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ORIGINAL RESEARCH

The Effect of *SOCS2* Polymorphisms on Type 2 Diabetes Mellitus Susceptibility and Diabetic Complications in the Chinese Han Population

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Background: *SOCS2* is downregulated in diabetes, which might be related to diabetes. We explored the effect of *SOCS2* polymorphisms on the development of type 2 diabetes mellitus (T2DM) and diabetic complications.

Methods: The subjects consisted of 500 patients with T2DM and 501 healthy controls. Five variants in *SOCS2* were genotyped by Agena MassARRAY system. RT-qPCR profiling was performed to detect the expression of *SOCS2* mRNA. Logistic regression analysis was utilized to calculate odds ratio (OR) and 95% confidence intervals (95% CIs).

Results: Rs3825199 (OR = 1.44, $p = 0.007$), rs11107116 (OR = 1.39, $p = 0.014$) and rs10492321 (OR = 1.48, $p = 0.004$) had an increased T2DM risk of T2DM. Moreover, the contribution of *SOCS2* polymorphisms to T2DM risk was associated with age, gender, smoking, drinking, and BMI. *SOCS2* variants also had a reduced risk for T2DM patients with diabetic nephropathy, diabetic retinopathy and coronary heart disease. *SOCS2* rs10492321 was the best single locus model. *SOCS2* mRNA was downregulated in patients with T2DM compared to healthy controls ($p = 0.029$).

Conclusion: This study firstly reported that rs3825199, rs11107116 and rs10492321 in *SOCS2* conferred to an increased risk for the occurrence of T2DM in the Chinese Han population. Moreover, *SOCS2* mRNA was downregulated in patients with T2DM, suggesting that *SOCS2* might have an important role in the occurrence of T2DM.

Keywords: type 2 diabetes mellitus, *SOCS2* variants, diabetic complications, life style

Introduction

Type 2 diabetes mellitus (T2DM) is a serious metabolic disorder with chronic hyperglycemia characterized by impaired insulin secretion and resistance.[1] Globally, the International Diabetes Federation (IDF) showed more than 451 million people with diabetes in 2017.[2] With the aging population and the westernization of lifestyle, the prevalence of diabetes in China has been rising rapidly from 0.67% in 1980 to 10.4% in 2013.[3] In China, there are approximately 11% of the population having diabetes but a significant proportion remaining undiagnosed.[4] The pathogenesis of T2DM is complicated and multifactorial, which is driven by environment, lifestyle, and genetic factors. Age, sex, cigarette smoking, alcohol drinking and overweight have been reported to be risk factors for T2DM.[5] In addition, genetic factors are strongly contributed to the etiology and manifestation of T2DM.[6,7] To date, a variety of risk loci affecting T2DM susceptibility have been recognized,[8–10] but numerous loci remain to be detected.

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Suppressor of cytokine signaling 2 (SOCS2) protein is a member of the suppressor of cytokine signaling family, which is a negative regulator of cytokine and growth factor signaling.[11,12] SOCS2 protein was reported to interact with the insulin-like growth factor-1 receptor (IGF1R) and decrease its biological actions.[13] SOCS2 was downregulated in diabetes, which might be related to either insulin deficiency or resistance.[14] SOCS2 was involved in hyperglycaemia and glucose intolerance caused by the abnormal regulation of proinsulin processing and insulin secretion in beta cells.[15] The overexpression of SOCS2 possesses a protective function in the development of diabetic nephropathy by reducing the expression of inflammatory cytokines and suppressing the activation of JAK/STAT pathway.[16] The physiological studies mentioned above proposed that SOCS2 might play an important role in diabetes, but the role of genetic polymorphism within *SOCS2* gene for T2DM predisposition has been less studied. Therefore, we chose *SOCS2* gene as a candidate gene to explore the effect of single-nucleotide polymorphisms (SNPs) in *SOCS2* on the development of T2DM.

Here, five SNPs (rs10859525, rs3825199, rs11107116, rs10492321, and rs10859563) in *SOCS2* were genotyped to examine the contribution of the genetic variants to the risk of the occurrence of T2DM at the interfaces of single-locus and combined SNPs. The present study also investigated whether the relationship of *SOCS2* polymorphisms with T2DM risk persists across age, gender, lifestyle, and body mass index (BMI), and explored the contribution of *SOCS2* polymorphisms to the susceptibility diabetic complications in the Chinese Han population.

Materials and Methods

Study Subjects

The study group consisted of 500 T2DM patients with T2DM and 501 healthy volunteers from the First Affiliated Hospital of Xi'an Jiaotong University. All enrolled subjects were unrelated Chinese Han ethnicity. Patients with T2DM were diagnosed as fasting plasma glucose ≥7.0 mmol/L according to WHO diagnostic criteria. Patients with type 1 diabetes, gestational diabetes, malignancy, acute infections, inflammation, other chronic diseases or other endocrine disease, and not receiving any drugs like antidiabetics were excluded. The controls were age and sex matched, no history of diabetes and other chronic diseases. Information on demographics, lifestyle factors and clinical characteristics of the participants was obtained from standardized questionnaires and medical records, including age, sex, BMI, smoking, drinking, fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), urea, creatinine, serum uric acid, glycated hemoglobin, and insulin (Table 1). The protocol of the study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (No: XJTU1AF2019LSK-007, Date: 2019.01.29) and conformed to the Declaration of Helsinki. All individuals signed written informed consent prior to sample collection.

SNP Genotyping

Five milliliters of venous blood samples were collected into the sample tubes for serum and ethylenediaminetetraacetic acid-evacuated tubes. Genomic DNA was obtained from peripheral leukocytes by GoldMag DNA isolation Kit (GoldMag Co. Ltd., Xi'an, China). Five SNPs (rs10859525 G>A, rs3825199 G>A, rs11107116 T>G, rs10492321 A>T, and rs10859563 C>G) in *SOCS2* were selected based on minor allele frequency (MAF) >5%, call rate >95%, and Hardy–Weinberg equilibrium (HWE) $p > 0.05$ (Suppl_Table 1). Genotyping of *SOCS2* polymorphism was determined by Agena MassARRAY system (Agena, San Diego, CA, USA) with incorporated software for primer design (Suppl_ Table 2) and data management.[17,18] The accordance rate of approximately 5% of the samples selected for replication was 100%.

