current study.

Abbreviations: *TCF7L2*, factor 7-like 2 gene; T2DM, type 2 diabetes mellitus; SNP, single nucleotide polymorphism; PCR–LDR, polymerase chain reaction–ligase detection reaction; OR, odds ratio; 95% CI, 95% confidence interval; PARP, population-attributable risk proportion; MAF, minor allele frequency.

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Results: The AG genotype of rs11196218 was associated with risk of T2DM in the Henan population (odds ratio 1.37, 95% confidence interval 1.06–1.78), and dominant model showed marginal significant association (1.28, 0.99–1.67). Meta-analysis of 10 studies revealed the dominant model associated with T2DM in the overall population (1.20, 1.05–1.36). When stratified by region (southern and northern China and Japan), both the AG genotype and the dominant model were associated with risk of T2DM in southern Chinese (1.31, 1.03–1.66; 1.27, 1.01–1.60, respectively).

Conclusion: The rs11196218 polymorphism in *TCF7L2* is associated with risk of T2DM in Asian population.

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Introduction

The transcription factor 7-like 2 gene (*TCF7L2*) is one of the genes associated with type 2 diabetes mellitus (T2DM) (Grant et al., 2006; Guinan, 2012). In 2007, rs11196218 single nucleotide polymorphism (SNP) in *TCF7L2* was first found associated with T2DM in Hong Kong Chinese (Ng et al., 2007). Following the initial report, there have been several association studies in different groups (Lin et al., 2010; Luo et al., 2009; Ma et al., 2009; Miyake et al., 2012; Qiao et al., 2012; Zhang, 2008; Zheng et al., 2012; Zhu, 2011). However, all of these replication studies were carried out in Asian populations, and most of them focused on Chinese (Lin et al., 2010; Luo et al., 2009; Ma et al., 2009; Qiao et al., 2012; Zhang, 2008; Zheng et al., 2012; Zhu, 2011), especially southern Chinese (Lin et al., 2010; Ma et al., 2009; Zhang, 2008; Zheng et al., 2012; Zhu, 2011), except for one Japanese study (Miyake et al., 2012). Although all participants were Asians, the results were confusing rather than conclusive, and showed strong regional variations. Some studies suggested that this SNP was associated with T2DM (Ng et al., 2007; Zhu, 2011) while the others reported contradictory results (Lin et al., 2010; Ma et al., 2009; Zhang, 2008; Zheng et al., 2012). This apparent difference among Asian populations may be due to regional variation or the relatively small sample sizes studied. Two previous meta-analyses had systematically reviewed the association of rs11196218 SNP and risk of T2DM, but one included only 3 studies (Luo et al., 2009) and the other focused on only Chinese studies (Wang et al., 2013); neither comprehensively reviewed the association of this SNP and T2DM in Asians.

In the present study, we evaluated the association of rs11196218 polymorphism and T2DM in the Han population in Henan Province in northern China, using a relatively large sample (1842 Chinese individuals with T2DM and 7777 normal glucose-tolerant controls). Then, we combined our data with those of all published studies for a meta-analysis to clarify the association of rs11196218 polymorphism in *TCF7L2* and risk of T2DM in Asians.

Materials and methods

Study design

A case–control study design was used to evaluate the association of rs11196218 polymorphism in *TCF7L2* and risk of T2DM. The software Sample Size Calculations (Mark Woodward, The George Institute International Health; Lesley Francis, MIS Consultants) was used to calculate the sample size and power. Because the minor allele frequency of rs11196218 is 0.407 in the Chinese population (HapMap-HCB), for an OR of 1.20 for the risk allele, with ratio of controls to cases 4 and two-sided significant level 5%, a total of 8079 participants (1616 cases and 6463 cases) were needed to guarantee 80% statistical power. We conducted a free diabetic screen for the adult residents of two random sampling communities in Henan province, northern China. Those having fasting plasma glucose (FPG) ≥ 7.0 mmol/L or previous diagnosis of T2DM (who was receiving insulin treatment or an oral hypoglycemic agent or presented with a history of diabetes during the interview) were included as cases, while those having FPG < 7.0 mmol/L and no

