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Original Article

Polymorphisms of the *KCNQ1* gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes

Qing LI[1, #], Ting-ting TANG[2, #], Feng JIANG[1], Rong ZHANG[1], Miao CHEN[1], Jun YIN[1], Yu-qian BAO[1], Xiang CHENG[2], Cheng HU[1, 3, *], Wei-ping JIA[1, *]

[1]*Department of Endocrinology & Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center of Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory for Diabetes Mellitus, Shanghai 200233, China;* [2]*Laboratory of Cardiovascular Immunology, Institute of Cardiology, Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430022, China;* [3]*Shanghai Jiao Tong University Affiliated Sixth People's Hospital South Campus, Shanghai 201499, China*

Abstract

KCNQ1 channel is a member of the voltage-gated potassium channel KQT-like subfamily. The *KCNQ1* gene has recently been identified as a susceptibility locus for type 2 diabetes mellitus (T2DM). In the present study, we examined the effects of *KCNQ1* variants on the therapeutic response to modified-release gliclazide (gliclazide MR) treatment in Chinese patients newly diagnosed with T2DM. A total of 100 newly diagnosed T2DM patients without a history of any anti-diabetic medications were treated with gliclazide MR for 16 weeks, but 91 patients completed the entire study. The anthropometric parameters were determined at baseline and at the final visit, while clinical laboratory tests were performed at baseline and on weeks 2, 4, 6, 12, 16. Two SNPs, rs2237892 and rs2237895, in the region of the *KCNQ1* gene were genotyped in all the participants. All calculations and statistical analyses were conducted using SPSS. The rs2237892 TT homozygotes exhibited significantly higher 2-h glucose levels at baseline (P<0.05) and a lower cumulative attainment rate of the target 2-h glucose level ($P_{log\text{-}rank}$=0.020) than the C allele carriers. Patients with greater numbers of rs2237892 T alleles exhibited larger augmentations (Δ) in the 2-h glucose levels (P=0.027); and patients with the rs2237892 TT genotype exhibited a higher Δ homeostasis model assessment of β-cell function (HOMA-β) than CC and CT genotype carriers (P=0.021 and P=0.043, respectively). Moreover, the rs2237895 C allele was associated with a greater decrement in Δ glycated hemoglobin (HbA1c) (P=0.024); and patients with the CC genotype exhibited greater variance than those with the AA and AC genotypes (P=0.005 and 0.021, respectively). Compared with the C allele, the odds ratio for treatment success among carriers of the rs2237892 T allele was 2.533 (P=0.007); and the rs2237895 C allele was associated with a 2.360-fold decrease in HbA1c compared with the A allele (P=0.009). *KCNQ1* polymorphisms are associated with gliclazide MR efficacy in Chinese patients with type 2 diabetes.

Keywords: potassium channel; *KCNQ1*; type 2 diabetes; sulfonylureas; gliclazide MR; pharmacogenetics

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Introduction

Type 2 diabetes mellitus (T2DM) is a genetically heterogeneous group of metabolic disorders that is characterized by chronic hyperglycemia resulting from a deficiency in insulin secretion and insulin resistance[1]. After metformin, sulfonylureas (SUs) are the most commonly used oral anti-diabetic agents for the treatment of T2DM. In the 2013 Dutch type 2 diabetes guidelines, gliclazide was recommended as the preferred second treatment option over other SUs[2]. Gliclazide is a second-generation SU that acts exclusively on the pancreatic sulfonylureas receptor 1 (SUR1) and increases plasma insulin concentration via β-cell stimulation[3].

Although most type 2 diabetic patients respond well to this agent, there is inter-individual variability in the responses to sulfonylureas. The genetic factors that were involved in drug absorption, distribution, metabolism, and targeting, partly attributed to inter-individual variability of drug response[4]. Pharmacogenomic studies have proved that variants in

# These authors contributed equally to this work.
*To whom correspondence should be addressed.
E-mail alfredhc@sjtu.edu.cn (Cheng HU);
wpjia@sjtu.edu.cn (Wei-ping JIA)
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ABCC8, *KCNJ11*, *CYP2C9*, *TCF7L2*, *PPARG*, *IRS1*, and *NOS1AP* were associated with the efficacy of sulfonylureas[5–11]. Recent studies have linked the voltage-gated potassium channel KQT-like sub-family, member 1 gene (*KCNQ1*) to T2DM susceptibility in East Asians[12, 13] and to obesity in China[14]. Specifically, KCNQ1 channels might play a role in the regulation of insulin secretion and participate in the regulation of cell volume, which is critically important for the regulation of metabolism by insulin[13, 15–18].

Moreover, it has been reported recently that *KCNQ1* rs2237897 is related to the efficacy of gliclazide monotherapy in Chinese patient who are newly diagnosed with type 2 diabetes[19]. Our previous pharmacogenetic study of gliclazide demonstrated that *KCNJ11* E23K can influence responses to gliclazide due to its effect on insulin secretion in Chinese patients who are newly diagnosed with T2DM[20]. The potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) gene is well known to encode a subunit of the inwardly rectifying potassium channel Kir6.2, which forms the K_{ATP} channels in pancreatic β cells[20]. However, *KCNQ1* is the gene that encodes the pore-forming subunit of a voltage-gated K^+ channel (KvLQT1) that plays key roles in the repolarization of the cardiac action potential and water and salt transport in epithelial tissues. This channel is expressed in a wide variety of tissues, including the heart, skeletal muscle, liver, and epithelia[21]. Additionally, *KCNQ1* is also expressed in pancreatic islets and cultured insulin-secreting INS-1 cells[22]. Therefore, both *KCNQ1* and *KCNJ11* have been associated with β cell function. Furthermore, one study observed a striking increase in insulin sensitivity in a *KCNQ1* knockout mouse model, raising the possibility that *KCNQ1* may be a novel element that affects insulin sensitivity[23]. Our previous study demonstrated that single-nucleotide polymorphisms (SNPs) in *KCNQ1* are associated with repaglinide efficacy and that the rosiglitazone response is related to improvements in insulin sensitivity rather than β cell function in Chinese patients with type 2 diabetes[24]. However, it remains unknown whether *KCNQ1* SNPs have the same influence on the therapeutic effects of sulfonylureas. Thus, we conducted this study to further explore the association of the *KCNQ1* polymorphisms and the therapeutic effect of modified-release (MR) gliclazide in Chinese patients who were newly diagnosed with T2DM.

