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Original Article

Transcription factor 7-Like 2 rs12255372, rs7903146 and rs290487 polymorphism is associated with the susceptibility to type 2 diabetes mellitus in a Chinese population

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Abstract: We conducted a hospital-based case-control study to evaluate the relationship between *TCF7L2* rs12255372, rs7903146 and rs290487 genetic polymorphisms and the susceptibility to type 2 diabetes mellitus in a Chinese Han population. Genotyping of *TCF7L2* rs12255372, rs7903146 and rs290487 was carried out using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. Statistical analysis was carried out using the SPSS 20.0 package (SPSS Inc., Chicago, IL, USA). By the chi-square test, a statistically significant difference was observed in the genotype frequencies of *TCF7L2* rs12255372 between type 2 diabetes mellitus patients and control subjects (χ^2=8.63, *P*=0.01), whereas no significant differences were found in the genotype frequencies of *TCF7L2* rs7903146 (χ^2=8.63, *P*=0.01) and rs290487 (χ^2=8.63, *P*=0.01) between the two investigated groups. Using unconditional logistic regression analysis, we observed that the TT genotype of *TCF7L2* rs12255372 was statistically significant associated with a elevated risk of development of type 2 diabetes mellitus compared to the wide-type genotype (adjusted OR=2.58, 95% CI=1.36-5.04). In the dominant model, the GT+TT genotype of *TCF7L2* rs12255372 significantly contributed to the susceptibility of type 2 diabetes mellitus, compared to the GG genotype (adjusted OR=1.74, 95% CI=1.16-2.58). In the recessive model, the TT genotype of *TCF7L2* rs12255372 was significant correlated with the risk of development of type 2 diabetes mellitus in comparison to the GG+GT genotype (adjusted OR=2.26, 95% CI=1.31-4.85). The findings of this study demonstrated that the TT genotype and T allele of *TCF7L2* rs12255372 polymorphism was associated with increased susceptibility to type 2 diabetes mellitus in a Chinese population.

Keywords: *TCF7L2*, rs12255372, rs7903146, rs290487, type 2 diabetes mellitus, Chinese population

Introduction

Type 2 diabetes mellitus (T2DM) is a common endocrine disease, which is associated with high morbidity worldwide. In China, it is estimated that about 92 million individuals suffer from type 2 diabetes mellitus and 148 million lives with prediabetes in China [1-4]. Previous studies have reported that the type 2 diabetes mellitus may be attributed to the high fat dietary, high cholesterol dietary, obesity or overweight, lack of physical activity practice and hypertension [5, 6]. However, environmental and dietary factors may play a part in the risk of developing type 2 diabetes mellitus, and genetic factors also contribute to the risk of developing this disease. Previous studies have implicated many genetic factors play an important role in the susceptibility to type 2 diabetes mellitus, such as Vitamin D receptor, ATP-Binding Cassette Transporter A1 gene, glutathione S-transferase genes, Methylenetetrahydrofolate reductase C677T gene, α-kinase 1 gene and Insulin receptor substrate-1 Gly972Arg gene [7-12].

Transcription factor 7-like 2 (*TCF7L2*), also called lymphatic factor-4 (TCF4), is located on the chromosome 10q25.3 with 216.86 kb in

Table 1. The primers, lengths of amplification fragment and restriction enzymes of *TCF7L2* rs12255372, rs7903146 and rs290487

TCF7L2	Primers (3'-5')	Restriction enzymes	Length of amplification fragment
rs12255372	Forward: AGGAGGCTGCCATATTGTTTACTT	*ACC*I	266 bp
	Reverse: ACACCTTTCTCATTTTTCAATTTCGC		
rs7903146	Forward: ACAATTAGAGAGCTAAGCACTTTTTAAATA	*SSP*I	139 bp
	Reverse: CTAACCTTTTCCTAGTTATCTGACATTG		
rs290487	Forward: AGGAGGCTGCCATATTGTTTACTT	*Rsa*I	153 bp
	Reverse: ACACCTTTCTCATTTTCAATTTCGC		

