**TCF7L2 rs290481 T>C polymorphism is associated with an increased risk of type 2 diabetes mellitus and fasting plasma glucose level**

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**ABSTRACT**

Genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene may be key agents in the etiology of type 2 diabetes mellitus (T2DM). In the present case-control study, we aimed to assess the possible relationship of TCF7L2 polymorphisms with T2DM and determine the effect of TCF7L2 polymorphisms on the level of fasting plasma glucose (FPG) in Eastern Chinese Han subjects. The TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms were genotyped by SNPscan genotyping assays in 502 subjects with T2DM and 782 non-diabetic controls. After adjusting for age, gender, drinking, smoking and body mass index (BMI), the association of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms with T2DM was determined. We found that TCF7L2 rs290481 T>C polymorphism increased the susceptibility of T2DM in the overall comparison. In subgroup analyses by age, sex, BMI, alcohol use and smoking status, a significantly increased risk of T2DM was also found in female, older subject and never drinking and BMI < 24 kg/m² subgroups. The relationship of TCF7L2 rs290481 T>C polymorphism with the biochemistry characteristics in controls was also assessed. We found that TCF7L2 rs290481 T>C polymorphism significantly increased the level of FPG in controls. Our findings suggest that TCF7L2 rs290481 T>C polymorphism is associated with T2DM in Eastern Chinese Han population and links to variations in FPG level. In addition, these relationships are more pronounced in female, older subject and never drinking and BMI < 24 kg/m² subgroups. A comprehensive fine-mapping study with functional investigation is needed to confirm or refute these potential correlations.
INTRODUCTION

Type 2 diabetes mellitus (T2DM), a chronic metabolic disease, is a common form of diabetes. Over the past decades, the incidence of T2DM in Chinese adult has increased dramatically and is about 11.6% [1]. T2DM is considered a serious public health threat. T2DM is primarily characterized by disturbance of energy metabolism, relative insulin deficiency and/or insulin resistance. Meanwhile, T2DM is a complex metabolic disorder resulting from multiple genetic components and environmental risk factors. The lipid metabolism and insulin signal transduction candidate genes may participate in the pathogenesis of T2DM. The variants of these candidate genes could change the expression of protein and also lead to abnormal signal transduction or metabolic disorder. Finally, these variants may influence the susceptibility of T2DM.

Transcription factor 7-like 2 (TCF7L2), a transcription factor, is a member of the high mobility group-box (HMGB) family [2] and exerting a variety of functions. TCF7L2 expresses in pancreatic β-cells [3] and plays an important role in glucose homeostasis. In addition, it is reported that TCF7L2 leads to the activation of Wnt target genes, and then it promotes the proliferation of pancreatic β-cells and the production of the incretin hormone glucagon-like peptide-1 in enteroendocrine cells [4]. Grant et al. reported that TCF7L2 polymorphisms may be associated with the risk of T2DM in an Icelandic population [5]. From then on, variants of TCF7L2 are considered as important genetic components in assessing the risk for T2DM worldwide [3, 6-8].

The TCF7L2 gene lies in chromosome 10q25.2-q25.3. TCF7L2 gene is polymorphic, and a number of loci have been identified, such as the rs10749127, rs10787475, rs11196224, rs12775879, rs17130188, rs290481, rs290487, rs290489, rs3750804, rs4918792, rs6585194, rs7085532, rs7094463, rs7919409, and rs966227, rs7903146, rs11196224, rs12775879, rs17130188, rs290481, rs290487, rs290489, rs3750804, rs4918792, rs6585194, rs7085532, rs7094463, rs7919409, and rs966227, rs7903146, rs11196205 and rs12255372 polymorphisms, etc. Among these single nucleotide polymorphisms (SNPs), the TCF7L2 rs7903146 polymorphism are widely studied for the potential relationship with T2DM susceptibility. Recently, several case-control studies found that TCF7L2 rs7903146 C>T is associated with the development of T2DM [9-12]. Then, a meta-analysis suggested that TCF7L2 rs7903146 C>T variants might confer an increased risk to T2DM in Chinese Han population [13]. However, in that meta-analysis, the number of included studies was moderate. Then, the power of the study may be limited. Several recent reports focused on the relationship of TCF7L2 rs290481 T>C with diabetes mellitus and the results were conflicting. Genetic variations of TCF7L2 genes, such as rs7903146C>T and rs290481 T>C, may contribute to the etiology of T2DM. Therefore, we designed a hospital-based case-control study with 502 T2DM cases and 782 healthy controls and selected TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms to explore the potential relationship of these SNPs with T2DM risk in an Eastern Chinese Han population.

