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ORIGINAL RESEARCH

The Influence of *SLC22A3* Genetic Polymorphisms on Susceptibility to Type 2 Diabetes Mellitus in Chinese Population

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Background: Solute carrier family 22 member 3 (*SLC22A3*) gene had been reported to be associated with the efficacy of metformin in type 2 diabetes mellitus (T2DM). However, few studies reported the relationship between *SLC22A3* polymorphism and T2DM. The aim of this study was to investigate the association of *SLC22A3* polymorphism and susceptibility to T2DM in Chinese population.
Methods: We identified *SLC22A3* rs555754, rs3123636, rs3088442 genotypes of 450 T2DM patients and 220 healthy controls from the Chinese population. The association between SNPs of *SLC22A3* and susceptibility of T2DM was evaluated.
Results: The clinical characteristics were significantly different between T2DM patients and healthy controls. The polymorphisms of *SLC22A3* rs555754 and rs3123636 were obviously associated with the susceptibility of T2DM which was adjusted for age, sex and BMI, while rs3088442 did not. And there was haplotype association of *SLC22A3* rs3088442-rs3123636 with T2DM susceptibility.
Conclusion: *SLC22A3* rs555754 and rs3123636 polymorphisms were associated with the susceptibility to T2DM in Chinese Han population. Large sample size studies would be required to verify this association.
Keywords: type 2 diabetes mellitus, *SLC22A3* gene, polymorphism, T2DM

Introduction

As one of the most common chronic metabolic diseases, diabetes characterized by hyperglycemia and abnormal insulin reaction, which severely threaten human health worldwide. It is estimated that 536.6 million people among 20–79 years were diagnosed with diabetes globally in 2021, accounting for about 10.5% of the global population, and type 2 diabetes mellitus (T2DM) is the major.[1] As we all known, T2DM is the results caused by the interaction of environmental factors and genetics.[2] Organic Cation Transporters (OCT) is a factor transferring many endogenous small molecules, drugs and environmental toxins, which will influence the development of various diseases and the efficacy of multiple drugs.[3]

The OCT family includes three organic cation transporters, and OCT3 is included. OCT3, encoded by the gene *SLC22A3*, which contains 12 putative transmembrane domains. *SLC22A3* is highly expressed at human blood–brain barrier, which suggest that OCT3 may be involved in the entry of diversity substrates into the CNS.[4] And it is reported that OCT3 can regulate the uptake of dopaminergic neurotransmission and behavior.[5] And it is a high-capacity transporter OCT3 is a critical transporter regulating the cardiac accumulation of doxorubicin, the deficiency of OCT3 can protect heart from acute and chronic doxorubicin-related damage.[6] What is more, *SLC22A3* is reported to be associated with esophageal cancer,[7,8] pancreatic adenocarcinoma[9] and acute myeloid leukemia.[10] *SLC22A3* is widely expressed in various tissues including liver, kidney, intestine, and other organs.[11] Any changes of *SLC22A3*, such as polymorphisms, methylation or epigenetic modification may influence the structure or function of OCT3, and then influence the transporting efficacy of many endogenous compounds.

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It is reported that the polymorphisms of *SLC22A3* were related to various disease including colon cancer, coronary artery disease[12] and T2DM.[3] As an organic cation transporter, more studies reported the influence of *SLC22A3* polymorphisms on metformin efficacy in T2DM,[13–15] but very few studies focused on the relationship between *SLC22A3* polymorphisms and T2DM,[11] especially in Chinese population. Thus, the aim of this study was to elucidate the association between *SLC22A3* polymorphisms and the susceptibility of T2DM in Chinese population.

