**Introduction**

Type 2 diabetes is a chronic complex metabolic disease, which is obviously influenced by genetic components and environmental factors\(^1\). Many studies focused on finding susceptibility gene loci for type 2 diabetes, including genome-wide linkage study, candidate gene study, and genome-wide association study (GWAS). Genome-wide linkage study showed that the peroxisome proliferators-activated receptor-γ2 (PPAR-γ2) gene was associated with type 2 diabetes\(^2\). PPAR-γ2 belongs to the nuclear hormone receptor superfamily of ligand-dependent transcription factors\(^3\) and is predominantly expressed in adipose tissue\(^4\). It is involved in adipocyte differentiation, regulating glucose and lipid homeostasis\(^4\). The most common polymorphism rs1801282 (Pro12Ala) occurs in 12% of the Finnish population\(^5\) and in 14% of the German population\(^6\). The rs1801282 is a missense mutation that causes the replacement of proline by alanine at codon 12 of PPAR-γ2 gene\(^7\). This gene affected type 2 diabetes patients not only on susceptibility but also on anti-diabetic therapeutic efficacy. Patients carrying CG genotype of rs1801282 showed a better rosiglitazone therapeutic efficacy than the CC genotype subjects\(^8\).

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**PPAR-γ2 and PTPRD gene polymorphisms influence type 2 diabetes patients’ response to pioglitazone in China**

Qi PE\(^1\), Qiong HUANG\(^3\), Guo-ping YANG\(^1\), Ying-chun ZHAO\(^5\), Ji-ye YIN\(^1\), Min SONG\(^4\), Yi ZHENG\(^1\), Zhao-hui MO\(^6\), * Hong-hao ZHOU\(^1\), Zhao-qian LIU\(^1\), *

\(^1\)Institute of Clinical Pharmacology, Hunan Key Laboratory of Pharmacogenetics, Central South University, Changsha 410078, China; \(^2\)Department of Pharmacy, Third Xiangya Hospital, Central South University, Changsha 410013, China; \(^3\)Institute of Clinical Pharmacology, Anhui Medical University, Hefei 230032, China; \(^4\)Center of Clinical Pharmacology, Third Xiangya Hospital, Central South University, Changsha 410013, China; \(^5\)Osteoporosis Research Center, Creighton University, Omaha, NE 68131, USA; \(^6\)Department of Endocrinology, Third Xiangya Hospital, Central South University, Changsha 410013, China

Aim: To investigate the influence of peroxisome proliferator-activated receptor γ2 (PPAR-γ2) gene polymorphism rs1801282 and protein tyrosine phosphatase receptor type D (PTPRD) gene polymorphism rs17584499 on the occurrence of type 2 diabetes and pioglitazone efficacy in a Chinese Han population.

Methods: One hundred ninety seven type 2 diabetes patients and 212 healthy controls were enrolled. Among them, 67 type 2 diabetes patients were administered pioglitazone (30 mg/d, po) for 3 months. All the subjects were genotyped for genetic variants in PPAR-γ2 and PTPRD using MALDI-TOF mass spectrometry. Fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin, serum triglyceride, total cholesterol, low-density and high-density lipoprotein-cholesterol were determined.

Results: The PPAR-γ2 gene rs1801282 polymorphism was significantly associated with type 2 diabetes susceptibility (OR=0.515, 95% CI 0.268–0.990) and the PTPRD gene rs17584499 polymorphism was also significantly associated with type 2 diabetes (OR=1.984, 95% CI 1.135–3.469) in a dominant model adjusted for age, gender and BMI. After pioglitazone treatment for 3 months, the type 2 diabetes patients with PPAR-γ2 rs1801282 CG genotypes significantly showed higher differential values of postprandial plasma glucose and serum triglyceride compared with those with rs1801282 CC genotype. The patients with PTPRD rs17584499 CT+TT genotypes showed significantly lower differential value of postprandial plasma glucose compared to those with rs17584499 CC genotype.

Conclusion: Diabetes risk alleles in PPAR-γ2 (rs1801282) and PTPRD (rs17584499) are associated with pioglitazone therapeutic efficacy.

