

Assessment of TCF7L2 Gene rs7903146 Polymorphism as Type 2 Diabetes Genetic Risk Factor within Southern Iraqi Population

Assessment of
TCF7L2 Gene
rs7903146
Polymorphism as
Type 2 Diabetes

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ABSTRACT

Objective: To investigate the association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes mellitus susceptibility in a southern Iraqi population

Study Design: Case-control study

Place and Duration of Study: This study was conducted at the Al-Fayhaa Teaching Hospital, Basrah, Iraq, from 1st November 2025 to 31st March 2026.

Methods: A total of 184 participants, including 103 patients with T2DM and 81 healthy controls were enrolled. Demographic and clinical data were collected, and genotyping of rs7903146 was performed using the tetra-primer amplification refractory mutation system polymerase chain reaction (Tetra-ARMS PCR). Selected samples were further validated by deoxyribonucleic acid (DNA) sequencing and basic local alignment search tool (BLAST) analysis.

Results: The frequency of C allele was significantly higher in controls (90.1%) than in patients (55.3%), suggesting a protective effect. In contrast, the T allele was more prevalent among patients (44.7%) than controls (9.9%), indicating its role as a risk allele. Significant associations were observed between the T allele and increased susceptibility to type 2 diabetes mellitus, with both heterozygous (CT) and homozygous (TT) genotypes showing elevated risk ($p < 0.01$ and $p < 0.002$, respectively).

Conclusion: A strong association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes mellitus susceptibility in the studied population.

Key Words: TCF7L2, rs7903146, Type 2 diabetes mellitus, Wnt signalling pathway.

Citation of article: Mohammed MQ, Saleh AA. Assessment of TCF7L2 Gene rs7903146 Polymorphism as Type 2 Diabetes Genetic Risk Factor within Southern Iraqi Population. Med Forum 2026;37(9):94-98. doi:10.60110/medforum.370918.

INTRODUCTION

Diabetes mellitus (DM) is known as a major induce for mortality and morbidity worldwide, influencing people across various residence, ethnicity, age, or sex¹. It classifies as modern society illness, as it represents a complicated, multifaceted metabolic condition², where the body failed to deal with sugar efficiently³. As a metabolic syndrome, diabetes has led to many related health issues for those affected and is categorized by the World Health Organization (WHO) as one of the most lethal diseases globally and a quiet threat⁴, these issues include but are not limited to diabetic

neuropathy, diabetic retinopathy, diabetic nephropathy, atherosclerosis and a cardiovascular risk (CVR) which is 2 to 3 times greater compared to those who do not have diabetes⁵. Also, individuals with diabetic Foot face a higher chance of experiencing foot ulcers, infections, and possibly amputations due to inadequate blood flow and nerve damage⁶. Diabetes caused an estimated 3.4 million deaths worldwide in 2024 and led to a staggering total health expenditure of about 1.015 trillion USD globally, with expenditures reaching 1.043 trillion USD in low- and middle-income countries⁷.

Diabetes mellitus has three main categories that can be identified. These are gestational diabetes, type 1 diabetes, and type 2 diabetes. The early phase of type 2 diabetes is characterized by insulin resistance, where cells fail to respond appropriately to insulin. As the condition progresses, there may be an insufficient supply of insulin, this disorder was previously known as "adult-onset diabetes" with clinical signs like frequent urination, excessive thirst, increased hunger, loss of weight, unclear vision, and difficulties with erectile function^{8,9}.

T2DM which makes up over 90% of diabetes incidences is influenced by a variety of interconnected

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Received: May, 2026

Reviewed: June-July, 2026

Accepted: August, 2026

risk factors that may be partially adjustable. The primary modifiable factors include dyslipidemia, characterized by elevated levels of cholesterol and triglycerides, along with excess body fat, both of which significantly drive the advancement of the disease⁷, also many Hormones include insulin, glucagon, incretin hormones play a vital role in the onset and regulation of the diabetes because of their impact on key metabolic functions such as appetite, insulin sensitivity, fat accumulation, and the burning of energy⁸. Conversely, non-modifiable factors encompass genetic susceptibility, which includes both personal and familial diabetes history particularly in first-degree relatives as well as inherited genetic variations that increase vulnerability to T2DM^{10,11}. Numerous genes are associated with T2DM, the polymorphisms rs7903146 of the TCF7L2 is among the most vulnerable genes identified related to T2DM so far¹². Genome-wide association studies (GWAS) have pinpointed more than 100 genetic locations associated with T2D, many of which pertain to insulin production, glucose control, and body fat¹³.

