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TCF7L2 rs7903146 Gene Variation Is Associated with Risk of Type 2 Diabetes in Turkish Population

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Abstract

Type 2 diabetes (T2D) results from combination of environmental factors and genetic determinants. Transcription factor 7-like 2 (TCF7L2) genes have been reported that it plays important role in T2D pathogenesis. In addition, TCF7L2 gene polymorphisms have been linked to T2D through many European populations. In the present study, we investigated TCF7L2 polymorphisms in healthy individuals and T2D patients and aimed to see whether TCF7L2 polymorphisms are associated with T2D in the Turkish population. We genotyped two SNPs of TCF7L2 gene, rs7903146 and rs12255372 in 100 healthy individuals and 100 patients. As a result of the genotype and allele distributions, we found that there were significantly associations between the TCF7L2 rs7903146 and risk of T2D (p=0.0172) in Turkish Population. However, there was no association for TCF7L2 rs12255372 (p=0.395) but GT genotype was higher in patient groups (p=0.0250). Similarly, our data shows that individuals who carry TCF7L2 rs7903146 polymorphism have significant risk of T2D in Turkish population.

Keywords Polymorphism; Association; T2D; TCF7L2

Introduction

T2D is a multifactorial metabolic disease which is characterized by hyperglycemia. Inadequate secretion of insulin or resistance to secreted insulin play important role in progression of T2D [1,2]. It also causes to various complications including cardiovascular and endothelial diseases [3,4]. The prevalence of T2D is increasing every year in worldwide. It has been reported that 366 million people were affected by diabetes in 2011 and expected to be double within next 20 years in the world [5,6].It has been reported that prevalence of diabetes in Turkey raised up to 14.58% in 2013 [7].

Genome wide analysis revealed that many genes involved in type-2 diabetes pathogenesis [8]. Especially, Transcription factor 7-like 2 (TCF7L2) gene is thought to be best candidate gene involved in from impairment of insulin secretion to development of T2D [9]. In addition, strong association between TCF7L2 polymorphism and T2D was reported in European populations [10]. The transcription factor 7 like 2 (TCF7L2) gene is an enteroendocrine transcription factor, which is localized to chromosome 10q and important component of Wnt signaling pathway [11]. Stimulation of Wnt catenin subsequently causes to assemble of β-catenin with BCL9, translocation into the nucleus and forms an active form with TCF7L2 [12,13]. The complex result in Wnt target genes activation that involves in cell proliferation, apoptosis and tissue invasion [14].

TCF7L2 gene play important role in T2D by regulating adipogenesis, myogenesis and pancreatic islands. It has an effect on function of beta cells and granules responsible for insulin secretion, regulates expression of protein involved in exocytosis of insulin granules [15]. It has been reported that individuals who carries risk alleles for SNPs within TCF7L2 showed impaired insulin secretion, increase in gastric inhibitor and impairment in glucose metabolism [16]. However, molecular mechanism of impaired insulin secretion due to TCF7L2 gene polymorphism is still not known [17]. Based on this background, we aimed to investigate whether TC7L2 polymorphisms are associated with T2D in Turkish patients.

Material and Methods

Subjects

The study includes 100 patients who were diagnosed as T2D in Mersin University, Faculty of Medicine, and Department of Endocrinology. Total of 100 individuals were recruited to this study as control group. The study was approved by the ethics committee of the Mersin University.

Genotyping of polymorphisms in TCF7L2

About 6-7 ml peripheral blood was collected in 2% EDTA-containing tubes and genomic DNA was extracted from leukocytes by high pure template preparation kit (Roche, Switzerland). Two SNPs of the TCF7L2, rs7903146 and rs12255372 were genotyped by real time PCR using the Light Cycler DNA Master Hybridization probes kit. The primer and probe sequences were given in Table 1. The PCR conditions for TCF7L2 genotypes were lay out as: 4 mmol/l MgCI, 0, 2 µmol/l of each PCR primers and 5 µL of the Light Cycler DNA Master Hybridization Mix and 50 ng of genomic DNA in a final volume of 50µL.

Statistical analysis

Chi- Square test was used to determine the genotype frequency of TCF7L2 polymorphisms in patient and control groups. The association between TCF7L2 polymorphisms and T2D was modelled in terms of binary logistic regression analysis. To determine T2D risk for the

genotypes Odds ratio (OR) and 95% confidence interval (95%) were calculated. Then, values of $p \leq 0.05$ was considered as the meaningful level and SPSS version 11.5 software program was used for statistical analysis.

Results

A total of 100 patients with T2D (male=59, female=41, mean age: 54, 24 ± 16, 52 years) and 100 control groups (male=56, femal =44 years) participated in this study. Frequency of genotypes for rs7903146 polymorphism was shown in Table 2. CC, CT and TT genotype percentage were 58%, 10% and 32% in controls, 36%, 22% and 42% in patients groups. There was significant difference between patients and controls for genotype frequency rs7903146 polymorphism ($p<0.05$). However, frequency of genotypes for rs12255372, GG, GT and TT were 82%, 9% and 9% in controls, 69%, 20% and 11% in patients groups. No difference was found between control and patient groups ($p>0.05$). However, there was significant difference between control and patient group in GT genotype frequency ($p<0.05$) (Tables 1-3).