length. Highly expression of transcription factor 7-like 2 is observed in fat cells and pancreatic cells, and this protein shows low expression in bone cells and muscle cells [13]. The *TCF7L2* encodes a transcription factor during the Wnt signaling pathway that contributes to the pancreatic islet development and adipogenesis [13]. Previous studies have reported that TCF7L2 combined with b-catenin to form heterodimers, and promote the expression of several kinds of genes, such as the insulinotropic hormone glucagon-like peptide 1 (GLP-1) gene and the insulin gene as well as genes that encode proteins during the processing and exocytose of insulin granule [14-16]. Several previous studies have reported the role *TCF7L2* genetic polymorphisms in the development of type 2 diabetes mellitus, but the results are conflicting [17-23]. In the present study, we attempted to determine whether the *TCF7L2* rs12255372, rs7903146 and rs290487 polymorphisms could influence the risk of development of type 2 diabetes mellitus in a Chinese Han population.

Materials and methods

Subjects

Our study consisted of 205 patients with type 2 diabetes mellitus and 226 healthy controls between March 2013 and February 2015. All the type 2 diabetes mellitus patients were recruited from the First Affiliated Hospital of Xiamen University. All the patients were diagnosed by laboratory evaluations based on the criteria from the American Diabetes Association [24]. The control subjects were recruited from individuals for regular health examination in the First Affiliated Hospital of Xiamen University. None of the control subjects were presence of diabetes or a family history of this disease. Study subjects who had had a history of acute or chronic infection disease, cancers, or end-stage liver or kidney diseases were excluded from our hospital.

The main characteristics of the type 2 diabetes mellitus patients were as follows: mean age was 56.44±9.45 years, and mean body mass index (BMI) was 26.17±2.53 kg/m^2. Males comprised 64.39% of the type 2 diabetes mellitus patients, and 48.29% of the patients had hypertension. The characteristics of the control subjects were as follows: mean age was 54.23±8.92 years, and mean body mass index (BMI) was 24.29±2.20 kg/m^2. Males comprised 57.52% of the type 2 diabetes mellitus patients, and 25.22% of the patients had hypertension.

A standard questionnaire was carried out to collect the demographic and lifestyle characteristics of type 2 diabetes mellitus patients and control subjects, including gender, sex, BMI, tobacco smoking, alcohol consumption and hypertension. The clinical data of type 2 diabetes mellitus were collected from medical records, including fasting glucose, fasting insulin, T serum total cholesterol (TC), triglycerides (TGs) and high density lipoprotein-cholesterol (HDL-C) as well as low density lipoprotein-cholesterol (LDL-C).

The informed consent forms were obtained from selected type 2 diabetes mellitus patients and controls prior to participating into this study. The ethics committee of the First Affiliated Hospital of Xiamen University authorized the performance of our study.

Genotyping methods

Each participant was asked to provide five mL peripheral blood after enrolling into our study,

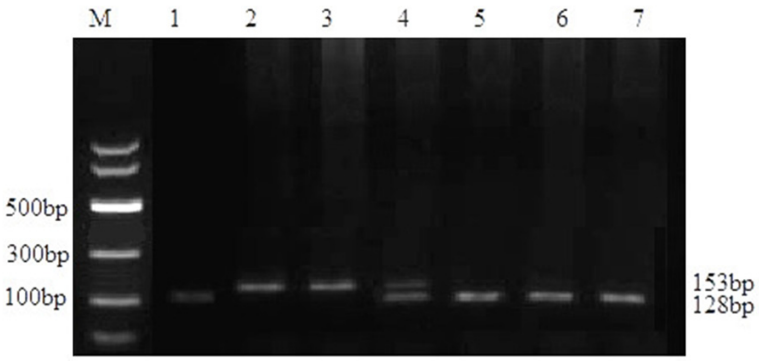

Figure 1. Agarose gel electrophoresis images for *TCF7L2* rs12255372. 1, 5-7 lanes: GG genotype; 2 and 3 lanes: 153 bp, 4 lane; GT genotype.