Materials and Methods

Study Population and Design

This study includes 450 T2DM patients (281 males and 169 females, mean age 56.98±13.60) and 220 healthy controls (111 males and 109 females, mean age 52.92 ± 12.83). All patients were diagnosed with T2DM according to the ADA standard[16] as fasting plasma glucose (FPG) ≥7.0 mmol / L or 2h plasma glucose (2h PG) during oral glucose tolerance test (OGTT) ≥11.1 mmol / L or glycosylated hemoglobin (HbA1c) ≥6.5%. And the healthy controls were recruited from health management center without history of diabetes and cardiovascular disease. The exclusion criteria of this study listed as follows, type 1 diabetes mellitus, chronic kidney disease, liver disease, myocardial infarction, stroke, and pregnancy. The demographic and clinical characteristics, including gender, age, body mass index (BMI), HbA1c, FBG, postprandial blood glucose (PBG), C-Peptide (CPO), postprandial C-Peptide (PCPO), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) of all participants are listed in Table 1. This study complies with the Declaration of Helsinki. The informed consent has obtained from all participants and this study was approved by the Ethics Committee of the Affiliated Zhuzhou Hospital of Xiangya School of Medicine CSU (Zhuzhou, Hunan, China) (2019–05031).

DNA Isolation and Genotyping

Three-milliliter peripheral blood was donated from each participant. Genomic DNA was isolated by the SQ Blood DNA Kit II (Omega Bio-Tek, Guangzhou, China) according to the manufacturer's protocol and stored at −20°C. Three SNPs of *SLC22A3* gene (rs555754, rs3123636 and rs3088442) was selected for further investigation according to bioinformatics

Table 1 The Demographic and Clinical Characteristics of T2DM Patients and Healthy Controls

Parameter	Healthy Controls (n=220)	T2DM Patients (n=450)	P value
Gender			
Male	111	281	**0.003***
Female	109	169	
Age(years)	52.92±12.83	56.98±13.60	**<0.001****
Height(cm)	165.75±8.21	165.48±10.20	0.736
Weight(kg)	63.02±8.89	67.58±11.81	**<0.001****
BMI(kg/m^2)	22.88±2.35	25.72±27.52	0.127
HbA1c(%)	5.49±2.68	8.65±2.38	**<0.001****
FBG(mmol/L)	5.31±1.37	8.60±3.20	**<0.001****
PBG(mmol/L)	6.51±2.94	14.10±5.87	**<0.001****
CPO(ng/mL)	2.64±1.43	2.38±1.71	0.091
TC(mmol/L)	5.12±4.25	4.62±1.26	**0.024***
TG(mmol/L)	1.78±3.76	2.07±2.12	0.203
LDL(mmol/L)	3.01±4.68	2.81±3.03	0.530
HDL(mmol/L)	1.45±0.45	3.40±47.96	0.545

Notes: Data are given as mean ± SD. Data were analyzed by independent sample *T*-test. *P<0.05, **P<0.001. The numbers in bold indicated statistically significant values.

Abbreviations: BMI, body mass index; HbA1c, glycosylated haemoglobin; FBG, fasting blood-glucose; PBG, postprandial blood glucose; CPO, C-Peptide; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

analysis and previous studies. High-throughput genotyping was relegated to Genesky Biotechnologies Inc. in Shanghai. The primers of these three SNPs were supplied in Table S1.

Statistics

The Hardy–Weinberg equilibrium (HWE) of SNPs was examined by a goodness-of-fit chi-square (χ^2) test. The demographic and clinical characteristics (apart from gender) of T2DM patients and health controls were compared using independent sample *T*-test and shown as mean ± SD. And the χ^2-test also conducted to compare the frequencies of genotypes and alleles between T2DM patients and healthy controls. The association between three SNPs of *SLC22A3* gene and susceptibility to T2DM was performed by binary logistic regression adjusted for age, gender, and BMI. Furthermore, the homozygote comparison, heterozygote comparison, dominant model, recessive model and haplotype analysis were also analyzed by binary logistic regression. Two-tailed p values less than 0.05 were considered to significance. All statistical analysis was performed by SPSS 23.0 and PLINK v1.07.

Results

Characteristics of Subjects

To find out the difference between healthy controls and T2DM patients, the characteristic analysis was conducted. After filtered, there were 220 healthy controls and 450 T2DM patients in accordance with the inclusion criteria (Figure 1). The differences of demographic and clinical characteristics between T2DM patients and healthy controls are displayed in Table 1. There were significant differences in gender, age, weight, HbA1c, FBG, PBG and TC between two groups (all p values < 0.05). In T2DM groups, there were 281 males and 169 females, aged 56.98 ± 13.60 years old, while in the healthy controls, 111 males and 109 females, aged 52.92 ± 12.83 years old were enrolled. Apart from these, the weight, HbA1c level, FBG, PBG of T2DM groups were significantly higher than the healthy controls (all p < 0.001). However, TC level of T2DM groups was lower than the healthy controls (p = 0.024).

