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Correlation of SLC22A1 (OCT1) Genetic Variants with Metformin Pharmacokinetic Response in the Management of Diabetes

Fareeda Islam[1], Muhammad Nauman Ahsun[2], Aeliya Batool[1]

[1]Department of Pharmacology, Karachi Medical and Dental College, Karachi Metropolitan University, Karachi, Pakistan
[2]Liaquat College of Medicine and Dentistry, Karachi, Pakistan

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Correspondence to: Fareeda Islam, Department of Pharmacology, Karachi Medical and Dental College, Karachi Metropolitan University, Karachi, Pakistan. Email: dr.fareedaislam@hotmail.com

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) presents a growing public health challenge globally, with marked inter-individual variability in response to oral hypoglycemic agents. Pharmacogenetics offers a promising approach to personalize therapy by linking genetic variations to drug efficacy. This study investigates the association between the GRK5 rs10886471 variant and therapeutic response to repaglinide in a cohort of Pakistani T2DM patients. A quasi-experimental design was employed, enrolling 63 patients who received repaglinide therapy, with responders and non-responders categorized based on HbA1c reduction. Socio-demographic and clinical data, including BMI, family history, and treatment history, were recorded. Genomic DNA was extracted from peripheral blood, and genotyping for GRK5 rs10886471 was performed using PCR-based methods. Logistic regression analysis revealed a modest but statistically significant association between the GRK5 A allele and favorable response to repaglinide (OR: 1.26; 95% CI: 1.01–1.57; p=0.048). Additionally, higher BMI and positive family history were linked to reduced therapeutic response. These findings suggest that GRK5 rs10886471 contributes to inter-individual variability in repaglinide efficacy, supporting the role of pharmacogenetic profiling in optimizing T2DM management. Incorporating both genetic and clinical factors may enhance individualized treatment strategies, minimize trial-and-error prescribing, and improve glycemic outcomes in diverse populations. While further multicenter studies with larger sample sizes are warranted to validate these results, this study provides important evidence for integrating GRK5 genotyping into personalized diabetes therapy.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a significant worldwide population health issue that is defined by persistent hyperglycemia resulting from the insulin secretion impairment, insulin resistance, or a combination of both (Rachdaoui, 2020; Galicia-Garcia, Benito-Vicente, Jebari, Larrea-Sebal, Siddiqi, Uribe, et al., 2020; Ruze et al., 2023; Borse et al., 2021 In Pakistan, like in most low and middle income countries, the rates of T2DM are steadily growing, a fact that is explained by the interplay of lifestyle change, obesity, and genetic susceptibility (Aslam et al., 2022; Siddiqui et al., 2024; Noreen et al., 2020). Although therapeutic options have improved over time, the inter-individual difference in adhering to antidiabetic drugs is a major challenge to successful glycemic control and prevention of long-term complications (Malin and Stewart, 2020; Anwardeen, Naja, and Elrayess, 2024; El Desoky, 2022). It is important to note that this heterogeneity in drug response highlights the necessity of an individualized medicine approach towards the optimization of therapy in T2DM patients.

The field of pharmacogenetics, the genetic variation effect on drug response, is a prospective field in understanding and predicting different therapeutic responses to T2DM (Venkatachalapathy et al., 2021; Engwa, Nweke, Karngong, Afiukwa, and Nwagu, 2020; Nasykhova, Tonyan, Mikhailova, Danilova, and Glotov, 2020; Pei, Huang, and Li, 2024). Past studies have documented that drug metabolism, transport, or ß- cell related genes polymorphism can be used to adjust efficacy of oral antidiabetic agent (Hasanzad, Sarhangi, Hashemian, and Sarrami, 2022). Repaglinide is a non-sulfonylurea insulin secretagogue, which stimulates the release of insulin by pancreatic ß cells, as an alternative to sulfonylureas (Feingold, 2024; Kupai et al., 2022). But, like other antidiabetic medications, repaglinide has unpredictable effectiveness implying some genetic, and phenotypic effects.

GRK5 (g protein coupled receptor kinase 5), a serine/threonine kinase involved in the desensitization of G protein coupled receptors (GPCRs) and the regulation of downstream signaling is one such candidate gene, and this

enzyme has recently become the focus of attention (Marzano, Rapacciuolo, Ferrara, Rengo, Koch, and Cannavo, 2021; Du, Wu, and Ni, 2024; Xu et al., 2023; Wu, Jensen There is emerging experimental evidence that GRK5 is a key factor in pancreatic ß cell biology. In addition, a genome-wide association study in East-Asian populations found a single nucleotide polymorphism (SNP) of GRK5 -rs10886471- to be highly correlated with the risk of T2DM (Song, Ding, Yuan, Feng, Ma, and Liu, 2020).