METHODS

This case-control study was conducted at Al-Fayhaa Teaching Hospital, Basrah, Iraq from 1st November 2025 to 31st March 2026 vide letter No. MEC-1101-UB/Approval/JSDJNS dated October 21, 2025. A total of 184 participants, including 103 patients with T2DM and 81 healthy controls were enrolled. The case group covered 62 females and 41 males, while the control group encompassed 40 females and 41 males. The diagnosis was validated according to the standards delineated by the American Diabetes Association (ADA), which encompass random blood glucose ≥ 140 mg/dL and/or HbA1c $\geq 6.5\%$ in addition to certain clinical signs and symptoms. The cohort act as control group exhibited comparable ages and lacked any family or personal medical history indicative of diabetes or cardiovascular disease¹⁴. Validated protocols were aligned with anthropometric measurements, including height and weight, to facilitate the calculation of BMI. Subsequent of efficient human genomic DNA extraction from blood samples in respective manufacturer protocol, from the Geneaid™ DNA Isolation Kit (Blood) from Taiwan. The PCR was performed with utilizing a Tetra primers ARMS technique and the theoretical frame works suggest that the copies of target sequence approximately reached a million.

The forward inner primer: (5-TAGAGAGCTAAGCACTTTTATAGATAC-3, reverse inner primer: (C 5-CTC ATA CGG CAA TTA AAT TAT ATA A-3), and two outer primers (forward outer: 5-AAT TTT TTC ACA TGT GAA GAC ATA C-3, reverse outer primer (5-TTT ATA GCG AAG AGA TGA AAT GTA G-3). 12.5 μ l of master mix (A

GoTaq® G2 Green Master Mix, Promega, USA), 1 μ l of each primer, 3 μ l of template DNA, and 5.5 μ l of nuclease free water mixed to reach a total volume of 25 μ l, and the PCR cycles begin with an initial denaturation phase at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, then annealing at temperature of 54°C for 60 second, extension at 72°C for 120 second, and conducted with a final extension at 72°C for 5 minutes. PCR products were exposed to gel electrophoresis on 2% agarose gels, visualized under ultraviolet light, and subsequently documented. Following sequencing, the resulting raw sequences were analyzed using the Basic Local Alignment Search Tool (BLAST) to identify similar sequences in the National Center for Biotechnology Information (NCBI) database. The samples, which exhibited different genotypes were categorized as heterozygotes (TC) or (TT) subsequently. The data was analyzed through SPSS-22. The Chi-squares test or the Fisher Exact Probability test was used, as well the T-test which utilized to make comparisons between two distinct numeric variables.

RESULTS

There was a significant variation in the CC genotype for SNP rs7903146 among T2DM patients, with 28 individuals (27.2%) in the patient group, compared to 67 individuals (82.7%) in the control group. furthermore, the results for the TT genotype (Homozygous) revealed a strong elevated in prevalence in T2DM patients compare to the control group. Additionally, a significant differentiation was observed in the CT genotype (heterozygous), with T2DM patients showing 58 cases (56.3%) versus 12 cases (14.8%) in the control group. In Table (1), C allele frequencies were recorded at 114 (55.3%) for patients and 146 (90.1%) for controls, while T allele frequencies were 92 (44.7%) for patients and 16 (9.9%) for controls. The differences observed in genotype and allele frequencies between T2DM patients and the control group were highly significant ($P=0.01$) for the C allele and $P=0.002$ for the T allele (Table 1).

Genotyping of the TCF7L2 rs7903146 (C>T) polymorphism was performed using (T-ARMS-PCR). The amplified products were resolved by 2% agarose gel electrophoresis and visualized under UV illumination. Genotypes were identified as CC (homozygous wild-type), CT (heterozygous), and TT (homozygous mutant) based on the observed banding patterns (Figs. 1-4).

Accurately determining DNA fragment nucleotide sequences was performed by utilizing Sanger sequencing technique, which known for its precision and dependability. Sanger sequencing reactions were carried out on the purified PCR products for both cases and control group, then the created sequence chromatograms are examined in the national center

biotechnology information (ncbi) to find nucleotide replacements related to SNP changes (Table 2). Chromatograms was used to view and comprehend Sanger sequencing chromatograms and evaluating

overlapping or separate signal peaks, which giving a raise to assess peak quality, find nucleotide sequences, and spot heterozygous or homozygous SNP variations. Chromatogram analysis showed in figure 2.

