# Ser1369Ala Variant in Sulfonylurea Receptor Gene *ABCC8* Is Associated With Antidiabetic Efficacy of Gliclazide in Chinese Type 2 Diabetic Patients

YAN FENG, MD, PHD[1]
GUANGYUN MAO, MD, PHD[1]
XIAOWEI REN, MD[1]
HOUXUN XING, MD[1]
GENFU TANG, MD[1]
QIANG LI, MD, PHD[2]
XUEQI LI, MD[3]
LIRONG SUN, MD[4]
JINQUI YANG, MD, PHD[5]
WEIQING MA, MD[6]
XIAOBIN WANG, MD, SCD[7]
XIPING XU, MD, PHD[1]

**OBJECTIVE** — The purpose of this study was to investigate whether genetic variants could influence the antidiabetic efficacy of gliclazide in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — A total of 1,268 type 2 diabetic patients whose diabetes was diagnosed within the past 5 years and who had no recent hypoglycemic treatment were enrolled from 23 hospitals in China. All of the patients were treated with gliclazide for 8 weeks. Fasting and oral glucose tolerance test 2-h plasma glucose, fasting insulin, and A1C were measured at baseline and after 8 weeks of treatment. We used two independent cohorts to test the associations of 25 single nuclear polymorphisms in 11 candidate genes with the antidiabetic efficacy of gliclazide. A general linear regression model was used to test the association with adjustment for important covariates.

**RESULTS** — After 8 weeks of gliclazide therapy, mean fasting plasma glucose (FPG) was reduced from 11.1 mmol/l at baseline to 7.7 mmol/l. In cohort 1, we genotyped all 25 SNPs ($n$ = 661) and found that Ser1369Ala of the *ABCC8* gene and rs5210 of the *KCNJ11* gene were significantly associated with decreases in FPG ($P$ = 0.002). We further genotyped Ser1369Ala in cohort 2 ($n$ = 607) and confirmed the association identified in cohort 1. In the pooled analysis, compared with subjects with the Ser/Ser genotype, subjects with the Ala/Ala genotype had a 7.7% greater decrease in FPG ($P < 0.001$), an 11.9% greater decrease in 2-h plasma glucose ($P$ = 0.003), and a 3.5% greater decrease in A1C ($P$ = 0.06) after 8 weeks of treatment with gliclazide.

**CONCLUSIONS** — In two independent cohorts of Chinese type 2 diabetic patients, we found consistent evidence that the Ser1369Ala variant in the *ABCC8* gene can influence the antidiabetic efficacy of gliclazide.

*Diabetes Care* 31:1939–1944, 2008

From the [1]Anhui Biomedical Institute, Anhui Medical University, Hefei, China; the [2]Division of Endocrinology, the Second Hospital, Harbin Medical University, Harbin, China; the [3]Division of Endocrinology, the First Hospital, Harbin Medical University, Harbin, China; [4]Tianjin Medical University Metabolic Hospital, Tianjin, China; the [5]Division of Endocrinology, Tongren Hospital, Capital Medical University, Beijing, China; the [6]Division of Endocrinology, the First Hefei People's Hospital, Hefei, China; and the [7]The Mary Ann and J. Milburn Smith Child Health Research Program, Children's Memorial Hospital and Children's Memorial Research Center, Chicago, Illinois.
Corresponding author: Xiping Xu, xipingxu18@gmail.com.
Received 26 November 2007 and accepted 21 June 2008.
Published ahead of print at http://care.diabetesjournals.org on 3 July 2008. DOI: 10.2337/dc07-2248.
Y.F. and G.M. contributed equally to this study.
Y.F. is currently affiliated with Bridgeport Hospital, Yale University School of Medicine, New Haven, Connecticut.


The epidemic of type 2 diabetes in the last decade in both developed and developing countries has made it a major threat to global public health. At least 171 million people worldwide had diabetes in 2000, and this figure is likely to more than double by 2030 to reach 366 million (1). The majority of diabetes is type 2 diabetes. Most of the recent rise in diabetes prevalence is probably a result of lifestyle and dietary changes, but there is also clear evidence for genetic predisposition to this complex disease. During the last decade, molecular genetic studies of type 2 diabetes have shown significant progress (2). Five genome-wide association studies have been published since February 2007, increasing the number of confirmed type 2 diabetes susceptibility loci from three (*PPARG, KCNJ11,* and *TCF7L2*) to 9 (with the addition of *CDKAL1, CDKN2A/B, IGF2BP2, HHEX/IDE, FTO*, and *SLC30A8*) (2). In addition, studies have lent support for the involvement of many other genes, such as *ABCC8* (3–6). In contrast, few studies have investigated whether genetic variants may modulate the response to antidiabetic agents in type 2 diabetic patients (7–9). Such information can assist clinicians in developing individualized treatment plans that will maximize therapeutic efficacy and minimize side effects.

