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Original Research Article

The T allele of TCF7L2 rs12255372 G/T Variant Can Predispose to Type 2 Diabetes Mellitus among Iraqi Population

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a polygenic metabolic disorder, resulting from the interaction of genetic and environmental factors. This study aimed to assess the association of TCF7L2 rs12255372 G/T variant with T2DM and insulin resistance (IR) in a sample of the Iraqi population. A total of 76 patients with T2DM and 54 healthy controls were genotyped for the TCF7L2 rs7903146 single nucleotide polymorphism (SNP). The association of different genotypes of this SNP with the development of T2DM as well and with IR and glycated hemoglobin (HbA1c) were assessed. The TT genotype showed a higher frequency in diabetic patients (17.11%) than controls (5.56%) with a significant difference (OR = 4.04, 95% CI = 1.04-15.71, p = 0.044). Furthermore, the T allele was more frequent in patients than controls (38.82% vs. 26.85%), with a significant difference (OR = 1.73, 95% CI = 1.01-2.95, p = 0.45). Mean HOMA-IR in patients carrying TT genotype was 2.91 ± 0.83 which was significantly higher than either GG or GT genotype (2.62 ± 0.63 and 2.71 ± 0.55, respectively). Thus, the T allele of TCF7L2 rs12255372 variant could be considered as a risk factor for developing T2DM. The study suggests that increase IR is the underlying mechanism by which this variant can predispose the individual for T2DM.

Keywords: Diabetes mellitus, TCF7L2 gene, rs12255372 variant, insulin resistance.

Introduction

Diabetes mellitus (DM) is a group of a chronic progressive metabolic disorder characterized by hyperglycemia caused by faults in insulin secretion, insulin activity, or both.[1] DM was considered as the seventh death causing disease affecting most communities in the world. A recent estimation considered that 425 million people (20–79 years of age) are suffering from the disease, over 90% of whom are type 2.[2] This figure is expected to be 629 million by 2045.[3] The International Diabetes Federation (IDF), in December 2011, stated that Iraq is considered as having a medium prevalence (9.3%) of diabetes.[4] Although the environmental factors and lifestyle play a major role in the development of T2DM, the susceptibility to the disease varies greatly between individuals exposed to almost similar environmental factors. Such observation highly suggests the significant role of genetic factors in this illness.

The TCF7L2 gene is located on chromosome 10q25.3 and spans about 215.9 Kb including 17 exons and 16 introns.[5] The protein encoded by this gene (T cell transcriptional factor-4 (TCF-4)) is a high-mobility group box that contains transcription factors belonging to a family of TCF/lymphoid enhancer factor (LEF).[6] This transcription factor is involved in Wnt signaling pathway,[7] which plays an important role in β-cell proliferation and insulin secretion.[8] Furthermore, TCF-4 controls the transcription of proglucagon gene which encodes for glucagon-like peptide 1 (GLP-1). The main functional role of GLP-1 is to induce insulin secretion while it inhibits glucagon secretion. As such, it is reasonable to assume that variants in the TCF7L2 gene might have a role in T2DM.[7] Moreover, TCF-4 has been functionally connected to impairment in insulin secretion, defect in the suppression of incretin- and glucose-induced glucagon, unusual insulin processing, and an increase in the release of hepatic glucose during fasting.[9]

Particularly, the most candidate single nucleotide polymorphism (SNP) in the TCF7L2 gene which was previously investigated due to its association with T2DM rs12255372. Several previous studies worldwide have suggested a significant impact of the TT genotype of this SNP as a risk factor for T2DM.[10-12] To the best of our knowledge, there is no previous study in Iraq that addressed this issue. Therefore, this study aimed to evaluate the role of rs12255372 in the incidence of T2DM and in insulin resistance (IR).

Materials and Methods

The study population

This cross-sectional study included 76 patients with T2DM who were attending Al-Imamain Al-Kadhumain Medical City, Baghdad during the period from September 2018 to August 2019. The diagnosis of T2DM was performed depending on the American Diabetes Association Guidelines.[13] A detailed history, physical examination, mode of antidiabetic therapy, and duration of DM were gathered. Pregnant women and patients receiving insulin by injections were excluded from the analysis.

Other 54 apparently healthy subjects that match the patients in age and gender were recruited to represent the control group. Those subjects were attending the same hospital for blood donation or as accompanying the patients. An approval of the Institutional Review Board (IRB) of the College of Medicine, Al-Nahrain (No. 2019/140) was obtained to conduct the study. Eligible participants were asked to sign an informed consent documenting their willingness to participate in the study.

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Data including weight, height, hip and waist circumference, family history of DM and smoking status were collected from each participant by direct interview.

