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The Association of UNC13B Gene Polymorphisms and Diabetic Kidney Disease in a Chinese Han Population

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Background: Polymorphisms in the UNC13B gene are associated with diabetic kidney disease (DKD) in the European population. Asian populations are more likely to suffer from complications of type 2 diabetes mellitus (T2DM), including diabetic kidney disease (DKD). This case-control study aimed to investigate the association between UNC13B gene polymorphisms and DKD in a Chinese Han population.

Material/Methods: Five single nucleotide polymorphism (SNP) *loci* (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) were genotyped in the UNC13B gene in 600 Chinese Han subjects. The study population included patients with T2DM with DKD (N=292) and control patients with T2DM without DKD (N=308). SNP genotyping was performed using a Sequenom MassARRAY system using chip-based matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS).

Results: There were no significant differences in the distribution of allele or genotype frequencies in the five UNC13B SNP markers (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) between the DKD group and control group of patients with T2DM. Haplotype analysis identified eight haplotypes for the combined effect of the five SNP markers in the UNC13B gene. The haplotype GGCCG was significantly associated with an increased risk of DKD.

Conclusions: This was the first study to demonstrate an association between UNC13B gene polymorphisms and the susceptibility to DKD in a Chinese Han population with T2DM. The haplotype GGCCG was significantly associated with an increased risk of DKD. The findings highlight the joint effect of SNP markers in the pathogenesis of DKD.

MeSH Keywords: Diabetic Nephropathies • Genetic Association Studies • Structural Homology, Protein

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Background

Diabetic kidney disease (DKD) is a chronic and severe microvascular complication of type 2 diabetes mellitus (T2DM). DKD can lead to end-stage renal disease (ESRD) and kidney failure and is closely associated with increased morbidity and mortality from cardiovascular disease [1]. Despite progress in the diagnosis and management of T2DM and its complications, the pathogenesis of DKD remains poorly understood. Epidemiological and familial population studies have shown that genetic factors play a key role in the pathogenesis of DKD, regardless of the type of diabetes [2–5]. The identification of the potential susceptibility genes and gene *loci* and the exploration of the molecular genetics of DKD are required to facilitate the early diagnosis and prevention of this complication.

Recently, the rs2281999 and rs13293564 polymorphisms of the UNC13B gene, or Unc-13 homolog B (*C. elegans*) on chromosome 9, are associated with an increased risk for DKD in three European populations, supporting its pivotal role as a novel candidate gene for DKD [6–8]. Asian populations are at an increased risk of complications of T2DM, including DKD, when compared with Western populations, regardless of environmental factors [9,10]. The susceptibility of UNC13B gene polymorphisms in DKD remains to be studied in Chinese populations that have a high incidence of DKD.

Therefore, this case-control study aimed to investigate the association between five single nucleotide polymorphisms (SNPs) (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) of the UNC13B gene in patients with T2DM with and without DKD in a Chinese Han population.

Material and Methods

Patients studied

A case-control study included 600 Chinese Han patients with type 2 diabetes mellitus (T2DM) and was conducted at the Jingzhou First People's Hospital in Hubei Province, China. The study included 292 patients with diabetic kidney disease (DKD) who were selected as the case group. The remaining 308 patients with T2DM, who had no history of DKD at the same time of hospital admission, were included in the control group. The controls were matched by nationality, age, and gender. T2DM was defined according to the 2012 criteria of the American Diabetes Association (ADA).

Cases with DKD had a urinary albumin excretion rate (UAER) ≥300 mg/24 h, or included patients with end-stage renal disease (ESRD) requiring renal transplantation or dialysis. The mean age was 60.53±7.14 years, and the mean duration of T2DM was 12.58±3.56 years. Patients in the control group had a maximum UAER <30 mg/24 h. The mean age was 59.68±6.22 years, and the mean duration of T2DM was 10.75±4.01 years. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Hospital Ethics Committee. All study participants signed informed consent to participate in the study.

Laboratory investigations

Fasting venous blood samples (3 ml) were extracted from each patient for the measurement of glycated hemoglobin A1c (HbA1c), creatinine, and lipids. HbA1c detection was performed using high-performance liquid chromatography (HPLC). Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by enzyme methods, according to the manufacturer's instructions. Blood pressure was evaluated after a 20-minute rest. The urinary albumin concentration was determined using immunoturbidimetry, with tests performed in triplicate.

