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The Correlation between *TCF7L2* (rs12255372) Polymorphism and the Incidence of Type 2 Diabetes Mellitus in Iraqi Patients

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Abstract

Type two diabetes mellitus (T2DM) is a chronic metabolic condition characterized by hyperglycemia, resulting from insulin resistance or inadequate insulin secretion. Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene demonstrate a significant correlation with T2DM among many ethnic populations. This study sought to assess the association between the TCF7L2 rs12255372 (G/T) polymorphism and the susceptibility to T2DM within a sample of the Iraqi population. The PCR-RFLP method was employed to investigate the TCF7L2 gene polymorphism in (50) T2DM patients and (25) healthy persons. All samples were obtained from the local community in Wasit province, Iraq. The results revealed substantial differences in rs12255372 genotypic and allele frequencies between patients and the control group ($P < 0.05$), with a heightened frequency of the G allele in patients (OR = 11.37, 95% CI 3.99–32.4, p = 0.0000021). The results suggest a possible association of the TCF7L2 rs12255372 (G>T) polymorphism with genetic susceptibility to T2DM, indicating that bearers of the G allele in the Iraqi population may have an elevated risk of disease onset.

Keywords: Gene polymorphism, Allele frequency, TCF7L2 gene, T2DM, PCR-RFLP.

العلاقة بين تعدد الأشكال الجينية TCF7L2 (rs12255372) وحدوث داء السكري من النوع الثاني لدى المرضى العراقيين

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الخلاصة

داء السكري من النوع 2 (T2DM) هو اضطراب أيضي مزمن يتميز بارتفاع مستوى السكر في الدم (ارتفاع السكر في الدم)، والذي يعزى إلى مقاومة الأنسولين أو ضعف إنتاج الأنسولين. تظهر الاختلافات في جين (TCF7L2)ارتباطًا قويًا مع T2DM عبر المجموعات العرقية المختلفة. هدفت هذه الدراسة إلى تقييم العلاقة بين تعدد الأشكال TCF7L2 rs12255372 (G/T) والقابلية للإصابة بـ T2DM في عينة من السكان العراقيين. تم استخدام تقنية PCR-RFLP لفحص تعدد أشكال الجينات TCF7L2 في (50) مصابا بالسكري T2DMو(25) من الأصحاء. تم جمع جميع العينات من المجتمع المحلي لمحافظة واسط، العراق. أظهرت النتائج اختلافات كبيرة في ترددات النمط الوراثي والأليل rs12255372 بين المرضى والسيطرة($P <0.05$) ، مع زيادة تردد أليل G في المرضى(OR = 11.37)، CI 3.99-32.4٪95، p = 0.0000021 تشير هذه البيانات إلى الدور المحتمل للمتغير TCF7L2 rs12255372 (G>T) في الاستعداد الوراثي لمرض T2DM، وقد يكون حاملو الأليل G في السكان العراقيين أكثر عرضة لخطر تطور المرض.

1.Introduction

Type 2 diabetes mellitus (T2DM) is a complicated metabolic disorder caused by various genetic and environmental conditions, defined by hyperglycemia, which can arise from various mechanisms, including reduced insulin secretion, peripheral tissue insulin resistance, and elevated glucose output by the liver. T2DM patients are more likely to develop peripheral circulation problems, blindness, renal failure, neuropathy, and cardiovascular disease [1–3]. Based on the International Diabetes Federation (IDF) research, 536.6 million people [10.5%] had type 2 diabetes worldwide in 2021, and 783.2 million people [12.2%] will have the disease by 2045 [4]. The occurrence of T2DM is linked with several risk factors, the most substantial of which is genetic predisposition. It has been established that certain genetic variants may lead to the inactivation or loss of gene function, hence promoting the pathophysiological processes that underlie the emergence and progress of the disorder [5]. Investigations on diabetes candidate genes have found an increasing number of genes connected with the potential danger of T2DM through their causative variations. The determination of these genetic variations may provide insight about the molecular pathways and mechanisms that lead to the development of T2DM [6].

Variations within transcription factor 7-like 2 (TCF7L2) have the highest connection with T2DM, making it the most major and potentially candidate gene among the identified genetic risk factors for the illness [7,8]. The *TCF7L2* gene is positioned on chromosome 10q25.3, spanning about 215 kb and having 17 exons. The TCF7L2 gene encodes a transcription factor that plays a critical role in the Wnt signaling pathway. This pathway includes a highly coordinated network of related proteins that are controlled at multiple levels, resulting in a variety of effects, and is principally linked with developmental biology [9,10]. The beginning and progression of diabetes are both significantly influenced by the Wnt signaling pathway. The basic Wnt ligand known as Wnt3a has the capacity to enhance the stability of β-catenin, control the expression of TCF7L2, encourage the proliferation of beta cells, and reduce the rate of apoptosis [11].

