Three single nucleotide polymorphisms associated with type 2 diabetes mellitus in a Chinese population

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Received August 17, 2016; Accepted November 10, 2016

DOI: 10.3892/etm.2016.3920

Abstract. An Indian study recently observed three new loci: rs9552911 in the *SGCG*, rs1593304 near *PLXNA4* and rs4858889 in *SCAP* associated with type 2 diabetes mellitus (T2DM) in a south Asian population. The present study aimed to validate these findings in a Chinese population. We genotyped the above three single-nucleotide polymorphisms (SNPs), rs9552911, rs1593304, and rs4858889, in a group of 1,972 Chinese individuals, comprising of 966 type 2 diabetic patients and 976 controls. Anthropometric variables and biochemical traits were measured in all the participants. The association analyses of genotype-disease and genotype-traits were estimated. The genotype frequency of rs9552911 differed statistically between the cases and controls (P=0.017). The difference was also evident between the cases and controls in non-obese participants (P=0.033). In addition, the SNP rs9552911 was associated with weight (P=0.033), total cholesterol (P=0.006) and low-density lipoprotein-cholesterol (P=0.007). The SNP rs1593304 was associated with β-cell function estimated by the homeostatic model assessment of β-cell function (P=0.041). However, there was no significant association between rs4858889 and T2DM. In conclusion, the results show that the SNP rs9552911 was associated with T2DM, possibly by affecting body mass index and lipid metabolism. The SNP rs1593304 may impair β-cell function.

Introduction

Diabetes is a major public health issue in China, especially type 2 diabetes mellitus (T2DM). There are 92.4 million adults with diabetes and 148.2 million adults with prediabetes (1). The prevalence of diabetes is continuously evolving in China (2). It may result in many complications including retinopathy, nephropathy, and peripheral neuropathy. Additionally, it leads to enhancement of the morbidity and mortality of coronary heart disease (3). T2DM is the result of complex interaction between genetic and environmental factors (4). Thus, investigations have focused on the genetic basis of T2DM that attracts increased attention worldwide.

The development of single-nucleotide polymorphism (SNP) typing technology of human genome has made it possible to perform a genome-wide association study (GWAS) with relative ease. It is now a powerful tool to search new disease susceptibility loci across the whole genome (5). Recently, Saxena *et al* (6) performed a GWAS and a multi-stage meta-analysis of T2DM in Punjabi Sikhs from India. Their findings showed 513 independent SNPs in Punjabi Sikhs and further replicated the top 66 SNPs through genotyping in a second batch of Punjabi Sikhs. On combined meta-analysis in other Sikh populations they identified a novel locus rs9552911 in association with T2DM at 13q12 in the *SGCG* gene. Subsequently, they undertook replication of the top 513 signals in non-Sikh south Asians and genotyped up to 31 top signals in 10,817 South Asians. In combined South Asian meta-analysis, they observed another two suggestive SNPs at chromosome 7q32 near *PLXNA4* (rs1593304), at 3p21 in *SCAP* (rs4858889) (6). The Sikhs are relative special population of ~26 million from the northwestern parts of India. They are south Asians with a distinct and unique religion born characteristics over 500 years ago in Punjab.

It is a well-known fact that the frequencies and the effects of genetic variations are different among ethnic groups and geographic regions. Therefore, investigating the 3 SNPs associated with type 2 diabetes in China is especially important. In this study, we aimed to validate whether the mutation of the reported 3 SNPs are associated with T2DM and diabetes-related metabolic traits in a Chinese population.

Materials and methods

Participants. The study sample included 1,972 Chinese from the The Second Affiliated Hospital of Harbin Medical University (Heilongjiang, China), comprised of 996 (type 2 diabetic) patients and 976 (non-diabetic) controls. All the type 2 diabetic patients were defined according to the

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Key words: type 2 diabetes mellitus, single-nucleotide polymorphisms, *SGCG*: rs9552911, *PLXNA4*: rs1593304, *SCAP*: rs4858889

1999 World Health Organization (WHO) criteria (7) and randomly recruited from the patients of the Department of Endocrinology and Metabolic Diseases. The controls had a fasting plasma glucose concentration <5.1 mmol/l, hemoglobin A1cv <6.0%, with no history of oral hypoglycaemic or lipid-regulating agents, or any related family history. We collected the medical history and demographic information of all the individuals. The Ethics Committee of the Harbin Medical University approved this study. The participants provided written informed consent. The PS: Power and Sample Size Calculation software version 3.0 (Biostatistics, Nashville, TN, USA) was used to assess the sample size. Assuming an allele frequency of 0.105 (MAF) in the control group, sample sizes of 874 in each group were adequate to detect an odds ratio (OR) of 1.5 at a power of 80% and significance level of 5%.