Extraction and Expression Examination of mRNA

Peripheral blood mononuclear cells (PBMCs) were isolated with lymphocyte separation medium from 50 patients with T2DM and 50 controls (PAA, GE Healthcare), and the total RNA was extracted from PBMC using TRI Reagent (Ambion, Life Technologies). The quantity of the total RNA was estimated by BioSpecnano spectrophotometer (Shimadzu Biotech). The reverse transcription (RT) reactions of GAPDH and *SOCS2* mRNA were performed by Takara-PrimeScript™ RT Master Mix (Perfect Real Time). SYBR Green-based qPCR profiling was performed using

Table 1 Characteristics of Patients with T2DM and Controls

Variable	Cases (n = 500)	Controls (n = 501)	*p*
Age (years, mean ± SD)	59.87 ± 12.87	59.85 ± 9.34	0.973
>60/≤60	240/260	268/233	
Gender, Male/Female	358/142	358/143	0.508
BMI (kg/m^2) <24/≥24	203/239	130/188	
Unavailable	58	183	
Smoking, Yes/No	219/280	98/164	
Unavailable	1	239	
Drinking, Yes/No	109/385	103/140	
Unavailable	6	258	
T2DM duration (years) >10/≤10	193/307		
Fasting blood glucose (mmol/L)	8.14 ± 3.35	5.65 ± 0.51	**<0.001**
Total cholesterol (mmol/L)	4.18 ± 2.01	4.93 ± 4.00	**<0.001**
Triglyceride (mmol/L)	1.91 ± 1.90	1.74 ± 0.97	0.088
LDL-C (mmol/L)	2.46 ± 0.90	2.61 ± 0.76	**0.012**
HDL-C (mmol/L)	1.05 ± 0.72	1.16 ± 0.55	**0.024**
Urea (mmol/L)	6.52 ± 3.26	5.42 ± 2.78	**<0.001**
Creatinine (μmol/L)	71.20 ± 52.66	68.74 ± 12.87	0.322
GFR (mL/min)	96.62 ± 22.22	96.07 ± 19.78	0.710
Serum uric acid (μmol/L)	333.17 ± 99.15	318.33 ± 76.64	**0.013**
Diabetic complications			
Diabetic nephropathy	146		
Diabetic retinopathy	69		
T2DM with coronary heart disease	126		
T2DM with hypertension	269		

Notes: *p* values were calculated by χ^2 test for continuous variables and Student's *t* test for categorical variables. Bold values indicate that $p < 0.05$ indicates statistical difference.

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UCRP, ubiquitin cross-reactive protein.

Takara-TB Green™ Premix Ex Taq™ II (Tli RNaseH Plus). The primer sequences were designed as follows: forward primer: GGAGCGAGATCCCTCCAAAAT, and reverse primer: GGCTGTTGTCATACTTCTCATGG for GAPDH; the forward primer: AGGATAAGCGGACAGGTCCAGAAG, and reverse primer: TTGTTAATGGTGAGCCTACAGA GATGC for *SOCS2* mRNA. The levels of miRNAs were normalized using GAPDH as reference RNA. The relative expression quantity (RQ) of mRNA was calculated as $RQ = 2^{-\Delta\Delta Ct}$ [$\Delta\Delta Ct$ = mean value of the study group ($Ct_{mRNA} - Ct_{GAPDH}$) – mean value of the control group ($Ct_{mRNA} - Ct_{GAPDH}$)].

Statistical Analysis

Differences in the distribution of demographic and clinical characteristics between patients with T2DM and the control group were analyzed using chi-square test or Student's *t*-test, as appropriate. The deviation from HWE for each SNP was determined using goodness-of-fit χ^2 test in controls. Logistic regression analysis after adjusting for age and gender was utilized to investigate the relationship of SNPs to T2DM predisposition by calculating odds ratio (OR) and 95% confidence intervals (95% CIs).[19] False-positive report probability (FPRP) analysis was used to evaluate the noteworthy associations of the significant findings. We set 0.2 as the FPRP threshold and assigned a prior probability of 0.1 for an association with genotypes under investigation. The influence of the combined SNPs on T2DM susceptibility was determined using haplotype analysis and multifactor dimensionality reduction (MDR) analysis. *SOCS2* mRNA expression differences between patients with T2DM and healthy controls were estimated by the independent sample *t* test. One-way ANOVA was used to assess the association between *SOCS2* mRNA levels and the genotype of *SOCS2* polymorphisms between the cases and controls. Data analyses were performed using IBM® SPSS version 18.0 (SPSS Inc., Chicago, IL), PLINK version 2.1.7, Haploview 4 version.2 software and MDR version 3.0.2 software. A p-value < 0.05 was considered the threshold for statistically significant, whereas a value of corrected $p < 0.05/5$ was considered significant after Bonferroni correction.

Results

Baseline Characteristics of Subjects

A total of 1001 subjects including 500 T2DM cases (59.87 ± 12.87 years, 358 males and 142 females) and 501 controls (59.85 ± 9.34 years, 358 males and 143 females) were recruited. The distribution in age and sex between patients with T2DM and controls was similar ($p = 0.973$ and $p = 0.508$, respectively). There were statistical differences between the two groups with respect to biochemical indexes including fasting blood glucose, total cholesterol, LDL-C, HDL-C, urea, and serum uric acid (all $p < 0.05$, Table 1).

Analysis for Association Between SOCS2 Variants and T2DM Susceptibility

As shown in Table 2, three SNPs in *SOCS2* (rs3825199, rs11107116 and rs10492321) were associated with an increased risk of the occurrence of T2DM. The risk genotypes of rs3825199-AG, rs11107116-GT and rs10492321-TA were more prevalent in patients with T2DM than controls exhibiting a higher susceptibility to T2DM (rs3825199, AG vs AA, OR = 1.44, 95% CI: 1.11–1.88, $p = 0.007$; rs11107116, GT vs GG, OR = 1.39, 95% CI: 1.07–1.81, $p = 0.014$; and rs10492321, TA vs TT, OR = 1.48, 95% CI: 1.13–1.93, $p = 0.004$, respectively). In addition, the elevated risk association with T2DM was also observed in the dominant model (rs3825199, OR = 1.35, 95% CI: 1.05–1.73, $p = 0.020$; rs11107116, OR = 1.30, 95% CI: 1.01–1.67, $p = 0.038$; and rs10492321, OR = 1.40, 95% CI: 1.09–1.81, $p = 0.009$). The significance of rs3825199 (AG vs AA), and rs10492321 (TA vs TT, and TA-AA vs TT) still existed after Bonferroni correction.