RESULTS

Baseline characteristics

Basic clinical characteristics (e.g. anthropometric data, demographics and risk factors) and biochemical laboratory are summarized in Table 1. Locus information of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms is listed in Table 2. All genotyping success rate for these SNPs was more than 99%. Minor allele frequency (MAF) in Chinese database and our controls is shown in Table 2. In addition, the deviations from the Hardy-Weinberg equilibrium (HWE) in controls are listed in Table 2.

Association of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms with T2DM

The genotype distributions of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms are summarized in Table 3. Genotype distributions for these two SNPs were tested for HWE and no significant deviation was identified in controls (Table 2). In the analysis of TCF7L2 rs290481 T>C SNP, differences in the distribution of the rs290481 TC genotype compared with the rs290481 TT genotype and rs290481 TC/CC genotype compared with the rs290481 TT genotype between 502 T2DM cases and 782 controls were found [TC vs. TT: crude odds ratio (OR) = 1.29, 95% confidence interval (CI) = 1.01–1.65, P = 0.042 and TC/CC vs. TT: crude OR = 1.27, 95% CI = 1.01–1.61, P = 0.044 (Table 3)]. Results of multivariate linear regression analysis demonstrated that TCF7L2 rs290481 T>C polymorphism was correlated with the development of T2DM in two genetic models. When the TCF7L2 rs290481 TT genotype was used as the reference group, the rs290481 TC and TC/CC genotype were correlated with the increased risk of T2DM [TC vs. TT: adjusted OR = 1.32, 95% CI = 1.03–1.69, P = 0.030 and TC/CC vs. TT: adjusted OR = 1.30, 95% CI = 1.02–1.64, P = 0.032 (Table 3)]. However, we found that TCF7L2 rs7903146C>T polymorphism was not associated with the development of T2DM (Table 3).

Association of TCF7L2 rs290481 T>C polymorphism with T2DM in different stratification groups

Table 4 summarizes the genotype frequencies of TCF7L2 rs290481 T>C polymorphism in the subgroup analyses. In female subgroup, after adjustment for age, body mass index (BMI), smoking status and alcohol use by logistic regression analysis, the TCF7L2 rs290481 CC genotype were associated with an increased risk of
T2DM compared with the TCF7L2 rs290481 TT and TC/TT genotypes [CC vs. TT: adjusted OR = 2.05, 95% CI 1.12–3.76, P = 0.020 and CC vs. TC/TT: adjusted OR = 1.83, 95% CI 1.05–3.21, P = 0.034 (Table 4)]. In ≥65 years subgroup, after adjustment for gender, BMI, smoking status and alcohol use by logistic regression analysis, the TCF7L2 rs290481 TC/CC and TC genotypes increased the risk of T2DM compared with the TCF7L2 rs290481 TT genotype [TC vs. TT: adjusted OR = 1.42, 95% CI 1.01–2.01, P = 0.047 and TC/CC vs. TT: adjusted OR = 1.41, 95% CI 1.01–1.95, P = 0.042 (Table 4)]. In never drinking subgroup, after adjustment for gender, age, BMI and smoking status by logistic regression analysis, the TCF7L2 rs290481 TC/CC and TC genotypes increased T2DM risk compared with the TCF7L2 rs290481 TT genotype [TC vs. TT: adjusted OR = 1.50, 95% CI 1.04–2.17, P = 0.031 and TC/CC vs. TT: adjusted OR = 1.49, 95% CI 1.05–2.12, P = 0.026 (Table 4)].

SNP haplotypes

Using SHESIS program [14], we constructed TCF7L2 haplotypes. We found there was no significant
difference in TCF7L2 haplotype distribution among T2DM cases and controls (Table 5).

