**Original Article**

# Association of a SLC30A8 Genetic Variant with Monotherapy of Repaglinide and Rosiglitazone Effect in Newly Diagnosed Type 2 Diabetes Patients in China*

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**Abstract**

**Objective** To investigate a potential relationship between Solute carrier family 30 (zinc transporter) member 8 (*SLC30A8*) rs13266634 variant and efficacy of rosiglitazone or repaglinide in treating newly diagnosed Chinese type 2 diabetes patients.

**Methods** A total of 209 diabetic patients without any antihyperglycemic history were recruited and treated with repaglinide or rosiglitazone randomly for 48 weeks (104 and 105 patients, respectively). Anthropometric measurements and clinical laboratory tests were carried out before and after the treatment. An non-synonymous variant rs13266634 was genotyped by matrix-assisted laser desorption ionization-time of flight mass spectroscopy.

**Results** Ninety-one patients in repaglinide group and ninety-three patients in rosiglitazone group completed the study. Δ value of homeostasis model assessment of beta cell function (HOMA-B) and Δ value of fasting proinsulin levels were statistically significant between three genotype groups (*P*=0.0149 and 0.0246, respectively) after rosiglitazone treatment. However, no genotype association was observed in the repaglinide or rosiglitazone group with other parameters.

**Conclusion** The *SLC30A8* variant was associated with the efficacy of insulin sensitizer monotherapy on insulin secretion in patients with newly diagnosed type 2 diabetes mellitus in Shanghai, China.

**Key words:** Pharmacogenetics; Single nucleotide polymorphisms; Solute carrier family 30 member 8; SLC30A8

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## INTRODUCTION

Type 2 diabetes is a complex metabolic disorder characterized by chronic hyperglycemia ascribing to insulin resistance and relative insulin secretion deficiency[1]. It is well known that the oral hypoglycemic agent including insulin secretagogue, methylbiguanide, inhibitor of alpha glucosidase and insulin sensitizer thiazolidinediones (TZDs) are commonly used for the therapy of type 2 diabetes mellitus with totally different physiological pathways. For instance,

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repaglinide, as a kind of non-sulfonylurea insulin secretagogue, contributes to stimulating insulin secretion via ATP-dependent potassium channels ($K_{ATP}$) of the pancreatic beta cells. Rosiglitazone, a representative of the thiazolidinediones, acts as agonists of the nuclear factor peroxisome proliferator–activated receptor γ (PPAR γ) and regulates the expression of genes involved in the glucose and lipid metabolism, thereby leading to the improvements of the insulin sensitivity, especially in the peripheral tissues[2-3]. However, the clinical response to these oral agents varies among individuals. It was reported that genetic polymorphisms had been increasingly recognized to play an important role in drug efficacy and estimated to account for 15%-30% and even 95% (for some certain drugs) of interindividual variability in drug metabolism and response[4]. The effects of genetic polymorphisms on insulin secretagogue and TZDs efficacy have been described in previous pharmacogenetical studies, suggesting that genetic variants might be associated with the different responses to the antihyperglycemic treatment[5-8].

*SLC30A8*, which was uniquely expressed in the pancreas (mainly in beta cells), was confirmed as a susceptible gene of type 2 diabetes in recent genetic studies and the non-synonymous Arg325Trp (C>T) variant of this gene (rs13266634) was indicated to have an impact on decreased pancreatic beta-cell function in different populations[9-13]. In addition, rs13266634 was associated with reduced first-phase insulin release in European non-diabetic offspring of type 2 diabetes patients according to the EUGENE2 study[14]. Moreover, such variant was detected to be associated with fasting glucose ($P$=0.0118) and type 2 diabetes in Chinese populations even after correction of multiple comparisons (OR 1.251, 95% CI 1.138-1.374, $P_{empirical}$=0.0002)[12]. The encoded protein, solute carrier family 30 (zinc transporter) member 8 (SLC30A8), also known as zinc transporter protein member 8 (ZnT8), is responsible for the transportation of zinc from the cytoplasm to extracellular spaces or to intracellular compartments, such as secretary granules and is of importance for the proinsulin processing, insulin maturation, storage and secretion from pancreatic beta cells[15]. The downregulation of ZnT8 in rat INS-1 insulinoma cells showed reduced intracellular insulin content and decreased insulin secretion after a hyperglycemic stimulus[16]. Moreover, the deletion of the mouse *slc30a8* is accompanied with modestly impaired insulin secretion without obvious changes in glucose metabolism[17]. In contrast, the overexpression of ZnT8 in cultured INS-1 cells showed a markedly increased insulin secretion in response to hyperglycemic challenge[16]. In this study, we analyzed the single-nucleotide polymorphism (SNP) rs13266634 in newly diagnosed type 2 diabetes patients who are the residents of Shanghai, China and had been treated with repaglinide or rosiglitazone solely for 48 weeks in order to evaluate its effects on the drug efficacy.

