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Association of *TCF7L2* Gene Variants with Glycemic Control During Metformin Therapy in Type 2 Diabetes Mellitus

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What is already known on this topic?

- *TCF7L2 is a major genetic risk factor for type 2 diabetes mellitus and plays an important role in β-cell function, insulin secretion, and glucose homeostasis.*
- TCF7L2 *variants have been associated with variability in glycemic response to glucose-lowering therapies, including metformin; however, evidence regarding their influence on glycemic control during metformin therapy remains limited and inconsistent.*

What this study adds on this topic?

- *Targeted next-generation sequencing identified multiple TCF7L2 variants, and the rs7903424 polymorphism was significantly associated with HbA1c levels in patients with type 2 diabetes receiving metformin therapy.*
- *Carriers of the rs7903424 GA genotype had higher HbA1c levels and poorer glycemic control than GG genotype carriers, suggesting that this variant may contribute to interindividual variability in glycemic control during metformin therapy.*

Abstract

Objective: The transcription factor 7-like 2 (*TCF7L2*) gene variants are among the strongest genetic risk factors for type 2 diabetes mellitus (T2DM). However, their influence on glycemic control during metformin therapy remains incompletely understood. This study aimed to investigate variants in the *TCF7L2* gene and to evaluate their association with glycemic control in patients with T2DM receiving metformin therapy.

Methods: Thirty-two patients diagnosed with T2DM were included in this study. The coding exons and exon–intron boundaries of the *TCF7L2* gene were analyzed using next-generation sequencing. Glycemic control was assessed using HbA1c levels, and genotype–phenotype associations were evaluated.

Results: Sequencing of the *TCF7L2* gene identified multiple genetic variants, the majority of which were located within intronic and untranslated regions. Among these, 3 common intronic variants, rs2296782 (c.382-458A>G), rs56913138 (c.685+126G>T), and rs7903424 (c.788+252G>A), were selected for genotype–phenotype analyses. The rs7903424 variant was significantly associated with glycemic control. Mean HbA1c levels were 6.22 ± 0.44%, 7.36 ± 1.68%, and 6.30 ± 0.71% for the GG, GA, and AA genotypes, respectively. The rs7903424 GA genotype was significantly associated with poorer glycemic control compared with the GG genotype, as indicated by higher HbA1c levels ($P = .020$).

Conclusion: The *TCF7L2* rs7903424 polymorphism was associated with glycemic control in patients with T2DM receiving metformin therapy. The rs7903424 GA genotype was associated with significantly poorer glycemic control, as reflected by higher HbA1c levels, compared with the GG genotype.

Keywords: *TCF7L2*, glycemic control, pharmacogenetics, polymorphism, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by insulin resistance and impaired insulin secretion.[1] Metformin is recommended as first-line pharmacological therapy in most international guidelines due to its efficacy, safety profile, and cardiovascular benefits.

Type 2 diabetes mellitus is a complex, polygenic disorder resulting from the interaction of multiple common genetic variants and environmental factors. Genome-wide association studies (GWAS) have identified over 400 susceptibility loci for T2DM.[2] Among these, variants in the transcription factor 7-like 2 (*TCF7L2*) gene represent the strongest and most consistently replicated risk factors across multiple ethnic populations.[3] Particularly, the intronic polymorphisms rs7903146 and rs12255372 have been associated with T2DM.[4,5]

Transcription factor 7-like 2 plays a central role in the Wnt signaling pathway, regulating pancreatic β-cell function, insulin secretion, and glucose homeostasis. The *TCF7L2* gene is located on chromosome 10q25.3. The gene has 18 exons and possesses highly conserved sequence regions to functional domain.[6] Functional studies have demonstrated that *TCF7L2* affects proglucagon expression and incretin signaling, thereby affecting insulin secretion dynamics.[7]

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Common intronic polymorphisms, particularly rs7903146 and rs12255372, are strongly associated with increased risk of T2DM, mainly through impaired insulin secretion rather than insulin resistance.[8] Beyond disease susceptibility, *TCF7L2* has also been investigated in pharmacogenetic studies due to its potential role in modulating response to glucose-lowering therapies.[9,10] Interindividual variability in response to metformin, the first-line treatment for T2DM, remains a major clinical challenge.[8,11,12] Although several studies have suggested that *TCF7L2* variants may influence glycemic response and insulin-related parameters after metformin therapy, the results remain inconsistent across populations.