**Relationship of TCF7L2 rs290481 T>C polymorphism with biochemistry characteristics**

Biochemistry characteristics of T2DM cases may be influenced by diet treatment and pharmacotherapy. Thus, in this stage, we assessed the relationship of TCF7L2 rs290481 T>C polymorphisms with the biochemistry characteristics in controls. The results are shown in Table 6. We found that TCF7L2 rs290481 T>C polymorphism significantly increased the level of fasting plasma glucose (FPG) and high-density lipoprotein cholesterol (HDL-C) in controls. When the FPG level of TCF7L2 rs290481 TT genotype was used as the reference, FPG level of the rs290481 CC genotypes significantly increased [CC vs. TT: \( P = 0.029 \) (Table 6)]. When the HDL-C level of TCF7L2 rs290481 TT genotype was used as the reference, HDL-C level of the rs290481 TC/CC genotypes significantly increased [TC/CC vs. TT: \( P = 0.030 \) (Table 6)].
Table 4: Stratified analyses between TCF7L2 rs290481 T>C polymorphism and T2DM risk by sex, age, smoking status, alcohol consumption and BMI

| Variable       | (case/control)* | Adjusted OR (95% CI): P |
|----------------|-----------------|-------------------------|
|                | TT              | TC                       | CC                       | TC/CC   | TT   | CC  | TC/CC   | CC vs. (TC/TT) |
| Sex            |                 |                          |                         |         |      |     |         |                  |
| Male           | 114/201         | 167/223                  | 48/95                   | 215/318 | 1.00 | 1.33 (0.98-1.81); 0.90 (0.59-1.37); 1.21 (0.91-1.62); 0.77 (0.53-1.13); | P: 0.564 |
|                |                 |                          |                         |         |      |     |         |                  |
| Female         | 58/112          | 79/118                   | 31/29                   | 110/147 | 1.00 | 1.27 (0.83-1.96); 2.05 (1.12-3.76); 1.47 (0.98-2.22); 1.83 (1.05-3.21); | P: 0.034 |
| Age (years)    |                 |                          |                         |         |      |     |         |                  |
| <65            | 80/153          | 112/175                  | 32/58                   | 144/233 | 1.00 | 1.21 (0.84-1.74); 1.05 (0.63-1.76); 1.19 (0.84-1.68); 0.95 (0.59-1.53); | P: 0.391 |
| ≥65            | 92/160          | 134/166                  | 47/66                   | 181/232 | 1.00 | 1.42 (1.01-2.01); 1.27 (0.80-2.01); 1.41 (1.01-1.95); 1.05 (0.69-1.60); | P: 0.097 |
| Smoking status |                 |                          |                         |         |      |     |         |                  |
| Never          | 114/217         | 160/239                  | 57/82                   | 217/321 | 1.00 | 1.29 (0.96-1.75); 1.36 (0.90-2.05); 1.31 (0.98-1.75); 1.18 (0.81-1.71); | P: 0.198 |
| Ever           | 58/96           | 86/102                   | 22/42                   | 108/144 | 1.00 | 1.35 (0.87-2.10); 0.79 (0.42-1.47); 1.24 (0.81-1.89); 0.69 (0.39-1.22); | P: 0.198 |
| Alcohol use    |                 |                          |                         |         |      |     |         |                  |
| Never          | 156/280         | 219/297                  | 74/110                  | 293/407 | 1.00 | 1.33 (1.02-1.74); 1.22 (0.85-1.74); 1.32 (1.03-1.70); 1.05 (0.75-1.45); | P: 0.097 |
| Ever           | 16/33           | 27/44                    | 5/14                    | 32/58   | 1.00 | 1.25 (0.58-2.70); 0.73 (0.22-2.40); 1.18 (0.56-2.51); 0.65 (0.22-1.96); | P: 0.445 |
| BMI (kg/m²)    |                 |                          |                         |         |      |     |         |                  |
| <24            | 65/175          | 108/190                  | 35/69                   | 143/259 | 1.00 | 1.50 (1.04-2.17); 1.36 (0.83-2.24); 1.49 (1.05-2.12); 1.08 (0.69-1.70); | P: 0.031 |
| ≥24            | 107/138         | 138/151                  | 44/55                   | 182/206 | 1.00 | 1.17 (0.83-1.64); 0.99 (0.62-1.69); 1.13 (0.82-1.67); 0.92 (0.59-1.42); | P: 0.097 |

* The genotyping was successful in 502 (99.00%) T2DM cases, and 782 (99.49%) controls for TCF7L2 rs290481 T>C; △ Adjusted for age, sex, BMI, alcohol use and smoking status (besides stratified factors accordingly) in a logistic regression model; Bold values are statistically significant (P<0.05)