Keywords: pioglitazone; type 2 diabetes; PPAR-γ2 rs1801282; PTPRD rs17584499; genetic polymorphisms; Chinese Han population

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*To whom correspondence should be addressed. E-mail liuzhaoqian63@126.com (Zhao-qian LIU); easd04mhzh@126.com (Zhao-hui MO)

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Recently, a Chinese Han GWAS reported several new genetic loci associated with type 2 diabetes\(^9\). Among them, protein tyrosine phosphatase receptor type D (PTPRD) gene showed the strongest association and largest odds ratio (ORs)\(^9\). PTPRD is a member of protein tyrosine phosphatases (PTPs) receptor type II A (R2A) subfamily\(^10\), which plays a significant role in diabetes\(^11\). The strongest associated polymorphism is rs17584499, which is located in the intron 10 of PTPRD gene\(^9\). Although the intronic single nucleotide polymorphisms (SNPs) is generally regarded to have no functional meaning, it may influence the splicing or the stability of mRNA\(^12\-^{14}\), and consequently changes the gene expression level. Additionally, the intronic SNP may be a marker of association with other functional polymorphisms.

Pioglitazone, a new insulin-sensitizing drug, belongs to thiazolidinedione (TZD), which is widely used for type 2 diabetes patients\(^15\-^{16}\). PPAR-γ2 gene is a target gene for pioglitazone. The binding of PPAR-γ2 and pioglitazone activates transcription of genes involved in glucose and lipid metabolism\(^17\-^{18}\). Type 2 diabetes patients treated with pioglitazone showed decrease in blood glycated hemoglobin (HbA1c)\(^19\), triglyceride, total cholesterol, and low-density lipoprotein-cholesterol (LDL-c) and increase in high-density lipoprotein-cholesterol (HDL-c)\(^20\). It has been reported that pioglitazone therapeutic efficacy in type 2 diabetes patients showed individual differences\(^20\-^{21}\).

In this study, we intend to explore the effect of PPAR-γ2 gene rs1801282 and PTPRD gene rs17584499 polymorphism on pioglitazone therapeutic efficacy in Chinese Han type 2 diabetes patients.

**Materials and methods**

**Subjects**

A total of 197 patients with type 2 diabetes and 212 healthy controls of Chinese Han population were recruited in the Third Xiangya Hospital, Central South University, Changsha in China. There were no significant differences with regard to age and sex between controls and cases, but a significant difference in body mass index (BMI) was found between controls and cases. Type 2 diabetes was diagnosed according to the World Health Organization criteria from 1999: fasting plasma glucose test (FPG) ≥ 7.0 mmol/L or 2 h postprandial plasma glucose test (PPG) ≥ 11.1 mmol/L. We excluded patients with type 1 diabetes, ischemic heart disease, congestive heart failure, kidney or liver diseases; patients receiving insulin treatment or other drugs, which affect the glucose metabolism (such as glucocorticoids); and pregnant or lactating patients. The inclusion criteria were as follows: (1) BMI between 19 and 30 kg/m\(^2\), (2) the duration of diabetes was more than three months, (3) no administration of any insulin secretagogue, agonist or inhibitor of CYP2C8, CYP3A4 in the past 3 months, (4) no TZD use, and (5) no change in medication in the last 3 months. The study protocol was approved by the Ethics Committee of Third Xiangya Hospital, Central South University and was in accordance with the Helsinki Declaration II. All subjects signed the informed consent prior to the beginning of study. Sixty seven patients were administered with 30 mg oral pioglitazone (Kasiping, Hangzhou, China) daily for 12 consecutive weeks. They were instructed to maintain the same levels of energy intake and physical activity throughout the entire study. We also applied for a clinical admission from Chinese Clinical Trial Registration (registration number: ChiCTR-RNC-12001949).

**Clinical measurements**

Venous blood samples were collected from subjects in the fasting state after an overnight fasting and 2 h after a standardized breakfast before and after 12 weeks of administration. Concentrations of FPG, PPG, TG, TC, HDL-c, LDL-c and HbA1c were determined as previously described\(^22\). Body mass index (BMI) was calculated as weight in kilograms divided by body height in squared meters.

