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Research article

GLP1R and *GIPR* gene sequencing for glycemic response to DPP-4 inhibitors in T2DM patients

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Abstract

Interindividual variability in glycemic response to dipeptidyl peptidase-4 (DPP-4) inhibitors remains a major challenge in the management of type 2 diabetes mellitus (T2DM). DPP-4 inhibitors exert their effects by inhibiting the degradation of incretin hormones. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are among these incretin hormones. Genetic variations in the receptor genes for these incretin hormones can influence both receptor function and incretin sensitivity. In this study, conducted on patients with T2DM receiving DPP-4 inhibitor therapy, we aimed to evaluate the relationship between variants in the relevant genes and glycemic response. Targeted next-generation sequencing (t-NGS) was used to sequence both the exons and the exon-intron boundary regions of the *GIPR* and *GLP1R* genes. A total of 42 T2DM patients undergoing DPP-4 inhibitor treatment were included in the study. Patients were divided into two groups based on their HbA1c levels: those with adequate glycemic control (≤7.0%) and those with inadequate glycemic control (>7.0%). Sequencing of the *GLP1R* and *GIPR* genes revealed 16 variants, including missense, intronic, synonymous, and non-coding region changes. The intronic variant rs767803082 in the *GLP1R* gene was classified as a VUS. Analysis of genotype distribution between the groups showed a nominally significant difference only for the *GIPR* gene variant rs34783010:G>T (p=0.043; BH q=0.172). When comparing the GG and GT genotypes, the GT genotype was predominantly observed in the group with adequate glycemic control, whereas the GG genotype was more frequent among patients with inadequate glycemic control (p=0.047). Our findings suggest that the *GIPR* rs34783010 variant may contribute to individual variability in the glycemic response to DPP-4 inhibitor therapy.

Keywords: *Genetic variation; GLP1R; GIPR; next-generation sequencing; single nucleotide polymorphism; T2DM*

1. Introduction

T2DM is a long-term metabolic disorder characterized by persistent hyperglycemia arising from a combination of impaired insulin secretion and reduced insulin sensitivity. The disease affects more than 400 million individuals worldwide (Młynarska et al., 2025). Data from the International Diabetes Federation indicate that approximately 9.6 million people in Turkey were living with diabetes in 2024, with projections suggesting that this number may surpass 14 million by 2050 (*IDF Diabetes Atlas 2025 | Global Diabetes Data & Insights*, n.d.). The growing prevalence of T2DM represents a substantial public health burden due to its strong association with neuropathy, cardiovascular disease, nephropathy, and other

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long-term complications (Satapathy et al., 2025). Type 2 diabetes (T2DM) can be controlled through personalized treatment, and the risk of complications can be reduced. Pharmacological treatment and/or insulin administration may be necessary to keep blood glucose levels as close to physiological limits as possible and to delay or prevent the onset of diabetes-related complications (Taylor et al., 2021). In addition, medical nutrition therapy and regular physical activity play an important role as fundamental and complementary elements in the comprehensive management of the disease (Artasensi et al., 2020). Recent therapeutic advances have focused on targeting key metabolic pathways involved in glucose homeostasis. SGLT2 inhibitors and GLP-1 receptor agonists represent important advances in T2DM therapy, with evidence supporting their ability to enhance glycemic control and mitigate cardiometabolic complications (Manolopoulos et al., 2011; Ansari et al., 2023). Despite the use of different antidiabetic drugs in T2DM, inter-individual variability still poses a challenge in the clinical management of the disease (Yaluri et al., 2025). DPP-4 inhibitors are widely used oral antidiabetic drugs and represent an important therapeutic option for glycemic control. DPP-4 inhibitors are commonly used oral antidiabetic drugs and represent an important treatment option for glycemic control. These oral antidiabetic drugs prevent the enzymatic degradation of GIP and GLP-1, thereby increasing incretin activity. As a result, glucose-dependent insulin secretion increases and glucagon secretion decreases (Lovshin and Drucker, 2009; Capuano et al., 2013). Following nutrient ingestion, GLP-1 is secreted from intestinal L cells, whereas GIP is released from K cells (Seino et al., 2010). These hormones potentiate glucose-stimulated insulin secretion in a glucose-dependent manner, thereby mediating the physiological incretin effect (Baggio and Drucker, 2007). GIP and GLP-1 constitute key components of the incretin effect by contributing to the enhancement of glucose-dependent insulin secretion following oral glucose intake. Consequently, the insulin response to oral glucose intake is more pronounced compared to intravenous glucose administration-a phenomenon defined as the “incretin effect.” This mechanism, mediated particularly by GLP-1 and GIP, plays a crucial role in regulating postprandial blood glucose levels and maintaining glucose homeostasis. In T2DM, incretin-induced insulin secretion is substantially diminished, largely attributable to impaired GLP-1 secretion; nevertheless, the insulinotropic response to exogenously administered GLP-1 remains predominantly intact. Beyond its insulinotropic effects, GLP-1 enhances glycemic regulation by inhibiting glucagon secretion, slowing gastric motility, and reducing food intake, which may also support weight loss (Yunusoglu, 2025). The clinical benefit of endogenous GLP-1 is limited due to its short half-life in circulation. Since GLP-1 is rapidly degraded and inactivated, particularly by the enzyme dipeptidyl peptidase-4 (DPP-4), it cannot maintain its effect for long under physiological conditions. This rapid enzymatic degradation leads to a rapid decrease in the effective circulating concentration of GLP-1, thus limiting its therapeutic potential (Todd and Bloom, 2007). GLP-1 and GIP exert their biological effects via GLP1R and GIPR. These receptors, which are structurally linked to G proteins, are found in the beta cells of the pancreas (Lovshin and Drucker, 2009). These receptors play a crucial role in stimulating insulin secretion in a glucose-dependent manner (Zheng et al., 2024). Variations in the genes encoding these receptors may influence receptor function, incretin hormone sensitivity, and ultimately, the clinical efficacy of DPP-4 inhibitors (Shilleh et al., 2024). By selectively inhibiting DPP-4, gliptins prevent rapid degradation of endogenous incretin hormones, notably GLP-1 and GIP. This pharmacodynamic effect augments circulating active incretin levels, promotes glucose-dependent insulin secretion, and partially corrects the attenuated incretin response characteristic of T2DM (Scheen, 2018). Current evidence indicates a potential role of *GLP1R* and *GIPR* polymorphisms in the variability of therapeutic responses to incretin-based treatments (Sathananthan et al., 2010; Javorský et al., 2016; Margoni et al., 2025; Yaluri et al., 2025). However, available studies remain limited and often evaluate single gene effects rather than the combined influence of both receptor pathways (La Vignera and Condorelli, 2026). A comprehensive evaluation of *GLP1R* and *GIPR* polymorphisms may therefore provide a more complete understanding of interindividual differences in DPP-4 inhibitor efficacy. Understanding the pharmacogenetic influence of *GLP1R* and *GIPR* gene variations could provide critical insights into personalized treatment approaches for T2DM, enabling more effective and targeted therapeutic strategies.