identifiable positive family history were recruited as controls. In total, 810 cases and 7777 normal glucose-tolerant controls were recruited from community populations. Additionally, we recruited 1032 cases from the outpatient clinics of 3 hospitals in Henan province in order to obtain enough cases. In hospitals, T2DM was diagnosed according to American Diabetes Association (ADA) criterion ([American Diabetes Association, 2005](#)). Participants with body mass index (BMI) ≤ 18.5 kg/m² and who were pregnant, handicapped, mentally disturbed, obese caused by disease or taking certain drugs, and had cancer were excluded. The study was approved by the ethics committee of Zhengzhou University, and informed consent was obtained from each participant before data collection.

Data collection

Demographic characteristics were collected by interviewer-administered questionnaire. Body weight, body height, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. Blood samples were collected for measuring FPG and lipid profile. Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured by use of an automatic biochemical analyzer (Hitachi 7600-020, Tokyo, Japan) with reagents purchased from Ningbo Rui Bio-technology (Ningbo, China). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula ([Friedewald et al., 1972](#)). Central obesity based on WC (WC ≥ 85 cm for men or WC ≥ 80 cm for women) was defined according to the recommended criteria for the Chinese population ([Zhou and Cooperative Meta-Analysis Group of the Working Group on Obesity in China, 2002](#)).

DNA isolation and genotyping

Genomic DNA was extracted from whole blood by use of a blood genome DNA extraction kit (Yaneng BIO, Shenzhen, China). PCR–ligase detection reaction (PCR–LDR) was used for genotyping. The PCR primers for the loci were 5'-AGC CAT TTC AAT TTC GTA CAT-3' (forward) and 5'-AAC ATC AAA CTC CAG AGG GTC-3' (reverse). PCR involved the LabCycler Gradient (SensoQuest GmbH, Göttingen, Germany) in a system with a total volume of 15 μ l, containing 1 μ l genomic DNA, 1.5 μ l 10 \times PCR buffer, 1.5 μ l MgCl₂, 0.25 μ l each primer, 0.3 μ l deoxyribonucleo-tide triphosphate (dNTP), 0.2 μ l Taq DNA polymerase (Qiagen GmbH, Hilden, Germany) and 10 μ l H₂O. The cycling parameters were 94 °C for 2 min; 35 cycles at 94 °C for 15 s, 55 °C for 15 s, 72 °C for 25 s; and a final extension step at 72 °C for 3 min. Probe sequences were 5'-AAC CAA CAT GGC TTG TTT TCA TAA A-3' (A specific), 5'-TTT AAC CAA CAT GGC TTG TTT TCA TAA G-3' (G specific), and 5'-P-CAC CCG AGA AGG TTT AAA TAA CAT T-FAM-3' (for LDR). For each PCR product, the ligation reaction was performed in a final volume of 10 μ l, including 2 μ l PCR product, 1 μ l 10 \times Taq DNA ligase buffer, 0.03 μ l probe mixture, 0.125 μ l Taq DNA ligase (New England Biolabs, Beverly, MA, USA) and 7 μ l H₂O. The LDR parameters were 30 cycles at 94 °C for 30 s and 56 °C for 2 min. The LDR reaction products were analyzed on the ABI 377 DNA sequencer (Applied Biosystems). Genotyping success rates in cases and controls were 97.9% and 98.6%, respectively. To confirm the accuracy of the PCR–LDR genotyping method, 5% samples were randomly selected for direct DNA sequencing. PCR–LDR genotyping showed 100% concordance with direct DNA sequencing of the randomly selected PCR products.