Clinical measurements. All the participants underwent a detailed physical examination. Anthropometric variables such as height, weight, waist and hip circumference and blood pressure were measured. Fasting plasma glucose levels, fasting insulin levels and haemoglobin A1c were measured. Lipid profiles including total cholesterol, triacylglycerol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol were also obtained. Homeostatic model assessment (HOMA) was used to assess insulin resistance (HOMA-IR) and β-cell function (HOMA-B) (8). Data are shown as means ± SD (Table I).

SNP genotyping. Blood samples were collected from all the participants. Genomic DNA was extracted from collected blood with the TIANamp Blood DNA kit (Tiangen Biotech Co., Ltd., Beijing, China). PCR was applied to amplified sample DNA according to the manufacturer's recommendations. SNPs were genotyped by a custom-by-design 48-Plex SNPscan™ kit. This kit was developed as patented SNP genotyping technology by Genesky Biotechnologies Inc. (Shanghai, China), which is based on double ligation and multiplex fluorescence PCR. GeneMapper v4.1 (Applied Biosystems Life Technologies, Foster City, CA, USA) was used to read the original sequenced information. In order to validate the genotyping accuracy, a 5% random sample of cases and controls was genotyped twice per all SNPs by different individuals In detail, we included 100 pairs of blind duplicates and the concordance rates were >98%.

Statistical analysis. Deviation from the Hardy-Weinberg equilibrium (HWE) was performed by the exact test (http://ihg.gsf.de/) in the cases and controls separately for each SNP before the association analysis. Continuous clinical data were compared by unpaired Student's t-tests between the case and control groups. The allelic frequencies and genotype counts between the cases and controls were compared using χ^2 tests. The SNP-disease association analyses were assessed by logistic regression under the additive model. OR with 95% confidence interval (CI) are presented. The association between genotype and diabetes-related quantitative traits was estimated using generalized linear regression. Statistical analyses were performed using the SPSS program for Windows software (version 17.0; SPSS, Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

Table I. Clinical characteristics of the study participants.

Characteristics	Cases	Controls	P-value
Number, n	996	976	
Men/women (n/n)	612/384	571/405	0.182
Age (years)	46.1±12.6	42.9±11.7	<0.05
Weight (kg)	73.1±13.4	66.6±12.4	<0.05
BMI (kg/m^2)	25.8±3.6	13.3±3.3	<0.05
Waist circumference (cm)	93.5±10.4	81.3±10.8	<0.05
Hip circumference (cm)	99.5±7.4	95.8±7.2	<0.05
Waist-to-hip ratio	0.94±0.06	0.85±0.07	<0.05
Systolic blood pressure (mmHg)	130.1±17.5	121.2±15.1	<0.05
Diastolic blood pressure (mmHg)	84.6±11.2	79.2±9.6	<0.05
Fasting blood glucose (mmol/l)	10.0±3.4	4.8±0.3	<0.05
Fasting insulin (mmol/l)	12.9±7.6	7.9±4.4	<0.05
Hemoglobin A1c (%)	9.3±2.4	5.1±0.5	<0.05
HOMA-IR	5.8±4.0	1.7±1.0	<0.05
HOMA-B	59.0±169.6	1,18.0±225.2	<0.05
Total cholesterol (mmol/l)	5.0±1.3	4.9±1.3	<0.05
Triacylglycerol (mmol/l)	2.4±2.3	1.4±1.0	<0.05
HDL-cholesterol (mmol/l)	1.2±0.3	1.5±0.4	<0.05
LDL-cholesterol (mmol/l)	2.9±1.0	2.9±0.9	0.687

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

Results

Clinical characteristics of the study population. The case-control cohort used in our investigation was matched for ethnicity, culture and geographical locations. The main clinical dates of case and control groups are presented in Table I. The proportion of males was slightly higher than that of females in the two groups, which may be due to a participation bias. Significant differences were detected for age, weight, body mass index (BMI), waist and hip circumference, waist-to-hip ratio, blood pressure, fasting plasma glucose levels, fasting insulin levels, hemoglobin A1c, HOMA-IR, HOMA-B, total cholesterol, triacylglycerol, and HDL-cholesterol between the cases and the controls (P<0.05).