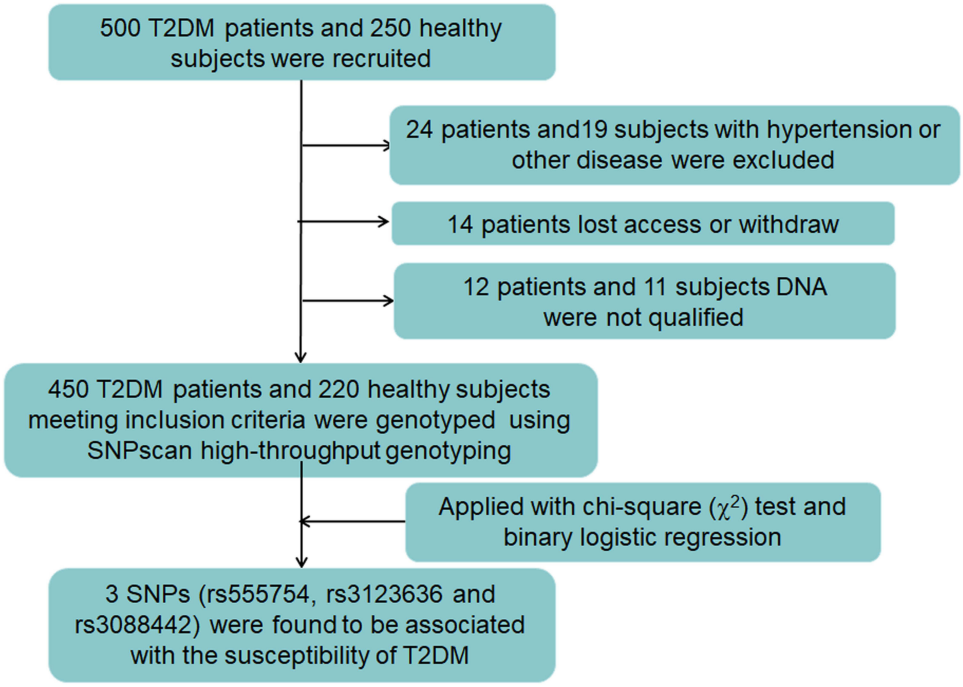

Figure 1 The experimental design routes of this study.

Association Study

In order to investigate the association of *SLC22A3* polymorphism and susceptibility to T2DM, χ^2-test and logistic regression was chosen for us. The genotypes and allelic frequencies of *SLC22A3* rs555754, rs3123636 and rs3088442 polymorphisms in the healthy controls and T2DM patients are listed in Table 2. All three SNPs were in accordance with the Hardy–Weinberg equilibrium (HWE p > 0.05, Table 2) and had a minor allele frequency > 5%. As for rs555754, the genotype frequencies of healthy controls were significantly different with T2DM patients (p = 0.034). The allelic frequencies were also different between healthy controls and T2DM patients (p = 0.012). As for rs3123636, there was a significant difference of genotype frequencies and allelic frequencies between the healthy controls and T2DM patients (p = 0.045 and p = 0.014, separately). However, we found no difference of rs3088442 in these two groups.

Further, we had applied different models to verify the influence of *SLC22A3* genetic polymorphisms on T2DM after adjusted for age, gender, and BMI (Table 3). In accordance with the results of χ^2-test, the influence of rs555754 and rs3123636 on the risk of T2DM was also confirmed by the results of binary logistic analysis adjusted by age, gender and BMI. The rs555754 genetic polymorphism was significantly associated with the increased susceptibility of T2DM in the homozygote comparison (AA vs GG: adjusted OR = 1.409, 95% CI = 1.049–1.892, p = 0.023) and recessive model (AA vs.GA/GG: adjusted OR = 1.365, 95% CI = 1.032–1.805, p = 0.029). As for rs3123636, there was a significant association of homozygote comparison with the decreased susceptibility to T2DM (CC vs TT: adjusted OR = 0.645, 95% CI = 0.449–0.927, p = 0.018). In