Statistical analysis

Categorical data are shown as number (percentage) and analyzed by chi-square test. Continuous data are shown as median (Q1, Q3) because data were non-normally distributed. Mann–Whitney–Wilcoxon and Kruskal–Wallis rank tests were used to assess differences in continuous data between cases and controls and among different genotypes in controls, respectively. Odds ratios (ORs), 95% confidence intervals (95% CIs) and corresponding *P* values for risk of T2DM were calculated by binary logistic regression analyses. Sex, age, anthropometric measurements (BMI, WC, SBP and DBP), and lipid levels (TC, TG, HDL-C and LDL-C) were covariates. All tests were two-sided and *P* < 0.05 was considered statistically significant. Statistical analysis involved SAS version 9.1 for Windows (SAS Institute Inc., NC, USA).

Meta-analysis

We searched MEDLINE, EMBASE, Cochrane, and Chinese databases (CNKI, CQVIP and Wan-fang Databases) for all articles published in English and Chinese between January 2007 and August 2013 using the keywords “TCF7L2”, “rs11196218”, “genetic polymorphism” and “T2D/T2DM”. The meta-analysis involved use of Review Manager version 5.0 (<http://www.cc-ims.net/RevMan>). Crude ORs with 95% CIs were used to assess the strength of association between rs11196218 polymorphism and T2DM risk. The allele model (G vs. A), the co-dominant model (GG vs. AA; AG vs. AA), the dominant model (GG + AG vs. AA) and the recessive model (GG vs. AG + AA) were used to evaluate the risk. Pearson’s goodness-of-fit chi-square test with 1 degree of freedom was used to assess departure from the Hardy–Weinberg equilibrium (HWE) for the control group in each study. To assess heterogeneity among the studies, Q-test and I^2 statistics were used. The fixed-effects model (the Mantel–Haenszel method) was used to calculate the pooled OR with $I^2 < 50\%$; otherwise, the random-effects model was used. Calculation of population-attributable risk proportion (PARP) was based on the estimated OR and risk genotype frequency of the SNP showing significant association with T2DM. Subgroup analyses were performed by region (southern and northern China and Japan).

Results

Association study of rs11196218 polymorphism and T2DM

Levels of BMI, WC, SBP, DBP, TC, TG, LDL-C were higher and level of HDL-C was lower for T2DM patients than controls (Table 1). Cases and controls differed in genotype distribution ($P = 0.001$) but not allelic distribution ($P = 0.579$). The AG genotype and dominant model of rs11196218 were associated with risk of T2DM (OR = 1.44, 95% CI = 1.14–1.80; OR = 1.32, 95% CI = 1.06–1.65, respectively) (Table 2). However, after adjusting for sex, age, anthropometric measurements, and lipid levels, only the AG genotype remained associated with risk of T2DM (OR = 1.37, 95% CI = 1.06–1.78), dominant model showed marginal significant associated with risk of T2DM (OR = 1.28, 95% CI = 0.99–1.67) (Table 2). The results changed with WC included as a covariant. When stratified by central obesity status, obese diabetics and non-obese controls differed in genotype distribution ($P < 0.001$) but not non-obese diabetics and non-obese controls ($P = 0.637$). The rs11196218 genotypes were not associated with clinical characteristics in controls. The power of this study was 100%.

Table 1
Demographic characteristics of the study participants.

Characteristics	Cases (n = 1842)	Controls (n = 7777)	P value
Male	925 (50.2)	3,214 (41.3)	<0.001
Age (year)	54.00 (45.0, 61.0)	49.00 (40.0, 58.0)	<0.001
BMI (kg/m ²)	27.38 (24.5, 30.7)	23.83 (21.6, 26.2)	<0.001
WC (cm)	90.50 (83.5, 101.3)	81.35 (74.9, 88.5)	<0.001
SBP (mm Hg)	128.33 (120.0, 140.0)	121.33 (110.7, 134.7)	<0.001
DBP (mm Hg)	81.33 (74.0, 90.0)	77.00 (70.7, 85.0)	<0.001
FPG (mmol/L)	7.62 (6.1, 9.9)	5.19 (4.8, 5.5)	<0.001
TC (mmol/L)	4.87 (4.2, 5.6)	4.28 (3.7, 4.9)	<0.001
TG (mmol/L)	1.73 (1.2, 2.6)	1.32 (1.0, 1.9)	<0.001
HDL-C (mmol/L)	1.10 (1.0, 1.3)	1.14 (1.0, 1.3)	<0.001
LDL-C (mmol/L)	2.81 (2.2, 3.4)	2.42 (2.0, 2.9)	<0.001

Data are presented as number (%) or median (Q1, Q3).