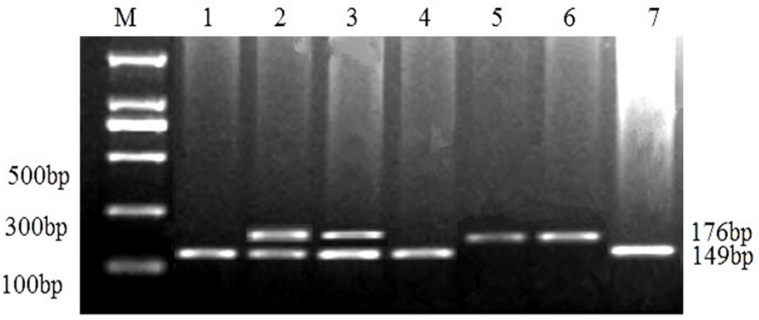

Figure 2. Agarose gel electrophoresis images for *TCF7L2* rs7903146. 5-6 lanes: TT genotype; 1,4 and 7 lanes: CC genotype; 2 and 3 lanes: CT genotype.

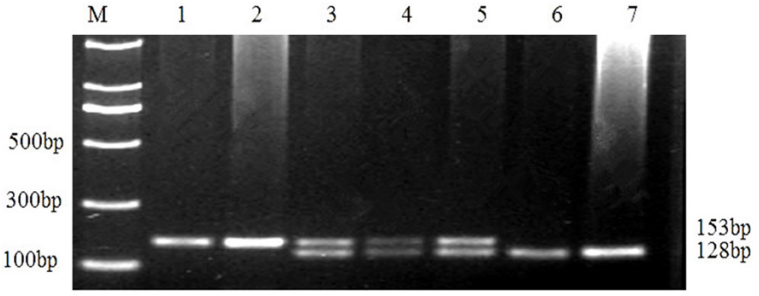

Figure 3. Agarose gel electrophoresis images for *TCF7L2* rs290487. 1 and 2 lanes: TT genotype; 3-5 lane: CT genotype; 6 and 7 lanes: CC genotype.

and the collected blood samples were kept in tubes with ethylenediamine tetra-acetic acid (EDTA) and stored at -20°C until utilization. DNA was extracted from peripheral blood sample using TIANGEN blood mini kit (TIANGEN Co. Limited, Beijing, China). Genotyping of *TCF7L2* rs12255372, rs7903146 and rs290487 was carried out using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. The forward and reverse primers, length of amplification fragment, and restriction enzymes of *TCF7-L2* rs12255372, rs7903146 and rs290487 used for PCR-RFLP were shown in **Table 1**.

The PCR analysis reaction were carried out at 94°C for 5 min, 30 cycles of 94°C for 30 s, 51°C for 30 s, and 72°C for 30 s and a final extension step of 72°C for 10 min. TThe amplified products were digested with *ACC*II restriction enzyme. The PCR product was analyzed using 3% agarose gel electrophoresis to identify the purity and integrity, and the results were confirmed ultraviolet light.

One fragment was observed for the TT genotype of rs12-255372, and the length was 153 bp. Two fragments were observed for the GG genotype of rs12255372, and the lengths were 128 bp and 25 bp. Three fragments were observed for the GT genotype of rs12255372, and the lengths were 153 bp, 128 bp and 25 bp (**Figure 1**). For rs7903146, the one enzyme-digested fragment was observed for the TT genotype (176 bp), two fragments were for the CC genotype (149 bp and 27 bp), and three fragments were for the CT genotype (176 bp, 149 bp and 27 bp) (**Figure 2**). For rs290487, the one enzyme-digested fragment was observed for the TT genotype (153 bp), three fragments were for the CT genotype (153 bp, 128 bp and 25 bp), and two fragments were for the CC genotype (128 bp and 25 bp) (**Figure 3**).