Materials and methods

Individuals and study design

The study commenced in 2012–2013 with the enrolment of 100 newly diagnosed type 2 diabetic patients without a history of any anti-diabetic medications. All patients were diagnosed according to World Health Organization criteria[25] and recruited from the outpatient clinics in Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. Detailed information in this study has been reported previously[20]. Diabetes education, including the introduction of T2DM and advice about diet and exercise, were provided to all patients. Then all subjects were treated with gliclazide MR for 16 weeks after a 2-week run-in period, subsequently visited the clinics on weeks 2, 4, 8, 12, and 16, and underwent designed clinical assessments. Nine patients were excluded from the study due to incomplete therapy, resulting in a sample of 91 patients (60 men and 31 women) who completed the 16-week gliclazide MR treatment. The initial minimum dosage of gliclazide was 30 mg per day. The dosage was increased to 60, 90, and 120 mg daily, in successively steps, until achievement of the target fasting plasma glucose (FPG) of ≤7 mmol/L (126 mg/dL) and/or 2-h plasma glucose (2-h PG) of ≤11 mmol/L (200 mg/dL). Patients exhibiting FPG >13 mmol/L (234 mg/dL) or 2-h PG >18 mmol/L (324 mg/dL) at two consecutive visits (at a maximal interval of 6 d) were excluded from the study.

Gliclazide presently is the first-line oral hypoglycemic medicine based on the standards of Care for Type 2 Diabetes in China[26]. For the purpose of this study, all participants were assigned to receive the gliclazide MR (Servier, Tianjin, China). And the escalating dose of gliclazide MR treatment was considered standard of care treatment for all patients. The study was approved by the Institutional Review Board of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. Written informed consent was obtained from each participant.

Anthropometric and biochemical measurements

The anthropometric measurements and clinical laboratory tests were described in detail previously[20]. In brief, anthropometric parameters containing height (m), weight (kg), waist and blood pressure were measured at baseline and at the final visit. Standard oral glucose tolerance tests were performed at baseline, and fasting blood samples and 2-h blood samples were collected at each visit for measurement of fasting and 2-h plasma glucose levels. Fasting and 2-h serum insulin levels, as well as serum lipid profiles were determined at baseline and at the final visit. Insulin sensitivity and β cell function were evaluated by homeostasis model assessment (HOMA) for insulin resistance index (HOMA-IR) and β cell function (HOMA-β)[27]. To evaluate potential β-cell function, the acute insulin response to arginine[28] was calculated after arginine stimulation tests at baseline and after 16 weeks of treatment.

Genotyping

Two SNPs in *KCNQ1*, rs2237892, and rs2237895, which were associated with type 2 diabetes in our previous study, were selected[24]. One primer set (forward primer: 5′-GCTGCAGCCCGTGTTCCT-3′; reverse primer: 5′-CGCATTCCGGGGGCTTCC-3′) were designed to amply DNA segment containing rs2237892 variant in *KCNQ1*. Another primer set for rs2237895 variant was 5′-TGGGGCAGGGGTGTCTTTA-3′ (forward primer) and 5′-TCTGCCTCTTGGTCTCATCTTTAC-3′ (reverse primer). Both PCR products were digested with Cfr9I (*Xma* I) (Thermo Fisher Scientific Inc, Waltham, MA, USA) at 37 °C for 4 h.

Definition of the response to gliclazide MR

In our study, HbA1c were reduced by 22% on average. Other

studies involving gliclazide treatment reported a decline of HbA1c by 15%-30%[29–32]. Therefore, responders were defined by two criterions. Criterion 1 was a decrease of >20% in the glycated hemoglobin level. Criterion 2 was a decrease of >30% in the glycated hemoglobin level.

Statistical analysis

Data are presented as the mean±SEM or *n* (%). Paired *t*-tests were used to compare values at baseline and 16 weeks after gliclazide MR. The allele frequencies were calculated by gene counting, and the results were then subjected to Hardy-Weinberg equilibrium tests. We set a FPG <7.0 mmol/L and a 2-h PG <7.8 mmol/L as attainment. The attainment rates between genotypes were estimated by Kaplan-Meier methodology and compared by the log-rank test and Cox regression model analysis adjusted for age, gender, and BMI at baseline. Data with a skewed distribution were $\log_{10}$-transformed prior to linear regression. The Δ values were calculated as the values at week 16 minus the values at baseline. Kruskal-Wallis test or ANOVA followed by the Student-Newman-Keuls multiple range test as appropriate were performed to analyze the differences among three genotype. After adjusting for age, gender, dosage and pathogenesis at baseline, multiple linear regressions under the additive genetic model were used to evaluate the differences in quantitative traits at baseline, 16 weeks and Δ values. Genotype distribution differences between responders and non-responders were compared by means of Fisher's exact test or χ^2-test. The odds ratio (OR) values are presented with 95% confidence intervals (CIs). Statistical significance was considered at $P<0.05$ (two-tailed). All calculations and statistics were performed using SPSS (version 20; SPSS Statistics, IBM Corporation, Armonk, NY, USA).

