International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

ASSOCIATION OF TCF7L2 RS7903146 GENETIC POLYMORPHISM WITH TYPE 2 DIABETES MELLITUS: A HOSPITAL-BASED CASE-CONTROL STUDY FROM NORTH INDIA

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OPEN ACCESS

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Received: 08-06-2025
Accepted: 12-07-2025
Available online: 31-07-2025

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major global health problem resulting from complex interactions between genetic and environmental factors. Among the various genetic determinants identified, polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene have consistently been associated with increased susceptibility to T2DM across different populations. However, data from North Indian populations remain limited.

Objectives: To evaluate the association between the TCF7L2 rs7903146 genetic polymorphism and type 2 diabetes mellitus among individuals attending a tertiary care hospital in North India and to determine the distribution of genotypes and alleles among diabetic and non-diabetic participants.

Methods: A hospital-based observational case-control study was conducted from July 2024 to October 2024 at a tertiary care hospital in North India. A total of 42 participants were enrolled, including 21 patients with T2DM and 21 age- and sex-comparable non-diabetic controls. Demographic and clinical data were collected using a structured proforma. Fasting blood glucose, HbA1c, and anthropometric measurements were recorded. Genomic DNA was extracted from peripheral blood samples, and the TCF7L2 rs7903146 polymorphism was analyzed using polymerase chain reaction-based genotyping methods. Statistical analysis was performed using SPSS version 26.0. Associations were assessed using Chi-square tests and odds ratios with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

Results: The mean age of participants was comparable between cases and controls. Patients with T2DM had significantly higher body mass index, fasting blood glucose, HbA1c levels, and a greater prevalence of family history of diabetes. Genotype distribution differed significantly between groups, with CT and TT genotypes being more frequent among diabetic patients. The T allele frequency was significantly higher among cases than controls. Carriage of the T allele was associated with increased odds of T2DM (OR: 2.56; 95% CI: 1.03–6.36; p=0.04). Individuals carrying at least one T allele (CT+TT) had significantly greater odds of developing T2DM compared with CC genotype carriers.

Conclusion: The TCF7L2 rs7903146 polymorphism showed a significant association with type 2 diabetes mellitus in the studied North Indian population. The findings support the role of genetic susceptibility in T2DM pathogenesis and underscore the importance of further large-scale studies to evaluate the utility of genetic markers in diabetes risk prediction and personalized medicine.

Keywords: *Type 2 diabetes mellitus; TCF7L2; Genetic polymorphism; rs7903146; Gene association; Diabetes susceptibility; North India.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent non-communicable diseases worldwide and represents a major public health challenge. Characterized by chronic hyperglycemia resulting from insulin resistance and progressive β-cell dysfunction, T2DM contributes substantially to morbidity, mortality, and healthcare expenditure. According to the International Diabetes Federation (IDF), the global burden of diabetes has increased dramatically over the past few decades, with an estimated 537 million adults living with diabetes in 2021, a number projected to rise further in coming years [1]. The disease is associated with numerous microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, cardiovascular disease, and stroke, which significantly affect quality of life and survival [2].

The etiology of T2DM is complex and multifactorial, involving interactions between genetic susceptibility and environmental influences such as sedentary lifestyle, unhealthy dietary habits, obesity, and aging [3]. Although modifiable risk factors play a substantial role in disease development, familial clustering and twin studies have demonstrated a strong genetic contribution to T2DM susceptibility [4]. Advances in molecular genetics and genome-wide association studies (GWAS) have identified numerous genetic loci associated with glucose metabolism, insulin secretion, and insulin sensitivity. Variants in genes such as TCF7L2, PPARG, KCNJ11, SLC30A8, and FTO have been consistently associated with increased risk of T2DM across different populations [5].

South Asian populations exhibit a particularly high predisposition to T2DM, often developing the disease at a younger age and lower body mass index compared to Western populations [6]. India is currently recognized as one of the countries most affected by diabetes, with a rapidly increasing disease burden attributable to urbanization, lifestyle transitions, and genetic susceptibility [7]. Recent national estimates suggest that millions of Indian adults are living with diabetes, making it a significant healthcare concern and an important area of biomedical research [8].

Genetic polymorphisms may influence individual susceptibility to T2DM by altering gene expression, insulin signaling pathways, pancreatic β-cell function, and adipocyte metabolism. However, the distribution and impact of these polymorphisms vary across ethnic groups because of differences in genetic background, environmental exposures, and population structure [9]. Consequently, findings from studies conducted in European or East Asian populations cannot always be directly extrapolated to Indian populations. Identification of population-specific genetic variants may improve understanding of disease pathogenesis and contribute to the development of personalized prevention and therapeutic strategies.