This investigation was designed to assess the influence of these genetic variants on glycemic responsiveness to DPP-4 inhibitor therapy in individuals with T2DM, thereby contributing to the development of precision therapeutic strategies in diabetes management.

2. Materials and methods

2.1. Study population and design

The study included 42 patients diagnosed with T2DM who were using DPP-4 inhibitors. Adult patients (≥18 years) diagnosed with T2DM according to the American Diabetes Association criteria and who had received stable DPP-4 inhibitor therapy (linagliptin or vildagliptin) for at least 24 weeks were eligible for inclusion. Ethics committee approval for this study was obtained from Halic University-Non-Interventional Clinical Research Ethics Commitee in accordance with the principles of the Declaration of Helsinki (Approval No: 2025/288). Between March and September 2025 written informed consent was obtained from all participants. Peripheral whole-blood samples were collected from all patients in EDTA tubes and stored at 4°C until genomic DNA isolation. Patients diagnosed with type 1 diabetes or other specific types of diabetes, with active malignancy or systemic inflammatory disease, using GLP-1 receptor agonists during the study period, and without sufficient clinical or laboratory data were excluded from the study. Baseline clinical and biochemical data included age, body mass index (BMI), sex, HbA1c, fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, and serum creatinine.

2.2. Targeted sequencing of GLP1R and GIPR genes

Genomic DNA was extracted from peripheral blood samples using the PureLink™ Genomic DNA Mini Kit (Invitrogen, Cat. No. K182002, USA). DNA concentration and purity were assessed with a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, Massachusetts, USA). The coding regions and exon–intron junctions of the GLP1R and GIPR genes were amplified using a C1000 thermal cycler (Bio-Rad, USA). Library preparation was performed with the TruSeq

Custom Amplicon v1.5 Library Preparation Kit (Illumina, Cat. No. 20018705, San Diego, USA), followed by next-generation sequencing on the NovaSeq 6000 platform (Illumina, San Diego, USA).

2.3. Raw data analysis

Following the FastQC raw data sequencing reads, adapter sequences were removed and low-quality reads were filtered out using Cutadapt. The resulting high-quality reads were aligned to the human reference genome GRCh38, following the workflow described in our previous studies (Pekkoc-Uyanik et al., 2023, 2025). Variant annotation was performed using the Ensembl Variant Effect Predictor (VEP) while processing the data through the DRAGEN analysis pipeline. The interpretation and filtering of all prioritized variants were conducted using the Ilyome Bioinformatics platform (Ilyome©, Turkey). Additionally, variant reads were visually inspected using the Integrative Genomics Viewer (IGV), which is integrated into the platform.

2.4. Statistical analyses

GraphPad Prism v10.6.1 (GraphPad Software, USA) was used for statistical analyses. The distribution of continuous variables was assessed using the Shapiro-Wilk normality test, and the data were analyzed using the Mann-Whitney U test or the t-test. Differences in sex distribution were assessed using the chi-square test, whereas Fisher's exact test was used when the expected cell frequencies were insufficient for the chi-square test. Continuous variables are presented as mean ± standard deviation (SD). Genotype and allele frequencies were calculated for each identified variant, and genotype distributions were assessed for conformity with Hardy-Weinberg equilibrium. Differences in genotype and allele distributions between the HbA1c-defined groups were evaluated using the chi-square test or Fisher's exact test. Linkage disequilibrium and haplotype distributions were also assessed for variants located within the *GIPR* region. P-values from multiple comparisons were adjusted using the Benjamini-Hochberg false discovery rate (FDR), yielding q-values . A multivariable logistic regression analysis was performed, including age, sex, and BMI. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

A total of 42 patients with T2DM were included in the study and stratified into two groups according to glycemic control (HbA1c ≤7.0% and >7.0%), as shown in Table 1. Clinical characteristics and demographic data were compared between the groups; no statistically significant difference was found regarding sex and age distribution. (p>0.05). Similarly, BMI, lipid parameters (triglycerides, total cholesterol, LDL-C, HDL-C), and creatinine levels were comparable between the groups (all p>0.05). HbA1c levels were significantly lower in the adequate glycemic control group compared to the inadequate control group (6.75±0.25 vs 8.75±1.12, p<0.001). In addition, fasting glucose levels differed significantly between the groups (*p*=0.0025). The groups were similar regarding demographic and most metabolic parameters, with significant differences observed primarily in glycemic control indicators.

