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Association between *ACAT1* rs1044925 and increased hypertension risk in Tongdao Dong

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Abstract

Hypertension is a multifactorial disease that partially caused by genetic factors, including variation in genes related to lipid metabolism. *ACAT1* gene is implicated in lipid metabolism for its encoding product, the enzyme acetyl-CoA acetyltransferase 1, catalyzing the synthesis of cholesteryl ester from cholesterol and playing an important role in the metabolism of cholesterol. Until now, there's little study on the relationship between *ACAT1* variants and hypertension. Here, we report a link between *ACAT1* rs1044925 and hypertension in Tongdao Dong population. Polymerase chain reaction-restriction fragment length polymorphism was used to detect the genotypes of the *ACAT1* SNP rs1044925 in a total of 637 subjects, including 406 hypertensive patients and 231 normotensive controls. The genotypic and allelic frequencies of rs1044925 were significantly different between the normotensive and hypertensive subjects ($P = .001$). AC/CC genotypes of rs1044925 were associated with an increased risk of hypertension (AC/CC vs AA: adjusted odds ratio = 1.723, 95% confidence interval = 1.160–2.559, $P = .007$). However, the AC/CC genotypes showed no relationship with serum lipid levels. The results suggest that the C carriers of *ACAT1* rs1044925 might increase the risk of hypertension in Tongdao Dong population, and the underlying mechanism needs to be further studied.

Abbreviations: ACAT1 = acetyl-CoA acetyltransferase 1, BMI = body mass index, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

Keywords: *ACAT1*, association, hypertension, rs1044925, SNP

1. Introduction

Hypertension, a major risk factor for cardiovascular diseases, affects nearly 1.4 billion adults worldwide, placing a substantial burden on healthcare systems.[1,2] Hypertension is a chronic and multifactorial disease caused by the interaction of both genetic and environmental factors.[3] Approximately 30% to 60% of blood pressure variation is attributed to genetic factors, including genes involved in lipid metabolism.[4] The human *ACAT* genes encode 2 isozymes, the enzyme acetyl-CoA acetyltransferase 1 (ACAT1) and ACAT2, with different intracellular localization and membrane topology, both playing an important role in cholesterol homeostasis by converting free cholesterol to cholesteryl ester.[5] ACAT1 is ubiquitously expressed in various tissues and cell types, including hepatocytes, macrophages, adrenals, skin and neurons, whereas ACAT2 is expressed only in the small intestine and hepatocytes.[6] Macrophage ACAT1 was reported to play a role in the formation of foam cells in atherosclerotic plaques, which is the characteristic of early-stage atherosclerosis, and so might be a potential target for the treatment of atherosclerosis and hypercholesterolemia.[7,8]

A number of studies have suggested that *ACAT1* gene polymorphisms modulate the serum lipid concentration and further play a role in the early stages of atherosclerotic plaques. Ohta et al[9] found that in hyperlipidemic subjects, plasma concentrations of high density lipoprotein cholesterol (HDL-C) and ApoAI were significantly higher with *ACAT1* 77G-A variant than without the variant. Wang et al[10] found that *ACAT1* gene rs1154556 and rs10913733 polymorphisms were associated with the development of coronary artery disease. Wu et al[11] reported the genotypic and allelic frequencies of *ACAT1* rs1044925 were significantly different between the patients with coronary artery disease or ischemic stroke and controls.

However, up to now, the genetic evidence on the association between *ACAT1* polymorphisms and hypertension is limited. Yin et al[12] reported that *ACAT1* rs1044925 was interacted with overweight/obesity to modulate blood pressure levels, and they also found *ACAT1* rs1044925 might partially attributed to the different blood pressure levels between nondrinkers and drinkers in Bai Ku Yao population, a minority ethnic group in China, suggesting rs1044925 might be associated with hypertension.[13] Furthermore, our previous study using of a DNA

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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pooling strategy to identify hypertension-related SNPs in Tongdao Dong population, with a prevalence rate of hypertension reaching 35.5%,[14] found that allele C on SNP rs1044925 of *ACAT1* only existed in pooled DNA samples isolated from 100 hypersensitive persons when compared with the samples from 100 healthy individuals, showing a connection between SNP rs1044925 and hypertension. So, in this study, we aimed to further explore the relationship between the *ACAT1* rs1044925 and hypertension in Tongdao Dong population.

