European Science Review 2025,
No 11–12
ISSN 2310-5577

PREMIER Publishing
ppublishing.org

Section 2. Biology

DOI:10.29013/ESR-25-11.12-9-16

STUDY OF GENETIC ASSOCIATION BETWEEN the rs1799817 POLYMORPHISM OF THE INSULIN RECEPTOR GENE and THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS

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Cite: *Saatov T.S., Toshtemirov A.E., Ibragimova E.A., Abdurakhimov S., Ibragimov Z.Z. (2025). Study of Genetic Association Between the Rs1799817 Polymorphism of the Insulin Receptor Gene and the Development of type 2 Diabetes Mellitus. European Science Review 2025, No 11–12*. https://doi.org/10.29013/ESR-25-11.12-9-16

Abstract

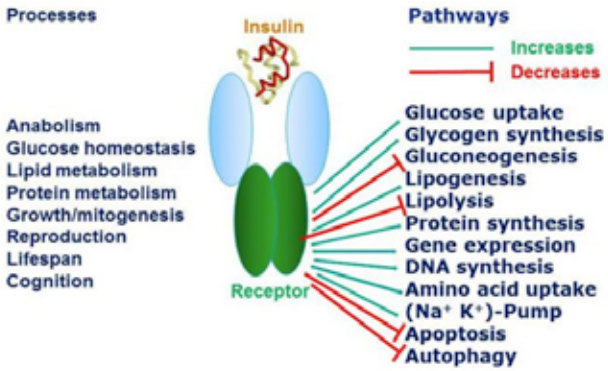
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by elevated blood glucose levels due to defects in insulin secretion or its signaling pathway. This disease develops as a result of the complex interaction between genetic, metabolic, and environmental factors. In this study, we investigated the association between the rs1799817 (C>T) polymorphism in exon 17 of the insulin receptor (INSR) gene and the risk of T2DM. A total of 144 participants were included in the study, with 66 diagnosed with T2DM and 78 healthy individuals as controls. Genetic analysis was performed by isolating DNA from peripheral blood samples and detecting the rs1799817 polymorphism using PCR and PmlI restriction enzyme digestion. Genotyping results showed no deviation from Hardy-Weinberg equilibrium in both groups. Although the overall genotype distribution did not reach statistical significance ($\chi^2 = 5.35$, $p = 0.069$), allelic analysis revealed a significant association. The C allele was less frequent in T2DM patients (54.5%) compared to controls (67.3%), while the T allele was more frequent in T2DM patients (45.5% vs 32.7%, $p = 0.028$). The C allele was associated with a protective effect against T2DM (OR = 0.58, 95% CI: 0.36–0.94). Further analysis using dominant and recessive models showed a trend toward reduced disease risk in carriers of the CC genotype (OR = 0.53, 95% CI: 0.28–1.00, $p = 0.05$), whereas the TT genotype did not show a significant association (OR = 1.69, 95% CI: 0.71–3.99, $p > 0.05$). These findings suggest that the rs1799817 polymorphism may influence susceptibility to T2DM, with the C allele potentially offering a protective effect. Further studies with larger sample sizes and mechanistic investigations are needed to validate these results and explore the biological mechanisms underlying this association.

Keywords: *type 2 diabetes mellitus, single nucleotide polymorphisms, genetic association, insulin receptor gene, Uzbek population*

Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by chronic hyperglycemia and impaired carbohydrate metabolism (Khokhar, P. B., Pentangelo, V., Palomba, F., Gravino, C., 2025). The pathogenesis of the disease is based on insulin resistance resulting from a deficiency in insulin secretion or a decrease in the sensitivity of peripheral tissues to insulin (Khokhar, P. B., Pentangelo, V., Palomba, F., Gravino, C., 2025; Młynarska, E., Czarnik, W., Dzieża, N., Jędraszak, W., Majchrowicz, G., Prusinowski, F., Franczyk, B., 2025). The main function of the hormone insulin is to exert its effects through the insulin receptor located in the liver, muscle, and adipose tissue. In particular, in liver cells, it increases the conversion of glucose to glycogen and reduces glucose excretion, and in muscle and adipose tissue, it increases glucose uptake via the GLUT4 transport protein. The insulin receptor belongs to the tyrosine kinase superfamily and becomes activated by autophosphorylation upon insulin binding. The activated receptor induces the IRS and PI3K/Akt signaling pathways (Figure 1). These mechanisms cause metabolic, mitogenic, and pleiotropic effects (Khokhar, P. B., Pentangelo, V., Palomba, F., Gravino, C., 2025; De Meyts P., 2016).