Table 2 Comparisons of Allelic Frequencies of *SLC22A3* rs555754, rs3123636 and rs3088442 Polymorphisms in T2DM Patients and Healthy Controls

Genotype	Healthy Controls (n=220)	T2DM Patients (n=450)	P value
SLC22A3 rs555754			
GG	106(48.2%)	183(40.7%)	**0.034**
GA	95(43.2%)	199(44.2%)	
AA	19(8.6%)	68(15.1%)	
Alleles			
G	307(69.8%)	565(62.8%)	**0.012**
A	133(30.2%)	335(37.2%)	
HWE P	0.940	0.522	
SLC22A3 rs3123636			
TT	113(51.4%)	276(61.3%)	**0.045**
TC	91(41.3%)	151(33.6%)	
CC	16(7.3%)	23(5.1%)	
Alleles			
T	343(78.0%)	733(81.4%)	**0.014**
C	97(22.0%)	167(18.6%)	
HWE P	0.923	0.924	
SLC22A3 rs3088442			
GG	54(24.5%)	137(30.5%)	0.275
GA	119(54.1%)	223(49.7%)	
AA	47(21.4%)	89(19.8%)	
Alleles			
G	227(51.6%)	497(55.3%)	0.195
A	213(48.4%)	401(44.7%)	
HWE P	0.469	0.995	

Notes: Data were analyzed by chi-square (χ^2) test. The numbers in bold indicated statistically significant values.
Abbreviations: T2DM, type 2 diabetes mellitus; HWE, Hardy–Weinberg equilibrium.

Table 3 The Association Between *SLC22A3* Genetic Polymorphisms and the Risk of T2DM (Adjusted for Age, Gender and BMI)

SNPs	Comparisons	Test of Association OR (95% CI)	P values
rs555754	AA vs GG (Homozygote comparison)	1.409(1.049–1.892)	**0.023**
	GA vs GG (Heterozygote comparison)	1.141(0.796–1.636)	0.473
	GA/AA vs GG (Dominant model)	1.335(0.956–1.347)	0.149
	AA vs GA/GG (Recessive model)	1.365(1.032–1.805)	**0.029**
rs3123636	CC vs TT (Homozygote comparison)	0.645(0.449–0.927)	**0.018**
	TC vs TT (Heterozygote comparison)	0.727(0.508–1.041)	0.082
	TC/CC vs TT (Dominant model)	0.824(0.694–0.978)	**0.027**
	CC vs TC/TT (Recessive model)	0.705(0.497–0.999)	**0.049**
rs3088442	AA vs GG (Homozygote comparison)	0.807(0.621–1.048)	0.107
	GA vs GG (Heterozygote comparison)	0.750(0.500–1.126)	0.165
	GA/AA vs GG (Dominant model)	0.858(0.707–1.040)	0.858
	AA vs GA/GG (Recessive model)	0.910(0.737–1.123)	0.380

Notes: Data were analyzed by binary logistic regression. The numbers in bold indicated statistically significant values.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4 Haplotype Analysis of *SLC22A3* rs3088442 and rs3123636 with the Risk of T2DM

Haplotypes[a]	Case Frequency	Control Frequency	OR (95% CI)	P value
AC	0.212	0.274	0.713(0.548–0.929)	**0.011**
AT	0.235	0.210	1.155(0.876–1.523)	0.305
GT	0.546	0.510	1.160(0.923–1.459)	0.203

Notes: Data were analyzed by the online software, SHEsis.[10] [a]Only haplotypes with frequency≥0.05 were shown. The numbers in bold indicated statistically significant values.
Abbreviations: T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

the dominant model, TT genotype of rs3123636 was selected as the reference, we found that the TC/CC genotype was shown to be the protective factor of T2DM (TC/CC vs TT: adjusted OR = 0.824, 95% CI = 0.694–0.978, p = 0.027). In the recessive model, when rs3123636 TC/TT genotype was used as the reference, the CC genotype was associated with a decreased risk of T2DM (CC vs TC/TT: adjusted OR = 0.705, 95% CI = 0.497–0.999, p = 0.049). However, there was no significant association between rs3088442 of *SLC22A3* and T2DM risk when analyzed by logistic regression adjusted for age, gender and BMI.

