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Protective Role of TRPC3 Gene Polymorphism (rs10518289) in Obstructive Sleep Apnea Hypopnea Syndrome Among Hypertensive Patients

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Obstructive sleep apnea-hypopnea syndrome (OSAHS) presents a significant health concern, particularly among individuals with essential hypertension (EH). Understanding the genetic underpinnings of this association is crucial for effective management and intervention. We investigated the relationship between TRPC3 gene polymorphisms and susceptibility to OSAHS in patients with EH.

Material/Methods: We enrolled 373 patients with EH hospitalized at the First Affiliated Hospital of Xinjiang Medical University between April 2015 and November 2017. Patients were categorized into EH (n=74) and EH+OSAHS (n=299) groups according to the apnea-hypopnea index. Sequenom detection technology was used for TRPC3 gene single-nucleotide polymorphism genotyping, including genotypes at rs953691, rs10518289, rs2292232, rs4995894, rs951974, and rs4292355.

Results: Sex, smoking history, alcohol history, hypertension duration, fasting blood glucose, urea, creatinine, total cholesterol, HDL-C, LDL-C, glycosylated hemoglobin, 24-h mean systolic BP, and 24-h mean diastolic BP were not significantly different between the 2 groups ($P>0.05$); however, age, BMI, triglyceride levels differed significantly ($P<0.05$). No significant difference was detected in distribution frequency of polymorphisms of TRPC3 gene between the 2 groups ($P>0.05$), while genotype, dominant genotype, and recessive genotype at rs10518289 and alleles at rs4292355 differed significantly ($P<0.05$). Logistic regression analysis showed age, BMI, and CG+GG genotypes at rs10518289 were risk factors for OSAHS in patients with EH. Interaction between TRPC3 (rs10518289) and obesity was not a risk of OSAHS with EH ($P>0.05$).

Conclusions: CC genotype of rs10518289 in the TRPC3 gene could be a protective genetic marker of OSAHS, and CG+GG genotype may be a risk genetic marker of OSAHS with EH.

Keywords: Sleep Apnea Syndromes • Essential Hypertension • TRPC3 Cation Channel • Polymorphism, Single Nucleotide

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Introduction

The latest study on the distribution of obstructive sleep apnea-hypopnea syndrome (OSAHS) showed there are approximately 936 million adults aged 30 to 69 years old living with OSAHS worldwide, and the proportion of Chinese patients accounted for 18.8% (176 million) of all patients with OSAHS [1]. OSAHS involves various complications and comorbidities, and one of the most common complications is hypertension. A previous study demonstrated that at least 30% of patients with hypertension have OSAHS, and approximately 50% to 60% of patients with OSAHS have hypertension [2]. Hypertension combined with OSAHS is often refractory and more likely to cause organ functional damage, such as proteinuria, left ventricular hypertrophy, and atrial fibrillation [3,4]. Although the incidence of OSAHS in patients with hypertension is relatively high, the pathogeneses and etiologies, as well as the mechanisms underlying the interaction between OSAHS and hypertension, remain elusive.

Intermittent hypoxia/reoxygenation is characteristic of OSAHS, involving the pathological change similar to ischemia/reperfusion injury, and calcium ion dyshomeostasis contributes significantly to the pathogenesis [5]. The transient receptor potential canonical (TRPC) channel is a group of calcium-permeable non-selective cation channels. TRPC3, as a member of the TRPCs subfamily, is composed of 836 amino acids and has 6 transmembrane structures on the cell membrane or organelles [6]. It holds significant importance in regulating microvascular permeability through the modulation of intracellular free Ca2+ concentrations. Liu et al [7] first reported that vascular TRPC3 did not change significantly before a blood pressure increase in spontaneously hypertensive rats, while its expression increased significantly after a blood pressure increase. TRPC3 inhibition helps counteract fibrosis caused by Ang II-induced hypertension and enhances blood pressure regulation [8]. In the process of myocardial ischemia/reperfusion injury, TRPC3 expression is significantly increased, leading to substantial Ca2+ inflow, increasing cardiomyocyte apoptosis and inflammatory response [9]. Consequently, this enhances peripheral resistance, resulting in elevated blood pressure. The regulation of TRPC3 is primarily governed by the TRPC3 gene; therefore, TRPC3 gene polymorphism could participate in the development and progression of OSAHS accompanied by hypertension.