Figure 1. *Pleiotropic effects of insulin and its receptor*



Notes: *Insulin regulates multiple physiological processes through its receptor (center), increasing (green lines) or decreasing (red lines) the activity of various intracellular metabolic pathways. These include glucose and lipid metabolism, protein synthesis, gene expression, cell growth, and cell-survival mechanisms (De Meyts P., 2016)*

In recent years, growing attention has been directed toward the genetic predisposition to T2DM. The rs1799817 polymorphism located in exon 17 of the insulin receptor (INSR) gene, lyes within the tyrosine kinase domain, structural alterations in this region may impair insulin signaling efficiency and increase T2DM risk (Gao, W., Deng, Z., Gong, Z., Jiang, Z., & Ma, L., 2025; Mekuria, A. N., Ayele, Y., Tola, A., & Mishore, K. M., 2019; Irgam, K., Reddy, B. S., Hari, S. G., Banapuram, S., Reddy, B. M., 2021). The INSR gene is located on the short (p) arm of chromosome 19 and consists of 22 exons and 21 introns. Exons 17–22 of the gene encode the tyrosine kinase domain, which is crucial for receptor function. Mutations within this domain can disrupt insulin signaling system (Figure 1), potentially leading to insulin resistance and compensatory hyperinsulinemia (Park, M., Kim, J. S., Park, Y. A., Lee, D. H., Choi, S. A., Chang, Y., Yee, J., 2025; Hubbard S. R., 2013; Feng, C., Lv, P. P., Yu, T. T., Jin, M., Shen, J. M., Wang, X., Jiang, S. W., 2013; Chandrasekaran, P., Weiskirchen, R., 2024).

The aim of the study: To investigate the genetic association between the rs1799817 polymorphism of the insulin receptor gene and the development of T2DM in individuals of Uzbek ethnicity.

Materials and Methods

A total of 144 participants were included in the study, comprising both individuals diag-

nosed with T2DM and healthy controls without symptoms characteristic of the disease. Of these, 66 individuals with clinically confirmed T2DM formed the main study group, while 78 healthy individuals served as the control group. Participants in the main group were selected from patients undergoing inpatient treatment at the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y. Kh. Turaqulov.

To ensure a comprehensive evaluation, a genealogical questionnaire was administered, and clinical indicators, medical history, and relevant biochemical analyses were assessed. For genetic analysis, DNA was isolated from peripheral blood samples, and the rs1799817 polymorphism of the INSR gene was detected using polymerase chain reaction (PCR) followed by restriction fragment length analysis.

Extraction of genomic DNA from peripheral blood

Genomic DNA was isolated from peripheral blood leukocytes using a salt-based precipitation method. To ensure high analytical accuracy and reproducibility, all procedures were conducted with the *DNeasy Blood & Tissue Kit (QIAGEN*, Germany) according to the manufacturer's protocol. The concentration and purity of the extracted DNA were assessed using a *NanoOne Ultra Micro* spectrophotometer (China). Absorbance measurements were recorded at 260 nm and 280 nm in TE buffer (Tris–EDTA), and samples with an A260/A280 ratio between 1.8 and 1.9 were considered of high purity. The integrity of each DNA sample was further confirmed by visualizing aliquots on agarose gel electrophoresis. All DNA samples were stored at –25 °C until further analysis to maintain molecular stability and prevent degradation.

PCR protocol for detection of the rs1799817 polymorphism of the insulin receptor gene

Detection of the rs1799817 (C>T) single nucleotide polymorphism (SNP) in the insulin receptor (INSR) gene was performed using a targeted polymerase chain reaction (PCR) assay. Primers specific to exon 17 of the INSR gene were designed by laboratory specialists using the reference genomic sequence to ensure optimal specificity and amplification efficiency (Table 1). Oligonucleotides were synthesized by Integrated DNA Technologies (IDT, USA) and validated for concentration and purity prior to use.