DNA extraction and single nucleotide polymorphism (SNP) genotyping

Genomic DNA was extracted and purified from peripheral blood using a genomic DNA extraction kit (Sangon Biotech, Shanghai, China), according to the manufacturer's instructions. The DNA concentration was determined with a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Five candidate SNPs (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) in the UNC13B gene were selected according to several large genome-wide association studies (GWAS) from other countries [6–8]. Genotyping of each SNP locus was conducted using a Sequenom MassARRAY system using chip-based matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Sequenom, San Diego, CA, USA).

Primers were synthesized and obtained on request by Sangon Biotech (Shanghai, China). Briefly, multiplex polymerase chain reaction (PCR) was designed using the Assay Designer software package (Sequenom, San Diego, CA, USA), and were processed with a specific iPLEX enzyme according to standard protocols for iPLEX chemistry (Sequenom, San Diego, CA, USA). The final genotyping reaction products were purified and dotted onto a 384-well SpectroCHIP array using a MassARRAY Nanodispenser and then analyzed by MALDI-TOF MS. The final genotype results were read in real-time using the MassARRAY real-time software system and analyzed with the MassARRAY Typer software version 3.4 (Sequenom, San Diego, CA, USA). Data quality analysis was performed with an ABI 3100 sequencer system (Applied Biosystems, Foster City, CA, USA). The results showed

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Table 1. Clinical characteristics of the patients with type 2 diabetes mellitus (T2DM) with or without diabetic kidney disease (DKD).

Variables	Control group (without DKD)	Case group (with DKD)	*P*-value
n	308	292	NS
Male (%)	153 (49.68)	148 (50.68)	0.805
Age (years)	59.68±6.22	60.53±7.14	0.120
Duration (years)	10.75±4.01	12.58±3.56	<0.001
Family history (%)	29 (9.42)	40 (13.70)	0.100
BMI (kg/m^2)	25.78±4.48	26.52±5.05	0.058
HbA1c (%)	7.88±2.62	8.25±3.03	0.110
Creatinine (μmol/L)	67.48±7.22	74.52±7.85	<0.001
SBP (mmHg)	125±9.62	138±10.25	<0.001
DBP (mmHg)	80.75±7.23	82.00±8.05	0.046
TG (mmol/L)	1.79±0.78	1.91±0.86	0.074
TC (mmol/L)	4.88±1.64	5.11±1.86	0.108
LDL-C (mmol/L)	2.58±0.98	2.84±1.25	0.005
HDL-C (mmol/L)	1.21±0.52	1.15±0.38	0.109
With retinopathy (%)	53 (17.21)	59 (20.21)	0.346
With hypertension (%)	72 (23.38)	96 (32.88)	0.010

HbA1c – hemoglobin A1c; SBP – systolic blood pressure; DBP – diastolic blood pressure; TG – triglyceride; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; BMI – body mass index. Data are presented as the mean±SD or the number (%). *P*-value <0.05 indicates statistical significance.

that the genotyping success rate was >95%, and the genotype concordance rate reached 100% between duplicate samples.

Statistical analysis

Clinical data were analyzed using the t-test and the chi-squared χ^2 test with SPSS version 20.0 software (IBM Corporation, Armonk, NY, USA). Values were presented as mean±SD or the number and percentage (%) based on the type of data. The Hardy–Weinberg equilibrium (HWE) was determined for each SNP locus in the cases and controls. All the SNPs were in accordance with the quality control standards, with a minor allele frequency >0.05, an SNP call rate >95% (HWE: χ^2 with 1 df) and *P*>0.05. The genetic odds ratio (OR) and 95% confidence interval (CI) were both estimated by logistic regression analysis. Linkage disequilibrium (LD), HWE, haplotype construction, and frequency analysis were performed with SHEsis software (*http://analysis.bio-x.cn/myAnalysis.php*) using expectation-maximization algorithms [11]. A *P*-value <0.05 (two-sided) was considered to be statistically significant.