Table 1
Demographic and clinical characteristics of patients with T2DM stratified by glycemic control.

Variable	Total population (n=42)	Adequate Glycemic Control HbA1c ≤7.0% (n=20)	Inadequate Glycemic Control HbA1c >7.0% (n=22)	*p*-value
Age (years)	62.19±7.50	64.20±6.99	60.36± 7.62	0.06
Sex (F/M)	22/20	9/11	13/9	0.54[#]
HbA1c (%)	7.80±1.30	6.75±0.25	8.75±1.12	<0.001
BMI (kg/m^2)	30.13±5.23	29.36±3.97	30.83±6.17	0.36
Fasting plasma glucose (mg/dL)	155.17±46.11	134.05±36.50	174.36±46.20	0.0025
Total cholesterol (mg/dL)	173.19±42.62	163.85±39.94	181.68±44.10	0.18
HDL-C (mg/dL)	43.38±10.76	44.8±9.63	42.09±11.76	0.36
LDL-C (mg/dL)	96.00±31.78	88.8±29.98	102.55±32.63	0.16
Triglycerides (mg/dL)	174.98±73.47	163.05±73.37	185.82±73.55	0.32
Creatinine (mg/dL)	0.94±0.25	0.96±0.19	0.92±0.29	0.33

HbA1c: glycated hemoglobin**;** BMI: Body Mass Index; HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides.
[#]: Chi-square test. Variables were analyzed using the Independent Samples t-test or Mann-Whitney U test.
Variables were presented as mean ± standard deviation for data.

A multivariable logistic regression analysis was performed to evaluate the independent effects of BMI, gender, and age on glycemic response. The estimated odds ratios were BMI (1.05, 95% CI: 0.92-1.21), age (0.92, 95% CI: 0.82-1.01), and sex (0.42, 95% CI: 0.10-1.56). No statistical significance was observed between the variables and the glycemic response. The detailed results of the multivariable logistic regression analysis are presented in Table 2.

Table 2
Multivariable logistic regression analysis of clinical factors associated with glycemic control in patients with T2DM.

Independent variables	β	OR	*p*-value	95% CI for OR
Age (years)	-0.086	0.918	0.069	0.823-1.006
Sex (F/M)	-0.870	0.419	0.199	0.099-1.563
BMI (kg/m^2)	0.044	1.045	0.515	0.915-1.206

OR: odds ratio; CI: confidence interval; BMI: Body Mass Index; Variables were presented as mean ± standard deviation for data.

3.2. Genotypes

Targeted next-generation sequencing of the *GLP1R* and *GIPR* genes identified 16 variants in patients with T2DM, including rare and common variants (Table 3).

These variants comprised intronic, missense, synonymous, and untranslated region (UTR) changes. Among the detected variants, the majority were classified as benign according to ACMG criteria. Specifically, 15 variants met benign classification criteria (BS2 or BA1).

Table 3
Common and rare *GLP1R and GIPR* gene variants detected in T2DM patients.

	T2DM Patients							
No	**Variant (HGVS cDNA)**	**dbSNP ID**	**Genomic Position (GRCh38)**	**Variant Type**	**ACMG Classification**	**Amino Acid Change**	**Highest population MAF**	**Pathogenic Criteria (Population Data)**
1	GLP1R:c.1182+35T>C	rs767803082	chr6-39079737 T>C	Intron variant	VUS	-	< 0.01	PM2
2	GLP1R:c.502G>A	rs6923761	chr6-39066296 G>A	Missense variant	Benign	p.Gly168Ser	0.40	BS2
3	GLP1R:c.1043+75_1043+76del	rs5875654	chr6-39079259 CAG>C	Intron variant	Benign	-	0.36	BS2
4	GLP1R:c.399A>G	rs6918287	chr6-39065826 A>G	Missense variant	Benign	p.Glu133=	0.06	BA1
5	GLP1R:c.1200A>C	rs1126476	chr6-39080715 A>C	Synonymous variant	Benign	p.Ile400=	0.50	BS2
6	GLP1R:c.20C>T	rs10305420	chr6-39048860 C>T	Missense variant	Benign	p.Pro7Leu	0.42	BS2
7	GLP1R:c.526A>C	rs2235868	chr6-39072878 A>C	Missense variant	Benign	p.Arg176=	0.50	BS2
8	GIPR:c.634-23C>T	rs11672660	chr19-45676926 C>T	Intron variant	Benign	-	0.30	BS2
9	GLP1R:c.780A>C	rs1042044	chr6-39073726 A>C	Missense variant	Benign	p.Leu260Phe	0.42	BS2
10	GLP1R:c.284-60A>T	rs910162	chr6-39065651 A>T	Intron variant	Benign	-	0.50	BS2
11	GIPR:c.1060G>C	rs1800437	chr19-45678134 G>C	Missense variant	Benign p.Glu354Gln		0.29	BS2
12	GLP1R:c.509+16C>T	rs10305457	chr6-39066319 C>T	Intron variant	Benign	-	0.24	BS2
13	GLP1R:c.284-67A>G	rs910163	chr6-39065644 A>G	Intron variant	Benign	-	0.50	BS2
14	GIPR:c.634-57A>G	rs4803846	chr19-45676892 A>G	Intron variant	Benign	-	0.31	BS2
15	GIPR:c.793+48G>T	rs34783010	chr19-45677156 G>T	Intron variant	Benign	-	0.29	BS2
16	GIPR:c.*24C>A	rs12709891	chr19-45681959 C>A	3' prime UTR variant	Benign	-	0.50	BS2