The power of the present study (α= 0.05)

For TCF7L2 rs290481 T>C polymorphism, the power value was 0.522 in TC vs. TT and 0.518 in TC/CC vs. TT. In the subgroup analyses, the results of power value were: 0.657 in CC vs. TT and 0.586 in CC vs. TC/TT among female subgroup; 0.518 in TC vs. TT and 0.551 in TC/CC vs. TT among ≥65 years subgroup; 0.569 in TC vs. TT and 0.597 in TC/CC vs. TT among never smoking subgroup, and 0.579 in TC vs. TT and 0.611 in TC/CC vs. TT among never drinking subgroup.

DISCUSSION

In the past decades, diabetes mellitus has become a public health concern worldwide. The characteristics of diabetes mellitus are the increased level of glucose, metabolism disturbance, and absolute and/or relative insulin resistance (IR). T2DM is one of the most common metabolic disorders in which a number of hereditary and environmental factors may contribute to its etiology. In this study, we focused on the association of energy metabolism and insulin-sensibility relative gene (TCF7L2) polymorphisms with T2DM susceptibility. We found TCF7L2 rs290481 T>C was associated with the development of T2DM and the increased level of FPG.

Transcription factor 7-like 2 (TCF7L2), a transcription factor, is expressed in pancreatic β-cells [3] and plays an important role in maintaining glucose homeostasis. It is well known that TCF7L2 gene is a candidate susceptibility gene of T2DM [3, 15, 16]. In this study, we selected two functional SNPs in TCF7L2 gene to explore the potential relationship of susceptibility to T2DM. TCF7L2 rs290481 T>C polymorphism is a locus in intron. Several recent reports suggested that TCF7L2 rs290481 T>C might play an important role in diabetes mellitus. Delgado-Lista et al. reported that this SNP was correlated with differences in insulin secretion, blood lipids, coagulation and blood pressure in metabolic syndrome (an entity often preceding T2DM) cases [17]. Another study indicated the rs290481 C allele near the 3’ end of TCF7L2 gene was associated with an increased
steady-state plasma glucose concentration, a higher 2-h post-challenge glucose and lower waist circumference in Chinese population [18]. However, a previous case-control study focused on the relationship of TCF7L2 rs290481 T>C polymorphism with gestational diabetes mellitus (GDM) in a Chinese Han population and suggested that this polymorphism was not a potential clinical value for the prediction of GDM [19]. In the present study, we identified a significant association between TCF7L2 rs290481 T>C polymorphism and the development of T2DM. In addition, the rs290481 T→C variant in TCF7L2 gene promoted the level of FPG. In the future, function of TCF7L2 rs290481 T>C polymorphism should be further studied to confirm or refute our primary findings.

Some studies reported that carriers of TCF7L2 rs7903146 T allele have higher susceptibility of T2DM [20]. This phenomenon might be due to impaired insulin secretory and/or insulinotropic effects of incretins rather than an insulin resistance [21, 22]. Recently, several case-control studies focused on the relationship of TCF7L2 rs7903146 C>T with the development of T2DM in China [7, 10, 11]. The results of a meta-analysis also indicated that TCF7L2 rs7903146 C>T variants might confer an increased risk to T2DM in Chinese population [13]. As shown in Table 4, we failed to establish a significant association between the TCF7L2 rs7903146 C>T variants and T2DM in Chinese Han individuals, which was not similar to results of the previous meta-analysis. The low penetrance of T2DM susceptibility from TCF7L2 rs7903146 C>T variants might be diluted by the interaction of gene-gene and gene-environment. Considering the complexity of T2DM etiology, other important genetic and environmental factors should not be ignored.

Like all epidemiological case–control studies, our investigation had several limitations. Firstly, T2DM cases and healthy controls were enrolled from two local hospitals in Eastern China and might therefore not be well-representative of the general Chinese population; the familial T2DM history of the participants was not considered, this bias might lead to spurious findings. Secondly, in this study, we only investigated two functional SNPs in TCF7L2 gene, which might not present an extensive view of the genetic variability of TCF7L2. In the future, further studies with larger sample size are needed to identify the potential genetic mechanism of T2DM by a comprehensive fine-mapping study. Thirdly, the number of participants included was moderate, the statistical power of the present study might be limited. Finally, environmental risk factors may be different between Eastern Chinese Han population and others. Thus, the risk of T2DM is likely to be affected by gene–gene and gene–environment interactions with different degrees. The association of TCF7L2 polymorphism with T2DM risk may differ in different ethnic subgroups.