**Genotyping**

Genomic DNA was extracted from peripheral blood leukocytes using the Promega DNA purification kit (Promega, Madison, WI, USA) and distributed on master plates with all steps recorded by a sample tracking system. Genotyping was performed using MALDI-TOF mass spectrometry of allele-specific primer extension products generated from amplified DNA sequences (MassARRAY, SEQUENOM Inc, San Diego, CA, USA). Primers were purchased from Metabion GmbH (Planegg-Martinsried, Germany).

**Statistical analysis**

Data were presented as mean±SD. Statistical analyses were performed with SPSS software (Version 17.0 for Windows; SPSS Inc, Chicago, IL, USA). The genotype frequencies were compared using Pearson χ\(^2\) analysis. Multivariate ORs were calculated using a logistic regression analysis while adjusting for age, gender and BMI. The differences before and after pioglitazone treatment were analyzed by paired t-tests. To compare changes between different genotypes after pioglitazone treatment, we used explored statistical analysis to determine the distribution of our data, and performed two-sample t test for normally distributed data and Mann-Whitney test for non-normally distributed data. Statistical power was calculated with power calculator software PASS (www.ncss.com). A two-sided P-value <0.05 was considered to be statistically significant.

**Results**

**Polymorphism distributions and association study**

We analyzed the distribution of PPAR-γ2 gene rs1801282 and PTPRD gene rs17584499 polymorphisms in 197 type 2 diabetes subjects and 212 healthy controls (Table 1). Both SNPs were found to be in Hardy-Weinberg equilibrium (P>0.05). We first studied the association of allelic frequencies of PPAR-γ2 gene rs1801282 and PTPRD gene rs17584499 polymorphisms with type 2 diabetes susceptibility, and found that the allelic frequencies of PPAR-γ2 gene rs1801282 polymorphism showed no significant differences between type 2 diabetes and con-
control ($P=0.052$), and that the allelic frequencies of PTPRD gene rs17584499 polymorphism showed significant association with type 2 diabetes ($P=0.009$). To further explore their correlation with type 2 diabetes susceptibility, we next analyzed their relationship stratified by genotypes. As a result, the PPAR-γ2 gene rs1801282 polymorphism heterozygote CG genotypic frequency was higher in the healthy control group than that in the type 2 diabetes patients group (15.09% vs 8.63%, $P<0.05$). The PPAR-γ2 gene rs1801282 polymorphism was significantly associated with type 2 diabetes and CG genotype carriers had a relative protection of 0.515 (95% CI 0.268–0.990, $P<0.05$) in a dominant model adjusted for age, gender and BMI. The PTPRD gene rs17584499 polymorphism homozygote TT genotypic frequency was higher in type 2 diabetes patients than that in healthy controls (1.52% vs 0.94%, $P<0.05$). Since the genotypic frequency of TT was very low (1.52%), we used dominant model (CC vs CT+TT) and compared CC and CT+TT in therapeutic efficacy analysis. The rs17584499 polymorphism was significantly associated with type 2 diabetes and CT+TT genotypes carriers had a relative risk of 1.984 (95% CI 1.135–3.469, $P<0.05$) in a dominant model adjusted for age, gender and BMI.

Comparisons of baseline characteristics between type 2 diabetes patients with different genotypes
A total of 67 type 2 diabetes patients (39 male, 28 female) were treated with 30 mg pioglitazone daily for 3 months. Pioglitazone significantly decreased the concentrations of FPG ($P<0.001$), PPG ($P<0.001$), HbA1c ($P<0.001$), total cholesterol ($P<0.01$), triglyceride ($P<0.01$) and LDL-c ($P<0.01$) in type 2 diabetes patients (Table 2).

| Parameters | Before          | After           | $P$ values |
|------------|----------------|-----------------|------------|
| BMI (kg/m$^2$) | 25.15±2.77   | 24.93±2.78     | 0.091      |
| FPG (mmol/L)  | 8.34±1.20     | 7.00±0.97      | <0.001$^c$ |
| PPG (mmol/L)  | 13.15±3.24    | 10.81±2.73     | <0.001$^c$ |
| HbA1c (%)     | 7.55±1.31     | 6.73±0.87      | <0.001$^c$ |
| TC (mmol/L)   | 5.01±0.93     | 4.69±0.84      | <0.002$^c$ |
| TG (mmol/L)   | 2.00±1.14     | 1.67±0.87      | <0.001$^c$ |
| HDL-c (mmol/L)| 1.12±0.31     | 1.18±0.34      | <0.224     |
| LDL-c (mmol/L)| 3.04±0.82     | 2.72±0.75      | <0.002$^c$ |

BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. Data are given as mean±SD. $P$ values are determined by paired student’s t test. $^cP<0.01$.