Most previous studies have focused on common intronic variants such as rs7903146, whereas the contribution of rare coding and regulatory variants within *TCF7L2* remains insufficiently characterized. Advances in next-generation sequencing (NGS) now allow comprehensive evaluation of both common and rare variants, providing deeper insight into the genetic architecture of T2DM and variability in treatment response.

In the present study, the authors aimed to sequence the highly conserved exonic regions of the *TCF7L2* gene and evaluate their association with HbA1c levels, a marker of glycemic control and disease progression, in patients with T2DM receiving metformin therapy.

Sequencing the *TCF7L2* gene in various ethnic groups will reveal rare and common variants, identify disease variants that predispose to *TCF7L2*, and allow for the provision of treatments to patients based on their genotypes. Therefore, the present study aimed to investigate genetic variants in the *TCF7L2* gene using NGS and to evaluate their association with glycemic control during metformin therapy, as assessed by HbA1c levels, in patients with clinically diagnosed T2DM.

Methods

Study Population and Clinical Data Collection

This preliminary study included 32 patients diagnosed with T2DM according to the American Diabetes Association (ADA) criteria. The samples were collected from March to May 2026. Written informed consent was obtained from all participants. İstanbul University-Cerrahpaşa Medical Research Ethics Committee approved the study protocol (Approval Number: 1598230; March 27, 2026) and the study was conducted in accordance with the principles of the Declaration of Helsinki. Peripheral blood samples were collected from all patients at the Ministry of Health, Sinan Sipahi Family Health Center, İstanbul, Türkiye, and molecular analyses were performed at the Haliç University, Faculty of Medicine, Department of Medical Biology, İstanbul, Türkiye. Patients aged 18 years or older with a confirmed diagnosis of T2DM were eligible for inclusion in the study. All participants had received metformin (1000 mg/day) as monotherapy for at least 6 months before enrollment. HbA1c values used in the analyses were obtained after at least 6 months of continuous metformin therapy and were considered to reflect glycemic control during treatment. Patients receiving insulin therapy and those with severe renal or hepatic impairment, pregnancy, or secondary forms of diabetes were excluded from the study. Demographic data were retrospectively obtained from medical records, whereas clinical parameters were determined from blood samples collected at the time of the study and analyzed in the laboratory. HbA1c levels were measured using an immunoturbidimetric assay method. The collected variables included age, sex, body mass index (BMI), and HbA1c.

Genetic Analysis

Genomic DNA was extracted from peripheral blood samples using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany; Cat. No. 11796828001). DNA concentration and purity were assessed before library preparation. Targeted sequencing libraries were generated using a designed amplicon panel. The coding exons and exon–intron boundary regions of the *TCF7L2* gene were analyzed using a targeted gene panel and NGS. Libraries were prepared and sequenced on the NovaSeq 6000 system platform (Illumina, San Diego). Sequencing data were generated with sufficient depth and coverage to ensure reliable variant detection across all targeted regions. The genotype distribution was in accordance with the Hardy–Weinberg equilibrium (HWE) ($P > .05$). Raw sequencing reads were quality-checked, trimmed, and aligned to the human reference genome (GRCh38) in the Illumina DRAGEN platform.[13] Raw sequencing reads were processed and analyzed using a previously established bioinformatic pipeline with minor modifications, as described in the previous studies.[14,15] Only variants with PASS status and a minimum read depth of 30× were retained.[16] Variant annotation and filtering were conducted using the Variant Effect Predictor (VEP). Variant data were further reviewed and managed using Ilyome© software (Ilyome©, Türkiye). Rare variants (minor allele frequency <5%) were prioritized and visually validated using Integrative Genomics Viewer (IGV). High-confidence variants were subsequently evaluated in relation to clinical findings.

Statistical Analysis

Data analysis was performed using GraphPad Prism version 10.6.1 (GraphPad Software, San Diego). Genotype distributions were tested for compliance with the HWE. The normality of continuous variables was assessed using the Shapiro–Wilk test. Comparisons among genotype groups were performed using the Kruskal–Wallis test, followed by Dunn's multiple-comparison test for post hoc analyses. Comparisons of continuous variables between 2 independent groups were conducted using the Mann–Whitney *U*-test. Continuous variables were expressed as mean ± SD. A 2-sided *P*-value of <.05 was considered statistically significant. To evaluate the potential influence of demographic factors on the association between the variant genotype and HbA1c levels, a multivariable linear regression analysis was performed with HbA1c as the dependent variable and genotype, age, BMI, and sex as independent variables.