The main mechanisms by which TCF7L2 variations cause disease include defect in pancreatic β-cell function and decreased insulin secretion, which may be caused by impaired incretin effect , i.e. impaired stimulatory effect of incretin hormones such as GIP and GLP-1 on insulin secretion. TCF7L2 acts within the Wnt/β-catenin signaling pathway to regulates transcription of genes associated with proinsulin production, insulin exocytosis, and incretin (GLP-1 and GIP) signaling, thereby contributing to hyperglycemia and the progression of diabetes mellitus [12–14]. The current study's objective was to examine the relationship between T2DM and the TCF7L2 rs12255372 (G/T) polymorphism in an Iraqi population sample.

2. Methodology

2.1 Study Design

To determine whether the *TCF7L2* (rs12255372) polymorphism and the chance of acquiring type 2 diabetes are related, a case-control study was carried out. There was a total of seventy-five people who took part in this research project. Of them, fifty were type 2 diabetes patients (22

men and 28 females) who were between the ages of 35 and 68 years old, and twenty-five were healthy persons who were closely matched in age and sex. They were all from the Wasit province in Iraq, and the collection of blood samples took place between February and May of 2025.

2.2 Sample Collection and DNA Extraction

Samples of peripheral blood, ranging from three to five milliliters, were collected from each participant in tubes containing EDTA. Utilizing a DNA extraction kit manufactured by intron biotechnology / Korea, genomic DNA was extracted. The concentration and purity of the DNA were determined by employing a Nanodrop spectrophotometer at a wavelength of 260/280 nm. The extracted DNA samples stored at–20 until further analysis.

2.3 Genotyping of TCF7L2 Gene Polymorphism (SNP rs12255372)

The TCF7L2 (rs12255372) was examined by the restriction fragment length polymorphism (RFLP) method. A specific fragment of the TCF7L2gene was amplified by polymerase chain reaction (PCR) using forward and reverse primers designed for the target region (Table 1) [15]. The amplified PCR products were digested with the restriction enzyme TasI (Tsp509I) (Thermo Scientific), following the manufacturer's instructions, the temperature and time of incubation were 37°C / 45 min. Based on the observed pattern of restriction fragments, genotypes were identified.

Table1 - Primer sequences for the TCF7L2 gene (rs12255372) genotyping.

Primer	Sequence	Tm (°C)	GC (%)	Product size
Forward	5'- CTTGAGGTGTACTGGAAACTAAGGC - 3'	63.0	48%	251
Reverse	5'- CTGTCTATTTGGCATTCAAATGGA- 3'	57.6	38%	base pair

2.4 Statistical Analysis

When comparing the genotype and allele frequencies of TCF7L2 (rs12255372) between controls and T2DM patients, we utilized the chi-square ($\chi 2$) test to analyze the data. To determine the extent of the connection, we used odds ratios (OR) with a confidence interval of 95%. All of the statistical analyses that were carried out with SPSS version 26, where the p-value was lower than 0.05, were regarded as statistically significant.

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3. Results

The TCF7L2 (rs12255372) polymorphism was genotyped in (50) type 2 diabetes patients and (25) healthy individuals. Genetic polymorphism analysis identified all three potential genotypes (GG, GT, and TT) for (rs12255372) SNP, as shown in Figures 1.

Current results showed that the GG genotype was more common among patients (62.06%) in comparison with the control group (20%), as well as the GT genotype being more frequent among patients (31.03%), while the TT genotype was significantly more frequent in control (73.3%) than in the patient group (6.89%) (P = 0.00003). The G allele was significantly more

common in T2DM patients (77.58%) than in controls (23.33%), in contrast, the T allele frequency was identified to be higher in the control (76.6%) in comparison with the patient (22.41%) (P = 0.00001), as shown Table 2.