Sampling

Five millilitres (5 mL) of venous blood were collected from each participant after fasting for at least 8 hours. The blood sample was divided into two aliquots; 3 mL in a plain tube for serum collection, while the other 2 mL were poured in EDTA tube.

Fasting blood sugar (FBS) was determined in serum samples using the glucose oxidase method. Total plasma cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were analyzed based on enzymatic methods. Glycosylated hemoglobin (HbA1c) was measured according to the ion-exchange chromatography method.

Molecular Assay

Genomic DNA was extracted from leukocyte using a ready commercial kit (SYNCTM DNA Extraction Kit/Genaid/Taiwan). The gene fragment corresponding to the rs12255372 polymorphism in the *TCF7L2* gene was amplified with conventional polymerase chain reaction (PCR) using two specific primers.[14] The reaction was performed in 50 µL of reaction mixture containing 2 µL of DNA template, 200 µM of each deoxynucleotide triphosphate (dNTP), 1.5–2.5 mM $MgCl_2$, 1 µL of each primer, and 0.6 unit Taq DNA polymerase (Bioneer/ Korea). The cycling conditions were as previously reported.[14] The PCR product was digested with Tsp509I restriction enzyme (New England Biolabs) at 65°C for 3 hours. The reaction consisted of 7 µL of amplicons, 1 × NEB buffer, 1U of the enzyme. The final volume was adjusted to 15 µL with nuclease-free water. The length of digested fragments was determined by 2.5% agarose gel electrophoresis stained by ethidium bromide. Allele discrimination was based on fragment size after digestion which was two bands (143 bp+ 104 bp) for GG (wild type), two bands (126 bp + 104 bp) for TT (mutant homozygote), and three bands (143 + 126 bp + 104 bp) for the mutant heterozygote GT.

Statistical analysis

Statistical Package for Social Sciences (SPSS version 25.0) was used for data analysis. Numerical variables were stated as a Mean ± standard deviation (SD), while categorical variables were stated as percentages. Demographic and clinical data were compared between groups using student's t-test or χ^2, as appropriate. Deviation of different genotypes from the Hardy–Weinberg equilibrium (HWE) was tested using χ^2 test. Bivariate logistic regression test was used to assess the statistically significant association between different genotypes and alleles of rs12255372 polymorphism and the development of DM. Odds ratios (OR) with 95% confidence interval (CI) were calculated from this test. The statistical tests were two-sided, and a $p \leq 0.05$ was considered statistically significant.

Results and Discussion

Table 1 shows the baseline characteristics of the study population. There were no significant differences between DM patients and controls in age, sex distribution, smoking habit, or family history of diabetes. However, diabetic patients had significantly higher BMI and WHR (28.06 ± 5.40 kg/m^2 and 0.91 ± 0.13, respectively) than controls (25.73 ± 6.20 kg/m^2 and 0.87 ± 0.10, respectively). Furthermore, Diabetic patients, both HbA1c and HOMA-IR were significantly higher in diabetic patients (8.86 ± 2.94% and 2.74 ± 0.81%, respectively) than in controls (5.33 ± 1.10% and 1.12 ± 0.48%, respectively).

Association of TCF7L2 rs12255372G/T polymorphism with DM

Based on enzymatic digestion pattern visualized in gel electrophoresis (Figure 1), TCF7L2 rs12255372G/T polymorphism appeared in three genotypes which were GG, GT and TT.

The frequency of different genotypes was in good accordance with HWE (Table 2). The TT genotype showed higher frequency in diabetic patients (17.11%) than controls (5.56%) with a significant difference (OR = 4.04, 95% CI = 1.04-15.71, p = 0.044). This effect seemed to be through a dominant model (OR = 3.51, 95% CI = 0.95-12.98, p = 0.048). At allelic level, the T allele was more frequent in patients than controls (38.82% *vs*. 26.85%), with a significant difference (OR = 1.73, 95% CI = 1.01-2.95, p = 0.45).

These results imply that the carrier of this genotype will be at about 4-time higher risk to have T2DM compared with those carrying GG genotype of the SNP. These results are in accordance with a large number of studies worldwide. Fortunately, some meta-analyses have summarized the results of these studies.

In one meta-analysis, Wang *et al*.[14] analyzed 42 studies with 34076 patients with T2DM and 36192 controls. These studies distributed as follows: 6 from Europe, 17 from Asia, 2 in Africa, 3 from America and 14 on Caucasian populations. The study has confirmed that T allele of SNP rs12255372 has a significant association with the susceptibility to T2DM in the global population. Almost similar results were obtained from more recent analyses including ten studies.[16]

However, some studies found no association between a TCF7L2 rs12255372 variant and T2DM such as that conducted among Chinese, Arabic or Pima Indian populations.[17-19]

Table 3 shows the association of different genotype of rs12255372 polymorphism with HbA1c and HOMA-IR in diabetic patients. Although patients carrying the TT genotype had slightly higher HbA1c than other genotypes, the difference was insignificant. In contrast, mean HOMA-IR in patients carrying TT genotype was 2.91 ± 0.83 which was significantly higher than either GG genotype (2.62 ± 0.63) or GT genotype (2.71 ± 0.55).

