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# Association among insulin receptor substrate-1 genetic polymorphism, sulfonylurea therapeutic efficacy, and insulin resistance in patients with type 2 diabetes mellitus

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## Abstract

### Background

Insulin receptor substrate-1 gene (IRS-1) is an endogenous substrate of the insulin receptor present in insulin-sensitive tissues, allowing insulin signaling to take place. The IRS-1, rs1801278 gene with Gly972Arg substitution polymorphism is one of the most commonly studied variants in relation with type 2 diabetes mellitus (T2DM).

### Objective

The objective of this study was to detect the genetic association of the IRS-1, rs1801278 gene polymorphism with secondary sulfonylurea (SU) failure and insulin resistance (IR) in T2DM in Egyptian patients.

### Patients and methods

A total of 81 T2DM Egyptian patients (49 nonresponders and 32 responders to SU) were recruited. Genotyping of IRS-1, rs1801278 single nucleotide polymorphism was done using a TaqMan allelic discrimination assay with allele-specific designed fluorescent probes.

### Results

Taking GG genotype and G allele as references, the genotypic and allelic frequency distribution of the IRS-1 Gly972Arg rs1801278 single nucleotide polymorphism showed a significant difference with GA + AA genotypes and A allele, being of higher frequency in the nonresponders group when compared with the responder group (odds ratio: 8.79; 95% confidence interval: 1.11–69.37) and in IR patients when compared with non-IR ones (odds ratio: 4.27; 95% confidence interval: 1.2–14.4). The association of the SU response with the presence or absence of IR showed a statistically significant difference, with more IR patients in the nonresponder group.

### Conclusion

IRS-1 rs1801278 gene with Gly972Arg substitution polymorphism may be a significant genetic associate for SU efficacy and IR in Egyptian patients with T2DM.

**Keywords:** Insulin receptor substrate-1 gene, insulin resistance, sulfonylurea, type 2 diabetes mellitus

## INTRODUCTION

Physiologically, insulin is secreted by the pancreatic  $\beta$  cells in response to elevated blood glucose level to maintain euglycemia [1]. Type 2 diabetes mellitus (T2DM) is a complex metabolic and endocrine disorder resulting from the interaction between genetic and environmental factors, which cause various degrees of alteration in insulin secretion and its action on peripheral tissues, as well as in the pancreatic  $\beta$  cells [2].

Patients with T2DM either secrete insulin in appropriate amounts or even in overabundance but cannot be used properly by their bodies, leading to a condition known as

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insulin resistance (IR), or secrete it in amounts less than those required to deal with the glucose in their bodies [3], and these are non-IR patients [4].

The oral antidiabetic agents sulfonylurea (SU) are insulin secretagogues that stimulate insulin release from pancreatic  $\beta$  cells and improve peripheral sensitivity to insulin by increasing the number of insulin receptors or changing the consequences of the insulin-receptor binding [5]. According to the WHO guidelines, SU have a long-term safety profile, are of low cost, and are highly effective (<http://www.who.int/diabetes/publications/guidelines-diabetes-medicines/en/>), so they are the most commonly prescribed oral antidiabetic agents in many developing Afro-Asian nations, including Egypt [3]. However, the continuous stimulated secretion of insulin by the  $\beta$  cells to overcome hyperglycemia may finally result in a decrease in  $\beta$ -cell mass, and 5–10% of those patients with T2DM whose blood glucose levels were initially adjusted by SU [6] experience what is known as secondary SU failure, being unable to keep up targeted A1C levels of the good diabetic control less than 7% [7].