The present study aimed to explore the association between TRPC3 gene polymorphism and the risk of OSAHS in patients with essential hypertension. The risk of OSAHS in patients with essential hypertension was predicted from the genetic level, which could provide scientific evidence for preventing OSAHS in patients with essential hypertension.

Material and Methods

Patient Population

This study was approved by human research Ethics Committee of Xinjiang Medical University, with approval number IACUC-20171214-09. Patients who were diagnosed with essential hypertension and were hospitalized in the First Affiliated Hospital of Xinjiang Medical University (Xinjiang, China) between April 2015 and November 2017 were recruited. In total, 373 patients met the inclusion and exclusion criteria, including 101 women and 272 men. The mean age was 47.02±10.07 years. They were divided into an essential hypertension group (EH group; n=74, age: 42.61±10.609 years) and essential hypertension with OSAHS group (EH+OSAHS group; n=299, age: 47.49±10.032 years old). The inclusion criteria were as follows: (1) patients with essential hypertension [10]; (2) patients who received a diagnosis of OSAHS according to the *Guidelines for Diagnosis and Treatment of Obstructive Sleep Apnea Syndrome* (OSAHS causes an apnea-hypopnea index ≥5 events/h) [11]; (3) diagnosis of hypertension accompanied by OSAHS in patients meeting the diagnostic criteria of hypertension and OSAHS at the same time; (4) patients aged between 18 and 65 years old; (5) patients who were Han people with no blood relationship or family history of miscegenation; and (6) patients who voluntarily participated and signed the informed consent form. The exclusion criteria were as follows: (1) patients who were clearly diagnosed with secondary hypertension other than hypertension induced by OSAHS; (2) patients with nasal diseases or chronic pulmonary diseases; (3) patients with heart valve disease, myocardial disease, congenital heart disease, or severe arrhythmia that have substantial influence on cardiac structures and functions; (4) patients with endocrine diseases (eg, type 1 or 2 diabetes), diseases induced by hyperthyroidism, or diseases induced by hypothyroidism; and (5) renal dysfunction in patients with chronic liver disease, chronic wasting disease, or malignant tumors.

Study Methods

Collection of Patients' General Characteristics and Blood Indicators

The following patients' data were collected: time of hospital admission, age, sex, history of alcohol consumption, smoking history, disease course of hypertension, height, and weight. Body mass index (BMI) was calculated using the following equation: BMI = body weight/height^2 (kg/m^2). Venous blood was obtained from all patients in the morning after fasting for 8 h, and then, an automatic biochemical analyzer (Roche C8000, Roche, Basel, Switzerland) was used to analyze the levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

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Table 1. Primers used for the amplification of TRPC3 genes.

SNP		Primer
Rs953691	Forward primer	ACG TTG GAT GCT GAC TGA TAA ACA GGA GGG
	Reverse primer	ACG TTG GAT GCT TTG AGC CAC TCA TCA CTG
Rs10518289	Forward primer	ACG TTG GAT GCC TCA AGA GTC TTT GTT GCC
	Reverse primer	ACG TTG GAT GGG CCA TCC CCA TTC TAT TAG
Rs2292232	Forward primer	ACG TTG GAT GTG TGA ATC ATG GAG GGT TTC
	Reverse primer	ACG TTG GAT GTA GAA TGG AAA TGA GAA GG
Rs4995894	Forward primer	ACG TTG GAT GTT CCT ATA CGA CTT GAC AGC
	Reverse primer	ACG TTG GAT GCC AGC TAG GTT TAA ATC TCT C
Rs951974	Forward primer	ACG TTG GAT GCA TTG CCA ACT ACG CAA AGC
	Reverse primer	ACG TTG GAT GCT GAG ATG GTA ACC ACC TAC
Rs4292355	Forward primer	ACG TTG GAT GTC CCA GAG ATC TGG TCT TTC
	Reverse primer	ACG TTG GAT GCT GGA TTA ACT GTC CTT GAG

(HDL-C), fasting blood glucose (FPG), urea, creatinine (Cr), and glycosylated hemoglobin (GHb).

Respiratory Monitoring During Sleep

All patients underwent 7 continuous respiratory monitoring cycles during sleep in the night, and the Com2pumedics2E polysomnography device (Australia) was used for simultaneous monitoring of blood oxygen saturation, thoracic and abdominal respiration, noise of snoring, and airflow of the mouth and nose. After the respiratory monitoring during sleep was completed, all data, including the apnea-hypopnea index and lowest blood oxygen saturation level, were analyzed by specifically trained professionals. Patients' height and body weight were measured on the day of respiratory monitoring during sleep in the night, and then, the BMI was calculated. The data analyses in this study included manual analysis and automatic computer-based analysis.