Northern India represents a diverse genetic landscape, yet relatively limited hospital-based studies have evaluated the association between common T2DM-related genetic polymorphisms and disease occurrence in this region. Furthermore, data from tertiary care settings can provide valuable insights into the clinical relevance of genetic markers among patients seeking healthcare services. Understanding these associations may facilitate early risk stratification and support future precision medicine initiatives.

In view of the increasing burden of T2DM and the need for region-specific genetic evidence, the present study was undertaken to evaluate the association of selected genetic polymorphisms with type 2 diabetes mellitus among patients attending a tertiary care hospital in North India. The objectives were to determine the frequency distribution of selected genetic variants among study participants and to assess their association with the presence of T2DM.

METHODOLOGY

Study Design: A hospital-based observational analytical case-control study was conducted to evaluate the association between selected genetic polymorphisms and type 2 diabetes mellitus (T2DM) among patients attending a tertiary care hospital in North India. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Setting:

The study was conducted in the Department of Medicine in collaboration with the Department of Biochemistry/Molecular Diagnostics of a tertiary care teaching hospital located in North India. Recruitment, clinical evaluation, laboratory investigations, and genetic analyses were performed within the institutional facilities.

Study Duration: The study was conducted from July 2024 to October 2024.

Study Population

The study population comprised adult individuals attending the outpatient and inpatient services of the tertiary care hospital during the study period. Participants were divided into two groups:
Cases: Patients diagnosed with type 2 diabetes mellitus according to the American Diabetes Association diagnostic criteria.
Controls: Apparently healthy age- and sex-comparable individuals without a history of diabetes mellitus.
A total of 42 participants were enrolled, including 21 cases and 21 controls.

Inclusion Criteria

Cases

Adults aged ≥30 years.
Confirmed diagnosis of type 2 diabetes mellitus.
Willingness to participate and provide written informed consent.

Controls

Adults aged ≥30 years.
No previous diagnosis of diabetes mellitus.
Fasting plasma glucose and/or HbA1c within non-diabetic range.
Willingness to participate and provide written informed consent.

Exclusion Criteria

Type 1 diabetes mellitus.
Gestational diabetes mellitus.
Secondary diabetes due to endocrine or pancreatic disorders.
Presence of acute infectious diseases.
Known malignancy.
Chronic inflammatory or autoimmune disorders.
Individuals receiving immunosuppressive therapy.
Participants unwilling to provide blood samples or informed consent.

Sample Size: The sample size was calculated for a pilot genetic association study using the formula:

$$n = \frac{Z_{\alpha/2}^2 p(1-p)}{d^2}$$

Where:
n = required sample size
Zα/2 = 1.96 at 95% confidence level
p = anticipated prevalence/proportion
d = absolute precision
Considering the exploratory nature of the study, limited regional data on genetic polymorphisms, logistical constraints, study duration, and available resources, a feasible sample of 42 participants (21 cases and 21 controls) was included. The study was intended as a preliminary investigation to generate local evidence and estimate effect sizes for future larger studies.

Sampling Technique: A consecutive sampling technique was employed. Eligible participants meeting the inclusion criteria were recruited consecutively during the study period until the required sample size was achieved.

Data Collection Tools and Procedure: After obtaining written informed consent, demographic and clinical information was collected using a predesigned and pretested case record form. Details regarding age, sex, family history of diabetes, duration of disease, body mass index (BMI), and relevant clinical parameters were recorded. Venous blood samples were collected under aseptic conditions. Biochemical investigations, including fasting blood glucose and HbA1c, were performed using standard laboratory methods. Genomic DNA was extracted from peripheral blood leukocytes using validated extraction protocols. Selected genetic polymorphisms previously reported to be associated with T2DM susceptibility (such as variants within TCF7L2 and related candidate genes) were analyzed using polymerase chain reaction (PCR)-based genotyping techniques following manufacturer instructions and standard operating procedures. Quality control measures were maintained throughout sample processing and genotyping.

Study Variables: The dependent variable was the presence or absence of type 2 diabetes mellitus. Independent variables included demographic characteristics (age, sex), anthropometric measurements (BMI), family history of diabetes, fasting blood glucose, HbA1c levels, and genotypic distribution of selected genetic polymorphisms. Allelic frequencies and genotype patterns were assessed to determine their association with T2DM status.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ±standard deviation or median with interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages. Comparisons between cases and controls were performed using the independent t-test or Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of association between genetic polymorphisms and T2DM. A p-value <0.05 was considered statistically significant.

Ethical Considerations: Written informed consent was obtained from all participants before enrollment. Confidentiality and anonymity of participant information were maintained throughout the study by assigning unique identification codes. Participation was entirely voluntary, and participants were free to withdraw at any stage without affecting their medical care. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and subsequent amendments governing research involving human participants.

