



ADIPOR2 variant is associated with higher fasting glucose level in non-diabetic Chinese Han population

Na Liu^{1,2,3} · Guihua Yang^{1,2,3} · Mei Hu^{1,2,3} · Jing Han^{1,2,3} · Yuyu Cai^{1,2,3} · Zhiying Hu^{1,2,3} · Chundi Jia^{1,2,3} · Man Zhang^{1,2,3} 

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Abstract

A high but normal fasting plasma glucose level in adults is a marker for insulin resistance and future development of type 2 diabetes mellitus. We aimed to investigate whether ADIPOR2 variants are associated with increased fasting plasma glucose (FPG) in non-diabetic Chinese Han subjects who had normal FPG levels. This study included 2038 subjects among the non-diabetic Chinese Han population. The ADIPOR2 polymorphisms were genotyped by the TaqMan method. For the analysis, participants were divided into low-normal FPG group (FPG < 4.88 mmol/L) and high-normal FPG group (6.1 mmol/L > FPG ≥ 4.88 mmol/L). We identified five single nucleotide polymorphisms (SNPs) of ADIPOR2 gene: rs10773989, rs2370055, rs9300298, rs10773983, and rs13611594. There was no significant difference in FPG levels between different genotypes of rs10773989, rs2370055, rs9300298, and rs13611594. Our data showed a significant association of rs10773983 with higher FPG levels, fasting insulin levels, and homeostatic model assessment of insulin resistance (HOMA-IR) in A-allele carriers ($p = 0.006$, $p < 0.001$, and $p < 0.001$, respectively). The subjects in high FPG group had higher median fasting insulin level (9.25 vs 8.16 $\mu\text{IU/mL}$, $p = 0.003$) and higher HOMA-IR (2.21 vs 1.58, $p < 0.001$) than those in normal FPG group. Subjects with the A-allele of rs10773983 compared to subjects with G-allele had 1.222-fold higher risk for high-normal FPG (OR = 1.222, 95%CI = 1.010–1.478, $p = 0.039$). Our findings suggest that ADIPOR2 rs10773983 polymorphism may be associated with an increased risk of high-normal FPG among non-diabetic Chinese Han subjects who have normal FPG levels.

Keywords Fasting plasma glucose · Single nucleotide polymorphisms · Genotype · Adiponectin receptor 2

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem, and a continuous increase in the prevalence of type 2 diabetes in China has occurred over a very short time [1]. Early identification of people at high risk of developing type 2 diabetes may help them delay or prevent the dysglycemia. Recent reports have suggested that a high but normal fasting

plasma glucose level in adults is a significant risk factor for future development of type 2 diabetes mellitus [2, 3]. Adiponectin is a hormone secreted by adipocytes that acts as an insulin-sensitizing and anti-diabetic adipokine [4, 5]. Two related receptors for adiponectin, termed adiponectin receptor 1 (ADIPOR1) and adiponectin receptor 2 (ADIPOR2), were identified as a mediator in the adiponectin signaling pathway through activation of 5' AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR α) [6]; ADIPOR2 is most abundantly expressed in the liver and correlates positively with insulin sensitivity [7]. Several studies have investigated the role of ADIPOR2 variants in the development of T2DM in several human populations, yielding controversial results [8–10]. However, it is still not clear whether ADIPOR2 variants are related to the increased fasting plasma glucose (FPG) within the normoglycemic range, which may indicate the earliest stages of insulin resistance or dysglycemic states. The aim of this study is to characterize the association between ADIPOR2

✉ Man Zhang
zhangman@bjsjth.cn

¹ Clinical Laboratory Medicine, Beijing Shijitan Hospital, Capital Medical University, 10 Teyi Road, Haidian District, Beijing 100038, China

² Peking University Ninth School of Clinical Medicine, 10 Teyi Road, Haidian District, Beijing 100038, China

³ Beijing Key Laboratory of Urinary Cellular Molecular Diagnostics, 10 Teyi Road, Haidian District, Beijing 100038, China

SNPs and FPG levels within the normal range (< 6.1 mmol/L) in non-diabetic Chinese Han population.