Blood Pressure Measurement

A blood pressure monitoring device (6100, Welch Allyn, Inc, Auburn, NY, USA) was used for the dynamic blood pressure monitoring. The intervals for dynamic blood pressure measurements were 30 min during the daytime and 60 min at night. The 24-h mean systolic blood pressure (24-h MSBP) and 24-h mean diastolic blood pressure (24-h MDBP) were documented.

Measurement of TRPC3 Gene Polymorphism

For DNA extraction, 5 mL fasting peripheral venous blood was collected in the morning, sealed in an EDTA anticoagulant tube, and stored at -70°C. The genomic DNA was extracted from the blood DNA extraction kit (TIANGEN), according to the manufacturers' instructions.

Polymerase Chain Reaction Amplification and Genotyping

The genotyping tools and MassARRAY platform provided by the Sequenom Inc (San Diego, CA, USA) were used to design primers for polymerase chain reaction (PCR) amplification and single-base extension. The multiplex PCR technique was used for PCR amplification, and the primers are shown in **Table 1**. The TYPER 4.0 software (Sequenom Inc) was used for the genotyping and illustration of results.

Statistical Analysis

SPSS 23.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis in this study. Normally distributed quantitative data are described as mean±standard deviation (mean±SD), and compared by the *t* test. Abnormally distributed quantitative data are presented as median (M; P25, P75) and compared using the Wilcoxon rank-sum test. Qualitative data are described as frequency and were compared using either the chi-square test or the Fisher's exact test. The representativeness of samples in the EH group and EH+OSAHS group was analyzed by the Hardy-Weinberg equilibrium. A logistic regression model was used to investigate the relationship between single-nucleotide polymorphisms and the accompaniment of OSAHS in patients with hypertension. After adjusting for sex, age, smoking history, history of alcohol consumption, disease course of hypertension, BMI, FPG, urea, Cr, TG, TC, HDL-C, LDL-C, GHb, 24-h MSBP, and 24-h MDBP, multivariate logistic regression analysis was used to explore the association between risk factors and the accompaniment of OSAHS in patients with hypertension, and crossover analysis was used in combination with multivariate logistic regression model to explore the interactions between genes and obesity. $P<0.05$ was considered statistically significant.

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Table 2. Comparison of clinical data between the EH group and EH+OSAHS group.

	EH group	EH+OSHAS group	*F*	*P*-value
Age (year)	42.61±10.609	47.49±10.032	-3.709	0.000
Gender (male/female)	49/25	223/76	2.102	0.147
Smoking history (yes/no)	31/42	131/168	0.043	0.835
Alcohol history (yes/no)	23/51	81/216	0.426	0.514
Hypertension history (months)	52±58.524	65.84±73.814	-1.487	0.138
BMI (kg/m^2)	25.376±3.239	27.390±3.269	-4.754	0.000
FPG (mmol/L)	4.872±1.136	5.024±1.513	-0.809	0.419
Urea (mmol/L)	5.223±1.497	5.343±1.300	-0.685	0.494
Creatinine (μmol/L)	71.280±20.024	71.90±16.315	-0.279	0.780
TG (mmol/L)	1.717±1.004	2.185±1.933	-2.888	0.004
TC (mmol/L)	4.239±0.922	4.244±0.862	-0.041	0.968
HDL-C (mmol/L)	1.134±0.312	1.086±0.286	1.265	0.206
LDL-C (mmol/L)	2.783±0.738	2.766±0.703	0.181	0.857
GHb (%)	5.652±0.704	5.783±0.885	-1.170	0.243
24-h MSBP (mm Hg)	135.80±12.905	136.21±15.268	-0.206	0.837
24-h MDBP (mm Hg)	87.77±11.275	86.56±11.953	0.775	0.439

Results

Comparison of General Clinical Data

Sex, smoking history, history of alcohol consumption, disease course of hypertension, FPG, urea, Cr, TC, HDL, LDL, GHb, 24-h MSBP, and 24-h MDBP were not significantly different between the EH group and EH+OSAHS group ($P>0.05$). In contrast, age, BMI, and TG were significantly higher in the EH+OSAHS group than in the EH group ($P<0.05$) (**Table 2**).

