ANALYSIS OF TCF7L2 (rs7903146) GENE POLYMORPHISM IN TYPE 2 DIABETIC POPULATION IN NORTH INDIA

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ABSTRACT

Background: Approximately 20% of T2DM cases are linked to TCF7L2. TCF7L2 is the first gene to be identified as the most potent gene for type 2 diabetes by genome-wide linkage studies and genomic linkage studies. One of the primary genetic variants affecting the likelihood of developing T2DM is the rs7903146 polymorphism.

Methods: This study employed a case-control design among patients with Type 2 diabetes mellitus and healthy individuals. Participants from both groups were genotyped for the rs7903146 (C/T) variant of the TCF7L2 gene using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique.

Results: A total of 125 cases of type 2 diabetes mellitus were included in the study, and 125 healthy individuals were enrolled as controls. The wild homozygous CC genotype, heterozygous CT genotype, and homozygous TT genotype were present in 28%, 42.4%, 37% of the case group, vs 36.8%, 52.8%, and 10.4% of the control group, respectively. TCF7L2 rs7903146 T allele, especially in the homozygous TT state, is significantly linked to unfavourable glycemic outcomes like high FBS, PPBS, and HbA1c levels in the North Indian population living with T2DM.

Conclusion: This study shows a significant association of the rs7903146(C/T) SNP of the TCF7L2 gene with type 2 diabetes mellitus in the north Indian population.

Key Words: Type 2 diabetes mellitus, hyperglycemia, and polymorphism.

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INTRODUCTION

Diabetes mellitus (DM) is a disease where the hallmark feature is elevated blood glucose concentration.[1] Type 1 Diabetes occurs due to autoimmune β-cells destruction, generally leading to complete insulin deficiency. Insulin resistance and a gradual loss in sufficient insulin production from β-cells cause type 2 diabetes.[2]

Globally, the incidence of T2DM is rising at a concerning pace, impacting the economy, living standards, public health, and the healthcare system.[3] The International Diabetes Federation (IDF) found that 589 million adults aged 20-79 years worldwide had diabetes in 2024; by 2050, that figure is expected to rise to 852.5 million. In India, 89.8 million individuals are suffering from diabetes in 2024, and it is expected to rise to 156.7 million by 2050.[4]

Previous genetic studies suggested that multiple genes are moderately associated with the pathogenesis of T2DM.[5] The risk for T2DM is not linked to one segment, and it seems to be the outcome of the epistasis of multiple genes spread all across the genome.[6] In previous studies, it has been discovered that some genetic variants (PPARG, KCNJ11, IGF2BP2, KCNQ1, TCF7L2, CDKAL1, and MTNR1B) were responsible for increasing the likelihood of T2DM.[7]

Characteristics of the TCF7L2 gene.

TCF7L2 (T-cell specific, HMG-box) (TCF7L2, also known as TCF4) is a key transcription factor involved in the canonical wingless-type MMTV integration site (WNT) signaling pathway. It is important for the control of secretion of insulin by pancreatic beta cells & for the maintenance of glucose homeostasis. It also participates in vascular remodelling by controlling the proliferation of smooth muscle cells and endothelial cell growth.[8] It also plays a part in pancreatic islet development.[9]

In humans, TCF4 is encoded by the TCF7L2 gene. The TCF7L2 gene in humans is located on chromosome 10q25.3. It encodes 596 amino acids, has 18 exons, and is 215,863 bases long. Since the link of this gene with diabetes risk was first discovered in 2006, other polymorphism sites have been found [7,10]first sequenced in cell lines from CRC. The 18 exons that make up TCF7L2 exhibit a complicated splicing pattern in

various tissues. Functional domains are represented by highly conserved sequences in this gene. Exon 1 of human TCF7L2 (hTCF4) belongs to the β-catenin binding domain, while exons 10 and 11 relate to the HMG box binding domain. Furthermore, the 30 region comprising exon 18 of TCF7L2 comprises conserved sequence motifs with conserved splicing patterns resembling those of the transcription factor T-cell factor 1 (TCF1) gene. The COOH-terminal region of the TCF7L2 isoforms has two conserved binding motifs that have been identified across time. As per the complicated TCF7L2 splicing pattern, several protein isoforms with both agonistic and antagonistic trans activation activities are produced by the alternative utilization of isoforms in the 30 region.[10]