## METERIALS AND METHODS

### *Patients and Study Design*

A total of 209 newly diagnosed type 2 diabetic patients, defined according to the World Health Organization criteria[18], were recruited from the outpatient clinics of 10 hospitals in Shanghai, China. Eligible patients, between 30 and 70 years of age with glycated hemoglobin ⩾6.5% and a body mass index (BMI) ⩾18.5 kg/m$^2$, had received no previous pharmacologic therapies for type 2 diabetes prior to the study and were divided into two groups randomly after the recruitment. One group including 104 and the other group including 105 newly diagnosed type 2 diabetic patients were treated with repaglinide and rosiglitazone for 48 weeks, respectively. Detailed information on the excluded criteria, withdrawn criteria as well as the medication methods were consistent with what was mentioned previously[8,19]. The study protocols were approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, and all the patients provided the written informed consent as well.

### *Anthropometric Measurements*

General anthropometric parameters, such as height (m), weight (kg), waist, and hip circumferences (cm) were included in the study. All the parameters were measured at the baseline and 48 weeks after the repaglinide or rosiglitazone monotherapy. BMI (kg/m$^2$) and waist-hip ratio were calculated as weight/height$^2$ and waist/hip, respectively.

### *Clinical Laboratory Tests*

Overnight, fasting and 2 h blood samples after a 75 g oral glucose tolerance test (OGTT) were collected. Plasma glucose concentrations were measured by the glucose oxidase-peroxidase assay kit (Shanghai Biological Products Institution,

Shanghai, China). Serum insulin and proinsulin concentrations were measured using the radioimmunoassay method (Linco Research, St Charles, MO, USA). Glycated hemoglobin values were determined by high-performance liquid chromatography method (Bio-Rad Laboratories, Hercules, CA, USA). The arginine stimulation tests were carried out to evaluate the potential pancreatic beta-cell function. Acute phase of insulin and proinsulin secretion in response to arginine stimulation was calculated as the mean insulin (proinsulin) level of the 2, 4, and 6 min samples minus fasting serum insulin (proinsulin) level. The efficiency of proinsulin processing was calculated as PI/I to estimate the beta-cell function in another aspect: PI/I=fasting proinsulin/fasting insulin. The homeostasis model assessment (HOMA) index was used to evaluate the IR and insulin secretion, with the following equation: HOMA-IR=fasting insulin×fasting glucose/22.5, HOMA of beta-cell function (HOMA-B)=20×fasting insulin/ (fasting plasma glucose-3.5). The Δ value was calculated in each parameter as the 48 weeks value minus the baseline value.

### *Genotyping*

Genomic DNA was extracted from peripheral leucocytes in whole blood samples. SNP was identified by PCR amplification and genotyped by matrix-assisted laser desorption ionization–time of flight mass spectroscopy using a MassARRAY Compact Analyzer (Sequenom, San Diego, CA, USA).

### *Statistical Analysis*

The allele frequencies were determined by gene counting and the Hardy-Weinberg equilibrium tests were performed as previously[20]. Data were shown as mean±SEM in Tables 1 and 2. Differences of the parameters between genotypes with normal distribution were tested using one-way ANOVA and multiple linear regression (adjusted for age, sex, BMI, and dosage), and differences of the parameters between genotypes with abnormal distribution were analyzed by Kruskal-Wallis Test. The Δ value was calculated in each parameter to evaluate the differences between the baseline prior to and 48 weeks after the drug therapy, using Paired T Test or Kruskal-Wallis Test when appropriate (data not shown). The genotype distribution in two groups was calculated using $\chi^2$-test. A two-tailed *P*-value ⩽0.05 was considered statistically significant. All statistical analysis and calculations were performed using SAS for Windows (version 6.12; SAS Institute, Cary, NC, USA).