Sulfonylurea is a widely used oral hypoglycemic agent. Most type 2 diabetic patients respond well to this agent, but variable efficacy is seen, and primary failure to sulfonylurea treatment is seen in a small portion of patients. Secondary failure of sulfonylurea monotherapy develops in ~34% of patients at 5 years (10). To explore the underlying genetic factors that may explain individual variable response to sulfonylurea, we conducted a hospital-based pharmacogenetic study. Our goal was to examine whether type 2 diabetes candidate gene variants can influence the antidiabetic efficacy of gliclazide, a commonly used sulfonylurea

hypoglycemic agent, in Chinese type 2 diabetic patients.

## RESEARCH DESIGN AND METHODS

— We conducted a hospital-based pharmacogenetic study of gliclazide in type 2 diabetic patients in China between December 2003 and August 2005. Patients were recruited from 23 hospitals located in Harbin of the Heilongjiang province, Beijing, Tianjin, and Hefei and Anqing of the Anhui province following the same study protocol. The 23 hospitals selected were the major hospitals in the study regions. These hospitals were all government owned but were run independently.

Type 2 diabetes was diagnosed according to American Diabetes Association criteria (11). To reduce the clinical heterogeneity of type 2 diabetes, this study was limited to Han Chinese subjects with onset of type 2 diabetes after the age of 35 years who also met all of the following criteria: *1*) diabetes diagnosed within the past 5 years and no antidiabetes treatment within the past 2 months, *2*) BMI <28 kg/m$^2$, and *3*) fasting plasma glucose (FPG) between 7.8 and 15.0 mmol/l. We excluded patients with any acute or chronic diabetes complications, unstable angina, myocardial infarction or heart failure, chronic gastrointestinal disease or abnormal liver function, renal insufficiency, or clinical problems potentially causing hyperglycemia, including infection, thyroid disease, or surgery. We also excluded those taking other medications, such as corticosteroids or estrogen, as well as cancer patients and pregnant or breast-feeding women.

Subjects were enrolled from the outpatient clinics of the participating hospitals. After giving written informed consent, patients started an 8-week treatment with gliclazide (Tianjin Huajin Pharmaceutical Company, Tianjin, China). The initial dose of gliclazide was 40 mg twice daily. The patients continued their initial dosage throughout the 8 weeks of treatment or had their dose increased to 80 mg twice daily if FPG was ≥7.0 mmol/l after 2 weeks and increased again by 40 mg (from 80 to 120 mg or from 40 to 80 mg) twice daily if FPG was ≥7.0 mmol/l after 4 weeks of treatment. The study was approved by the institutional review boards of Anhui Medical University and all participating hospitals.

### Data collection and clinical laboratory methods

At the first visit (screening), a standard questionnaire was administered to collect information on medical history and medication, diet, exercise, and lifestyle factors including smoking and alcohol drinking, household income, educational level, and occupation. Height, weight, waist circumference, and blood pressure were measured using a standard protocol. Overnight (>10 h) fasting blood samples were collected to determine FPG, insulin, A1C, lipid profile, liver and renal function, and routine blood cell counts. All study patients underwent a 75-g oral glucose tolerance test (OGTT) unless FPG was ≥13.0 mmol/l, and blood samples were collected after 2 h to determine plasma glucose. Diabetes education was also provided to all potentially eligible subjects during the screening visit. The education included a brief introduction on type 2 diabetes, with a particular focus on diet and physical exercise. In addition, a handbook with more detailed information was given to the subjects for them to read.

All study patients returned for follow-up every 2 weeks. A follow-up questionnaire was administered to monitor patients' medications, diet, exercise, and side effects of gliclazide. Specifically, the research staff documented whether the subjects complied with the treatment and followed the instruction for diet (with a grade of very good, fair, and poor) and exercise time. The side effects of gliclazide that we monitored in our study included hypoglycemia, abnormal liver function, skin rash, or any other symptoms reported by patients.

FPG (at the 29th day) or fasting fingerstick glucose (at the 13th and 43rd days) were measured for each subject. At the last visit (57th day), blood was drawn at fasting and 2 h after the OGTT to repeat all of the tests that the patients had at their first visit.

Plasma glucose, serum lipids, and liver and renal function were measured at the local hospitals using an automatic analyzer (Hitachi 7020; Hitachi, Tokyo, Japan, or a similar model). The A1C values were determined with a high-performance liquid chromatography method at four major participating hospitals using the unique standard procedure and the same reagents. Serum insulin was measured using an electrochemiluminescence method on an Elecsys 2010 system (Roche Diagnostics, Basel, Switzerland) at our central laboratory. The insulin secretion (HOMA-B) and resistance index of homeostatic model assessment (HOMA-IR) were calculated according to fasting glucose and insulin level using the HOMA2 calculator (http://www.dtu.ox.ac.uk/homa).