Insulin receptor substrate-1 (IRS-1) gene, located on chromosome 2q36, encodes one of the IRS protein substrate family. The encoded IRS-1 is an endogenous substrate of the insulin receptor present in insulin-sensitive tissues and allows insulin signaling to take place. Binding of insulin to its receptor initiates certain actions in the insulin receptor  $\beta$  subunit and IRS-1 protein, respectively [8], which in turn activates a pathway mediating the vast majority of insulin metabolic effects [9]. The IRS-1, rs1801278 gene with Gly972Arg substitution polymorphism, where glycine residue changes to arginine at codon 972, is the most commonly studied single nucleotide polymorphism (SNP) of this gene [10]. In T2DM, this aforementioned SNP was nearly 50% less in patients who responded effectively to SU compared with those who showed secondary SU failure [11] and was shown to be related to IR [12] acting as a competitive inhibitor of the insulin receptor [13].

The aim of this study was to detect the genetic association of IRS-1 Gly972Arg rs1801278 SNP with secondary SU failure and IR in T2DM in Egyptian patients.

## PATIENTS AND METHODS

This study was performed during the period from January 2018 to January 2019. A total of 81 Egyptian patients who were screened for this study based on American Diabetes Association (ADA) 2016 T2DM diagnostic criteria [14] were selected from the Department of Internal Medicine of the National Institute of Diabetes and Endocrinology, Cairo, Egypt. These patients' age ranged from 40 to 70 years old. Inclusion criterion was the use of SU as the oral antidiabetic treatment. Exclusion criteria included malignancies; anemias; hemoglobinopathies; hepatic, renal or cardiovascular diseases; and exogenous insulin therapy. Full history taking and full clinical assessment including general examination and anthropometric measurements were fulfilled for all the patients

participating in the study. They were divided into two groups according to their response to SU using A1C less than or equal to 7.0% as a cutoff. The first group included 49 (60.49%) patients with an A1C more than 7.0% (nonresponders) and the second group, the control group, included 32 (39.51%) patients with an A1C less than or equal to 7.0% (responders). A written consent was acquired from all participating patients. This study has earned approval by the General Organization of Teaching Hospitals and Institutes research ethics committee.

### Sample collection

Venous blood was collected after an overnight fasting with no caloric intake. Overall, 2 ml of EDTA plasma (stored at  $-80^{\circ}\text{C}$ ) was used for molecular analysis using real-time PCR assay. Another 2 ml of EDTA plasma was used for A1C analysis utilizing D-10 HPLC ion exchange chromatography (Bio-Rad, Hercules, California, USA). Two milliliters of sodium fluoride plasma was used to measure fasting blood glucose (FBG). Four milliliters of serum was used for routine biochemical analysis of lipid profile [total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c)] and creatinine levels by utilizing ARCHITECT 8000 science analyzer (Abbott, Abbott Park, Illinois, USA). After performing the routine biochemical tests, the serum was stored at  $-20^{\circ}\text{C}$  before assaying fasting insulin using commercially available insulin DRG solid-phase enzyme-linked immunosorbent assay kit based on the sandwich principle according to the manufacturer's instructions (DRG International Inc., Springfield, New Jersey, USA). Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as follows = fasting insulin ( $\mu\text{IU/ml}$ ) $\times$ fasting glucose ( $\text{mg/dl}$ )/405 [15]. The cutoff values for HOMA-IR may differ in various populations according to the ethnic group [16], so we applied the HOMA-IR cut-off more than 2.72 for both sexes together which was assumed for adult Egyptian patients by the study of Ahmed *et al.* [17].

### Insulin receptor substrate-1 genotyping

The genomic DNA was extracted from 200  $\mu\text{l}$  of whole blood samples using the Qiagen Extract kit (Qiagen, Hilden, Germany), as indicated by the manufacturer's protocol for each patient recruited in the study. The quantity and quality of DNA was estimated by Nano-Drop ND-1000 spectrophotometer (Thermo Scientific, Waltham, Massachusetts, USA) [18]. Genotyping of IRS-1, rs1801278 Gly972Arg SNP located on chromosome 2q36 was done utilizing a TaqMan allelic discrimination assay with allele-specific designed fluorescent probes, acquired from Applied Biosystems (Foster City, California, USA). The forward and reverse primers were 5'AGTCTGGCTACTTGTCTGGC3' and 5'ATGAGTTGTCCCCGTCAGA3' respectively. Amplification of DNA was performed on 3  $\mu\text{l}$  of genomic DNA. The assay consisted of 15  $\mu\text{l}$  of Taq PCR master mix kit (Qiagen), and 2  $\mu\text{l}$  of the two oligonucleotide primers. The assay was led by utilizing an Applied Biosystems Instrument Prism 7500 Sequence Detection System (Applied Biosystems), with optimized thermal cycle (initial denaturation at  $95^{\circ}\text{C}$  for 2 min, denaturation at  $95^{\circ}\text{C}$  for 30 s followed by annealing