Table No. 1: TCF7L2 rs7903146 variant exhibits strong genetic association with T2DM across multiple inheritance models

Genotype/SNP	Patients (n=103)	Control (n=81)	Chi-square	P-value	OR(C.I)
Codominant					
C/C	28 (27.2%)	67 (82.7%)	55.98	0.01	Reference
T/T	17 (16.5%)	2 (2.5%)	9.647	0.002	4.52(1.74 to 11.72)
C/T	58 (56.3%)	12 (14.8%)	32.124	0.01	5.76(3.17 to 10.47)
Dominant					
TT+CT	75 (84.3%)	14 (15.7%)	0.49	0.48	1.75(8.63-0.35)
Recessive					
CC+CT	86 (52.1%)	79 (47.9%)	45.0	0.01	0.086(0.185-0.04)
Allele					
C	114 (55.3%)	146 (90.1%)	52.77	0.01	0.19(0.12to 0.29)
T	92 (44.7%)	16 (9.9%)	52.916	0.01	5.33(3.39to 8.37)

Table No. 2: BLAST analysis of sequenced sample with homo sapiens reference sequence

Name	Scientific name	Similarity %	Accession No.
J41	Homosapiens	99.39	PQ-074218.1
J40	Homosapiens	99.38	PQ-074218.1
J39	Homosapiens	99.37	PQ-074218.1
J38	Homosapiens	99.38	PQ-074222.1
J37	Homosapiens	99.37	PQ-074222.1
J34	Homosapiens	99.13	NG-012631.1

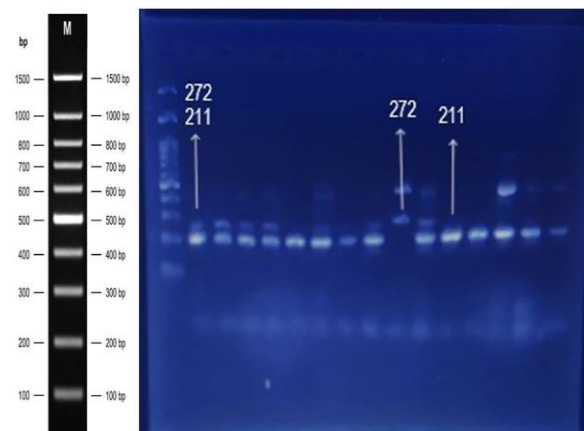


Figure No. 1: Resolution of Tetra-Primer ARMS-PCR Products for TCF7L2 rs7903146 (C>T) Genotyping by 2% Agarose Gel Electrophoresis showing Allele-specific banding patterns (272 bp and 211 bp)

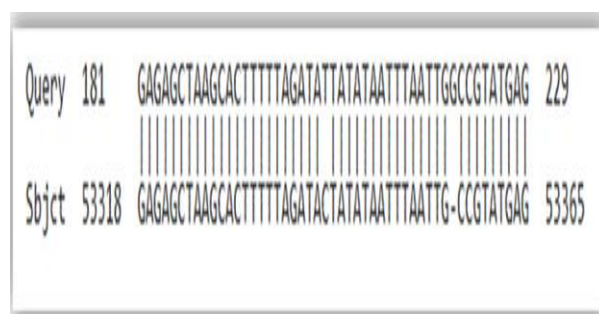


Figure No. 2: Chromatogram by Sanger sequencing (T allele a trs7903146)

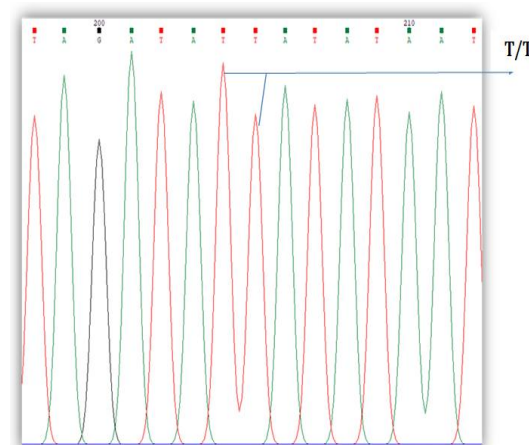


Figure No.3: Alignment of the sample sequence with the reference TCF7L2 gene sequence

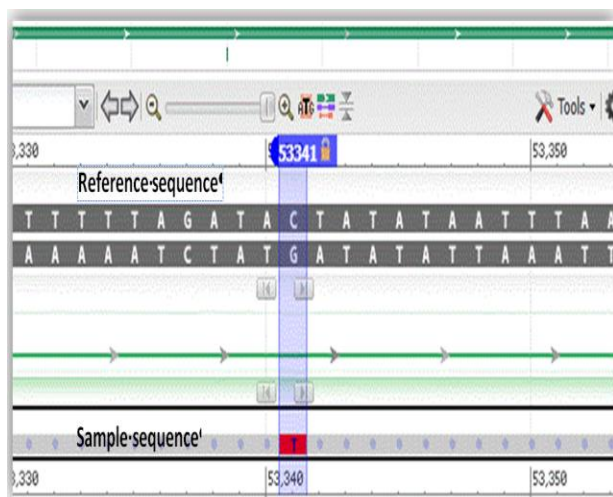


Figure No. 4: Detection of SNP variation by DNA sequence alignment analysis (C>T substitution)

DISCUSSION

The genotype distributions reflect a pronounced skew toward the CC genotype in control subjects (82.7%), whereas patients revealed a predominance of the CT genotype (56.3%), focusing on the possibility of risk allele classification and statistical precision was implemented through chi-square analyses (55.98 for codominant CC versus other categories, $P=0.01$), along with odds ratios with 95% confidence intervals to ascertain effect sizes in the present study.