TCF7L2 is the first gene to be identified as the most potent gene for type 2 diabetes by genome-wide linkage studies and genomic linkage studies. One of the strongest genetic connections found in research on complex disorders is that of TCF7L and T2DM, which has been reliably reproduced in a number of populations with varying genetic backgrounds. The TCF7L2 variants linked to type 2 diabetes work in a genetic paradigm that is multiplicative. Approximately 20% of T2DM cases are linked to TCF7L2.[10]

Variants of TCF7L2 that are frequently observed include rs7901695, rs7903146, rs7895340, rs11196205, and rs12255372.[11] One of the primary genetic variants affecting the likelihood of developing T2DM is the rs7903146 polymorphism.[12] Hence, in this study, TCF7L2 polymorphism was analyzed to check its role in etiopathogenesis of T2DM, and further can be utilized for better patient management and reducing mortalities.

MATERIAL AND METHOD

A Case-control study was planned to detect the contribution of TCF7L2 rs7903146 polymorphism in type diabetes mellitus patients. This study was conducted on patients attending the OPD of the department of General Medicine and the department of Biochemistry of Santosh Medical College & Hospital, Ghaziabad, Uttar Pradesh. 125 pre-diagnosed type 2 diabetic patients were taken as the study group, and the same number of healthy individuals were taken as the control group. Inclusion criteria were to include subjects with a confirmed diagnosis of T2DM, aged 35 to 55 years of age. Before registering for the study, informed written consent was taken from the participants, expressing their willingness to participate in the study. Individuals suffering from Type 1 Diabetes mellitus, hemochromatosis, chronic kidney disease, chronic liver disease, thyroid disorders, malignancies, and patients taking lipid-lowering drugs were excluded from the study.

After 10 to 12 hours of overnight fasting, 5ml of blood was obtained from each participant using standard venipuncture procedure under aseptic precautions, of which 3ml was transferred in EDTA vial for HbA1c and RFLP, and 2ml in fluoride vial for blood sugar analysis.

Blood glucose estimation was done by the hexokinase method, and HbA1c by **the** immunoturbidimetric method. Participants from both groups were genotyped for the rs7903146 (C/T) variant of the TCF7L2 gene in DNA obtained from the peripheral blood using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique. PCR amplification of the rs7903146 (C/T) variant of the TCF7L2 gene mutation region was done using previously described primers.

Gene	Primers	PCR product size	Restriction Enzyme	Recognition site	Cleavage Site
TCF7L2 (rs7903146)	**Forward Primer**: 5′GAGAGCTAAGCACTTTTAGGTA-3′	113 bp	RsaI	5′-GTAC-3′	5′-G ↓ TAC-3′
	Reverse Primer: 5′-CTGACATTGACTAAGTTACTTGC-3′				

The PCR reaction was set in a total reaction volume of 20 µL containing 50 ng genomic DNA, 5 pmol each primer (Sigma-Aldrich, St Louis, MO), 10 µL 2X DreamTaq PCR Master Mix (Fermentas, Hanover, MD) containing DreamTaq DNA Polymerase, 2X DreamTaq buffer, deoxynucleotide triphosphate (dNTPs), and 4 mmol/L MgCl2. Initial denaturation was done at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 sec, annealing at 58°C for 40 sec, and extension at 72°C for 40 sec. This was followed by a final extension step of 10 min at 72°C. The 113 bp fragment generated was restriction digested with two units of RsaI (Fermentas) at 37°C for 8 h. The digested products were then separated on 3% agarose gel along with a 100 bp DNA ladder (Fermentas).