Methods

Subjects This cross-sectional community study initially included 2472 Han Chinese subjects who were referred for health screening at Beijing Shijitan Hospital between January 2012 and December 2013. The physical examination included determination of the height, weight, waist circumference, and seated BP. BMI (kg/m^2) was calculated as weight (kg) divided by height (m) [2]. Lipid profile and HbA1c were tested and recorded for all the subjects. Family history of diabetes, according to self-report questionnaire data, was recorded. Exclusion criteria for this study included either diagnosed type 1 or type 2 diabetes; fasting plasma glucose level ≥ 6.1 mmol/L [11]; HbA1c $\geq 6.0\%$ [12]; medical history of cardiovascular or cerebrovascular diseases; history of cancer; chronic renal, liver, or inflammatory bowel disease; and BMI (in kg/m^2) < 20 and > 35 . After these exclusions, 2038 subjects were included in this study. The study protocol was approved by the Beijing Shijitan Hospital Ethics Committee, Capital Medical University. Written informed consent was obtained from all the participants before their enrolment in the study.

SNP selection and genotyping Total genomic DNA samples were obtained from the whole blood samples using the RelaxGene Blood DNA System (Tiangen Biotech, Beijing, China). SNPs located in different haplotype blocks of ADIPOR2 genes for this study were selected based on HapMap using Data Release 27 for the Chinese population (Chinese Han from Beijing-CHB). Tag SNPs were chosen in SNPs with minor allele frequency ≥ 0.1 and Hardy–Weinberg equilibrium (HWE) p value > 0.05 , using Tagger in Haploview software (Broad Institute, Cambridge, MA). The criterion for r^2 was set at 0.8. We used the pairwise mode and obtained a minimal set of tagging SNPs: rs10773989, rs2370055, rs9300298, rs10773983, and rs13611594. The SNPs were genotyped using the TaqMan real-time PCR assays (Applied Biosystems). The TaqMan genotyping reaction was amplified on a GeneAmp PCR system 7000 (Applied Biosystems) (95°C for 3 min, followed by 40 cycles of 95°C for 3 s and 60°C for 20 s), and fluorescence was detected on an ABI Prism sequence detector (Applied Biosystems).

Biochemical measurements Blood samples were drawn from subjects after an overnight fast and were immediately centrifuged at 2800 rpm for 15 min at 4°C . The plasma was kept at -80°C . The concentrations of plasma glucose levels, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglyceride (TG), and total cholesterol (TC) were detected by an automatic biochemical

analyzer (Hitachi 7080, Tokyo, Japan). HbA1c levels were conducted using automated glycohemoglobin analyzer (TOSOH HLC-723G8, Tokyo, Japan). Quantitative measurements of plasma insulin concentration were measured by a chemiluminescent immunoassay using a Liaison analyzer (DiaSorin, Saluggia, Italy). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated following a method previously described by Matthews et al.

Statistical analysis Continuous variables are presented as mean \pm standard deviation if symmetrically distributed or as medians and interquartile ranges if distributed asymmetrically (lipid parameters, fasting plasma glucose level, fasting plasma insulin levels). The differences between groups were tested by independent samples t test or Mann-Whitney U tests. Hardy–Weinberg equilibrium test was assessed for each SNP with Pearson's chi-square test. Demography, metabolic parameters, and genotype distribution of rs10773983 were compared between low-normal FPG and high-normal FPG groups using the chi-square test, independent samples t test, or Mann-Whitney U test as appropriate. Multivariate logistic regression analysis was used to analyze association between rs10773983 polymorphism and high-normal FPG by adjusting for other variables, such as age, sex, family history of diabetes, BMI, triglyceride, total cholesterol, HDL-c, and LDL-c. A two-tailed p value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 22.0 (SPSS Inc. Chicago, IL, USA).