2. Materials and methods

2.1. Subjects

The study population consisted of 637 subjects of Dong nationality who reside in the Tongdao Dong Autonomous County that located in the southwestern part of Hunan Province in China. 406 hypertensive patients with systolic blood pressure (SBP) ≥ 140 mm Hg and/or a diastolic blood pressure (DBP) ≥ 90 mm Hg, aged 34 to 93 years were recruited in the hypertensive group. 231 individuals with normotension aged 33 to 93 years were recruited in the control group. All subjects gave their signed informed consent and the study protocol was approved by the Hunan Ethical Committee of Hunan University of Medicine, China.

All subjects gave measurements included height, weight and body mass index (BMI) which calculated as weight in kilograms divided by the square of height in meters. SBP and DBP were measured 3 times with 10-minute intervals in a sitting position by the same physician, and the average of 3 measurements was taken into further analysis. A history of secondary hypertension, coronary artery disease, chronic kidney disease, congenital and mental disorders, and endocrine disorders were defined as additional criteria for exclusion from this study.

2.2. Sample collection

We collected 2 blood samples (4 mL for each) from each volunteer. One blood sample was collected without anticoagulant after a 12-hour fast and the serum was used for the determination of lipids from all subjects. The collected blood for serum preparation was kept in an upright position at room temperature for 30 minutes followed by centrifugation at 2000 rpm for 15 minutes. The supernatant (serum) was carefully aspirated at room temperature and transferred into tubes. Unturbid samples were aliquoted into cryovials and stored at −80°C for subsequent analysis. The other Blood was collected in vacutainer tubes with EDTA for analysis of DNA. Genomic DNA was extracted from peripheral blood leukocytes.

2.3. Biochemical parameters investigations

Four lipid parameters (total cholesterol [TC], triglycerides [TG], HDL, and low density lipoprotein cholesterol [LDL-C]) were measured. The levels of serum TC, TG in samples were determined by enzymatic methods with commercially available kits.[15] HDL-cholesterol concentrations were determined by enzymatic assay after phosphotungstic acid and magnesium precipitation.[16] LDL-C was calculated according to Friedewald's formula.[17] All values were measured in mmol/L.

2.4. DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method. The ACAT genes was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) assay. PCR amplification was performed in 25 μL mixture containing 4 ng of DNA template, 1.5 μL of 4 μM each primer (5′ TATATTAAGGGGATCAGAAGT 3′ as forward primer and 5′ CCACCTAAAAACATACTACC 3′ as reverse primer, annealing with 53°C, PCR products with the size of 389 bp) as same as Wu et al described,[18] 1.5 μL of 25 mM Mg^{2+}, 2.5 μL of 10x buffer, 2.5 μL of 2 μM dNTP, 0.3 μL of 5 U/μL Taq polymerase. PCR conditions were 95°C for 5 minutes, 35 cycles of denaturation at 95°C for 45 seconds, annealing at 53°C for 30 seconds, and extension at 72°C for 50 seconds, followed by a final 10 minutes extension at 72°C. Then, electrophoresis on a 1% agarose gels. After the run was completed, the gel was visualized under UV light. RFLP assay was performed using 1 U of *Rsa I* restriction enzyme which was added to 15 μL PCR products and digested at 37°C for 5 hours. Digested products were electrophorized on 0.5% agarose gel containing ethidium bromide (2%). After the run was completed, the gel was visualized under UV light. Taking Ladder Marker as reference, only 1 fluorescent band was AA genotype (electrophoretic band: 389 bp), 2 fluorescent bands were CC genotype (electrophoretic band: 279 and 110 bp), and 3 fluorescent bands were AC genotype (electrophoretic band: 389, 279, and 110 bp). Finally, 2 PCR products of AA, AC and CC genotypes were randomly selected by PCR-RFLP were furtherly confirmed by direct sequencing (Tsingke Biological Technology Co., Beijing, China).