Results

A total of 32 patients with T2DM receiving metformin therapy were included in the study. The baseline demographic and clinical characteristics of the participants are summarized in Table 1.

TCF7L2 Gene Sequencing Results

Individuals diagnosed with T2DM underwent sequencing of the *TCF7L2* gene, including the coding regions and exon–intron boundaries. Multiple variants were identified across the *TCF7L2* locus. The majority of detected variants were located within intronic and untranslated regions (UTRs), whereas no pathogenic or likely pathogenic coding variants were identified in the study cohort. The characteristics of the detected variants are summarized in Table 2.

Several common intronic variants were observed at relatively high frequencies, including rs2296782 (c.382−458A>G), rs56913138 (c.685+126G>T), and rs7903424 (c.788+252G>A), which were subsequently selected for genotype–phenotype analyses. Additional intronic and UTR variants were detected at lower

Table 1. Demographic and Clinical Profile of the Study Cohort

Demographic and Clinical Characteristics	Total (N = 32)
Sex, n (%)	
Female	20 (62.5)
Male	12 (37.5)
Age (years)	62.6 ± 9.81
Height (cm)	166 ± 10.2
Weight (kg)	84.9 ± 12.4
BMI (kg/m²)	31.0 ± 5.02
BMI category, n (%)	
Normal weight	1(3.1%)
Overweight	17(53.1%)
Obese	14(43.8%)
TC (mg/dL)	191 ± 38.8
HDL-C (mg/dL)	44 ± 10.3
LDL-C (mg/dL)	115 ± 33.4
Triglycerides (mg/dL)	159 ± 79.1
ALT (IU/L)	22.6 ± 17.2
AST (IU/L)	20.0 ± 8.77
Glucose (mg/dL)	127 ± 47.2
Urea (mg/dL)	34.6 ± 11.1
Creatinine (mg/dL)	0.84 ± 0.20
Uric acid (mg/dL)	5.54 ± 1.56
Hemoglobin (Hb, g/dL)	13.2 ± 1.96
HbA1c %	6.69 ± 1.24
fT4 (ng/dL)	1.20 ± 0.12
TSH (mIU/L)	2.80 ± 4.04
PSA (ng/dL)	1.27 ± 0.68*

Data are presented as mean ± SD for continuous variables and as number (percentage) for categorical variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; fT4, free thyroxine; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PSA, prostate-specific antigen; TC, total cholesterol; TSH, thyroid-stimulating hormone.
*PSA values were available for male participants only (n = 12).

frequencies and were predominantly classified as benign, likely benign, or variants of uncertain significance (VUS) according to the American College of Medical Genetics and Genomics (ACMG) criteria.

The sequencing analysis demonstrated genetic variability within the *TCF7L2* locus among patients with T2DM, with most identified variants located in non-coding regions. These findings support the potential contribution of regulatory genetic variation to interindividual differences in glycemic control during metformin therapy.

The most frequently detected coding alteration was the heterozygous frameshift variant c.1454del (p.Lys485Serfs*23; rs745872748), which was identified in 7 of 32 patients (21.9%). This variant is predicted to introduce a premature termination codon, resulting in protein truncation. According to ACMG criteria, it was classified as likely pathogenic based on the PVS1 and PM2 evidence.

The intronic deletion variant c.1319−4del (rs761045930), located within the polypyrimidine tract upstream of the splice acceptor site, was identified in 27 of 32 patients (84.4%), all of whom were heterozygous carriers. According to ACMG criteria, the variant was classified as VUS. Although the variant is situated in the splice-site region, its functional consequences remain unclear, and no definitive evidence currently supports an effect on *TCF7L2* function or disease phenotype.

Association Between TCF7L2 Variants and Glycemic Control During Metformin Therapy

Sequencing of the *TCF7L2* gene among these, 3 common intronic variants, rs2296782 (c.382-458A>G), rs56913138 (c.685+126G>T), and rs7903424 (c.788+252G>A), were selected for genotype–phenotype analyses because of their relatively high allele frequencies. The selected variants are presented in Table 2.