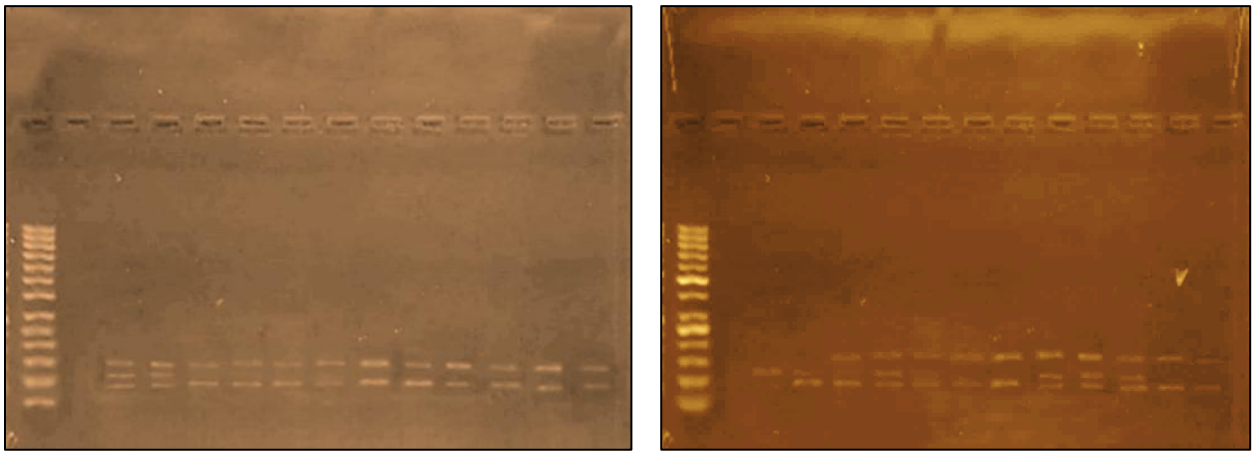

Figure -1 PCR–RFLP analysis of the TCF7L2 (rs12255372) polymorphism using the restriction enzyme TasI (Tsp509I). The estimated product sizes for GG, 143 bp, 104 bp; TT, 126 bp, 104 bp; and GT, 143, 126, and 104 bp, correspondingly. A 100 bp DNA ladder was used as a molecular size marker.

Table 2- The allelic and genotypic frequency of the TCF7L2 gene G>T rs12255372 polymorphism in both controls and diabetes patients.

Groups	Genotype Frequency (%)			Allele Frequency (%)	
	GG	GT	TT	G	T
Control(N=25)	20.000	6.66	73.333	23.33	76.66
Patients(N=50)	62.069	31.03	6.897	77.58	22.41
Chi square		21.018		24.075	
P-value		0.00003		0.00001	
Significance		Sig.		Sig.	

P-value < 0.05 (significant)

3.1 Correlation between TCF7L2 (rs12255372) Polymorphism and T2DM

To determine if there is a link between the TCF7L2 (rs12255372) polymorphism and type 2 diabetes risk, we calculated the odds ratio (OR) with 95% CI for the genotype and allele. Table 3 shows that those with the GG genotype are more likely to develop type 2 diabetes (OR = 6.5, 95% CI = 1.39 to 25.85, p = 0.011), whereas those with the TT genotype had a much lower risk of developing type 2 diabetes (OR = 0.02, 95% CI = 0.004 to 0.162, p = 0.000003). Research has shown that having the G allele of TCF7L2 (rs12255372) increases the risk of type 2 diabetes mellitus (T2DM) in the population studied (odds ratio OR =11.37, 95% CI = 3.99-32.41, p = 0.0000021). On the other hand, the T allele seemed to provide protection against T2DM, as it was more commonly found in healthy subjects than in patients (OR = 0.088, 95% CI = 0.03-0.250). According to these results, the G allele at rs12255372 may be a risk factor for type 2 diabetes mellitus (T2DM), but the T allele may be a protective factor.

Table -3 Relationship between T2DM susceptibility and the TCF7L2 rs12255372 (G/T) polymorphism

Genotype/ allele	OR	95%CI	P-Value	Significance
GG	6.5	1.392 to 25.858	0.011	Sig.
GT	6.3	0.682 to 52.752	0.076	Ns.
TT	0.026	0.004 to 0.162	0.000003	Sig.
G allele	11.37	3.99–32.41	0.0000021	Sig.
T allele	0.088	0.031–0.250	0.000002	Sig.