Stratified Analysis for the Relationship of SOCS2 Variants to T2DM Risk

Stratified analyses were performed to explore the relationship between *SOCS2* SNPs and T2DM risk factors, including age, gender, smoking, drinking, and BMI. When stratified by gender, rs3825199, rs11107116 and rs10492321 were conferred to an increased T2DM risk among males not females under the allele, genotype, dominant and additive models (Suppl_Table 3). Based on age, the study population was stratified into two groups: older than 60 years and younger than or equal to 60 years. No significant relation of *SOCS2* variants to T2DM risk in those aged older than 60 years was observed. While high-risk association was found in rs3825199, rs11107116 and rs10492321 in subjects aged ≤60 years (Suppl_Table 3). The significance of rs3825199, rs11107116 and rs10492321 still existed after Bonferroni correction in males and subjects aged ≤60 years.

In smoker, increased risk of T2DM development was found for rs10492321 (Suppl_Table 4). Among non-smokers, the risk effect of rs3825199, rs11107116 and rs10492321 on the occurrence of T2DM was observed under the genotype and dominant models. In drinker, rs10859525 was a protective factor for T2DM developing, while rs3825199 increased T2DM susceptibility. In non-drinkers, a trend of the higher risk of developing T2DM was also found in subjects with the

Table 2 Correlation Between *SOCS2* Variants and T2DM Risk

SNPs ID	Models	Genotype	Case	Control	Adjusted by Age and Gender	
					OR (95% CI)	*p*
rs3825199	Allele	A	646	676	1	
		G	354	326	1.14 (0.94–1.37)	0.176
	Genotype	AA	200	237	1	
		AG	246	202	**1.44 (1.11–1.88)**	**0.007***
		GG	54	62	1.03 (0.68–1.56)	0.881
	Dominant	AG-GG vs AA			**1.35 (1.05–1.73)**	**0.020**
	Recessive	GG vs AA-AG			0.86 (0.58–1.26)	0.437
	Log-additive	AA+AG+GG			1.14 (0.94–1.37)	0.177
rs11107116	Allele	G	653	679	1	
		T	347	323	1.12 (0.93–1.35)	0.243
	Genotype	GG	205	238	1	
		GT	243	203	**1.39 (1.07–1.81)**	**0.014**
		TT	52	60	1.01 (0.66–1.52)	0.978
	Dominant	GT-TT vs GG			**1.30 (1.01–1.67)**	**0.038**
	Recessive	TT vs GG-GT			0.85 (0.58–1.27)	0.430
	Log-additive	GG+GT+TT			1.12 (0.93–1.35)	0.243
rs10492321	Allele	T	617	656	1	
		A	383	346	1.18 (0.98–1.41)	0.080
	Genotype	TT	183	224	1	
		TA	251	208	**1.48 (1.13–1.93)**	**0.004***
		AA	66	69	1.17 (0.79–1.73)	0.428
	Dominant	TA-AA vs TT			**1.40 (1.09–1.81)**	**0.009***
	Recessive	AA vs TT-TA			0.95 (0.66–1.37)	0.791
	Log-additive	TT+TA+AA			1.18 (0.98–1.41)	0.081

Notes: *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold values indicate that $p < 0.05$ means the data are statistically significant.*p indicates that after Bonferroni correction ($p < 0.05/5$) means the data are statistically significant.
Abbreviations: SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus; OR, odds ratio; 95% CI, 95% confidence interval.

AG/AG-GG genotypes of rs3825199, GT genotype of rs11107116 and TA/TA-AA genotypes of rs10492321 (Suppl_Table 4). Among subjects with BMI >24 kg/m^2, rs10859563 was associated with the reduced T2DM predisposition. In subjects with BMI ≤24 kg/m^2, rs3825199-AG genotype and rs11107116-GT genotype had 1.66- and 1.64-fold increased risk of developing T2DM than their reference genotype, respectively (Suppl_Table 5). The significance of rs3825199 (AG vs AA), rs11107116 (GT vs GG), and rs10492321 (TA vs TT) in non-smokers and the significance of rs10859563 (CC vs GG) among subjects with BMI >24 kg/m^2 still existed after Bonferroni correction.

Table 3 Association of *SOCS2* Variants with Diabetic Nephropathy and Diabetic Retinopathy in T2DM Patients

SNP ID	Model	DN vs No DN		DR vs No DR	
		OR (95% CI)	*p*	OR (95% CI)	*p*
rs10859525	G vs A	0.68 (0.50–0.94)	**0.017**	0.63 (0.41–0.99)	**0.042**
	AG vs AA	0.74 (0.49–1.12)	0.152	0.53 (0.29–0.95)	**0.034**
	GG vs AA	0.47 (0.20–1.12)	0.087	0.53 (0.19–1.50)	0.232
	AG-GG vs AA	0.69 (0.46–1.03)	0.069	0.53 (0.31–0.92)	**0.025**
	GG vs AA-AG	0.53 (0.23–1.25)	0.147	0.70 (0.25–1.91)	0.480
	AA+AG+GG	0.71 (0.51–0.99)	**0.040**	0.63 (0.40–0.98)	**0.042**
rs10859563	C vs G	0.72 (0.55–0.96)	**0.022**	1.01 (0.69–1.48)	0.965
	GC vs GG	0.65 (0.42–1.00)	0.051	1.04 (0.56–1.92)	0.899
	CC vs GG	0.51 (0.28–0.91)	**0.024**	1.01 (0.44–2.32)	0.980
	GC-CC vs GG	0.61 (0.40–0.91)	**0.016**	1.03 (0.58–1.86)	0.912
	CC vs GG-GC	0.65 (0.38–1.11)	0.113	0.99 (0.47–2.06)	0.969
	GG+GC+CC	0.70 (0.53–0.93)	**0.013**	1.01 (0.68–1.51)	0.956

Notes: *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold values indicate that $p < 0.05$ indicates statistical significance.
Abbreviations: T2DM, type 2 diabetes mellitus; SNP, single-nucleotide polymorphism; DN, diabetic nephropathy; DR, diabetic retinopathy; OR, odds ratio; 95% CI, 95% confidence interval.