T2DM, Type 2 Diabetes Mellitus; ACMG classification was performed according to the 2015 ACMG/AMP guidelines
VUS, variant of uncertain significance. MAF: Minor Allele Frequency. 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.
Pathogenicity was evaluated in accordance with the ACMG guidelines. PM2, Pathogenic Moderate 2 (variant absent or at extremely low frequency in population data/databases); BS2, Benign Strong 2 (variant observed in healthy individuals in population data); BA1, Benign Stand-Alone 1 (allele frequency greater than expected for the disorder based on population data; stand-alone evidence for benign classification).

In contrast, only one variant, *GLP1R* c.1182+35T>C (rs767803082), was categorized as a variant of uncertain significance (VUS) due to its very low population frequency (MAF<0.01) and insufficient functional evidence.

Missense variants were observed in both genes, including *GLP1R* rs6923761 (p.Gly168Ser), rs10305420 (p.Pro7Leu), and rs1042044 (p.Leu260Phe), as well as *GIPR* rs1800437 (p.Glu354Gln). Despite their protein-altering effects, all of these variants were classified as benign and exhibited relatively high minor allele frequencies. Synonymous variants, such as *GLP1R* rs1126476 (p.Ile400=) and rs6918287 (p.Glu133=), were also identified and classified as benign, with high population frequencies supporting a lack of functional impact. In addition, a substantial proportion of the detected variants were located in intronic regions, including *GIPR* rs11672660, rs4803846, and rs34783010, as well as multiple intronic variants in *GLP1R*. These variants demonstrated moderate to high allele frequencies, consistent with common genetic variation. A single 3′ UTR variant, rs12709891 in the *GIPR* gene, was also detected and classified as benign. Although non-coding variants may have regulatory potential, no functional data were available to support a pathogenic role for this variant.

The genetic landscape observed in this cohort was dominated by common, benign polymorphisms with relatively high allele frequencies. No pathogenic or likely pathogenic variants were identified in either *GLP1R* or *GIPR*, suggesting that rare high-impact variants in these genes are unlikely to play a major role in the variability of DPP-4 inhibitor response in this study population.

Genetic analyses were performed for the *GIPR* gene variants rs11672660, rs1800437, rs4803846, and rs34783010. The IGV reads for these variants are presented in Fig. 1: rs4803846 (a), rs1800437(b), rs11672660 (c), and rs34783010 (d), showing the variant positions and sequencing reads. Genotype distribution analysis revealed that only the *GIPR* rs34783010:G>T variant showed a nominally significant diffe-

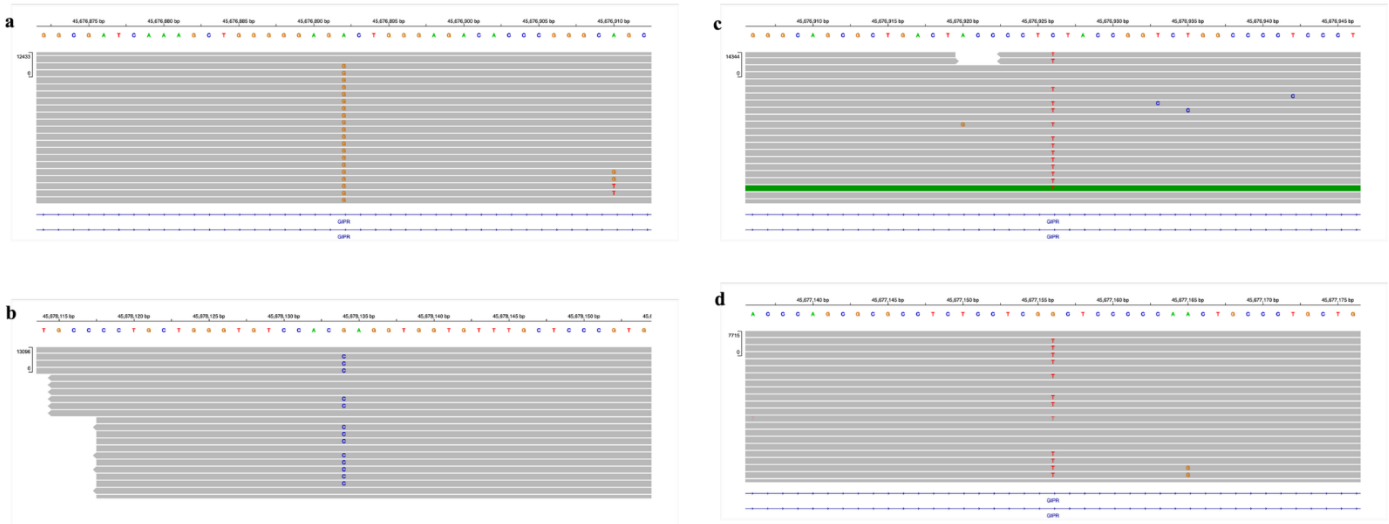


Fig. 1. The IGV illustrating the reads of the *GIPR* gene rs4803846 (a), rs1800437 (b), rs11672660 (c), and rs34783010 (d) variations.

rence between inadequate and adequate glycemic control groups (p=0.043), FDR (BH q=0.172) (Table 4, Fig. 2). In the comparison of GG vs GT genotypes, the GT genotype was predominantly observed in the adequate glycemic control group, while the GG genotype occurred more often among patients with inadequate glycemic control (p=0.047). *GIPR* gene rs11672660, rs1800437, and rs4803846 variants showed no significant differences (all p>0.05).