## RESULTS

Of the total 209 patients participated, 91 patients and 93 patients completed the 48-week study in the repaglinide and the rosiglitazone group, respectively. No significant differences were observed regarding to the patients' baseline characteristics such as age, sex, BMI, fasting plasma glucose, 2-h plasma glucose, fasting insulin, HOMA-B or HOMA-IR between repaglinide and rosiglitazone group (*P*>0.05. Data were not shown). The patients were subdivided into 3 subgroups according to the *SLC30A8* rs13266634 genotype distribution as CC, CT, and TT in each therapeutic group. The genotype distribution was in agreement with Hardy-Weinberg equilibrium in both groups (*P*=0.612 and 0.466, respectively) and the risk allele was C allele with the frequency 0.654 and 0.608 in repaglinide and rosiglitazone group, respectively. No significant difference was observed in allele frequency between the two groups (*P*=0.3574). The call rate of the SNP rs13266634 were 100% in both groups.

Association between the *SLC30A8* genetic variant and the clinical features in the rosiglitazone group was shown in Table 1. Here, the Δ value of HOMA-B was detected to be statistically significant among the three genotype groups (*P*=0.0149), without significant differences at baseline (*P*=0.6357). The increasing value was greater in the CC and CT carriers (from 57.32 to 116.70 and 55.08 to 117.03, respectively) as compared with the TT carriers (from 73.80 to 83.40), indicating that the risk allele C carriers responded more actively on the rosiglitazone treatment. Δ value of fasting proinsulin level showed a significantly statistical difference among the three genotype groups after rosiglitazone therapy for 48 weeks (*P*=0.0246, adjusted for age, sex, BMI, and dosage). No significant differences were found in proinsulin conversion (PI/I) or the insulin resistance among the three groups.

Relationship of the *SLC30A8* genetic variant and the clinical characteristics in the repaglinide group was summarized in Table 2. No significant differences were detected in the 3 subgroups (CC, CT, and TT) in regards with clinical parameters such as HbA1c, FPG, HOMA-B, HOMA-IR or acute insulin secretion.