Statistical analysis

The baseline information and clinical data between the patients and controls were compared using independent sample t-test or Chi-

Table 2. The general information and clinical data of patients and control subjects

Characteristics	Patients N=205	%	Controls N=226	%	*t* test or χ^2 test	*P* value
Age, years	56.44±9.45		54.23±8.92		2.50	0.01
Gender						
Female	73	35.61	96	42.48		
Male	132	64.39	130	57.52	2.13	0.14
BMI, kg/m^2	26.17±2.53		24.29±2.20		8.25	<0.05
Tobacco smoking						
No	140	68.29	164	72.57		
Yes	65	31.71	62	27.43	0.94	0.33
Alcohol consumption						
No	133	64.88	152	67.26		
Yes	72	35.12	74	32.74	0.27	0.60
Hypertension						
No	106	51.71	169	74.78		
Yes	99	48.29	57	25.22	24.78	<0.001
Fasting glucose, mmol/l	8.21±2.87			4.92±1.64	14.78	<0.001
Fasting insulin, mmol/l	58.65±14.72			52.50±15.62	4.20	<0.001
TC, mg/dL	182.62±17.51			154.53±11.25	20.00	<0.001
TG, mg/dL	163.42±21.47			135.63±20.29	13.81	<0.001
HDL-c, mg/dL	48.50±10.65			47.42±12.43	0.96	0.17
LDL-c, mg/dL	132.15±15.32			121.50±12.43	7.96	<0.001

Table 3. Genotype distribution of *TCF7L2* rs12255372, rs7903146 and rs290487 polymorphisms between type 2 diabetes mellitus patients and control subjects

TCF7L2	Patients N=205	%	Controls N=226	%	χ^2 value	*P* value	χ^2 value for HWE	P for HWE	Minor allele frequency	
rs12255372								In controls	In NCBI database	In controls
GG	87	42.44	122	53.98						
GT	85	41.46	85	37.61						
TT	33	16.10	19	8.41	8.63	0.01	0.58	0.45	0.2139	0.2721
rs7903146										
CC	104	50.73	126	55.75						
CT	90	43.90	93	41.15						
TT	11	5.37	7	3.10	2.02	0.36	4.35	0.04	0.2278	0.2367
rs290487										
TT	93	45.37	112	49.56						
TC	92	44.88	98	43.36						
CC	20	9.76	16	7.08	1.38	0.50	0.77	0.38	0.2536	0.2876

square (χ^2) test. Genotypic frequencies and allele frequencies in control subjects for *TCF7L2* rs12255372, rs7903146 and rs290487 were tested for departure from HWE using the goodness-of-fit χ^2-test. Association between *CF7L2* rs12255372, rs7903146 and rs290487 genetic polymorphism and type 2 diabetes mellitus were analyzed using unconditional logistic regression analyses, and the odds ratio (OR) and 95% confidence intervals (95% CI) were calculated adjusted for potential confounding factors. Statistical analysis was carried out using the SPSS 20.0 package (SPSS Inc., Chicago, IL, USA). All *P* values in this study were two-sided. A *P*=0.05 was considered the threshold for statistical significance.

Table 4. Association between *TCF7L2* rs12255372, rs7903146 and rs290487 polymorphisms and risk of type 2 diabetes mellitus

TCF7L2 rs12255372	Patients N=205	%	Controls N=226	%	Crude OR	*P* value	OR (95% CI)[1]	*P* value
Co-dominant								
GG	87	42.44	122	53.98	1.0 (Ref.)	-	1.0 (Ref.)	-
GT	85	41.46	85	37.61	1.40 (0.91-2.15)	0.10	1.52 (0.95-2.42)	0.07
TT	33	16.1	19	8.41	2.44 (1.25-4.84)	0.005	2.58 (1.36-5.04)	0.002
Dominant								
GG	87	42.44	122	53.98	1.0 (Ref.)	-	1.0 (Ref.)	-
GT+TT	118	57.56	104	46.02	1.59 (1.07-2.37)	0.02	1.74 (1.16-2.58)	0.007
Recessive								
GG+GT	172	83.9	207	91.59	1.0 (Ref.)	-	1.0 (Ref.)	-
TT	33	16.1	19	8.41	2.09 (1.11-4.03)	0.01	2.26 (1.31-4.85)	0.005
rs7903146								
Co-dominant								
CC	104	50.73	126	55.75	1.0 (Ref.)	-	1.0 (Ref.)	-
CT	90	43.9	93	41.15	1.17 (0.78-1.76)	0.42	1.26 (0.86-1.92)	0.37
TT	11	5.37	7	3.1	1.90 (0.65-6.00)	0.19	2.07 (0.73-6.52)	0.28
Dominant								
CC	104	50.73	126	55.75	1.0 (Ref.)	-	1.0 (Ref.)	-
CT+TT	101	49.27	100	44.25	1.22 (0.82-1.82)	0.30	1.35 (0.87-1.99)	0.23
Recessive								
CC+CT	194	94.63	219	96.90	1.0 (Ref.)	-	1.0 (Ref.)	-
TT	11	5.37	7	3.10	1.77 (0.61-5.50)	0.24	1.85 (0.65-5.64)	0.17
rs290487								
Co-dominant								
TT	93	45.37	112	49.56	1.0 (Ref.)	-	1.0 (Ref.)	-
TC	92	44.88	98	43.36	1.13 (0.75-1.71)	0.54	1.27 (0.81-1.87)	0.47
CC	20	9.76	16	7.08	1.51 (0.70-3.29)	0.26	1.63 (0.74-3.38)	0.32
Dominant								
TT	93	45.37	112	49.56	1.0 (Ref.)	-	1.0 (Ref.)	-
TC+CC	112	54.64	114	50.44	1.18 (0.80-1.76)	0.38	1.22 (0.86-1.93)	0.42
Recessive								
TT+TC	185	90.25	210	92.92	1.0 (Ref.)	-	1.0 (Ref.)	-
CC	20	9.76	16	7.08	1.42 (0.68-3.02)	0.32	1.55 (0.76-3.29)	0.32

