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Deletion Polymorphism of Angiotensin Converting Enzyme Gene is Associated with Left Ventricular Hypertrophy in Uighur Hypertension-Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) Patients

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Background: This study aimed to explore the association of angiotensin converting enzyme (ACE) gene insertion/deletion polymorphisms with left ventricular hypertrophy (LVH) in Han and Uighur hypertension-OSAHS (obstructive sleep apnea hypopnea syndrome) patients in China.

Material/Methods: A total of 162 Han and 72 Uygur patients with hypertension-OSAHS were independently subdivided into an LVH group and a non-LVH (NLVH) group based on the left ventricular mass index. The insertion/deletion polymorphisms of ACE gene were determined by polymerase chain reaction. The association of ACE gene insertion/deletion polymorphisms with LVH was assessed by chi-squared test. Logistic regression analysis was performed to obtain the odds ratios and 95% confidence intervals for the risk of LVH after adjusting for confounding factors.

Results: In Uighur patients, the distributions of D allele and DD genotype showed significant differences between the LVH group and the NLVH group. The difference of DD genotype remained significant after multivariate adjustment. In contrast, no significant differences were observed in the distributions of D allele and DD genotype between the LVH group and the NLVH group in Han patients. Moreover, moderate-severe OSAHS was an independent risk factor for LVH.

Conclusions: D allele and DD genotype of ACE gene are possible genetic markers for the risk of LVH in Uighur but not Han hypertension-OSAHS patients.

MeSH Keywords: Angiotensin-Converting Enzyme Inhibitors • Hypertension, Portal • Polymorphism, Single Nucleotide

Abbreviations: **ACE** – angiotensin converting enzyme; **AHI** – apnea hypoventilation index; **LVMI** – left ventricular mass index; **LVH** – left ventricular hypertrophy; **NLVH** – non-left ventricular hypertrophy; **OSAHS** – obstructive sleep apnea-hypopnea syndrome; **RAS** – renin-angiotensin-aldosterone system

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Background

Left ventricular hypertrophy (LVH) is defined by an increase in left ventricular mass (LVM), and has been a common heart disease generally caused by increased pressure and/or volume load. Epidemiological studies have indicated that LVH is an independent risk factor for cardiovascular morbidity and mortality [1,2]. Hypertension and obstructive sleep apnea hypopnea syndrome (OSAHS) are common clinical diseases that seriously threaten human health, and a close relationship has been shown between them. Available studies have revealed that 30% to 50% of hypertension patients have concomitant OSAHS, and 50% to 60% of OSAHS patients develop hypertension [3]. In recent years, a variety of studies have shown that the coexistence of hypertension with OSHAS significantly increases the severity of LVH in patients [4,5]. However, the mechanism remains elusive.

When hypertension coexists with OSHAS, the intermittent hypoxia and hypercapnia may stimulate sympathetic activities, and the abnormal activity of the renin-angiotensin-aldosterone system (RAS) is crucial for the development of LVH. Angiotensin-converting enzyme (ACE) is a central component of the RAS. It can hydrolyze the peptides by removing a dipeptide from the C-terminus to convert the inactive decapeptide angiotensin I to the octapeptide angiotensin II. ACE inhibitors have different performances in inhibiting ACE activity in patients with distinct ACE genotypes [6]. Recent studies have suggested that genetic variations of RAS are implicated in the development of LVH 7. It has been demonstrated that the DD genotype of ACE gene is accompanied by increased plasma ACE activity, and it is believed that angiotensin II at a higher concentration may promote inappropriate vascular wall thickening and myocardial hypertrophy [8].

Based on the association between ACE and cardiac remodeling, we hypothesized that ACE genetic polymorphisms may predispose patients with hypertension-OSAHS to LVH. This study was to investigate the association of ACE gene insertion/deletion polymorphisms with LVH in Han and Uighur patients with hypertension-OSAHS.

