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Original Article

# *IGF2BP2* variations influence repaglinide response and risk of type 2 diabetes in Chinese population

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**Aim:** To investigate whether the insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) rs1470579 and rs4402960 polymorphisms are associated with the development of type 2 diabetes mellitus (T2DM) and the repaglinide therapeutic efficacy in Chinese T2DM patients.
**Methods:** A case-control study of a total of 350 patients with T2DM and 207 healthy volunteers was conducted to identify their genotypes for the *IGF2BP2* rs1470579 and rs4402960 polymorphisms using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Forty-two patients were randomly selected to undergo an 8-week repaglinide treatment (3 mg/d). Fasting plasma glucose (FPG), postprandial plasma glucose (PPG), glycated hemoglobin (HbAlc), fasting serum insulin (FINS), postprandial serum insulin (PINS), homeostasis model assessment for insulin resistance (HOMA-IR), serum triglyceride, total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-c), and high-density lipoprotein-cholesterol (HDL-c) were determined before and after repaglinide treatment.
**Results:** The frequencies of the *IGF2BP2* rs1470579 C allele and the rs4402960 T allele were higher in T2DM patients than in healthy controls ($P<0.05$ and $P<0.001$, respectively). The effects of the repaglinide treatment on FPG ($P<0.05$) and PPG ($P<0.05$) were reduced in patients with the rs1470579 AC+CC genotypes compared with AA genotype carriers. Patients with the rs4402960 GT+TT genotypes exhibited an enhanced effect of repaglinide treatment on PINS ($P<0.01$) compared with GG genotype subjects.
**Conclusion:** The *IGF2BP2* rs1470579 and rs4402960 polymorphisms may be associated with the development of T2DM, and these polymorphisms may affect the therapeutic efficacy of repaglinide in Chinese T2DM patients.

**Keywords:** *IGF2BP2*; genetic polymorphism; type 2 diabetes mellitus; repaglinide

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## Introduction

The rapidly increasing prevalence of type 2 diabetes mellitus (T2DM) is a tremendous public health problem throughout the world. T2DM affects more than 170 million patients worldwide, and the total number of diabetes patients is estimated to increase from 20.8 million in 2000 to 42.3 million in 2030[1]. T2DM is a polygenic disease that is characterized by impaired insulin secretion and insulin resistance. Genetic variants in combination with environmental factors are thought contributive to the development of this disease. Recent genome-wide association studies (GWASs) and meta-analyses have identified several novel diabetes susceptibility loci. These loci may play roles in insulin secretion and pancreatic β-cell function[2–7]. Some variations in CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), cyclin dependent kinase inhibitor 2A-2B (*CKDN2A-2B*), zinc transporter member 8 (*SLC30A8*), and insulin-like growth factor 2 mRNA-binding protein 2 gene (*IGF2BP2*) have been shown to be associated with development of T2DM, and these findings have been confirmed in a Han Chinese population. SNPs in *CDKAL1*, *SLC30A8*, and *IGF2BP2* are also thought to be associated with impaired β-cell function[8].

*IGF2BP2* belongs to an mRNA-binding protein family that plays roles in RNA localization, stability and translation[9]. *IGF2BP2* is highly expressed in pancreatic islets and binds to insulin-like growth factor 2 (IGF-2), which is an important growth and insulin signaling molecule[5]. *IGF2BP2* is a homolog of *IGF2BP1*, which binds to the 5′UTR of IGF2

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mRNA and regulates IGF2 translation[10]. Several GWASs have found that study subjects carrying mutant alleles of SNPs rs1470579 and rs4402960 showed a moderately increased risk of T2DM. Several studies have confirmed this result in Asian populations[6–8, 11]. T2DM patients with different *IGF2BP2* genotypes showed various levels of insulin secretion. It has been demonstrated that variants in *IGF2BP2* affect first-phase insulin secretion and the disposition index detected by hyperglycemic clamps[12].

Repaglinide is an insulin secretagogue agent, which acts as an effective medication for treating T2DM[13, 14]. Repaglinide can reduce the concentration of blood glucose by enhancing the secretion of insulin from pancreatic β-cells, inhibiting ATP-sensitive $K^+$ channels (KATP), and activating $Ca^{2+}$ channels[13]. Individual differences in the repaglinide therapeutic efficacy have been reported. However, the possible mechanism is still unknown. Recent studies have shown that polymorphisms in the cytochrome P450 (CYP) 2C8, 3A4, and organic anion-transporting polypeptide 1B1 (*OATP1B1*) gene could influence the plasma concentration of repaglinide[15–17]. Therefore, it is possible that polymorphisms in other genes may also affect the repaglinide efficacy. *IGF2BP2* participates in the insulin signaling pathway and insulin secretion. Repaglinide also reduces glucose levels by increasing insulin secretion. Thus, the study we present here aimed to explore the correlation of *IGF2BP2* genetic polymorphisms with the therapeutic efficacy of repaglinide in Chinese T2DM patients.