Our findings suggest that TCF7L2 rs290481 T>C polymorphism is associated with T2DM susceptibility in Eastern Chinese Han population and links to variations in FPG level. In addition, these relationships are more pronounced in female, older subjects and never drinking and BMI < 24 kg/m² subgroups. A comprehensive fine-mapping study with functional investigation is needed to confirm the potential correlation between TCF7L2 polymorphisms and the development of T2DM.

### Table 5: TCF7L2 haplotype frequencies (%) in cases and controls and risk of type 2 diabetes

| Haplotypes | Cases (n=1004) | Controls (n=1564) | Crude OR (95% CI) | P |
|------------|----------------|------------------|-------------------|---|
| T<sup>rs290481</sup>C<sup>rs7903146</sup> | 575(58.32) | 933(59.96) | 1.00 | 0.743 |
| C<sup>rs290481</sup>C<sup>rs7903146</sup> | 392(39.76) | 580(37.28) | 1.10(0.93-1.29) | 0.292 |
| T<sup>rs290481</sup>T<sup>rs7903146</sup> | 13(1.32) | 34(2.19) | 0.62(0.32-1.19) | 0.170 |
| C<sup>rs290481</sup>T<sup>rs7903146</sup> | 6(0.61) | 9(0.58) | 1.08(0.38-3.06) | 1.000 |

### Table 6: Associations of the TCF7L2 rs290481 T>C genetic variants with biochemistry characteristics in healthy controls

| Genotype | Controls (n=782) | FPG (mmol/L) | P | Total cholesterol (mmol/L) | P | Triglyceride (mmol/L) | P | HDL-C (mmol/L) | P | LDL-C (mmol/L) | P |
|----------|-----------------|--------------|---|--------------------------|---|----------------------|---|---------------|---|----------------|---|
| TT       | 313             | 5.11±0.49    | 1.0| 4.84±1.13               | 1.0| 1.66±1.06             | 1.0| 1.27±0.36     | 1.0| 3.13±0.91     | 1.0|
| TC       | 341             | 5.13±0.50    | 0.627| 4.88±0.95             | 0.794| 1.53±0.85            | 0.349| 1.32±0.38     | 0.064| 3.13±0.74     | 0.966|
| CC       | 124             | 5.22±0.43    | 0.029| 4.96±0.93            | 0.359| 1.50±0.98          | 0.341| 1.34±0.36     | 0.062| 3.19±0.80     | 0.477|
| TC<CC    | 465             | 5.15±0.48    | 0.224| 4.90±0.95           | 0.560| 1.52±0.89         | 0.258| 1.33±0.37     | 0.030| 3.15±0.76     | 0.743|

FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Bold values are statistically significant (P <0.05)
MATERIALS AND METHODS

Subjects

The patient group consisted of 502 subjects with T2DM diagnosed at the Department of Endocrinology in the Affiliated People’s Hospital of Jiangsu University and Fujian Medical University Union Hospital. Patients with a confirmed diagnosis following the World Health Organization 1999 guidelines of T2DM were enrolled to participate in this case-control study: a FPG level of ≥ 7.0 mmol/L and/or a 2h postprandial plasma glucose (PPG) ≥ 11.1 mmol/L after an oral glucose tolerance test [23]. The healthy control group consisted of 782 subjects who attended health check in these hospitals. The major including criteria for controls were: (a) no history of T2DM, (b) PPG < 7.8 mmol/L and (c) fasting plasma glucose (FPG) < 6.1 mmol/L [24]. T2DM patients and healthy controls were recruited between October 2014 and May 2016 consecutively. There was no significant difference in the distribution of sex or age between these two groups. Our study was approved by the Ethics Committee of Jiangsu University and Fujian Medical University, and all participants signed a written informed consent. All subjects were interviewed by two experienced doctors and answered a questionnaire regarding demographic variables and risk factors. Systolic blood pressure, diastolic blood pressure, weight and height were measured. Biochemistry characteristics [e.g. total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), serum triglycerides and FPG] were also tested. BMI was assessed as weight (kg) divided by height (meter) squared. BMI ≥ 24 was used as the criteria for overweight and obesity in Chinese adults [25, 26].