### Candidate gene and SNP selection and genotyping method

We selected 11 type 2 diabetes candidate genes on the basis of the published literature (see Table 2). For each gene, one to six nonsynonymous or haplotype-tagging SNPs, according to the HapMap data (http://www.hapmap.org/), were selected. In our central laboratory, we genotyped all 25 selected SNPs for all of the subjects in cohort 1, which consisted of 661 patients from 12 participating hospitals located in northern China. We further genotyped one significant nonsynonymous SNP (rs757110) identified in cohort 1 for all subjects in cohort 2, which consisted of 607 patients from the remaining 11 participating hospitals located in southern China. The reasons for the two-phase genotyping were twofold: reduce the genotyping cost and minimize the multiple testing problem, which could inflate type I error.

DNA was extracted from leukocytes in peripheral blood using standard techniques. Genotyping was performed by TaqMan genotyping assays that were designed and manufactured by Applied Biosystems (Foster City, CA).

**Statistical analysis.** All data analyses were performed using SAS (version 8; SAS Institute, Cary, NC). The phenotype data are shown as mean ± SD and the differences between groups were tested using *t* tests or one-way ANOVA. The associations between quantitative phenotypes (FPG, 2-h plasma glucose, or A1C decrease [percent]) and genotypes were tested using linear regression models. The associations between binary phenotypes (response/nonresponse) and genotypes were tested using a logistic repression model. All analyses were performed with or without adjustment for age, sex, BMI, total gliclazide dosage, and baseline HOMA-B and HOMA-IR. All *P* values were two tailed.

## RESULTS

— We enrolled a total of 1,464 patients; 196 patients were lost to follow-up during the course of treatment. The major reason for those lost to follow-up was inconvenience because they lived too far from the study hospitals. The

subjects who completed the study and those who were lost to follow-up were similar ($P > 0.05$) in major baseline demographic and clinical characteristics, including age (50.1 ± 8.4 vs. 49.2 ± 9.4 years), sex (men 54 vs. 49%), age of diagnosis of type 2 diabetes (49.4 ± 8.4 vs. 48.5 ± 10.4 years), fasting glucose (11.1 ± 2.9 vs. 11.4 ± 3.2 mmol/l), insulin (5.6 ± 2.2 vs. 5.3 ± 2.5 μIU/ml), A1C (8.4 ± 1.9 vs. 8.1 ± 2.1%), and blood pressure (126.1 ± 17.3/81.3 ± 10.8 vs. 125.6 ± 17.4/80.5 ± 10.2 mmHg). Some difference was noted for total cholesterol (5.2 ± 1.4 vs. 5.6 ± 4.2 mmol/l, $P = 0.01$) and triglycerides (2.1 ± 1.7 vs. 2.8 ± 4.1 mmol/l, $P < 0.01$).

We analyzed the data of 1,268 patients who completed the entire study procedures. Most patients followed the instructions for diet and exercise well. The percentage of patients with poor diet control was consistently <6% throughout the whole trial, 42 and 53% of patients had fair or good diet control, respectively, at day 57. The mean weekly exercise time was 8 h. In 245 and 111 patients, respectively, the dose of gliclazide was increased at days 15 and 29 according to the study protocol to achieve better glycemic control. The demographic and clinical characteristics of the study patients are summarized in Table 1. The mean age of the patients was 50.4 years and 54.4% of the patients were male. After 8 weeks of gliclazide therapy, the patients' mean FPG decreased from 11.1 mmol/l at baseline to 7.7 mmol/l (mean ± SD decrease 3.4 ± 2.8 mmol/l), and 43.7 and 63.0% patients lowered their FPG to <7.0 and 7.8 mmol/l, respectively. A1C decreased from 8.1 ± 1.9 to 6.9 ± 1.3% (1.4 ± 1.6%). Mean fasting insulin level and HOMA-B increased by 22 and 122%, respectively, but the mean HOMA-IR did not change significantly (Table 1). The patients included in the cohort 1 and 2 studies were similar with regard to age and sex distribution. However, patients in cohort 2 had lower BMI and a lower level of A1C, fasting insulin, HOMA-B, and HOMA-IR than those in cohort 1 (Table 1). This may reflect population differences across geographic differences between cohort 1 patients, who were mainly from northern China, and cohort 2 patients, who were from southern China.

We first explored the possible influence of demographic and clinical variables, including age, sex, BMI, total dosage of gliclazide during the 8 weeks of treatment, and baseline HOMA-B and HOMA-IR, on percent decrease in FPG after 8 weeks of gliclazide therapy. We found that the last three factors were significantly associated with the antidiabetic efficacy of gliclazide ($P < 0.001$). Thus, these factors, along with age and sex, were adjusted in the subsequent genetic association analyses. The distribution of patients with different levels of diet control (good, fair, or poor) and average exercise hours among three genotype groups of Ser1369Ala polymorphism were not significantly different (data not shown).