Material and Methods

Patients

All patients gave written informed consent and the study protocols were approved by the Ethics Committees of the First Affiliated Hospital of Xinjiang Medical University (approval no. 20160218-41, dated Feb 18, 2016). A total of 234 patients with hypertension-OSAHS (mean age: 48.76±9.89 years) including 162 Han Chinese and 72 Uygur Chinese were recruited from the First Affiliated Hospital of Xinjiang Medical University (Urumqi, Xinjiang, China). The diagnosis of hypertension was initially made during January 2015 to December 2016. These patients were subdivided into 2 groups: LVH group (LVMI ≥115 g/m^2 [male] or ≥95 g/m^2 [female]), and non-LVH (NLVH) group (LVMI <115 g/m^2 [male], LVMI <95/m^2 [female]) based on the LVM index (LVMI) according to the recommendations of the European Guidelines for Hypertension [9]. Inclusion criteria were as follows: 1) diagnosis of hypertension was based on the 2010 Chinese Guideline for the Management of Hypertension [10]. 2) The diagnosis of OSAHS was based on the pre-existing Diagnosis and Treatment of OSAHS. 3) Hypertension with OSAHS was defined as coexistence of hypertension and OSAHS. 4) Patients were 18 to 65 years old (mean age: 48.76±9.89 years). 5) All the participants signed the informed consent prior to the study. Exclusion criteria were as follows: 1) patients were diagnosed with secondary hypertension except for OSAHS. 2) Patients had chronic obstructive lung diseases. 3) Patients had valvular heart disease, cardiomyopathy, advanced heart disease, severe heart arrhythmia, and other diseases that can affect heart structure and function. 4) Patients had endocrine system diseases including diabetes, hyperthyroidism, hypothyroidism. 5) Patients had acute-on-chronic liver failure (ACLF), renal failure, chronic wasting disease, and cancer.

Sleep apnea monitoring

All patients were given 7-hour sleep monitoring at night, using the Australian PSG instrument E-type analyzer. The blood oxygen saturation, abdominal or diaphragmatic breathing, snoring, nasal airflow, apnea hypoventilation index (AHI), and the lowest oxygen saturation ($LSaO_2$) were monitored. Height and weight were measured in the evening before the examination, and body mass index (BMI) was calculated.

Blood pressure measurements

The blood pressure was dynamically monitored (ABPM6100, Welch Allyn, Inc., USA) with an interval of 30 minutes between 2 measurements during daytime and 60 minutes at night. In addition, the 24-hour mean systolic blood pressure (24-hour SBP), 24-hour mean diastolic blood pressure (24-hour DBP) and 24-hour mean pulse pressure (24-hour PP) were recorded. According to the 2010 Guidelines for Prevention and Treatment of Hypertension in China, hypertension was defined as: 1) SBP ≥140 mmHg and/or DBP ≥90 mmHg, 2) 24-hour ambulatory blood pressure: mean 24-hour blood pressure ≥130/80 mmHg, mean daytime blood pressure ≥135/85 mmHg, mean nighttime blood pressure ≥120/70 mmHg.

Echocardiography

Philips iE33 3-dimensional (3D) ultrasound scanner (Philips, Andover, MA, USA) was used for echocardiography. The left

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Table 1. Patients' clinical information.

Characteristic	Uygur			Han		
	Total	LVH (n=24)	NLVH (n=48)	Total	LVH (n=43)	NLVH (n=119)
Gender (M/F)	46/26	13/11	33/15	130/32	26/17	104/15
Age (years)	50.79±8.39	52.33±6.18	50.02±9.27	48.50(41, 55.25)	50.30±11.09	46.98±10.02
Smoking (yes/no)	29/43	10/14	19/29	76/86	16/27	60/59
Drinking (yes/no)	29/43	8/16	21/27	82/80	15/28*	67/52
Family history (yes/no)	58/14	19/5	39/9	116/46	31/12	85/34
BMI (kg/m^2)	28.93 (26.75, 31.08)	29.37 (26.93, 31.85)***	28.70 (26.70, 31.08)	27.30 (25.30, 29.70)	27.80 (25.70, 29.70)	27.10 (25.30, 29.40)
TG (mmol/L)	1.57 (1.14, 2.22)	1.52 (1.26, 2.14)	1.58 (1.06, 2.34)	1.69 (1.18, 2.19)	1.72 (1.28, 3.05)	1.69 (1.06, 2.15)
TC (mmol/L)	4.14±1.05	4.56 (3.29, 5.03)	4.02 (3.32, 4.91)	4.13 (3.66, 4.78)	4.08 (3.58, 4.75)	4.16 (3.68, 4.80)
HDL-C (mmol/L)	0.99 (0.87, 1.16)	1.03±0.23***	1.00±0.28	1.06 (0.89, 1.27)	1.03 (0.88, 1.18)	1.09 (0.89, 1.28)
LDL-C (mmol/L)	2.83 (2.20, 3.43)	2.84±0.95	2.76±0.84	2.70 (2.36, 3.22)	2.64 (2.42, 3.18)	2.82 (2.35, 3.28)
24-hour SBP (mmHg)	134 (122, 143)	137.54±16.18	133.73±14.75	135 (127, 145)	145 (135, 158)*	135 (126, 141)
24-hour DBP (mmHg)	80 (76, 88)	80.33±8.64**,***	81.69±10.61	86 (79, 94)	90 (80, 98)*	85 (79, 91)
AHI	20.55 (9.92, 26.80)	25.37 (16.38, 34.53)*	15.65 (8.50, 26)	21.15 (11.78, 39.60)	32.10 (18.70, 57.60)*	18.20 (9.40, 38.30)