There was no significant difference in baseline levels of clinical and biochemical characteristics between patients with CC genotype and CG genotype of PPAR-γ2 rs1801282 polymorphism or between patients with CC genotype and CT+TT genotypes of PTPRD rs17584499 polymorphism (Table 3).

Influence of PPAR-γ2 and PTPRD gene polymorphisms on therapeutic efficacy of pioglitazone in type 2 diabetes patients
After treatment with pioglitazone for 3 months, type 2 diabetes patients carrying rs1801282 CG genotypes showed higher FPG DV values (mmol/L) (DV -2.24±0.82) and TG DV

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### Table 1. Distribution of gene polymorphisms and association results for type 2 diabetes.

| Genotype frequency | Type 2 diabetes patients group | Healthy control group | $\Delta P$ | OR (95% CI) (Univariate analysis) | $\delta P$ | OR (95% CI) (Multivariate analysis) |
|--------------------|--------------------------------|-----------------------|------------|------------------------------------|------------|------------------------------------|
| PPAR-γ2 rs1801282  |                                |                       |            |                                    |            |                                    |
| CC                 | 180                            | 180                   | 1          | 1                                  | 1          | 1                                  |
| CG                 | 17                             | 32                    | 0.044$^b$  | 0.531 (0.285–0.991)                | 0.047$^b$  | 0.515 (0.268–0.990)                |
| PTPRD rs17584499   |                                |                       |            |                                    |            |                                    |
| CC                 | 145                            | 179                   | 1          | 1                                  | 1          | 1                                  |
| CT                 | 49                             | 31                    | 0.026$^a$  | 1.945 (1.194–3.169)                | 0.008$^a$  | 1.984 (1.135–3.469)                |
| TT                 | 3                              | 2                     | 0.042$^a$  |                                    |            |                                    |

$^aP$ values: for comparison between type 2 diabetes patients and healthy control by χ$^2$ test; $^bP$ values and their ORs: for comparison between genotypes by logistic regression analysis in dominant model; $^cP$ values and their ORs: for multivariate analyses after adjusted for age, gender and BMI. $^dP<0.05$, $^eP<0.01$. 

### Table 2. Clinical characteristics of all type 2 diabetes patients before and after pioglitazone treatment ($n=67$).

| Parameters          | Before        | After         | $P$ values |
|---------------------|--------------|--------------|------------|
| BMI (kg/m$^2$)      | 25.15±2.77   | 24.93±2.78   | 0.091      |
| FPG (mmol/L)        | 8.34±1.20    | 7.00±0.97    | <0.001$^c$ |
| PPG (mmol/L)        | 13.15±3.24   | 10.81±2.73   | <0.001$^c$ |
| HbA1c (%)           | 7.55±1.31    | 6.73±0.87    | <0.001$^c$ |
| TC (mmol/L)         | 5.01±0.93    | 4.69±0.84    | <0.002$^c$ |
| TG (mmol/L)         | 2.00±1.14    | 1.67±0.87    | <0.001$^c$ |
| HDL-c (mmol/L)      | 1.12±0.31    | 1.18±0.34    | <0.224     |
| LDL-c (mmol/L)      | 3.04±0.82    | 2.72±0.75    | <0.002$^c$ |

BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. Data are given as mean±SD. $P$ values are determined by paired student’s t test. $^cP<0.01$. 

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values (mmol/L) (DV -0.89±0.48) compared with those with rs1801282 CC genotype (DV -1.23±1.24, P<0.05; DV -0.27±0.82, P<0.05, respectively) (Table 4, Figure 1).