## Materials and methods

### Subjects

A total of 350 unrelated T2DM patients (178 male and 172 female), aged 25–70 years (mean 49.06±10.75 years), and 207 healthy controls (117 male and 90 female), aged 25–70 years (mean 47.96±10.78 years), were recruited for this study. T2DM patients were recruited from the Department of Endocrinology, the Second Xiangya Hospital and Diabetic Center of Xiangya Hospital of Central South University, and the control subjects were from the Health Screening Center of Xiangya Hospital of Central South University, Changsha, China. All subjects were evaluated through collecting medical histories and conducting physical examinations and routine clinical laboratory tests. T2DM was diagnosed according to a fasting plasma glucose (FPG ≥7.0 mmol/L) and/or postprandial plasma glucose test (PPG ≥11.1 mmol/L) (World Health Organization criteria, 1999). The criteria for enrollment were that the subjects fell within the body mass index (BMI) range from 18.5 to 30 kg/m$^2$ and had not been treated with any insulin secretagogue, agonist or inhibitor of CYP2C8, CYP3A4, and OATP1B1 in the past 3 months. Patients with type 1 diabetes mellitus, a history of ketoacidosis, ischemic heart disease, congestive heart failure or trauma, kidney or liver diseases, patients receiving insulin treatment and pregnant or lactating women were excluded from this study. All of the healthy volunteers had normal fasting plasma glucose levels and blood pressure (data not shown). The clinical characteristics of the study groups are given in Table 1. The study protocol was approved by the Ethics Committee of Xiangya School of Medicine, Central South University and were in accordance with the Helsinki Declaration II. Written informed consent was obtained from each individual before the start of this study. We applied for clinical admission to the Chinese Clinical Trial Register (registration number: ChiCTR-CCC00000406). A total of 42 T2DM patients (23 male and 19 female) with different *IGF2BP2* rs1470579 and rs4402960 genotypes and the same *CYP2C8* and *OATP1B1* genotypes took oral doses of 3 mg repaglinide daily (1 mg×3/per day preprandial treatment) for 8 consecutive weeks.

### Genotyping analysis

Genomic DNA was isolated from peripheral blood leukocytes using an SQ Blood DNA Kit (Omega, Colorado, USA). Genotypes for the *IGF2BP2* polymorphisms were analyzed using a PCR-RFLP assay. For the rs4402960 locus, the following primer pairs were used: sense primer: 5′-AGACCAGCCTTGGCAATGTAGTG-3′, antisense primer: 5′-CTAAAGCACTGAGAGAAACAGCCCT-3′. The 439-bp PCR products of rs4402960 were digested with *Mbo* II (Fermentas, Maryland, USA) into fragments of 282 bp and 157 bp (rs4402960 homozygosity resulted in the production of a single 439-bp fragment). To determine the genotyping success rate, *Mse* I (Fermentas, Maryland, USA) was used to digest DNA from rs4402960 homozygotes into fragments of 284 bp and 155 bp, while DNA from individuals who were wild type for rs4402960 resulted in production of only a single 439-bp fragment. For amplification of the rs1470579 locus, the following primer pairs were used: sense primer: 5′-CAGGGGTAGATGATGTAAGTGGT-3′, antisense primer: 5′-ACCTAATTTGATTTTGAGTTTCC-3′. The 460-bp PCR products of rs1470579 were digested with *Mse* I (Fermentas, Maryland, USA) into fragments of 226 bp, 157 bp, 61 bp, and 16 bp (rs1470579 homozygosity resulted in as the production of fragments of 287 bp, 157 bp, and 16 bp). For the same purpose, *Fok* I (Fermentas, Maryland, USA) was used to digest DNA from rs1470579 homozygotes into fragments of 396 bp and 64 bp, while DNA from individuals who were wild type for rs1470579 produced only a single 460-bp fragment. Direct sequencing of randomly selected samples confirmed the accuracy of genotyping results. The genotyping success rate was >98%, and genotyping of duplicate samples revealed no errors.

### Clinical laboratory tests

After an overnight fast, venous blood samples were collected both in the fasting state and 2 h after a standardized breakfast on study d 0 and on the 8th weekend after treatment administration. Concentrations of FPG, TC, and triglyceride were determined by enzymatic colorimetric assay. HDL-c concentration was measured by lipoprotein electrophoresis. LDL-c concentration was calculated according to the Friedewald formula[18]. Plasma insulin and HbAlc levels were measured using a radioimmunoassay kit (BNIBT, Beijing, China) and by high performance liquid chromatography (HPLC) assay, respectively. The HOMA-IR value was used to estimate the

level of insulin sensitivity and calculated according to the following formula: fasting serum insulin (mU/L)×fasting blood glucose (mmol/L)/22.5[19].

### Statistical analysis

Statistical analyses were performed with SPSS software (Version 15.0 for Windows; SPSS Inc, Chicago, IL, USA). All continuous variables were given as means±SD and confidence intervals (95% CI). Variables that were not normally distributed were log-transformed before analysis. Hardy-Weinberg equilibrium and allelic frequencies in different groups were assessed with Pearson $\chi^2$ test of goodness-of-fit in the study sample. Student's *t*-test was used to compare continuous variables between the T2DM and control groups. Paired Student's *t*-tests and ANOVA tests were used to compare the differences in the degree of reduction or increase in plasma concentrations among the different genotypic groups before and after repaglinide treatment. LD between SNPs was estimated using Haploview version 3.2. The association between each SNP and the risk of T2DM was examined using logistic regression. All association analyses assumed an additive effect of the risk allele and were adjusted for sex, age, and BMI. A two-sided test with the type error level (α) set at 5% was used in all statistical analysis. Results were regarded as significant when $P<0.05$. Statistical power was calculated using a power calculator software PASS (www.ncss.com).

## Results

### Clinical and biochemical characteristics

The clinical and biochemical characteristics of all subjects in the current study were summarized in Table 1. There were no significant differences in age, BMI, waist/hip ratio (WHR) and HDL-c, but the levels of FPG, triglycerides, TC, and LDL-c were higher in T2DM cases than in healthy controls ($P<0.01$ and $P<0.001$, respectively).

