JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

# CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients

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**Keywords**
*CYP2C9**3, Gliclazide, Type 2 diabetes mellitus

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*J Diabetes Investig* 2016; 7: 764–768

doi: 10.1111/jdi.12486

## ABSTRACT

**Aims/Introduction:** The objective of the present study was to investigate the effects of *CYP2C9**3 polymorphisms on the therapeutic response to gliclazide in type 2 diabetes patients.

**Materials and Methods:** A total of 746 incident type 2 diabetes patients were included in this study. After enrolment, patients went on 4-week gliclazide monotherapy. Fasting plasma glucose was measured before and after treatment. Hypoglycemia episodes and lifestyle information were collected by weekly follow up. Genotyping of rs1057910 was carried out using the single base primer extension method. The *t*-test, analysis of variance and chisquare-test were used to evaluate the effects of rs1057910 alleles on the therapeutic response to gliclazide.

**Results:** After the therapy, fasting plasma glucose decreased significantly from 11.2 ± 2.7 mmol/L to 8.0 ± 2.2 mmol/L ($P < 0.001$). Patients with AC/CC genotypes of rs1057910 had a greater reduction of fasting plasma glucose (3.6 vs 3.0 mmol/L, $P < 0.001$; 31.4 vs 24.5%, $P < 0.001$) and a higher rate of treatment success (54.7 vs 37.5%, $P < 0.001$; 51.4 vs 32.3%, $P < 0.001$; 71.6 vs 48.3%, $P < 0.001$ for criterion 1, 2 and 3, respectively).

**Conclusions:** The present study showed that the polymorphism at rs1057910 significantly affected the therapeutic response of gliclazide in type 2 diabetes mellitus patients. The risk allele is associated with a greater decrease of fasting blood glucose and a higher rate of treatment success with gliclazide monotherapy.

## INTRODUCTION

Sulfonylureas (SUs) have been a cornerstone of type 2 diabetes mellitus pharmacotherapy for over 50 years, and are among the most widely used oral hypoglycemic agents[1,2]. They work by stimulating the secretion of insulin from pancreatic β-cells[3]. It is well recognized that a substantial interindividual variability exists in the response to SUs[1]. In addition to some environmental factors, such as age, sex, disease status, drug and food interactions, and comorbidity[4], genetic polymorphisms in the gene coding for enzymes involved in the metabolism of SUs play an important role in the therapeutic response among individuals.

Most SUs are intensively metabolized in the liver, and cytochrome P450 (CYP) 2C9 is a major enzyme mediating the metabolism of SUs[4]. Previous studies in healthy volunteers have shown that the polymorphisms in the *CYP2C9* gene seriously affected the catalytic capacity of the enzyme[5–9]. The most common *CYP2C9* variant alleles, namely *CYP2C9**3 (rs1057910), are responsible for the majority of poor metabolizer phenotypes[6,7,10–12].

A few studies have assessed the effects of rs1057910 on the response to SUs in type 2 diabetes[13–21]. However, most of them merely focused on an adverse effect, hypoglycemia, and scarce evidence exists to support a better therapeutic response as a result of this common variant. Meanwhile, because of limited sample size, different study designs and outcome definitions, these studies yielded controversial results. In the present

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Received 19 May 2015; revised 19 November 2015; accepted 18 January 2016

prospective study, we aimed to investigate the association between rs1057910 and the efficacy as well as adverse effect of gliclazide in Chinese type 2 diabetes patients.

## MATERIALS AND METHODS

### Study design and patient selection

The present study was carried out in the outpatient clinic of the Second Affiliated Hospital of Shantou University Medical College. Type 2 diabetes was diagnosed according to the World Health Organization criterion[22]. Patients were eligible for the study if they were newly diagnosed patients with type 2 diabetes and could not attain an appropriate fasting plasma glucose level (fasting plasma glucose [FPG] <7.8 mmol/L) through lifestyle modification, and drug-naïve patients. Patients with any acute or chronic diabetes complications, malignancies, endocrine disorders, myocardial infarction or heart failure, chronic gastrointestinal disease or liver dysfunction, renal insufficiency, systemic inflammatory disease, surgery and corticosteroids treatment were excluded. Pregnant and lactating women were also excluded. This study was approved by the ethics committee of Shantou University Medical College. Written informed consent to this study was obtained from all participants.

After enrolment, all the participants started 4-week treatment with gliclazide (Tianjin Huajin Pharmaceutical Company, Tianjin, China). The initial dose of gliclazide was 40 mg twice daily (half an hour before breakfast and supper). The dosage was adjusted according to FPG at the 15th day. Another 40 mg was added when FPG was ≥7.0 mmol/L.