at 62°C for 30 s, elongation at 72°C for 45 s, and the final extension step at 72°C for 5 min). The genotyping was conducted at Clinilab Laboratories (Clinilab, Maadi, Cairo, Egypt) facility according to the manufacturer's protocol, and the success rate was superior to 95%, with a calculated error based on PCR duplicates of less than 1%.

### Statistical analyses

Statistical analysis was performed using the statistical package for social sciences SPSS, version 13.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The K-S test and Shapiro–Wilk's test were conducted to test for the normality of the statistical samples. For normally distributed samples, data are presented as mean  $\pm$  SD; comparison between means was done by Student *t* test. For samples with non-Gaussian distribution, data are represented as median (minimum–maximum). The median values between two groups were compared by the Mann–Whitney *U* test. Fisher's exact test was used to assess significance for  $2 \times 2$ -crosstabulation tables, whereas the Mantel-Haenszel test was used to assess significance of the common odds ratio estimate. A *P* value less than 0.05 was considered statistically significant.

## RESULTS

A total of 81 Egyptian patients with T2DM who were included in the current study had undergone analysis for IRS-1, (rs1801278) gene Gly972Arg polymorphism. All the recruited patients were investigated for secondary failure to SU using A1c less than or equal to 7.0% as a cutoff. Patients with A1c more than 7.0% (nonresponders) were 49/81 (60.49%) patients, whereas patients with A1c less than or equal to 7.0% (responders) were 32/81 (39.51%) patients. Comparison between nonresponders and responders regarding demographic and biochemical features is summarized in Table 1. FBG, A1c, TG, and HOMA-IR were significantly higher in the nonresponders than the responder group ( $P < 0.001$ ,  $P < 0.001$ ,  $P = 0.016$ , and  $P = 0.036$ , respectively), whereas fasting insulin and HDL-c were significantly lower in the nonresponders than the responder group ( $P = 0.008$  and  $0.040$ , respectively). No significant differences ( $P > 0.05$ ) were found regarding other parameters between the two studied groups.

Regarding IRS-1, rs1801278 gene, taking GG genotype as a reference, the GG genotype frequency was 83.95% ( $n = 68/81$ ) and for GA + AA was 16.05% ( $n = 13/81$ ). Demographic and biochemical features of GG genotype group in comparison with GA + AA genotype group are mentioned in Table 2. FBG, A1c, and HOMA-IR were significantly lower in the GG than the GA + AA genotype group ( $P = 0.016$ ,  $P < 0.001$ , and  $P = 0.005$ , respectively), whereas cholesterol and LDL-c were significantly higher in the GG than the GA + AA genotype group ( $P = 0.012$  and  $0.041$ , respectively). Regarding the other parameters, no significant differences were observed between the two studied groups ( $P > 0.05$ ).

The genotypic and allelic frequency distribution of IRS-1, rs1801278 (Gly972Arg) SNP among nonresponders and