**Table 1.** Clinical and biochemical characteristics of T2DM patients and healthy controls. Data are expressed as means±SD (95% CI). *P* values were determined by a two sample Student's *t*-test. $^cP<0.01$.

| Variable | T2DM patients *n*=350 | Healthy controls *n*=207 | *P* values |
|---|---|---|---|
| N (male/female) | 350 (178/172) | 207 (117/90) | |
| Age (years) | 49.06±10.75 (47.80, 50.32) | 47.96±10.78 (46.59, 49.34) | 0.139 |
| BMI (kg/m$^2$) | 25.04±3.46 (24.63, 25.45) | 24.08±2.82 (23.71, 24.45) | 0.365 |
| WHR | 0.91±0.06 (0.91, 0.92) | 0.90±0.05 (0.89, 0.91) | 0.175 |
| FPG (mmol/L) | 9.29±3.90 (8.85, 9.74) | 4.99±0.44 (4.92, 5.06) | 0.000$^c$ |
| Triglyceride (mmol/L) | 2.79±2.99 (2.41, 3.17) | 1.45±0.89 (1.32, 1.59) | 0.000$^c$ |
| TC (mmol/L) | 4.67±2.10 (4.42, 4.93) | 4.49±0.75 (4.37, 4.61) | 0.001$^c$ |
| HDL-c (mmol/L) | 1.43±0.81 (1.32, 1.54) | 1.42±0.32 (1.37, 1.47) | 0.597 |
| LDL-c (mmol/L) | 2.98±1.18 (2.84, 3.12) | 2.42±0.67 (2.31, 2.52) | 0.000$^c$ |

### Genotyping analysis and allelic frequencies

A total of 350 T2DM patients (178 male and 172 female) and 207 (117 male and 90 female) healthy volunteers were genotyped unambiguously for *IGF2BP2* rs1470579 and rs4402960 polymorphisms. The genotypic distributions of rs1470579 and rs4402960 SNPs were in agreement with Hardy-Weinberg equilibrium ($P>0.05$). The frequency of the rs1470579 C allele was higher in the T2DM group than in the control group (30.29% *vs* 24.64%, $P<0.05$). The frequency of the T allele at the rs4402960 locus was 27.14% in T2DM patients, which was higher than in healthy controls (27.14 *vs* 21.26%, $P<0.001$). We found significant linkage disequilibrium between the rs1470579 locus and the rs4402960 locus (D′=0.642, $r^2$=0.358, $P<0.05$, Table 2). There was no significant difference with respect to clinical parameters among the different haplotype groups (data not shown).

**Table 2.** Genotypes and frequencies of the *IGF2BP2* rs1470579 and rs4402960 polymorphisms in T2DM patients and healthy subjects. The allelic frequencies are indicated in absolute values (percentage). *P* values were determined by the Pearson $\chi^2$ test. $^bP<0.05$, $^cP<0.01$.

| Genotype | T2DM patients *n*=350 (frequency) | Healthy controls *n*=207 (frequency) | *P* value |
|---|---|---|---|
| *rs1470579* genotypes | | | |
| AA | 177 (50.57%) | 125 (60.39%) | |
| AC | 134 (38.29%) | 62 (29.95%) | |
| CC | 39 (11.14%) | 20 (9.66%) | 0.076 |
| *rs1470579* alleles | | | |
| A | 488 (69.71%) | 312 (75.36%) | |
| C | 212 (30.29%) | 102 (24.64%) | 0.025$^b$ |
| *rs4402960* genotypes | | | |
| GG | 188 (53.71%) | 129 (62.32%) | |
| GT | 134 (38.29%) | 68 (32.85%) | |
| TT | 28 (8.00%) | 10 (4.83%) | 0.097 |
| *rs4402960* alleles | | | |
| G | 510 (72.86%) | 326 (78.74%) | |
| T | 190 (27.14%) | 88 (21.26%) | 0.000$^c$ |

### Comparison of baseline characteristics of T2DM patients with different rs1470579 and rs4402960 genotypes

The baseline clinical characteristics of 350 T2DM patients with different rs1470579 and rs4402960 genotypes were summarized in Table 3. There were no significant differences in sex, age, BMI, or WHR between different genotype groups. In patients with the *IGF2BP2* rs1470579 genotype, there were significant differences in FPG (mmol/L) (8.66±3.87 *vs*

**Table 3.** The baseline clinical and biochemical characteristics of different genotypes of *IGF2BP2* gene in 350 T2DM patients. Data are given as means±SD (95% CI). *P* values represent the statistical difference between the AA and AC+CC (GG and GT+TT) genotype groups that were assessed by a two-sample *t*-test. $^{\Delta}P$ values are determined by Pearson $\chi^2$ test. $^{\dagger}$indicates that data were transformed to logarithmic values. $^{b}P<0.05$, $^{c}P<0.01$.