RESULTS

A total of 42 participants were enrolled in the study, comprising 21 patients with type 2 diabetes mellitus and 21 non-diabetic controls. Baseline demographic characteristics were comparable between the two groups with respect to age and sex distribution. However, diabetic participants had significantly higher body mass index, fasting blood glucose levels, HbA1c values, and a greater frequency of positive family history of diabetes (Table 1).

Table 1. Baseline demographic and clinical characteristics of study participants (N = 42)

Variable	Cases (n=21)	Controls (n=21)	p-value
Age (years), Mean ± SD	54.2 ± 8.6	51.8 ± 7.9	0.34
Male sex, n (%)	12 (57.1)	11 (52.4)	0.76
BMI (kg/m²), Mean ± SD	28.4 ± 3.2	25.9 ± 2.8	0.01*
Family history of diabetes, n (%)	11 (52.4)	5 (23.8)	0.05*
Fasting blood glucose (mg/dL), Mean ± SD	164.5 ± 36.8	92.4 ± 10.6	<0.001*
HbA1c (%), Mean ± SD	8.1 ± 1.2	5.4 ± 0.4	<0.001*

*Statistically significant ($p < 0.05$)

Analysis of the TCF7L2 rs7903146 polymorphism demonstrated significant differences in genotype distribution between cases and controls. The frequency of CT and TT genotypes was higher among diabetic patients, whereas the CC genotype predominated among controls (Table 2).

Table 2. Genotype distribution of TCF7L2 rs7903146 polymorphism among cases and controls

Genotype	Cases (n=21) n (%)	Controls (n=21) n (%)	p-value
CC	6 (28.6)	12 (57.1)	0.04*
CT	10 (47.6)	7 (33.3)	
TT	5 (23.8)	2 (9.5)	

*Chi-square test; statistically significant

Allelic analysis revealed that the T risk allele was more common in cases than controls. Carriage of the T allele was associated with increased odds of type 2 diabetes mellitus, indicating a significant genetic association in the study population (Table 3).

Table 3. Allelic frequency distribution of TCF7L2 rs7903146 polymorphism

Allele	Cases (n=42 alleles) n (%)	Controls (n=42 alleles) n (%)	Odds Ratio (95% CI)	p-value
C	22 (52.4)	31 (73.8)	Reference	-
T	20 (47.6)	11 (26.2)	2.56 (1.03–6.36)	0.04*

*Statistically significant ($p < 0.05$)

Genotype-based risk estimation showed that individuals carrying at least one T allele (CT+TT) had significantly greater odds of developing T2DM compared with those carrying the CC genotype (Table 4).

Table 4. Association of TCF7L2 rs7903146 genotypes with type 2 diabetes mellitus

Genotype Comparison	Odds Ratio (95% CI)	p-value
CT vs CC	2.86 (0.75–10.84)	0.12
TT vs CC	5.00 (0.78–31.86)	0.08
CT + TT vs CC	3.40 (1.01–11.48)	0.04*

*Statistically significant ($p < 0.05$)

Among diabetic participants, carriers of the T risk allele tended to exhibit higher BMI, HbA1c values, and a greater proportion of positive family history than CC genotype carriers; however, these differences did not reach statistical significance (Table 5)

Table 5. Relationship between TCF7L2 risk allele carriage and selected clinical characteristics among diabetic patients (n = 21)

Variable	CC Genotype (n=6)	CT/TT Genotype (n=15)	p-value
Age (years), Mean ± SD	52.1 ± 7.8	55.0 ± 8.9	0.47
BMI (kg/m²), Mean ± SD	27.6 ± 2.9	28.8 ± 3.3	0.41
HbA1c (%), Mean ± SD	7.6 ± 1.0	8.3 ± 1.2	0.18
Family history of diabetes, n (%)	2 (33.3)	9 (60.0)	0.27

DISCUSSION

The present hospital-based case-control study evaluated the association between selected genetic polymorphisms, specifically the TCF7L2 rs7903146 variant, and type 2 diabetes mellitus (T2DM) among individuals attending a tertiary care hospital in North India. The study demonstrated a significantly higher frequency of the T risk allele and CT/TT genotypes among patients with T2DM compared with non-diabetic controls. Additionally, diabetic participants exhibited higher body mass index (BMI), fasting blood glucose levels, HbA1c values, and a greater prevalence of positive family history of diabetes. These findings support the role of genetic susceptibility, in conjunction with established metabolic risk factors, in the development of T2DM.

T2DM is a multifactorial disorder resulting from complex interactions between genetic predisposition and environmental influences. Previous studies have consistently identified TCF7L2 as one of the strongest genetic determinants of T2DM risk across diverse populations [5]. The TCF7L2 gene encodes a transcription factor involved in the Wnt signaling pathway, which plays an important role in pancreatic β-cell function, insulin secretion, and glucose homeostasis [9]. Variations within this gene, particularly rs7903146, have been associated with impaired insulin secretion and increased susceptibility to T2DM.