Haplotype Analysis

After correlation analysis, we also conducted the linkage disequilibrium (LD) analysis by the online software, SHEsis[17] (Figures S1 and S2). And we found there was LDs between *SLC22A3* rs3123636 and rs3088442, with the r square value of rs3088442-rs3123636 is 0.332, and the D′ value is 0.948.

Then, haplotype analysis between T2DM and healthy controls was conducted. According to the results, there were only *SLC22A3* rs3088442-rs3123636 in a block, and the frequency of haplotypes with p values <0.05 was ignored. So, there were only three haplotypes analyzed in this study. Among them, only one haplotype was significantly related to the risk of T2DM (Table 4). The haplotype of AC with rs3088442-rs3123636 was considered as the protective factor of the susceptibility to T2DM (OR = 0.713, 95% CI = 0.548–0.929, p = 0.011).

Discussion

SLC22A3 is a candidate gene related to various diseases, including cancer,[8,18] cardiovascular disease[6,19] and metabolic disease.[20,21] Ren et al found that rs420038 in *SLC22A3* was related to lower risk of colorectal cancer and influenced the expression of this gene.[18] In addition, Wang et al revealed that rs3088442 in *SLC22A3* was associated with both plasma lipoprotein(a) level and the risk of coronary artery disease in Chinese population.[19] Paquette et al demonstrated that rs2048327

SNP of *SLC22A3* gene was significantly associated with lipoprotein(a) level and cardiovascular disease events in hypercholesterolemia subjects.[22] Further, rs3088442 G>A and rs2292334 G>A in *SLC22A3* had been reported to be associated with the susceptibility of T2DM.[11] At the same time, these two variants (rs2292334[23] and rs3088442[24]) had been reported to be related to the efficacy of metformin in different population. As for Indian males, rs2292334 was identified as the risk factor for the development of T2DM.[25] In Iranians, rs3088442 G>A was identified as a protective factor with T2DM, while rs2292334 G>A as the risk.[11] In Pakistan population, rs3088442 was suggested to be a protective allele and was associated with metformin efficacy with T2DM patients.[26] In the latest follow-up study, rs543159 and rs1317652 in *SLC22A3* gene was suggested to be associated with variability in response to metformin therapy in T2DM patients.[20] However, no studies have shown the relationship between *SLC22A3* polymorphism and the risk of T2DM in Chinese.

In the present study, we firstly investigated the distribution of rs555754, rs3123636 and rs3088442 genetic polymorphism of *SLC22A3* gene, and discussed the roles of these three SNPs on the susceptibility of T2DM on 450 T2DM patients and 220 healthy controls in Chinese population. And we found significant difference of rs555754 and rs3123636 distribution between T2DM patients and healthy controls (Table 2). Compared to the wild-type, our data indicated the increased risk of T2DM patients carrying mutant-type of rs555754. In other words, the allele A and genotype AA of rs555754 in *SLC22A3* gene could lead to the occurrence of T2DM in Chinese population. As for rs3123636 genetic polymorphism, the mutant type was a significantly protective factor of T2DM. What's more, the haplotype of AC with rs3088442-rs3123636 was deemed as the protective factor of T2DM in our study. By means of bioinformatics analysis, we found the rs555754 polymorphism was the 5′ UTR variant, and rs3123636 was the intron variant. Like other reported regulatory genetic variants (such as *SLC22A3* −1603 G>A[26] and rs2229611[27]), rs555754 and rs3123636 could also influence the expression or function of *SLC22A3* gene by affecting the activity of splicing site or transcription factor. Thus, we hypothesized that rs555754 and rs3123636 genetic polymorphism of *SLC22A3* play similar roles in the susceptibility of T2DM. And the function of these two variants needs further investigations in the future.

In conclusion, this is the first time to analyze the effect of rs555754, rs3123636 and rs3088442 genetic polymorphisms in SLC22A3 gene on the susceptibility of T2DM, especially in Chinese population. We found that rs555754 and rs3123636 of *SLC22A3* gene were associated with the susceptibility of T2DM in Chinese population. Further studies in larger different population are needed to confirm our finding, and the research of the molecular mechanisms of these two variants will be the next steps of our team.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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Disclosure

The authors declare no conflict of interests in this study.

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