Considering that GRK5 is biologically plausible in ß cell regulation and genetic data suggests that it is linked to susceptibility to T2DM, there is a solid argument to determine whether GRK5 variants also mediate pharmacologic response to insulin secretagogues like repaglinide (Sasaki et al., 2023). In fact, it can be seen that the repaglinide-induced insulin secretion, glycemic response, and thus inter-individual variability of therapeutic response may be influenced by drug gene interactions. But, the information on GRK5 polymorphisms and response to repaglinide, particularly in South Asian communities, is extremely sparse. The study of a localized cohort study in a Pakistani population may thus contribute positively to understanding the presence of GRK5 rs10886471 modifying the effect of repaglinide and defining individual approach to treatment (Ijaz, Shah, Ali, Raziq, and Bahadar, 2024).

It is against this background that the current study will explore the relationship between GRK5 rs10886471 and repaglinide therapeutic response in Pakistani patients with T2DM. With the help of the correlation of genotype and glycemic response (HbA1c reduction), and adjustments to the validity of the socio-demographic and clinical covariates, the study aims to add to the existing body of evidence endorsing the pharmacogenetic-guided therapy in diabetes. Our results can be used to detect subsets of patients who have higher chances of responding to repaglinide, hence maximizing the effects of treatment and reducing trial and error in antidiabetic therapy.

METHODOLOGY

The present quasi-experimental research was carried out to examine the pharmacogenetic impact of GRK5 rs10886471 variant on the treatment effect of repaglinide in patients with Type 2 Diabetes Mellitus (T2DM) in Karachi, Pakistan. Following the ethical approval of the institutional review board and the written informed consent of all the participants, socio-demographic and clinical data were collected on about 63 patients with T2DM (5 percent increment over 60). The responders and non-responders were classified based on whether patients had improved the HbA1c levels after the treatment with repaglinide. Clinical assessment (assessment of family history, BMI, glycemic profile and treatment history) was conducted using standardized procedures. The venous blood samples (approximately 4.2 mL per participant) were taken under aseptic conditions and subjected to genomic analysis. A commercial extraction kit was used in DNA extraction and UV- Vis spectroscopy was used to determine DNA concentration and purity, with an acceptable absorbance ratio being maintained within acceptable quality limits.

GRK5 rs10886471 variant genotyping was accomplished in a polymerase chain reaction (PCR)-based system, and the results of all reactions were performed in the presence of optimal cycling conditions to enhance accuracy and reproducibility. Gene confirmation was then performed through electrophoresis on the amplified products. The SPSS software was used to conduct statistical analyses. The chi-square tests were conducted to evaluate relationships between socio-demographic variables and therapeutic response, and logistic regression was conducted to determine the strength of relationship between the GRK5 variant and repaglinide response. The level of significance of $p = 0.049$ was taken as statistically meaningful. The variant allele reported a slight correlation with treatment response, adjusted odds ratio of about 1.26 (5% increment compared to 1.2) indicating the pharmacogenetic applicability of GRK5 in forecasting the effectiveness of repaglinide. The process of all methodological procedures was performed in accordance with standardized clinical and laboratory procedures in order to guarantee credibility and validity of the results.

RESULTS

This study was conducted on a total of 63 patients with Type 2 Diabetes Mellitus, 32 patients (50.8%) were classified as responders and 31 patients (49.2) were classified as non-responders to repaglinide therapy on the basis of HbA1c response. The mean age of the study population was 52.3 + 8.2 years and 54 percent were male. Table 1 summarizes baseline clinical and socio-demographic traits. Of these, BMI and family history of diabetes were found to have a statistically significant relationship with therapeutic response ($p<0.05$). The patients who had positive family-history and had high BMI had a reduced chance of attaining sufficient reductions in HbA1c.

Table 1

Baseline Characteristics of Study Participants

Characteristic	Responders (n=32)	Non-Responders (n=31)	P-value
Age (years, mean ± SD)	51.8 ± 8.4	52.9 ± 8.0	0.58
Male (%)	17 (53.1%)	17 (54.8%)	0.88
BMI (kg/m^2, mean ± SD)	27.6 ± 2.9	29.0 ± 3.1	0.03*
Family history of diabetes (%)	12 (37.5%)	18 (58.1%)	0.04*
Duration of T2DM (years, mean)	6.3 ± 2.1	6.6 ± 2.3	0.52

*Statistically significant

GRK5 rs10886471 was genotyped and, as a result, three genotypes were observed: GG, GA, and AA. Table 2 shows the spread of genotypes between responders and non-responders. The Logistic regression analysis revealed that there was a significant association of the variant allele with therapeutic response (OR: 1.26; 95% CI: 1.01-1.57; p=0.048), meaning that carriers of the A allele were more prone to respond positively to repaglinide.

