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Effects of *ABCA1* variants on rosiglitazone monotherapy in newly diagnosed type 2 diabetes patients[1]

Jie WANG[2], Yu-qian BAO[2], Cheng HU[2], Rong ZHANG[2], Cong-rong WANG[2], Jun-xi LU[2], Wei-ping JIA[2,3], Kun-san XIANG[2]

Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

Key words

pharmacogenetics; rosiglitazone; ATP-binding cassette transporter subfamily A number 1; single nucleotide polymorphisms

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[3]Correspondence to Dr Wei-ping JIA.
Phn 86-21-6436-9181, ext 8922.
Fax 86-21-6436-8031.
E-mail wpjia@sjtu.edu.cn

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Abstract

Aim: The aim of the present study was to investigate the relationship between R219K, M883I, and R1587K variants of the ATP-binding cassette transporter subfamily A number 1 (*ABCA1*) gene and response to rosiglitazone treatment in newly diagnosed patients with type 2 diabetes. **Methods:** A total of 105 diabetic patients with no history of antihyperglycemia medication were treated with rosiglitazone (4 or 8 mg daily) for 48 weeks. Three non-synonymous variants R219K, M883I, and R1587K, were genotyped in all patients. **Results:** Ninety-three patients completed the entire study. The R219K variant of *ABCA1* had an effect on rosiglitazone response with the per-allele odds ratio of 2.04 for treatment failure ($P<0.05$). The RR homozygotes had a better improvement in indicators of insulin sensitivity, as determined by a significantly greater decrease in the homeostasis model assessment index of insulin resistance (–2.39±0.46 *vs* –0.69±0.51, $P<0.05$). No genotype-phenotype association was detected for M883I and R1587K. **Conclusion:** The R219K variant of *ABCA1* was associated with the therapeutic effect of rosiglitazone. The RR homozygotes had a better response to rosiglitazone treatment in terms of insulin sensitivity improvement than minor K allele carriers. Neither the M883I nor R1587K variant of the *ABCA1* gene was associated with rosiglitazone response.

Introduction

Type 2 diabetes is a progressive and complex metabolic disorder, which is characterized by chronic hyperglycemia resulting from insulin resistance (IR) and deficiency in insulin secretion[1]. Reduced insulin action in the liver, adipose tissue, and skeletal muscle plays a major role in the pathogenesis of type 2 diabetes[2]. Insulin sensitizer thiazolidinediones (TZDs) are oral hypoglycemic agents acting predominantly by enhancing peripheral insulin sensitivity, reducing glucolipotoxicity, and endogenous insulin secretory demands, and preserving β-cell function[3]. They are agonists of nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ) that heterodimerizes with the retinoid X receptor, thereby leading to the transcription of genes involved in glucose and lipid homeostasis[4]. As a new generation of oral antidiabetic drug, TZDs improve insulin sensitivity and reduce glycemia, insulinemia, and dyslipidemia in patients with type 2 diabetes[5].

However, it is reported that the clinical response to TZDs varies. The Prevention of Diabetes study observed that approximately 36% patients did not respond to troglitazone treatment effectively[6]. Wide interindividual variability in drug response may be due to multiple factors, including age, sex, race, accommodation, organ function, placebo effect, clinical stage, and the severity of disease. Genetic polymorphisms in the targets of drug therapy have been increasingly recognized as an important mechanism responsible for the interindividual differences in drug efficacy[7]. Previous pharmacogenetical research of TZDs analyzed single nucleotide polymorphisms (SNPs) on *PPARG*, *ADIPOQ*, and *CYP2C8*[8–14], indicating that genetic variants might be related to variations in the response to TZD treatment.