Hardy-Weinberg Equilibrium

The distributions of genotypes in the EH and EH+OSAHS groups were in agreement with the Hardy-Weinberg equilibrium ($P>0.05$), indicating that samples in both groups had population representativeness (**Table 3**).

Comparison of Genotype Frequencies Between EH Group and EH+OSAHS Group

The distributions of genotypes at rs953691, rs2292232, rs4995894, and rs951974, as well as different models, were not significantly different between the EH group and EH+OSAHS group ($P>0.05$). The genotype distribution, dominant genotype (CC/CG+GG), and recessive genotype (GG/CG+CC) at rs10518289 were significantly different between the 2 groups ($P<0.05$). The distribution of alleles at rs4292355 was significantly different between the 2 groups ($P<0.05$) (**Table 4**).

Exploring the Risk Factors of OSAHS in Hypertension by Logistic Regression Analysis

The accompaniment of OSAHS in patients with hypertension was used as the dependent variable, and sex, age, smoking history, history of alcohol consumption, disease course of hypertension, BMI, FPG, urea, Cr, TG, TC, HDL-C, LDL-C, GHb, 24-h MDBP, 24-h MSBP, and dominant genotype at rs10518289 were used as the independent variables for logistic regression analysis. The findings showed that age, BMI, and dominant genotype of the TRPC3 gene at rs10518289 (CC vs CG+GG) were independent risk factors of OSAHS in hypertension patients ($P<0.05$) (**Table 5**).

Effects of the Interaction Between TRPC3 (Rs10518289) Gene and Obesity on Risk of OSAHS in Patients with Essential Hypertension

The TRPC3 (rs10518289) gene and BMI were found as risk factors for the occurrence of OSAHS in patients with essential hypertension, and thus, the genetic-environmental interactions were explored. BMI ≤30 kg/m^2 was defined as obesity. Then, crossover analysis was used to explore the interaction between the TRPC3 (rs10518289) gene and obesity (additive model),

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Table 3. Hardy-Weinberg equilibrium for EH group and EH+OSHAS group.

TRPC3 locus	Genotype	EH groug (n=74)			EH+OSHAS group (n=299)		
		Actual	Expected	*P* value	Actual	Expected	*P* value
Rs953691	GG	23	20	0.254	99	91	0.063
	GT	32	36		132	148	
	TT	19	19		68	60	
Rs10518289	CC	23	20	0.254	48	45	0.465
	CG	32	37		136	142	
	GG	19	16		115	112	
Rs2292232	CC	25	22	0.184	97	90	0.129
	CT	31	37		135	148	
	TT	18	15		67	60	
Rs4995894	AA	55	54	0.626	220	218	0.437
	CA	17	18		71	74	
	CC	2	1		8	6	
Rs951974	AA	19	16	0.173	68	62	0.185
	GA	31	37		137	148	
	GG	24	21		94	88	
Rs4292355	CC	50	52	0.096	205	204	0.700
	CT	24	20		84	86	
	TT	0	2		10	9	

which showed no statistical significance ($P>0.05$). Multivariate logistic regression analysis showed that the interaction between the CG+GG genotype of TRPC3 (rs10518289) and obesity was not significantly associated with the occurrence of OSAHS in patients with hypertension ($P>0.05$) (**Table 6**).

Discussion

This research demonstrated a link between TRPC3 gene variations and the occurrence of OSAHS in patients with essential hypertension, indicating that the presence of the CG+GG genotype at rs10518289 might increase the likelihood of developing OSAHS among these patients. In other words, carrying the CC allele reduced the risk of OSAHS in patients with essential hypertension.

Studies have shown that OSAHS is independently associated with hypertension, while the association between OSAHS and hypertension is mutual, and the diseases share a similar etiology. Our previous studies indicated that hypertension patients with OSAHS have an increased risk of target organ damage (early renal dysfunction and left ventricular hypertrophy) in clinical practice, which is positively linked to the intensity of OSAHS [12,13]. Currently, the diagnostic value of OSHAS is often overlooked, except in cases in which it coexists with essential hypertension, resistant hypertension, and cardiovascular disease [12]. Despite the acknowledged effectiveness of continuous positive airway pressure for OSAHS, between 39% and 50% of patients prescribed nocturnal continuous positive airway pressure for OSAHS do not adhere to its use [14,15]. Thus, prompt identification and management of OSAHS in individuals with primary hypertension are essential for enhancing their health outcomes.