**Table 1.** Association between SNP rs13266634 of *SLC30A8* and Clinical Characteristics in Rosiglitazone Group

| Parameter | | CC (*n*=36) | CT (*n*=41) | TT (*n*=16) | *P* Value |
|---|---|---|---|---|---|
| Dosage (mg/d) | | 5.41±0.33 | 5.20±0.29 | 6.40±0.52 | 0.1203 |
| Age (year) | | 53.72±1.52 | 51.88±1.42 | 48.94±2.24 | 0.2131 |
| Sex (male/female) | | 22/14 | 30/11 | 13/3 | 0.3252 |
| BMI (kg/m$^2$) | Baseline | 25.38±0.51 | 24.83±0.45 | 25.84±0.78 | 0.4740 |
| | 48 weeks | 24.93±0.66 | 24.63±0.49 | 25.45±1.04 | 0.7336 |
| | Δ value | -0.80±0.40 | 0.01±0.20 | 0.01±0.47 | 0.3136 |
| Glycated Hemoglobin (%) | Baseline | 8.01±0.21 | 8.45±0.27 | 8.59±0.41 | 0.4111 |
| | 48 weeks | 6.31±0.11 | 6.34±0.11 | 6.52±0.40 | 0.9964 |
| | Δ value | -1.53±0.25 | -2.14±0.29 | -1.65±0.35 | 0.3694 |
| Fasting Plasma Glucose (mmol/L) | Baseline | 8.82±0.25 | 9.04±0.30 | 9.45±0.53 | 0.6461 |
| | 48 weeks | 6.65±0.24 | 6.39±0.17 | 7.09±0.30 | 0.1721 |
| | Δ value | -2.23±0.36 | -2.67±0.28 | -2.18±0.66 | 0.5187 |
| 2 h Plasma Glucose (mmol/L) | Baseline | 12.59±0.51 | 13.73±0.45 | 14.16±0.90 | 0.3275 |
| | 48 weeks | 9.31±0.47 | 8.27±0.31 | 9.66±0.67 | 0.0685 |
| | Δ value | -3.22±0.65 | -5.31±0.56 | -4.87±1.32 | 0.0780[b] |
| Fasting Insulin (pmol/L) | Baseline | 83.12±6.46 | 81.55±5.73 | 110.68±15.11 | 0.1694 |
| | 48 weeks | 98.81±10.98 | 98.47±9.74 | 90.02±9.36 | 0.9417 |
| | Δ value | 15.16±9.27 | 16.27±10.00 | -20.66±16.75 | 0.0896 |
| Fasting Proinsulin (μU/mL) | Baseline | 126.67±15.56 | 126.71±11.91 | 184.23±25.13 | 0.0653 |
| | 48 weeks | 95.08±12.09 | 79.45±9.13 | 113.34±27.31 | 0.2282 |
| | Δ value | -37.65±9.46 | -45.90±14.58 | -80.63±39.19 | **0.0246**[b*] |
| PI/I | Baseline | 1.65±0.16 | 1.70±0.18 | 1.71±0.17 | 0.5864 |
| | 48 weeks | 0.98±0.07 | 0.85±0.08 | 1.25±0.26 | 0.1106 |
| | Δ value | -0.69±0.17 | -0.82±0.17 | 0.51±0.29 | 0.8130 |
| HOMA-B | Baseline | 57.32±5.30 | 55.08±5.00 | 73.80±15.89 | 0.6357 |
| | 48 weeks | 116.70±9.46 | 117.03±9.88 | 87.40±10.92 | 0.1040 |
| | Δ value | 57.86±8.94 | 61.10±8.37 | 6.60±20.16 | **0.0149**[*] |
| HOMA-IR | Baseline | 5.32±0.40 | 5.48±0.42 | 7.61±1.01 | 0.0707 |
| | 48 weeks | 5.28±0.78 | 4.42±0.45 | 4.79±0.71 | 0.4381 |
| | Δ value | -0.31±0.65 | -1.18±0.49 | -3.31±1.12 | 0.1026 |
| Acute Insulin Secretion (pmol/L) | Baseline | 66.41±11.94 | 84.79±12.55 | 77.98±26.24 | 0.6259 |
| | 48 weeks | 48.51±8.53 | 44.62±7.38 | 72.26±17.98 | 0.5912 |
| | Δ value | -27.44±10.93 | -40.18±11.16 | -10.81±28.72 | 0.8224 |
| Acute Proinsulin Secretion (pmol/L) | Baseline | 65.70±10.29 | 73.04±10.81 | 67.18±22.60 | 0.6784 |
| | 48 weeks | 41.79±7.35 | 38.44±6.36 | 62.25±15.49 | 0.4073 |
| | Δ value | -23.64±9.42 | -34.61±9.61 | -9.32±24.74 | 0.7274 |
| Total Cholesterol(mmol/L) | Baseline | 5.29±0.21 | 5.39±0.16 | 5.26±0.26 | 0.2367 |
| | 48 weeks | 5.33±0.19 | 5.59±0.20 | 5.38±0.26 | 0.2177 |
| | Δ value | 0.02±0.20 | 0.20±0.16 | 0.06±0.19 | 0.8069[b] |
| Triglyceride(mmol/L) | Baseline | 1.62±0.15 | 2.22±0.26 | 3.23±0.67 | <0.0001 |
| | 48 weeks | 1.76±0.19 | 2.40±0.31 | 3.07±0.54 | <0.0001 |
| | Δ value | 0.10±0.18 | 0.14±0.33 | -0.22±0.51 | 0.8095 |
| HDL-C(mmol/L) | Baseline | 1.28±0.05 | 1.22±0.04 | 1.06±0.04 | <0.0001 |
| | 48 weeks | 1.36±0.06 | 1.28±0.04 | 1.26±0.10 | 0.0009 |
| | Δ value | 0.05±0.05 | 0.08±0.03 | 0.20±0.10 | 0.2901 |
| LDL-C(mmol/L) | Baseline | 3.40±0.18 | 3.27±0.13 | 3.06±0.21 | 0.3770 |
| | 48 weeks | 3.21±0.15 | 3.25±0.14 | 2.89±0.23 | <0.0001 |
| | Δ value | -0.23±0.13 | -0.03±0.15 | -0.32±0.27 | 0.7336 |