P-value < 0.05 (significant)

4. Discussion

The purpose of this study was to investigate the connection between the TCF7L2 (rs12255372) genetic variation and the likelihood of acquiring type 2 diabetes among individuals from the Iraqi community. The results of the analysis showed that there were statistically significant differences in the genotypic and allelic distribution of the rs12255372 polymorphism between the patients and the control group ($P < 0.05$, Table 2). The higher frequency of the G allele in T2DM group (77.5%) relative to controls (23.3%), with an OR = 11.3, 95%CI = 3.99–32.41, proposes association with T2DM predisposition. In contrast, the frequency of the T allele was higher in the control group (76.6%) compared to the patient group (22.4%), indicating a protective role against T2DM (OR = 0.088, 95%CI = 0.031–0.250). Numerous studies among various ethnic populations showed that variations in the TCF7L2 gene have been persistently associated with T2DM and may serve as a prospective genetic indicator in T2DM patients. These polymorphisms contribute to T2DM by several mechanisms including impaired insulin production, deficiencies in glucose-mediated glucagon suppression, defect in insulin biosynthesis and processing, and increased hepatic glucose output in the fasting [7,16,17]. The current results are in agreement with Yang *et al*. (2015), they found statistical differences between the T2DM patients and the control group in both the genotypic and allelic frequencies at rs12255372 ($P < 0.01$). Furthermore, the frequency of the (rs12255372) G allele was significantly greater in the group with type 2 diabetes (90.1% versus 75.2% in the healthy group), with an odds ratio of 1.198. The T allele, on the other hand, was found more frequently in the healthy group (24.8%) than in the group of people with type 2 diabetes (9.9%) with OR= 0.400. The results of this study suggest that the G allele may be considered a risk factor for type 2 diabetes, but the T allele is considered a protective factor [15].

A study conducted by Mandour *et al*. (2018) in the Egyptian society further supported these findings, which discovered that the frequency of the T allele was higher among healthy individuals (51.7%), while in T2DM individuals (39.2%), and not connected with T2DM (OR = 0.602, 95% CI = 0.361-1.005, $P = 0.052$), whereas the G allele frequency (48.3%) in control group and (60.8%) in the diabetic group [18]. As opposed to our findings, the T allele of (rs12255372) has been detected as a predisposing factor for diabetes in both Chinese and Cameroonian populations [19,20]. According to Barros *et al*. (2014), there was no significant correlation between the allele and genotype distribution of rs12255372 with the risk of type 2

diabetes [21]. On the other hand, Shokouhi *et al*. (2014) demonstrated that the T allele of the (rs12255372) SNP of *TCF7L2* was associated with type 2 diabetes within the Kurdish people in Iran [22]. Alami *et al*. (2012), investigate the relationship between TCF7L2 (rs12255372) and T2DM in an Iranian community and detect that the minor T allele of TCF7L2 (rs12255372) is strongly linked with the probability of developing T2DM, with OR = 1.458 (95% CI 1.108-1.918, p = 0.007) [23].

Numerous investigations carried out in the Saudi and UAE populations revealed a slight or no connection between rs12255372 and T2DM, whereas a study conducted in an Arab Tunisian cohort demonstrated a relationship of the T allele of rs12255372 with T2DM [24–26]. The correlation between TCF7L2 gene variants and the incidence of T2DM has been further supported by a number of studies conducted in different ethnic groups, such as British, Dutch, Swedish, French, Indian, American, and Japanese [27–33].

The variations among populations could be due to ethnic differences, environmental effects, gene-gene interactions, and differences in sample size that affect the functional outcome of TCF7L2 polymorphisms. As a result, whereas the T allele is widely recognized as a risk factor worldwide, the reverse association observed in our findings and others indicates the need for additional studies in different ethnic populations to explain the population-specific effects of TCF7L2 polymorphisms on diabetes predisposition.

The TCF7L2 (rs12255372) polymorphism is situated within a non-coding intronic sequence of the gene and reveals a strong correlation with T2DM. The precise mechanism by which a genetic alteration within the TCF7L2 gene's intron causes vulnerability to type 2 diabetes is still unclear. Genetic variants located close to the 3’ end of the TCF7L2 gene may disturb its expression by modulating alternative splicing [34,35].

All of the TCF7L2 gene's identified polymorphisms are situated so far in the intronic sequence. Thus, it is crucial to describe how the TCF7L2 gene's expression is affected by intronic alterations. In this regard, Srinivasan *et al*. (2018), showed that (rs12255372) T allele carriers revealed a substantial rise of TCF7L2 mRNA expression in pancreas islets of humans, that was linked with reduce secretion of insulin, and increased the rate of liver glucose output. Also, it has indirectly influenced through changing GLP-1 levels, which are transcriptionally controlled by TCF7L2 [36].

5. Conclusion

This study indicated that the rs12255372 (G>T) variation is related to the vulnerability to T2DM in a sample from the Iraqi population. Further research is needed to support the current findings in larger and more ethnically diverse populations. Considering the crucial role of TCF7L2 genetic variants in disease development, additional research into TCF7L2's functional role in type 2 diabetes is critically required.

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Ethical Considerations

The participants provided consent, and the Iraqi Ministry of Health's ethical commission approved the collection of blood samples.

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