[1]Adjuted for age, sex, BMI, hypertension, levels of fasting glucose, fasting insulin, TC, TG, HDL-c and LDL-c.

Results

The demographic and lifestyle characteristics of type 2 diabetes mellitus patients and control subjects were shown in **Table 2**. Using independent sample t-test or χ^2 test, the type 2 diabetes mellitus patients were comparable in sex (χ^2=2.13, *P*=0.14), tobacco smoking (χ^2=0.94, *P*=0.33) and alcohol consumption (χ^2=0.27, *P*=0.60) as well as level of HDL-c (*t*=0.96, *P*=0.17). However, a statistically significant difference was found between type 2 diabetes mellitus patients and control subjects with respect to age (*t*=2.50, *P*=0.01), BMI (*t*=8.25, *P*<0.05), hypertension (χ^2=24.78, *P*<0.001), and levels of fasting glucose (*t*=14.78, *P*< 0.001), fasting insulin (*t*=4.20, *P*<0.001), TC (*t*=20.00, *P*<0.001), TG (*t*=13.81, *P*<0.001) and LDL-c (*t*=7.96, *P*<0.001).

The genotype frequencies of *TCF7L2* rs12255372, rs7903146 and rs290487 polymorphism between type 2 diabetes mellitus patients and control subjects were presented in

Table 3. By the chi-square test, a statistically significant difference was observed in the genotype frequencies of *TCF7L2* rs12255372 between type 2 diabetes mellitus patients and control subjects (χ^2=8.63, *P*=0.01), whereas no significant differences were found in the genotype frequencies of *TCF7L2* rs7903146 (χ^2=2.02, *P*=0.36) and rs290487 (χ^2=1.38, *P*=0.50) between the two investigated groups. The genotype frequencies of *TCF7L2* rs12255372 (χ^2=0.58, *P*=0.45) and rs290487 (χ^2=0.77, *P*=0.38) were in agreement with the Hardy-Weinberg equilibrium in controls using the goodness-of-fit χ^2-test, while the genotype frequencies of rs7903146 (χ^2=4.35, *P*=0.04) were not. The minor allele frequencies (MAFs) of *TCF7L2* rs12255372, rs7903146 and rs290487 in controls appear similar to the MAFs in NCBI database (http://www.ncbi.nlm.nih.gov/snp).