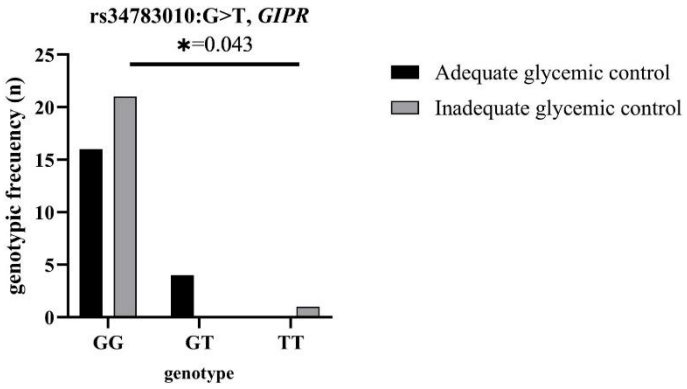


Fig. 2. Genotype distribution of the *GIPR* rs34783010:G>T polymorphism according to glycemic control status. * The difference between groups is statistically significant, as indicated by the asterisk.

3.3. Linkage disequilibrium and haplotype analysis of GIPR gene

Haplotype analysis and Linkage disequilibrium (LD) of the *GIPR* gene demonstrated that the four analyzed SNPs (rs4803846, rs11672660, rs34783010, and rs1800437) formed a single haplotype block spanning approximately 1 kb (Fig. 3). *GIPR* gene rs4803846 variation showed a significant deviation from Hardy–Weinberg equilibrium (p < 0.001) and was excluded from further analyses (Table 5). Pairwise LD values indicated moderate to high linkage among the variants, with the strongest LD observed between rs34783010 and rs1800437, followed by rs4803846 and rs1800437. When grouped according to HbA1c levels, no significant differences in LD structure, haplotype block were observed between the groups.

Haplotype analysis of the four *GIPR* variants did not reveal any statistically significant association with treatment response in T2DM patients using gliptins. However, the haplotype constructed from the rs34783010 and rs1800437 variants showed a trend toward statistical significance (χ^2 = 3.322, p = 0.068) (Table 6).

Table 4
Genotype distribution of *GIPR* polymorphisms in adequate and inadequate glycemic control groups.

Variation	Genotype	Adequate glycemic control group (n=20)	Inadequate glycemic control group (n=22)	*p* value	BH q-value
rs11672660 (C>T)	CC	18 (90.0%)	20 (90.9%)	0.999	0.999
	CT	2 (10.0%)	2 (9.1%)		
	TT	0 (0%)	0 (0%)		
rs1800437 (G>C)	GG	16 (80.0%)	20 (90.9%)	0.400	0.800
	GC	4 (20.0%)	2 (9.1%)		
	CC	0 (0%)	0 (0%)		
rs34783010 (G>T)	GG	16 (80.0%)	21 (95.5%)	0.043	0.172
	GT	4 (20.0%)	0 (0%)		
	TT	0 (0%)	1 (4.5%)		
rs4803846 (A>G)	AA	14 (70.0%)	17 (77.3%)	0.852	0.999
	AG	1 (5.0%)	1 (4.5%)		
	GG	5 (25.0%)	4 (18.2%)		

Chi-square test, n: Number of samples. Values are given as the number of subjects (n) and percentages (%).
BH: Benjamini–Hochberg FDR-adjusted.

Table 5
GIPR gene common variations in haplotype analysis markers.

Gene	Marker	Polymorphism	Allele Change	Contig Position	MAF
GIPR	**Marker 1**	rs4803846	A>G	45676892	0.238
	Marker 2	rs11672660	C>T	45676926	0.048
	Marker 3	rs34783010	G>T	45677156	0.060
	Marker 4	rs1800437	G>C	45678134	0.071

MAF: Minor allele frequency.

4. Discussion

This pilot study examined the potential contribution of *GLP1R* and *GIPR* genetic variants to variability in glycemic res-

Table 6
Single and block haplotype analysis of variations in the *GIPR* gene.

			Frequencies			
Marker	**Haplotype**	**Frequency**	**Adequate glycemic control group**	**Inadequate glycemic control group**	**Chi square**	***p* value**
M2	**C**		0.955	0.950	0.01	0.922
M3	**G**		0.955	0.925	0.327	0.567
M4	**G**		0.955	0.900	0.94	0.332
M3+M4	**CTA**	0.904	0.909	0.898	0.030	0.861
M3+M4	**CTT**	0.037	0.045	0.027	0.199	0.655
M3+M4	**TCA**	0.035	0.000	0.073	3.322	0.068
M3+M4	**TCT**	0.025	0.045	0.002	1.626	0.202