Results

Clinic characteristics of the study cohort

Of the 100 enrolled patients, 91 (60 men and 31 women, mean age 55.00±11.00 years old) completed the entire study, and 9 patients lost to follow-up. The baseline and post-therapy clinical characteristics of the study group are summarized in Table 1. Blood pressure, blood glucose, glycated hemoglobin levels and lipid profiles (LDL-C) decreased significantly after 16 weeks of gliclazide MR therapy compared with baseline (all $P<0.01$). Moreover, there were significant improvements in homeostasis model assessment of insulin resistance (HOMA–IR, $P<0.01$) and homeostasis model assessment of β-cell function (HOMA–β, $P<0.01$).

Table 1. Clinical characteristics of patients before and after gliclazide modified release treatment.

	Baseline	16 weeks	*P* value
BMI (kg/m^2)	24.96±0.28	25.38±0.26	0.160
Waist (cm)	90.14±0.91	90.25±0.79	0.641
Waist-hip ratio	0.93±0.01	0.93±0.01	0.129
SBP (mmHg)	136.65±1.91	132.00±1.56	0.007
DBP (mmHg)	82.73±1.20	79.41±1.13	0.004
FPG (mmol/L)	9.29±0.26	6.89±0.15	<0.001
2-h PPG (mmol/L)	16.52±0.46	9.37±0.37	<0.001
HbA1c (%)	8.45±0.16	6.47±0.07	<0.001
Fasting insulin (pmol/L)	10.64±0.68	11.32±0.84	0.184
2-h insulin (pmol/L)	46.07±4.25	47.05±5.04	0.625
HOMA-IR	4.00±0.30	3.37±0.28	0.004
HOMA-β	46.65±3.56	80.23±6.07	<0.001
Acute insulin secretion (μU/mL)	27.46±2.36	27.01±2.39	0.263
Total cholesterol (mmol/L)	5.23±1.71	4.91±1.36	0.061
HDL-C (mmol/L)	1.13±1.70	1.10±1.34	0.107
LDL-C (mmol/L)	3.06±1.14	2.93±1.11	<0.001
Triglyceride (mmol/L)	2.16±0.26	1.84±0.19	0.102

Data represent the mean±SEM. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, post-prandial plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

KCNQ1 SNPs and glucose metabolism during gliclazide MR treatment

To assess the effects of *KCNQ1* genetic polymorphisms (rs2237892 and rs2237895) on blood glucose during treatment, then we analyzed the changes in fasting glucose and 2-h glucose levels during treatment among different genotype groups. The genotype distributions of all SNPs conformed to Hardy-Weinberg equilibrium. The mean values of these parameters over time are displayed in Figure 1. Fasting glucose was not significantly different among patients with the CC, CT, and TT genotypes of rs2237892 (Figure 1A). Patients with the TT genotype of rs2237892 displayed higher 2-h glucose levels than the C allele carriers at baseline and at the fifth visit (all $P<0.05$, Figure 1B). Regarding rs2237895, there were no apparent variations among carriers of the AA, AC, and CC genotypes in terms of FPG or 2-h PG during the treatment (Figures 2A and 2B). After <7.0 mmol/L and <7.8 mmol/L were set as the fasting glucose and 2-h glucose standards respectively, the survival analyses showed that there was a trend towards a lower attainment rate of 2-h glucose in patients with the rs2237892 TT genotype ($P_{\text{log-rank}}=0.020$, Figure 1D). The significant difference remained after adjusting for age, gender, and BMI at baseline analyzed by Cox regression ($P_{Cox\text{-}regression}=0.019$, Figure 1D). No significant differences in the attainment rate of FPG and 2-h PG among patients with different rs2237895 genotype were found ($P_{\text{log-rank}}=0.481$ and 0.946, respectively, Figures 2C and 2D).

Next, we further explored the relevance of *KCNQ1* SNPs to quantitative traits. After adjusting for age, gender, dosage and pathogenesis at baseline, there were significant linear relationships between the number of rs2237892 T alleles and the augmentations in Δ2-h glucose levels according to multiple stepwise regressions ($P=0.027$, Table 2). Additionally, trends towards such associations were observed in ΔHbA1c ($P=0.058$), ΔHOMA-β ($P=0.094$), and (Δ) acute insulin response ($P=0.058$), as illustrated in Table 2. Significant differences in