Analysis for Association Between SOCS2 Variants and Diabetic Nephropathy or Diabetic Retinopathy in Patients with T2DM

We next investigated the association between *SOCS2* variants and diabetic nephropathy or diabetic retinopathy in patients with T2DM (Table 3). We found that rs10859525 (G vs A, OR = 0.68, $p = 0.017$; AA+AG+GG, OR = 0.71, $p = 0.040$) and rs10859563 (C vs G, OR = 0.72, $p = 0.022$; CC vs GG, OR = 0.51, $p = 0.024$; GC-CC vs GG, OR = 0.61, $p = 0.016$; and GG+GC+CC, OR = 0.70, $p = 0.013$) had a reduced risk of diabetic nephropathy in patients with T2DM. Moreover, the protective effect of rs10859525 on the risk of diabetic retinopathy in patients with T2DM was observed under the allele (OR = 0.63, $p = 0.042$), genotype (OR = 0.53, $p = 0.034$), dominant (OR = 0.53, $p = 0.025$), and additive (OR = 0.63, $p = 0.042$) models.

Association of SOCS2 Variants in T2DM Patients with Coronary Heart Disease or Hypertension versus Controls

Additionally, the association of *SOCS2* variants with the combined effect of T2DM and coronary heart disease/hypertension was examined (Table 4). We found that rs3825199 (GG vs AA, OR = 0.35, $p = 0.035$; and GG vs AA-AG, OR = 0.31, $p = 0.014$), rs11107116 (TT vs GG, OR = 0.28, $p = 0.020$; and TT vs GG-GT, OR = 0.25, $p = 0.009$), and rs10859563 (C vs G, OR = 0.70, $p = 0.015$; CC vs GG, OR = 0.48, $p = 0.020$; and GG+GC+CC, OR = 0.70, $p = 0.018$) had the reduced risk for T2DM patients with coronary heart disease compared with healthy controls. In addition, the significance of rs11107116 (TT vs GG-GT) still existed after Bonferroni correction. However, there was no significant association for T2DM patients with hypertension.

Influence of Combined SNPs on Susceptibility to T2DM

Pairwise linkage disequilibrium (LD) and haplotype analyses were conducted for *SOCS2* variants. Figure 1 revealed an LD block in *SOCS2* SNPs (rs3825199, rs11107116 and rs10492321), and the D' values of rs3825199-rs11107116, rs11107116-rs10492321 and rs3825199-rs10492321 were all 0.99. The frequencies of haplotypes (GTA, AGA and AGT)

Table 4 Association of *SOCS2* Variants in T2DM Patients with Coronary Heart Disease or Hypertension versus Controls

SNP ID	Model	T2DM Patients with CHD		T2DM Patients with Hypertension	
		OR (95% CI)	*p*	OR (95% CI)	*p*
rs3825199	G vs A	0.90 (0.66–1.21)	0.470	1.12 (0.90–1.4)	0.303
	AG vs AA	1.33 (0.88–2.01)	0.182	1.38 (1.00–1.91)	0.050
	GG vs AA	0.35 (0.13–0.93)	**0.035**	1.02 (0.61–1.70)	0.951
	AG-GG vs AA	1.11 (0.74–1.66)	0.617	1.30 (0.96–1.77)	0.095
	GG vs AA-AG	0.31 (0.12–0.79)	**0.014**	0.86 (0.53–1.40)	0.548
	AA+AG+GG	0.88 (0.65–1.20)	0.419	1.12 (0.89–1.40)	0.344
rs11107116	T vs G	0.87 (0.65–1.18)	0.381	1.11 (0.89–1.39)	0.353
	GT vs GG	1.29 (0.85–1.95)	0.225	1.33 (0.96–1.84)	0.083
	TT vs GG	0.28 (0.10–0.82)	**0.020**	1.00 (0.60–1.68)	0.999
	GT-TT vs GG	1.07 (0.72–1.61)	0.738	1.26 (0.93–1.71)	0.144
	TT vs GG-GT	0.25 (0.09–0.71)	**0.009***	0.87 (0.53–1.42)	0.566
	GG+GT+TT	0.85 (0.62–1.16)	0.309	1.10 (0.88–1.38)	0.414
rs10859563	C vs G	0.70 (0.53–0.93)	**0.015**	0.93 (0.75–1.15)	0.489
	GC vs GG	0.75 (0.48–1.16)	0.190	0.82 (0.58–1.16)	0.258
	CC vs GG	0.48 (0.25–0.89)	**0.020**	0.87 (0.57–1.34)	0.533
	GC-CC vs GG	0.66 (0.44–1.00)	0.052	0.84 (0.61–1.15)	0.272
	CC vs GG-GC	0.56 (0.31–1.00)	0.050	0.98 (0.67–1.43)	0.913
	GG+GC+CC	0.70 (0.52–0.94)	**0.018**	0.92 (0.74–1.14)	0.435

Notes: *p* values were calculated by logistic regression analysis with adjustments for age and gender. Bold values indicate that $p < 0.05$ indicates statistical significance. *p indicates that after Bonferroni correction ($p < 0.05/5$) means the data are statistically significant.

Abbreviations: T2DM, type 2 diabetes mellitus; SNP, single-nucleotide polymorphism; CHD, coronary heart disease; OR, odds ratio; 95% CI, 95% confidence interval.

and the result of haplotype analysis was shown in Table 5. No significant association between *SOCS2* haplotypes and T2DM risk in the whole population was discovered, whereas GTA and AGT haplotypes conferred to an increased T2DM risk in males (OR = 1.29, 95% CI: 1.03–1.60, $p = 0.026$ and OR = 1.34, 95% CI: 1.08–1.66, $p = 0.008$).

FPRP Analysis for Significant Findings

FPRP analysis was carried out to detect whether the significant findings were deserving attention (Table 6). At the prior probability level of 0.1, the significant association for rs3825199, rs11107116, and rs10492321 remained noteworthy in the overall analysis. The significant findings remained noteworthy for rs3825199, rs11107116, and rs10492321 in males, the subgroup at age ≤60 years, non-smokers, and non-drinkers. The associations of rs10859563 for BMI >24 kg/m^2, rs10859563 for diabetic nephropathy, and rs10859563 for T2DM patients with CHD were also positive at the prior probability level of 0.1. Moreover, GTA and AGT haplotypes were also positive in males.