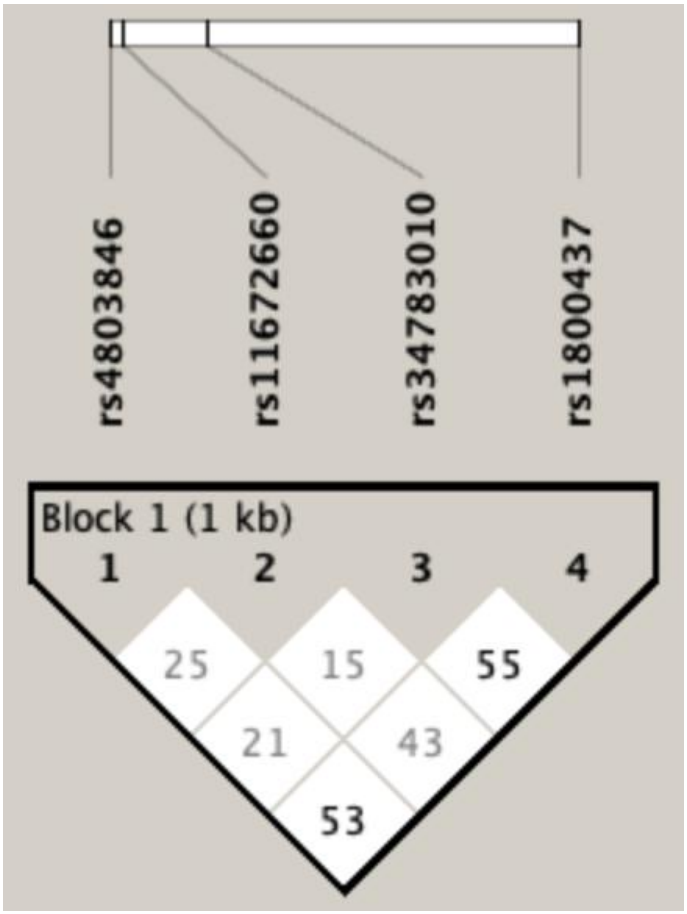


Fig. 3. Linkage disequilibrium (LD) structure and haplotype block of four *GIPR* gene variants.

ponse to DPP-4 inhibitor therapy among patients with T2DM. Receptor genes often contain genetic variants, the majority of which are silent and preserve the wild-type receptor structure (Koole et al., 2010). However, variants that alter the protein sequence in G protein-coupled receptors may influence physiological processes, contribute to disease progression, or affect therapeutic responsiveness. Therefore, genetic variability may contribute to interindividual variability in glycemic response by altering the pharmacodynamic mechanisms of treatment (Ahmad et al., 2025; Yaluri et al., 2025; La Vignera & Condorelli, 2026; Su et al., 2026). These effects may arise through modifications in ligand–receptor interactions involving receptors such as GLP-1R and GIPR, potentially leading to receptor-specific conformational alterations that affect activation efficiency. In addition, genetic variants may influence receptor expression levels, downstream signaling pathways, and receptor sensitivity. Thus, contributing to variability in biological responses and clinical outcomes among patients receiving treatment (Succurro et al., 2022). The effects of *GLP-1R* variations, the primary pharmacological target for T2DM and obesity, on receptor function, and consequently the individual variability and metabolic characteristics in clinical response to hypoglycemic drugs, are not sufficiently defined (Lee et al., 2026; Su et al., 2026). Similarly, genetic variations in *GIPR* have been reported to influence metabolic traits such as insulin secretion, glucose homeostasis, and body mass index, although their impact on treatment response remains incompletely understood (Saxena et al., 2010).

In this cohort, comparison of biochemical characteristics and clinical parameters between two groups showed no significant differences in age, sex, BMI, lipid profile, or serum creatinine. However, fasting plasma glucose levels were significantly lower in the adequate glycemic control group. Therefore, genetic factors may represent one of several contributors to interindividual variability in glycemic response to DPP-4 inhibitor therapy. However, the absence of strong associations for most variants suggests that the effect sizes of individual polymorphisms are likely modest, consistent with the polygenic nature of pharmacogenetic traits in T2DM.Among the analyzed study variants, *GIPR* gene rs34783010:G>T variant showed a nominally significant difference between inadequate and adequate glycemic control groups (p=0.043), FDR (BH q=0.172). In the comparison of GG vs GT genotypes, the GT genotype was predominantly observed in the adequate glycemic control group, while the GG genotype occurred more often among patients with inadequate glycemic control (p=0.047). Although this association was not strong after considering the limited sample size, it may still suggest a potential contribution of GIPR-mediated signaling pathways to therapeutic response or glycemic control. Given the growing recognition of GIP as an important component of incretin physiology, even subtle changes in receptor function or expression may influence insulin secretion and glycemic control. The literature also presents growing evidence supporting the simultaneous consideration of both GLP-1 and GIP pathways in incretin-based therapies. (Campbell and Drucker, 2025; La Vignera and Condorelli, 2026).

In a study, the minor T allele of the rs34783010 variant in the *GIPR* gene was found to be associated with lower BMI, as well as with high HbA1c levels and increased hepatic triglyceride (Jamialahmadi et al., 2025). In addition, the biological significance of the identified intronic rs34783010 variant has not been sufficiently investigated. Further functional analyses are required to elucidate the potential regulatory effects of the intronic rs34783010 variant on gene splicing and expression. Although most of our analyzed variants did not show statistically significant associations with HbA1c-based glycemic control groups. A large-scale pharmacogenomic study conducted on patients recently treated with gliptins has revealed

potentially significant associations between genetic variants and glycemic response (Pilon et al., 2026).