The minor allele frequencies of the SNPs we genotyped in the cohort 1 study ranged from 1 to 50% (Table 2). Genotypes of all SNPs were in Hardy-Weinberg equilibrium. We found that 2 of the 25 SNPs, rs757110 and rs5210, were significantly associated with percent decrease of FPG, even after Bonferroni correction for multiple testing ($P = 0.002$) (Table 2). SNP rs757110, which is located in exon 33 of the *ABCC8* gene (encoding the sulfonylurea receptor), results in an amino acid substitution of Ser/Ala. SNP rs5210, which is located in the 3′ untranslated region of KCNJ11, is located in the same chromosome as rs757110 and is only 10 kb apart. However, the two SNPs are not in significant linkage disequilibrium (LD) ($D' = 0.08$, $R^2 = 0.006$).

We genotyped rs757110 for all of the study patients in the cohort 2 study and confirmed the significant association identified in cohort 1 ($P = 0.002$, additive model). In the pooled analysis (combining cohort 1 and cohort 2 patients), we found that patients with Ser/Ala and Ala/Ala genotypes had 2.8% ($P = 0.076$) and 7.7% ($P < 0.001$) greater decreases in FPG, and 10.8% ($P = 0.001$) and 11.9% ($P = 0.003$) greater decreases in OGTT 2-h plasma glucose, respectively, compared with those with the Ser/Ser genotype (Table 3). The decrease in A1C after 8 weeks of treatment with gliclazide was 3.5% greater in patients with the Ala/Ala

**Table 1—*Characteristics of patients in cohort 1 and cohort 2***

| Characteristics | Cohort 1 | Cohort 2 | Pooled |
|---|---|---|---|
| *n* | 661 | 607 | 1,268 |
| Age (years) | 50.2 ± 8.0 | 50.5 ± 8.6 | 50.4 ± 8.3 |
| Men (%) | 54.8 | 54.0 | 54.4 |
| Age at diagnosis (years)* | 49.0 ± 7.8 | 49.1 ± 8.5 | 49.1 ± 8.1 |
| Duration of diabetes (months)* | 14.2 ± 19.9 | 14.6 ± 22.3 | 14.4 ± 20.9 |
| BMI (kg/m$^2$) | 24.9 ± 2.9 | 24.3 ± 3.4† | 24.9 ± 8.4 |
| Waist circumference (cm) | 88.7 ± 9.0 | 86.7 ± 9.5† | 87.8 ± 9.3 |
| Baseline | | | |
| FPG(mmol/l) | 10.8 ± 2.6 | 11.4 ± 3.2† | 11.1 ± 2.9 |
| 2-h plasma glucose (mmol/l)‡ | 18.9 ± 4.4 | 18.3 ± 5.0† | 18.6 ± 4.7 |
| A1C (%)§ | 8.5 ± 1.8 | 8.3 ± 2.1 | 8.1 ± 1.9 |
| Fasting insulin (μIU/ml)‖¶ | 6.7 ± 2.0 | 5.0 ± 2.2† | 5.5 ± 2.2 |
| HOMA-B‖¶ | 20.1 ± 2.0 | 14.9 ± 2.5† | 18.2 ± 2.2 |
| HOMA-IR‖¶ | 1.0 ± 2.0 | 0.8 ± 2.0† | 0.9 ± 2.0 |
| Total cholesterol (mmol/l) | 5.1 ± 1.1 | 5.2 ± 1.6 | 5.2 ± 1.4 |
| HDL cholesterol (mmol/l) | 1.3 ± 0.4 | 1.5 ± 3.2 | 1.4 ± 2.2 |
| Triglyceride (mmol/l) | 2.2 ± 1.6 | 2.0 ± 1.9 | 2.1 ± 1.7 |
| FPG at day 29 (mmol/l) | 7.9 ± 2.1 | 8.1 ± 2.4 | 8.0 ± 2.3 |
| At day 57 | | | |
| FPG(mmol/l) | 7.7 ± 2.1 | 7.7 ± 2.4 | 7.7 ± 2.3** |
| 2-h plasma glucose (mmol/l)†† | 14.6 ± 4.4 | 13.9 ± 5.1† | 14.3 ± 4.7** |
| A1C (%)‡‡ | 7.1 ± 1.3 | 6.6 ± 1.4† | 6.9 ± 1.3** |
| Fasting insulin (μIU/ml)‖§§ | 7.4 ± 2.0 | 5.5 ± 2.5† | 6.7 ± 2.2** |
| HOMA-B‖§§ | 44.7 ± 1.8 | 33.1 ± 2.5† | 40.4 ± 2.2** |
| HOMA-IR‖§§ | 1.1 ± 2.0 | 0.8 ± 2.0† | 1.0 ± 2.0 |