MDR Analysis for SNP-SNP Interactions

MDR analysis was used to assess the influence of SNP-SNP interaction in *SOCS2* (Figure 2 and Table 7). Table 7 displays the results obtained from MDR analysis for one- to five-locus models. *SOCS2* rs10492321 was the best single-factor model (testing accuracy = 0.533; cross–validation consistency = 6/10). Moreover, the best combination was five-locus model (Testing accuracy = 0.33; cross–validation consistency = 10/10).

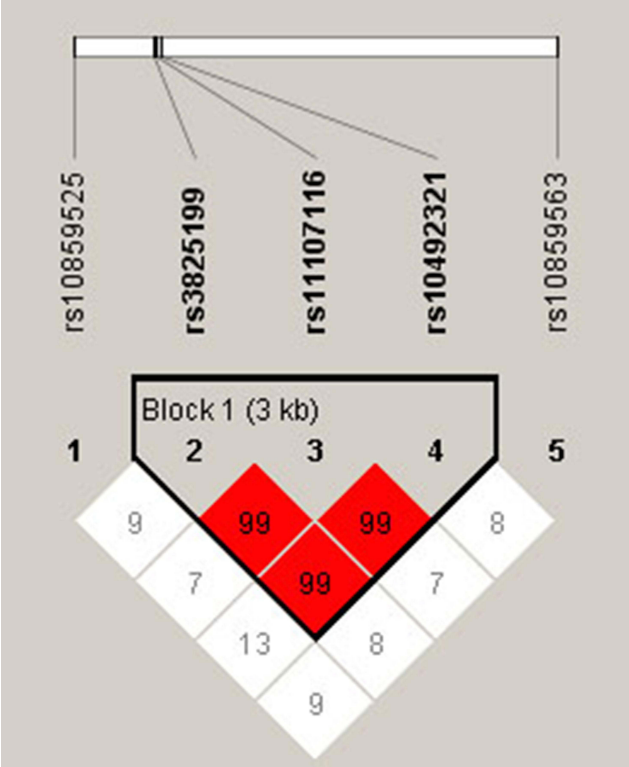

Figure 1 Haplotype block map for the linkage disequilibrium between the genetic variants in *SOCS2*. Bold indicated a LD block in *SOCS2* SNPs (rs3825199, rs11107116 and rs10492321). The numbers of matrices represent the D′ value for the SNP pairs.

Expression of mRNA and Association of mRNA Levels and Genotype of These SNPs

We measured the expression of *SOCS2* mRNA between the controls and patients with T2DM. We found that *SOCS2* mRNA was downregulated in patients with T2DM compared to healthy controls (p = 0.029, Figure 3). Next, the association between mRNA levels and the genotype of these SNPs was measured. However, no significant association

Table 5 Correlation of *SOCS2* Haplotypes with T2DM Risk in the Whole Population and Males

SNP	Haplotype	Frequency		χ^2	p^a	Adjusted by Age and Gender	
		Case	Control			OR (95% CI)	p^b
Whole population							
rs3825199|rs11107116|rs10492321	GTA	0.346	0.319	1.60	0.206	1.13 (0.94–1.36)	0.206
rs3825199|rs11107116|rs10492321	AGA	0.028	0.023	0.51	0.474	1.23 (0.70–2.17)	0.468
rs3825199|rs11107116|rs10492321	AGT	0.383	0.349	2.45	0.118	1.15 (0.96–1.38)	0.121
Males							
rs3825199|rs11107116|rs10492321	GTA	0.360	0.305	5.04	**0.025**	**1.29 (1.03–1.60)**	**0.026**
rs3825199|rs11107116|rs10492321	AGA	0.028	0.021	0.73	0.392	1.35 (0.68–2.69)	0.388
rs3825199|rs11107116|rs10492321	AGT	0.398	0.330	7.24	**0.007**	**1.34 (1.08–1.66)**	**0.008**

Notes: p^a values were calculated by χ^2 test. p^b values were calculated by logistic regression analysis with adjustments for age and gender. Bold values indicate that $p < 0.05$ respects the data are statistically significant.

Abbreviations: T2DM, type 2 diabetes mellitus; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

Table 6 False-Positive Report Probability Values for the Associations Between *SOCS2* Polymorphisms and T2DM Susceptibility

Group/SNPs ID	Model	OR (95% CI)	*p*	Statistical Power	Prior Probability				
					0.25	0.1	0.01	0.001	0.0001
Overall									
rs3825199	AG vs AA	1.44 (1.11–1.88)	0.007	0.618	**0.034**	**0.097**	0.541	0.922	0.992
	AG-GG vs AA	1.35 (1.05–1.73)	0.020	0.797	**0.062**	**0.167**	0.687	0.957	0.996
rs11107116	GT vs GG	1.39 (1.07–1.81)	0.014	0.714	**0.057**	**0.155**	0.668	0.953	0.995
	GT-TT vs GG	1.30 (1.01–1.67)	0.038	0.869	**0.122**	0.293	0.820	0.979	0.998
rs10492321	TA vs TT	1.48 (1.13–1.93)	0.004	0.539	**0.021**	**0.060**	0.411	0.876	0.986
	TA-AA vs TT	1.40 (1.09–1.81)	0.009	0.701	**0.042**	**0.116**	0.591	0.936	0.993
Male									
rs3825199	G vs A	1.32 (1.06–1.64)	0.014	0.876	**0.040**	**0.111**	0.579	0.933	0.993
	AG vs AA	1.69 (1.23–2.31)	0.001	0.855	**0.003**	**0.010**	**0.104**	0.539	0.921
	AG-GG vs AA	1.61 (1.20–2.17)	0.002	0.923	**0.006**	**0.017**	**0.159**	0.656	0.950
	AA+AG+GG	1.31 (1.06–1.64)	0.015	0.881	**0.059**	**0.159**	0.675	0.954	0.995
rs11107116	T vs G	1.28 (1.03–1.59)	0.029	0.924	**0.077**	0.200	0.733	0.965	0.996
	GT vs GG	1.61 (1.18–2.20)	0.003	0.913	**0.009**	**0.027**	0.232	0.753	0.968
	GT-TT vs GG	1.54 (1.14–2.07)	0.004	0.958	**0.013**	**0.038**	0.304	0.815	0.978
	GG+GT+TT	1.28 (1.02–1.59)	0.030	0.924	**0.077**	0.200	0.733	0.965	0.996
rs10492321	A vs T	1.37 (1.10–1.70)	0.004	0.795	**0.016**	**0.046**	0.346	0.842	0.982
	TA vs TT	1.72 (1.25–2.37)	0.001	0.822	**0.003**	**0.010**	**0.099**	0.526	0.917
	TA-AA vs TT	1.69 (1.25–2.28)	0.001	0.865	**0.002**	**0.006**	**0.064**	0.407	0.873
	TT+TA+AA	1.37 (1.10–1.69)	0.005	0.801	**0.012**	**0.036**	0.289	0.804	0.976
≤60 years									
rs3825199	AG vs AA	1.99 (1.35–2.94)	0.001	0.510	**0.003**	**0.010**	**0.096**	0.518	0.915
	AG-GG vs AA	1.73 (1.20–2.49)	0.003	0.782	**0.012**	**0.035**	0.287	0.802	0.976
rs11107116	GT vs GG	1.78 (1.21–2.62)	0.003	0.723	**0.014**	**0.041**	0.322	0.827	0.980
	GT-TT vs GG	1.54 (1.08–2.21)	0.018	0.922	**0.059**	**0.157**	0.673	0.954	0.995
rs10492321	TA vs TT	1.86 (1.26–2.74)	0.002	0.643	**0.008**	**0.023**	0.206	0.724	0.963
	TA-AA vs TT	1.61 (1.12–2.30)	0.010	0.883	**0.029**	**0.083**	0.499	0.909	0.990
Non-smoker									
rs3825199	AG vs AA	1.92 (1.25–2.94)	0.003	0.574	**0.014**	**0.040**	0.317	0.824	0.979
	AG-GG vs AA	1.64 (1.11–2.43)	0.013	0.839	**0.047**	**0.128**	0.617	0.942	0.994
rs11107116	GT vs GG	1.80 (1.18–2.76)	0.006	0.685	**0.030**	**0.085**	0.504	0.911	0.990
	GT-TT vs GG	1.57 (1.06–2.32)	0.024	0.888	**0.074**	**0.193**	0.724	0.964	0.996