Genotype	Restriction Pattern	Expected Band Sizes (bp)
TT (Homozygous)	No RsaI restriction site	113bp
CT (Heterozygous)	Partial digestion	Two bands (~113 bp & ~91 bp)
CC	Complete	Two bands

(Homozygous)	digestion	(~91& & 22 bp)

RESULTS

Allelic and genotypic frequencies in patients and controls were estimated by direct counting. Comparisons between the groups were done using a t-test comparing 2 groups. Genotype and allele frequencies were compared between the T2DM and the control groups using logistic regression. Odds ratio (OR) with 95% confidence intervals was calculated. p-values less than 0.05 were considered statistically significant. All calculations were performed using SPSS 21.0.

Table 1: Genotype distribution in T2DM (Study group) and Control group

Genotype	Control Group (n=125)	T2DM Group (n=125)
CC	46 (36.80%)	35 (28.00%)
CT	66 (52.80%)	53 (42.40%)
TT	13 (10.40%)	37 (29.60%)

Genotype distribution of TCF7L2 polymorphism in T2DM patients and healthy controls. The CT genotype was the most common genotype in both groups, found in 53 (42.4%) T2DM patients and 66 (52.8%) controls. The TT genotype was more prevalent among T2DM patients [37 (29.6%)] than in non-diabetic controls [13 (10.4%)], and the CC genotype was less prevalent among T2DM patients [35 (28.0%)] than in controls [46 (36.8%)]. The results suggest that the TT genotype is increasing in T2DM patients in the studied population.

Table 2: Association of TCF7L2 rs7903146 Genotypes (CC, CT, TT) with Glycemic Parameters and BMI in the T2DM group (Study Group)

Parameter	CC (n=35)	CT (n=53)	TT (n=37)	F-value	p-value
FBS (mg/dL)	151.17 ± 57.09	149.47 ± 60.68	195.38 ± 81.59	6.005	**0.003***
PPBS (mg/dL)	210.91 ± 74.15	213.70 ± 85.95	285.43 ± 118.39	7.847	**0.001***
HbA1c (%)	7.53 ± 0.74	7.66 ± 1.08	8.96 ± 1.40	19.489	**<0.001***
BMI (Kg/m^2)	27.80± 3.97	28.77± 3.34	26.73± 3.53	3.567	**0.031***

***Shows statistically significant**

Values are presented as mean ± standard deviation. Means were compared between genotype groups using one-way ANOVA.

TCF7L2 (rs7903146) genotypes were significantly different statistically in glycemic parameters. The mean levels of FBS, PPBS and HbA1c were higher in TT genotype individuals than CC and CT genotypes ($p < 0.05$). Post hoc analysis showed that these differences were between the TT group and the CC and CT groups, but there was no significant difference between CC and CT groups. Mean values of glycemic parameters increased from CC to CT to TT genotypes. Among the parameters studied, the largest difference between groups was observed for HbA1c.

Table 3: Association of TCF7L2 rs7903146 Genotypes (CC, CT, TT) with Glycemic Parameters and BMI in Control Group

Parameter	CC (n=46)	CT (n=66)	TT (n=13)	F-value	p-value
FBS (mg/dL)	87.57 ± 9.57	86.44 ± 10.86	93.69 ± 10.70	2.648	0.075
PPBS (mg/dL)	117.41 ±12.26	117.47 ±14.00	124.54 ± 14.62	1.619	0.202
HbA1c (%)	4.73 ± 0.37	4.88 ± 0.37	5.04 ± 0.35	4.129	**0.018***
BMI (kg/m^2)	26.26 ± 2.44	25.77 ± 2.15	27.46 ± 4.27	2.498	0.086

***Shows statistically significant**

Values are displayed as mean ± standard deviation. Difference in means were evaluated between genotype groups using one-way ANOVA.