Integrative Genomics Viewer visualizations of the *TCF7L2* variants rs56913138, rs2296782, and rs7903424 are shown in Figure 1A, 1B, and 1C, respectively. The rs7903424 (c.788+252G>A) variant was identified in 32 patients with T2DM. Genotype frequencies were 53.1% (n = 17) for GG, 40.6% (n = 13) for GA, and 6.3% (n = 2) for AA. The mean HbA1c levels were 6.22 ± 0.44%, 7.36 ± 1.68%, and 6.30 ± 0.71% for the GG, GA, and AA genotypes, respectively. The heterozygous GA genotype exhibited higher HbA1c values compared with the GG and AA genotypes.

The rs7903424 polymorphism was analyzed according to genotype groups (GG, GA, and AA). Post hoc Dunn's multiple-comparison test following the Kruskal–Wallis analysis revealed a significant difference in HbA1c levels between the GG and GA genotypes (P = .020), with individuals carrying the GA genotype exhibiting higher HbA1c levels than those with the GG genotype (Figure 2). No significant differences were observed between the GG and AA genotypes or between the GA and AA genotypes after multiple comparisons. However, these comparisons should be interpreted with caution because only 2 patients carried the homozygous mutant AA genotype, substantially limiting the statistical power to detect genotype-specific differences. To assess the potential influence of demographic factors, a multivariable linear regression analysis was performed including age, BMI, and sex as covariates. After adjustment, the overall association between the rs7903424 genotype and HbA1c was attenuated and showed borderline significance (P = .079). Age (P = .212), BMI (P = .865), and sex (P = .204) were not significantly associated with HbA1c levels.

Discussion

Transcription factor 7-like 2 is one of the most extensively studied susceptibility genes for T2DM.[4,17,18] In the present study, the authors investigated the association between *TCF7L2* gene variants and glycemic control in patients with T2DM receiving metformin therapy. The exonic regions of *TCF7L2* are highly conserved, resulting in a relatively low frequency of coding variants.[6] Most genetic variants investigated in association studies have been located within intronic regions. *TCF7L2* is one of the most extensively studied genes associated with T2DM. Previous research has largely focused on a limited number of common intronic variants, particularly rs7903146 and rs12255372.[19]

Table 2. Common *TCF7L2* Variants Selected for Genotype–Phenotype Analysis

T2DM Patients							
No	**Variant (HGVS cDNA)**	**dbSNP ID**	**Genomic Position (GRCh38)**	**Variant Type**	**ACMG Classification**	**Amino Acid Change**	**Highest Population MAF**
1	*TCF7L2*:c.382−458A>G	rs2296782:A>G	chr10-112964098 A>G	Intron	Benign	—	0.43
2	*TCF7L2*:c.685+126G>T	rs56913138:G>T	chr10-113141442 G>T	Intron	Benign	—	0.32
3	*TCF7L2*:c.788+252G>A	rs7903424:G>A	chr10-113144277 G>A	Intron	Benign	—	0.32

The highest minor allele frequency observed in any population, including 1000 Genomes Phase 3, ESP, and gnomAD. Gene variant, position, ACMG classification, amino acid change, and pathogenic criteria taken from Franklin Bioinformatics. Variation type and the highest population MAF are taken from Ensembl.
ACMG, The American College of Medical Genetics and Genomics; ESP, Exome Sequencing Project; MAF, minor allele frequency; T2DM, type 2 diabetes mellitus.

The present study aimed to identify common, low-frequency, and rare variants within the *TCF7L2* gene by sequencing exon and exon–intron boundary regions and to evaluate their association with HbA1c levels in patients with T2DM. Targeted sequencing of the *TCF7L2* gene identified a wide range of genetic variants, including common, low-frequency, and rare polymorphisms. The majority of these variants were located within intronic and UTRs, particularly in exon–intron boundary regions.

The *TCF7L2* gene has some variants, such as rs176632, rs2296784, and rs17686448, that have previously been reported in the literature in association with diseases.[18,20,21] The predominance of intronic variants observed in the cohort is consistent with the highly conserved nature of the coding regions of *TCF7L2* and supports previous observations that genetic variation within this locus is concentrated in non-coding regions. These findings highlight the extensive genetic diversity of the *TCF7L2* locus and suggest that many variants identified through NGS approaches remain functionally unexplored. Further studies in larger cohorts and functional investigations are needed to determine their potential contribution to glycemic regulation and T2DM susceptibility.

rs2296784 has previously been reported by Amin et al[18] in a family-based study investigating *TCF7L2* variants in Italian families with polycystic ovary syndrome, where the variant was identified among the loci showing evidence of linkage and/or linkage disequilibrium with disease susceptibility. Although the clinical phe-notype investigated differed from T2DM, this finding supports the potential relevance of rs2296784 as a genetic marker within the *TCF7L2* locus and suggests that further studies are warranted to clarify its functional significance across metabolic disorders.