Parameter	Patients	Controls	p- Value
n (total)	100	100	
Age (years)	54,24	51,32	0.189
Gender			
Female (%)	41	44	0.775
Male n(%)	59	56	

Table 1: The number of controls and patients according to age and gender (n- number of sample)

Gene	PCR Primers	Hybridization Probes
rs7903146	5'- AGAGCTAAGCACTTTTTAGGT -3'	5'-TAGAGAGCTAAGCACTTTTTAGATA[C/T]
	5'- GATGAAATGTAGCAGTGAAGT -3'	TATATAATTTAATTGCCGTATGAGG -3'
rs12255372	5'- CCAGGAATATCCAGGCAAGGAT -3'	5'- TGCCCAGGAATATCCAGGCAAGAAT[G/T]
	5'-GGCATTCAAATGGAGGCTGA -3'	ACCATATTCTGATAATTACTCAGGC -3'

Table 2: The sequence of primers and probes for rs7903146 and rs12255372

Genotype OR (95%CI)	Healthy Controls	Cases with T2DM	χ2
	N (%)	N (%)	p value
(rs7903146)			
CC (Reference)	58	36	**0.0172**
CT **(1.39-7.42)**	10	22	**3.222**
TT **(1.11- 3.80)**	32	42	**2.05**
(rs7903146)			
GG (Reference)	82	69	**0.1041**
GT **[2.641(1.13-6.17)]**	9	20	
TT **(0.57- 3.71)**	9	11	**1.452**

Table 3: Analysis of TCF7L2 SNPs genotype frequency in controls and T2D patients (Note: Statistically important results are shown as bold)

Discussion

TCF7L2 is a high mobility group box containing transcription factor and play important role in cell and regulatory metabolism [18]. It is important component of Wnt signal pathway. Wnt complex with TCF7L2 transcriptionally regulate expression of proglucagon in gut endocrine L cells [19]. Thus, variant of TCF7L2 can change level of proglukagon gene product, glucagon- like protein-1 (GLP-1) and insulinotropic hormone [20]. GLP-1 and insulin together keep blood glucose level in balance. Altered level of GLP-1 can affect susceptibility to T2D [21]. There are lots of study about TCF7L2 polymorphisms and its risk for T2D. Most of study reports that significant association between the TCF7L2 rs7903146, rs12255372 and risk of T2DM [22-24]. However, there are some studies suggest that no association between TCF7L2 rs12255372 and risk of T2D [25].

In our study, there was significant difference between patient and control groups on rs7903146 (C/T) polymorphism (p=0.0172). The number of TT mutant genotype in patients group is more than twice the number in control groups. This result suggests that individuals who carry this mutant allele have more risk of developing of T2D. However, there was no significant difference for rs12255372 (G/T) polymorphism (p=0.1041). Surprisingly, GT genotype was higher in patient groups (p=0.0250). This results shows that it might be associated with T2D if the number of sample is increased.

Jyothi et al. [26] studied TCF7L2 gene polymorphisms on 758 T2D patients and 621 controls. They found that significant association between T2D and rs7903146 (OR 1.88, $p<0.001$) and rs12255372 (OR 1.50, $p<0.001$). Sladek et al. [21] performed 392,935 SNP analyses on 1363 French populations with T2D. Similarly, they reported that especially TCF7L2 rs7903146 gene variant has highly significant effect on developing of T2DM ($p=3.2 \times 10-17$). Mayans et al. [27] performed similar study on 872 T2D patients and 857 controls in Swedish populations. They found significant associations between TCF7L2 polymorphism and T2D (rs7901346, P=0.00002; and rs12255372, P=0.000004). TCF7L2 have been also reported to be associates with different types of cancer. Chen et al. [28] studied TCF7L2 gene polymorphism on different types of cancer in American population. As result of Meta analyses, they found that especially rs7903146 have significant association in breast, lung prostate and colon cancer.

Regarding of all those results, rs79013146 gene polymorphism is a major risk factor almost all ethnicity. This shows that TCF7L2 is one of the important genes for susceptibility to T2D. In addition, finding of relation between TCF7L2 polymorphisms and different types of cancer

shows that it is also susceptible gene to cancer. If the number of study with different ethnicity is increased on this gene, it will be helpful to enlighten of association between cancer and diabetes. In conclusion, our data show that significant association between TCF7L2 rs7903146 and T2D risk. However, further studies with larger number will be required to confirm our data. In addition, there are other factors including age, sex, alcohol using, and ethnicity contributing to progress of T2D. Those factors may affect the genes and predispose individuals to T2D.

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Conflict of Interest

No conflicts of interests were disclosed by the authors.

ABBREVIATIONS

T2D Type 2 diabetes

DM Diabetus mellitus

EDTA Ethylene diamine tetraacetic acid

OR Odds ratio

TCF7L2 Transcription factor 7-like 2

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