2.5. Statistical analyses

Quantitative variables were presented as mean and standard deviation. The Hardy–Weinberg equilibrium was assessed by chi-square test. Differences of general characteristics and serum lipid levels between normotensives and hypertensives were analyzed by independent *t* test and chi-square test. Allele and genotypic frequencies for *ACAT1* rs1044925 was calculated with the gene counting method, and the differences in genotype and allele distributions between 2 groups were obtained using Fisher's exact test and chi-square test. Furthermore, we applied ANOVA to analysis association between quantitative variables and genotypes. Logistics regression analysis was used to assess the odds ratio for detecting the association between hypertension and genotypes. All statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL), and a *P* value of less than .05 was considered statistically significant.

3. Results

3.1. General characteristics

The general characteristics of the patients with hypertension and the healthy controls were presented in Table 1. The average age, body weight, BMI, SBP, DBP, and serum TC, TG, LDL-C, HDL-C levels of hypertensive group were significantly higher than that of control group. There were no differences in the ratio of male to female and body height between 2 groups.

Furthermore, the factors significantly different between the 2 groups, together with the exception of gender were introduced into the logistic regression model, and the model showed that age, BMI, TC and LDL-C were associated with increased risk of hypertension (Table 2).

3.2. Genotypic and allelic frequencies

The genotyping of rs1044925 polymorphism confirmed by PCR-RFLP was shown in Figure 1. AA genotype presented only 1 band at 389 bp, AC genotype presented 3 bands at 389, 279, and 110 bp, CC genotype showed 2 bands at 279 and 110 bp. These 3 genotypes were finally confirmed by direct sequencing (Fig. 2).

The genotypic and allelic frequencies of rs1044925 were in accordance with the Hardy–Weinberg equilibrium. The genotype distributions of rs1044925 polymorphism in normotensive controls and hypertensive patients were indicated in Table 3. The alleles frequencies in the controls were 90.0% for the A allele and 10.0% for the C allele, and 83.0% for the A allele and 17.0% for the C allele in the patients with hypertension.

Table 1

General characteristics and serum lipid levels in normotensive controls and hypertensive patients.

Characteristics	Control group (n = 231)	Hypertensive group (n = 406)	$t(x^2)$	*P*
Male/female	90/141	169/237	0.401	.526*
Age (yr)	62.18 ± 12.31	66.53 ± 10.30	–4.550	<.001†
30–44	13	6	34.837	<.001*
45–59	94	93		
60 and above	124	307		
Height (cm)	153.81 ± 9.63	153.39 ± 8.80	0.564	.573†
Weight (kg)	55.66 ± 9.85	57.56 ± 11.32	–2.222	.027†
BMI (kg/m^2)	23.47 ± 3.17	24.37 ± 3.84	–3.210	.001†
SBP (mm Hg)	120.81 ± 12.09	160.15 ± 17.05	–33.868	<.001†
DBP (mm Hg)	72.37 ± 11.31	90.92 ± 13.54	–18.500	<.001†
TC (mmol/L)	5.50 ± 1.03	5.78 ± 1.35	–2.927	.004†
TG (mmol/L)	1.77 ± 1.47	2.09 ± 2.31	–2.147	.032†
LDL-C (mmol/L)	2.71 ± 1.24	3.15 ± 1.31	–4.253	<.001†
HDL-C (mmol/L)	1.35 ± 0.43	1.44 ± 0.45	–2.402	.017†

BMI = body mass index, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

*$\chi 2$ test.

†Independent *t* test between control group and hypertensive group.

Table 2

Correlative risk factors for hypertension.

Factor	OR	95% CI	*P*
Age (yr)	1.041	1.025–1.058	<.001
BMI (kg/m^2)	1.081	1.029–1.136	.002
TC (mmol/L)	1.176	1.016–1.361	.030
LDL-C (mmol/L)	1.249	1.084–1.438	.002

P values were obtained by logistic regression analysis.