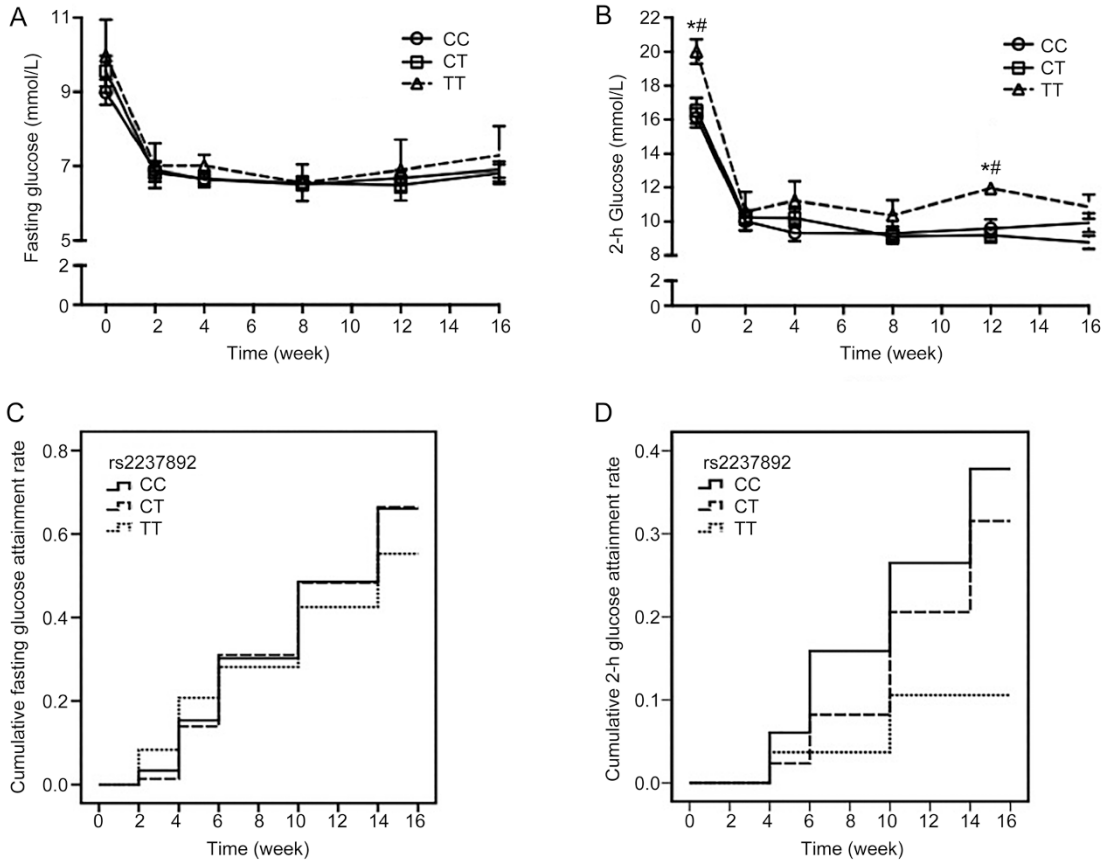

Figure 1. Association of rs2237892 with fasting glucose and 2-h glucose levels during gliclazide MR treatment. (A and B) Mean fasting glucose and 2-h glucose levels among carriers of the CC, CT, and TT genotypes. The data are presented as the mean±SEM. $^{*}P<0.05$ between CC and TT genotype carriers; $^{\#}P<0.05$ between CT and TT genotype carriers. (C and D) Associations of rs2237892 with attainment rates of the target values for fasting glucose and 2-h glucose, respectively, among carriers of the CC, CT, and TT genotypes. (C) $P_{log\text{-}rank}=0.752$, $P_{Cox\text{-}regression}=0.797$; and (D) $P_{log\text{-}rank}=0.020$, $P_{Cox\text{-}regression}=0.019$. The $P_{Cox\text{-}regression}$ values were adjusted for age, gender, and body mass index at baseline.

ΔHOMA-β were detected; *ie*, the patients with the TT genotype exhibited higher variance than those with the CC and CT genotypes (P=0.021 and P=0.043, respectively, Table 2). Similarly, as illustrated in Table 3, there were obvious linear relationships between the number of rs2237895 C alleles and the decrease in ΔHbA1c (P=0.024). Significant differences in the changes in ΔHbA1c were detected among the three groups; patients with the CC genotype exhibited a higher variance than those with the AA and AC genotypes (P=0.005 and 0.021, respectively; Table 3). Patients with the rs2237895 AC genotype exhibited a lower 2-h insulin level after treatment than AA homozygotes (P=0.014, Table 3).

KCNQ1 SNPs and response to gliclazide MR treatment

To identify the association of the *KCNQ1* genetic polymorphisms with the response rate to gliclazide MR treatment, the genotype frequencies according to the therapeutic responses are illustrated in Table 4. Based on the first criterion, no significant effects of the variances in rs2237892 or rs2237895 on gliclazide MR treatment were observed; however, the rs2237892 TT homozygotes and rs2237895 CC homozygotes exhibited good responses to gliclazide MR therapy. According to the second criterion, both rs2237892 and rs2237895 were associated with the response to gliclazide MR treatment. Regarding rs2237892, there were more responders among the rare TT allele homozygotes TT; 57.1% of the TT homozygotes responded, compared with only 15.9% of the CC homozygotes. The heterozygote CT group exhibited an intermediate response rate. The odds ratio for the T allele with respect to treatment success was 2.533 (95% CI: 1.283–4.999, P=0.007) compared with the rs2237892 C allele. Similarly, the rs2237895 C allele was associated with a 2.360-fold decrease in glycated hemoglobin compared with the A allele (95% CI: 1.225–4.550, P=0.009).

Discussion

Gliclazide MR is a new formulation of a second-generation SU drug that was designed for once-daily administration[33]. Gliclazide MR initiates insulin secretion by closing potassium channels. Our previous research indicated that the *KCNJ11* E23K variant is associated with the therapeutic effect of gliclazide in Chinese patients with T2DM[20]. However, the