Results

The overall study population consisted of 2038 subjects. The demographic and clinical characteristics of the population studied are shown in Table 1. We genotyped the SNPs

Table 1 Basic characteristics of the people studied

Characteristics	All ($n = 2038$)
Male, % (n)	51.7 (1053)
Age (years)	46.8 ± 12.8
Family history of diabetes, % (n)	7.65 (156)
BMI (kg/m^2)	24.0 (21.8–26.3)
FPG (mmol/L)	5.19 (4.83–5.55)
Total cholesterol (mmol/L)	5.34 (4.61–6.14)
Triglycerides (mmol/L)	1.32 (0.91–2.04)
HDL-c (mmol/L)	1.33 (1.12–1.57)
LDL-c (mmol/L)	3.19 (2.49–3.74)
HbA1c (%)	4.9 (4.8–5.2)
Fasting insulin ($\mu\text{IU}/\text{mL}$)	15.62 (9.56–22.06)

Data are shown as mean \pm SD or median (interquartile range)

FPG fasting plasma glucose, HDL high-density lipoprotein, LDL low-density lipoprotein, BMI body mass index

(rs10773989, rs2370055, rs9300298, rs10773983, and rs13611594) in ADIPOR2 in the cohort. All of the tested ADIPOR2 SNPs were in Hardy–Weinberg equilibrium ($p > 0.05$). None of the rs10773989, rs9300298, rs2370055, or rs13611594 was significantly associated with FPG, HDL-c, LDL-c, BMI, triglycerides, and total cholesterol levels. For the sequence variant identified in rs10773983, 707 (34.7%) had homozygote form of G/G, while 338 (16.6%) were homozygote (A/A), and 993 (48.7%) were heterozygotes (G/A). The association between the rs10773983 genotypes and clinical characteristics was analyzed further under three different genetic models as shown in Table 2. No significant difference was observed in age, BMI, HbA1c, TC, family history of diabetes, TG, and LDL-c between different variants of rs10773983. However, there was a significant association of rs10773983 with higher FPG levels, fasting insulin levels, and HOMA-IR in A-allele carriers ($p = 0.006$, $p < 0.001$, and $p < 0.001$, respectively).

Subjects were further divided into two groups according to their FPG levels: low-normal FPG group with FPG < 4.88 mmol/L and high-normal FPG group with FPG ≥ 4.88 mmol/L. The median FPG level in high-normal FPG group was higher than that of normal group (5.37 vs 4.57 mmol/L, $p < 0.001$). The subjects in high FPG group were significantly older (48.8 ± 12.1 years vs 41.7 ± 12.9 years, $p < 0.001$) and had higher median total cholesterol level (5.56 vs 4.86 mmol/L, $p < 0.001$), higher median triglyceride level (1.44 vs 1.09 mmol/L, $p < 0.001$), higher median LDL-c level (3.22 vs 2.79 mmol/L, $p < 0.001$), higher medial BMI (24.2 vs 23.3 kg/m², $p < 0.001$), higher median fasting insulin level (9.25 vs 8.16 μ IU/mL, $p = 0.003$), higher

HOMA-IR (2.21 vs 1.58, $p < 0.001$) than those in normal FPG group as shown in Table 3. In addition, more individuals in the high-normal FPG group have family history of diabetes than those in normal FPG group (8.54 vs 5.41%, $p = 0.036$). No significant difference in gender distribution or HDL-c level was observed between the two groups (Table 3). We subsequently investigated the distribution of genotypes for the rs10773983 polymorphisms between the two groups. The frequencies of GA and AA genotypes are significantly higher in subjects with high-normal FPG than those in the low-normal FPG group as shown in Table 3.

The effects of the genotypes of rs10773983 were analyzed further under three different genetic models using logistic tests (Table 4). Multivariate logistic regression analysis showed that after adjustment for age, sex, family history of diabetes, and BMI, the GA and AA genotypes and the combined AA+GA genotype of ADIPOR2 rs10773983 were significantly associated with a higher risk of high-normal FPG (OR = 1.423, 95%CI = 1.110–1.825; OR = 1.718, 95%CI = 1.211–2.439; OR = 1.491, 95%CI 1.179–1.886 respectively; $p < 0.01$). The findings showed that subjects with the A-allele of rs10773983 compared to subjects with G-allele had 1.222-fold higher risk for high-normal FPG (OR = 1.222, 95%CI = 1.010–1.478, $p = 0.039$).