CI = confidence intervals, OR = odds ratio.

The frequencies of the AA, AC and CC genotypes were 80.1%, 19.9%, and 0% in the controls, 70.0%, 26.1%, and 3.9% in the hypertensive patients respectively. The genotypic and allelic frequencies were significantly different between the controls and hypertensive patients (*P* = .001), and there's no difference in the genotypic and allelic frequencies between males and females in both normotensive and hypertensive groups (*P* > .05).

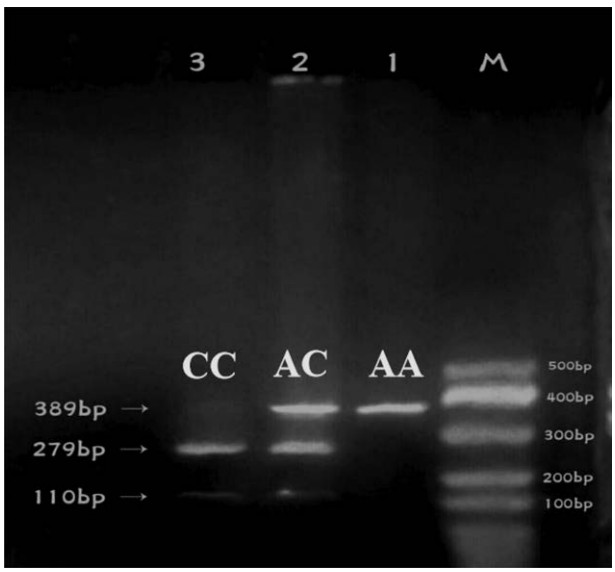

Figure 1. Genotyping of rs1044925 polymorphism in the ACAT1 gene performed by polymerase chain reaction-restriction fragment length polymorphism.

3.3. Association between genotypes and general characteristics

Table 4 shows the association between the C allele of rs1044925 and general characteristics. DBP level was significantly higher in the subjects with TC/CC genotype when compared with the subjects with AA genotype (*P* = .034), and values for all other parameters were similar between the subjects with AA genotype and the subjects with TC/CC genotype (*P* > .05).

3.4. ACAT-1 SNP rs1044925 and the risk of hypertension

Logistic regression was employed to further confirm the effect of *ACAT1* rs1044925 on the risk of hypertension. As presented in Table 5, the TC/CC genotype of *ACAT1* rs1044925 was associated with an increased risk of hypertension (adjusted odds ratio = 1.723, 95% confidence interval = 1.160–2.559, *P* = .007).

4. Discussion

ACAT1, an enzyme involved in the formation of cholesterolesters, plays an important role in cholesterol homeostasis. Cholesterol metabolism is a dynamic process involving intracellular transport, cholesterol esterification, and cholesterol ester hydrolysis.[19] ACAT1 converts cholesterol to cholesterol esters, which are stored in lipid droplets in the cytoplasm of phagocytes, which releases cholesterol efflux by hydrolysis by neutral cholesterol hydrolase.[20] Notably, ACAT1 is associated