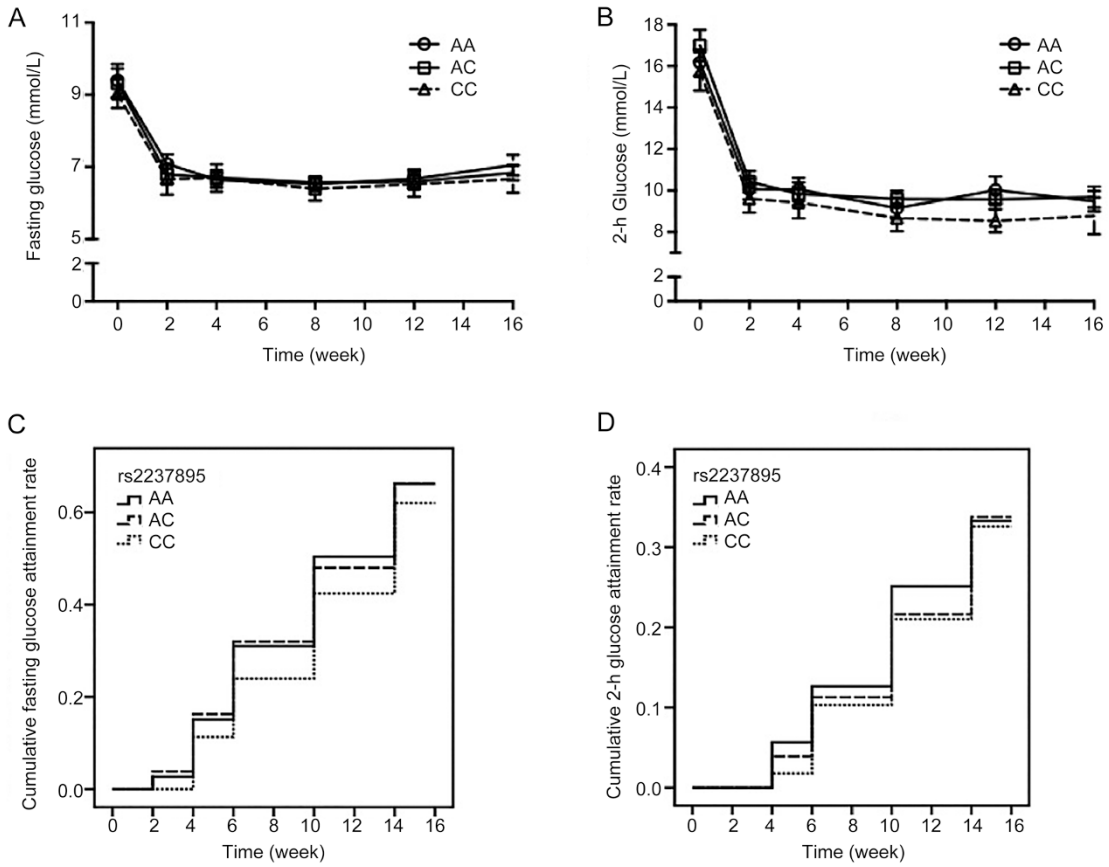

Figure 2. Association of rs2237895 with fasting glucose and 2-h glucose levels during gliclazide MR treatment. (A and B) Mean fasting glucose and 2-h glucose levels among carriers of the CC, CT, and TT genotypes. The data are presented as the mean±SEM. (C and D) The associations between rs2237895 and the attainment rates of target values for fasting glucose and 2-h glucose levels, respectively, among carriers of the CC, CT, and TT genotypes. (C) $P_{log\text{-}rank}$=0.481, $P_{Cox\text{-}regression}$=0.542; and (D) $P_{log\text{-}rank}$=0.946, $P_{Cox\text{-}regression}$=0.891. The $P_{Cox\text{-}regression}$ values were adjusted for age, gender, and body mass index at baseline.

relationship between *KCNQ1* and gliclazide has rarely been reported. Based on the original genome-wide association scans and replication studies, common variants in *KCNQ1* (rs2237892, rs2237895, and rs2237897) demonstrate the strongest associations with T2DM[12, 13, 18, 34]. A recent study focusing on Chinese patients with T2DM confirmed that rs2237897 but not rs2237892 is related to the efficacy of gliclazide monotherapy according to FPG alone[19]. Thus far, no studies have reported data for the relationship between rs2237895 and SUs. Rs2237892 and rs2237895, in moderate linkage disequilibrium (LD), are located in intron 15 of the *KCNQ1* gene on chromosome 11p15, and encode the pore-forming α subunit of the KvLQT1 channel. It has previously been shown that various *KCNQ1* polymorphisms (rs2237892 and rs2237895) are associated with an increased risk of T2DM due to not only decreasing levels of various measures of insulin secretion[13, 15–18] but also effects on insulin sensitivity[23, 24]. Therefore, we aimed to identify the relationships between *KCNQ1* polymorphisms (rs2237892 and rs2237895) and the therapeutic effect of gliclazide in Chinese populations.

Our present study revealed that the *KCNQ1* SNPs were associated with the response to gliclazide MR therapy in newly diagnosed T2DM patients. Regarding rs2237892, the TT homozygotes exhibited a lower treatment failure rate, and there was a significant linear relationship between the number of rs2237892 T alleles and the augmentation of Δ2-h glucose levels. Therefore, even if the 2-h glucose levels and cumulative attainment rate of the target 2-h glucose level among TT patients were higher than those of CC and CT patients, the patients with the T alleles exhibited a greater reduction in 2-h glucose levels following gliclazide treatment. Furthermore, we also identified some genotype-related differences with respect to improvements in blood glucose (HbA1c) and β-cell function (HOMA-β and acute insulin response); the patients with the T alleles displayed lower HbA1c and improved β-cell function. These findings suggest that the rs2237892 T allele improved the efficiency of gliclazide. The K_V channels encoded by *KCNQ1* play important roles in mediation of the repolarization of the membrane that terminates Ca^{2+} influx and insulin secretion in pancreatic β-cells[35], and the rs2237892 T allele has been found to be associated with higher second-phase glucose-stimulated insulin secretion via the hypergly-

Table 2. Associations of the single-nucleotide polymorphism rs2237892 in *KCNQ1* with the clinical features of the gliclazide cohort.