For PTPRD gene rs17584499, CT+TT genotypes carriers showed lower PPG DV levels (mmol/L) (DV -0.63±3.26) compared with those with CC genotype (DV -3.18±3.37, P<0.01) after treated with pioglitazone for 3 months (Table 4, Figure 2).

**Discussion**
In the present study, we explored the effects of PPAR-γ2 rs1801282 and PTPRD rs17584499 polymorphisms on pioglitazone response in Chinese Han type 2 diabetes patients. Our study suggested that diabetes risk alleles in PPAR-γ2 rs1801282 and PTPRD rs17584499 polymorphisms were asso-

**Table 3.** The baseline characteristics of all type 2 diabetes patients with various genotypes for the PPAR-γ2 rs1801282 and PTPRD rs17584499 polymorphisms before the administration of pioglitazone (n=67).

| Parameters          | PPAR-γ2 rs1801282 |          |          | PTPRD rs17584499 |          |          |
|---------------------|-------------------|----------|----------|------------------|----------|----------|
| No (male/female)    | 60 (35/25)        | 7 (4/3)  | 0.952b   | 45 (24/21)       | 22 (15/7) | 0.247a   |
| Age (year)          | 56.77±8.34        | 55.43±10.41 | 0.704c   | 55.62±7.98       | 58.68±9.33 | 0.100d   |
| Duration (month)    | 41.67±35.22       | 67.71±63.57 | 0.367d   | 42.16±39.34      | 48.96±39.58 | 0.389d   |
| BMI                 | 25.29±2.79        | 23.91±2.39 | 0.213e   | 25.18±2.59       | 25.07±3.17 | 0.713d   |
| FPG (mmol/L)        | 8.25±1.18         | 9.16±1.12 | 0.056f   | 8.36±1.28        | 8.30±1.05  | 0.989d   |
| PPG (mmol/L)        | 13.17±3.30        | 12.94±2.89 | 1.000f   | 13.48±3.24       | 12.46±3.20 | 0.225d   |
| HbA1c (%)           | 7.49±1.26         | 8.03±1.78 | 0.492g   | 7.65±1.29        | 7.34±1.36  | 0.216d   |
| TC (mmol/L)         | 4.99±0.92         | 5.23±1.08 | 0.608h   | 5.09±0.98        | 4.86±0.82  | 0.530d   |
| TG (mmol/L)         | 1.96±1.14         | 2.40±1.17 | 0.223i   | 2.06±1.22        | 1.88±0.97  | 0.694d   |
| HDL-c (mmol/L)      | 1.10±0.32         | 1.24±0.29 | 0.223i   | 1.13±0.36        | 1.09±0.19  | 0.298d   |
| LDL-c (mmol/L)      | 3.02±0.82         | 3.18±0.89 | 0.697i   | 3.06±0.90        | 2.98±0.64  | 0.841d   |

BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. *P values are determined by Pearson χ² test. †P values are assessed by two-sample t-test. ‡P values are determined by Mann-Whitney test.

**Table 4.** Comparisons of differential values (DV, post-administration minus pre-administration) in type 2 diabetes patients with different PPAR-γ2 rs1801282 and PTPRD rs17584499 polymorphisms after pioglitazone treatment (n=67).

| Parameters          | PPAR-γ2 rs1801282 |          |          | PTPRD rs17584499 |          |          |
|---------------------|-------------------|----------|----------|------------------|----------|----------|
| No (male/female)    | 60 (35/25)        | 7 (4/3)  | 0.952b   | 45 (24/21)       | 22 (15/7) | 0.247a   |
| DV FPG (mmol/L)     | -1.23±1.24        | -2.24±0.82 | 0.015i   | -1.36±1.17       | -1.29±1.39 | 0.830d   |
| DV PPG (mmol/L)     | -2.56±3.55        | -0.45±2.78 | 0.260j   | -3.18±3.37       | -0.63±3.26 | 0.006k   |
| DV HbA1c (%)        | -0.75±1.24        | -1.39±0.93 | 0.132l   | -0.92±1.31       | -0.61±1.01 | 0.303m   |
| DV TC (mmol/L)      | -0.36±0.79        | -0.10±0.66 | 0.539l   | -0.40±0.85       | -0.17±0.75 | 0.130n   |
| DV TG (mmol/L)      | -0.27±0.82        | -0.89±0.48 | 0.010l   | -0.35±0.82       | -0.30±0.79 | 0.530m   |
| DV HDL-c (mmol/L)   | -0.08±0.36        | -0.08±0.62 | 0.830l   | -0.09±0.40       | -0.00±0.38 | 0.857l   |
| DV LDL-c (mmol/L)   | -0.34±0.80        | -0.16±0.99 | 0.580i   | -0.39±0.83       | -0.18±0.77 | 0.400l   |