Another pharmacogenetic study involving patients with T2DM treated with metformin has demonstrated an association between *SLC22A1* gene variants and treatment response. These studies further support the contribution of genetic variations to the differences observed among individuals receiving antidiabetic treatment. (Todurga-Seven et al., 2026). In conclusion, our findings suggest that the *GIPR* gene rs34783010 polymorphism may influence the glycemic response to DPP-4 inhibitors. Further studies involving larger cohorts and functional analyses are needed to better elucidate the role of incretin receptor genetics in personalized diabetes treatment. Integrating pharmacogenetic data into clinical practice could improve treatment decisions and glycemic outcomes for patients with T2DM. There are certain limitations to the results of this study. The small sample size (n=42) limits statistical power, particularly in association analyses involving genotype data. The fact that some variant genotypes were present in very few individuals may affect statistical analysis; therefore, the results should be considered as preliminary data. It should be noted that basing the glycemic response on HbA1c levels of ≤7.0% or >7.0% reflects glycemic control rather than a comprehensive measure of treatment response. The study does not include data on baseline and follow-up HbA1c levels, duration of diabetes, or lifestyle factors. Consequently, these factors should be considered when interpreting the findings. Future studies incorporating more detailed clinical and treatment-related parameters are needed. Another limitation is that clinical and environmental factors, such as diet, can influence glycemic outcomes but could not be fully controlled for in this study. Finally, functional validation of the identified variants was not performed, which limited mechanistic interpretation. The observed associations require confirmation in larger, independent cohorts and external validation to determine their potential clinical utility.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The study was performed in accordance with the Declaration of Helsinki on medical research consisting of a human study group. The protocol was approved by the Ethics Committee of the Halic University (App. No. 2025/288).

References

Ahmad, F., Abubakar, S., Syed Alwi, S. S., & Chuan, N. O. (2025). Genetic determinants of variable anti-diabetic therapy responses across diverse populations with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Research and Clinical Practice*, *226*. https://doi.org/10.1016/j.diabres.2025.112337

Ansari, M. A., Chauhan, W., Shoaib, S., Alyahya, S. A., Ali, M., Ashraf, H., Alomary, M. N., & Al-Suhaimi, E. A. (2023). Emerging therapeutic options in the management of diabetes: recent trends, challenges and future directions. *International Journal of Obesity (2005)*, *47*(12), 1179–1199. https://doi.org/10.1038/S41366-023-01369-3

Artasensi, A., Pedretti, A., Vistoli, G., & Fumagalli, L. (2020). Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. *Molecules (Basel, Switzerland)*, *25*(8). https://doi.org/10.3390/MOLECULES25081987

Baggio, L. L., & Drucker, D. J. (2007). Biology of Incretins: GLP-1 and GIP. *Gastroenterology*, *132*(6), 2131-2157. https://doi.org/10.1053/j.gastro.2007.03.054

Campbell, J. E., & Drucker, D. J. (2025). Therapeutic Targeting of the GIP Receptor-Revisiting the Controversies. *Diabetes*, *74*(8), 1320-1325. https://doi.org/10.2337/DB25-0393

Capuano, A., Sportiello, L., Maiorino, M. I., Rossi, F., Giugliano, D., & Esposito, K. (2013). Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy--focus on alogliptin. *Drug Design, Development and Therapy*, *7*, 989-1001. https://doi.org/10.2147/DDDT.S37647

IDF Diabetes Atlas 2025 | Global Diabetes Data & Insights. (n.d.). Retrieved April 10, 2026, from https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/

Jamialahmadi, O., Mujica, E., Morris, L., Mancina, R. M., Ciociola, E., Qadri, S. F., ... & Romeo, S. (2025). Genome-wide interaction study with body mass index identifies CYP7A1 and GIPR as genetic modulators of metabolic dysfunction-associated steatotic liver disease. *Clinical and Molecular Hepatology*, *31*(4), 1252-1268. https://doi.org/10.3350/cmh.2025.0159

Javorský, M., Gotthardová, I., Klimčáková, L., Kvapil, M., Židzik, J., Schroner, Z., Doubravová, P., Gala, I., Dravecká, I., & Tkáč, I. (2016). A missense variant in GLP1R gene is associated with the glycaemic response to treatment with gliptins. *Diabetes, Obesity & Metabolism*, *18*(9), 941-944. https://doi.org/10.1111/DOM.12682

Koole, C., Wootten, D., Simms, J., Valant, C., Sridhar, R., Woodman, O. L., Miller, L. J., Summers, R. J., Christopoulos, A., & Sexton, P. M. (2010). Allosteric ligands of the glucagon-like peptide 1 receptor (GLP-1R) differentially modulate endogenous and exogenous peptide responses in a pathway-selective manner: implications for drug screening. *Molecular Pharmacology*, *78*(3), 456-465.

La Vignera, S., & Condorelli, R. A. (2026). Personalization of incretin therapy: can GLP-1 and GIP receptor polymorphisms influence therapy response? *Journal of the Endocrine Society*, *10*(8), bvag149.

Lee, H., Christie, H. E., Lee, J. S., Kwon, W. I., Moon, M. K., Choi, S. H., ... & Park, K. S. (2026). The gain-of-function GLP1R R131Q variant preserves β-Cell function and enhances response to GLP-1 receptor agonists. *Diabetes Care*, dc260662.

Lovshin, J. A., & Drucker, D. J. (2009). Incretin-based therapies for type 2 diabetes mellitus. *Nature Reviews. Endocrinology*, *5*(5), 262-269. https://doi.org/10.1038/NRENDO.2009.48

Manolopoulos, V. G., Ragia, G., & Tavridou, A. (2011). Pharmacogenomics of oral antidiabetic medications: current data and pharmacoepigenomic perspective. *Pharmacogenomics*, *12*(8), 1161-1191. https://doi.org/10.2217/PGS.11.65

Margoni, A., Papavassiliou, K. A., & Papavassiliou, A. G. (2025). Deliberating the striking effect of dual GLP-1R and GIPR agonists on "Diabesity" in light of precision medicine and pharmacogenomics. *Metabolism Open*, *28*, 100409. https://doi.org/10.1016/J.METOP.2025.100409