The intronic variant rs176632 has previously been reported in an indigenous Mexican population by Acosta et al[21], who identified it as one of the few variants shared between indigenous individu-als, the 1000 Genomes Project, and the SIGMA Project datasets. Notably, rs176632 exhibited an exceptionally high minor allele fre-quency and was considered a potential ancestral variant that may have persisted through selective sweep events within the *TCF7L2* locus. In this cohort, rs176632 was also detected in the majority of individuals (29/32), supporting the notion that this variant rep-resents a highly conserved and widely distributed polymorphism within the *TCF7L2* gene. However, despite its high prevalence, the functional significance of rs176632 in glycemic regulation and T2DM remains unclear and warrants further investigation.

The intronic variant rs17686448 has been described previ-ously within the *TCF7L2* locus; however, evidence regarding its functional relevance remains limited.[20] In the present study, rs17686448 was detected in 2 individuals, highlighting the genetic heterogeneity of non-coding regions within *TCF7L2*.

Previous studies have primarily focused on common *TCF7L2* variants, particularly rs7903146, and have demonstrated significant associations with T2DM susceptibility, insulin secretion, and therapeutic response.[22] Connor et al[23] further emphasized the biological relevance of *TCF7L2* and noted that the clinical significance of many less frequently studied variants remains largely unexplored.[23] Consistent with these observations, data regarding rs7903424 are limited, particularly with respect to glycemic control and response to metformin therapy. In the present study, rs7903424 was the only variant that showed a significant association with HbA1c levels, suggesting that this relatively understudied intronic variant may contribute to interindividual differences in glycemic regulation among patients with T2DM.

In this study, sequencing of the *TCF7L2* gene identified that the majority of detected variants were located within the exon–intron boundary region, intronic region, and UTRs. However, the authors focused on sequencing variants located in exon–intron boundary regions of the *TCF7L2* gene. Among these, 3 common intronic variants, rs2296782 (c.382-458A>G), rs56913138 (c.685+126G>T), and rs7903424 (c.788+252G>A), were selected for genotype–phenotype analyses, but only rs7903424 demonstrated a significant association with HbA1c levels. The most important finding of this study was the significantly higher HbA1c levels observed among individuals carrying the heterozygous GA genotype of rs7903424 compared with those carrying the wild type GG genotype. Patients with the GA genotype exhibited a median HbA1c level of 7.0%, whereas the median HbA1c level in the GG group was 6.2%. Furthermore, the GA genotype group showed the highest mean rank values, suggesting poorer glycemic control despite metformin treatment. These findings indicate that genetic variation within *TCF7L2* may contribute to interindividual differences in glycemic control during metformin therapy. In contrast, no statistically significant difference was observed between the homozygous mutant AA and wild-type GG genotypes. However, this finding should be interpreted with caution because only 2 patients carried the homozygous mutant genotype (n = 2), substantially limiting the statistical power to detect genotype-specific di erences.

Interestingly, c.1319−4del (rs761045930) was detected at a high frequency in the cohort. Despite its location within the splice polypyrimidine tract, the clinical significance of this variant remains uncertain, and further studies are required to determine whether it represents a population-specific polymorphism o r has functional relevance.