This is in accordance with an Iranian study among Kurdish ethnic group,[20] and with Velayutham's study among the Indian population.[21] However, an Iranian case-control study concluded the lack of association between TCF7L2 rs12255372 and IR.[22]

This discrepancy between different studies can be attributed to variation in the selection criteria of patients and controls, demographic characteristics like ethnicity and race, and to different sample sizes.

The underlying mechanisms of different genotypes of TCF7L2 SNP in the development of T2DM is still uncertain. Notably, the TCF7L2 rs12255372 is located in the intronic region of the gene, and accordingly, the change from guanine to thymine base do not influence the amino acid sequence of the encoded protein.

Mondal *et al*.[23] assumed that TCF7L2 variants might affect alternative splicing of the encoded mRNAs, which in turn might have a distinct effect on the translated protein and its physiologic roles in inducing T2DM. The mechanism(s) implemented by this alternative transcript to increase individual's susceptibility to T2DM is(are) controversial.

One hypothesis attributed this effect to the physiological role of TCF-4 in Wnt signaling pathway. The alternative transcript could affect this pathway as TCF-4 controls the transcription of the proglucagon gene through the Wnt signaling pathway. The proglucagon gene encodes the incretin hormone GLP-1,[24] which has a plethora of physiological activities. One of these activities is sustaining glucose homeostasis via the stimulation of insulin secretion, inhibition of glucagon secretion, and slowing gastric emptying.[25] In addition, GLP-1 promotes insulin gene transcription, stimulates pancreatic β-cell proliferation and neogenesis, and inhibits β-cell apoptosis.[26] Supporting this hypothesis is the study of Cauchi *et al*.[27] who found T allele of TCF7L2 rs12255372 G/T gene polymorphism can downregulate each of insulin secretion as well as insulin sensitivity to sugar. Another investigation demonstrated that subjects with the T allele of this polymorphism had relatively high levels of glucose during 2-h post-meal and along fasting period. Those individuals also showed a relatively low insulin production compared with those with G allele. All these factors render them more prone to T2DM.[28]

An alternative hypothesis assumes that variants in TCF7L2 interrupt adipogenesis and/or adipocyte normal physiological activity by affecting the transcriptional regulation of PPARG causing precipitation of triglycerides in body tissues (i.e., muscle and liver) with a consequence increase in IR, or, at least, there is an exacerbation in the defect on insulin secretion that is already present through free fatty acid (FFA)-induced IR.[29]

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On the other hand, Acyl-CoA synthetase 5(ACSL5) has an important physiologic role in lipid biosynthesis and FA degradation, which could be linked with IR. In this regard, Xia *et al.*[30] showed that the TCF7L2 variants reside in an element that controls the expression of ACSL5 and hypothesized that the TCF7L2 can regulate ACSL5 expression. Taking the correlation between ACSL5 and insulin sensitivity into account, inhibition of ACSL5 enzyme activity could be a promising treatment for T2DM.

Table 1: Demographic and clinical characteristics of the study population

Characteristic	Patients (n = 76)	Controls (n = 54)	*p*-value
Age, years, Mean ± SD	52.41 ± 12.6	49.18 ± 11.5	0.731
BMI, kg/m^2, Mean ± SD	28.06 ± 5.4	25.73 ± 6.2	0.024
WHR	0.91 ± 0.13	0.87 ± 0.11	0.011
Sex, No (%)			
Male	43 (56.58%)	33 (61.11%)	0.605
Female	33 (43.42%)	21 (38.89%)	
Smoking, No (%)			
Never	52 (68.42%)	38 (70.37%)	0.812
Ex/current	24 (31.58%)	16 (29.63%)	
Family History, No (%)			
No	67 (88.16%)	52 (96.3%)	0.10
Yes	9 (11.84%)	2 (3.7%)	
HbA1c (%)	8.86 ± 2.94	5.33 ± 1.1	<0.001
HOMA-IR (%)	2.74 ± 0.81	1.12 ± 0.48	<0.001

BMI: body mass index, WHR: waist: hip circumference ratio, HbA1c: Hemoglobin A1c, HOMA-IR: homeostatic model assessment of insulin resistance