Associations of the three SNPs with T2DM. The genotype distributions of the three SNPs were in HWE in cases and controls. The allele and genotype distribution are summarized in Tables II and III, respectively. Allele frequencies of the three SNPs were not statistically significant between the cases and controls (OR=1.012, 95% CI=0.848-1.207, P=0.898 for rs1593304, OR=1.032, 95% CI=0.873-1.221, P=0.712 for rs4858889 and OR=1.058, 95% CI=0.907-1.234, P=0.472 for rs9552911). As for rs9552911, the genotype frequency was statistically different between the cases and controls with

Table II. The allele distribution and association analysis of three SNPs for type 2 diabetes.

SNPs Allele	Groups	Allele distribution, n (%) A	G	Risk allele	P-value	OR (95% CI)	P-value[a]	OR[a] (95% CI)[a]
rs1593304	Case	289 (14.5)	1,703 (85.5)	G	0.898	1.012 (0.848-1.207)	0.837	1.020 (0.844-1.232)
	Control	286 (14.7)	1,666 (85.3)					
rs4858889	Case	1,667 (83.7)	325 (16.3)	A	0.712	1.032 (0.873-1.221)	0.972	0.997 (0.832-1.194)
	Control	1,625 (83.2)	327 (16.8)					
rs9552911	Case	403 (20.2)	1,589 (79.8)	G	0.472	1.058 (0.907-1.234)	0.734	1.029 (0.872-1.214)
	Control	445 (21.2)	1,663 (78.8)					

[a]Adjusted for age, gender and BMI. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table III. The genotype distribution and the effect on the risk of type 2 diabetes.

SNPs	Genotype	Case, n (%)	Control, n (%)	P-value in χ^2 test	P-value[a]	OR[a] (95% CI)	P-value[a,b]
rs1593304	G/G	726 (72.9)	714 (73.2)	0.662			
	G/A	251 (25.2)	238 (24.4)		0.727	1.037 (0.845-1.273)	0.771
	A/A	19 (1.9)	24 (2.5)		0.422	0.779 (0.423-1.434)	0.393
rs4858889	A/A	695 (69.8)	682 (69.9)	0.403			
	G/A	277 (27.8)	261 (26.7)		0.690	1.041 (0.853-1.271)	0.489
	G/G	24 (2.4)	33 (3.4)		0.218	0.714 (0.417-1.220)	0.363
rs9552911	G/G	642 (64.5)	595 (61.0)	**0.017**			
	G/A	305 (30.6)	349 (35.8)		0.030	0.810 (0.670-0.979)	0.076
	A/A	49 (4.9)	32 (3.3)		0.135	1.419 (0.879-2.246)	0.103

[a]P-value for genogype in additive model. [b]P-value adjusted for age, gender and BMI. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; BMI, body mass index. Bold text, statistically significant.

Table IV. Genotype frequencies between the cases and controls in non-obese participants with χ^2 tests.

SNPs	Genotype	Genotype distribution, n (%) Case	Control	P-value in χ^2 test	P-value[a]	OR (95% CI)[a]	P-value[a,b]
rs1593304	G/G	532 (73.0)	653 (72.7)	0.798			
	G/A	182 (25.0)	222 (24.7)		0.957	1.006 (0.802-1.263)	0.743
	A/A	15 (2.0)	23 (2.6)		0.509	0.801 (0.414-1.550)	0.440
rs4858889	A/A	507 (69.5)	627 (69.8)	0.856			
	G/A	200 (27.4)	240 (26.7)		0.790	1.031 (0.826-1.286)	0.833
	G/G	22 (3.1)	31 (3.5)		0.647	0.878 (0.502-1.535)	0.607
rs9552911	G/G	460 (63.1)	543 (60.5)	**0.033**			
	G/A	230 (31.6)	325 (36.2)		0.093	0.835 (0.677-1.030)	0.085
	A/A	39 (5.3)	30 (3.3)		0.088	1.535 (0.938-2.510)	0.096

[a]The additive model was used in the association analyses. [b]P-value adjusted for age and gender. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval. Bold text, statistically significant.