Discussion

The aim of this investigation was to reveal the possible association of ADIPOR2 rs10773983 polymorphisms with high-normal FPG level in the Chinese Han population. Our results

Table 2 Comparison of serum lipid levels and BMI with the GG, GA, and AA genotypes of the SNP rs10773983

	rs10773983 genotypes			P_{add}	P_{dom}	P_{rec}
	GG $n = 707$	GA $n = 993$	AA $n = 338$			
Age (years)	46.7 \pm 13.3	47.1 \pm 12.5	46.8 \pm 12.4	0.605	0.352	0.959
Total cholesterol (mmol/L)	5.29 (4.58–6.11)	5.41 (4.63–6.15)	5.32 (4.61–6.15)	0.308	0.196	0.849
Triglyceride (mmol/L)	1.34 (0.89–2.02)	1.31 (0.90–2.04)	1.27 (0.96–2.09)	0.695	0.455	0.635
LDL-c (mmol/L)	3.05 (2.48–3.70)	3.14 (2.48–3.75)	3.14 (2.57–3.77)	0.362	0.170	0.683
HDL-c (mmol/L)	1.30 (1.10–1.52)	1.35 (1.12–1.59)	1.32 (1.14–1.56)	0.138	0.160	0.460
HbA1c (%)	5.00 (4.80–5.20)	4.90 (4.75–5.20)	4.90 (4.80–5.10)	0.751	0.521	0.835
FPG (mmol/L)	5.13 (4.75–5.49)	5.21 (4.86–5.58)	5.23 (4.92–5.58)	0.017	0.006	0.227
Fasting insulin (μ IU/mL)	7.82 (5.15–12.26)	9.41 (5.58–13.32)	9.47 (6.59–12.78)	< 0.001	< 0.001	0.037
HOMA-IR	1.78 (1.14–2.81)	2.13 (1.26–3.09)	2.16 (1.47–2.96)	< 0.001	< 0.001	0.070
BMI (kg/m ²)	23.80 (21.7–26.4)	24.1 (22.07–26.40)	23.90 (21.62–26.10)	0.660	0.564	0.727
Family history of diabetes, % (n)	8.2 (58)	6.7 (67)	8.8 (30)	0.404	0.554	0.377

Data are shown as mean \pm SD or median (interquartile range). BMI was adjusted for age and gender

HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; BMI, body mass index; FPG, fasting blood glucose; P_{add} , p value under an additive inheritance model (GG vs AA vs GA); P_{dom} , p value under a dominant inheritance model (AA+GA vs GG); P_{rec} , p value under recessive model (AA vs GA+GG)

Table 3 Clinical and metabolic characteristics of study participants categorized by fasting plasma glucose

	Low-normal FPG (<i>n</i> = 564)	High-normal FPG (<i>n</i> = 1474)	<i>p</i> value
Male (%)	273 (48.5%)	779 (52.9%)	0.111
Age (years)	41.7 ± 12.9	48.8 ± 12.1	< 0.001
Total cholesterol (mmol/L)	4.86 (4.21–5.68)	5.56 (4.80–6.22)	< 0.001
Triglyceride (mmol/L)	1.09 (0.77–1.60)	1.44 (0.98–2.14)	< 0.001
LDL-c (mmol/L)	2.79 (2.33–3.33)	3.22 (2.59–3.81)	< 0.001
HDL-c (mmol/L)	1.35 (1.16–1.57)	1.32 (1.10–1.57)	0.222
FPG (mmol/L)	4.57 (4.31–4.75)	5.37 (5.13–5.66)	< 0.001
Fasting insulin (μU/mL)	8.16 (5.07–12.09)	9.25 (5.76–13.06)	0.003
HOMA-IR	1.58 (1.02–2.37)	2.21 (1.36–3.16)	< 0.001
BMI (kg/m ²)	23.3 (21.1–25.5)	24.2 (22.2–26.5)	< 0.001
Family history of diabetes (%)	5.41%	8.54%	0.036
rs10773983 (%)			
GG	234 (41.5%)	473 (32.1%)	0.001
GA	254 (45.0%)	738 (50.1%)	
AA	76 (13.5%)	263 (17.8%)	
Allele G	59.6%	54.7%	0.032
Allele A	40.4%	45.3%	

Data are presented as mean values±SD or median (interquartile range). BMI was adjusted for age and gender. HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance

provided evidence that rs10773983 was a susceptible genetic variant for high-normal FPG (FPG ≥ 4.88 mmol/L) in Chinese Han people.

