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/m² [male] or >95 g/m² [female]), and non-LVH (NLVH) group (LVMI <115 g/m² [male], LVMI <95/m² [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 (LSaO₂) 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
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:

\[
LVM = 0.8 \times 1.04 \times [(IVST + LVPWT + LVEDD)^2 - LVEDD^2] + 0.0061 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.1529, 
\]

where LVM (g) = LVM/surface area.

**Genotyping**

The peripheral venous blood (5 mL) was collected from each patient, 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’-CTGGAGACCACCTCCCACATCTTCT-3’, and the reverse primer was 5’-GATGTGGCCATCATCGTGCAGAT-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), ID (heterozygote), or DD (homozygote for the deletion allele).

| Characteristic | Uygur | Han |
|---------------|-------|-----|
| Gender (M/F)  | Total  | LVH (n=24) | NLVH (n=48) | Total  | LVH (n=43) | NLVH (n=119) |
| Age (years)   | 46/26 | 13/11 | 33/15 | 130/32 | 26/17 | 104/15 |
| 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/m²)  | 28.93 | (26.75, 31.08) | (26.93, 31.85)** | 28.70 | (26.70, 31.08) | (25.30, 29.70) |
| TG (mmol/L)  | 1.57 | (1.14, 2.22) | (1.26, 2.14) | 1.58 | (1.06, 2.34) | (1.18, 2.19) |
| TC (mmol/L)  | 4.14±1.05 | (3.29, 5.03) | (3.32, 4.91) | 4.13 | (3.66, 4.78) | (3.58, 4.75) |
| HDL-C (mmol/L) | 0.99 (0.87, 1.16) | 1.03±0.23*** | 1.00±0.28 | 1.06 | (0.89, 1.27) | (0.88, 1.18) |
| LDL-C (mmol/L) | 2.83 | (2.20, 3.43) | 2.84±0.95 | 2.76±0.84 | 2.70 | (2.36, 3.22) |
| 24-hour SBP (mmHg) | 134 (122, 143) | 137.5±16.18 | 133.73±14.75 | 135 (127, 145) | 134/145 | 135 (126, 141) |
| 24-hour DBP (mmHg) | 80 (76, 88) | 80.33±8.64**** | 81.69±10.61 | 86 | (79, 94) | 90 (80, 98)* |
| AHI | 20.55 | (9.92, 26.80) | 25.37 | (16.38, 34.53)* | 15.65 | (8.50, 26) |

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-hour systolic blood pressure; 24-h 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.
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).

![Figure 1](image1.png)

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

| Ethnicity | Group | Genotype | II (%) | ID (%) | DD (%) | Allele frequency | I (%) | D (%) | χ² value | P value | Allele frequency | I (%) | D (%) | χ² value | P value |
|-----------|-------|----------|--------|--------|--------|----------------|-------|-------|---------|---------|----------------|-------|-------|---------|---------|
| Uygur     | LVH   | II       | 9 (37.50) | 5 (20.83) | 10 (41.67) | 6.75 | 0.03 | 23 (48) | 25 (52) | 4.70 | 0.03 |
|           | NLVH  | II       | 23 (47.92) | 18 (37.50) | 7 (14.58) | 0.50 | 0.78 | 64 (67) | 32 (33) | 0.18 | 0.68 |
| Han       | LVH   | II       | 22 (51.16) | 15 (34.88) | 6 (13.96) | 5.55 | 0.02 | 59 (68.60) | 27 (31.40) | 0.35 | 0.56 |
|           | NLVH  | II       | 62 (52.10) | 45 (37.82) | 12 (10.08) | 0.73 | 0.70 | 169 (71.01) | 69 (28.99) | 0.61 | 0.43 |

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

| Group     | Ethnicity | Genotype | II (%) | ID (%) | DD (%) | Allele frequency | I (%) | D (%) | χ² value | P value | Allele frequency | I (%) | D (%) | χ² value | P value |
|-----------|-----------|----------|--------|--------|--------|----------------|-------|-------|---------|---------|----------------|-------|-------|---------|---------|
| LVH       | Uygur     | II       | 9 (37.50) | 5 (20.83) | 10 (41.67) | 6.59 | 0.03 | 23 (48) | 25 (52) | 5.55 | 0.02 |
|           | Han       | II       | 22 (51.16) | 15 (34.88) | 6 (13.96) | 5.55 | 0.02 | 59 (68.60) | 27 (31.40) | 0.35 | 0.56 |
| NLVH      | Uygur     | II       | 23 (47.92) | 18 (37.50) | 7 (14.58) | 0.73 | 0.70 | 64 (67) | 32 (33) | 0.61 | 0.43 |
|           | Han       | II       | 62 (52.10) | 45 (37.82) | 12 (10.08) | 0.73 | 0.70 | 169 (71.01) | 69 (28.99) | 0.61 | 0.43 |
**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/m²)        | <28=0, ≥28=1       |
| TG (mmol/L)        | <1.70=0, ≥1.70=1   |

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

| Risk factors | β     | SE    | Wald χ² value | P value | OR value | 95% CI           |
|--------------|-------|-------|---------------|---------|----------|------------------|
| **Uygur**    |       |       |               |         |          |                  |
| Female       | 1.50  | 0.95  | 7.41          | 0.01    | 4.16     | 1.69~10.22       |
| 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           | 0.40  | 0.86  | 0.08          | 0.81    | 0.85     | 0.37~2.37        |
| TG            | 0.47  | 0.72  | 0.44          | 0.51    | 1.61     | 0.40~6.53        |
| TC            | 0.70  | 1.66  | 7.34          | 0.01    | 5.27     | 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        |
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 Uighur 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 were 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 Uyghur 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.