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Table 2

Association of rs11196218 polymorphism and type 2 diabetes mellitus (T2DM) in different models.

Genetic models	Cases	Controls	P value	OR (95% CI)	P value*	OR (95% CI)*
Allele model						
A	967 (26.82)	4041 (26.37)	–	1.00	–	–
G	2639 (73.18)	11,287 (73.63)	0.579	0.98 (0.90, 1.06)	–	–
Co-dominant model						
AA	98 (5.44)	540 (7.05)	–	1.00	–	1.00
AG	771 (42.76)	2961 (38.64)	0.002	1.44 (1.14, 1.80)	0.018	1.37 (1.06, 1.78)
GG	934 (51.80)	4163 (54.31)	0.067	1.24 (0.99, 1.55)	0.173	1.20 (0.93, 1.55)
Dominant model						
AA	98 (5.44)	540 (7.05)	–	1.00	–	1.00
AG + GG	1705 (94.56)	7124 (92.95)	0.014	1.32 (1.06, 1.65)	0.060	1.28 (0.99, 1.67)
Recessive model						
AG + AA	869 (48.20)	3501 (45.69)	–	1.00	–	1.00
GG	934 (51.80)	4163 (54.31)	0.054	0.90 (0.82, 1.00)	0.118	0.91 (0.81, 1.02)

Data are presented as number (%).

OR, odds ratio; 95% CI, 95% confidence interval.

* Adjusted by sex, age, BMI, WC, SBP, DBP, TC, TG, HDL-C and LDL-C.

Results of the meta-analysis

We included 9 eligible published articles (Lin et al., 2010; Luo et al., 2009; Ma et al., 2009; Miyake et al., 2012; Ng et al., 2007; Qiao et al., 2012; Zhang, 2008; Zheng et al., 2012; Zhu, 2011) and current study, for 8342 cases and 13,445 controls. Six studies were for southern China, 3 for northern China, and only one study was for Japan. The distributions of genotypes in controls for all studies were in Hardy–Weinberg equilibrium (Table 3). Because of absence of genotype data, ten studies were used for the allele model, with 8 studies for the other genetic models. We found the dominant model of rs11196218 significantly associated with risk of T2DM in the overall population (OR = 1.20, 95% CI = 1.05–1.36) (Fig. 1). The PARP for the dominant model was 15.5%. On subgroup analysis by region, the results suggested a consistent association of the dominant model and T2DM risk in southern Chinese (OR = 1.27, 95% CI = 1.01–1.60) but not northern Chinese and Japanese populations. The AG genotype was associated with T2DM risk in southern Chinese (OR = 1.31, 95% CI = 1.03–1.66) (Table 4).

Discussion

T2DM is a complex disease affected by both genetic and environmental factors (Gujral et al., 2013). Many genetic association studies have suggested that several genes and specific SNPs are associated with risk of T2DM (Nair et al., 2012; Ng et al., 2008; Rai et al., 2012; Yu et al., 2013). In fact, *TCF7L2* is considered the most influential gene in determining genetic susceptibility for T2DM in humans (Luo et al., 2009; Ng et al., 2008; Qiao et al., 2012; Wang et al., 2013). Mechanistic studies suggested that *TCF7L2* could impair β -cell function and down-regulate the expression of glucagon-like peptide 1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIP-R), thus reducing insulin level (Le-Bacquer et al., 2011; Shu et al., 2009; Vazquez-Roque et al., 2011). However, because of the low frequency of the at-risk allele of the SNP variants rs7903146, rs12255372 and rs11196205, originally reported in European populations, the association of these variants and T2DM in Asian populations varies among studies (Guinan, 2012).