At the first visit, an experienced physician completed a questionnaire for each participant to collect information on demographic characteristics, medical history and medication, and lifestyle factors (including diet, exercise, smoking and alcohol consumption). Anthropometric parameters, such as height, weight, waist circumference, hip circumference and blood pressure, were measured according to standard protocols. An overnight (>10 h) fasting blood sample was drawn for determination of FPG, lipid profile, liver and renal function, and routine blood cell counts. Diabetes education including a brief introduction to type 2 diabetes, as well as advice on diet and exercise, was provided to all participants.

Participants came back for clinical follow up every 2 weeks. A clinical follow-up questionnaire was implemented by a trained physician for each participant to monitor their medication compliance, diet, exercise and side-effects. FPG was measured at each clinical follow up. At day 8 and day 22, a call was made by the same physician to complete a questionnaire about the medication compliance, diet, exercise and side effects for each participant.

### Laboratory methods

Plasma glucose was profiled by the glucose oxidase method. Lipid profile, and liver and renal function were tested using an automatic biochemical analyzer. Genomic deoxyribonucleic acid was isolated from peripheral blood leukocytes using the method of protein precipitation according to standard procedures. Genotyping of rs1057910 and rs1799853 were carried out using the GenomeLab SNP stream Genotyping System (Beckman Coulter Inc., Fullarton, CA, USA) according to the manufacturer's instructions[23]. Only data from rs1057910 was analyzed as a result of the low frequency of the minor allele for the rs1799853 (the genotype frequency of CC, CT, and TT are 99.6, 0.40 and 0%, respectively).

### Definition of outcomes

Three kinds of outcomes were used in the present study to evaluate the effects of rs1057910 alleles on the therapeutic response to gliclazide. The primary outcome for this study was the decrease of FPG at day 29 (both absolute and percentage value of the FPG reduction). The second outcome was the success of the gliclazide treatment. As for this outcome, we used three criteria to compare with other studies. They were as follows: (i) FPG <7.8 mmol/L at day 29, this was the same as another study from China[24]; (ii) FPG <7.0 mmol/L, this was the same as the study of Ren *et al.*[25]; and (iii) FPG <7.2 mmol/L and FPG ≥3.9 mmol/L, this was in line with the China Guideline for type 2 diabetes[26]. We also compared the number of hypoglycemia episodes among different genotypes of rs1057910. Hypoglycemia in the present study was ascertained by self-report. A hypoglycemia episode was ascertained if any of the following symptoms occurred: palpitations, tremor, sweating, hunger, anxiety, behavioral changes, difficulty in concentrating and thinking, confusion, cognitive impairment, convulsions, and coma[26].

### Statistical analysis

Continuous variables were presented as mean ± standard deviation, and compared by *t*-test or ANOVA among groups. The frequency distributions of categorical variables among groups were compared by Pearson's chisquare-test. SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

## RESULTS

A total of 746 type 2 diabetes patients were available for data analysis in the present study. The frequencies of rs1057910 genotype AA, AC, and CC were 90.08, 9.65 and 0.27%, respectively. The allele frequencies were in Hardy–Weinberg equilibrium. There were no significant differences in age, sex, body mass index, rice intake, sugar intake and exercise time among the genotype at baseline (Table 1).

Participants in the present study performed good management of their diet and exercise behavior during the follow-up period. Compared with day 1, the frequency of non-sugar intake at day 29 was significantly increased ($P < 0.001$), while there was no significant difference in the rice intake ($P = 0.440$) and exercise time ($P = 0.184$). After 4 weeks of gliclazide treatment, the FPG decreased significantly from

**Table 1** | Comparison of baseline characteristics of the participants among different genotypes of rs1057910 in the present study

| Variable | Rs1057910 | | | *P*-value |
|---|---|---|---|---|
| | AA ($n$ = 672) | AC ($n$ = 72) | CC ($n$ = 2) | |
| Age, years (SD) | 49.5 ± 8.2 | 50.3 ± 7.6 | 53.7 ± 6.9 | 0.3155 |
| BMI, kg/m$^2$ (SD) | 24.7 ± 3.0 | 24.9 ± 2.8 | 25.0 ± 2.1 | 0.7610 |
| Male (%) | 402 (59.8) | 45 (62.5) | 1 (50.0) | 0.757 |
| FPG, mmol/L (SD) | 11.3 ± 2.8 | 11.0 ± 2.6 | 10.5 ± 1.1 | 0.2169 |
| Duration of diabetes, years (SD) | 1.26 ± 2.6 | 1.29 ± 2.1 | 1.23 ± 1.7 | 0.6857 |
| Rice, g/day (SD) | 370 ± 120 | 370 ± 135 | 325 ± 65 | 0.7855 |
| Exercise time, h/day (SD) | 0.9 ± 0.7 | 0.8 ± 0.7 | 0.5 ± 0.6 | 0.5963 |
| Sugar | | | | |
| None (%) | 455 (67.7) | 52 (72.3) | 2 (100.0) | 0.404 |
| 1–2/week(%) | 162 (24.2) | 14 (19.4) | 0 (0.0) | |
| ≥3/week(%) | 55 (8.1) | 6 (8.3) | 0 (0.0) | |

BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation.