***Note.*** Data are shown as mean±SEM. Δ value=$T_{48\ weeks}$ value - baseline ($T_0$) value. *P* value: comparison among 3 genotypes (ANOVA or Kruskal-Wallis test). [*]*P*<0.05 vs baseline in each genotype. [b]Adjusted for age, sex, BMI and each genotype. BMI, body mass index; HOMA-B, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 2.** Association between SNP rs13266634 of *SLC30A8* and Clinical Characteristics in Repaglinide Group

| Parameter | | CC (*n*=40) | CT (*n*=39) | TT (*n*=12) | *P* Value |
|---|---|---|---|---|---|
| Dosage (mg/d) | | 2.58±0.23 | 2.41±0.25 | 2.48±0.48 | 0.8103 |
| Age (year) | | 52.92±1.36 | 51.90±1.47 | 52.58±3.35 | 0.8854 |
| Sex (male/female) | | 30/10 | 21/18 | 11/1 | 0.0269 |
| BMI (kg/m$^2$) | Baseline | 25.42±0.48 | 25.72±0.47 | 24.93±0.71 | 0.7034 |
| | 48 weeks | 25.53±0.47 | 25.31±0.52 | 24.42±0.74 | 0.5006 |
| | Δ value | 0.11±0.21 | -0.23±0.21 | -0.51±0.36 | 0.3306 |
| Glycated Hemoglobin (%) | Baseline | 8.49±0.26 | 8.36±0.22 | 7.75±0.31 | 0.4310 |
| | 48 weeks | 6.27±0.14 | 6.36±0.14 | 6.14±0.24 | 0.5226 |
| | Δ value | -2.21±0.31 | -2.00±0.23 | -1.61±0.39 | 0.4240[b] |
| Fasting Plasma Glucose (mmol/L) | Baseline | 9.35±0.32 | 9.59±0.31 | 8.93±0.46 | 0.5709 |
| | 48 weeks | 6.94±0.17 | 7.05±0.30 | 6.76±0.42 | 0.8049 |
| | Δ value | -2.41±0.32 | -2.60±0.32 | -2.17±0.59 | 0.5889[b] |
| 2 h Plasma Glucose (mmol/L) | Baseline | 13.90±0.51 | 13.70±0.45 | 13.31±1.08 | 0.8378 |
| | 48 weeks | 9.20±0.43 | 9.18±0.51 | 9.47±0.90 | 0.9505 |
| | Δ value | -4.49±0.64 | -4.43±0.73 | -3.83±1.71 | 0.9548[b] |
| Fasting Insulin (pmol/L) | Baseline | 80.19±6.64 | 83.75±5.18 | 63.66±10.81 | 0.1393 |
| | 48 weeks | 101.80±6.90 | 104.93±9.03 | 94.89±8.83 | 0.8130 |
| | Δ value | 21.61±6.08 | 18.16±9.19 | 31.23±15.76 | 0.8803[b] |
| Fasting Proinsulin (pmol/L) | Baseline | 123.12±12.63 | 96.21±15.31 | 96.97±16.50 | 0.0495 |
| | 48 weeks | 133.74±13.58 | 104.09±12.87 | 75.28±12.93 | 0.0154 |
| | Δ value | 10.62±15.22 | 2.97±14.37 | -21.69±16.51 | 0.4305 |
| PI/I | Baseline | 1.91±0.21 | 1.12±0.16 | 1.83±0.40 | 0.0019 |
| | 48 weeks | 1.38±0.11 | 1.22±0.19 | 0.79±0.12 | 0.0101 |
| | Δ value | -0.54±0.20 | 0.05±0.24 | -1.04±0.41 | 0.0592 |
| HOMA-B | Baseline | 56.34±10.77 | 50.53±4.08 | 46.40±11.76 | 0.3944 |
| | 48 weeks | 110.07±10.68 | 125.04±17.32 | 116.90±20.48 | 0.9319 |
| | Δ value | 54.40±10.39 | 72.27±15.35 | 70.51±26.35 | 0.8980 |
| HOMA-IR | Baseline | 5.31±0.39 | 5.91±0.38 | 4.03±0.59 | 0.0599 |
| | 48 weeks | 5.06±0.35 | 5.54±0.53 | 4.86±0.63 | 0.8256 |
| | Δ value | -0.13±0.41 | -0.57±0.58 | 0.82±0.85 | 0.9485[b] |
| Acute Insulin Secretion (pmol/L) | Baseline | 187.01±24.67 | 203.67±22.81 | 188.02±27.27 | 0.5318 |
| | 48 weeks | 172.24±18.43 | 186.47±27.53 | 198.50±17.89 | 0.4233 |
| | Δ value | -14.77±24.17 | -22.48±23.49 | 10.48±27.56 | 0.8029[b] |
| Acute Proinsulin Secretion (pmol/L) | Baseline | 70.84±7.70 | 65.81±10.94 | 46.42±10.37 | 0.2397 |
| | 48 weeks | 54.08±7.29 | 33.46±8.28 | 40.80±9.73 | 0.0810 |
| | Δ value | -16.76±7.15 | -34.86±8.11 | -5.62±14.98 | 0.6840[b] |