Results

Clinical data analysis

A total of 600 Chinese Han patients with type 2 diabetes mellitus (T2DM) were included in this study. There were 292 patients with diabetic kidney disease (DKD) who were selected as the case group, and the remaining 308 patients without DKD from the same time in hospital were included in the control group. The clinical characteristics of the patients in the study are shown in Table 1. Both study groups had a similar distribution of age and gender (Table 1). There were significant differences between the two groups in the duration of T2DM, creatinine levels, blood pressure, and low-density lipoprotein cholesterol (LDL-C) levels between the two groups (p<0.05) (Table 1). However, there was no significant difference for family history, body mass index (BMI), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) between the case and control groups (*P*>0.05) (Table 1).

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Table 2. Distribution of allele frequencies of the five single nucleotide polymorphisms (SNPs) in the UNC13B gene in the case-control cohort.

SNP ID	Allele	n (% frequency)		*P*-value	OR	95% CI
		Case	Control			
rs2281999	G	377 (0.646)	401 (0.651)	0.844	0.976	0.770–1.238
	A	207 (0.354)	215 (0.349)			
rs13293564	G	558 (0.955)	576 (0.935)	0.121	1.490	0.897–2.475
	T	26 (0.045)	40 (0.065)			
rs661712	C	360 (0.616)	359 (0.583)	0.235	1.151	0.913–1.450
	T	224 (0.384)	257 (0.417)			
rs17360668	G	473 (0.810)	521 (0.846)	0.100	0.777	0.575–1.050
	A	111 (0.190)	95 (0.154)			
rs10114937	T	384 (0.658)	423 (0.687)	0.282	0.876	0.688–1.115
	C	200 (0.342)	193 (0.313)			

SNP – single nucleotide polymorphism; OR – odds ratio; CI – confidence interval. *P*-value <0.05 indicates statistical significance.

Table 3. Genotype frequencies of the five single nucleotide polymorphisms (SNPs) in the UNC13B gene in cases and control groups of patients with type 2 diabetes mellitus (T2DM) with and without diabetic kidney disease (DKD).

SNP ID	Major/minor allele	Group	AA (%)	AB (%)	BB (%)	*P*-value
rs2281999	G/A	Case	143 (0.490)	91 (0.312)	58 (0.199)	0.691
		Control	148 (0.481)	105 (0.341)	55 (0.179)	
rs13293564	G/T	Case	273 (0.935)	12 (0.041)	7 (0.024)	0.160
		Control	276 (0.896)	24 (0.078)	8 (0.026)	
rs661712	C/T	Case	126 (0.432)	108 (0.370)	58 (0.199)	0.547
		Control	120 (0.390)	119 (0.386)	69 (0.224)	
rs17360668	G/A	Case	209 (0.716)	55 (0.188)	28 (0.096)	0.364
		Control	234 (0.760)	53 (0.172)	21 (0.068)	
rs10114937	T/C	Case	135 (0.462)	114 (0.390)	43 (0.147)	0.402
		Control	149 (0.484)	125 (0.406)	34 (0.110)	

AA represents the wild-type homozygote; AB represents the heterozygote; BB represents the polymorphic homozygote. *P*-value <0.05 indicates statistical significance.

Allele and genotype association analysis

In this study, five single nucleotide polymorphisms (SNPs) were analyzed (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) in the UNC13B gene in the case and control groups after removing non-analyzed genotype samples. The distribution of allele and genotype frequencies of the SNP markers are summarized in Tables 2 and 3. All the SNP markers were accorded with the Hardy-Weinberg equilibrium (HWE), and the minor allele frequencies were >0.05. However, the results showed that there was no significant difference in the distribution of allele or genotype frequencies in the five UNC13B SNP markers between the DKD group and the control group (Tables 2, 3) (*P*>0.05).

Haplotype analysis showed a significant association with an increased risk of DKD

The haplotype structures of the UNC13B gene distributed on chromosome 9 were analyzed, and five SNPs *loci* were identified

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Table 4. Haplotype frequencies of UNC13B gene in cases and controls.