11.2 ± 2.7 mmol/L to 8.0 ± 2.2 mmol/L ($P < 0.001$). These results are shown in Table 2.

Table 3 shows the association between the rs1057910 genotype and therapeutic response to gliclazide. Owing to the low frequency of CC genotype for rs1057910, pooling individuals with AC and CC genotype was carried out in the association analysis. Patients with AC and CC genotypes had greater reduction of FPG (3.6 vs 3.0 mmol/L, $P < 0.001$; 31.4 vs 24.5%, $P < 0.001$), and a higher rate of treatment success (54.7 vs 37.5%, $P < 0.001$; 51.4 vs 32.3%, $P < 0.001$; 71.6 vs 48.3%, $P < 0.001$ for criterion 1, 2 and 3, respectively); whereas in the comparison of hypoglycemic events, rice intake, sugar intake, diet control and exercise time, the differences between AA and AC/CC were not statistically significant, as shown in Table 3.

## DISCUSSION

In the present prospective cohort study, we investigated the association of *CYP2C9**3 with the therapeutic response of gliclazide in type 2 diabetes patients. Our results showed that rs1057910 was a major source of interindividual variability in the response to gliclazide treatment. Compared with the wild genotype (AA), patients with the genotype of AC or CC had a greater reduction of FBG after a 4-week gliclazide monotherapy.

**Table 2** | Comparison of fasting plasma glucose and life behavior before and after the treatment

| Variable | Day 1 | Day 29 | *P*-value |
|---|---|---|---|
| FPG, mmol/L (SD) | 11.2 (2.7) | 8.0 (2.2) | <0.001 |
| Sugar intake | | | |
| None (%) | 510 (68.4) | 646 (86.6) | <0.001 |
| 1-2/week (%) | 175 (23.5) | 82 (11.0) | |
| ≥3/week (%) | 61 (8.1) | 18 (2.4) | |
| Rice intake, g/day (SD) | 370 (135) | 365 (125) | 0.440 |
| Exercise time, h/day (SD) | 0.81 (0.7) | 0.82 (0.7) | 0.184 |

FPG, fasting plasma glucose; SD, standard deviation.

Gliclazide is widely used in the treatment of type 2 diabetes, and it has been reported that *CYP2C9* was a major contributor to gliclazide metabolic clearance with some contribution of *CYP2C19*[27]. The existing evidence derived from pharmacokinetic studies carried out in healthy volunteers showed that *CYP2C9**3 (rs1057910) was responsible for the majority of poor metabolizer phenotypes[4,28]. There appeared to be great interindividual differences in the dose–response relationship for gliclazide, both with respect to the glucose and the insulin response[29,30]. Monitoring of gliclazide plasma concentrations has therefore been proposed to reduce the cases of individual toxicity or lack of efficacy caused by relative overdosage or underdosage, respectively[31]. A reduction in variability of plasma concentrations could be achieved if homozygous and heterozygous carriers of *CYP2C9* allele *3 received lower doses. It is common sense in clinical pharmacology that a reduction in the variability of dose–concentration relationships could result in more predictable efficacy and lower incidence of adverse events. To achieve similar plasma concentration profiles, slow metabolizers (genotype *CYP2C9**3/*3) should receive less than 50% of the dose that is adequate for rapid metabolizers. Carriers of the *3/*3 genotype of *CYP2C9* might have a substantially higher rate of drug accumulation, particularly when a twice-daily dosing scheme is applied. Therefore, it is logical to hypothesize that patients with *3 alleles will have a lower clearance of SUs and a higher plasma SUs level, and this will eventually produce a better therapeutic response and a greater risk for hypoglycemia.