Table 1. *PCR mixture composition and the sequences of used oligonucleotide primers*

Reagents	Volume	Note
HiGenoMB PCR TaqMixture (2×)	15 µL	HiGenoMB PCR TaqMixture – Specific PCR mixture, dNTPs – Nucleoside triphosphate mixture, HiGenoMB Taq-polymerase – Specific Taq-polymerase)
HiGenoMB Taq-polymerase (5 U/µl)	0.3 µL	
dNTPs (10 mM)	0.6 µL	
Forward primer (For p INSR1)	0.65 µL (15 pmol);	
Reverse primer (Rev p INSR2)	0.65 µL (15 pmol);	
Deionized water	9.8 µL	
DNA matrix	3 µL	
Total volume	30 µL	
Forward primer (For p INSR1)	5'- TCAGGAAAGCCAGCCCATGTC –3'	
Reverse primer (Rev p INSR2)	5'- CCAAGGATGCTGTGTAGATAA –3'	

PCR amplification was carried out on a StepOne Real-Time PCR System (Applied Biosystems, USA) under optimized thermal cycling conditions. Reaction mixtures contained genomic DNA template, forward and reverse primers, dNTPs, $MgCl_2$, and Taq DNA polymerase in volumes prepared according to standardized laboratory protocols. Amplification success was verified through electrophoretic separation of PCR products on agarose gel. The resulting amplicons were subsequently subjected to restriction fragment length polymorphism (RFLP) analysis for genotype determination.

Restriction Enzyme and Reagents for Polymorphism Identification

The hydrolysis of amplified DNA fragments was conducted in accordance with the manufacturer's guidelines (New England Biolabs, NEB, USA). Specifically, PCR products were subjected to digestion using the PmlI restriction enzyme (Eco72I, 10 U/μL, NEB, USA) in conjunction with 10× Tango buffer. The digestion reaction was performed in a total volume of 15 μL and incubated at 37 °C for 4 hours to facilitate endonuclease hydrolysis. The 10× Tango buffer utilized for the PmlI enzyme comprised 33 mM Tris-acetate (pH 7.9), 10 mM magnesium acetate, 66 mM potassium acetate, and 0.1 mg/mL Bovine Serum Albumin (BSA).

Visualization of PCR Products

To visualize the PCR results and assess the efficacy of the restriction analysis, gel electrophoresis was performed on a 2.5% agarose gel. The electrophoresis was conducted at a voltage of 150 V for a duration of 25 minutes. Prior to loading the PCR products onto the gel, bromophenol blue and glycerol were incorporated into the samples to facilitate well deposition and to monitor the progress of the electrophoresis. A 1× TBE buffer solution (pH 8.0) was employed during the electrophoresis process. For DNA fragment visualization, the gel was stained with Ethidium Bromide (EtBr). Following electrophoresis, DNA fragments were visualized using a UV transilluminator (Life Technologies E-Gel Imager, USA), and their sizes were estimated in comparison to a 50 bp DNA ladder.

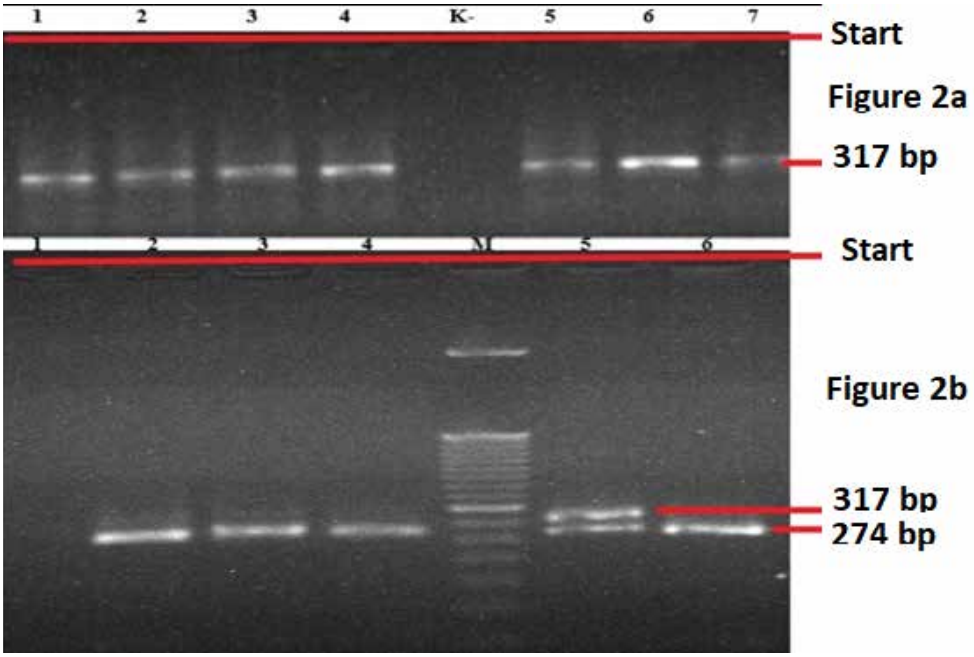
Statistical Analysis of Results

Statistical analyses of the obtained data were performed using the statistical software packages "WINPEPI 2016 (Version 11.65)" and "Doctor Stat 2013 (Version 1.9)." To evaluate the population characteristics regarding the distribution of genotypes and alleles of the studied polymorphism, statistical analyses were based on the criteria of Hardy-Weinberg equilibrium (HWE).