In a 2008 study involving a “gene-based approach” to test all common genetic variants within *TCF7L2* in a Chinese population, rs11196218 was found associated with T2DM in Hong Kong Chinese (G vs. A: OR = 1.43, 95% CI = 1.14–1.79) (Ng et al., 2007). Since then, some replication studies have been performed in Chinese and Japanese populations (Lin et al., 2010; Luo et al., 2009; Ma et al., 2009; Miyake et al., 2012; Qiao et al., 2012; Zhang, 2008; Zheng et al., 2012; Zhu, 2011); the minor allele frequency (MAF) of rs11196218 was >20% in Asians. Even for the common SNP, discrepancies existed among studies performed in the same ethnic groups (Lin et al., 2010; Ma et al., 2009; Ng et al., 2007; Zhang, 2008; Zheng et al., 2012; Zhu, 2011). Therefore, with the existing information, evaluating the impact of this gene on the

Table 3
Characteristics of the studies included in the meta-analysis.

Authors	Year	Region	Source of controls	Genotyping method	Cases					Controls					P value*
					GG	AG	AA	G	A	GG	AG	AA	G	A	
Current study	–	NC	Community	PCR–LDR	934	771	98	2639	967	4163	2961	540	11,287	4041	0.67
Ng et al.	2007	SC	Community	MALDI-TOF	–	–	–	676	190	–	–	–	599	239	–
Lin et al.	2010	SC	Community	ABI SNaPshot	–	–	–	2174	884	–	–	–	2023	855	–
Luo et al.	2009	NC	Hospital	ABI SNaPshot	250	184	34	684	252	257	182	29	696	240	0.67
Ma et al.	2009	SC	Hospital	PCR-PFLP	93	123	43	309	209	67	106	31	240	168	0.30
Qiao et al.	2012	NC	Hospital	PCR–LDR	382	261	53	1025	367	292	235	30	819	295	0.05
Zhang et al.	2008	SC	Hospital	Taqman	253	210	31	716	272	235	153	34	623	221	0.20
Zheng et al.	2012	SC	Hospital	MALDI-TOF	128	84	15	340	114	80	58	14	218	86	0.46
Zhu et al.	2010	SC	Hospital	Taqman	14	127	159	155	445	10	102	188	122	478	0.39
Miyake et al.	2008	Japan	Community	Taqman	1316	724	93	3356	910	1112	612	100	2836	812	0.19

NC, northern China; SC, southern China.

* P value for Hardy–Weinberg equilibrium.

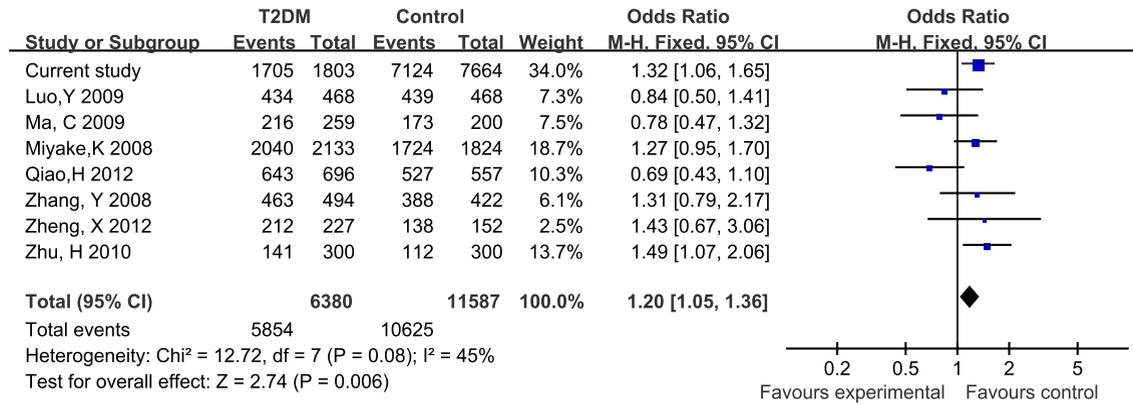


Fig. 1. Forest plot for the dominant model of rs11196218 polymorphism and T2DM.