χ^2 tests (P=0.017). In an additive model, the genotype GA was significantly less frequent in case patients with logistic regression (P=0.033). However, there were no statistical differences with adjustment for age, gender and BMI. On

Table V. Association of the three candidate SNP variant genotypes with clinical characteristics.

SNPs	Weight (kg)	BMI (kg/m^2)	Hemoglobin A1c (%)	HOMA-IR	HOMA-B	Total cholesterol (mmol/l)	Triacylglycerol (mmol/l)	HDL-cholesterol (mmol/l)	LDL-cholesterol (mmol/l)
rs1593304									
G/G	69.67±13.37	24.52±3.68	7.19±2.67	3.67±3.52	94.58±197.03	4.94±1.19	1.88±1.71	1.34±0.37	2.92±0.94
G/A	70.44±13.32	24.68±3.70	7.34±2.81	4.01±3.79	69.31±219.41	4.95±1.19	2.02±2.08	1.34±0.36	2.91±0.88
A/A	70.87±12.43	24.6±3.52	7.21±2.47	3.33±3.36	89.40±68.90	4.94±1.18	1.71±1.29	1.40±0.34	2.98±0.87
P-value	0.230	0.474	0.361	0.230	0.041	0.917	0.347	0.781	0.854
rs4858889									
G/G	69.60±13.58	24.10±3.47	6.95±2.76	2.91±2.38	86.73±74.65	5.00±1.13	1.93±1.79	1.37±0.31	2.86±0.96
G/A	69.67±14.23	24.49±3.87	7.30±2.77	3.82±3.52	85.33±253.57	4.95±1.27	1.89±1.75	1.33±0.35	2.93±0.96
A/A	69.98±12.97	14.61±3.61	7.21±2.67	3.75±3.65	89.38±180.73	4.93±1.16	1.91±1.82	1.35±0.38	2.92±0.91
P-value	0.635	0.288	0.901	0.522	0.717	0.626	0.911	0.455	0.940
rs9552911									
G/G	70.37±13.30	24.67±3.66	7.31±2.76	3.77±3.54	84.22±192.41	4.99±1.19	1.92±1.75	1.34±0.37	2.96±0.94
G/A	69.14±13.30	24.36±3.70	7.03±2.56	3.58±3.58	95.73±226.56	4.88±1.18	1.92±1.90	1.35±0.36	2.85±0.92
A/A	68.46±13.81	24.47±3.69	7.47±2.77	4.70±4.17	88.12±75.62	4.69±1.12	1.66±1.78	1.37±0.38	2.80±0.75
P-value	0.033	0.117	0.221	0.606	0.335	0.006	0.507	0.552	0.007

Data are shown as means ± SD. P-value is adjusted for age, gender and BMI. SNPs, single-nucleotide polymorphisms; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-B, homeostatic model assessment of β-cell function; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the other hand, SNPs (rs1593304 and rs4858889) were not significantly associated with T2DM as observed by χ^2 tests or logistic regression. To gain a better understanding of weight and T2DM, we stratified the participants into obese (BMI, ≥28 kg/m^2) and non-obese (BMI, <28 kg/m^2). The genotype frequency of rs9552911 showed statistical significant differences between the cases and controls in non-obese participants with χ^2 tests (P=0.033) (Table IV).

Associations of the candidate SNP variant genotypes with clinical characteristics. We tested the effect of SNPs on a series of diabetes-related clinical characteristics, including BMI, weight, hemoglobin A1c, total cholesterol, triacylglycerol, LDL-cholesterol, HDL-cholesterol, HOMA-IR and HOMA-B in all the samples (Table V). The multiple linear regression analysis after adjusting gender, age and BMI revealed a significant association of rs9552911 with weight (P=0.033), total cholesterol (P=0.006) and LDL-cholesterol (P=0.007) levels. Thus, the genotype AA was associated with lower weight, total cholesterol and higher LDL-cholesterol. In addition, the SNP rs1593304 was associated with β-cell function estimated by HOMA-B (P=0.041).

Discussion

Previous studies in Punjabi Sikhs from India suggested that rs9552911, rs1593304 and rs4858889 made a significant contribution to T2DM susceptibility (6). In the present study, we aimed to confirm the association of three SNPs (rs1593304, rs4858889 and rs9552911) in 1,972 case-control samples in the main land Chinese population.