| Parameters | rs1470579 genotypes | | *P* values | rs4402960 genotypes | | *P* values |
|---|---|---|---|---|---|---|
| | AA | AC+CC | | GG | GT+TT | |
| N (male/female) | 177(92/85) | 173(86/87) | 0.748$^{\Delta}$ | 188 (89/99) | 162 (89/73) | 0.165$^{\Delta}$ |
| Age (years) | 48.15±10.78 (46.35, 49.94) | 49.98±10.68 (48.19, 51.76) | 0.154 | 48.86±11.02 (46.98, 50.74) | 50.18±10.59 (48.35, 52.01) | 0.319 |
| BMI (kg/m$^2$) | 25.27±3.46 (24.68, 25.85) | 24.81±3.47 (24.23, 25.40) | 0.277 | 25.26±3.55 (24.65, 25.87) | 25.23±3.34 (24.64, 25.81) | 0.935 |
| WHR | 0.91±0.06 (0.90, 0.92) | 0.91±0.06 (0.90, 0.92) | 0.785 | 0.91±0.05 (0.90, 0.92) | 0.92±0.06 (0.91, 0.93) | 0.438 |
| FPG (mmol/L) | 8.66±3.87 (8.05, 9.28) | 9.96±3.82 (9.33, 10.59) | 0.004$^{\dagger c}$ | 8.26±3.23 (7.73, 8.79) | 10.45±4.23 (9.74, 11.17) | 0.000$^{\dagger c}$ |
| PPG (mmol/L) | 15.49±5.69 (14.50, 16.48) | 16.80±6.49 (15.73, 17.88) | 0.116$^{\dagger}$ | 15.21±5.36 (14.25, 16.16) | 17.06±6.61 (15.94, 18.18) | 0.044$^{\dagger b}$ |
| FINS (mU/L) | 9.91±5.79 (8.91, 10.92) | 9.72±6.55 (8.58, 10.87) | 0.546$^{\dagger}$ | 9.52±5.45 (8.53, 10.50) | 10.30±6.31 (9.19, 11.42) | 0.461$^{\dagger}$ |
| PINS (mU/L) | 44.95±40.04 (37.89, 52.00) | 60.60±47.92 (52.73, 68.46) | 0.000$^{\dagger c}$ | 47.74±38.01 (40.87, 54.61) | 60.90±49.29 (52.54, 69.25) | 0.038$^{\dagger b}$ |
| HOMA-IR | 26.35±34.77 (20.19, 32.50) | 28.96±37.72 (22.36, 35.55) | 0.247$^{\dagger}$ | 25.17±30.95 (19.50, 30.84) | 30.80±36.24 (24.38, 37.21) | 0.241$^{\dagger}$ |
| HbA1c (%) | 9.50±6.29 (8.37, 10.64) | 8.62±2.57 (8.16, 9.08) | 0.107$^{\dagger}$ | 9.21±6.31 (8.06, 10.36) | 8.86±2.69 (8.37, 9.35) | 0.890$^{\dagger}$ |
| Triglyceride (mmol/L) | 3.12±3.57 (2.49, 3.76) | 2.44±2.20 (2.04, 2.84) | 0.154$^{\dagger}$ | 2.85±3.03 (2.29, 3.40) | 2.59±2.71 (2.10, 3.09) | 0. 539$^{\dagger}$ |
| TC (mmol/L) | 4.52±2.40 (4.12, 4.91) | 4.86±1.64 (4.56, 5.16) | 0.010$^{\dagger b}$ | 4.43±2.43 (4.02, 4.83) | 4.94±1.44 (4.68, 5.21) | 0.000$^{\dagger c}$ |
| HDL-c (mmol/L) | 1.51±1.01 (1.33, 1.70) | 1.35±0.53 (1.25, 1.44) | 0.249$^{\dagger}$ | 1.47±1.13 (1.25, 1.68) | 1.36±0.57 (1.25, 1.46) | 0.699$^{\dagger}$ |
| LDL-c (mmol/L) | 2.91±1.09 (2.71, 3.11) | 3.17±1.27 (2.96, 3.38) | 0.003$^{c}$ | 2.91±1.09 (2.71, 3.11) | 2.98±1.26 (2.76, 3.19) | 0.655 |

9.96±3.82, *P*<0.01), PINS (mU/L) (44.95±40.04 *vs* 60.60±47.92, *P*<0.001), TC (mmol/L) (4.52±2.40 *vs* 4.86±1.64, *P*<0.05) and LDL-c (mmol/L) (2.91±1.09 *vs* 3.17±1.27, *P*<0.01) between subjects with the AA and AC+CC genotype (Table 3, Figure 1). We also found that there were significant differences in FPG (mmol/L) (8.26±3.23 *vs* 10.45±4.23, *P*<0.001), PPG (mmol/L) (15.21±5.36 *vs* 17.06±6.61, *P*<0.05), PINS (mU/L) (47.74±38.01 *vs* 60.90±49.29, *P*<0.05) and TC (mmol/L) (4.43±2.43 *vs* 4.94±1.44, *P*<0.001) between individuals with the rs4402960 GG and GT+TT genotypes (Table 3, Figure 2).

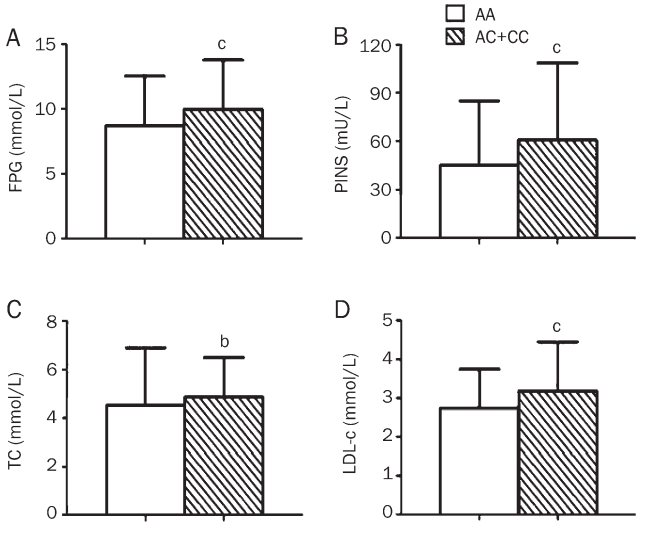


**Figure 1.** Comparison of the baseline levels of FPG (A), PINS (B), TC (C), and LDL-c (D) in T2DM patients with different *IGF2BP2* rs1470579 genotypes. Data are expressed as means±SD. $^{b}P<0.05$, $^{c}P<0.01$ compared with the AA genotype. *n*=350.