***Note.*** Data are shown as mean±SEM. Δ value=$T_{48\ weeks}$ value - baseline ($T_0$) value. *P* value: comparison among 3 genotypes (ANOVA or Kruskal-Wallis test). [b]Adjusted for age, sex, BMI and each genotype. BMI, body mass index; HOMA-B, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

## DISCUSSION

Pharmacogenetics evolved in the late 1950s to investigate mainly the genetic differences in drug response has been increasingly employed by the clinicians for its function of allowing individual therapies due to the genetic differences in drug responses and also providing new drug targets at the molecular level[4]. TZDs, a kind of insulin sensitizer, was mainly reported to improve the insulin resistance in peripheral tissues and delay the

progression from glucose intolerance to overt diabetes[21]. Small clinical studies were however focused on the beta-cell preservation with TZDs therapy[22-24]. Results from ADOPT showed that rosiglitazone treatment could delay the progressive loss of glycemic control and maintain the mean level of glycated hemoglobin at less than 7% for a longer period so as to preserve the beta-cell function[25].

The genome-wide association studies has confirmed *SLC30A8* to be an susceptible gene of type 2 diabetes in different populations, and the risk allele C was associated with impaired insulin release[9-13]. In this study, we found that *SLC30A8* rs13266634 variant was associated with rosiglitazone therapy in HOMA-B among three genotype distributions in newly diagnosed type 2 diabetes patients. The mean level of HOMA-B in C carriers was lower than that in T carriers at baseline, which was consistent with the forthcoming studies[9-13]. Interestingly, the C allele carriers showed a more active response to the drug in the aspect of HOMA-B, the latter of which is a homeostasis index indicating the insulin secretion and beta-cell function. Such phenomenon demonstrated that a kind of compensation mechanism of insulin secretion might exist which may improve the insulin secretion defect to a certain extent especially after rosiglitazone therapy. Another possibility is that rs13266634 might work as a genetic marker in linkage disequilibrium with other causal variants in the *SLC30A8* region.

We were not able to find any association with insulin secretion or proinsulin conversion after arginine stimulation in CC, CT, and TT carriers. Kirchhoff et al.[26] found that the rs13266634 was associated with reduced proinsulin conversion to insulin after intravenous glucose tolerance test (IVGTT), whereas the same association was not replicated after OGTT in the same population. We supposed that due to the compensatory mechanism during the early stage of diabetes, the effect of the variant on beta-cell function might be limited, even without any changes in insulin or proinsulin levels. Another possibility is that a strongly increased secretary demand such as IVGTT can induce the impaired insulin secretion with the defect in proinsulin processing.

There are several limitations in our study. First, the sample size is relatively small, and consequently we may not have enough statistical power to detect effects of genetic variants and proinsulin conversion to insulin after the arginine-load. Kirchhoff et al.[26] has confirmed the association between rs13266634 variant and impaired proinsulin secretion. However, we failed to replicate the similar association, and therefore the effect of the small sample size cannot be excluded. Second, the patients included in our study were newly diagnosed and those under unsatisfactory glycemic control were withdrawn in the process of our study, and how much influence the compensatory mechanism exert on the results at the early stage of the disease and how the effect can be on rosiglitazone therapy in patients with unfavorable glycemic control still need further investigation. Third, the Krusal-Wallis test was mainly used to analyze the Δ value of parameters among three genotypes due to the abnormal distribution, and hence the confounding factors such as age, sex, BMI could not be adjusted.

In conclusion, our data suggest that the *SLC30A8* rs13266634 variant be associated with HOMA-B in diabetic patients with rosiglitazone therapy. Further studies with larger sample size and longer-term follow up are needed to confirm the results from our study so as to guide the individualized drug therapy for the clinicians in combination with pharmacogenomic information.