Data are means ± SD. *The sample sizes of cohort 1, cohort 2, and total are 383, 291, and 674, respectively. †$P < 0.05$ compared with cohort 1. ‡The sample sizes of cohort 1, cohort 2, and total are 534, 429, and 963, respectively. §The sample sizes of cohort 1, cohort 2, and total are 378, 321, and 699, respectively. ‖Log transformed before the analysis; geometric mean and anti-log SD are presented. ¶The sample sizes of cohort 1, cohort 2, and total are 572, 465, and 1,037, respectively. **$P < 0.05$ compared with baseline, *t* test. ††The sample sizes of cohort 1, cohort 2, and total are 646, 520, and 1,166, respectively. ‡‡The sample sizes of cohort 1, cohort 2, and total are 460, 249, and 709, respectively. §§The sample sizes of cohort 1, cohort 2, and total are 598, 304, and 902, respectively.

**Table 2—*Associations of 25 candidate SNPs with percentage decrease in FPG after 8-week gliclazide treatment in type 2 diabetic patients of cohort 1***

| Gene | Encoded protein | SNP | Codon | Amino acid change | Minor allele frequency | Association with FPG decrease (*P*)* |
|---|---|---|---|---|---|---|
| *ABCC8* | Sulfonylurea receptor (SUR1) | rs757110 | 1,369 | Ser→Ala | 0.432 | 0.002 |
| | | rs1799854 | — | — | 0.416 | 0.498 |
| | | rs2074312 | — | — | 0.500 | 0.031 |
| | | rs2237984 | — | — | 0.369 | 0.616 |
| | | rs2237981 | — | — | 0.256 | 0.046 |
| *Kir6.2* (*KCNJ11*) | ATP-sensitive potassium channel, Kir6.2 | rs5210 | — | — | 0.480 | 0.002 |
| *ENSA* | Endosulfine alpha | rs7517 | — | — | 0.222 | 0.085 |
| *PPARG* | Peroxisome proliferative activated receptor γ | rs2972164 | — | — | 0.084 | 0.284 |
| | | rs10510412 | — | — | 0.346 | 0.480 |
| | | rs2959273 | — | — | 0.412 | 0.332 |
| *CAPN10* | Calpain 10 | rs10933620 | — | — | 0.342 | 0.462 |
| | | rs3792267 | — | — | 0.107 | 0.765 |
| | | rs2975760 | — | — | 0.106 | 0.958 |
| *TCF1* | Hepatocyte nuclear factor 1α | rs2464195 | — | — | 0.498 | 0.490 |
| | | rs1169300 | — | — | 0.499 | 0.457 |
| *IRS1* | Insulin receptor substrate 1 | rs1801278 | 972 | Gly→Arg | 0.009 | 0.905 |
| | | rs9653366 | — | — | 0.189 | 0.065 |
| | | rs10498210 | — | — | 0.073 | 0.336 |
| | | rs12052364 | — | — | 0.172 | 0.039 |
| *GLP1R* | Glucagon-like peptide 1 receptor | rs1042044 | 260 | Phe→Leu | 0.492 | 0.496 |
| *UCP2* | Uncoupling protein 2 | rs660339 | 55 | Val→Ala | 0.467 | 0.739 |
| *PPARGC1A* | Peroxisome proliferative activated receptor γ, coactivator 1α | rs8192678 | 482 | Ser→Gly | 0.425 | 0.596 |
| | | rs3736265 | 612 | Thr→Met | 0.175 | 0.780 |
| *ADRB2* | $\beta_2$-Adrenergic receptor | rs1042713 | 16 | Arg→Gly | 0.422 | 0.386 |
| | | rs1042714 | 27 | Gln→Glu | 0.099 | 0.897 |

*Linear regression under additive model with adjustment for age, sex, total gliclazide dose, baseline HOMA-B, and HOMA-IR.

genotype than in those with the Ser/Ser genotype ($P = 0.06$) (Table 3). The mean gliclazide dosage requirements for Ser/Ser, Ser/Ala, and Ala/Ala genotypes were 83.7, 77.6, and 78.4 mg/day, respectively. When we define FPG at day 57 as <7.8mmol/l in response to gliclazide therapy, the patients with the Ser/Ala and Ala/Ala genotypes had odds ratios of 1.4 (95% CI 1.0–2.1, $P = 0.06$) and 2.2 (1.4–3.6, $P = 0.001$), respectively, for response to gliclazide therapy compared with subjects with Ser/Ser genotype.