Parameter		CC	CT	TT	*P* value
Age (year)		55.80±1.77	53.88±1.76	55.57±5.41	0.743
Gender (male/female)		31/13	23/17	6/1	0.266
Dosage (mg/d)		45.39±3.43	41.03±2.95	54.20±13.59	0.984
BMI (kg/m^2)	Baseline	25.26±0.30	24.74±0.48	24.78±1.15	0.607
	16 Weeks	25.40±0.30	25.20±0.46	25.72±1.20	0.884
	Δ value	0.03±0.15	0.33±0.23	0.33±0.38	0.463
Waist (cm)	Baseline	91.46±0.98	89.57±1.74	92.00±1.06	0.463
	16 Weeks	90.76±1.06	89.39±1.31	91.25±3.33	0.770
	Δ value	-0.70±0.70	-0.18±0.96	0.75±0.85	0.764
Waist-hip ratio	Baseline	0.94±0.01	0.93±0.01	0.96±0.03	0.429
	16 Weeks	0.93±0.01	0.92±0.01	0.97±0.02	0.154
	Δ value	-0.01±0.01	-0.02±0.01	0.01±0.02	0.605
Fasting glucose (mmol/L)	Baseline	8.99±0.34	9.56±0.41	9.96±1.37	0.162
	16 Weeks	6.90±0.21	6.81±0.22	7.30±0.77	0.531
	Δ value	-2.06±0.27	-2.78±0.39	-2.90±1.11	0.153
2-h glucose (mmol/L)	Baseline	16.11±0.57	16.54±0.75	20.02±0.73$^{*\#}$	0.184
	16 Weeks	9.94±0.57	8.76±0.38	10.88±0.71	0.879
	Δ value	-6.10±0.66	-7.92±0.78	-10.45±1.72	0.041
Glycated hemoglobin (%)	Baseline	8.05±0.16	8.81±0.30	8.60±0.57	0.195
	16 Weeks	6.46±0.10	6.49±0.10	6.40±0.46	0.649
	Δ value	-1.59±0.19	-2.33±0.31*	-2.40±0.45	0.058
Fasting insulin (pmol/L)	Baseline	10.22±0.77	10.83±0.87	9.29±2.90	0.909
	16 Weeks	10.96±0.84	11.74±1.30	11.18±3.25	0.268
	Δ value	0.73±0.58	0.90±0.96	1.89±2.67	0.247
Log10 (2-h insulin) (pmol/L)	Baseline	1.59±0.05	1.53±0.05	1.70±0.08	0.758
	16 Weeks	1.57±0.06	1.61±0.05	1.69±0.05	0.341
	Δ value	-0.03±0.05	0.08±0.04	-0.03±0.04	0.257
Log10 HOMA-IR	Baseline	0.52±0.03	0.55±0.03	0.45±0.15	0.616
	16 Weeks	0.47±0.03	0.45±0.04	0.50±0.14	0.736
	Δ value	-0.05±0.02	-0.11±0.03	0.03±0.07	0.887
Log10 HOMA-β	Baseline	1.60±0.04	1.56±0.05	1.50±0.11	0.395
	16 Weeks	1.84±0.04	1.82±0.05	1.92±0.08	0.789
	Δ value	0.23±0.03	0.26±0.04	0.46±0.06$^{*\#}$	0.094
Log10 (acute insulin response) (pmol/L)	Baseline	1.38±0.04	1.37±0.04	1.34±0.10	0.609
	16 Weeks	1.33±0.04	1.36±0.05	1.38±0.09	0.451
	Δ value	-0.06±0.03	-0.01±0.03	0.04±0.06	0.058

Data are presented as the mean±SEM. The Δ values were calculated as the values at weeks 16 minus the values at baseline. $^{*}P<0.05$ compared with the CC genotype (one-way ANOVA followed by the Student-Newman-Keuls multiple range test). $^{\#}P<0.05$, compared with the CT genotype (one-way ANOVA followed by the Student-Newman-Keuls multiple range test). *P* values were adjusted for age, gender, dosage, and pathogenesis at baseline when linear regression models were adopted. BMI, body mass index; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

cemic clamp[36]. Therefore, we hypothesized that the *KCNQ1* rs2237892 T allele may increase insulin release after gliclazide treatment. Nevertheless, how the *KCNQ1* rs2237892 polymorphism affects the electrical change of the β-cell membrane following gliclazide MR treatment remains unknown and should be further investigated.

Recently, some researchers indicated that the *Kcnq1* molecule affected insulin sensitivity via glucose metabolism[23]. In our previous study investigating *KCNQ1* SNPs and repaglinide efficacy, the rs2237892 TT genotype was associated with better 2-h glucose normalization accompanied by greater improvements in insulin sensitivity[24]. However, in the present study, we failed to detect an influence of *KCNQ1* rs2237892 on insulin sensitivity following gliclazide MR treatment, which was most likely due to the ability of repaglinide to improve insulin sensitivity[37] or to the small sample size assessed in the present study. Based on all these findings, we propose the tentative hypothesis that the better 2-h glucose normalization observed in individuals with the rs2237892 TT genotype might be due to greater improvements in islet β-cell function in these individuals. Specifically, the rs2237892 T allele could improve the gliclazide response with respect to stimulation of insulin secretion and lowering of blood glucose levels; however, the underlying mechanism remains to be elucidated.

Table 3. Associations of the single-nucleotide polymorphism rs2237895 in KCNQ1 with the clinical features of the gliclazide cohort.