### Effects of the rs1470579 and rs4402960 polymorphisms on therapeutic efficacy of repaglinide treatment in patients with T2DM

A total of 42 T2DM patients (23 male and 19 female) were treated with 3 mg of repaglinide daily for 8 weeks. Repaglinide significantly decreased the concentrations of FPG (*P*<0.001), PPG (*P*<0.001), HbA1c (*P*<0.001), TC (*P*<0.05), and LDL-c (*P*<0.001), while treatment increased the levels of FINS (*P*<0.01), PINS (*P*<0.001), and HDL-c (*P*<0.01) in T2DM patients (Table 4). As shown in Table 5 and Figure 3, there

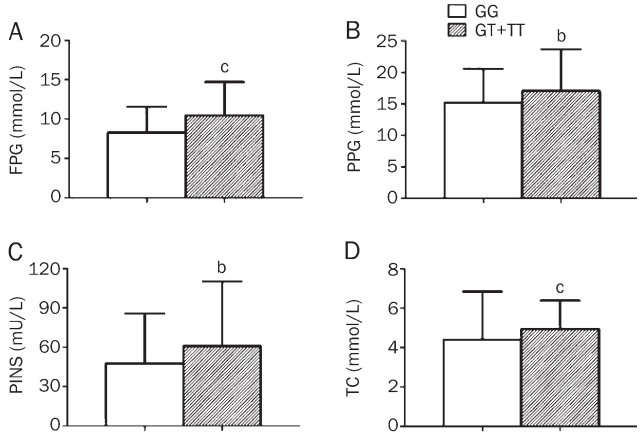


**Figure 2.** Comparison of the baseline levels of FPG (A), PPG (B), PINS (C), and TC (D) in T2DM patients with different *IGF2BP2* rs4402960 genotypes. Data are expressed as means±SD. $^{b}P<0.05$, $^{c}P<0.01$ compared with the GG genotype. $n$=350.

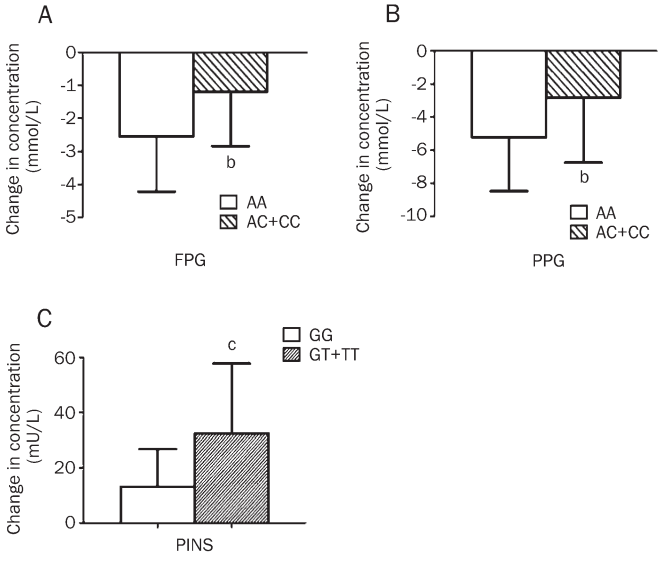


**Figure 3.** Comparison of differential values (post-administration minus pre-administration) of FPG (A) and PPG (B) between the AA genotype and the AC+CC genotypes of the *IGF2BP2* rs1470579 polymorphism in T2DM patients after repaglinide treatment, respectively. Comparison of differential values of PINS (C) between the GG genotype and the GT+TT genotypes of the *IGF2BP2* rs4402960 polymorphism in T2DM patients after repaglinide treatment. Data are expressed as means±SD. $^{b}P<0.05$, $^{c}P<0.01$. $n$=42.

**Table 4.** Clinical characteristics of all T2DM patients before and after repaglinide treatment ($n$=42). Data are expressed as means±SD (95% CI). $P$ values were determined by a paired Student's $t$-test. $^{b}P<0.05$, $^{c}P<0.01$.

| Parameters | Before | After | $P$ values |
|---|---|---|---|
| FPG (mmol/L) | 8.75±1.95 (8.14, 9.36) | 6.81±1.55 (6.33, 7.29) | 0.000$^{c}$ |
| PPG (mmol/L) | 15.72±3.77 (14.55, 16.90) | 11.56±3.00 (10.63, 12.50) | 0.000$^{c}$ |
| `FINS (mU/L) | 7.81±6.37 (8.84, 9.74) | 11.61±6.45 (9.57, 13.64) | 0.001$^{c}$ |
| PINS (mU/L) | 37.91±24.71 (30.21, 45.61) | 58.07±28.91 (49.06, 67.08) | 0.000$^{c}$ |
| HOMA-IR | 2.98±2.56 (2.18, 3.78) | 3.43±2.10 (2.77, 4.09) | 0.335 |
| HbA1c (%) | 8.59±1.72 (8.05, 9.12) | 6.84±1.10 (6.49, 7.19) | 0.000$^{c}$ |
| Triglyceride (mmol/L) | 2.26±1.75 (1.71, 2.80) | 2.28±1.48 (1.81, 2.74) | 0.948 |
| TC (mmol/L) | 5.28±1.22 (4.90, 5.66) | 4.79±0.97 (4.49, 5.09) | 0.014$^{b}$ |
| HDL-c (mmol/L) | 1.34±0.39 (1.22, 1.46) | 1.46±0.45 (1.32, 1.61) | 0.001$^{b}$ |
| LDL-c (mmol/L) | 3.10±1.13 (2.74, 3.46) | 2.39±0.95 (2.08, 2.69) | 0.000$^{c}$ |

were significantly lower repaglinide effects in patients with the *IGF2BP2* rs1470579 AC+CC genotype on FPG (mmol/L) (from 8.27±2.02 to 7.08±1.51, DV -1.19±1.64) and PPG (mmol/L) (from 14.80±4.09 to 11.96±3.43, DV -2.84±3.91) compared with rs1470579 AA genotype carriers (from 9.14±1.84 to 6.59±1.57, DV -2.56±1.65, $P$<0.05; from 16.49±3.38 to 11.23±2.61, DV -5.25±3.23, $P$<0.05, respectively). However, patients with the GT+TT genotypes of rs4402960 showed an enhanced effect of repaglinide treatment on PINS (mU/L) (from 31.76±27.59 to 64.13±29.39, DV 32.37±25.42) compared with individuals with the GG genotype (from 40.99±27.59 to 55.04±28.71, DV 13.16±13.64, $P$<0.01) (Table 5).