Calcium homeostasis imbalance is one of the important mechanisms of hypertension combined with OSHAS. The intermittent hypoxia-triggered augmentation of store-operated Ca2+ entry via store-operated calcium channels significantly contributes to the elevated [Ca2+] [16]. Mitochondria are the most important calcium stores in the cell. TRPC3 is an important component of store-operated calcium channels and is the only isotype located on mitochondria in the TRPC family [17]. TRPC3 mediates Ca2+ uptake by mitochondria from the endoplasmic

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Table 4. Comparison of the frequency distribution of TRPC3 genotypes in the EH group and EH+OSAHS group.

TRPC3 gene	Type	Genotype	EH group (n=74) n (%)]	EH+OSHAS group (n=299) [n (%)]	χ^2 value	*P* value
Rs953691	Genotype	GG	23 (31.1)	99 (33.1)	0.305	0.85948
		GT	32 (43.2)	132 (44.1)		
		TT	19 (25.7)	68 (22.7)		
	Allele	G	55 (51.9)	231 (53.6)	0.100	0.752
		T	51 (48.1)	200 (46.4)		
	Dominant model	GG	23 (31.1)	99 (33.1)	0.111	0.739
		TT+GT	51 (68.9)	200 (66.9)		
	Recessive model	TT	19 (25.7)	68 (22.7)	0.285	0.593
		GG+GT	55 (74.3)	231 (77.3)		
	Additive model	CT	32 (43.2)	132 (44.1)	0.020	0.888
		CC+TT	42 (56.8)	167 (55.9)		
Rs10518289	Genotype	CC	23 (31.1)	48 (16.1)	9.803	0.007
		CG	32 (43.2)	136 (45.5)		
		GG	19 (25.7)	115 (38.5)		
	Allele	C	55 (51.9)	184 (42.3)	3.177	0.075
		G	51 (48.1)	251 (57.7)		
	Dominant model	CC	23 (31.1)	48 (16.1)	8.692	0.003
		GG+CG	51 (68.9)	251 (83.9)		
	Recessive model	GG	19 (25.7)	115 (38.5)	4.213	0.040
		CC+CG	55 (74.3)	184 (61.5)		
	Additive model	CG	32 (43,2)	136 (45.5)	0.120	0.729
		CC+GG	42 (56.8)	163 (54.5)		
Rs2292232	Genotype	GG	25 (33.8)	97 (32.4)	0.270	0.874
		GT	31 (41.9)	135 (45.2)		
		TT	18 (24.3)	67 (22.4)		
	Allele	G	56 (53.3)	232 (53.5)	0.001	0.982
		T	49 (46.7)	202 (46.5)		
	Dominant model	GG	25 (33.8)	97 (32.4)	0.049	0.826
		TT+GT	49 (66.2)	202 (67.6)		
	Recessive model	TT	18 (24.3)	67 (41.9)	5.156	0.023
		GG+GT	56 (75.7)	232 (58.1)		
	Additive model	GT	31 (41.9)	135 (45.2)	0.255	0.614
		GG+TT	43 (58.1)	164 (54.8)		

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Table 4 continued. Comparison of the frequency distribution of TRPC3 genotypes in the EH group and EH+OSAHS group.