Parameter		AA	AC	CC	*P* value
Age (year)		55.65±2.21	55.05±1.69	52.85±2.87	0.755
Gender (male/female)		19/14	30/15	10/3	0.435
Dosage (mg/d)		46.01±4.71	43.58±2.84	40.63±4.94	0.902
BMI (kg/m^2)	Baseline	24.95±0.47	25.33±0.40	24.91±0.67	0.973
	16 Weeks	25.09±0.48	25.50±0.36	25.23±0.53	0.771
	Δ value	0.14±0.22	0.16±0.19	0.32±0.35	0.894
Waist (cm)	Baseline	89.86±1.59	91.46±1.44	89.33±1.74	0.856
	16 Weeks	89.46±1.50	90.91±1.15	89.67±1.39	0.594
	Δ value	-0.40±0.78	-0.55±0.89	0.33±1.22	0.859
Waist-hip ratio	Baseline	0.93±0.01	0.94±0.01	0.92±0.02	0.551
	16 Weeks	0.92±0.01	0.93±0.01	0.91±0.02	0.861
	Δ value	0.00±0.01	-0.02±0.01	-0.01±0.01	0.599
Fasting glucose (mmol/L)	Baseline	9.39±0.46	9.32±0.40	9.03±0.39	0.947
	16 Weeks	7.05±0.28	6.84±0.21	6.66±0.37	0.335
	Δ value	-2.31±0.35	-2.50±0.38	-2.51±0.35	0.338
2-h glucose (mmol/L)	Baseline	16.16±0.62	16.99±0.75	15.73±0.92	0.730
	16 Weeks	9.48±0.49	9.68±0.51	8.77±0.89	0.569
	Δ value	-6.97±0.70	-7.15±0.83	-7.41±1.21	0.742
Glycated hemoglobin (%)	Baseline	8.15±0.21	8.40±0.24	9.29±0.54*	0.071
	16 Weeks	6.55±0.11	6.48±0.11	6.15±0.18	0.500
	Δ value	-1.59±0.17	-1.94±0.27	-3.13±0.49$^{*\#}$	0.024
Fasting insulin (pmol/L)	Baseline	11.75±1.02	9.40±0.78	10.53±1.16	0.241
	16 Weeks	12.69±1.14	10.56±1.18	10.37±0.85	0.207
	Δ value	0.93±0.82	1.15±0.84	-0.16±1.23	0.733
Log10 (2-h insulin) (pmol/L)	Baseline	1.62±0.06	1.56±0.05	1.50±0.06	0.131
	16 Weeks	1.72±0.07	1.51±0.05*	1.60±0.03	0.088
	Δ value	0.04±0.06	-0.01±0.04	0.07±0.06	0.948
Log10 HOMA-IR	Baseline	0.57±0.04	0.48±0.03	0.58±0.04	0.825
	16 Weeks	0.52±0.04	0.43±0.04	0.43±0.05	0.313
	Δ value	-0.05±0.03	-0.05±0.03	-0.15±0.05	0.383
Log10 HOMA-β	Baseline	1.59±0.05	1.54±0.04	1.63±0.08	0.958
	16 Weeks	1.85±0.05	1.81±0.03	1.89±0.05	0.513
	Δ value	0.26±0.04	0.26±0.03	0.26±0.07	0.583
Log10 (acute insulin response) (pmol/L)	Baseline	1.43±0.04	1.34±0.04	1.34±0.07	0.146
	16 Weeks	1.38±0.05	1.31±0.04	1.36±0.08	0.642
	Δ value	-0.04±0.04	-0.03±0.03	0.02±0.05	0.286

Data are presented as the mean±SEM. The Δ values were calculated as the values at weeks 16 minus the values at baseline. $^*P<0.05$ compared with the AA genotype (one-way ANOVA followed by the Student Newman Keuls multiple range test). $^\#P<0.05$ compared with the AC genotype (one-way ANOVA followed by the Student-Newman-Keuls multiple range test). *P* values were adjusted for age, gender, dosage, and pathogenesis at baseline when linear regression models were adopted. BMI, body mass index; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 4. Genotype and allele distributions of responders and non-responders carrying the *KCNQ1* rs2237892 and rs2237895 variants.

	Criterion 1				Criterion 2			
rs2237892	CC	CT	TT	*P* value	CC	CT	TT	*P* value
Responder (%)	21 (47.7)	21 (52.5)	5 (71.4)	0.563	7 (15.9)	15 (37.5)	4 (57.1)	0.014
Non-responder (%)	23 (52.3)	19 (47.5)	2 (28.6)		37 (84.1)	25 (62.5)	3 (42.9)	
rs2237895	AA	AC	CC	*P* value	AA	AC	CC	*P* value
Responder (%)	16 (48.5)	22 (48.9)	9 (69.2)	0.391	6 (18.2)	12 (26.7)	8 (61.5)	0.014
Non-responder (%)	17 (51.5)	23 (51.1)	4 (30.8)		27 (81.8)	33 (73.3)	5 (38.5)	

Criterion 1: Responders were defined by a greater than 20% decrease in HbA1c. Criterion 2: Responders were defined by a greater than 30% decrease in HbA1c.