## Discussion

In this study, we examined the effects of *IGF2BP2* variations on the therapeutic efficacy of repaglinide treatment in Chinese T2DM patients. Our results suggested that the *IGF2BP2* gene may represent a susceptibility gene for T2DM. We observed that the two variants in *IGF2BP2* fell within one LD block ($r^2$=0.358 for rs1470579 and rs4402960) and were significantly associated with T2DM [odds ratios 1.284 (1.175, 1.346), $P$=0.036 for rs1470579 and odds ratios 1.499 (1.021, 2.199), $P$=0.039 for rs4402960]. This study also found that patients with the rs1470579 AC+CC genotypes had poor responses to repaglinide treatment with respect to FPG and PPG compared with individuals with the AA genotype ($P$<0.05). Patients with the GT+TT genotypes of rs4402960 also showed a better repaglinide therapeutic effect on PINS compared with individuals with the GG genotype ($P$<0.01).

IGFs and IGF binding proteins (IGFBPs) regulate cellular growth and proliferation. Targeting mRNA binds to the 5'UTR, 3'UTR or coding region of IGFBPs[9]. IGF2 belongs to the insulin family of polypeptide growth factors, which is involved in the development and stimulation of insulin action[3]. IGF2BP2, also named IMP2, is an mRNA-binding protein that post-translationally regulates IGF2, which is a

**Table 5.** The comparisons of DV in T2DM patients with different *IGF2BP2* rs1470579 and rs4402960 genotypes before and after repaglinide treatment. Data are given as means±SD (95% CI). *P* values represent the statistical difference between the AA and AC+CC (GG and GT+TT) groups that were assessed by a two-sample *t*-test. $^{\Delta}P$ values are determined by Pearson $\chi^2$ test. $^{\dagger}$indicates that data were transformed to logarithmic values. $^{b}P<0.05$, $^{c}P<0.01$.