**Table 1: Comparison between sulfonylurea nonresponders and responders regarding demographic and biochemical features**

Parameters	Nonresponders [ <i>n</i> =49 (60.49%)]	Responders [ <i>n</i> =32 (39.51%)]	<i>P</i>
Age (years)	50 (40-68)	51 (41-68)	0.660 <sup>‡</sup>
Duration (years)	8.0 $\pm$ 4.0	8.0 $\pm$ 5.0	0.600 <sup>†</sup>
BMI (kg/m <sup>2</sup> )	32.2 $\pm$ 4.5	31.7 $\pm$ 4.2	0.647 <sup>†</sup>
FBG (mg/dl)	182 (67-562)	134 (64-284)	<0.001 <sup>***</sup>
A1c (%)	8.4 (7.1-13.5)	6.5 (5.1-7)	<0.001 <sup>***</sup>
FBI (mIU/l)	4.2 (0.9-12.0)	5.6 (2.1-15.8)	0.008 <sup>*</sup>
HOMA-IR	2.0 (0.8-3.2)	1.8 (1.2-2.5)	0.036 <sup>*</sup>
Chol. (mg/dl)	206 $\pm$ 48	203 $\pm$ 34	0.718 <sup>†</sup>
TG (mg/dl)	171 (62-565)	141 (69-300)	0.016 <sup>**</sup>
LDL-c (mg/dl)	122 (42-250)	124 (70-185)	0.996 <sup>‡</sup>
HDL-c (mg/dl)	43 $\pm$ 10	47 $\pm$ 9	0.040 <sup>**</sup>
Creat. (mg/dl)	0.7 (0.5-2)	0.7 (0.5-1.4)	0.692 <sup>‡</sup>

A1c, glycated hemoglobin; Chol, cholesterol; Creat., creatinine; FBG, fasting blood glucose; FBI, fasting blood insulin; HDL-c, high-density lipoprotein density cholesterol; HOMA, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides. <sup>†</sup>*t*-test. <sup>‡</sup>Mann-Whitney *U*. <sup>\*</sup>Significant ( $P < 0.05$ ). <sup>\*\*</sup>Highly significant ( $P < 0.001$ ).

**Table 2: Demographic and biochemical characteristics of the insulin receptor substrate-1 (G972R) gene polymorphism (GG) genotype group in comparison with GA+AA genotype group**

Parameters	GG [ <i>n</i> =68 (83.95%)]	GA + AA [ <i>n</i> =13 (16.05%)]	<i>P</i>
Age (years)	53.0 $\pm$ 9.0	52.0 $\pm$ 7.0	0.553 <sup>†</sup>
Duration (years)	9.0 (1-20)	5.0 (1-15)	0.188 <sup>‡</sup>
BMI (kg/m <sup>2</sup> )	32.5 $\pm$ 5.2	31.9 $\pm$ 4.3	0.667 <sup>†</sup>
FBG (mg/dl)	157 (64-473)	201 (67-562)	0.016 <sup>**</sup>
A1c (%)	7.4 (5.1-13.4)	9.9 (7-13.5)	<0.001 <sup>***</sup>
Fasting insulin (mIU/l)	4.9 $\pm$ 2.4	4.9 $\pm$ 2.6	0.921 <sup>†</sup>
HOMA-IR	1.8 $\pm$ 0.4	2.3 $\pm$ 0.5	0.005 <sup>**</sup>
Chol. (mg/dl)	239 $\pm$ 48	199 $\pm$ 39	0.012 <sup>**</sup>
TG (mg/dl)	150 (62-565)	208 (65-440)	0.136 <sup>‡</sup>
LDL-c (mg/dl)	156 $\pm$ 48	125 $\pm$ 33	0.041 <sup>**</sup>
HDL-c (mg/dl)	44 $\pm$ 9	44 $\pm$ 10	0.915 <sup>†</sup>
Creat. (mg/dl)	0.7 (0.5-2)	0.8 (0.6-1.1)	0.404 <sup>‡</sup>

A1c, glycated hemoglobin; Chol, cholesterol; Creat., creatinine; FBG, fasting blood glucose; FBI, fasting blood insulin; HDL-c, high-density lipoprotein density cholesterol; HOMA, homeostasis model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides. <sup>†</sup>*t*-test. <sup>‡</sup>Mann-Whitney *U*. <sup>\*</sup>Significant ( $P < 0.05$ ). <sup>\*\*</sup>Highly significant ( $P < 0.001$ ).