The ATP-binding cassette transporter subfamily A number 1 (*ABCA1*) gene is located on chromosome 9q31.1 and is composed of 50 exons extending across a genomic region of

147 kb. The encoded transmembrane protein functions as a transporter of cellular cholesterol and phospholipid to lipid-poor apolipoproteins, especially apolipoprotein A1, which is crucial for high-density lipoprotein biogenesis, as well as the reverse cholesterol transport[15]. Genetic studies have shown that *ABCA1* might be a candidate gene of type 2 diabetes. Several genetic variants were associated with diabetes and prediabetic intermediate traits[16,17]. A recent study by Brunham *et al*[18] further investigated its functional role in β cells. They demonstrated that Abca1 probably had an effect on islet cholesterol homeostasis, subsequently influencing glucose tolerance and insulin secretion. In addition, they found that Abca1 influenced rosiglitazone response in mice. However, whether ABCA1 plays a similar role in humans is yet an unanswered question. Thus, we hypothesized that variants of *ABCA1* might contribute to interindividual variation in response to rosiglitazone therapy. In this study, we selected 3 non-synonymous variants of *ABCA1*, R219K, M883I, and R1587K, to evaluate their effects on rosiglitazone treatment in newly diagnosed patients with type 2 diabetes.

Materials and methods

Patients and study design A total of 105 newly diagnosed patients with type 2 diabetes, defined according to the World Health Organization criteria[19], were derived from the outpatient clinics at 10 hospitals in Shanghai. All patients were naive to prior antidiabetic therapy and treated with rosiglitazone for 48 weeks. We enrolled patients 30–70 years of age, glycated hemoglobin ≥6.5%, and a body mass index (BMI) ≥18.5 kg/m^2. For the female patients, postmenopause, surgical sterilization, or effective contraception was required. Excluded criteria were: (i) type 1 diabetes, gestational diabetes, or other specific types; (ii) acute or chronic complications in need of insulin therapy; (iii) significant cardiocerebral, hepatic or nephric disease; (iv) malignant tumor, hematological disease, autoimmune disease, psychiatric disease, or significant digestion and absorption disturbances; (v) current exposure to medication affecting glucose metabolism, such as glucocorticoid; (vi) long-term alcohol or drug abuse; (vii) fasting plasma glucose >13 mmol/L (234 mg/dL) and/or 2 h post-load plasma glucose >18 mmol/L (364 mg/dL); and (viii) blood pressure >180/110 mmHg.

The initial dose was 4 mg/d and escalated to 8 mg/d in patients who failed to attain glycemic targets of fasting plasma glucose >7 mmol/L (126 mg/dL) and/or 2 h plasma glucose >11 mmol/L (200 mg/dL). Patients with glycated hemoglobin was ≥8% or fasting plasma glucose >13 mmol/L (234 mg/dL) or 2 h plasma glucose >18 mmol/L (364 mg/dL) twice (a maximal interval of 6 d) were withdrawn from the study. This study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Shanghai, China). Each patient provided written informed consent before participating in the study.

Anthropometric measurements General anthropometric parameters, including height (in m), weight (in kg), waist and hip circumferences (in cm), and systolic and diastolic blood pressure (in mmHg) were measured in all patients at baseline and 48 weeks after the initiation of rosiglitazone therapy. BMI and waist–hip ratio were calculated as weight/height^2 and waist/hip, respectively.

Clinical laboratory tests Blood samples were collected after an overnight fast and 2 h after a 75 g oral glucose tolerance test (OGTT). Plasma glucose concentrations were measured using the glucose oxidase-peroxidase method with commercial kits (Shanghai Biological Products Institution, Shanghai, China). Glycated hemoglobin values were determined by high-performance liquid chromatography performed on a Bio-Rad Variant II hemoglobin testing system (Bio-Rad Laboratories, Hercules, CA, USA). Serum lipid profiles, including total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured with a type 7600-020 Automated analyzer (Hitachi, Tokyo, Japan). An arginine stimulation test was performed to estimate acute insulin secretion of islet β cells. The serum levels of insulin and proinsulin were measured in duplicate at 0, 2, 4, and 6 min ($insulin_0$, $insulin_2$, $insulin_4$, $insulin_6$; $proinsulin_0$, $proinsulin_2$, $proinsulin_4$, $proinsulin_6$) after an intravenous injection of 50 mL arginine solution at the concentration of 10%, using radioimmunoassay (Linco Research, St Charles, MO, USA). The intra-assay coefficients of variation were less than 10%. The evaluation of IR and β-cell secretion at baseline was calculated using the homeostasis model assessment (HOMA) index[20], with the following formula: HOMA–IR=fasting insulin×fasting plasma glucose/22.5, HOMA of β-cell function (HOMA–B)=20×fasting insulin/(fasting plasma glucose–3.5). The amount of acute phase insulin and proinsulin secretion after arginine stimulation was calculated with the following equation: Acute insulin secretion=($insulin_2$+$insulin_4$+$insulin_6$)/3–$insulin_0$; acute proinsulin secretion=($proinsulin_2$+$proinsulin_4$+$proinsulin_6$)/3–$proinsulin_0$.