| Parameters | rs1470579 genotype | | *P* value | rs4402960 genotype | | *P* value |
|---|---|---|---|---|---|---|
| | AA | AC+CC | | GG | GT+TT | |
| N (male/female) | 24 (13/11) | 18 (10/8) | 0.929$^{\Delta}$ | 28 (18/10) | 14 (5/9) | 0.079$^{\Delta}$ |
| FPG (mmol/L) | | | | | | |
| Pre- | 9.14±1.84 (8.35, 9.94) | 8.27±2.02 (7.30, 9.25) | 0.153 | 8.89±1.70 (8.23, 9.55) | 8.47±2.41 (7.08, 9.66) | 0.518 |
| Post- | 6.59±1.57 (5.91, 7.27) | 7.08±1.51 (6.35, 7.81) | 0.257$^{\dagger}$ | 6.86±1.47 (6.28, 7.43) | 6.72±1.74 (5.72, 7.72) | 0.717$^{\dagger}$ |
| DV | -2.56±1.65 (-3.27, -1.84) | -1.19±1.64 (-1.98, -0.40) | 0.011$^{b}$ | -2.03±1.60 (-2.65, -1.41) | -1.75±2.11 (-2.97, -0.53) | 0.630 |
| PPG (mmol/L) | | | | | | |
| Pre- | 16.49±3.38 (15.02, 17.95) | 14.80±4.09 (12.83,16.77) | 0.151 | 16.23±3.15 (15.01,17.45) | 14.71±4.75 (11.97,17.45) | 0.221 |
| Post- | 11.23±2.61 (10.10, 12.36) | 11.96±3.43 (10.31,13.61) | 0.442 | 11.53±2.96 (10.38, 12.68) | 11.63±3.17 (9.80, 13.46) | 0.917 |
| DV | -5.25±3.23 (-6.65, -3.86) | -2.84±3.91 (-4.72, -0.96) | 0.034$^{b}$ | -4.70±3.46 (-6.04, -3.36) | -3.07±4.09 (-5.43, -0.71) | 0.183 |
| FINS (mU/L) | | | | | | |
| Pre- | 7.04±5.75 (4.55, 9.53) | 8.74±6.75 (5.48, 11.99) | 0.274$^{\dagger}$ | 7.94±6.34 (5.48, 10.40) | 7.55±6.15 (4.00, 11.10) | 0.812$^{\dagger}$ |
| Post- | 11.60±6.37 (8.84, 14.35) | 11.62±6.74 (8.27,14.97) | 0.993 | 12.83±6.56 (10.24,15.42) | 9.25±5.74 (5.93,12.56) | 0.092 |
| DV | 4.56±6.79 (1.62, 7.50) | 2.48±5.86 (-0.44, 5.39) | 0.308 | 4.65±6.75 (1.98, 7.32) | 1.70±5.39 (-1.41,4.81) | 0.165 |
| PINS (mU/L) | | | | | | |
| Pre- | 36.47±22.87 (26.58,46.36) | 39.65±27.30 (26.50,52.81) | 0.683 | 40.99±27.59 (30.29,51.69) | 31.76±27.59 (30.29,51.69) | 0.259 |
| Post- | 56.96±25.70 (45.85,68.08) | 59.41±33.05 (43.48,75.34) | 0.789 | 55.04±28.71 (43.91,66.17) | 64.13±29.39 (47.15,81.10) | 0.343 |
| DV | 19.84±21.86 (10.39,29.30) | 19.23±18.78 (10.17,28.28) | 0.923 | 13.16±13.64 (7.87,18.45) | 32.37±25.42 (17.69,47.05) | 0.003$^{c}$ |
| HOMA-IR | | | | | | |
| Pre- | 2.83±2.39 (1.79, 3.86) | 3.17±2.80 (1.82, 4.52) | 0.631$^{\dagger}$ | 3.12±2.65 (2.09, 4.14) | 2.72±2.44 (1.31, 4.12) | 0.506$^{\dagger}$ |
| Post- | 3.43±2.20 (2.48, 4.38) | 3.44±2.02 (2.43, 4.44) | 0.599$^{\dagger}$ | 3.88±2.21 (3.01, 4.75) | 2.57±1.60 (1.64, 3.49) | 0.097$^{\dagger}$ |
| DV | 0.60±2.84 (-0.63, 1.83) | 0.11±2.12 (-0.94, 1.16) | 0.540 | 0.66±2.61 (-0.37, 1.70) | -0.15±2.36 (-1.51, 1.21) | 0.335 |
| HbA1c (%) | | | | | | |
| Pre- | 8.99±2.00 (8.12, 9.86) | 8.10±1.16 (7.54, 8.66) | 0.096 | 8.69±1.52 (8.10, 9.28) | 8.40±2.11 (7.18, 9.61) | 0.614 |
| Post- | 6.91±1.24 (6.36, 7.46) | 6.74±0.93 (6.28, 7.21) | 0.639 | 6.90±1.23 (6.41, 7.40) | 6.72±0.85 (6.22, 7.21) | 0.615 |
| DV | -2.15±2.18 (-3.12, -1.19) | -1.43±1.05 (-1.95, -0.91) | 0.366 | -1.91±1.50 (-2.51, -1.30) | -1.68±2.27 (-2.99, -0.37) | 0.472 |
| Triglyceride (mmol/L) | | | | | | |
| Pre- | 2.51±2.24 (1.54, 3.47) | 1.95±0.81 (1.56, 2.34) | 0.441$^{\dagger}$ | 2.29±2.06 (1.49, 3.09) | 2.18±0.89 (1.67, 2.70) | 0.571$^{\dagger}$ |
| Post- | 2.27±1.09 (1.80, 2.74) | 2.28±1.89 (1.37, 3.19) | 0.383$^{\dagger}$ | 2.25±1.12 (1.81, 2.68) | 2.33±2.08 (1.13, 3.53) | 0.553$^{\dagger}$ |
| DV | -0.24±0.28 (-1.22, 0.75) | 0.32±1.51 (-0.40, 1.06) | 0.930$^{\dagger}$ | -0.05±2.03 (-0.84, 0.74) | 0.15±1.90 (-0.95, 1.25) | 0.107$^{\dagger}$ |
| TC (mmol/L) | | | | | | |
| Pre- | 5.00±1.40 (4.00, 5.60) | 5.61±0.89 (5.19, 6.04) | 0.105 | 5.16±1.28 (4.67, 5.66) | 5.51±1.09 (4.88, 6.14) | 0.393 |
| Post- | 4.63±0.90 (4.24, 5.02) | 5.00±1.03 (4.49, 5.49) | 0.147$^{\dagger}$ | 4.88±1.03 (4.48, 5.28) | 4.62±0.84 (4.14, 5.10) | 0.539$^{\dagger}$ |
| DV | -0.37±1.46 (-1.00, 0.26) | -0.62±0.90 (-1.06, -0.19) | 0.513 | -0.28±1.30 (-0.79, -0.22) | -0.89±0.98 (-1.46, -0.32) | 0.134 |
| HDL-c (mmol/L) | | | | | | |
| Pre- | 1.30±0.34 (1.15, 1.45) | 1.38±0.45 (1.16, 1.60) | 0.514 | 1.23±0.34 (1.10, 1.37) | 1.55±0.43 (1.30, 1.79) | 0.013 |
| Post- | 1.41±0.32 (1.27, 1.55) | 1.53±0.57 (1.26, 1.81) | 0.397 | 1.38±0.47 (1.20, 1.56) | 1.64±0.37 (1.42, 1.85) | 0.084 |
| DV | 0.11±0.15 (0.04, 0.18) | 0.18±0.27 (0.05, 0.31) | 0.321 | 0.17±0.20 (0.09, 0.24) | 0.09±0.24 (-0.05, 0.22) | 0.268 |
| LDL-c (mmol/L) | | | | | | |
| Pre- | 3.04±1.37 (2.43, 3.64) | 3.18±0.78 (2.79, 3.57) | 0.701 | 3.01±1.22 (2.52, 3.50) | 3.27±0.97 (2.71, 3.83) | 0.493 |
| Post- | 2.46±1.06 (1.99, 2.93) | 2.30±0.81 (1.90, 2.70) | 0.600 | 2.36±1.01 (1.95, 2.77) | 2.44±0.86 (1.94, 2.93) | 0.811 |
| DV | -0.57±0.71 (-0.88, -0.26) | -0.64±1.02 (-1.15, -0.14) | 0.795 | -0.59±0.78 (-0.90, -0.27) | -0.63±0.99 (-1.20, -0.06) | 0.884 |

fetal growth factor that is involved in several developmental stages[10]. IGF2BP2 is involved in binding IGF-2 transcripts and regulating their translation[10]. The IGFBP homolog is necessary for pancreas development in Xenopus[20], and IGF2BP3 transgenic mice exhibit acinar-ductal pancreatic metaplasia[21]. IGF2BP2 also acts in the regulation of mRNA stability. Interactions between genetic variation in *IGF2BP2* and T2DM may be exerted through this IGF2 pathway and through the insulin pathway. The *IGF2BP2* gene is located at chromosome 3q27.2. Intron 2 is the longest intron in the *IGF2BP2* gene among mammalian species. SNPs rs1470579 and rs4402960 are located in a 50-kb region of this intron. Diabetes-predisposing variants may, therefore, affect regulation of IGF2BP2 expression[3].

In the present study, we found that the distributions of both the rs1470579 and the rs4402960 alleles were in accordance with Hardy-Weinberg equilibrium. The frequency of the C allelic of rs1470579 and the T allele of rs4402960 were higher in T2DM subjects than in healthy controls ($P$<0.05 and $P$<0.001, respectively). Our data showed that the allelic frequency of *IGF2BP2* SNPs in the Chinese population is different from their frequencies in Japanese[6], Finns Swedish[22], English[23], and French Caucasian populations[24]. *IGF2BP2* rs1470579 SNPs have dramatically different allele frequencies in white and black populations[25].