TCF7L2 (rs7903146) genotypes were significantly different statistically in glycemic parameters. The mean levels of FBS, PPBS and HbA1c were higher in TT genotype individuals than CC and CT genotypes ($p < 0.05$). Post hoc analysis demonstrated that these differences were among the TT group and the CC and CT groups, but the analysis did not reveal any significant difference between CC and CT groups. The mean values of glycemic parameters were increased from CC to CT to TT genotypes. The greatest difference across groups was observed in HbA1c of the parameters studied.

Table 4:Frequencies and univariate analysis of SNP genotypes and alleles in the study group and control group.

Genotype	T2DM (Study group) (n=125)	Healthy Subjects (Control group) (n=125)	OR (95 % CI)	p-value
CC	35(28.0	46(36.8%)	1.00 (Re	-

	%)		f)	
CT	53 (42.4 %)	66(52.8%)	1.055 (0.59-1.86)	0.85
TT	37 (29.6 %)	13(10.4%)	3.74 (1.73-8.08)	0.0006*
C allele	123 (49.2%)	158 (64%)	1.0 (Ref)	
T allele	127 (50.8%)	92 (36%)	1.77 (1.24-2.54)	0.002*

***Shows statistically significant**

Univariate analysis was applied to compare the genotype and allele frequency of TCF7L2 rs7903146 polymorphism in T2DM patients and healthy controls. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with the CC genotype and C allele as reference groups. Statistical significance was calculated by Chi-square test and p-value <0.05 was taken as significant statistically.

Table 5: Genetic Model Analysis between Control and T2DM Groups

Genetic Model	**Genotype Grouping**	**Control (n=125)**	**T2DM (n=125)**	**Odds Ratio (OR)**	**95% CI**	**Chi-square (x^2)**	**p-value**
Dominant (TT+CT vs CC)	CT+TT vs CC	79 vs 46	90 vs 35	**1.50**	0.87-2.60	2.2	0.138
Recessive (TT vs CT+CC)	TT vs CC+CT	13 vs 112	37 vs 88	**3.63**	1.83-7.20	13.9	**<0.001***
Additive (T vs C allele)	T vs C	92 vs 158	127 vs 123	**1.77**	1.24-2.54	9.92	**0.002***

***Shows statistically significant**

The genetic model calculations revealed that the recessive model (TT vs. CT+CC) was significantly linked with T2DM (OR = 3.63, p < 0.001). The finding shows that there is a strong correlation between TT genotype and T2DM risk.

The additive (allelic) model was also significantly linked (OR = 1.77, p = 0.002) hinting to a dose-dependent effect of the T allele on disease risk.

However, the dominant model (TT+CT vs CC) did not reveal significance (p = 0.138) indicating that the presence of a minimum of one T allele may not be sufficient enough to significantly increase the risk.

DISCUSSION

TCF7L2 is transcription factor which is highly polymorphic and has been implicated in insulin secretion and in an increased rate of hepatic glucose synthesis. It has been found to protect pancreatic cells death caused by interleukin-1 and interferon.[13]