LVH – left ventricular hypertrophy; NLVH – non-left ventricular hypertrophy; AHI – apnea hypopnea index; BMI – body mass index; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; 24-h SBP – 24-h mean systolic blood pressure; 24-hr DBP – 24-h mean diastolic blood pressure. Comparison between LVH group and NLVH group in the same ethnicity * $P<0.05$; Comparing LVH in different ethnicity ** $P<0.05$; Comparing NLVH in different ethnicity *** $P<0.05$.

ventricular end-diastolic diameter, left ventricular end-diastolic dimension (LVEDd), left ventricular contraction at the end of the inner diameter, left ventricular end-systolic dimension (LVESD), interventricular septum thickness (interventricular septal thickness, IVST) and left ventricular posterior wall thickness (LVPWT) were measured by an experienced cardiologist. All these parameters were continuously measured in 3 different cardiac cycles. The mean value of 3 readings was used to calculate LVM, according to the Devereux's formula: LVM (g)=0.8×1.04×[(IVST+LVPWT+LVEDD)^3–LVEDD^3]+0.6. The size of body surface was calculated with the Stevenson's formula: surface area (m^2)=0.0061×height (cm)+0.0128×weight (kg)–0.1529, LVMI (g/m^2)=LVM/surface area.

Genotyping

The peripheral venous blood (5 mL) was collected from each patients, anti-coagulated with ethylenediamine tetra acetic acid (EDTA) (TIANGEN Biotech, Beijing, China), and stored at –70°C for further use. Briefly, DNA was extracted from whole blood samples using TIANamp Genomic DNA Kit (TIANGEN Biotech). The ACE gene insertion/deletion polymorphisms were determined by polymerase chain reaction (PCR) using intron-specific primers as described previously [11]. The forward primer was 5'-CTGGAGACCACTCCCATCCTTTCT-3', and the reverse primer was 5'-GATGTGGCCATCACATTCGTCAGAT-3'. The primers would anneal outside the insertion/deletion region in the intron 16 of ACE gene, yielding PCR product of 490 bp in case of insertion allele or 190 bp in case of deletion allele. The genotypes were classified as II (homozygote for the insertion allele), DD (homozygote for the deletion allele), or ID (heterozygote). Amplification was performed in a mixture (20 μL) containing 100 ng of genomic DNA, 0.5 mmol/L dNTPs, 0.7 μmol/L each primer (Sangon Biotech, Shanghai, China) and 1 U of Taq DNA polymerase (TIANGEN Biotech). The PCR conditions were as follows: 94°C for 300 seconds, followed by 35 cycles of 94°C for 45 seconds, 58°C for 45 seconds, and 72°C for 45 seconds, and a final extension at 72°C for 420 seconds. PCR products

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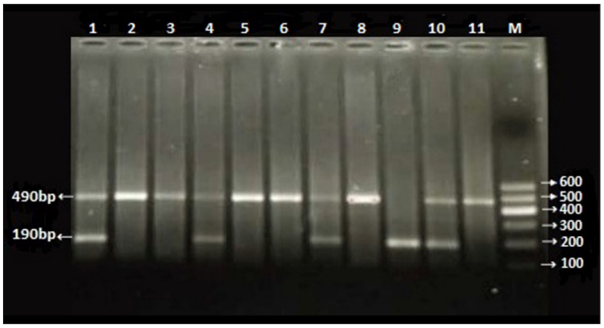

Figure 1. The genotypes of 11 patients. Fragment sizes are 190 bp for D allele and 490 bp for I allele. M: marker. Lane 1, 4, 7, 10: Type ID; Lane 2, 3, 5, 6, 8, 11: Type II; Lane 9: Type DD.

were separated on 2% agarose gels with 100 bp DNA ladder as the marker.

Statistical analysis

SPSS version 23.0 (SPSS Inc., IL, USA) was used for statistical analysis. Quantitative data with normal distribution were expressed as mean ± standard deviation (SD). The quantitative data with abnormal distribution as expressed as median and interquartile range, and analyzed with the Wilcoxon test. The qualitative data are expressed as constituent ratios, and analyzed with the chi-square test. Hardy-Weinberg equilibrium (HWE) for the different polymorphisms was calculated using the chi-square test [12,13]. LVH was considered as dependent variable, while the relevant factors as the independent variables in the logistic regression analysis. A value of $P<0.05$ was considered statistically significant.