The existing evidence around a better therapeutic response of SUs as a result of *CYP2C9* polymorphisms is scarce and inconclusive. A population pharmacogenetic study of incident sulfonylurea users found that type 2 diabetes patients with *CYP2C9**2/*2, *2/*3, or *3/*3 genotypes were 3.4-fold ($P = 0.0009$) more likely to achieve a treatment hemoglobin $A_{1C}$ level <7% than patients with two wild-type *CYP2C9* alleles, and this corresponded to a 0.5% ($P = 0.003$) greater reduction in hemoglobin $A_{1C}$ concentration[15]. Another prospective study

**Table 3** | Association of rs1057910 genotype with the therapeutic response to gliclazide in type 2 diabetes patients

| | Rs1057910 | | |
|---|---|---|---|
| | AA ($n$ = 672) | AC/CC ($n$ = 74) | $P$-value |
| FPG[†] | | | |
| After, mmol/L (SD) | 8.3 (2. 3) | 7.3 (1.8) | <0.001 |
| Change(ab), mmol/L (SD) | 3.0 (2.6) | 3.6 (2.2) | <0.001 |
| Change(per) (SD) | 24.5 (19.2) | 31.4 (14.9) | <0.001 |
| Treatment suc[‡] | | | |
| C1, $n$ (%) | 252 (37.5) | 41 (54.7) | <0.001 |
| C2, $n$ (%) | 217 (32.3) | 38 (51.4) | <0.001 |
| C3, $n$ (%) | 325 (48.3) | 53 (71.6) | <0.001 |
| No. hypo, (SD)[§] | 1.0 (2.7) | 1.3 (2.9) | 0.1830 |
| Total dose, pill (SD) | 39.0 (8.3) | 38.0 (7.6) | 0.1661 |
| Rice, g/day (SD) | 7.4 (2.5) | 7.0 (2.4) | 0.1053 |
| Exercise time, h/day (SD) | 0.8 (0.7) | 0.8 (0.7) | 0.1981 |
| Diet control | | | |
| Poor (%) | 43 (6.2) | 8 (10.8) | 0.081 |
| Fair (%) | 258 (38.4) | 32 (43.2) | |
| Good (%) | 372 (55.4) | 35 (47.3) | |
| Sugar | | | |
| None (%) | 585 (87.1) | 62 (83.8) | 0.493 |
| 1–2/week(%) | 72 (10.7) | 9 (12.2) | |
| ≥3/week(%) | 15 (2.2) | 3 (4.0) | |

[†]After: after the gliclazide treatment; change(ab): the absolute value of FPG reduction; change(per): the percentage value of the FPG reduction. The comparisons among different genotype groups were analyzed by $t$-test. [‡]The success of the gliclazide treatment. C1, C2 and C3 correspond to criterion 1, criterion 2 and criterion 3, respectively. The chis-quare-test was used to compare the different frequency of treatment success among different genotype groups. [§]The number of the hypoglycemic events during the follow-up period. This variable was analyzed by $t$-test.

from Japan yielded a similar result that the reduction in the hemoglobin $A_{1C}$ was significantly larger ($P$ = 0.05) among the *CYP2C9**1/*3 participants than that of the *CYP2C9**1/*1 participants[16]. Whereas, if the decrease of FPG was taken as the outcome, two studies from the Netherlands found no significant difference in the decrease of FPG between carriers of *CYP2C9**2 or *CYP2C9**3 alleles and homozygous carriers of the *CYP2C9**1 allele[17,32]. In the present study, significantly different decreases of FPG resulting from polymorphism at rs1057910 were observed. Our study might not have an immediate impact on clinical practice; however, before such a model of care can be implemented, research is required to more clearly quantify the association of genetic variation with treatment outcomes and adverse effects.

As with all observational studies, there were limitations to the present study. We only studied the initial response to gliclazide for a short period, the association of CYP2C9*3 variant with the long-term response to gliclazide remains unknown and further studies with a longer follow-up period are worth considering. In addition, our study was carried out by use of a single-dose design. Further studies of patients with different *CYP2C9*3* genotypes with multiple dosing will be required to verify the conclusions, and will be beneficial to the investigation of individual rational dosages and decreasing the risks of adverse effects.

The strengths of the present study include the prospective study design, relatively large sample size and the monotherapy of gliclazide. Like other cohort studies, the prospective design itself is an excellent method to control information bias. Compared with previous studies[13,20,29], our findings with 746 incident type 2 diabetes patients therefore provide relatively more powerful evidence for the association between *CYP2C9**3 variant and the therapeutic response to gliclazide. The monotherapy of gliclazide avoids the influence of co-medication and the heterogeneous metabolism of SUs, as discussed above.

In conclusion, the results of the present study showed that polymorphism at rs1057910 significantly affected therapeutic response to gliclazide in type 2 diabetes patients. The risk allele is associated with greater decrease of FBG and a higher rate of treatment success with gliclazide monotherapy.

## ACKNOWLEDGMENTS

We thank the staff of the Department of Endocrinology of the Second Affiliated Hospital of Shantou University Medical College for their support in the recruiting and management of the study participants.

## DISCLOSURE

The authors declare no conflict of interest.

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