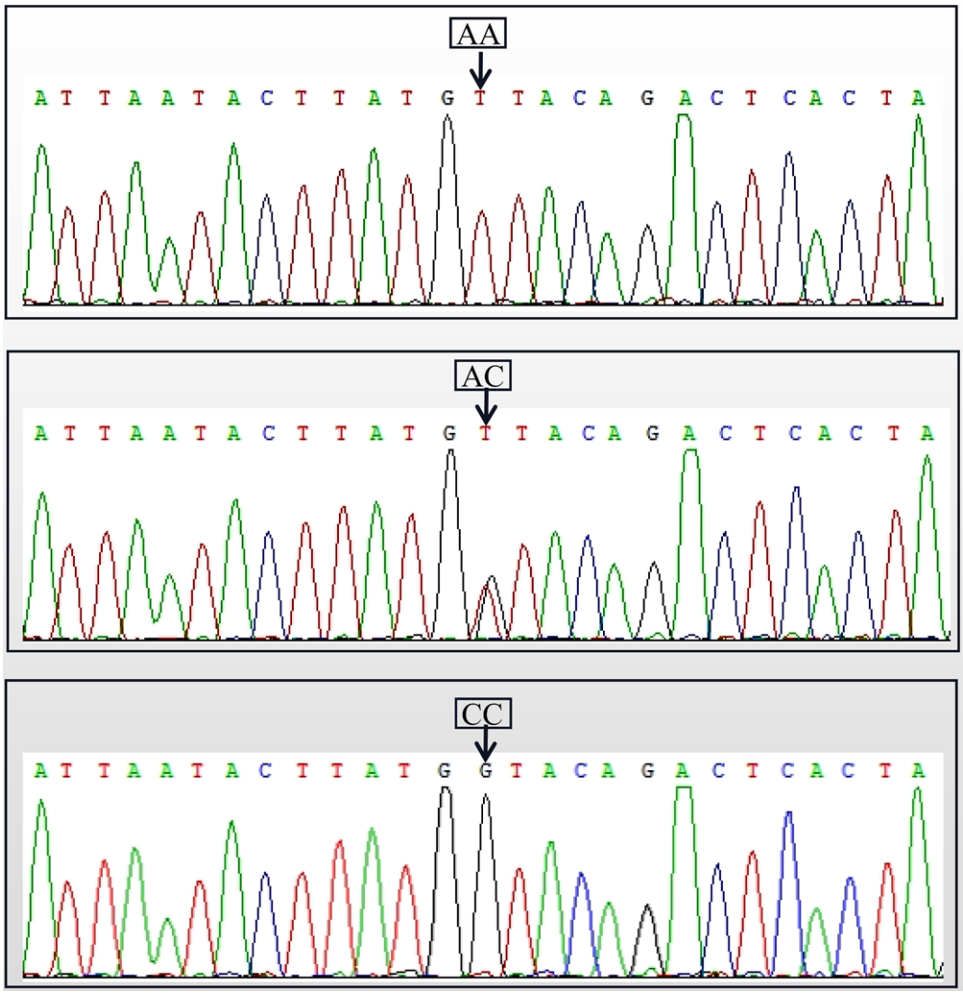

Figure 2. The nucleotide sequences of rs1044925 polymorphism performed by direct sequencing.

Table 3

The genotype and allele distributions of rs1044925 in normotensive controls and hypertensive patients.

		Genotype, n (%)					Allele, *n* (%)			
Group	**n**	**AA**	**AC**	**CC**	χ^2	***P***	**A**	**C**	χ^2	***P***
Normotensive controls	231	185 (80.1)	46 (19.9.0)	0 (0)	15.677	.000*	416 (90.0)	46 (10.0)	11.805	.001†
Hypertensive patients	406	284 (70.0)	106 (26.1)	16 (3.9)			674 (83.0)	138 (17.0)		
Normotensives										
Male	90	72 (80.0)	18 (20.0)	0 (0)	0.001	1.000†	162 (90.0)	18 (10.0)	0.001	.980†
Female	141	113 (80.1)	28 (19.9)	0 (0)			254 (90.1)	28 (9.9)		
Hypertensives										
Male	169	126 (74.6)	35 (20.7)	8 (4.7)	4.571	.100†	287 (84.9)	51 (15.1)	1.492	.222†
Female	237	158 (66.7)	71 (30.0)	8 (3.4)			387 (81.6)	87 (18.4)		

*P value was calculated using Fisher's exact test.

†P values were calculated using chi-square test.

with atherosclerosis,[21] Alzheimer's disease,[22] and cancers.[23] However, up to now, there is little study on it's relationship with hypertension. In this manuscript, we first explored the association between the *ACAT1* rs1044925 and hypertension in Tongdao Dong population. We found that the frequencies of AC and CC genotype, and also C allele of rs1044925 in *ACAT1* gene were higher in hypertensive patients of Tongdao Dong when compared with local normotensive controls, and the carriers of C allele of rs1044925 had higher DBP than those with AA genotype, suggesting *ACAT1* rs1044925 might presumably be correlated with hypertension. The logistic regression analysis further revealed that AC+CC genotype carriers had a 72.3% increased risk of hypertension relative to those with AA genotype. The correlation between *ACAT1* rs1044925 and DBP levels was also observed in the Bai Ku Yao Population,[24] in which the genotypic frequencies of rs1044925 were found to be different in hypertensives between males and females and the carriers of C allele showed lower DBP than those with AA genotype in female hypertensives which was inconsistent with our findings. The reason for the discrepancy is unclear but may be explained by the racial and ethnic specificity of gene polymorphism and different environmental factors.