Results

General characteristics

The general characteristics of the LVH group and the NLVH group in Uygur patients and Han patients are shown in Table 1.

ACE genotype and allele frequency in the 2 groups

PCR products corresponded to either 490-bp fragment (I allele) or 190-bp fragment (D allele), and 3 genotypes were identified: II, ID, and DD. The wild-type homozygous type II resulted in a 490-bp fragment, the mutant heterozygous type ID resulted in a 490-bp fragment and a 190-bp fragment, and the mutant homozygous type DD resulted in a 190-bp fragment (Figure 1). The distribution of genotypes and allele frequency between the LVH group and the NLVH group were significantly different ($P=0.03$, $P=0.03$) in Uygur patients, while the differences were not statistically significant in Han patients ($P=0.78$, $P=0.68$; Table 2). Moreover, significant differences in the distributions of ACE genotype and allele frequency between Uyghur and Han people were noted in the LVH group ($P=0.03$; $P=0.02$), but not the NLVH group ($P=0.70$; $P=0.43$) (Table 3).

Table 2. Comparing ACE genotype and allele frequency between LVH group and NLVH group.

Ethnicity	Group	Genotype			χ^2 value	*P* value	Allele frequency		χ^2 value	*P* value
		II (%)	ID (%)	DD (%)			I (%)	D (%)		
Uygur	LVH	9 (37.50)	5 (20.83)	10 (41.67)	6.75	0.03	23 (48)	25 (52)	4.70	0.03
	NLVH	23 (47.92)	18 (37.50)	7 (14.58)			64 (67)	32 (33)		
Han	LVH	22 (51.16)	15 (34.88)	6 (13.96)	0.50	0.78	59 (68.60)	27 (31.40)	0.18	0.68
	NLVH	62 (52.10)	45 (37.82)	12 (10.08)			169 (71.01)	69 (28.99)		

Table 3. Comparing ACE genotype and allele frequency between Uygur and Han people.

Group	Ethnicity	Genotype			χ^2 value	*P* value	Allele frequency		χ^2 value	*P* value
		II (%)	ID (%)	DD (%)			I (%)	D (%)		
LVH	Uygur	9 (37.50)	5 (20.83)	10 (41.67)	6.59	0.03	23 (48)	25 (52)	5.55	0.02
	Han	22 (51.16)	15 (34.88)	6 (13.96)			59 (68.60)	27 (31.40)		
NLVH	Uygur	23 (47.92)	18 (37.50)	7 (14.58)	0.73	0.70	64 (67)	32 (33)	0.61	0.43
	Han	62 (52.10)	45 (37.82)	12 (10.08)			169 (71.01)	69 (28.99)		

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Table 4. Variable assignment.

Risk factors	Variable assignment
Gender	Female=0, Male=1
Smoking	No=0, Yes=1
Drinking	No=0, Yes=1
Family history	No=0, Yes=1
BMI (kg/m^2)	<28=0, ≥28=1
TG (mmol/L)	<1.70=0, ≥1.70=1
TC (mmol/L)	<5.72=0, ≥5.72=1
HDL-C (mmol/L)	<1.16=1, ≥1.16=0
LDL-C (mmol/L)	<3.10=0, ≥3.10=1
AHI	<15=0, ≥15=1
Genotype	II=0, ID=1, DD=2

Table 5. Logistic regression analysis of LVH in Uygur and Han hypertension-OSAHS patients.