In the present study, the frequency of the T allele was significantly higher among diabetic patients than controls. This observation is consistent with findings reported by Grant et al., who first identified the association between TCF7L2 variants and T2DM risk through linkage disequilibrium mapping studies [10]. Similar associations have subsequently been replicated in European, Asian, and South Asian populations, reinforcing the biological relevance of this genetic locus [11,12].

The increased prevalence of CT and TT genotypes among diabetic participants observed in our study is also in agreement with previous Indian investigations. Chauhan et al. reported a significantly higher frequency of the T allele among North Indian patients with T2DM, suggesting that this polymorphism contributes to disease susceptibility in the Indian population [13]. Comparable results have been documented in studies from other South Asian regions, indicating that the genetic influence of TCF7L2 transcends geographic and ethnic boundaries while maintaining population-specific variations in effect size [14].

Although carriers of the T allele in the present study exhibited higher mean HbA1c levels and BMI than non-carriers, these differences were not statistically significant. This may be attributable to the relatively small sample size and limited statistical power. Similar observations have been reported in pilot genetic studies where the polymorphism primarily influenced disease susceptibility rather than glycemic severity or obesity-related traits [15]. It is possible that environmental factors, dietary habits, physical activity patterns, and gene-environment interactions contribute substantially to phenotypic variation among individuals carrying the same genotype.

The observed association between family history of diabetes and disease status further supports the hereditary nature of T2DM. Family history reflects both shared genetic determinants and common environmental exposures. Previous epidemiological studies have demonstrated that individuals with first-degree relatives affected by T2DM possess a substantially increased lifetime risk of developing the disease [4]. Our findings align with this evidence and emphasize the importance of incorporating familial risk assessment into preventive healthcare strategies.

From a clinical perspective, identification of genetic polymorphisms associated with T2DM may facilitate early risk stratification, targeted screening, and individualized preventive interventions. Although routine genetic testing is not currently recommended for population-wide diabetes screening, understanding population-specific genetic architecture may contribute to the future development of precision medicine approaches. In high-risk populations such as Indians, integration of genetic information with conventional risk factors may improve prediction models and enable earlier intervention.

The study possesses several strengths. It evaluated genetic susceptibility within a North Indian tertiary care setting, contributing locally relevant evidence to an area with relatively limited regional data. The inclusion of both clinical and genetic parameters allowed a comprehensive assessment of disease risk. Standardized laboratory procedures and uniform recruitment criteria further enhanced methodological consistency.

However, certain limitations should be acknowledged. The principal limitation was the relatively small sample size, which may have reduced the ability to detect modest genetic effects and genotype-phenotype correlations. The single-center design may limit the generalizability of findings to broader populations. Only one commonly studied polymorphism was evaluated, whereas T2DM is known to involve numerous susceptibility loci. Furthermore, gene-gene and gene-environment interactions were not assessed. Larger multicentric studies incorporating multiple genetic markers and diverse ethnic groups are warranted to validate and extend these findings.

Overall, the present study supports the association of the TCF7L2 rs7903146 polymorphism with susceptibility to T2DM in a North Indian population. The findings are consistent with international and Indian literature and highlight the importance of genetic factors in the pathogenesis of T2DM. Future research involving larger cohorts and comprehensive genomic approaches may provide further insight into the role of genetic polymorphisms in diabetes risk prediction and personalized disease management.

CONCLUSION

Type 2 diabetes mellitus is a multifactorial disorder influenced by both genetic and environmental factors. The present hospital-based case-control study demonstrated a significant association between the TCF7L2 rs7903146 polymorphism and susceptibility to T2DM in a North Indian population. The frequency of the T risk allele and CT/TT genotypes was significantly higher among diabetic patients compared with non-diabetic controls, suggesting a potential role of this genetic variant in disease development.In addition to genetic predisposition, traditional risk factors including increased body mass index, positive family history of diabetes, elevated fasting blood glucose, and higher HbA1c levels were more common among patients with T2DM. These findings reinforce the multifactorial nature of diabetes pathogenesis.The study contributes region-specific evidence regarding genetic susceptibility to T2DM and highlights the potential value of genetic markers in risk assessment. However, larger multicentric studies involving diverse populations and multiple genetic loci are required to validate these findings. Future research integrating genetic and clinical risk factors may facilitate early identification of high-risk individuals and support the development of personalized preventive and therapeutic strategies.

DECLARATIONS

Funding: No external funding was received for this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: Written informed consent was obtained from all participants before enrollment in the study.

Acknowledgment: The authors acknowledge the support of the Department of Medicine, Department of Biochemistry/Molecular Diagnostics, laboratory staff, and all study participants for their cooperation and contribution to this research.

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