Results: Familial Predisposition and PCR Specificity

Genealogical analyses indicated that 71.2% of patients with Type 2 Diabetes Mellitus (T2DM) reported a familial predisposition to the disease.

Figure 2. *Visualization of the rs1799817 polymorphism of the INSR gene after PCR analysis and endonuclease hydrolysis*



Regarding the standard PCR results for the rs1799817 polymorphism in the insulin receptor (IR) gene, a single distinct DNA fragment of 317 bp was clearly visualized, with no evidence of non-specific amplification or primer-dimer formation. This observation

confirms both the specificity of the primers for the targeted genetic locus and the successful execution of the PCR reaction (Figure 2 a).

Figure 2.

(a) *PCR amplification showing a specific 317 bp product in samples 1–7, with no band in the negative control (K-).*

(b) *PCR products reflect the results after restriction enzyme digestion (RFLP – Restriction Fragment Length Polymorphism). M – DNA marker 50 bp; lane 1 – negative control; lanes 2,3,4,6- samples with a 274 bp fragment, homozygous TT genotype of mutant type; 5 – sample with a heterozygous CT genotype, with a combination of 317 bp and 274 bp fragments.*

Results of Restriction Fragment Length Polymorphism (RFLP) Analysis

The outcomes of the RFLP analysis, illustrated in Figure 2b, revealed distinct patterns among the samples based on the selective cleavage of the amplified DNA fragments. The intact 317 bp fragment corresponds to the homozygous reference genotype (CC). In contrast, the presence of both the 317 bp and 274 bp fragments indicates the heterozygous genotype (CT), while the exclusive appearance of the 274 bp fragment signifies the homozygous mutant genotype (TT).

Assessment of Hardy-Weinberg Equilibrium for Genotypes and Alleles

To evaluate the population equilibrium of the genotypes and alleles under investigation, we employed the chi-square (χ^2) test to assess Hardy-Weinberg equilibrium (HWE). The distribution of genotypes for the rs1799817 (C>T) polymorphism in the insulin receptor (INSR) gene was analyzed in both Type 2 Diabetes Mellitus (T2DM) patients and control subjects. Within the T2DM cohort (CC = 19, CT = 34, TT = 13; n = 66), the observed genotype frequencies conformed to Hardy-Weinberg expectations, yielding $\chi^2 = 0.10$ with a p-value of 0.75.

Table 2. *Genotype and allele frequencies of polymorphism rs1799817 gene INSR in T2DM patients and controls*

Group	Genotyp	Observed	Expected	χ^2	p-value
T2DM (n=66)	CC	19	19.4	0.10	0.75
	CT	34	33.2		
	TT	13	13.4		
Controls (n=78)	CC	37	36.7	0.74	0.39
	CT	31	32.6		
	TT	10	8.7		

Assessment of Hardy-Weinberg Equilibrium in Control Group

In the control group (CC = 37, CT = 31, TT = 10; n = 78), we observed no significant deviation from Hardy-Weinberg equilibrium ($\chi^2 = 0.74$, p = 0.39). These findings suggest that both studied populations are in genetic equilibrium, with no evidence indicating genotyping errors or population stratification.

Evaluation of the Association Between the rs1799817 Polymorphism in the INSR Gene and Type 2 Diabetes Mellitus

This study investigated the association between the rs1799817 (C>T) polymorphism in the insulin receptor (INSR) gene and the risk of Type 2 Diabetes Mellitus (T2DM). Genotyping results for the T2DM group (CC = =19, CT = 34, TT = 13; n = 66) and the normoglycemic control group (CC = 37, CT = 31, TT = 10; n = 78) demonstrated adherence to Hardy-Weinberg equilibrium (T2DM: χ^2 = = 0.10, p = 0.75; controls: $\chi^2 = 0.74$, p = = 0.39), confirming appropriate sample distribution (Table 2).

While the overall genotype distribution did not reach statistical significance (χ^2 = = 5.35, df = 2, p = 0.069), allelic analysis revealed a significant association. The frequency of the C allele was notably lower in T2DM patients (54.5%) compared to controls

(67.3%), whereas the frequency of the T allele was higher among cases (45.5% vs. 32.7%). The allelic chi-square test confirmed this difference as statistically significant ($\chi^2 = 4.78$, df = 1, p = 0.028), with an odds ratio of 0.58 (95% CI: 0.36–0.94). This suggests a potential protective effect of the C allele against the development of T2DM.