DV, differential value (3 months post-administration minus 0 month pre-administration); FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. *P values are determined by Pearson χ² test. †P values are assessed by two-sample t-test. ‡P values are determined by Mann-Whitney test.

**Figure 1.** Comparisons of differential values (post-administration minus pre-administration) of (A) fasting plasma glucose (FPG) and (B) triglyceride (TG) between the CC genotypes and CG genotypes of the PPAR-γ2 rs1801282 polymorphism in type 2 diabetes patients after treatment with pioglitazone. ‡P<0.05.
PTPRD was associated with type 2 diabetes and involved in insulin signal pathway. The association was first reported in a Chinese Han population GWAS. We confirmed this result and found that rs17584499 polymorphism was significantly associated with type 2 diabetes, and CT+TT genotypes carriers had a relative risk of 1.984 (95% CI 1.135–3.469, P<0.05) in a dominant model adjusted for age, gender and BMI. PTPRD, which belongs to the R2A subfamily of PTPs, was assumed to act in the regulation of insulin signaling. The R2A PTP subfamily also includes LAR, PTPRS and PTPRD, which are involved in neural development, cancer, and diabetes. LAR- and PTPRS-deficient mice showed glucose homeostasis disorders and insulin sensitivity change. PTPs play an important role in cellular insulin action regulation. The similar structure in PTPs family proteins indicate that they perform similar functions in various tissues. PTPRD may play an important role in type 2 diabetes pathogenesis but should be investigated in detail.

This is the first study to investigate the effect of PTPRD rs17584499 polymorphism on the therapeutic efficacy of pioglitazone. CT+TT genotypes patients showed lower PPG DV levels compared with those carrying CC genotype after treated with pioglitazone for 3 months. We propose that PTPRD expressed in skeletal muscle may be one of targets for pioglitazone. Thiazolidinediones improved insulin sensitivity, dependent or independent of PPAR-γ activation. It directly inhibited the mitochondrial fuel oxidation in rat isolated skeletal muscle. It also increased glucose transport in skeletal muscle cells. Furthermore, new thiazolidinedione derivative benzylidene-2,4-thiazolidinedione showed activation on PPAR-γ and inhibition on PTP1B, another member of PTPs superfamily. Rosiglitazone also inhibits PTP1B and enhances insulin activity in skeletal muscle of diabetic rats. So PTPRD might be inhibited by pioglitazone. However, further investigation is needed to validate this hypothesis.

One of the limitations of this study is the relatively small sample size. Therefore, we calculated the power values of each analysis, which ranged from 75% to 98%. Thus, we are confident that our result is reliable. Another limitation is the unavailability of pioglitazone plasma concentration. Since pioglitazone is mainly metabolized by CYP2C8, we selected patients with the CYP2C8*1*1 genotype to avoid any possible effects of CYP2C8 polymorphism on pioglitazone efficacy due to variations in the pharmacokinetics of pioglitazone.

In summary, diabetes risk alleles in PPAR-γ2 (rs1801282) and PTPRD (rs17584499) are associated with pioglitazone therapeutic efficacy. These findings may be helpful for targeted treatment with pioglitazone for type 2 diabetes. However, further studies, including studies with a large sample size, more strict clinical experiment and mechanistic studies, are needed in the future.
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Author contribution
Zhao-qian LIU, Zhao-hui MO and Hong-hao ZHOU designed the research; Qi PEI, Qiong HUANG, Min SONG and Yi ZHENG performed the research; Qiong HUANG and Guo-ping YANG analyzed the data; and Qi PEI, Ying-chun ZHAO, Ji-ye YIN and Zhao-qian LIU wrote the paper.

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