T2DM, acknowledged as a worldwide metabolic disorder characterized by the impairment of glucose, protein, and lipid metabolism arising from decline tissue responsiveness to insulin, which in consequence leads to impaired insulin secretion. The key clinical manifestation of T2DM including without limitation to elevated blood glucose concentrations and insulin resistance. Despite the Genetic factors considerably effect the etiology of the disease, environmental elements involving an unhealthy diet, excess weight, lack of physical activity, and certain environmental influences, further aid in the onset of diabetes¹².

Table 1 showed a deep analysis of the TCF7L2 rs7903146 differentiation within a case and control groups and revealed a significant allelic imbalance, with more frequent TT genotype among the patients (16.5% compared to 2.5%), leading to OR of 4.52 (95% CI:1.74-11.72, $\chi^2=9.647$, $P=0.002$). While the CT heterozygous genotype is prevalent in-patient groups (56.3% vs. 14.8%), although this is reflected in contrasting recessive patterns (CC-CT versus TT: OR=5.76 CI: 3.17-10.47, $P=0.01$), evidenced the affected by deficiencies in beta-cell in cretin and disturbances in the Wnt/ β -catenin pathway. In dominant models (TT-CT vs. CC), findings were considered non-significant (OR=1.75 [0.35-8.63], $P=0.48$). coupled with the above, allelic analysis explicitly identifies the

T allele as a risk allele (44.7% in cases versus 9.9% in controls; OR=5.33 [3.39–8.37], $\chi^2=52.916$, $P=0.01$).

Correspondingly, Iranian study conducted by Amoli et al¹⁵ demonstrated a robust linked between the rs7903146 T allele and T2DM onset. Their study result given a prove support to the herein conclusions and focused on the crucial role of this SNP as a significant genetic predictor of T2DM. Along the same trajectory, a meta-analysis carried out by Wang and others¹⁶ in China in 2013 evidenced that within the Chinese population, the rs7903146 T allele is conspicuous as one of the most influential genetic contributors to T2DM susceptibility. They noticed that both the CT and TT genotypes strongly linked with T2DM risk, closely aligned with the findings of the current study. Moreover, Mustafa and Younus¹⁷, Iraqi researchers conducted a study in 2021 among the Kurdish people in Erbil, and revealed that, the CT and TT genotypes had significant relation with T2DM onset tendency. They demonstrated that patients with T allele had a significantly elevated risk of developing T2DM, agree with the current outcome, which shows that the T allele founded in 44.7% of patients and purely 9.9% of healthy participants. Similarly, Chaudhary and colleagues¹⁸ in Kuwait in 2024 study the TCF7L2 polymorphisms and demonstrated significant association with increased T2DM susceptibility, especially among participants carrying alleles linked β -cell dysfunctionality, insulin production and activity. Their findings evidenced the existing concept that the T allele is major contributor to both disease susceptibility an dim paired metabolic regulation In same direction, Nouri and Altaee¹⁹ in Iraq during 2025 revealed a strong relation between the TCF7L2 rs7903146 polymorphism and T2DM onset, with the T allele being more frequencies in case cohort. Their outcomes reinforcement the existed findings, particular in regarding to prevalence of CT and TT genotypes in patients and the protective function of the C allele and considerable concordances with previous studies from Iraq, Iran, Kuwait, and China, thus supporting the significant role of the TCF7L2 rs7903146 polymorphism in increasing T2DM susceptibility.

CONCLUSION

Overall, the TCF7L2 rs7903146 differentiation considered as strongest genetic factor play a robust role in glucose homeostasis within patient group, with T allele revealed a significant odds ratio of 5.33 (95% CI:3.39–8.37). -his allele affected beta-cell function by negative regulatory and inducing in cretin resistance. This reveals a critical requirement for the necessity of genetic mapping configurations in Arabian genetic and scapes to establish personalized endocrinological defenses against the T2DM susceptibility.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Manar Qasim Mohammed, Afrodet A. Saleh
Drafting or Revising Critically:	Manar Qasim Mohammed, Afrodet A. Saleh
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No. MEC-1101_UB/
Approval/JSDJNS Dated 21.10.2025

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