Association between *COL4A3* variant rs55703767 and susceptibility to diabetic kidney disease in patients with type 2 diabetes mellitus: results from the INDEED cohort study

Zihan Li[1,2,3,4], Zijun Sun[1,2,3,4], Dongyuan Chang[1,2,3,4], Li Zhu[1,2,3,4], Min Chen[1,2,3,4], Minghui Zhao[1,2,3,4,5]

[1]Department of Renal Medicine, Peking University First Hospital, Beijing 100034, China;
[2]Institute of Nephrology, Peking University, Beijing 100034, China;
[3]Key Laboratory of Renal Disease, Ministry of Health of China, Beijing 100034, China;
[4]Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing 100034, China;
[5]Peking-Tsinghua Center for Life Sciences, Beijing 100034, China.

To the Editor: Diabetic kidney disease (DKD) is the leading cause of the end-stage renal disease nowadays.[1] The etiology of DKD is complex and remains largely unknown.[2] A genome-wide association study showed that a common missense variant in *COL4A3*, rs55703767, played a protective role in DKD in type 1 diabetes mellitus in Europeans, and this effect depended on blood glucose levels.[3] However, data from type 2 diabetes mellitus (T2DM) are insufficient.

This case-control study enrolled patients with T2DM from the incidence, development, and prognosis of diabetic kidney disease (INDEED) study.[4] The research complied with the *Declaration of Helsinki* and was approved by the Ethics Committee of Peking University First Hospital (No. 2016-1026). Informed consent was obtained from each participant.

Patients were diagnosed with T2DM according to the American Diabetic Association criteria,[5] and among these T2DM patients, those who developed kidney damage (estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2 or urinary albumin-to-creatinine ratio [uACR] >3.0 mg/mmol for >3 months) excluding coexisting nondiabetic-related renal diseases were classified as T2DM with the DKD group. All patients were required to have a minimum diabetes duration of 10 years. Finally, a total of 1311 T2DM patients including 580 with DKD and 731 without DKD were recruited in our study [Supplementary Figure 1, http://links.lww.com/CM9/A902].

Demographic data were gathered using standardized questionnaires. Triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, and fasting blood glucose (FBG) were tested. Urinary creatinine, uACR, and urinary α1-microglobulin were measured in the central laboratory in Peking University First Hospital.

DNA was extracted from peripheral blood samples. TaqMan SNP Genotyping Assay (4351379, Applied Biosystems) was used for the genotyping of rs55703767 using the ViiA™ 7 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA).

Categorical variables, frequencies of alleles, and genotypes between two groups were compared using the χ^2 test. Continuous variables were compared using the Student's *t*-test. The Hardy-Weinberg equilibrium (HWE) was tested using the Chi-square test with one degree of freedom. All *P* values were calculated based on two-tailed tests of statistical significance. The *P* value <0.05 was considered to be statistically significant. Statistical power was calculated by QUANTO. The statistical analysis of the data was calculated using the SPSS version 23.0 software (IBM SPSS, Armonk, NY, USA).

General data of these two groups were presented in Supplementary Table 1, http://links.lww.com/CM9/A902. Patients with DKD had significantly higher levels of systolic and diastolic blood pressure, abdominal circumference, body mass index, triglycerides, total cholesterol, FBG and serum creatinine, and lower level of eGFR than those without DKD [Supplementary Table 1, http://links.lww.com/CM9/A902]. Both groups were in accordance with the HWE, suggesting the suitability of the population for genetic analysis [Supplementary Table 2, http://links.lww.com/CM9/A902].

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Correspondence to: Min Chen, Department of Renal Medicine, Peking University First Hospital, Beijing 100034, China
E-Mail: chenmin74@sina.com

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Table 1: Association between *COL4A3* variant rs55703767 and susceptibility to DKD in T2DM patients.

Genetic models		T2DM with DKD ($n = 580$)	T2DM without DKD ($n = 731$)	OR (95% CI)	*P*
Dominant	GG	451 (77.8)	589 (80.6)	1.186 (0.907–1.551)	0.217
	GT+TT	129 (22.2)	142 (19.4)		
Recessive	TT	5 (0.86)	7 (0.95)	0.899 (0.284–2.849)	0.857
	GG + GT	575 (99.1)	724 (99.0)		
Overdominant	GT	124 (21.4)	135 (18.5)	1.201 (0.914–1.577)	0.209
	GG + TT	456 (78.6)	596 (81.5)		
Additive	TT	5 (0.9)	7 (0.9)	0.778 (0.241–2.514)	0.674
	GT	124 (21.4)	135 (18.5)	0.933 (0.294–2.958)	0.906
	GG	451 (77.8)	589 (80.6)		

Data were shown as *n* (%). CI: Confidence interval; DKD: Diabetic kidney disease; OR: Odds ratio; T2DM: Type 2 diabetes mellitus.

The frequency distributions of COL4A3 variant rs55703767 (G/T) genotypes in T2DM without DKD group were as follows: GG, 589 (80.6%); GT, 135 (18.5%); and TT, 7 (0.9%). The distributions in T2DM with the DKD group were as follows: GG, 451 (77.8%); GT, 124 (21.4%); and TT, 5 (0.9%). There was no significant difference in the genotypic distribution between these two groups [Supplementary Table 2, http://links.lww.com/CM9/A902]. Minor allele frequencies (MAFs) were found to be 0.116 and 0.102 for the "T" allele of rs55703767 in T2DM without DKD and T2DM with DKD group, respectively, and it was consistent with the frequency of the Asian population (MAF = 0.11) provided by the ALFA project (Asian) [Supplementary Table 3, http://links.lww.com/CM9/A902]. Dominant, recessive, overdominant, and additive model analyses were performed [Table 1] for the COL4A3 variant rs55703767 and no significant difference in the genotypic distribution between the two groups was identified in any model. The association analysis of rs55703767 genotypes with the investigated clinical parameters was shown in Supplementary Table 4, http://links.lww.com/CM9/A902 using two of the most common genetic models. In T2DM with the DKD group, a significantly higher level of HbAlc was found in individuals with TT genotype compared with those with GT/GG genotypes ($P = 0.025$; Supplementary Table 4, http://links.lww.com/CM9/A902).

The association analysis between rs55703767 and the risk of DKD was conducted by stratifying HbA1c below or above 7.5%, and there was no significant difference between them [Supplementary Table 5, http://links.lww.com/CM9/A902]. In addition, we further analyzed the association by stratifying different cut-off levels of HbA1c from 6.0% to 9.0% in our participants but no significant difference was observed. The different results between our study and the study by Salem *et al*[3] regarding hyperglycemia specificity might be explained by the following reasons. First, hyperglycemia specificity of the renal protective effect of rs55703767 may be different among various races. Second, our study focused on type 2 diabetes, and the study by Salem et al[3] focused on type 1 diabetes. The etiology and pathogenesis of these two types are obviously different. Third, the association between glucose level and rs55703767 can be affected by confounding factors, such as hypoglycemic drugs.

There are some limitations to our study. First, in the current study, although we enrolled patients who had regular follow-up visits from 2006 to 2016 to ensure that all patients have minimum diabetes duration of 10 years, we did not have the information of their exact diabetes duration. Second, we used QUANTO (https://pphs.usc.edu/download-quanto/) to calculate the statistical power of our study, and there was only 25.59% power to detect the association. Therefore, larger sample size is warranted in future studies. Third, it was a single SNP study, and false-negative results can occur due to population structure.

To conclude, our findings suggested that there was no detectable association between COL4A3 variant rs55703767 and the susceptibility to DKD in the Chinese T2DM population.

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Conflicts of interest

None.

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