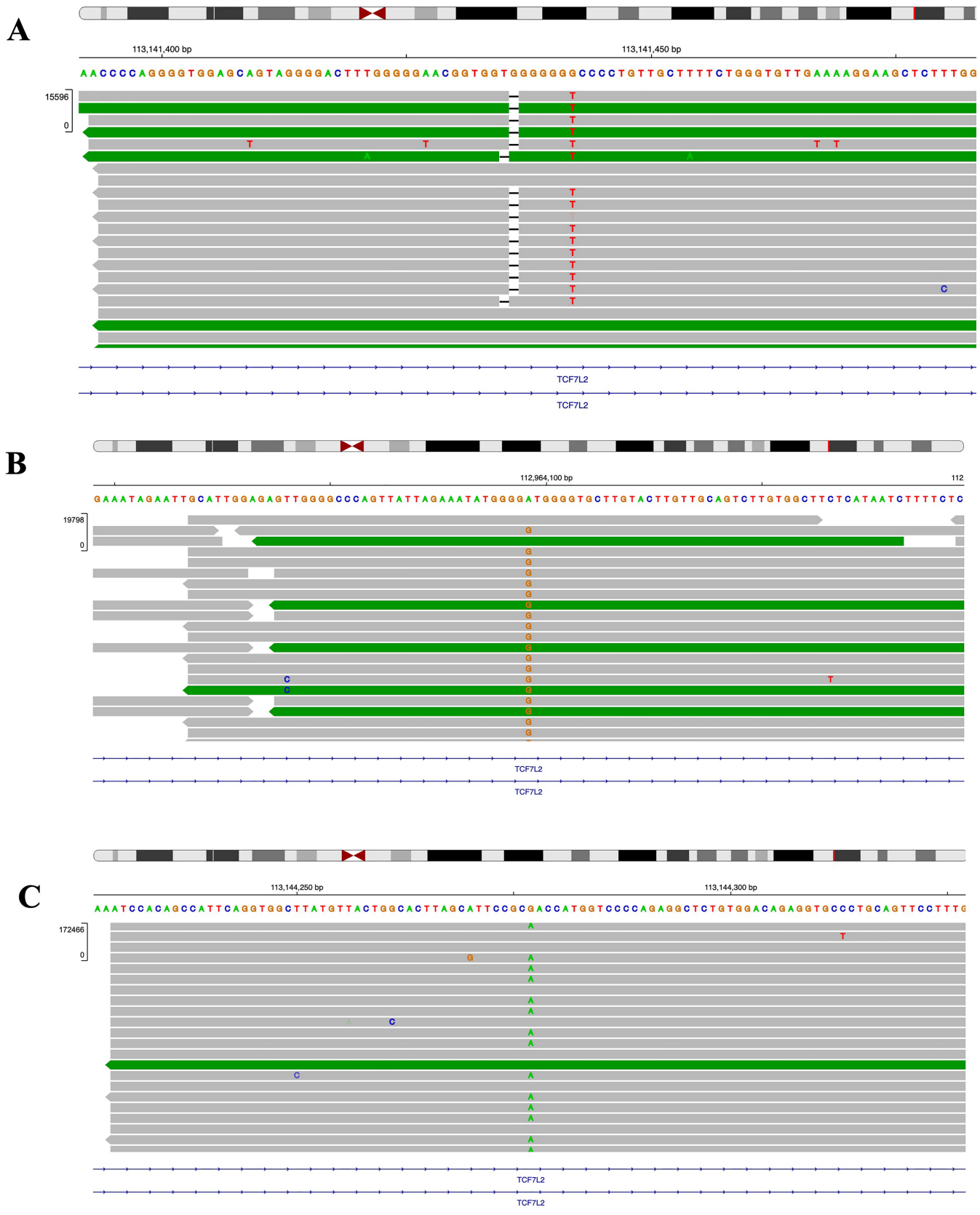

Figure 1. IGV visualization of the *TCF7L2* gene variants rs5691318, rs2296782, and rs7903424. IGV, Integrative Genomics Viewer; *TCF7L2*, transcription factor 7-like 2.