Genotyping Genomic DNA was extracted from peripheral blood leucocytes in the whole-blood samples. The SNPs were detected by the PCR restriction fragment length polymorphism. PCR amplification was performed on the GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA, USA). Amplicons were subsequently digested

overnight with restriction enzymes. Following electrophoresis in 12% polyacrylamide gels, the digestion products were stained with ethidium bromide and visualized in the Gel Doc 2000 gel documentation system (Bio-Rad Laboratories, USA). Sixteen random samples were duplicated to confirm the genotyping accuracy, and no discrepancy was detected.

Definition of rosiglitazone responsiveness As there are no generally accepted criteria to divide patients into responders and non-responders, we used 2 methods to define the response to rosiglitazone treatment based on previous clinical studies[11,21–23]. Criterion 1 is a decrease of >15% in all glycemic measures of glycated hemoglobin, fasting, and 2 h plasma glucose after a 75 g glucose OGTT. Criterion 2 is a decrease of 0.5% in glycated hemoglobin. The withdrawals owning to inadequately controlled blood glucose or glycated hemoglobin were defined as non-responders in the analysis.

Statistical analysis Data were shown as mean±SEM or N (%). Allele frequencies were calculated by gene counting. Tests of the Hardy–Weinberg equilibrium were performed[24]. Pairwise linkage disequilibrium was determined by calculating $|D'|$ and r^2 using Haploview (version 3.32)[25]. The differences between groups were tested using Student's *t*-test or Kruskal–Wallis test when appropriate. Genotype distribution differences between responders and non-responders were compared by Fisher's exact test or χ^2-test. Considering few subjects of rare allele homozygotes, the genotype–phenotype associations were analyzed between common allele homozygotes and rare allele carriers. A 2-tailed *P*-value ≤0.05 was considered statistically significant. All statistical analyses were performed using SAS for Windows (version 6.12; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of the patients before and after rosiglitazone treatment Of the 105 patients enrolled, 93 patients (65 men and 28 women, mean age 52.09±9.09 years) completed the entire study. Twelve patients were withdrawn, among whom 5 patients were attributed to inadequately controlled blood glucose or glycated hemoglobin levels; 1 patient had abnormal liver function and 6 patients were lost to follow up.

The baseline and post-therapy clinical characteristics of the study group are summarized in Table 1. After 48 weeks of rosiglitazone therapy, the blood glucose and glycated hemoglobin levels significantly decreased in comparison with baseline ($P<0.01$). Meanwhile, significant improvements in HOMA–IR ($P<0.01$), HOMA–B ($P<0.01$), and acute proinsulin secretion after arginine stimulation ($P<0.01$) were observed. With regards to the lipid profiles, only the increase in HDL-C level was observed ($P<0.01$).

Table 1. Clinical characteristics of the study group at baseline and after 48 weeks of rosiglitazone treatment. $^cP<0.01$ *vs* baseline.