We did not find any significant association between the Ser1369Ala polymorphism and fasting insulin level, HOMA-B, and HOMA-IR, either at baseline or after treatment, or the change in fasting insulin level or HOMA-B after gliclazide treatment. Interestingly, however, mean HOMA-IR decreased significantly

**Table 3—*Association of Ser1369Ala genotype with percentage decrease in FPG, 2-h plasma glucose, and A1C after 8 weeks of gliclazide treatment in type 2 diabetic patients (pooled sample of cohort 1 and cohort 2)***

| Outcome phenotype | Genotype | *n* | Baseline | Day 57 | Decrease (%) | Regression, β (Se)* | *P* |
|---|---|---|---|---|---|---|---|
| FPG (mmol/l) | Ser/Ser | 363 | 11.1 ± 2.9 | 7.9 ± 2.4 | 26.1 ± 20.2 | — | — |
| | Ser/Ala | 562 | 11.0 ± 2.9 | 7.6 ± 2.0 | 27.9 ± 18.9 | 2.8 (1.6) | 0.076 |
| | Ala/Ala | 224 | 11.5 ± 3.3 | 7.6 ± 2.5 | 31.6 ± 19.8 | 7.7 (1.9) | <0.001 |
| 2-h plasma glucose (mmol/l) | Ser/Ser | 269 | 18.9 ± 4.7 | 15.2 ± 5.9 | 22.3 ± 22.8 | — | — |
| | Ser/Ala | 404 | 18.4 ± 4.7 | 14.0 ± 4.1 | 23.3 ± 23.4 | 10.8 (3.3) | 0.001 |
| | Ala/Ala | 157 | 18.8 ± 4.4 | 13.9 ± 4.4 | 27.6 ± 20.3 | 11.9 (4.1) | 0.003 |
| A1C (%) | Ser/Ser | 151 | 8.4 ± 1.9 | 7.0 ± 1.5 | 14.2 ± 17.6 | — | — |
| | Ser/Ala | 251 | 8.3 ± 2.0 | 6.8 ± 1.2 | 15.8 ± 15.3 | 1.9 (1.4) | 0.195 |
| | Ala/Ala | 106 | 8.7 ± 2.0 | 7.0 ± 1.4 | 17.4 ± 13.5 | 3.5 (1.8) | 0.060 |

Data are means ± SD unless otherwise indicated. *Multiple line regression model, outcome variables were percent decrease in FPG, 2-h plasma glucose, and A1C, respectively. The analysis adjusted for age, gender, total gliclazide dose, and baseline HOMA-B and HOMA-IR. β (Se), regression coefficient (SE) for genotype using Ser/Ser as reference.

(0.15 ± 1.10, $P = 0.04$) in patients with the Ala/Ala genotype, but not in patients with the Ser/Ser or Ser/Ala genotypes (data not shown).

Of the 1,268 study subjects, 273 (21.5%) met the criteria for metabolic syndrome. However, we did not find any association between the Ser1396Ala polymorphism and BMI or metabolic syndrome, and further adjustment for metabolic syndrome in the analysis did not alter the association between the Ser1396Ala polymorphism and antidiabetic efficacy (data not shown).

**CONCLUSIONS** — The sulfonylurea receptor (SUR1), encoded by the *ABCC8* gene, is the internal molecular target for gliclazide. Genetic variants of *ABCC8*, such as exon 16 −3t/c, exon 18 T759T, and most recently the missense mutation Y356C, have been reported to be associated with type 2 diabetes (3,5,12,13). Some missense mutations other than Ser1369Ala in the *ABCC8* gene have been identified as causing neonatal diabetes (14). To our knowledge, this study is the first to report the association between a genetic variant of the *ABCC8* gene and therapeutic efficacy of sulfonylurea in type 2 diabetic patients.

The major strengths of this study include large sample size, multiple well-measured phenotypes, and a prospective design. However, cautions are needed in interpreting our findings. First, we only studied the response to gliclazide for a short period, i.e., the initial response to monotherapy with a sulfonylurea. The association of Ser1369Ala with the long-term response to gliclazide remains unknown. Second, we excluded obese patients. The InterASIA study, a recent large-scale nationwide epidemiological study in China, showed that 18.7% of diabetic subjects were obese (BMI ≥28 kg/m$^2$) (15). Thus, our study sample should represent >80% of type 2 diabetic patients in China.

Population admixture, which may lead to false-positive association, is a major concern in a genetic association study. Given the obvious difference between the northern and southern Han Chinese, we analyzed the two cohorts separately to minimize potential confounding due to population admixture. The differential baseline characteristics of the two study cohorts may affect antidiabetic efficacy of the treatment; however, it would not be likely to influence the main purpose of this pharmacogenetic study. The fact that consistent associations were observed in the two different cohorts strengthens the genetic association and its generalizability across populations.