TRPC3 gene	Type	Genotype	EH group (n=74) n (%)]	EH+OSHAS group (n=299) [n (%)]	χ^2 value	*P* value
Rs4995894	Genotype	GG	55 (74.3)	220 (73.6)	0.020	0.990
		GC	17 (23.0)	71 (23.7)		
		CC	2 (2.7)	8 (2.7)		
	Allele	G	72 (79.1)	291 (78.6)	0.010	0.921
		C	19 (20.9)	79 (21.4)		
	Dominant model	GG	55 (74.3)	220 (73.6)	0.017	0.896
		CC+CG	19 (25.7)	79 (26.4)		
	Recessive model	CC	2 (2.7)	8 (2.7)	0.000	0.990
		GG +CG	72 (97.3)	291 (97.3)		
	Additive model	CG	17 (23)	71 (23.7)	0.020	0.889
		CC+GG	57 (77)	228 (76.3)		
Rs951974	Genotype	GG	19 (25.7)	68 (22.7)	0.441	0.840
		GT	31 (41.9)	137 (45.8)		
		TT	24 (32.4)	94 (31.4)		
	Allele	G	50 (47.6)	205 (47.0)	0.012	0.912
		T	55 (52.4)	231 (53)		
	Dominant model	GG	19 (25.7)	68 (22.7)	0.285	0.593
		GT +TT	55 (74.3)	231 (77.3)		
	Recessive model	TT	24 (32.4)	94 (31.4)	0.027	0.869
		GG+GT	50 (67.6)	205 (68.6)		
	Additive model	GT	31 (41.9)	137 (45.8)	0.370	0.543
		TT+ GG	43 (58.1)	162 (54.2)		
Rs4292355	Genotype	CC	50 (67.6)	205 (68.6)	2.869	0.732
		CT	24 (32.4)	84 (28.1)		
		TT	0 (0)	10 (3.3)		
	Allele	C	74 (75.5)	289 (96.7)	42.143	0.000
		T	24 (24.5)	10 (3.3)		
	Dominant model	CC	50 (67.6)	205 (68.6)	0.027	0.869
		CT+TT	24 (32.4)	94 (31.4)		
	Recessive model	TT	0 (0)	10 (3.3)	2.543	0.111
		CT+CC	74 (100)	289 (96.7)		
	Additive model	CT	24 (32.4)	84 (28.1)	0.543	0.461
		CC+TT	50 (67.6)	215 (71.9)		

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Table 5. Logistic regression analysis of factors influencing OSAHS in patients with essential hypertension.

	B	SE	Wald χ^2	*P* value	OR value	95% CI
Rs10518289 dominant model (CC vs CG+GG)	-0.774	0.348	4.961	0.026	0.461	0.233~0.911
Genger	-0.074	0.486	2.315	0.128	0.477	0.184~1.238
Smoking history	0.187	0.378	0.244	0.621	1.205	0.575~2.529
Alcohol history	-0.331	0.383	0.749	0.387	1.393	0.659~2.949
Hypertension history	-0.002	0.003	0.603	0.438	0.998	0.993~1.003
Age	0.074	0.020	13.833	0.000	1.077	1.036~1.120
FPG	-0.070	0.137	0.257	0.612	0.933	0.713~1.221
BMI	0.235	0.057	16.919	0.000	1.265	1.131~1.415
TG	0.310	0.225	1.904	0.168	1.364	0.878~2.119
TC	0.030	0.561	0.003	0.958	1.030	0.343~3.092
HDL-C	0.524	0.682	0.589	0.443	1.688	0.443~6.432
LDL-C	-0.105	0.617	0.029	0.865	0.900	0.269~3.016
GHb	0.041	0.240	0.029	0.866	1.042	0.651~1.668
urea	-0.039	0.123	0.102	0.749	0.961	0.755~1.224
Creatinine	-0.014	0.011	1.500	0.221	0.986	0.965~1.008
24-h MSBP	-0.002	0.020	0.013	0.910	1.002	0.964~1.042
24-h MDBP	-0.005	0.026	0.039	0.844	0.995	0.946~1.046

EH=0, EH+OSAHS=1; genger (male=1, female=0); smoking history (yes=1, no=0); alcohol history (yes=1,no=0); Rs10518289 genotype (CC=1,CG+GG=2).

Table 6. Interaction between genotype of TRPC3 gene at rs10518289 and obesity.

TRPC3 (Rs10518289)	Obesity	EH group	EH+OSAHS group	OR value	*P* value	RER1	AP	S
CG+GG	Yes	39	216	-2.9235	0.9711	-41.377	-18.042	0.031
CG+GG	No	12	35	-1.7252	0.9744			
CC	Yes	14	42	3.7535	0.9711			
CC	No	9	6	1				

Obesity (BMI ≥30).

reticulum or intracellularly, regulates the spatiotemporal distribution pattern of calcium, increases the production of reactive oxygen species (the generation of reactive oxygen species can stimulate the activation of mitochondrial calcium channels [18]), and participates in the occurrence and development of hypertension. Studies have shown that the improvement of ischemia/reperfusion injury significantly reduces the activity and expression of TRPC3. With the inhibition of TRPC3, Ca2+ inflow decreases, resulting in the reduction of nitric oxide production and the improvement of blood pressure [9]. Therefore, TRPC3 may become a new target for the treatment of hypertension combined with OSHAS.