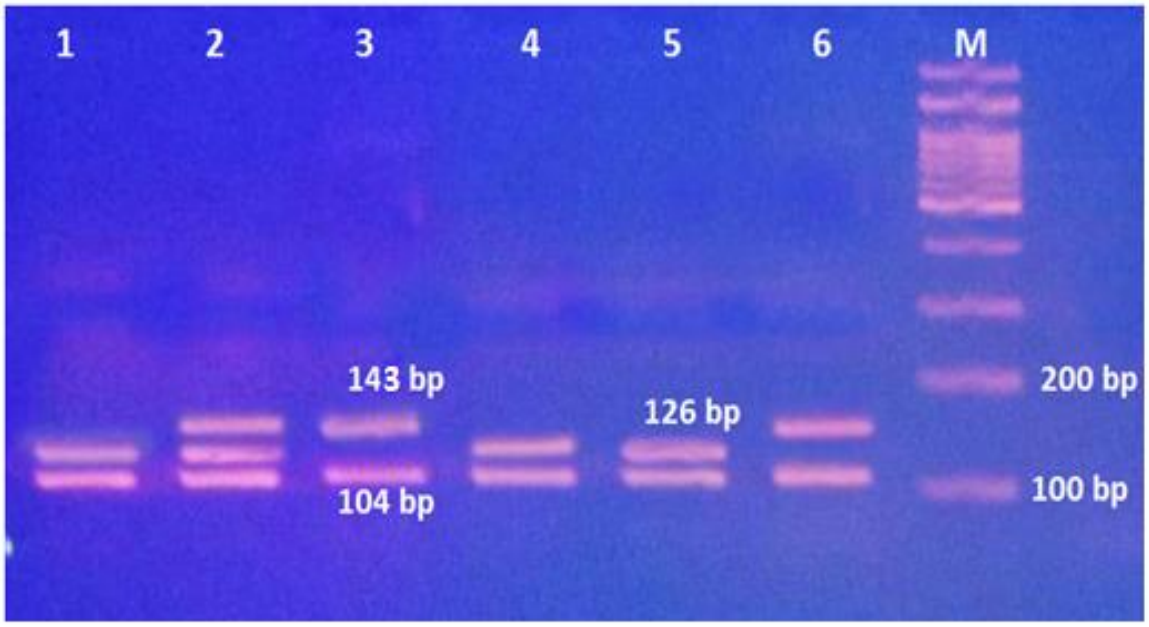

Figure 1: TCF7L2 rs12255372G/T genotype patterns in DM patients after digestion with Tsp509I restriction enzyme, visualized under U. V light after staining with ethidium bromide. Lanes 1,4 and 5: TT genotype; lane 2: GT genotype; lanes 3 and 6: GG genotype; M: 100 bp molecular ladder.

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Table 2: The frequency of different genotypes and allele of TCF7L2 rs12255372G/T polymorphism in T2DM patients and controls

rs12255372 Polymorphism	Patients (n = 76)	Controls (n = 54)	*P*-value	OR (95% CI)
Genotypes				
GG	30 (39.47%)	28 (51.85%)	0.126	1.0 ref.
GT	33 (43.42%)	23 (42.59%)	0.440	1.34 (0.64-2.81)
TT	13 (17.11%)	3 (5.56%)	0.044	4.04 (1.04-15.71)
HWE	0.454	0.563		
Dominant model				
GG+GT	63 (82.89%)	51 (94.44%)	0.048	ref.
TT	13 (17.11%)	3 (5.56%)		3.51 (0.95-12.98)
Recessive model				
GG	30 (39.47%)	28 (51.85%)	0.116	1.0 ref.
GT+TT	46 (60.53%)	26 (48.15%)		1.65 (0.82-3.34)
Alleles				
G	93 (61.18%)	79 (73.15%)	0.045	ref.
T	59 (38.82%)	29 (26.85%)		1.73 (1.01-2.95)

Table 3: Association of different genotypes of rs12255372 polymorphism with HbA1c and HOMA-IR in Diabetic Patients

rs12255372 Polymorphism	GG genotype (n = 30)	GT genotype (n = 33)	TT genotype (n = 13)	p-value
HbA1c (%)	8.32 ± 1.22	8.38 ± 1.08	8.60 ± 1.43	0.219
HOMA-IR (%)	2.62 ± 0.63[a]	2.71 ± 0.55[a]	2.91 ± 0.83[b]	0.014

Different small letters indicate significant differences

Conclusion

The present study highly suggests the role of T allele of TCF7L2 rs12255372 variant as a risk factor for developing T2DM. Furthermore, the study suggests that increase IR is the underlying mechanism by which this variant can predispose the individual for T2DM. The study recommends a regular checking for diabetes in individual carrying the TT genotype of the polymorphism. The effect of other polymorphisms in the third intron of the TCF7L2 gene on susceptibility to T2DM, and the possible linkage disequilibrium between these polymorphisms should be investigated in order to further clarify the genetic predisposing factors for T2DM among the Iraqi population.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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