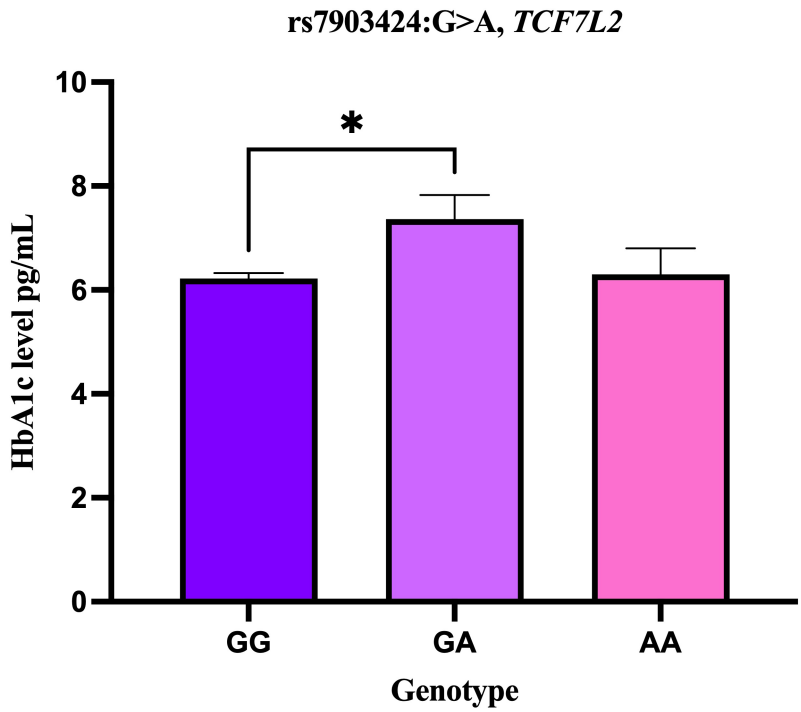

Figure 2. Comparison of HbA1c levels among rs7903424 genotypes of the *TCF7L2* gene in patients with T2DM. T2DM, type 2 diabetes mellitus; *TCF7L2*, transcription factor 7-like 2.

In the present study, the rs7903424 GA genotype was associated with significantly higher HbA1c levels compared with the GG genotype. Given the limited literature available on rs7903424, the findings provide novel evidence supporting a potential role of this variant in treatment-related glycemic outcomes. Although rs7903424 has been investigated less frequently, the findings suggest that this variant may also influence glycemic outcomes in patients with T2DM.

The biological mechanism underlying the association between rs7903424 and HbA1c levels remains unclear. Because the variant is located within an intronic region, it is unlikely to directly alter protein structure. However, intronic variants may influence gene expression through effects on transcriptional regulation, alternative splicing, chromatin organization, or interactions with regulatory elements. Such mechanisms could potentially affect *TCF7L2* activity and consequently alter glucose metabolism and treatment response. In contrast, no significant associations were observed between rs2296782 or rs56913138 and the evaluated clinical parameters. Although these variants are relatively common within the popula-tion, the results do not support a major effect on glycemic control in this cohort. Nevertheless, the limited sample size may have reduced the statistical power to detect modest genetic effects.

The findings suggest that *TCF7L2* gene variations may influ-ence glycemic control during metformin therapy in patients with T2DM. The rs7903424 variant has been associated with impaired insulin secretion, which may partially explain differences in glyce-mic outcomes.

In conclusion, targeted sequencing of the *TCF7L2* gene iden-tified a broad spectrum of common, low-frequency, and rare variants in patients with T2DM receiving metformin therapy. Consistent with the highly conserved nature of the coding regions of *TCF7L2*, most detected variants were located within intronic and untranslated regions, particularly at exon–intron bound-aries. Among the variants evaluated, rs7903424 was the only polymorphism significantly associated with HbA1c levels. The GA genotype was associated with poorer glycemic control, as reflected by significantly higher HbA1c levels, compared with the GG genotype. These findings suggest that genetic variation within *TCF7L2* may contribute to interindividual differences in glycemic control during metformin therapy. Furthermore, the identification of numerous rare and poorly characterized variants highlights the value of targeted sequencing approaches for uncovering genetic diversity beyond well-established *TCF7L2* risk loci. Larger studies and functional analyses are needed to validate the observed asso-ciation and to clarify the biological mechanisms through which rs7903424 and other non-coding variants may influence glycemic control during metformin therapy in T2DM.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, although an a priori sample size cal-culation was performed during the study design phase, the final number of recruited participants was lower than the initially esti-mated sample size because recruitment was restricted to eligible patients who met the inclusion criteria during the study period. Therefore, the study may have had limited ability to detect genetic variants with small effect sizes. Second, the absence of a healthy control group prevented assessment of variant frequencies in the general population. Third, functional studies were not performed to determine the biological effects of the identified variants. Finally, environmental factors, treatment adherence, disease duration, and lifestyle characteristics may also influence HbA1c levels and could not be fully controlled.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Istanbul University-Cerrahpaşa (Approval No.: 2026/1598230; Date: March 27, 2026).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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Author Contributions: Concept – K.Ç.P-U., . Z.G.T-S.; Design – K.Ç.P-U., Z.G.T-S.; Supervision – K.Ç.P-U., Z.G.T-S., S.O.; Resources – E.R.A; Materials – E.R.A.; Data Collection and/or Processing – E.R.A., M.Y.B., M.F.A.; Analysis and/or Interpretation – K.Ç.P-U., Z.G.T-S.; Literature Search – K.Ç.P-U.; Writing – K.Ç.P-U., Z.G.T-S.; Critical Review – K.Ç.P-U.

Declaration of Interests: The authors have no conflict of interest to declare.

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