Risk factors	β	SE	Wald χ^2 value	*P* value	*OR* value	95% CI
Uygur						
Female	1.50	0.95	2.47	0.12	4.46	0.69~28.86
Smoking	0.85	0.92	0.84	0.36	2.33	0.38~14.21
Drinking	0.40	0.86	0.22	0.64	1.49	0.28~8.02
Family history	0.20	0.74	0.08	0.78	1.23	0.29~5.19
BMI	–0.60	0.67	0.81	0.37	0.55	0.15~2.04
TG	0.47	0.72	0.44	0.51	1.61	0.40~6.53
TC	–2.63	1.66	2.50	0.11	0.07	0.00~1.87
HDL-C	–0.43	0.76	0.33	0.57	0.65	0.15~2.88
LDL-C	0.91	0.64	2.06	0.15	2.49	0.72~8.70
AHI	1.83	0.75	5.98	0.01	6.20	1.44~26.77
Genotype ID *vs.* II	0.08	0.78	0.01	0.92	1.07	0.24~5.03
Genotype DD *vs.* II	1.53	0.76	4.08	0.04	4.61	1.05~20.31
Han						
Female	1.68	0.61	7.59	0.00	5.39	1.63~17.85
Smoking	0.08	0.51	0.02	0.88	1.08	0.40~2.92
Drinking	–0.30	0.49	0.36	0.55	0.74	0.28~1.95
Family history	–0.46	0.48	0.90	0.34	0.63	0.25~1.63
BMI	0.53	0.42	1.57	0.21	1.69	0.74~3.86
TG	–0.16	0.43	0.15	0.70	0.85	0.37~1.96
TC	–0.14	0.90	0.02	0.88	0.87	0.15~5.11
HDL-C	0.85	0.48	3.15	0.08	2.33	0.92~5.94
LDL-C	0.16	0.50	0.11	0.75	1.18	0.44~3.12
AHI	1.77	0.56	10.16	0.00	5.88	1.98~17.46
Genotype ID *vs.* II	–0.01	0.45	0.00	0.98	0.99	0.41~2.38
Genotype DD *vs.* II	0.35	0.66	0.27	0.60	1.41	0.39~5.18

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Logistic regression analysis

LVH served as a dependent variable, while gender, smoking, drinking, family history, BMI, TG, TC, HLD-C, LDL-C, AHI, and genotype as independent variables in the logistic regression analysis (Table 4). Results showed AHI and DD genotype were the effective factor for the LVH group ($P<0.05$) in Uyghur patients, and AHI and female gender were the effective factor for the LVH group ($P<0.05$) in Han patients (Table 5).

Discussion

In this study, our results showed the different ACE genotypes in LVH between Han patients and Uyghur patients, and DD genotype of ACE gene was a risk factor for LVH in Uighur hypertension-OSAHS patients but not in Han hypertension-OSAHS patients.

LVH is a predictor for various cardiovascular diseases, but the genetic factors related to LVH are poorly understood. In recent years, several studies have investigated the association between ACE gene insertion/deletion polymorphisms and LVH in different populations, but results are controversial [14]. There is evidence showing that ACE gene insertion/deletion polymorphisms ware associated with the development of LVH [15,16], but the relationship between ACE gene polymorphisms and LVH is not confirmed in other studies [17,18]. In this study, our results showed ACE gene insertion/deletion polymorphisms were associated with LVH in Uighur hypertension-OSAHS patients.

In addition, in Uighur hypertension-OSAHS patients, the frequencies of DD genotype and D allele were significantly higher in the LVH group than in the NLVH group. The differences remained significant after multivariate adjustment. These findings suggest Uighur hypertension-OSAHS patients carrying the DD genotype of ACE gene have a higher risk for LVH. Bahramali et al. [19] and Schunkert et al. [20] reported that DD genotype was an independent risk factor for LVH. Li et al. performed meta-analysis and confirmed that the incidence of LVH in DD genotype patients significantly increased [21]. However, no significant differences in the distributions of ACE I insertion/deletion polymorphisms were found between the LVH group and the NLVH group in Han hypertension-OSAHS patients in the present study. Moreover, AHI and female gender were risk factors of LVH, which was consistent with previously reported [22,23]. The differences in ecological environment, genetic characteristics, diet habits and lifestyles between Uygur and Han Chinese might lead to distinct effects of same genotypes in Han and Uighur hypertension-OSAHS patients. For example, Uighur Chinese mainly eat high-calorie foods such as pasta, beef, mutton and dairy products, and their intake of vegetables, fruits, and rice are less as compared to Han Chinese. A recent study reported that many factors affect the phenotypes of hypertrophic cardiomyopathy in genetic carriers [24]. This might explain different effects of same genotypes in Han and Uighur hypertension-OSAHS patients.

In our study, the effects of drugs on blood pressure and LVH were excluded because only patients who were initially diagnosed with hypertension and not treated were recruited into present study. However, there were several limitations in the present study. The sample size was small and patients with hypertension alone were not recruited as controls. The selection of hypertension-OSAHS patients was limited. This was a single center study. Thus, more multi-center studies with larger sample sizes are recommended to confirm the association between ACE gene insertion/deletion polymorphisms and LVH in hypertension-OSAHS patients.

Conclusions

In conclusion, DD and D allele frequency of ACE gene are possible genetic markers for the risk of LVH among Uighur hypertension-OSAHS patients. In clinical practice, it is thus recommended to individually prevent and control various risk factors in hypertension-OSAHS patients based on the race.

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Conflict of interest

The authors declare that there is no conflict of interest.

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