(*Continued*)

Table 6 (Continued).

Group/SNPs ID	Model	OR (95% CI)	*p*	Statistical Power	Prior Probability				
					0.25	0.1	0.01	0.001	0.0001
rs10492321	TA vs TT	1.77 (1.16–2.71)	0.008	0.713	**0.035**	**0.098**	0.544	0.923	0.992
	TA-AA vs TT	1.62 (1.09–2.40)	0.016	0.853	**0.054**	**0.145**	0.652	0.950	0.995
Alcohol drinker									
rs10859525	G vs A	0.63 (0.42–0.96)	0.030	0.859	**0.099**	0.249	0.784	0.973	0.997
	AA+AG+GG	0.65 (0.43–0.98)	0.041	0.895	**0.118**	0.286	0.815	0.978	0.998
rs3825199	AG vs AA	1.87 (1.04–3.35)	0.037	0.589	**0.153**	0.351	0.856	0.984	0.998
Not alcohol drinker									
rs3825199	AG vs AA	1.70 (1.12–2.59)	0.014	0.775	**0.050**	**0.136**	0.633	0.946	0.994
	AG-GG vs AA	1.52 (1.03–2.25)	0.035	0.915	**0.107**	0.264	0.798	0.975	0.997
rs11107116	GT vs GG	1.61 (1.06–2.44)	0.026	0.843	**0.069**	**0.183**	0.711	0.961	0.996
rs10492321	TA vs TT	1.67 (1.10–2.54)	0.016	0.800	**0.058**	**0.157**	0.672	0.954	0.995
	TA-AA vs TT	1.57 (1.06–2.33)	0.023	0.885	**0.078**	0.203	0.738	0.966	0.996
BMI >24 kg/m^2									
rs10859563	C vs G	0.70 (0.53–0.92)	0.011	0.637	**0.047**	**0.130**	0.621	0.943	0.994
	CC vs GG	0.46 (0.26–0.81)	0.008	0.386	**0.053**	**0.143**	0.647	0.949	0.995
	CC vs GG-GC	0.53 (0.32–0.87)	0.013	0.591	**0.058**	**0.155**	0.669	0.953	0.995
	GG+GC+CC	0.69 (0.52–0.92)	0.010	0.593	**0.055**	**0.148**	0.657	0.951	0.995
BMI ≤24 kg/m^2									
rs3825199	AG vs AA	1.66 (1.03–2.68)	0.037	0.777	**0.128**	0.306	0.829	0.980	0.998
rs11107116	GT vs GG	1.64 (1.02–2.64)	0.042	0.793	**0.136**	0.321	0.839	0.981	0.998
Diabetic nephropathy									
rs10859525	G vs A	0.68 (0.50–0.94)	0.017	0.548	**0.097**	0.243	0.780	0.973	0.997
	AA+AG+GG	0.71 (0.51–0.99)	0.040	0.645	**0.168**	0.378	0.870	0.985	0.999
rs10859563	C vs G	0.72 (0.55–0.96)	0.022	0.700	**0.098**	0.245	0.781	0.973	0.997
	CC vs GG	0.51 (0.28–0.91)	0.024	0.527	**0.114**	0.279	0.810	0.977	0.998
	GC-CC vs GG	0.61 (0.40–0.91)	0.016	0.835	**0.053**	**0.143**	0.647	0.949	0.995
	GG+GC+CC	0.70 (0.53–0.93)	0.013	0.632	**0.062**	**0.165**	0.685	0.956	0.995
Diabetic retinopathy									
rs10859525	G vs A	0.63 (0.41–0.99)	0.042	0.842	**0.138**	0.325	0.841	0.982	0.998
	AG vs AA	0.53 (0.29–0.95)	0.034	0.578	**0.146**	0.339	0.850	0.983	0.998
	AG-GG vs AA	0.53 (0.31–0.92)	0.025	0.582	**0.110**	0.271	0.804	0.976	0.998
	AA+AG+GG	0.63 (0.40–0.98)	0.042	0.847	**0.125**	0.300	0.825	0.979	0.998

(*Continued*)

Table 6 (Continued).