Table 3. *Association analysis of rs1799817 genotypes and alleles with T2DM*

Comparison	Model	χ^2 (df)	p-value	OR (95% CI)	Interpretation
C vs T allele	Allelic	4.78 (1)	0.028	0.58 (0.36–0.94)	C allele protective
Genotype (CC vs CT vs TT)	Codominant	5.35 (2)	0.069	–	No significant association
TT+CT vs CC	Dominant (T carrier)	–	> 0.05	1.90 (0.99–3.64)	Borderline tendency
TT vs CC+CT	Recessive (T risk)	–	> 0.05	1.69 (0.71–3.99)	Not significant

Further Analysis of the rs1799817 Polymorphism under Dominant and Recessive Models

Subsequent analyses utilizing dominant and recessive genetic models revealed that individuals carrying the CC genotype exhibited a trend toward reduced susceptibility to Type 2 Diabetes Mellitus (T2DM) (OR = 0.53, 95% CI: 0.28–1.00, p = 0.05). Conversely, the recessive TT model did not demonstrate a statistically significant association (OR = 1.69, 95% CI: 0.71–3.99, p > 0.05). Collectively, these findings suggest that the rs1799817 polymorphism in the insulin receptor (INSR) gene may modulate T2DM susceptibility at the allelic level, despite the genotypic distribution failing to reach a statistically significant threshold. The observed protective effect of the C allele underscores potential functional implications for the regulation of insulin receptor signaling, thereby necessitating further investigation in larger cohorts and mechanistic studies to elucidate its biological role in T2DM pathogenesis.

This study provides preliminary scientific evidence that contributes to the expansion of the ethnic and geographic spectrum of genetic association studies related to T2DM.

Discussion

This investigation focused on the genetic association between the rs1799817 polymorphism of the INSR gene and T2DM development among individuals of Uzbek ethnicity. The INSR gene, located on chromosome 19, encodes the insulin receptor protein, composed of two subunits, α and β. The principal function of this receptor is to bind insulin and initiate a cascade of intracellular signaling pathways that facilitate glucose uptake by cells, thereby lowering blood glucose levels (Zerón H. M., Maldonado A. N., Sánchez M. M., 2025). Disruptions in insulin receptor functionality due to mutations or polymorphisms can lead to insulin resistance, a critical factor in the onset of diabetes and other metabolic disorders. Such disruptions adversely affect normal insulin signaling, diminishing the body's capacity to effectively regulate blood sugar levels.

The polymorphism examined herein plays a pivotal role in modulating both transcriptional and translational efficiency of the INSR gene, thereby influencing the overall expression of the insulin receptor protein. While this nucleotide change may not alter protein conformation, it can significantly affect transcription and translation processes, potentially reducing protein synthesis levels. This reduction may disrupt the activation of signaling cascades associated with the insulin receptor.

The frequency of the rs1799817 polymorphism exhibits variation across different ethnic groups. In European populations, the prevalence of the T allele ranges from 30% to 35%, whereas in East Asian populations, it is notably higher, reaching 40% to 45%. Conversely, African populations typically exhibit lower prevalence rates for the T allele, generally ranging

from 20% to 25% (Adam, A. R., Ozbakir, B., Ozay, A. C., Tulay, P., 2022). These disparities may be attributed to genetic heterogeneity and variations in the prevalence of metabolic diseases among different ethnic groups, consequently impacting susceptibility to insulin resistance and diabetes-related complications.

Previous studies conducted among Japanese populations have indicated that carriers of the T allele face a heightened risk of insulin resistance and an increased likelihood of developing T2DM compared to carriers of the C allele. This association has been corroborated in various Asian and European populations (https://www.snpedia.com/index.php/Rs1799817). Our findings suggest that this polymorphism exerts a similar effect within the Uzbek population.

Research Funding

This research was financially supported by the Ministry of Higher Education, Science and Innovation of the Republic of Uzbekistan (project F-OT-2021–153).

Legal and Ethical Standards: The study received approval from the Ethics Committee of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y. Kh. Turaqulov under the Ministry of Health of the Republic of Uzbekistan, as well as from the Institute of Biophysics and Biochemistry at the National University of Uzbekistan named after Mirzo Ulugbek. The research was conducted in accordance with the principles outlined in the Declaration of Helsinki (revised in 2018).

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submitted 01.09.2025;
accepted for publication 04.12.2025;
published 30.12.2025

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