The correlation of *TCF7L2* rs12255372, rs7903146 and rs290487 polymorphisms with the risk of developing type 2 diabetes mellitus was shown in **Table 4**. Using unconditional logistic regression analysis, we observed that the TT genotype of *TCF7L2* rs12255372 was statistically significant associated with a elevated risk of development of type 2 diabetes mellitus compared to the wide-type genotype (adjusted OR=2.58, 95% CI=1.36-5.04). In the dominant model, the GT+TT genotype of *TCF7L2* rs12255372 significantly contributed to the susceptibility of type 2 diabetes mellitus, compared to the GG genotype (adjusted OR=1.74, 95% CI=1.16-2.58). In the recessive model, the TT genotype of *TCF7L2* rs12255372 was significant correlated with the risk of development of type 2 diabetes mellitus in comparison to the GG+GT genotype (adjusted OR=2.26, 95% CI=1.31-4.85). However, the rs7903146 and rs290487 polymorphisms did not associate with the risk of development of type 2 diabetes mellitus in co-dominant, dominant and recessive models.

Discussion

In previous studies, *TCF7L2* has perhaps the greatest influence on type 2 diabetes mellitus susceptibility [25]. In the present study, we investigated the role of *TCF7L2* rs12255372, rs7903146 and rs290487 genetic polymorphisms in the susceptibility to type 2 diabetes mellitus, and our findings have demonstrated that the *TCF7L2* rs12255372 polymorphism significantly influences the susceptibility to type 2 diabetes mellitus in comparison to the wide-type genotype in a Chinese population.

TCF7L2 gene is an critical member of the Wnt signaling pathway, which is involved in the development of embryonic cellular [26]. Previous experimental study has indicated that the Wnt signaling pathway is closely associated with the insulin secretion [27]. Furthermore, the *TCF7L2* gene regulates insulin and glucagon gene secretion through the Wnt signaling pathway. An experimental study reported that high expression of *TCF7L2* in the pancreatic beta cells is involved in glucose metabolism through regulation of the beta cell mass in mouse [28]. Cauchi et al. conducted a study in a French population, and they reported that *TCF7L2* is expressed in most human tissues, including mature pancreatic beta-cells, with the exception of the skeletal muscle. In the subcutaneous and omental fat from obese type 2 diabetic subjects, *TCF7L2* expression significantly decreased compared with obese normoglycemic individuals [26].

Currently, many previous studies have observed a statistically association between *TCF7L2* rs12255372 genetic variation and risk of development of type 2 diabetes mellitus [19-22]. Acharya et al. conducted a study in a Saudi Arabian population, and they reported that *TCF7L2* rs12255372 and rs4506565 was associated with an increased risk of developing type 2 diabetes mellitus [20]. Rafati et al. performed a study in an Iranian population, and reported that the *TCF7L2* rs12255372 genetic variation increased the risk of development of the type 2 diabetes mellitus [22]. Yao et al. suggested that the genetic polymorphisms of the *TCF7L2* rs12255372 gene was correlated with the risk of type 2 diabetes mellitus in a Chinese population [19]. Yang et al. carried out a study with 111 type 2 diabetes mellitus subjects and 109 healthy individuals, and suggested that *TCF7L2* rs12255372 genetic variation was an important risk factor for the development of type 2 diabetes mellitus [21]. However, three studies have reported inconsistent findings with the above mentioned studies, they reported that no association was found between *TCF7L2* rs12255372 polymorphism and risk of

type 2 diabetes mellitus [18, 29, 30]. Recently, Wang et al. conducted a meta-analysis with 34,076 patients and 36,192 controls, and they reported that *TCF7L2* rs12255372 was significantly associated with susceptibility to type 2 diabetes mellitus in the global population [31]. Our study reported that the *TCF7L2* rs12255372 could affect the susceptibility to type 2 diabetes mellitus in a Chinese population. The conflicting results about the role of *TCF7L2* rs12255372 polymorphism in type 2 diabetes mellitus may due to the different types of cancers studied and the various ethnic populations.

The current study has some limitations. First, selection bias could not be avoided in this study due to a hospital-based case-control study design. Second, the sample size of this study was relative small, which may influence the statistical power to find differences between groups. Further large scale studies with more ethnicities are greatly required to verify the results of our study.

The findings of this study demonstrated that the *TCF7L2* rs12255372 polymorphism was associated with increased susceptibility to type 2 diabetes mellitus in co-dominant, dominant and recessive models. Due to the importance of the *TCF7L2* genetic polymorphisms in the development of diseases, further investigations into the functional role of *TCF7L2* in type 2 diabetes mellitus are greatly required.

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Disclosure of conflict of interest

None.

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