References:

1. Kannel WB, Gordon T, Offutt D: Left ventricular hypertrophy by electrocardiogram. Prevalence, Incidence, and mortality in the Framingham study. Ann Intern Med, 1969; 71: 89–105
2. Levy D, Garrison RJ, Savage DD et al: Prognostic implication of echocardiographically determined left ventricular mass in the Framingham heart study. N Engl J Med, 1990; 322: 1561–66
3. Elmasry A, Lindberg E, Hedner I et al: Obstructive sleep apnea and urine catecholamines in hypertensive males: A population-based study. Eur Respir J, 2002; 19: 511–17
4. Tomiyama H, Takata Y, Shinya K et al: Concomitant existence and interaction of cardiovascular abnormalities in obstructive sleep apnea subjects with normal clinic blood pressure. Hypertens Res, 2009; 32: 201–6
5. Sekizuka H, Osada N, Akashi YJ: Impact of obstructive sleep apnea and hypertension on left ventricular hypertrophy in Japanese patients. Hypertens Res, 2017; 40: 477–82
6. Rigat B, Hubert C, Al Lange Galas F et al: An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Chin Invest, 1990; 86: 1343–46
7. Bahramali E, Firouzabadi N, Rajabi M et al: Association of renin-angiotensin-aldosterone system gene polymorphisms with left ventricular hypertrophy in patients with heart failure with preserved ejection fraction: A case-control study. Clin Exp Hypertens, 2017; 39: 371–76
8. Lindpaintner K, Ganten D: The cardiac renin-angiotensin system. An appraisal of present experimental and clinical evidence. Circ Res, 1991; 68: 905–21
9. Manica G, Fagard R, Narkiewicz K et al: 2013 ESH/ESC guideline for the management of arterial hypertension: The task force for the management of arterial hypertension of European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J, 2013; 34: 2159–219
10. Revision committee of China’s guidelines for the prevention and treatment of hypertension. Guidelines for prevention and treatment of hypertension in China 2010. China Hypertension J, 2011; 19: 701–43
11. Rigat B, Hubert C, Corvol P et al: PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) [dipeptidyl carboxypeptidase I]. Nucleic Acids Res, 1992; 20: 1433
12. Laurito S, Cueto JA, Perez J et al: The impact of paralog genes: Detection of copy number variation in spinal muscle atrophy patients. Biocell, 2018; 42: 87–91
13. Nemer AO, Al Anazi MS, Bhat RS et al: Association between preterm birth risk and polymorphism and expression of the DNA repair genes OGG1 and APE1 in Saudi women. Biocell, 2018; 42: 1–6
14. Gomez-Angelats E, de la Sierra A, Enjuto M et al: Lack of association between ACE gene polymorphism and left ventricular hypertrophy in essential hypertension. J Hum Hypertens, 2000; 14: 47–49
15. Iwai N, Ohmichi N, Nakamura Y et al: DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy. Circulation, 1994; 90: 2622–28
16. Kato N, Tatara Y, Ohishi M et al: Angiotensin-converting enzyme single nucleotide polymorphism is a genetic risk factor for cardiovascular disease: A cohort study of hypertensive patients. Hypertension Res, 2011; 34: 728–34
17. López-Contreras J, Blanco-Vaca F, Borrás X et al: Usefulness of the I/D angiotensin-converting enzyme genotype for detecting the risk of left ventricular hypertrophy in pharmacologically treated hypertensive men. J Hum Hypertens, 2000; 14: 327–31
18. Shlyakhto EV, Shwartz EI, Nefedova YB et al: Lack of association of the renin-angiotensin system genes polymorphisms and left ventricular hypertrophy in hypertension. Blood Pressure, 2001; 10: 135–41
19. Bahramali E, Rajabi M, Jamshidi J et al: Association of ACE gene D polymorphism with left ventricular hypertrophy in patients with diastolic heart failure: A case control study. BMJ Open, 2016; 6: e010282
20. Schunkert H, Hense HW, Holmer SR et al: Association between a deletion polymorphism of the angiotensin-converting enzyme and left ventricular hypertrophy. N Engl J Med, 1994; 330: 1634–38
21. Li X, Li Y, Jia N et al: Angiotensin-converting enzyme gene deletion allele increases the risk of left ventricular hypertrophy: Evidence from a meta-analysis. Mol Biol Rep, 2012; 39: 10063–75
22. Iwashima Y, Horio T, Kamide K et al: Additive interaction of metabolic syndrome and chronic kidney disease on cardiac hypertrophy, and risk of cardiovascular disease in hypertension. Am J Hypertens, 2010; 23: 290–98
23. Li H, Pei F, Shao L et al: Prevalence and risk factors of abnormal left ventricular geometrical patterns in untreated hypertensive patients. BMC Cardiovasc Disord, 2014; 14: 136
24. Pérez-Sánchez J, Romero-Puche AJ, García-Molina Sáez E et al: Factors influencing the phenotypic expression of hypertrophic cardiomyopathy in genetic carriers. Rev Esp Cardiol (Engl Ed), 2018; 71: 146–54