(Table 2) The results revealed significant differences in FBS, PPBS, HbA1c and BMI in different genotypic groups indicating that the rs7903146 polymorphism affects glycemic control & metabolic characteristics in T2DM group. The mean FBS level was highest in persons with the TT genotype (195.38 ± 81.59 mg/dL) compared to those with the CC genotype (151.17 ± 57.09 mg/dL) and CT genotype (149.47 ± 60.68 mg/dL). The difference was found to be statistically significant (F = 6.005, p = 0.003). Similarly The TT genotype had significantly higher PPBS values (285.43 ± 118.39 mg/dL) than the CT (213.70 ± 85.95 mg/dL) and CC (210.91 ± 74.15 mg/dL) genotype carriers (F = 7.847, p = 0.001). Similar result are also shown by **Van der Kroef et al.** the average nocturnal blood glucose levels in the T allele (CT/TT genotypes) carriers were significantly higher (4.67 mmol/L) compared to those with the CC genotype (4.48 mmol/L; p = 0.03).[14] Furthermore **Lu YC et al**. also displayed that the *TCF7L2* rs7903146 T allele was linked with an elevated likelihood of T2DM and higher fasting glucose. Individuals with the CT and TT genotypes had significantly elevated FBS levels compared to those with the CC genotype among both the overall cohort and control group ($p < 0.05$).[15] Higher postprandial glucose levels in TT carriers may reflect defective incretin-mediated insulin secretion. TCF7L2 is a major player in the Wnt signaling pathway and regulates the activity of the glucagon-like peptide-1 (GLP-1), a key factor in postprandial insulin secretion.[16] Studies conducted earlier have displayed that the rs7903146 T allele is linked with a decreased incretin effect that causes exaggerated postprandial hyperglycemia.[17,18] This finding is in agreement with earlier studies that reported elevated blood glucose concentrations in carriers of the rs7903146 T allele. **Lyssenko et** al showed that the T allele was linked to impaired insulin secretion and decreased β-cell function, leading to higher glucose levels and an increased likelihood of diabetes.[19]

HbA1c is considered the best marker for long-term glycemic control. In the current, we detected that

HbA1c levels were markedly higher in TT genotype carriers (8.96 ± 1.40%) compared to CT (7.66 ± 1.08%) and CC (7.53 ± 0.74%) carriers (F = 19.489, p < 0.001). This very significant difference reveals that subjects with the TT genotype sustain hyperglycemia over time. The findings of **Chandak et al.** are in line with study that have demonstrated a link of the T allele of rs7903146 with inadequate blood glucose regulation and high HbA1c levels.[20] TT carriers may have high HbA1c due to chronic β-cell dysfunction with insufficient secretion of insulin and sustained hyperglycemia. **Pearson et al.** described that the carriers of the TCF7L2 risk allele have defects in insulin processing and secretion, which have contributed to the deterioration of glycemic status.[21] Similarly, **Florez et al.** reported that risk allele carriers showed progressive deterioration of glucose homeostasis due to defects in insulin secretion and not in insulin sensitivity.[22] The present results support these observations and suggest that the TT genotype is a contributor to poor blood glucose regulation and diabetes progression.

The genotype of rs7903146 was also observed (Table 2) being significant with BMI (F = 3.567, p = 0.031). Interestingly, the mean BMI of the carriers of TT genotype was lower (26.73 ± 3.53 kg/m2) than the carriers of CT (28.77 ± 3.34 kg/m2) and CC (27.80 ± 3.97 kg/m2) genotypes. This result has likewise with several studies demonstrating that the diabetogenic effect of TCF7L2 is largely independent of obesity.[23,24] In contrast to other diabetes susceptibility genes like FTO, which affect body weight and adiposity, TCF7L2 mainly affects pancreatic β-cell function and insulin secretion. Thus, individuals having the T allele may develop diabetes although they have lower BMI. TCF7L2 risk variants predispose to diabetes through mechanisms independent of the obesity-related pathways.[25] Similar results have been observed in South Asian populations, where TCF7L2-related diabetes occurs even at modest BMI values.[26]

Other researches have demonstrated that rs7903146 (C/T) polymorphism in TCF7L2 gene is the most frequent SNP linked with the likelihood of T2DM.[27,28] In our research, we investigated the association of TCF7L2 polymorphisms rs7903146 and likelihood to T2DM in North Indian T2DM patients and healthy controls.