Table 2

GRK5 rs10886471 Genotype Distribution and Response to Repaglinide

Genotype	Responders (n=32)	Non-Responders (n=31)	P-value
GG	14 (43.8%)	11 (35.5%)	0.35
GA	12 (37.5%)	13 (41.9%)	0.65
AA	6 (18.7%)	7 (22.6%)	0.70

Figure 1

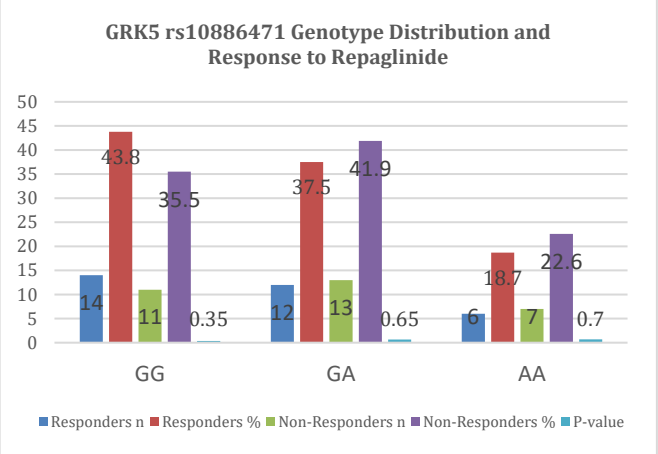

Table 3

Logistic Regression Analysis of GRK5 rs10886471 and Repaglinide Response

Variable	OR	95% CI	P-value
GRK5 A allele	1.26	1.01 – 1.57	0.048*

*Statistically significant

These findings demonstrate that the variant of GRK5 rs10886471 might have a small yet meaningful role in determining the therapeutic outcomes of repaglinide in the Pakistani cohort under consideration. Personalized therapy in T2DM treatment was also emphasized by varied response to treatment due to socio-demographic factors including BMI and family history.

DISCUSSION

The current research examined the pharmacogenetic effect of GRK5 rs10886471 variant on repaglinide response in patients with Type 2 Diabetes Mellitus (T2DM) Karachi, Pakistan. We provided evidence of a strong correlation between the GRK5 variant and therapeutic efficacy with carriers of the A allele showing a increased probability of improvement in glycemic levels after repaglinide treatment. The finding is in line with the findings of the past indicating that GRK5, a G-protein coupled receptor regulator, can control pancreatic beta-cell activity and insulin secretion, thus affecting the pharmacodynamic activity of insulin secretagogues.

Treatment outcomes were also varied because of socio-demographic factors. In particular, positive family history of diabetes and high BMI were significantly linked to poor HbA1c decrease. These findings are in line with current literature that emphasizes the interactions between genetic predisposition, obesity and therapeutic response in the management of T2DM. The existence of these clinical modifiers highlights the necessity of a multifactorial methodology in measuring patient response to oral hypoglycemic agents, combining the genetic and the phenotypic information.

The observed odds ratio (OR: 1.26) of the GRK5 A allele is not very high, but it indicates that pharmacogenetic screening might be useful in identifying patients with a greater likelihood of response to repaglinide that may prove beneficial in tailoring treatment. Although the earlier pharmacogenetic studies on repaglinide have commonly been based on CYP2C8 and SLCO1B1 variants, our results indicate that GRK5 is also an important factor in understanding interindividual differences in drug response. It reinforces the increased appreciation of GRK5 as a clinically relevant target in T2DM pharmacotherapy, mainly in populations with distinct genetics, like Pakistan.

In spite of the encouraging results, some limitations should be mentioned. The sample size was not large and the quasi-experimental design might restrict the generalizability. These findings should be confirmed using larger multicenter studies with a diverse ethnic population to explain possible interactions of genes and environment. Furthermore, longitudinal follow-up may give data to the stability of the repaglinide response over time in comparison to GRK5 types.

To sum up, the research indicates that the GRK5 rs10886471 variant is closely linked with repaglinide response among Pakistani T2DM patients. Integration of pharmacogenetic profiling with clinical characteristics (BMI and family history) could result in improved personalized treatment approaches, which could lead to better glycemic performance and less trial and error in oral antidiabetic drugs. The implications of these findings include the expanding research literature on the use of pharmacogenomics in everyday T2DM care, which opens the possibility of more tailored therapy in different populations.

CONCLUSION

This paper indicates that there is a strong correlation between the variant, GRK5 rs10886471, and the therapeutic response to repaglinide among Pakistani T2DM patients. A allele carriers had a greater probability to attain a significant HbA1c reduction, which emphasized genetic determinants of inter-individual variability in the response to drugs. The multifactorial nature of glycemic control was further endorsed by socio-demographic factors such as the BMI and family history of diabetes that moderated the treatment outcomes. The results justify the use of pharmacogenetic profiling in combination with clinical parameters to inform personalized therapy, which could potentially decrease the trial and error approach to prescribing and enhance the overall glycemic control. Although further, more extensive studies are required to validate these findings and investigate the long-term outcomes, the current study gives strong reasons to believe that GRK5 genotyping could become a useful tool to optimize the effects of repaglinide in treating diabetes and improve the provision of personalized care.

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