Group/SNPs ID	Model	OR (95% CI)	*p*	Statistical Power	Prior Probability				
					0.25	0.1	0.01	0.001	0.0001
T2DM patients with CHD									
rs3825199	GG vs AA	0.35 (0.13–0.93)	0.035	0.237	0.308	0.572	0.936	0.993	0.999
	GG vs AA-AG	0.31 (0.12–0.79)	0.014	0.158	0.211	0.446	0.898	0.989	0.999
rs11107116	TT vs GG	0.28 (0.10–0.82)	0.020	0.145	0.295	0.557	0.932	0.993	0.999
	TT vs GG-GT	0.25 (0.09–0.71)	0.009	0.097	0.223	0.463	0.905	0.990	0.999
rs10859563	C vs G	0.70 (0.53–0.93)	0.015	0.632	**0.062**	**0.165**	0.685	0.956	0.995
	CC vs GG	0.48 (0.25–0.89)	0.020	0.448	**0.117**	0.284	0.814	0.978	0.998
	GG+GC+CC	0.70 (0.52–0.94)	0.018	0.627	**0.078**	0.203	0.737	0.966	0.996
Males									
rs3825199| rs11107116| rs10492321	GTA	1.29 (1.03–1.60)	0.026	0.915	**0.063**	**0.168**	0.689	0.957	0.996
rs3825199| rs11107116| rs10492321	AGT	1.34 (1.08–1.66)	0.008	0.849	**0.025**	**0.073**	0.463	0.897	0.989

Notes: *p* values were calculated by logistic regression analysis with adjustments for age. Statistical power was calculated using the number of observations in the subgroup and the OR and *p* values in this table. The level of false-positive report probability threshold was set at 0.2, and noteworthy findings are presented. Bold values indicate that prior probability< 0.2 indicates noteworthy findings.

Abbreviations: T2DM, type 2 diabetes mellitus; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; CHD, coronary heart disease.

between the expression of *SOCS2* mRNA and the genotype of these SNPs in patients with T2DM and the controls was observed ($p > 0.05$, Suppl_Figure 1).

Discussion

In our study, we detected the potential effect of *SOCS2* genetic variants on T2DM incidence and found that three SNPs in *SOCS2* (rs3825199, rs11107116 and rs10492321) were associated with increasing the risk towards the occurrence of T2DM in the Chinese Han population (Table 2). Specially, the contribution of *SOCS2* polymorphisms to T2DM risk

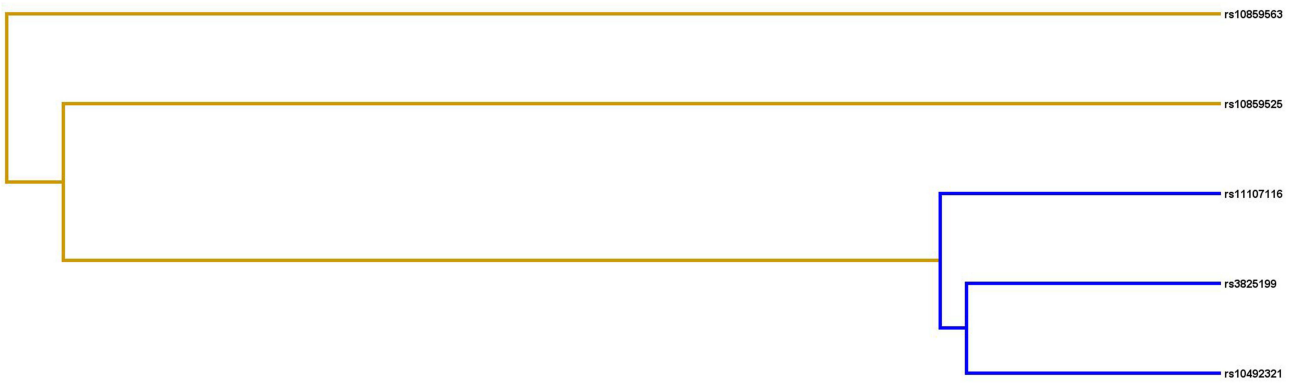

Figure 2 The interaction dendrogram for *SOCS2* SNP-SNP interaction. Yellow line indicates synergistic interaction, blue color indicates redundant interactions.

Table 7 SNP-SNP Interaction Models in *SOCS2* for T2DM Risk by MDR Analysis

Best Combination	Training Bal. Acc.	Testing Bal. Acc.	CVC	χ^2	*p*	OR (95% CI)
rs10492321	0.545	0.533	6/10	7.80	**0.0052**	1.42 (1.11–1.83)
rs10859525, rs10492321	0.556	0.526	5/10	11.70	**0.0006**	1.55 (1.20–1.98)
rs10859525, rs10492321, rs10859563	0.577	0.517	5/10	22.02	**<0.0001**	1.82 (1.42–2.34)
rs10859525, rs11107116, rs10492321, rs10859563	0.587	0.513	5/10	28.46	**<0.0001**	1.98 (1.54–2.55)
rs10859525, rs3825199, rs11107116, rs10492321, rs10859563	0.589	0.533	10/10	29.81	**<0.0001**	2.01 (1.56–2.59)

Notes: *p* values were calculated using χ^2 tests. Bold values indicate that $p < 0.05$ indicates statistical significance.
Abbreviations: MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross–validation consistency; OR, odds ratio; CI, confidence interval.

might be associated with age, gender, lifestyle (smoking and drinking), and BMI (Suppl Tables 3–5). Among patients with T2DM, rs10859525 and rs10859563 had a reduced risk of diabetic nephropathy, and rs10859525 had the protective effect on the risk of diabetic retinopathy (Table 3). Additionally, rs3825199, rs11107116, and rs10859563 had a reduced risk for T2DM patients with coronary heart disease compared with healthy controls (Table 4). Moreover, GTA and AGT haplotypes had higher T2DM susceptibility among males (Table 5). The results combined SNPs revealed that rs10492321 was the best single factor model, and the best combination was five-locus model (Table 7). Moreover, we found that *SOCS2* mRNA was downregulated in patients with T2DM compared with healthy controls. This is the first study reporting the association between *SOCS2* variants and T2DM predisposition in the Chinese Han population.

SOCS2 gene, located on chromosome 12q22, has emerged as the negative regulator on insulin and growth hormone pathways. Several studies reported that *SOCS2* genetic variants were associated with a large number of diseases, including acromegaly, growth hormone deficiency, and extreme obesity.[20–22] *SOCS2* gene as risk gene was identified to be associated with the molecular networks of T2DM.[23] The increasing evidence reveals that SOCS2 protein plays an important role in T2DM development, involving regulation of the insulin signaling and pancreatic β-cell function.[24] However, little is known about the impact of *SOCS2* genetic variants on the occurrence of T2DM. Only one reported study did *SOCS2* SNPs are related to the risk of T2DM in Japanese.[25] No previous studies have reported the association between these SNPs (rs10859525, rs3825199, rs11107116, rs10492321, and rs10859563) and T2DM risk. Here, our findings firstly demonstrated that *SOCS2* rs3825199, rs11107116 and rs10492321 might be risk factors towards increased T2DM predisposition among the Chinese Han population (Table 2). Our study suggested that *SOCS2* variants might contribute to the pathogenesis of T2DM.