responders to SU, which are represented in Table 3, showed statistically significant differences ( $P = 0.014$  and  $0.016$ , respectively), provided that the GG genotype [75.51% (37/49)] was lower in the nonresponders group than the responders group [96.88% (31/32)], whereas the GA + AA genotype was higher in the nonresponder group [24.49% (12/49)] than the responder group [3.13% (3/32)]. Similarly, frequencies of G and A alleles were 87.8% (86/98) and

12.2% (12/98), respectively, in the nonresponders compared with 98.4% (63/64) and 1.6% (3/64), respectively, in responder group. That is to say, nonresponders had a higher GA + AA genotype and A allele frequency and a lower GG genotype and G allele frequency. The common odds ratio was found to be statistically significant ( $P = 0.039$ ), with odds ratio (OR): 8.79; 95% confidence interval (CI): 1.11–69.37, indicating that the relative risk of being a nonresponder is more likely to occur in the GA + AA genotype and A allele groups by 8.79 times greater than the GG genotype and G allele groups.

Data in Table 4 show that 12/81 (24.4%) patients were IR and 69/81 (85.2%) patients were non-IR. The genotypic and allelic frequency distributions of IRS-1 rs1801278 (Gly972Arg) SNP between the IR and non-IR groups were statistically significant ( $P = 0.021$  and  $0.027$ , respectively). The GG genotype [(58.3%) 7/12] was lower in the IR group than the non-IR group [(88.4%) 61/69], whereas the GA + AA genotype [(41.7%) 5/12] was higher in the IR than the non-IR group [(11.6%) 8/69]. Showing similar results, allele frequencies of G and A alleles were 79.2% (19/24) and 20.8% (5/24) in the IR group compared with (94.2%) 130/138 and (5.8%) 8/138 in non-IR group, respectively. These results demonstrate a higher frequency of GA + AA genotype and A allele in the IR group and a higher frequency of GG genotype and G allele in the non-IR group. The common odds ratio was found to be statistically significant ( $P = 0.019$ ) with OR: 4.27; 95% CI: 1.2–14.4, indicating that the relative risk of being IR is 4.27 times greater for GA + AA genotype and A allele compared with GG genotype and G allele.

## DISCUSSION

The recently applied trend of studies was markedly concerned with pharmacogenetics information investigating the interindividual variation in the oral antidiabetic agents' response, proving significant gene–drug interaction that may help in tailoring personalized medicine [19]. From previously reported candidate gene studies, the associations between the IRS-1 Gly972Arg polymorphism, the progressively increased risk of secondary SU treatment failure [20], and IR [21] were observed worldwide in patients with T2DM. This will help the early identification and management of patients with T2DM for whom SU are less beneficial [22]. As ethnicity is a definite and important determinant of these associations [23], this study attempted to elucidate these associations in Egyptian patients with T2DM.

In this study, patients with secondary failure to SU (nonresponders) showed significant differences of biochemical parameters in the form of higher FBG, A1c, TG, and HOMA-IR and lower fasting insulin and HDL-c as compared with patients achieving the well-controlled glycemic target (responders).

There were also significant differences in the biochemical characteristics between patients carrying the Gly972Arg variant (GA + AA) compared with homozygous wild-type patients (GG), with higher FBG, A1c, and HOMA-IR and lower cholesterol and LDL-c in GA + AA group. The patients carrying IRS-1 Gly972Arg variant were associated with secondary failure to SU compared with those who were noncarriers, with a relative risk of being a nonresponder more likely to occur in the GA + AA genotype and the A allele groups by 8.79 times greater than the GG genotype and the

**Table 3: Genotypic and allelic distribution of the insulin receptor substrate-1 (G972R) gene polymorphism among sulfonylurea nonresponder and responder groups**

IRS-1 (rs1801278)	Nonresponders [n (%)]	Responders [n (%)]	$P^a$	Allelic OR (95% CI) <sup>b</sup>
n (%)	49 (60.5)	32 (39.5)	0.014	$P=0.039$ 8.79 (CI: 1.11-69.37)
GG (68)	37 (75.5)	31 (96.9)		
GA+AA (13)	12 (24.5)	1 (3.1)		
n (%)	98 (60.5)	64 (39.5)	0.016	
G (149)	86 (87.8)	63 (98.4)		
A (13)	12 (12.2)	1 (1.6)		

CI, confidence interval; IRS-1, insulin receptor substrate-1; OR, odds ratio. <sup>a</sup>Fisher's exact test. <sup>b</sup>Mantel-Haenszel for common odds ratio estimate.