Our data also demonstrated that patients with T2DM who carried the C allele of rs1470579 had higher levels of FPG, PINS, TC, and LDL-c compared with individuals with the AA genotype. The *IGF2BP2* variant (rs4402960) was associated with insulin sensitivity, FPG, glucose AUC, and FPG[24]. rs4402960 was also associated with reductions in first-phase insulin secretion and in the disposition index, which reflects the failing adaptive capacity of pancreatic β-cells[12] resulting in hyperglycemia including FPG and PPG. SNP rs4402960 has also been shown to be associated with the disposition index in Hispanic Americans[26], HOMA-β in non-diabetic Japanese individuals and lower acute insulin release and tolerance[27]. SNP rs4402960 is strongly associated with an increased risk of T2DM and increased AUC of glucose in individuals of Dutch descent[28]. Our findings were, thus, in accord with several previous reports.

We also found that patients with T2DM who carried the T allele of rs4402960 had higher levels of FPG, PPG, PINS, and TC compared with subjects with the GG genotype. The results of our research agree with the observations of Wu *et al*, who observed a significant association of SNPs (rs1470579 and rs4402960) in *IGF2BP2* [1.17 (1.03–1.32); $P$=0.014] with combined IFG (impaired fasting glycemia)/T2DM group. The association of these SNPs with HOMA-β reduction suggested that *IGF2BP2* confers T2DM risk through a reduction of β-cell function[8].

The underlying pathophysiological mechanisms that are affected by *IGF2BP2* variations could be linked to nearby SNPs that have an effect on microRNAs, larger non-coding transcripts, or even antisense mRNA transcribed from intron 2[9]. Doria *et al* pointed out that protein phosphatase 1, regulatory subunit 2 (*PPP1R2*) and insulin-sensitizing adipokine adiponectin (*ADIPOQ*), which are implicated in metabolism and regulation of insulin activity, are located in proximity to *IGF2BP2*[29]. Replication of this research has indicated that *IGF2BP2* variants were more likely to be associated with reduced β-cell function[12, 27, 30]. Because *IGF2BP2* was shown to affect insulin secretion in a previous study, we hypothesized that patients with deteriorative β-cell function would have a poorer response to repaglinide treatment.

This study explored the influences of the rs1470579 and rs4402960 polymorphisms of *IGF2BP2* on the therapeutic efficacy of repaglinide treatment in T2DM patients. In this study, to avoid the influence of pharmacokinetic changes in the action of repaglinide on its therapeutic efficacy, we selected patients with the same *CYP2C8* (*3) and *OATP1B1* (*1B, *5 and *15) genotypes. After T2DM patients were treated with 3 mg repaglinide daily for 8 consecutive weeks, there were significantly augmented repaglinide effects in patients with the rs1470579 AC+CC genotypes on FPG and PINS compared to subjects with the rs1470579 AA genotype ($P$<0.05, $P$<0.05, respectively). Moreover, patients with GT+TT genotypes of rs4402960 showed lower effects of repaglinide treatment on PINS compared with individuals with the GG genotype ($P$<0.01). Repaglinide acts to inhibit ATP-sensitive $K^+$ (KATP) currents in pancreatic β-cells and to stimulate an increase in $[Ca^{2+}]_i$ to promote insulin secretion[31]. Repaglinide is metabolized in the liver by the cytochrome P450 (CYP) 2C8 and 3A4 enzymes[15]. Hepatic uptake by OATP1B1 is an important step preceding the metabolism of this drug, and genetic polymorphisms in these enzymes affect the pharmacokinetics of repaglinide metabolism[16,17]. In this study, to avoid the influence of pharmacokinetic changes in repaglinide action on its therapeutic efficacy, we selected patients with the same *CYP2C8* (*3) and *OATP1B1* (521T>C) genotypes to participate in this study (data not show).

One of the limitations of our study was its relatively small sample size. Another limitation was that the mechanisms through which *IGF2BP2* contributes to the development of T2DM are not fully understood. The power values for detecting the two polymorphisms we investigated were 80%–98%. The influence of *IGF2BP2* polymorphisms on the therapeutic efficacy of treatments for T2DM in large samples of T2DM patients is worthy of continued investigation.

In conclusion, we showed that variants in the *IGF2BP2* gene are associated with T2DM, and also associated with reduced therapeutic efficacy of repaglinide treatment. However, understanding the biological mechanism by which variants in *IGF2BP2* could mediate these effects on the biphasic pattern of insulin secretion will require further investigation.

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## Author contribution

Zhao-qian LIU had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Zhao-qian LIU and Qiong HUANG designed the research; Zhao-qian LIU, Qiong HUANG, Ji-ye YIN, Xing-ping DAI, Min DONG, Zhi-guang ZHOU, Xi HUANG, Hong-hao ZHOU, and Min YU performed the research; Zhao-qian LIU, Qiong HUANG and Qi PEI analyzed the data; Zhao-qian LIU and Qiong HUANG wrote the paper.

## Abbreviations

GWASs, genome-wide association studies; SNPs, single nucleotide polymorphisms; T2DM, type 2 diabetes mellitus; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; IGF2, insulin-like growth factor 2; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2 gene; BMI, body mass index; WHR, waist to hip ratio; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbAlc, glycated hemoglobin; FINS, fasting serum insulin; PINS, postprandial serum insulin; HOMA-IR, homeostasis model assessment for insulin resistance; TC, total cholesterol; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; DV, differential value (post-administration minus pre-administration); Pre-, pre-administration; Post-, post-administration.

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# Stroke and Atrial Fibrillation: risks, prevention and management of stroke in AF patients

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