T2DM is the result of the combined effects of genetic background, gender, aging, lifestyle, obesity and other factors.[6,7,26] Age and gender differences in the risk, onset, and progress of T2DM were found in previous studies.[27,28] When stratified by gender and age, rs3825199, rs11107116, and rs10492321 were conferred to an increased T2DM risk among males, and among the subjects aged ≤60 years (Suppl Table 3). Haplotype analysis revealed that GTA and AGT

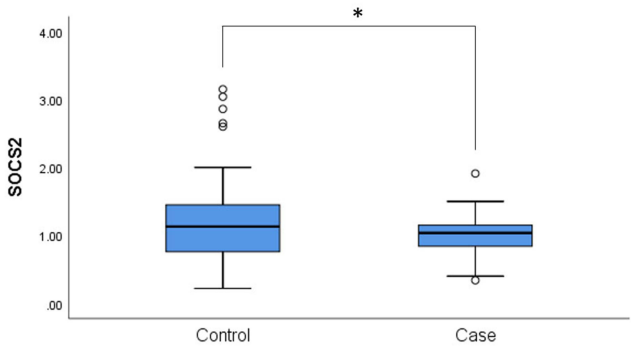

Figure 3 The expression levels of *SOCS2* in the PBMCs samples of 50 cases and 50 controls. Statistical significance of expression level with *for $p < 0.05$. PBMCs, peripheral blood mononuclear cells.

haplotypes had the higher T2DM susceptibility among males (Table 5). Our finding suggested that the association between *SOCS2* polymorphisms and T2DM susceptibility was gender- and age-specifics. In addition, active smoking is reported to be a risk factor for T2DM, and moderate alcohol consumption is related to a reduced T2DM risk.[29,30] Epidemiological studies showed that obesity had the important role on the occurrence of T2DM, and nearly 90% of the incidence of patients with T2DM is associated with being overweight.[31,32] Our results displayed that rs3825199 and rs11107116 conferred to the higher T2DM susceptibility in non-smokers (Suppl_Table 4). *SOCS2* rs10859525 showed a protective effect on T2DM risk among drinkers, while rs11107116 and rs10492321 had the higher risk for T2DM developing in non-drinkers (Suppl_Table 4). When stratified by BMI, rs3825199 and rs11107116 were associated with an increased T2DM susceptibility in subjects with BMI ≤24 kg/m^2, whereas rs10859563 was related to a reduced T2DM risk among subjects with BMI >24 kg/m^2 (Suppl_Table 5). These results showed that smoking, alcohol drinking, and BMI might influence *SOCS2* polymorphisms to T2DM risk.

With the increase in the incidence of T2DM, a rise in the prevalence of secondary comorbidities including diabetic nephropathy and diabetic retinopathy is anticipated.[33] Our results showed that rs10859525 and rs10859563 had a reduced risk of diabetic nephropathy, and rs10859525 had the protective effect on the risk of diabetic retinopathy among patients with T2DM (Table 3). Considering that coronary artery diseases and hypertension are related to the occurrence and development of T2DM,[34,35] we examined the association of *SOCS2* variants with the combined effect of T2DM and coronary heart disease/hypertension. We found that rs3825199, rs11107116, and rs10859563 had a reduced risk for T2DM patients with coronary heart disease compared with healthy controls, but not significantly associated with hypertension (Table 4). A study reported that *SOCS2* overexpression might alleviate diabetic nephropathy in rats by inhibiting the TLR4/NF-κB pathway.[36] *SOCS2* was upregulated in myocardial tissues in mice after ischemia-reperfusion (I/R) injury.[37] We hypothesized that these SNPs may affect the occurrence of diabetic nephropathy and T2DM patients with coronary heart disease by affecting *SOCS2* expression. However, no significant correlation between *SOCS2* mRNA expression and SNPs genotypes was found, which may be caused by a small sample size. Recently, there is no report about the role of *SOCS2* gene on diabetic retinopathy and hypertension. However, our results should be necessary to confirm the results in a larger sample size.

Inevitably, this study has several limitations. First, all subjects were Han nationality recruited from the same hospital, which may not be generalized to other ethnicities. Second, the quantity of the chosen variants are too small to represent the genetic polymorphisms in *SOCS2* thoroughly. Third, the sample size for stratification analysis is too insufficient to exclude the false-positive results. Finally, the functional and mechanistic studies of *SOCS2* polymorphisms on T2DM are not performed. Although we found no significant correlation between SNPs genotype and mRNA expression of *SOCS2*because of the small sample size, the further experimental verification is needed. Therefore, large-scale and multicenter future studies are needed to authenticate our findings, and studies for multiple SNPs and the functional effect of SNPs on *SOCS2* are also desired.

Conclusion

In summary, this is the first study to report that rs3825199, rs11107116 and rs10492321 in *SOCS2* were conferred to an increased risk towards the occurrence ofT2DM in the Chinese Han population and might be associated with age, gender, lifestyle (smoking and drinking), and BMI. *SOCS2* polymorphisms were also associated with a reduced risk for T2DM patients with diabetic nephropathy, diabetic retinopathy, and coronary heart disease. Furthermore, GTA and AGT haplotypes had the higher T2DM susceptibility among males, and risk accumulation effect on the incidence of T2DM was found in SNP-SNP interaction. Moreover, *SOCS2* mRNA was downregulated in patients with T2DM, suggesting that *SOCS2* might have an important role in the occurrence of T2DM. Our findings may help increase the understanding of *SOCS2* genetic polymorphisms in the pathogenesis T2DM in the Chinese Han population.

Data Sharing Statement

All data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author (Jing Xu, 254309205@qq.com).

Compliance with Ethical Standards

The protocol of this study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTUAF2019LSK-007) and conformed to the Declaration of Helsinki.

Informed Consent

All individuals provided written informed consent prior to sample collection.

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The authors thank all participants and volunteers in this study. A preprint of this article has previously been published.[38]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Juan Pan and Rui Tong are co-first authors for this study.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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