Table 4

Meta-analysis of the association between rs11196218 polymorphism and T2DM in different models.

Study populations	G vs. A		GG vs. AA		AG vs. AA		(GG + AG) vs. AA		GG vs. (AG + AA)	
	OR (95% CI)	<i>P</i> value*	OR (95% CI)	<i>P</i> value*	OR (95% CI)	<i>P</i> value*	OR (95% CI)	<i>P</i> value*	OR (95% CI)	<i>P</i> value*
Overall	1.03 (0.99, 1.08)	0.06	1.15 (1.00, 1.33)	0.42	1.16 (0.94, 1.44) ^a	0.04	1.20 (1.05, 1.36)	0.08	0.97 (0.90, 1.04)	0.40
Region										
Southern China	1.13 (0.99, 1.29) ^a	0.04	1.22 (0.89, 1.67)	0.74	1.31 (1.03, 1.66)	0.32	1.27 (1.01, 1.60)	0.23	0.98 (0.81, 1.18)	0.35
Northern China	0.98 (0.91, 1.05)	0.87	1.08 (0.90, 1.31)	0.09	0.95 (0.55, 1.64) ^a	0.01	0.95 (0.62, 1.48) ^a	0.02	0.94 (0.86, 1.02)	0.28
Japan	1.06 (0.95, 1.18)	–	1.27 (0.95, 1.71)	–	1.27 (0.94, 1.72)	–	1.27 (0.95, 1.70)	–	1.03 (0.91, 1.17)	–

* *P* value for heterogeneity.^a Estimates for random-effects model.

genetic susceptibility of T2DM is difficult. Studies with larger sample size and sufficient power as well as a well-designed meta-analysis are needed to clarify this issue.

With 1842 T2DM and 7777 normal controls in our study, the power to detect the association of rs11196218 polymorphism and T2DM reached 100%. Our results suggest that the GA genotype and the dominant rs11196218 model are associated with risk of T2DM. Our findings are similar to those of Anhui population (Zhu, 2011) but opposite to those of Beijing (Luo et al., 2009), Chongqing (Zheng et al., 2012) and Japan (Miyake et al., 2012) populations. This inconsistency may be due to the intricate substructure of study populations, but confounding cannot be neglected. In the present study, the association of the dominant model of rs11196218 polymorphism and T2DM disappeared after adjustment for sex, age, anthropometric measurements, and lipid levels. The results of different adjustments show that WC was the confounder. For controls, we found no association of anthropometric or metabolic measurements and rs11196218 genotypes.

In our meta-analysis, the dominant model of rs11196218 was associated with risk of T2DM in the overall population. However, when stratified by region, this association was found in only the southern Chinese population, not northern Chinese or Japanese populations. In the southern Chinese population, the AG genotype was associated with increased risk of T2DM. The main reason might be due to the complex composition of the Chinese and Japanese populations and the great differences among ethnic groups in genetics and living environment. As well, studies of rs11196218 polymorphism and T2DM have focused on southern Chinese populations. Except for our study, with only 2 studies of northern Chinese (Luo et al., 2009; Qiao et al., 2012) and 1 study of Japanese (Miyake et al., 2012), the number of studies is relatively less. More independent replication studies with a large sample size in these regions are needed to verify the results.

Although our study combined data from all qualified studies and had a large sample size with sufficient power to assess the rs11196218 polymorphism in *TCF7L2* in the Asian population, the possible heterogeneity among subjects recruited from different studies might be a limitation. Moreover, we lacked detailed information on sex, age, anthropometric measurements and metabolic measurements for the meta-analysis, so the effects of these factors could not be adequately addressed.

In conclusion, both our case-control study and meta-analysis suggest an association of rs11196218 polymorphism in *TCF7L2* and risk of T2DM in Chinese population.

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