DNA extraction and genotyping

Peripheral blood sample was collected in EDTA vacutainer tubes for the extraction of genomic DNA using the Promega Genomic DNA Purification Kit (Promega, Madison, USA). TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms were determined by the SNPscan™ genotyping assay (Genesky Biotechnologies Inc., Shanghai, China), which is a double ligation and multiplex fluorescence PCR [27]. Fifty-two DNA samples were randomly selected and tested again for quality control. The genotypes of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms were confirmed.

Statistical analysis

Continuous variables [e.g. age, BMI, FPG, total cholesterol, triglyceride, HDL-C and LDL-C levels] are expressed as means ±standard deviation (SD). Comparisons between T2DM patients and healthy controls were performed with Student’s t-test. The categorical variables (e.g. TCF7L2 genotypes, sex, age, smoking status, drinking and BMI) were compared with Chi-square test (χ²). Deviations from the HWE in controls were determined by an internet-based calculator (http://ihg.gsff.de/cgi-bin/hw/hwa1.pl). The relationship of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms with T2DM risk was evaluated by odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Multivariate linear regression was harnessed to determine the association of TCF7L2 rs7903146C>T and rs290481 T>C polymorphisms with quantitative traits. All multivariate linear regression analyses were adjusted for age, sex, alcohol use, smoking status and BMI. Analysis was performed with SAS software Version 9.4 (SAS Institute, Cary, NC). A P < 0.05 with two-tailed test was defined as the criterion of statistical significance. In this study, the Power and Sample Size Calculator software (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize) was used to calculate the power value (α = 0.05). SHESIS software (Bio-X Inc., Shanghai, China, http://analysis.bio-x.cn/myAnalysis.php), an online haplotype calculator, was used to construct TCF7L2 haplotypes [14].

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CONFLICTS OF INTERESTS

The authors have no potential financial conflicts of interests.

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REFERENCES

1. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, Xu M, Li Y, Hu N, et al. Prevalence and control of diabetes in Chinese adults. Jama. 2013; 310:948-959.
2. Duval A, Busson-Leconiat M, Berger R, Hamelin R. Assignment of the TCF-4 gene (TCF7L2) to human chromosome band 10q25.3. Cytogenetics and cell genetics. 2000; 88:264-265.

3. Cauchi S, Meyre D, Dina C, Choquet H, Samson C, Gallina S, Balkau B, Charpentier G, Pattou F, Stetsuyk V, Scharfmann R, Staels B, Fruebbe G, Froguel P. Transcription factor TCF7L2 genetic study in the French population: expression in human beta-cells and adipose tissue and strong association with type 2 diabetes. Diabetes. 2006; 55:2903-2908.

4. Jin T, Liu L. The Wnt signaling pathway effector TCF7L2 and type 2 diabetes mellitus. Molecular endocrinology. 2008; 22:2383-2392.

5. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkdottir U, Magnusson KP, Walters GB, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature genetics. 2006; 38:320-323.

6. Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hinney A, Hansen T, et al. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nature genetics. 2007; 39:218-225.

7. Lin Y, Li P, Cai L, Zhang B, Tang X, Zhang X, Li Y, Xian Y, Yang Y, Wang L, Lu F, Liu X, Rao S, et al. Association study of genetic variants in eight genes/loci with type 2 diabetes in a Han Chinese population. BMC medical genetics. 2010; 11:97.

8. Chang YC, Chang TJ, Jiang YD, Kuo SS, Lee KC, Chiu KC, Chuang LM. Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. Diabetes. 2007; 56:2631-2637.

9. Erkoc Kayda D, Arikoglu H, Kayis SA, Ozturk O, Gonen MS. Transcription factor 7-like 2 (TCF7L2) gene polymorphisms are strong predictors of type 2 diabetes among nonobese diabetics in the Turkish population. Turkish journal of medical sciences. 2017; 47:22-28.

10. Jia HY, Li QZ, Lv LF. Association between transcription factor 7-like 2 genetic polymorphisms and development of type 2 diabetes in a Chinese population. Genetics and molecular research : GMR. 2016; 15.