Regarding rs2237895, Jonsson *et al* conducted a prospective population-based study and found that the rs2237895 C allele indeed increased the risk of future T2DM and that this effect was due to failure of β-cell function[15]. In the present study, the carriers of greater numbers of C alleles at rs2237895 consistently exhibited higher HbA1c at baseline, which is in agreement with our previous research on the efficacy of repaglinide[24]. Furthermore, the rs2237895 CC patients exhibited greater augmentation in ΔHbA1c following treatment, potentially accounting for the lower failure rate of gliclazide therapy among the CC homozygotes. However, we also failed to detect a change in insulin sensitivity or β-cell function in the rs2237895 carriers following gliclazide treatment. Thus far, to the best of our knowledge, two studies have assessed the *KCNQ1* gene and the therapeutic response to SU treatment. The first study evaluated *KCNQ1* (rs163184) and the therapeutic response (FPG, HbA1c) to sulfonylurea treatment[38]. However, the patients who were not newly diagnosed with T2DM in this study were not treated with SU monotherapy, and other parameters related to insulin sensitivity and β-cell function were not assessed. In the other study published latest, Duan *et al* found that *KCNQ1* rs2237897 was associated with the efficacy of gliclazide accessed by FPG after 8-week monotherapy in Chinese type 2 diabetic patients. Specifically, the FPG reduction and treatment success rate were significantly higher in carriers of rs2237897 CT and TT genotypes, whereas no significant difference was found in the FPG reduction and treatment success rate among different genotype of rs2237892[19]. Similar with our study, the enrolled patients were newly diagnosed T2DM and treated with gliclazide monotherapy for perspective research. And the FPG reduction had no significant difference for rs2237892, which also confirmed by our present study. However, Duan *et al* measured only FPG but no other glucose metabolic parameters, such as 2-h PG, HbA1c, insulin sensitivity and islet β-cell function. Besides, the 8-week follow-up was not enough to observe a long-term effect of *KCNQ1* polymorphisms on the efficacy of gliclazide treatment. And rs22237895 was not analyzed in Duan's study. So our study was not a replication study and added more findings about *KCNQ1* rs2237892 and rs2237895 to this field.

To sum up, we found that the newly diagnosed T2DM patients carrying the *KCNQ1* rs2237892 T allele and the rs2237895 C allele were inclined to achieve better therapeutic results with gliclazide following prospective monotherapy for 16 weeks. Interestingly, consistent with our findings, Dai *et al* found that T2DM patients with the rs2237892 T allele and the rs2237895 C allele following repaglinide treatment were more likely to have a positive effect on postprandial glucose levels than patients with the rs2237892 CC and rs2237895 AA genotype[39]. In addition, our previous study demonstrated that patients with rs2237892 TT homozygotes had lower glucose levels following repaglinide treatment, while the rs2237895 C risk allele in those patients was associated with greater increments in fasting insulin[24]. Because the rs2237892 and rs2237895 markers are located near the outside of a *KCNQ1* exon, they do not change the amino acid sequence. These SNPs acted as biological markers may play a more direct role in gliclazide metabolism by affecting the gene's function. However, only biological markers can not explain gene function, which need more intelligent guesswork. Therefore, how the rs2237892 and rs2237895 *KCNQ1* polymorphisms affect the outcomes of gliclazide treatment remain unknown, and why the non-risk T allele of rs2237892 is associated with a better therapeutic outcome but the risk C allele of 2237895 is related to a greater beneficial effect require further investigation.

Several limitations to this study should be considered. First, the sample size was relatively small, which implies that the statistical power was insufficient and may account for the failure to detect an association between the *KCNQ1* SNPs and insulin sensitivity. But the effect of an inadequate follow-up period also cannot be ruled out. Second, the possibility of a false-positive finding cannot be excluded due to the lack of adjustment for multiple comparisons. However, because the analyzed SNPs were present in modest linkage disequilibrium and the quantitative traits were highly related, the influences of multiple comparisons may be limited. Third, no placebo group were included in the present study, so the effects of lifestyle modifications cannot be completely eliminated. Nevertheless, all patients were provided the same diabetes education according to guidelines on diet and exercise. And in the view of ethics, drug intervention as soon as possible to target blood glucose will benefit glycemic control as well as delay the occurrence of diabetic complications, lacking of placebo group in pharmacogenomics research focusing on well established anti-diabetic drug is reasonable and in accordance with study design performed by international counterparts[3, 8, 40–47]. Fourth, the glucose metabolic parameters like HbA1c, insulin sensitivity and islet β-cell function during the 16-week treatment were not measured, which might further strengthen our findings. However, in our previous pharmacogenetics study[24], blood glucose level decreased obviously within 12 weeks after treatment and kept at a steady state then. So the follow-up time were shortened to 16 weeks in this study design. And in our opinion, as for the newly diagnosed T2D patients without any anti-diabetic drug, the changes of blood glucose are sensitive and insulin secretions are unstable at the beginning of monotherapy. In the current study, there were two major visit time-point (baseline and 16 weeks) and four intermediate visit time-point (2, 4, 8, and 12 weeks). We determine the basic clinic traits at four intermediate visits, and comprehensive assessment at two major visits, this design can greatly save research cost as well as avoid too much blood drawing from the patients. Fifth, the mechanism underling is still unclear due to lacking of functional study.

In conclusion, the *KCNQ1* polymorphism is associated with the therapeutic response to sulfonylurea treatment in Chinese patients who are newly diagnosed with type 2 diabetes. Further investigations with a lager sample size and a placebo control group are necessary to confirm our findings.

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Author contribution

Cheng HU and Wei-ping JIA conceived and designed research; Qing LI, Ting-ting TANG, Feng JIANG, Rong ZHANG, and Miao CHEN performed the experiments; Jun YIN, Yu-qian BAO, and Xiang CHENG contributed new reagents or analytic tools; Qing LI, Ting-ting TANG, and Cheng HU analyzed the data; Qing LI, Ting-ting TANG, Cheng HU, and Wei-ping JIA wrote the paper.

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