	Baseline	48 weeks
BMI (kg/m^2)	25.08±0.31	24.85±0.37
Waist (cm)	88.58±0.90	87.37±0.96
Waist–hip ratio	0.91±0.01	0.90±0.01
Systolic blood pressure (mmHg)	129.19±1.63	125.41±1.84
Diastolic blood pressure (mmHg)	83.44±0.99	79.22±0.99^c
Fasting plasma glucose (mmol/L)	9.09±0.18	6.58±0.13^c
2 h plasma glucose (mmol/L)	13.51±0.30	8.87±0.25^c
Glycated hemoglobin (%)	8.24±0.15	6.36±0.09^c
Fasting insulin (μU/mL)	14.22±0.69	16.33±1.02
HOMA-IR	5.69±0.28	4.80±0.37^c
HOMA-B	57.51±3.76	114.17±6.43^c
Acute insulin secretion (μU/mL)	30.69±2.38	30.15±2.85
Acute proinsulin secretion (μU/mL)	11.05±1.10	7.28±0.81^c
Total cholesterol (mmol/L)	5.28±0.11	5.46±0.13
HDL-C(mmol/L)	1.22±0.03	1.31±0.03^c
LDC-C (mmol/L)	3.26±0.09	3.18±0.09
Triglyceride (mmol/L)	2.17±0.17	2.25±0.19

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Association between *ABCA1* genetic variants and the response rate of rosiglitazone treatment The genotype distributions of 3 SNPs were consistent with the Hardy–Weinberg equilibrium. By calculating $|D'|$ and r^2, a low extent of linkage disequilibrium was detected among them (Table 2). Therefore, the effects of 3 SNPs on rosiglitazone treatment were analyzed, respectively.

The total response rate of the cohort was 0.398 and 0.782 defined by the 2 criteria, respectively. The genotype fre-

Table 2. Pairwise linkage disequilibrium analyses among *ABCA1* gene R219K, M883I and R1587K variants.

$\|D'\|$ \ r^2	R219K	M883I	R1587K
R219K		0.041	0.027
M883I	0.372		0.031
R1587K	0.191	0.377	

Linkage disequilibrium estimates are shown as $|D'|$ in the lower triangle and r^2 in the upper triangle.

quencies according to the therapeutic responses are shown in Table 3. According to the first criterion, R219K was associated with response to rosiglitazone treatment with more treatment failures in the rare allele homozygotes KK. Eighty-eight percent of the KK homozygotes failed compared with only 52% of the RR homozygotes. The heterozygote RK group showed an intermediate response rate. The per-allele odds ratio for treatment failure was 2.04 (P<0.05). According to the second criterion, although not significant, the same trend was observed; the KK homozygotes had a poor response to rosiglitazone therapy. No significant effect of M883I or R1587K on rosiglitazone therapy was observed.

Association between *ABCA1* genetic variants and the effect of rosiglitazone treatment on clinical features The association between R219K and clinical features is shown in Table 4. Here we detected a significantly higher 2-h plasma glucose (P<0.05) and waist–hip ratio (P<0.05) at baseline in the RR homozygotes compared with minor K allele carriers. The RR homozygotes also showed greater though non-significant reductions in fasting and 2-h plasma glucose as well as the glycated hemoglobin level after 48 weeks' treatment. With respect to insulin sensitivity, the decline in the HOMA–IR value was significantly greater in RR homozygotes (P<0.05). As for the lipid profiles, we found no significant differences between the 2 groups. Neither M883I nor R1587K was observed to be associated with clinical features at baseline or after treatment (Tables 5 and 6).

Discussion

Pharmacogenetics involve the study of contributions of inherited differences in drug disposition or drug targets to drug response, with the ultimate goal to select the optimal drug therapy and dosages through the use of genetically-guided, individualized treatment[26]. Rosiglitazone, a member of TZDs, is a widely used insulin sensitizer. Data from ADOPT[22] and DREAM[27] showed that initial treatment with rosiglitazone could slow the progressive loss of glycemic control in diabetic patients and reduce diabetes incidences, as well as regress to normoglycemia in individuals with impaired fasting glucose and/or impaired glucose tolerance.