11. Hsiao TJ, Lin E. A common rs7903146 variant of the transcription factor 7-like 2 gene is associated with type 2 diabetes mellitus and fasting glucose in a Taiwanese population. Diabetes & metabolism. 2017; 15:1149-1160.

12. Yako YY, Madubedube JH, Kengne AP, Erasmus RT, Pillay TS, Matsha TE. Contribution of ENPP1, TCF7L2, and FTO polymorphisms to type 2 diabetes in mixed ancestry ethnic population of South Africa. African health sciences. 2015; 15:1149-1160.

13. Dou H, Ma E, Yin L, Jin Y, Wang H. The association between gene polymorphism of TCF7L2 and type 2 diabetes in Chinese Han population: a meta-analysis. PloS one. 2013; 8:e59495.

14. Shi YY, He L. SHesis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell research. 2005; 15:97-98.

15. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. The Journal of clinical investigation. 2007; 117:2155-2163.

16. Hayashi T, Iwamoto Y, Kaku K, Hirose H, Maeda S. Replication study for the association of TCF7L2 with susceptibility to type 2 diabetes in a Japanese population. Diabetologia. 2007; 50:980-984.

17. Delgado-Listas J, Perez-Martinez P, Garcia-Rios A, Phillips CM, Williams CM, Gulseth HL, Helal O, Blaak EE, Kiec-Wilk B, Basu S, Drevon CA, Defoort C, Saris WH, et al. Pleiotropic effects of TCF7L2 gene variants and its modulation in the metabolic syndrome: from the LIPGENE study. Atherosclerosis. 2011; 214:110-116.

18. Chang YC, Chiu YF, Ho LL, Ting CT, Shih KC, Curb JD, Chen YD, Li HY, Chuang LM. TCF7L2 genetic variants and progression to diabetes in the Chinese population: pleiotropic effects on insulin secretion and insulin resistance. Journal of molecular medicine. 2010; 88:183-192.

19. Ye D, Fei Y, Ling Q, Xu W, Zhang Z, Shu J, Li C, Dong F. Polymorphisms in TCF7L2 gene are associated with gestational diabetes mellitus in Chinese Han population. Scientific reports. 2016; 6:30686.

20. Florez JC. Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? Diabetologia. 2008; 51:1100-1110.

21. Florez JC. The new type 2 diabetes gene TCF7L2. Current opinion in clinical nutrition and metabolic care. 2007; 10:391-396.

22. Pilgaard K, Jensen CB, Schou JH, Lyssenko V, Wegner L, Brons C, Vilsboll T, Hansen T, Madsbad S, Holst JJ, Volund A, Poulsen P, Group L, et al. The T allele of rs7903146 TCF7L2 is associated with impaired insulinotropic action of incretin hormones, reduced 24 h profiles of plasma insulin and glucagon, and increased hepatic glucose production in young healthy men. Diabetologia. 2009; 52:1298-1307.

23. Yao M, Wu Y, Fang Q, Sun L, Li T, Qiao H. Association of ADIPOQ Variants with Type 2 Diabetes Mellitus Susceptibility in Ethnic Han Chinese from Northeast China. Journal of diabetes investigation. 2016.

24. Fan Y, Li X, Zhang Y, Fan X, Zhang N, Zheng H, Song Y, Shen C, Shen J, Ren F, Yang J. Genetic Variants of TPCN2
Associated with Type 2 Diabetes Risk in the Chinese Population. PloS one. 2016; 11:e0149614.

25. Zhai Y, Zhao WH, Chen CM. [Verification on the cut-offs of waist circumference for defining central obesity in Chinese elderly and tall adults]. Zhonghua liu xing bing xue za zhi. 2010; 31:621-625.

26. Zhang X, Zhang S, Li Y, Detrano RC, Chen K, Li X, Zhao L, Benjamin EJ, Wu Y. Association of obesity and atrial fibrillation among middle-aged and elderly Chinese. International journal of obesity. 2009; 33:1318-1325.

27. Yin J, Wang X, Wei J, Wang L, Shi Y, Zheng L, Tang W, Ding G, Liu C, Liu R, Chen S, Xu Z, Gu H. Interleukin 12B rs3212227 T > G polymorphism was associated with an increased risk of gastric cardiac adenocarcinoma in a Chinese population. Diseases of the esophagus. 2015; 28:291-298.