## COMPETING INTERESTS

Authors declare that they have no competing interests.

## REFERENCES

1. Stumvoll M, Goldstein BJ, and Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy.Lancet, 2005; 365, 1333-46.
2. Elte JW and Blickle JF. Thiazolidinediones for the treatment of type 2 diabetes. Eur J Intern Med, 2007; 18, 18-25.
3. Rosen ED and Spiegelman BM. PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem, 2001; 276, 37731-4.
4. Eichelbaum M, Ingelman-Sundberg M and Evans WE. Pharmacogenomics and individualized drug therapy. Annu Rev Med, 2006; 57, 119-37.
5. Kirchheiner J, Thomas S, Bauer S, et al. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. Clin Pharmacol Ther, 2006; 80, 657-67.
6. Kang ES, Park SY, Kim HJ, et al. The influence of adiponectin gene polymorphism on the rosiglitazone response in patients with type 2 diabetes. Diabetes Care, 2005; 28, 1139-44.
7. Snitker S, Watanabe RM, Ani I, et al. Changes in insulin sensitivity in response to troglitazone do not differ between subjects with and without the common, functional Pro12Ala peroxisome proliferator-activated receptor-gamma2 gene variant: results from the Troglitazone in Prevention of Diabetes (TRIPOD) study. Diabetes Care, 2004; 27, 1365-8.
8. He YY, Zhang R, Shao XY, et al. Association of KCNJ11 and

ABCC8 genetic polymorphisms with response to repaglinide in Chinese diabetic patients. Acta Pharmacol Sin, 2008; 29, 983-9.
9. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature, 2007; 445, 881-5.
10. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science, 2007; 316, 1341-5.
11. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science, 2007; 316, 1336-41.
12. Hu C, Zhang R, Wang C, et al. PPARG, KCNJ11, CDKAL1, CDKN2A-CDKN2B, IDE-KIF11-HHEX, IGF2BP2 and SLC30A8 are associated with type 2 diabetes in a Chinese population. PLoS One, 2009; 4, e7643.
13. Xiang J, Li XY, Xu M, et al. Zinc transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J Clin Endocrinol Metab, 2008; 93, 4107-12.
14. Boesgaard TW, Zilinskaite J, Vanttinen M, et al. The common SLC30A8 Arg325Trp variant is associated with reduced first-phase insulin release in 846 non-diabetic offspring of type 2 diabetes patients--the EUGENE2 study. Diabetologia, 2008; 51, 816-20.
15. Chimienti F, Favier A and Seve M. ZnT-8, a pancreatic beta-cell-specific zinc transporter. Biometals, 2005; 18, 313-7.
16. Fu Y, Tian W, Pratt EB, et al. Down-regulation of ZnT8 expression in INS-1 rat pancreatic beta cells reduces insulin content and glucose-inducible insulin secretion. PLoS One, 2009; 4, e5679.
17. Pound LD, Sarkar SA, Benninger RK, et al. Deletion of the mouse Slc30a8 gene encoding zinc transporter-8 results in impaired insulin secretion. Biochem J, 2009; 421, 371-6.
18. Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med, 1998; 15, 539-53.
19. Wang J, Bao YQ, Hu C, et al. Effects of ABCA1 variants on rosiglitazone monotherapy in newly diagnosed type 2 diabetes patients. Acta Pharmacol Sin, 2008; 29, 252-8.
20. Wigginton JE, Cutler DJ, and Abecasis GR. A note on exact tests of Hardy-Weinberg equilibrium. Am J Hum Genet, 2005; 76, 887-93.
21. Yki-Jarvinen H.Thiazolidinediones. N Engl J Med, 2004; 351, 1106-18.
22. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. Diabetes, 2002; 51, 2796-803.
23. Knowler WC, Hamman RF, Edelstein SL, et al. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes, 2005; 54, 1150-6.
24. Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet, 2006; 368, 1096-105.
25. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med, 2006; 355, 2427-43.
26. Kirchhoff K, Machicao F, Haupt A, et al. Polymorphisms in the TCF7L2, CDKAL1, and SLC30A8 genes are associated with impaired proinsulin conversion. Diabetologia, 2008; 51, 597-601.