The results of this study indicated that age, BMI, and TG level were elevated in the EH+OSAHS group, compared with that in the EH group, which was in agreement with the findings of previous studies [19]. It is well known that age is a risk factor of OSAHS occurrence. With the increase of age, the prevalence

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and severity of OSAHS increases [20]. In addition, the findings could be associated with the ethnical differences in susceptibility to age increase. Dyslipidemia is a common disease in patients with obstructive sleep apnea. Our studies have shown that in patients with OSAHS, elevation of TG level and reduction of HDL-C level were frequently observed [19]. Studies have also demonstrated that OSAHS-relevant TG elevation could be associated with ethnicity and is determined by genetic factors [21]. Obesity and OSAHS share various common comorbidities and have significant influences on cardiovascular and endocrine systems. Our previous studies have shown that in patients with hypertension, BMI elevation could increase the occurrence of OSAHS. The associations among dyslipidemia, inflammatory markers, apnea-hypopnea index, and BMI have already been demonstrated [22], and OSAHS could increase the incidence of cardiovascular events in patients with obesity [23]. Carratù et al [24] reported that, inconsistent with apnea-hypopnea index, a higher BMI in patients with OSA was closely associated with the risk of cardiovascular diseases. Therefore, obesity and OSAHS could be not only independent risk factors that play roles in the occurrence and progression of such diseases, but could also interact with each other by a more sophisticated mode than only additive or subordinative effects.

The present study revealed significant differences in the distribution of the rs10518289 genotype, dominant genes (CC/CG+GG), and recessive model (GG/CG+CC) between patients with hypertension and OSAHS and those with simple hypertension. Logistic regression analysis indicated that the CG+GG genotype of rs10518289 could be an independent risk factor for an independent risk factor for the co-occurrence of hypertension and OSAHS. The possible mechanisms underlying this phenomenon are as follows. (1) Intermittent hypoxia stimulation enhances vascular TRPC3 expression. TRPC3 acts upstream of the calcium/calmodulin-dependent protein kinase-nuclear factor of activated T-cell signaling pathway. Activated calcium/calmodulin-dependent protein kinase phosphatase dephosphorylates and activates nuclear factor of activated T cells, which then translocates to the nucleus and further promotes TRPC3 gene transcription, leading to persistent expression. Excessive intracellular calcium concentration causes persistent myocardial cell contractions and excessive proliferation, thereby increasing peripheral resistance and elevating blood pressure [25]. (2) Intermittent hypoxia stimulation augments mitochondrial TRPC3 expression in vascular tissues. TRPC3 promotes mitochondrial calcium uptake, reactive the generation of reactive oxygen species generation and vascular constriction, thus raising blood pressure [26]. (3) Hypoxia-inducible factor-1 is one of the biomarkers for diagnosing OSAHS. TRPC3 participates in hypoxia-inducible factor-1-induced smooth muscle cell proliferation, contributing to increased blood pressure [27]. Finally, (4) intermittent hypoxemia and circadian rhythm disruption regulate TRPC3, potentially mediating the transforming growth factor-β (TGF-β)/Smad signaling pathway involvement in the co-occurrence of OSHAS and hypertension [28,29]. A study conducted by Wang et al showed that the TRPC3 gene polymorphism (rs111887471) is associated with sleep-related blood pressure regulation [30]. Although the studied gene locus differs from ours, both studies suggest that TRPC3 variations can play a role in sleep-related blood pressure regulation.

The results of the current study revealed that the interaction between the CG+GG genotype of TRPC3 (rs10518289) and obesity was not associated with the occurrence of OSAHS, indicating that their influences on OSAHS occurrence in patients with hypertension could be independent.

There were several limitations in this study. For instance, we did not deeply investigate the exact pathogenic mechanisms of TRPC3 in the occurrence of OSAHS in patients with essential hypertension. Also, no healthy control group was involved in this study. The findings of this study need to be further validated via additional large-scale studies.

Conclusions

In conclusion, this study demonstrated that TRPC3 gene polymorphism was associated with the incidence of OSAHS in patients with essential hypertension, and the CC genotype of rs10518289 in TRPC3 gene could be a protective genetic marker of OSAHS. Age and BMI may be risk factors, and the CG+GG genotype at rs10518289 may be a risk genetic marker of OSAHS in patients with essential hypertension. The findings of this study enhanced understanding about mechanisms underlying the occurrence of OSAHS in patients with essential hypertension and provided a reliable foundation for exploring the pathogeneses of OSAHS occurrence in these patients.

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