Młynarska, E., Czarnik, W., Dzieża, N., Jędraszak, W., Majchrowicz, G., Prusinowski, F., Stabrawa, M., Rysz, J., & Franczyk, B. (2025). Type 2 diabetes mellitus: new pathogenetic mechanisms, treatment and the most important complications. *International Journal of Molecular Sciences*, *26*(3). https://doi.org/10.3390/IJMS26031094

Pekkoc-Uyanik, K. C., Aslan, E. I., Kilicarslan, O., Ser, O. S., Ozyildirim, S., Yanar, F., Yildiz, A., Ozturk, O., & Yilmaz-Aydogan, H. (2023). Next-generation sequencing of prolidase gene identifies novel and common variants associated with low prolidase in coronary artery ectasia. *Molecular Biology Reports*, *50*(2), 1349-1365. https://doi.org/10.1007/S11033-022-08142-1

Pekkoc-Uyanik, K. C., Todurga-Seven, Z. G., Shahzadi, A., Sonmez, H., Mercan, S., Mete, B., & Tabak, F. (2025). Next-generation sequencing of CCR5, CXCR4, and IFNAR1 variants in relation to HIV-1 disease progression and ART response. *Scientific Reports*, *15*(1).

Pilon, M. O., de Denus, S., Asselin, G., Legault, M. A., Ngongang Kwandjang, H. B., Barhdadi, A., ... & Dubé, M. P. (2026). Pharmacogenomic study of the effects of saxagliptin on glucose control and hypoglycemic events. *BMC Medical Genomics*, *19*(1), 72.

Satapathy, P., Pratima, P., Gaidhane, A. M., Vadia, N., Menon, S. V., Chennakesavulu, K., ... & Bushi, G. (2025). Prevalence and impact of microvascular complications in type 2 diabetes mellitus on cognitive impairment and depression: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome*, *17*(1), 187.

Sathananthan, A., Man, C. D., Micheletto, F., Zinsmeister, A. R., Camilleri, M., Giesler, P. D., ... & Vella, A. (2010). Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. *Diabetes care*, *33*(9), 2074-2076. https://doi.org/10.2337/DC10-0200

Saxena, R., Hivert, M. F., Langenberg, C., Tanaka, T., Pankow, J. S., Vollenweider, P., ... & Giant Consortium. (2010). Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nature genetics*, *42*(2), 142-148. https://doi.org/10.1038/NG.521

Scheen, A. J. (2018). The safety of gliptins: updated data in 2018. *Expert Opinion on Drug Safety*, *17*(4), 387-405. https://doi.org/10.1080/14740338.2018.1444027

Seino, Y., Fukushima, M., & Yabe, D. (2010). GIP and GLP-1, the two incretin hormones: Similarities and differences. *Journal of Diabetes Investigation*, *1*(1-2), 8-23. https://doi.org/10.1111/J.2040-1124.2010.00022.X

Shilleh, A. H., Viloria, K., Broichhagen, J., Campbell, J. E., & Hodson, D. J. (2024). GLP1R and GIPR expression and signaling in pancreatic alpha cells, beta cells and delta cells. *Peptides*, *175*. https://doi.org/10.1016/j.peptides.2024.171179

Su, Q. J., Ashenhurst, J. R., Xu, W., Tran, V., Ryanne Wu, R., Weldon, C. H., ... & 23andMe Research Team. (2026). Genetic predictors of GLP1 receptor agonist weight loss and side effects. *Nature*, *653*(8115), 770–775. https://doi.org/10.1038/s41586-026-10330-z

Succurro, E., Sciacqua, A., Klen, J., & Dolžan, V. (2022). Glucagon-like Peptide-1 Receptor Agonists in the Management of Type 2 Diabetes Mellitus and Obesity: The Impact of Pharmacological Properties and Genetic Factors. *International Journal of Molecular Sciences 2022, Vol. 23, Page 3451*, *23*(7), 3451. https://doi.org/10.3390/IJMS23073451

Taylor, S. I., Yazdi, Z. S., & Beitelshees, A. L. (2021). Pharmacological treatment of hyperglycemia in type 2 diabetes. *The Journal of Clinical Investigation*, *131*(2). https://doi.org/10.1172/JCI142243

Todd, J. F., & Bloom, S. R. (2007). Incretins and other peptides in the treatment of diabetes. *Diabetic Medicine: A Journal of the British Diabetic Association*, *24*(3), 223-232. https://doi.org/10.1111/J.1464-5491.2006.02071.X

Todurga-Seven, Z. G., Pekkoc-Uyanik, K. C., Irmak-Aksan, H., Akdemir, M. F., Agay, E. R., & Ozyazgan, S. (2026). Association of SLC22A1 gene variants with metformin response in patients with Type 2 diabetes mellitus. *International Journal of Medical Biochemistry*, *9*(3), 141-150. https://doi.org/10.14744/IJMB.2026.31644

Yaluri, A. S., Ürgeová, A., Maršálek, M., Javorský, M., & Tkáč, I. (2025). Pharmacogenetics of incretin-based therapies. *Postgraduate Medical Journal*. https://doi.org/10.1093/POSTMJ/QGAF232

Yunusoglu, O. (2025). GLP-1 receptor agonists: Mechanisms, clinical applications, and future directions. In F. Demirkaya Miloglu & E. Dilek (Eds.), Current studies in pharmacology (1st ed., pp. 1-30). Livre de Lyon.

Zheng, Z., Zong, Y., Ma, Y., Tian, Y., Pang, Y., Zhang, C., & Gao, J. (2024). Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*, *9*(1). https://doi.org/10.1038/S41392-024-01931-Z

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