**Table 4: Genotypic and allelic distributions of the insulin receptor substrate-1 (Gly972R) gene polymorphism among insulin resistance and noninsulin resistance groups**

IRS-1 (rs1801278)	IR [n (%)]	Non-IR [n (%)]	$P^a$	Allelic OR (95% CI) <sup>b</sup>
n (%)	12 (14.8)	69 (85.2)	0.021	$P=0.019$ 4.27 (CI: 1.2-14.4)
GG (68)	7 (58.3)	61 (88.4)		
GA+AA (13)	5 (41.7)	8 (11.6)		
n (%)	24 (14.8)	138 (85.2)	0.027	
G (149)	19 (79.2)	130 (94.2)		
A (13)	5 (20.8)	8 (5.8)		

CI, confidence interval; IR, insulin resistance; IRS-1, insulin receptor substrate-1; OR, odds ratio. <sup>a</sup>Fisher's exact test. <sup>b</sup>Mantel-Haenszel for common odds ratio estimate.

G allele groups (OR: 8.79; 95% CI: 1.11–69.37;  $P = 0.039$ ). In approval with our findings, three Italian case–control studies indicated this association between IRS-1 Gly972Arg polymorphism and failure to oral hypoglycemic treatment, mostly SU [24–26]. Similar findings were also claimed by other studies [20,22,27]. The odds of SU failure varied according to the ethnic group recruited in each study. It was lower in Egyptian patients with T2DM (OR: 1.75; 95% CI: 1.08–12.4;  $P = 0.041$ ) [28] compared with the Italian patients (OR: 2.1; 95% CI: 1.18–3.70;  $P = 0.01$ ) [24].

There was a significant association between the IRS-1 Gly972Arg polymorphism and IR in the studied Egyptian patients with T2DM with a relative risk of being IR is 4.27 times greater for GA + AA genotype and A allele compared with GG genotype and G allele (OR: 4.27; 95% CI: 1.2–14.4;  $P = 0.019$ ). This is in convenience with the findings of some studies which assumed that IRIS-1 gene Gly972Arg SNP was associated with and involved in the pathogenesis of IR in T2DM, with rs1801278 GA genotype and A allele reflecting a substantially higher proportion in IR groups when compared with non-IR ones [12,28,29]. However, this finding was opposed by other studies which had detected no such association between the Arg972 IRS-1 polymorphism and IR [11,30,31].

The current study also investigated the association of the efficacy of SU treatment response with the presence or absence of IR. It showed a statistically significant difference ( $P = 0.02$ ), where all responders [ $(n = 32)$  100%] were non-IR. This was in agreement with two studies [27,32] but in disagreement with Chen *et al.* [33]. The limitations in our study included the comparatively small sample size and that we investigated a single genetic polymorphism. Further studies with larger sample sizes, in various ethnic groups, and investigating multiple SNPs simultaneously are required to be able to accomplish the real benefit and the aimed role of pharmacogenetics in personalized therapy of each patient individually.

## CONCLUSION

Gly972Arg SNP in IRS-1 gene (rs1801278) is associated with each of both secondary failure to SU and IR in Egyptian patients with T2DM. Such criteria could help prescribing the best therapeutic plan to efficiently individualize T2DM treatment. It might enable the identification of whether SU will be ‘the right drug for the right patient.’

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equipment facility except the genotyping was conducted at Clinilab Laboratories (Clinilab, Maadi, Cairo, Egypt) facility.

## Conflicts of interest

There are no conflicts of interest.

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