SNP rs9552911 is located in the *SGCG* gene at 13q12. The SNP is associated with T2DM, especially in male and non-obese people. It is shown that the genotype frequency was statistically different among the cases and controls. In an additive model, the genotype GA reduced the risk of T2DM (OR=0.810, 95% CI=0.670-0.979) compared with GG. It was similar to the previous study in India that had the protective allele (OR=0.67, 95% CI=0.58-0.77). Additionally, the genotype frequency of rs9552911 was statistically different between the cases and controls in non-obese participants (P=0.033). Thus, we suggest that the SNP may be related to T2DM in non-obese people. Thus, rs9552911 may give us a new understanding of the etiology of T2DM in non-obese people. Although non-obese diabetes has not been widely addressed, it should attract more public attention. In addition, the SNP rs9552911 was significantly associated with weight (P=0.033), total cholesterol (P=0.006) and LDL-cholesterol (P=0.007). Bioactive lipid metabolites accumulation may result in cellular dysfunction and insulin resistance (9), which in turn led to impaired regulation of postprandial blood glucose (10). It is known that insulin promoted the synthesis of lipids, and inhibited their degradation. Insulin resistance increased the levels of serum lipids (11). It has been proposed that the high levels of serum lipids were not only crucial for the development of insulin resistance but also for inflammation, coronary heart disease and fatty liver disease (12-14). Thus, the disorder of lipid metabolism is a risk factor for T2DM and many other chronic diseases. We inferred that rs9552911 is likely to be related to insulin resistance via influence of lipid metabolism.

The gene *SGCG* encodes gamma (γ)-sarcoglycan, one of several sarcolemmal transmembrane glycoproteins that interact with dystrophin (15). It was shown that the sarcoglycan null mice, which lacked the sarcoglycan complex in skeletal muscle and adipose tissue, were glucose-intolerant and exhibited whole body insulin due to impaired insulin-stimulated glucose uptake in skeletal muscles (16). However, the molecular mechanism of the relationship between *SGCG* and glycol metabolism is still unclear. To clarify the role of *SGCG* to T2DM, further research focused on the function of SNP and other causative variants in this extended region is needed.

Rs1593304 located near *PLXNA4* of 7q32 and rs4858889 in *SCAP* of 3p21. We found GA carriers of rs1593304 showed the lowest HOMA-B compared with other genotype. HOMA-B is a method for assessing β-cell function from basal (fasting) glucose and insulin or C-peptide concentrations (17). Several mechanisms underlying the causes of pancreatic β-cell failure have been reported, including gene mutation, decreased insulin signalling and inflammation. Numerous susceptibility genes for T2DM also have been identified in humans (18). This indicated that rs1593304 may have decreased β-cell function, thereby elevating the risk of diabetes. However, neither the frequency of the risk alleles nor the genotypes was associated with T2DM after the adjustment for gender, age and BMI. We failed to identify any association of SNP rs4858889 with T2DM in Chinese population, which was inconsistent with the results of Saxena *et al* (6). The possible reason could be the genetic heterogeneity, ethnicity and different lifestyle. Our results were confirmed in a Chinese population. Frequencies of some genetic variations may be variable among different ethnic groups and different geographic regions. As mentioned above, the Sikhs is a relative special population. They are in the absence of conventional risk factors such as smoking, obesity, and a diet rich in meats. Sikhs neither smoke nor chew tobacco and over 50% of them are lifelong vegetarians (6). While the East Asian Chinese belong to the largest population and ethnic group in the world (19). The prevalence rate of diabetes is 9.7% in China and is ranked second after India where prevalence is observed to be 12.1% (1,20). Unlike the Sikhs, Chinese have a higher smoking rate, alcohol consumption and intake of fatty diet. Therefore, our results were not as statistically significant as those in Sikhs. Further, investigation in other populations is necessary for the concrete conclusion. Certain limitations of this study were the cases and controls were enrolled from hospitals hence, not representing the general population. Secondly, large sample size is also needed to overcome additional genetic and environmental modifiers.

In conclusion, the SNP rs9552911 variants were associated with T2DM, especially in non-obese people. The rs1593304 may lower β-cell function and increase the risk of diabetes. These results could be utilized for further research on the pathogenesis of T2DM.

Acknowledgements

The present study was funded by the National Natural Science Foundation of China (81473053), the Natural Science Foundation of Heilongjiang Province (ZD201220), and the National Basic Research Program of China (2014CB542401, SQ2013CB051164).

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