In this study, we found that the R219K variant of the *ABCA1* gene was associated with response to rosiglitazone therapy in newly diagnosed type 2 diabetes patients. The RR homozygotes showed a lower failure rate and a better improvement in insulin sensitivity after 48 weeks' treatment. Rosiglitazone increases the expression of *ABCA1* through a PPARγ-LXRα-ABCA1 pathway, thereby regulating cholesterol homeostasis[28,29]. It is well recognized that accumulation of lipids in tissues leads to β-cell dysfunction and IR[30–32]. Brunham *et al*[18] further demonstrated that *Abca1* had an effect on β-cell function through its role on cholesterol accumulation in islets. Their results indicated that Abca1 mainly affected insulin secretion. However, we failed to find any association between *ABCA1* genetic variants and acute insulin or proinsulin secretion after arginine stimulation. The main outcome of our study was that R219K was associated with insulin sensitivity improvement. The underlying mechanism is still unknown.

We did not detect significant differences in lipid profiles between the RR homozygotes and minor K allele carriers, although the latter were suggested to be associated with decreased triglyceride and a trend toward increased HDL-C in some[33,34], but not all[35] association studies. As serum cholesterol levels are influenced by many factors, we sup-

Table 3. Genotype and allele distributions between responders and non-responders of *ABCA1* genetic variants. [b]P<0.05 *vs* responder by criterion 1.

	Criterion 1			Criterion 2		
R219K						
	RR	RK	KK	RR	RK	KK
Responder	14 (0.483)	19 (0.452)	2 (0.118)	24 (0.889)	33 (0.767)	11 (0.647)
Non-responder[b]	15 (0.517)	23 (0.548)	15 (0.882)	3 (0.111)	10 (0.233)	6 (0.353)
M883I						
	MM	MI	II	MM	MI	II
Responder	15 (0.319)	15 (0.455)	5 (0.625)	33 (0.717)	29 (0.878)	6 (0.750)
Non-responder	32 (0.681)	18 (0.545)	3 (0.375)	13 (0.283)	4 (0.121)	2 (0.250)
R1587K						
	RR	RK	KK	RR	RK	KK
Responder	13 (0.394)	18 (0.400)	4 (0.400)	26 (0.788)	37 (0.822)	5 (0.556)
Non-responder	20 (0.606)	27 (0.600)	6 (0.600)	7 (0.212)	8 (0.178)	4 (0.444)

Table 4. Association between ABCA1 R219K variant and clinical features. [b]$P<0.05$ *vs* RR.

Parameter		RR (n=29)	KX (n=64)
Drug dose		5.47±0.36	5.66±0.25
Fasting plasma glucose (mmol/L)	Baseline	9.28±0.29	8.99±0.22
	48 weeks	6.57±0.19	6.59±0.17
	Δ value	−2.79±0.30	−2.28±0.27
2-h Plasma glucose (mmol/L)	Baseline	14.42±0.49	13.06±0.37[b]
	48 weeks	9.64±0.48	8.53±0.29[b]
	Δ value	−4.72±0.77	−4.27±0.50
Glycated hemoglobin (%)	Baseline	8.15±0.22	8.28±0.19
	48 weeks	6.20±0.15	6.43±0.11
	Δ value	−2.09±0.27	−1.73±0.22
HOMA-IR	Baseline	5.77±0.41	5.64±0.37
	48 weeks	3.93±0.30	5.16±0.51
	Δ value	−2.39±0.46	−0.69±0.51[b]
HOMA-B	Baseline	56.05±6.22	58.21±4.72
	48 weeks	102.15±11.20	119.27±7.79
	Δ value	43.89±7.72	57.14±9.12
Fasting insulin (μU/mL)	Baseline	14.31±1.09	14.18±0.87
	48 weeks	13.38±0.73	17.64±1.44
	Δ value	−1.40±1.04	2.93±1.50
Acute insulin secretion (μU/mL)	Baseline	30.96±4.24	30.57±2.89
	48 weeks	29.64±4.93	30.37±3.52
	Δ value	−2.54±4.79	−1.06±4.23
Acute proinsulin secretion (μU/mL)	Baseline	10.17±1.43	11.47±1.49
	48 weeks	5.86±1.04	8.06±1.07
	Δ value	−5.02±1.67	−4.03±1.55
BMI (kg/m^2)	Baseline	25.33±0.60	24.97±0.35
	48 weeks	24.56±0.74	24.98±0.42
	Δ value	−0.34±0.27	0.05±0.16
Waist (cm)	Baseline	90.74±1.82	87.58±1.00
	48 weeks	87.67±2.13	87.23±1.02
	Δ value	−2.00±0.94	−0.35±0.61
Waist-hip ratio	Baseline	0.93±0.01	0.90±0.01[b]
	48 weeks	0.90±0.01	0.90±0.01
	Δ value	−0.02±0.01	−0.00±0.01
HDL-C (mmol/L)	Baseline	1.15±0.03	1.25±0.03
	48 weeks	1.29±0.05	1.32±0.04
	Δ value	0.13±0.06	0.07±0.03

HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol

Table 5. Association between ABCA1 M883I variant and clinical features.

Parameter		MM (n=49)	IX (n=44)
Drug dose		5.68±0.28	5.51±0.29
Fasting plasma glucose (mmol/L)	Baseline	8.89±0.23	9.29±0.27
	48 weeks	6.53±0.17	6.65±0.21
	Δ value	−2.24±0.29	−2.65±0.31
2-h plasma glucose (mmol/L)	Baseline	13.54±0.46	13.48±0.39
	48 weeks	8.93±0.29	8.80±0.43
	Δ value	−4.24±0.60	−4.60±0.57
Glycated hemoglobin (%)	Baseline	8.30±0.23	8.18±0.18
	48 weeks	6.40±0.12	6.31±0.13
	Δ value	−1.84±0.29	−1.84±0.17
HOMA-IR	Baseline	5.71±0.39	5.66±0.41
	48 weeks	4.53±0.39	5.10±0.66
	Δ value	−1.38±0.49	−0.98±0.62
HOMA-B	Baseline	60.73±5.75	54.11±4.78
	48 weeks	107.63±6.94	121.73±11.28
	Δ value	42.38±9.45	65.68±9.56
Fasting insulin (μU/mL)	Baseline	14.60±1.02	13.81±0.91
	48 weeks	16.03±1.33	16.62±1.63
	Δ value	1.05±1.67	2.17±1.36
Acute insulin secretion (μU/mL)	Baseline	31.15±3.49	30.21±3.25
	48 weeks	27.69±3.35	33.30±4.87
	Δ value	−3.37±4.70	0.63±4.45
Acute proinsulin secretion (μU/mL)	Baseline	10.43±1.65	11.70±1.46
	48 weeks	6.88±1.07	7.97±1.24
	Δ value	−3.64±1.88	−5.15±1.32
Waist (cm)	Baseline	88.05±1.19	89.13±1.37
	48 weeks	86.98±1.24	87.80±1.49
	Δ value	−0.53±0.75	−1.24±0.71
BMI (kg/m^2)	Baseline	24.92±0.45	25.25±0.41
	48 weeks	24.47±0.54	25.27±0.49
	Δ value	−0.16±0.22	0.02±0.18
Waist–hip ratio	Baseline	0.90±0.01	0.91±0.01
	48 weeks	0.90±0.01	0.90±0.01
	Δ value	−0.01±0.01	−0.01±0.01
HDL-C (mmol/L)	Baseline	1.22±0.04	1.21±0.03
	48 weeks	1.35±0.05	1.26±0.04
	Δ value	0.12±0.04	0.05±0.03

HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol

pose that a small change in *ABCA1* activity could affect rosiglitazone response without markedly impacting circulating cholesterol profiles.