We did not examine the association of a common variant of the *KCNJ11* gene in cohort 2. It is possible that Ser1396Ala SNP is not a causal variant. Instead, the association between Ser1396Ala and antidiabetic efficacy may be a result of other functional mutations that are in high LD with Ser1396Ala. Future studies should screen for mutations within both the *SUR1* gene and nearby genes, such as *KCNJ11*.

The association between A1C and the Ser1369Ala polymorphism was only marginally significant. We speculate that significance would have been achieved if we had extended the trial for another 4 weeks, because hemoglobin turns over every 3 months. Another reason was that missing data for A1C may have affected our statistical power to detect a significant association.

Finally, we excluded patients with longstanding diabetes (>5 years), who were more likely to have decreased β-cell function and to have complications of the disease (which may affect the therapeutic response to gliclazide). Caution is needed in generalizing our findings to patients with longstanding diabetes.

Although our study may not have an immediate impact on clinical practice, it may stimulate more investigations in this area. Pharmacogenetics is an emerging discipline investigating the influence of genetic variants on drug response. It is an important path toward personalized medicine. So far, only a few pharmacogenetic studies on diabetes have been reported. Patients with maturity-onset diabetes of the young who had the hepatocyte nuclear factor-1α mutation were reported to be extremely sensitive to the hypoglycemic effects of sulfonylureas (16). Recently, Shu et al. (9) took a multipronged approach, using cell-based experiments, in vivo studies in mice, and in vitro human trials (healthy volunteers), and demonstrated that genetic variances of organic cation transporter 1 (OCT1) had a significant impact on response to metformin, a common antidiabetic agent for type 2 diabetes. However, a small study ($n = 24$ responders and 9 nonresponders) did not confirm the association of *OCT1* gene polymorphisms and response to metformin in diabetic patients (8). Sesti et al. (17) reported that the E23K variants in *KCNJ11* are associated with increased risk for secondary failure of sulfonylurea treatment in type 2 diabetic patients. The E23K polymorphism is in high LD ($D' = 0.98$, $R^2 = 0.87$) with the Ser1369Ala of the *ABCC8* gene (5), so we did not include the E23K polymorphism in our study. However, we did find that a common variant of *KCNJ11*, rs5210, was associated with gliclazide response in our cohort 1 study.

SUR1 is an important subunit of the ATP-sensitive $K^+$ channel, which is a key component in regulation of insulin secretion from pancreatic β-cell membranes. The Ser1369Ala variant is located in the second nucleotide-binding fold, a functionally important region of the *ABCC8* gene. It has not been found to be associated with type 2 diabetes in either Caucasians (13) or Japanese (5,18). Interestingly, the *ABCC8* Ser1369Ala polymorphism was recently reported to influence progression to diabetes (6). Although the Ser1369Ala is a missense polymorphism, its influence on SUR1 function still remains uncertain. Florez et al. (6) found the Ala/Ala carriers had a significantly lower insulin index, i.e., insulin secretion function, compared with Ser/Ser carriers in subjects with impaired glucose tolerance. However, other studies did not find any association between the Ser1369Ala variant and insulin secretion in nondiabetic subjects (19,20). We also did not find any association between the Ser1369Ala variant and fasting plasma insulin level or HOMA-B, an indicator for insulin secretion, either at baseline or after gliclazide treatment. The improvement in insulin resistance (HOMA-IR) in the Ser/Ser genotype group was probably due to good glucose control after gliclazide treatment.

In summary, we found that a common variant in the *ABCC8* gene, Ser1369Ala, was significantly associated with the antidiabetic efficacy of gliclazide in nonobese type 2 diabetic patients in China. Patients with the Ala/Ala genotype appeared to respond significantly better to gliclazide than did patients with the Ser/Ser genotype. Although the difference may have limited impact on clinical practice, our results did demonstrate that genetic variation can be a significant determinant of response to oral hypoglycemic drugs.

**Acknowledgments**— The study was supported by Tianshili Pharmaceutical Company, Tianjin, China.

We greatly appreciate the participation of the 23 hospitals in the study. We are grateful to Dr. Rongh Qian for input and support of the study and Dr. Scott A. Venners for his editing of the manuscript.