Table 4

Association between genotypes (AA, AC+CC) and parameters including physical parameters, biochemical parameters.

	Genotype			
ACAT	**AA (n = 469)**	**AC+CC (n = 168)**	***t***	***P***
Age (yr)	64.66 ± 11.658	65.79 ± 10.31	–1.178	.240
Height (cm)	153.76 ± 9.14	152.93 ± 9.01	1.012	.312
Weight (kg)	57.16 ± 11.12	56.07 ± 10.02	1.113	.266
BMI (kg/m^2)	24.10 ± 3.78	23.895 ± 3.21	0.689	.491
SBP (mm Hg)	145.03 ± 25.39	148.27 ± 21.35	–1.604	.110
DBP (mm Hg)	83.49 ± 16.36	86.15 ± 12.98	–2.127	.034
TC (mmol/L)	5.65 ± 1.22	5.75 ± 1.33	–0.816	.415
TG (mmol/L)	1.97 ± 2.04	1.98 ± 2.08	–0.056	.955
LDL-C (mmol/L)	2.97 ± 1.28	3.06 ± 1.36	–0.721	.471
HDL-C (mmol/L)	1.40 ± 0.43	1.42 ± 0.47	–0.580	.562

Results of ANOVA analysis.

ACAT1 = acetyl-CoA acetyltransferase 1, BMI = body mass index, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

Table 5

ACAT rs61044925 and the risk of hypertension.

SNP	Genotype	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P**
rs1044925	AA	1	.006	1	.007
	AC+CC	1.728 (1.174–2.542)		1.723 (1.160–2.559)	

Results of logistic regression analysis.

ACAT1 = acetyl-CoA acetyltransferase 1, CI = confidence intervals, OR = odds ratio.

*Adjusted for sex, age and BMI.

Though we found the relationship between the genetic variants of *ACAT1*, one of a lipid metabolism-related genes, and the risk of hypertension, nothing is known about the underlying mechanism. Usually, the genetic variants in lipid metabolism-related genes may influence the expression levels of corresponding proteins, subsequently resulting in abnormal lipid metabolism, which may finally associated with a consequent of increased/decreased risk of hypertension.

In this study, we found TC and LDL-C levels were associated with increased risk of hypertension in Tongdao Dong population that was consistent with our previous study,[25] but the serum lipid levels were similar between the subjects with AA genotype and the subjects with TC/CC genotype. The association between *ACAT1* rs1044925 and serum lipid levels has been reported in several previous studies with inconsistent results. Wu et al[11] reported that the C allele carriers of *ACAT1* rs1044925 had higher serum HDL-C level in hyperlipidemic subjects. Li et al[26] showed that serum LDL-C and non-HDL-C levels were lower in the C allele carriers than in the C allele noncarriers. Thus, the relationship between rs10444925 and serum lipid levels needs to be further clarified.

5. Limitations

There are 2 potential limitations to the present study. First, hypertension is resulted from the interaction of both environmental and genetic factors, such as smoking, drinking and diet, which were not included in this study. Second, we found the rs1044925 C allele was associated with an increased risk of hypertension, but the relationship between rs1044925 and the expression level of ACAT1 is still unclear, which is crucial for the functional study of this SNP, and we will explore this issue in our next study.

Author contributions

XJ, TZ, and HY designed the study and recruited the subjects and collected the data. HW recruited the subjects, collected the data and accomplished data analysis. NL and YX performed the experiments. TZ and HY wrote the paper. XJ reviewed and edited the manuscript. All authors read and approved the manuscript.

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