In the present research we have analysed the link of TCF7L2 rs7903146 (C>T) polymorphism with susceptibility of North Indian population for T2DM. The results of the study displayed a significant link between the rs7903146 variant and likelihood of T2DM in genotype and allele frequencies. (Table 4) Genotype distribution showed that CC genotype was found in 28.0% of T2DM patients and 36.8% of healthy controls and considered as the reference genotype. The CT genotype was present in 42.4% of diabetic subjects and 52.8% of controls (OR = 1.055, 95% CI: 0.59-1.86; p = 0.85) and indicate no significant link with the susceptibility to T2DM. However, the TT genotype was markedly higher in T2DM patients (29.6%) as compared to controls (10.4%). Carrying the TT genotype was linked with a 3.74-fold elevated risk of T2DM in comparison with the CC genotype (OR = 3.74, 95% CI: 1.73-8.08; p = 0.0006). These results reflect that homozygous for T allele is substantially linked with raised susceptibility of T2DM in the studied population. This was further supported by allelic analysis (Table 4). The occurrence of T allele was markedly elevated in T2DM group (50.8%) than in control group (36.0%). The occurrence of C allele was lower in cases (49.2%) than in controls (64.0%). The T allele was identified to be considerably linked with increased susceptibility of T2DM (OR = 1.77, 95% CI: 1.24–2.54; p = 0.002). This means that the T allele enhances the risk of causing diabetes by about 77%.The results obtained in our research are in agreement with several previous international and Indian studies. **Sagawah Phu et al.** showed significantly high prevalence of T allele in T2DM patients (45%) compared with controls (28%). The rs7903146 T allele is linked with an higher likelihood of T2DM relative to C allele with an allelic odds ratio of 2.07 (95% CI 1.39 - 3.09) (p = 0.004).[29] **Grant et al.** first identified the strong link between the **TCF7L2 rs7903146 variant** and T2DM, reporting that the T allele significantly increased diabetes risk across different populations.[16] Subsequent studies by **Saxena et al. and Scott et al.** further confirmed the contribution of TCF7L2 variants to impaired glucose metabolism and insulin secretion.[30,31] Also, analogous outcomes have been reported in Asian and Indian populations, suggesting that the diabetogenic effect of the T allele is consistent across ethnic groups.[20,32] Similar results to our findings was also demonstrated by **Elhourch et al.** who reported that the T allele was more frequent in diabetic individuals (45.3%) than in healthy controls (34.5%) and is linked with an elevated likelihood of diabetes (odds ratio = 2.13; 95% CI = 1.12-7.31; P = 0.005) in Moroccan population.[33] Furthermore, **Bahaaeldin et al**. discovered that the occurance of the T allele was elevated in subjects with T2DM (32.9%) relative to controls (26.7%) in an Egyptian study, yielding an odds ratio of 1.35 (95% CI 0.68-2.6); however, this result was insignificant (p>0.05).[34]

The present research also investigated the link of TCF7L2 (rs7903146) gene polymorphism with susceptibility to T2DM in North Indian population using dominant, recessive and additive genetic models (Table 5). Results demonstrated statistically significant link between T allele and increased

likelihood of T2DM especially in recessive and additive inheritance models.

(Table 5) In the dominant model (TT+CT versus CC) the occurance of T allele carriers was elevated among T2DM patients (90) than among controls (79). The calculated OR (OR = 1.50; 95% CI = 0.87–2.60) indicated a 1.5-fold elevated likelihood of T2DM in T allele carriers. However, the link was statistically non-significant (p = 0.138). This finding indicates that the appearance of a single T allele could failed to be sufficient alone to confer a strong diabetic risk in the studied population. Similar non-significant associations under the dominant model have been reported in certain Asian populations, suggesting ethnic variability in the genetic effect of rs7903146 polymorphism.[24,35]

In contrast, the recessive model (TT vs CC+CT) showed a highly significant link with T2DM. Individuals having the TT genotype were noticeably more prevalent among diabetic subjects (37) compared to controls (13). The odds ratio of 3.63 (95% CI = 1.83–7.20) indicated that individuals carrying the homozygous TT genotype had approximately 3.6 times greater likelihood of developing T2DM compared to carriers of the C allele. This correlation was markedly significant ($\chi2$ = 13.9, p < 0.001). These results give an indication that the diabetogenic effect of rs7903146 is more pronounced in the homozygous form of the T allele. This finding exhibit similarity with earlier studies reporting a strong link of TT genotype with reduced insulin secretion and β-cell dysfunction.[19,22] The higher frequency of TT genotype and T allele in the present study further supports the evidence that rs7903146 is a major contributor to diabetes susceptibility in North Indians.