There are several limitations of this study that should be noted. First, the sample size of this study is relatively small, thus we do not have enough statistical power to detect effects of genetic variants and HDL-C levels. Although previous studies reported that M883I had an impact on ABCA1 function[36] and R1587K was associated with HDL-C level[33,37], we failed to detect any effect of these 2 variants on rosiglitazone treatment. We cannot exclude the possibility that the sample size may be one of the reasons. Second, as most variables of our study are in skew distribution, the Kruskal–Wallis test was the main method used to analyze the association between genotypes and phenotypes, thus we could not adjust for the effect of confounding factors, such as drug dose.

Table 6. Association between *ABCA1* R1587K variant and clinical features.

Parameter		RR (n=32)	KX (n=61)
Drug dose		5.49±0.33	5.67±0.26
Fasting plasma glucose (mmol/L)	Baseline	9.26±0.31	8.97±0.21
	48 weeks	6.69±0.21	6.53±0.17
	Δ value	–2.47±0.39	–2.42±0.25
2-h plasma glucose (mmol/L)	Baseline	13.49±0.48	13.53±0.39
	48 weeks	8.46±0.37	9.08±0.33
	Δ value	–4.44±0.75	–4.40±0.50
Glycated hemoglobin (%)	Baseline	8.05±0.19	8.36±0.21
	48 weeks	6.23±0.12	6.43±0.12
	Δ value	–1.76±0.18	–1.88±0.25
HOMA-IR	Baseline	6.04±0.55	5.47±0.30
	48 weeks	5.54±0.88	4.41±0.32
	Δ value	–0.99±0.92	–1.30±0.35
HOMA-B	Baseline	60.24±7.69	55.83±3.84
	48 weeks	116.63±11.45	112.88±7.81
	Δ value	50.85±13.44	54.43±7.71
Fasting insulin (μU/mL)	Baseline	14.90±1.35	13.80±0.73
	48 weeks	18.73±2.47	14.94±0.80
	Δ value	3.08±2.63	0.73±0.87
Acute insulin secretion (μU/mL)	Baseline	29.55±3.80	31.40±3.07
	48 weeks	37.06±6.26	26.47±2.73
	Δ value	6.08±7.33	–5.80±2.86
Acute proinsulin secretion (μU/mL)	Baseline	9.71±1.84	11.87±1.38
	48 weeks	8.49±1.53	6.79±0.94
	Δ value	–2.22±2.31	–5.45±1.33
Waist (cm)	Baseline	88.32±1.28	88.74±1.24
	48 weeks	86.73±1.45	87.71±1.26
	Δ value	–1.28±0.96	–0.64±0.60
BMI (kg/m^2)	Baseline	25.03±0.44	25.11±0.42
	48 weeks	24.56±0.62	25.00±0.46
	Δ value	–0.39±0.25	0.10±0.17
Waist-hip ratio	Baseline	0.90±0.01	0.91±0.01
	48 weeks	0.89±0.01	0.90±0.01
	Δ value	–0.01±0.01	–0.01±0.01
HDL-C (mmol/L)	Baseline	1.26±0.05	1.19±0.03
	48 weeks	1.34±0.07	1.29±0.04
	Δ value	0.11±0.05	0.08±0.03

HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta cell function; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol

However, we did not detect a significant difference in drug dose between groups. The K allele carriers of the R219K variant showed a relatively higher mean drug dose compared with the RR homozygotes, which may also reflect a poorer response to rosiglitazone treatment. Third, a 48 week follow-up period might be inadequate to see the thorough therapeutic effect, but as documented in the ADOPT study[22], the maximal treatment effect of rosiglitazone on glycated hemoglobin was achieved within one year. Considering the compliance of patients, the effect of genotypes on long-term drug response would be better studied in a carefully controlled clinical trial.

In conclusion, we provide evidence that the R219K variant of the *ABCA1* gene either directly or as a marker with additional functional variant in linkage disequilibrium, has an effect on response to rosiglitazone treatment. Never-theless, we are at an early stage of defining pharmacogenetic determinants of rosiglitazone treatment response. Long-term follow-up studies with large samples are needed to further confirm our findings and allow individualizing therapy based on genomic information.

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