**References**


1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
2. Zeggini E: A new era for type 2 diabetes genetics, *Diabet Med* 24:1181–1186, 2007
3. Tarasov AI, Nicolson T, Riveline JP, Taneja TK, Baldwin SA, Baldwin JM, Charpentier G, Gautier JF, Froguel P, Vaxillaire M, Rutter GA: A rare mutation in *ABCC8*/SUR1 leading to altered $K_{ATP}$ channel activity and β-cell glucose sensing is associated with type 2 diabetes mellitus in adults. *Diabetes* 57:1595–1604, 2008
4. Sakamoto Y, Inoue H, Keshavarz P, Miyawaki K, Yamaguchi Y, Moritani M, Kunika K, Nakamura N, Yoshikawa T, Yasui N, Shiota H, Tanahashi T, Itakura M: SNPs in the *KCNJ11-ABCC8* gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. *J Hum Genet* 52:781–793, 2007
5. Yokoi N, Kanamori M, Horikawa Y, Takeda J, Sanke T, Furuta H, Nanjo K, Mori H, Kasuga M, Hara K, Kadowaki T, Tanizawa Y, Oka Y, Iwami Y, Ohgawara H, Yamada Y, Seino Y, Yano H, Cox NJ, Seino S: Association studies of variants in the genes involved in pancreatic β-cell function in type 2 diabetes in Japanese subjects. *Diabetes* 55:2379–2386, 2006
6. Florez JC, Jablonski KA, Kahn SE, Franks PW, Dabelea D, Hamman RF, Knowler WC, Nathan DM, Altshuler D: Type 2 diabetes–associated missense polymorphisms *KCNJ11* E23K and *ABCC8* A1369S influence progression to diabetes and response to interventions in the Diabetes Prevention Program. *Diabetes* 56:531–536, 2007
7. Sesti G, Hribal ML: Pharmacogenetics in type 2 diabetes: polymorphisms in candidate genes affecting responses to antidiabetic oral treatment. Curr Pharmacogenomics 4:69–78, 2006
8. Shikata E, Yamamoto R, Takane H, Shigemasa C, Ikeda T, Otsubo K, Ieiri I: Human organic cation transporter (OCT1 and OCT2) gene polymorphisms and therapeutic effects of metformin. *J Hum Genet* 52:117–122, 2007
9. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, Ianculescu AG, Yue L, Lo JC, Burchard EG, Brett CM, Giacomini KM: Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J Clin Invest* 117:1422–1431, 2007
10. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355: 2427–2443, 2006
11. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 29:S43–S48, 2006
12. Hani EH, Clement K, Velho G, Vionnet N, Hager J, Philippi A, Dina C, Inoue H, Permutt MA, Basdevant A, North M, Demenais F, Guy-Grand B, Froguel P: Genetic studies of the sulfonylurea receptor gene locus in NIDDM and in morbid obesity among French Caucasians. *Diabetes* 46:688–694, 1997
13. Inoue H, Ferrer J, Welling CM, Elbein SC, Hoffman M, Mayorga R, Warren-Perry M, Zhang Y, Millns H, Turner R, Province M, Bryan J, Permutt MA, Aguilar-Bryan L: Sequence variants in the sulfonylurea receptor (SUR) gene are associated with NIDDM in Caucasians. *Diabetes* 45:825–831, 1996
14. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, Bryan J, Aguilar-Bryan L, Vaxillaire M, Froguel P: Activating mutations in the *ABCC8* gene in neonatal diabetes mellitus. *N Engl J Med* 355:456–466, 2006
15. Hu D, Xie J, Fu P, Zhou J, Yu D, Whelton PK, He J, Gu D: Central rather than overall obesity is related to diabetes in the Chinese population: the InterASIA study. *Obesity (Silver Spring)* 15:2809–2816, 2007
16. Pearson ER, Liddell WG, Shepherd M, Corrall RJ, Hattersley AT: Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1α gene mutations: evidence for pharmacogenetics in diabetes. *Diabet Med* 17:543–545, 2000
17. Sesti G, Laratta E, Cardellini M, Andreozzi F, Del Guerra S, Irace C, Gnasso A, Grupillo M, Lauro R, Hribal ML, Perticone F, Marchetti P: The E23K variant of *KCNJ11* encoding the pancreatic β-cell adenosine 5′-triphosphate-sensitive potassium channel subunit Kir6.2 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. *J Clin Endocrinol Metab* 91:2334–2339, 2006
18. Ohta Y, Tanizawa Y, Inoue H, Hosaka T, Ueda K, Matsutani A, Repunte VP, Yamada M, Kurachi Y, Bryan J, Aguilar-Bryan L, Permutt MA, Oka Y: Identification and functional analysis of sulfonylurea receptor 1 variants in Japanese patients with NIDDM. *Diabetes* 47:476–481, 1998
19. Hansen T, Echwald SM, Hansen L, Moller AM, Almind K, Clausen JO, Urhammer SA, Inoue H, Ferrer J, Bryan J, Aguilar-Bryan L, Permutt MA, Pedersen O: Decreased tolbutamide-stimulated insulin secretion in healthy subjects with sequence variants in the high-affinity sulfonylurea receptor gene. *Diabetes* 47:598–605, 1998
20. Rissanen J, Markkanen A, Karkkainen P, Pihlajamaki J, Kekalainen P, Mykkanen L, Kuusisto J, Karhapaa P, Niskanen L, Laakso M: Sulfonylurea receptor 1 gene variants are associated with gestational diabetes and type 2 diabetes but not with altered secretion of insulin. *Diabetes Care* 23:70–73, 2000