The additive model (T vs C allele), also supported the significant contribution of T allele towards diabetes susceptibility. The frequency of T allele was significantly higher in T2DM subjects (127) than controls (92) with an OR of 1.77 (95% CI = 1.24–2.54) and statistically significant p-value (0.002). This finding indicates that the chance of developing T2DM rises by ~1.8-fold for each additional T allele. The T allele of rs7903146 has been detected to be one of the strongest genetic determinants of T2DM in multiple ethnic populations in previous GWAS and meta-analyses.[16,25]

The biological basis of this linkage may be impaired insulin secretion and altered incretin signalling. A transcription factor is codded by the TCF7L2 gene which is an important part of the Wnt signaling pathway. The Wnt signaling pathway regulates pancreatic β-cell proliferation and insulin secretion. The rs7903146 T allele has been the main reason for reduced β-cell function, decreased secretion of insulin, increased release of hepatic glucose, leading to hyperglycemia and the development of T2DM.[19] Also, decreased glucagon-like peptide-1 (GLP-1) mediated secretion of insulin in T allele carriers has been identified to further increase diabetes susceptibility.[17] Therefore, the much higher prevalence of TT genotype among diabetic patients in the present study may reflect the deleterious effect of this variant on pancreatic β-cell function.

Our findings are concordant with several Indian and international studies. **Chandak et al.** reported a significant linkage of the rs7903146 T allele with T2DM in Indian populations.[20] Similarly, **Saxena et al.** and **Grant et al.** found that the T allele was markedly linked with the development of diabetes in different ethnic populations.[16,30] However, some studies in East Asian populations reported weaker linkages, which may be attributed to lower T allele frequency and ethnic genetic heterogeneity.[36]

The lack of a significant linkage for the heterozygous CT genotype indicates that the diabetogenic effect of rs7903146 is more pronounced in individuals with dual copies of the risk allele. The risk of the disease is directly linked with TT genotype. Similar genotype-specific effects were seen in previous studies.[22,23,24]

The elevated prevalence of the T allele and TT genotype in the study group (T2DM) in relation to the control group in this study underlines the significance of genetic screening to identify high-risk individuals in the North Indian population. As T2DM is a multifactorial disorder influenced by both environmental and genetic factors, understanding the contribution of TCF7L2 polymorphism may help in early diagnosis, preventive strategies, and personalized therapeutic approaches.

Overall, the present findings indicate that the TCF7L2 rs7903146 T allele, especially in the homozygous TT state, is closely linked with an elevated likelihood of T2DM in the North Indian population. These outcomes corroborate earlier studies with TCF7L2 being a major genetic determinant of T2DM & suggest that it could be useful as a genetic marker to identify individuals at an elevated likelihood of developing diabetes.

SUMMARY AND CONCLUSION

These current findings reveal that the TCF7L2 rs7903146 T allele, especially in the homozygous TT state, is significantly linked to unfavourable glycemic outcomes like high FBS, PPBS, and HbA1c levels in the North Indian population living with T2DM. Although TT genotype carriers displayed markedly reduced BMI than CT and CC carriers, they had demonstrated markedly impaired glycemic control, suggesting that the effect of TCF7L2 on diabetes susceptibility is mediated mainly through β-cell dysfunction and impaired secretion of insulin rather than through obesity. These findings further support the potential importance of polymorphism of rs7903146 in the

pathogenesis and progression of T2DM & establish it as key genetic marker for early risk assessment, disease prediction, and personalized management of T2DM.

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