Haplotype	12345	Case (%)		Control (%)		P-value	OR	95% CI
1	GATCG	35.00	(0.060)	25.20	(0.041)	0.109	1.536	0.905–2.606
2	GGCCG	45.60	(0.078)	29.72	(0.048)	0.025	1.724	1.066–2.788
3	GGCTA	33.02	(0.057)	38.22	(0.062)	0.752	0.925	0.570–1.501
4	GGCTG	49.51	(0.085)	62.16	(0.101)	0.391	0.841	0.565–1.250
5	GGTCA	72.54	(0.124)	88.42	(0.144)	0.390	0.862	0.613–1.211
6	GGTCG	140.92	(0.241)	154.01	(0.250)	0.878	0.979	0.744–1.288
7	GGTTA	26.97	(0.046)	32.80	(0.053)	0.629	0.878	0.519–1.486
8	GGTTG	56.60	(0.097)	64.96	(0.105)	0.708	0.930	0.635–1.361

Five variations constituted eight major haplotypes. 1: rs13293564 (G/T); 2: rs17360668 (G/A); 3: rs10114937 (T/C); 4: rs661712 (C/T); 5: rs2281999 (G/A). Haplotype frequencies were analyzed using SHEsis software. OR, odds ratio; CI, confidence interval. *P*-value <0.05 indicates statistical significance.

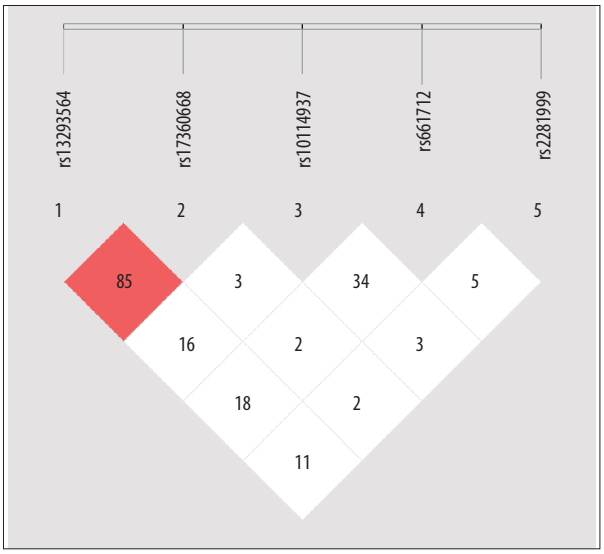

Figure 1. Diagram of the haplotypes and pair-wise linkage disequilibrium (LD) of the five single nucleotide polymorphism (SNP) *loci* (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) that were genotyped in the UNC13B gene in 600 Chinese Han subjects. The five SNPs and orientations in the UNC13B gene, located on chromosome 9, are shown at the top of the figure. The darker color indicates a greater linkage disequilibrium (LD), and the lighter color indicates a lower LD. Haplotype construction and LD analysis were performed using SHEsis software [11].

in the UNC13B gene that constituted a haplotype block, among which eight haplotypes were identified, as shown in Table 4 and Figure 1. The red square of the UNC13B linkage disequilibrium (LD) block indicated a strong linkage between the marker rs13293564 and rs17360668, as shown in Figure 1 (D'=0.85).

Also, the results showed that haplotype 2 (GGCCG) of the UNC13B gene was significantly associated with an increased risk of DKD (OR 1.724; 95% CI, 1.066~2.788; *P*=0.025) (Table 4). There was no significant difference between the other UNC13B haplotype frequencies between the cases and controls, as shown in Table 4 (*P*>0.05).

Discussion

Recently, the pivotal role of genetic susceptibility in the pathogenesis of diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM) has been supported by epidemiological studies and familial aggregation studies in diabetic patient populations [2–5]. Genetic associations at rs2281999 located in the UNC13B gene have recently been observed in the Finnish population of patients with DKD [6]. Another UNC13B single nucleotide polymorphism (SNP), rs13293564, was reported to be significantly correlated with DKD in four studies in Europe, and the T allele carriers of rs13293564 were shown to be at high risk of DKD [6–8]. Also, an association was identified between rs2281999 and rs13293564, which were in strong linkage disequilibrium (LD) on chromosome 9. However, these associations fell short of statistical significance from those observed in French populations [6]. However, a limitation of previous studies was that most failed to investigate haplotype and disease correlation at the candidate gene locus [12,13]. These findings highlight that studies on the UNC13B gene in other populations with DKD is important as there may be different environmental and ethnic differences that are biologically relevant and involved in DKD in T2DM.