Elevated FPG, even within the normal range according to the World Health Organization definition [13], may be associated with insulin resistance and pre-diabetes. Tirosch et al. found that glucose levels within the normal range independently predicted incident diabetes mellitus (DM) during a 6-

year follow-up [14]. O'Malley et al data suggested that insulin sensitivity declines when moving from low- to high-normal FPG in pre-pubertal and pubertal obese youth, independently of age, BMI, and sex [15]. The present study showed the similar results for increased fasting insulin levels and decreased insulin sensitivity in subjects with FPG ≥ 4.88 mmol/L in Chinese Han people.

Furthermore, high-normal fasting glucose level may play an important role in the pathophysiology of atherosclerotic disease. Shaye et al. found that elevated fasting glucose level, within the normal range, is an independent predictor of cardiovascular disease (CVD) in men without type 2 DM [16]. Neurologic studies suggested that even in the normal range and in the absence of diabetes, a high-normal fasting glucose level was associated with changes in brain structure and cognitive function [17, 18]. However, the genetic factors contributing to the high-normal fasting glucose level are still incompletely understood. Adiponectin is an adipose tissue hormone secreted by adipocytes and exerts multiple biological effects, such as insulin sensitization, anti-inflammation, and anti-atherogenesis [19], throughout the body mediated by the specific receptors ADIPOR1, ADIPOR2, and T-cadherin. ADIPOR2 is predominantly expressed in the liver and regulates glucose and lipid metabolism by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPARα) pathways [20], leading to increased insulin sensitivity and glucose uptake. In a study of an Amish population diagnosed with type 2 DM, five SNPs (rs1029629, rs12342, rs11061971,

Table 4 Effects of rs10773983 genotypes on the risk of high-normal FPG under different genetic models

Genetic model	<i>p</i> value ^a	OR (95%CI) ^a
Additive model		
GG		1.000
GA	0.005	1.423 (1.110–1.825)
AA	0.002	1.718 (1.211–2.439)
Dominant model		
GG		1.000
AA+GA	0.001	1.491 (1.179–1.886)
Recessive model		
GA + GG		1.000
AA	0.038	1.408 (1.020–1.943)
Allele		
G		1.000
A	0.039	1.222 (1.010–1.478)

OR, odds ratio; 95%CI, 95% confidence interval

^a Adjusted for sex, age, family history of diabetes, and BMI

rs1044471, and AR2-8f) for ADIPOR2 were found to be associated with type 2 DM and impaired glucose tolerance, while another research on the French population suggested association between SNPs rs767870 of ADIPOR2 and type 2 DM. In this study, we examined the SNPs (rs10773989, rs2370055, rs9300298, rs10773983, and rs13611594) in ADIPOR2 in the non-diabetic Chinese Han population. The results of the present study revealed that only the haplotype containing the A allele of rs10773983 in the ADIPOR2 was significantly associated with the higher normal fasting glucose levels and type 2 diabetes risk in a population consisting of individuals within normal fasting glucose range. There was no association between rs10773983 in ADIPOR2 and BMI. Phenotypic, genotypic, and environmental features of different populations may be the explanation of the discrepancies between our study and past researches [21].

There were a few limitations to our study. One such limitation is the lack of the measurement of the ADIPOR2 expression. Because rs10773983 is an intron variant and does not alter ADIPOR2 amino acid sequence, it might therefore influence ADIPOR2 expression at the transcriptional level rather than altering protein functions. Further studies are required to explain the mechanisms underlying the association between rs10773983 and ADIPOR2 function expression. Also, without routinely testing oral glucose tolerance test of our study population, there might be some participants with impaired blood glucose or even diabetes recruited in our study population and may interfere with the final analysis. Further studies with oral glucose tolerance test, together with HbA1c and FPG, are needed to better verify the relationships between rs10773983 SNPs, high-normal fasting glucose, and insulin resistance in the non-diabetic Chinese Han population.

Conclusions

Our findings suggest that ADIPOR2 rs10773983 polymorphism may be associated with an increased risk of high-normal FPG among non-diabetic Chinese Han subjects who have normal FPG levels.

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Compliance with ethical standards

The study protocol was approved by the Beijing Shijitan Hospital Ethics Committee, Capital Medical University. Written informed consent was obtained from all the participants before their enrolment in the study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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