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The present study was the first to investigate the association between UNC13B gene polymorphisms and DKD in a Chinese Han population, which is a population with a high incidence of DKD and a more rapid progression of renal involvement. The findings showed that there was no significant difference in the distribution of allele or genotype frequencies in the five UNC13B SNPs, rs13293564, rs17360668, rs10114937, rs661712, and rs2281999, between the DKD case group and the control group. Some of the study findings were consistent with those observed in Europeans with DKD due to type 1 diabetes mellitus [14], but were discordant with those reported in the population of Finland [6]. This finding may be attributed to environmental and ethnic differences, inappropriate sample size, genetic heterogeneity, or other unknown biological factors in this complex disease [15–17].

The findings from the present study, combined with those from previous studies, highlight that investigation of candidate genes for the complex disease of DKD in other populations is essential to resolve the disparate effects of the candidate genes for disease susceptibility. However, the finding that eight haplotypes reflected the combined effect of the five SNP markers in the UNC13B gene and were identified, the GGCCG haplotype was significantly associated with an increased risk of DKD. This haplotype of the UNC13B gene might be a potential genetic marker for DKD in the Chinese Han population. To our knowledge, this was the first report to investigate the role of haplotypes of the UNC13B gene in the pathogenesis of DKD in a Chinese population. Further genetic association studies are required to further explore the correlations between haplotype and disease cat the candidate gene locus. Importantly, single-gene variation is rarely the only cause of this complex disease, and the combined effect of haplotype should be emphasized and investigated in other countries and ethnic groups to investigate the biological mechanisms of DKD further.

The human UNC13B gene contains a C1 diacylglycerol (DAG) domain and three C2 (calcium) binding domains, UNC13B has been found to be highly expressed in human neurons and renal cells, including renal cortical tubular cells, glomerular mesangial cells, and also in podocytes that have a role as a charge barrier to prevent proteinuria [6,18,19]. In addition to the role in synaptic transmission in neurons [20,21], functional studies have shown that UNC13B binds to DAG and that DAG is activated in the presence of hyperglycemia, resulting in upregulation and activation of renal cells that express UNC13B, resulting in the apoptosis of these cells in the human kidney [19]. Because hyperglycemia activates DAG and increases its intracellular levels to induce apoptosis in human UNC13B-expressing renal tissues further, there is a possibility that UNC13B has a potential role in inducing apoptosis and mediating acute and chronic renal cell injury under hyperglycemic conditions [19]. Also, apoptosis of glomerular podocytes results in albuminuria [22,23], and this supports that the DAG-activated signaling pathway underlies an early stage of renal injury, rather than a late outcome of the renal injury in DKD [6]. Also, a protein kinase C (PKC)-dependent signaling pathway that regulates cell proliferation and differentiation has been identified as another DAG-activated pathway [19]. However, the underlying biological mechanisms that mediate these changes have not been fully clarified, and it remains unclear whether there is an association between the DAG-activated signaling pathway and the effects of UNC13B variants on apoptosis and other renal injuries in DKD. Therefore, further studies are required to determine the detailed molecular mechanisms underlying these signaling pathways and molecular associations in the pathogenesis of DKD.

Conclusions

This case-control study aimed to investigate the association between UNC13B gene polymorphisms and diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM) in a Chinese Han population. Five single nucleotide polymorphism (SNP) *loci* (rs13293564, rs17360668, rs10114937, rs661712, and rs2281999) were genotyped in the UNC13B gene in 600 Chinese Han subjects using a Sequenom MassARRAY system using chip-based matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). The GGCCG haplotype was significantly associated with an increased risk of DKD. Single gene variations showed no significance, but the joint effect of the haplotype may be another biological mechanism in DKD. The findings highlight the combined effect of SNP markers in the pathogenesis of DKD. Further studies on the UNC13B gene in genome-wide association studies (GWAS) in large samples involving other ethnicities are required to investigate this relationship further. Also, future functional studies of the gene variants in patients with T2DM may provide further insights into the pathogenesis of DKD.

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