

# Association between Carotid Intima-media Thickness and Aldehyde Dehydrogenase 2 Glu504Lys Polymorphism in Chinese Han with Essential Hypertension

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## Abstract

**Background:** Aldehyde dehydrogenase 2 (ALDH2) is involved in the pathophysiological processes of cardiovascular diseases. Recent studies showed that mutant *ALDH2* could increase oxidative stress and is a susceptible factor for hypertension. In addition, wild-type *ALDH2* could improve the endothelial functions, therefore reducing the risk of developing atherosclerosis. The aim of the present study was to explore the frequency of the Glu504Lys polymorphism of the *ALDH2* gene and its relation to carotid intima-media thickness (CIMT) in a group of patients with essential hypertension (EH) and to investigate the association between the Glu504Lys polymorphism and CIMT in Chinese Han patients with EH.

**Methods:** In this study, 410 Chinese Han patients with EH who received physical examinations at the People's Hospital of Sichuan Province (China) were selected. DNA microarray chip was used for the genotyping of the Glu504Lys polymorphism of the *ALDH2* gene. The differences in CIMT among patients with different Glu504Lys *ALDH2* genotypes were analyzed.

**Results:** The mean CIMT of the patients carrying AA/AG and GG genotypes was  $1.02 \pm 0.31$  mm and  $0.78 \pm 0.28$  mm, respectively. One-way ANOVA showed that the CIMT of the patients carrying the AA/AG genotype was significantly higher than in the ones carrying the GG genotype ( $P < 0.001$ ). Multivariate logistic regression showed that the Glu504Lys AA/AG genotype of the *ALDH2* gene was one of the major factors influencing the CIMT in patients with EH (odds ratio = 3.731, 95% confidence interval = 1.589–8.124,  $P = 0.001$ ).

**Conclusions:** The Glu504Lys polymorphism of the *ALDH2* gene is associated with the CIMT of Chinese Han patients with EH in Sichuan, China.

**Key words:** Aldehyde Dehydrogenase 2; Carotid Intima-media Thickness; Essential Hypertension; Glu504Lys Polymorphism

## INTRODUCTION

Essential hypertension (EH) is a global health problem that is especially severe in China.<sup>[1]</sup> EH is one of the major causes of cardiovascular death. Previous studies have shown that hypertension is a disease mainly affecting the large and small arteries all over the body. Atherosclerosis (AS) is the major vascular damage caused by hypertension.<sup>[2]</sup>

AS is one of the major presentations of the systemic AS.<sup>[3]</sup> During development and progression of AS, the carotid intima-media is the earliest affected region. Measuring the carotid intima-media thickness (CIMT) with ultrasonography

could provide excellent objective imaging evidence for the early diagnosis of AS.<sup>[4]</sup> AS is the pathophysiological basis of EH, and EH in turn could promote the development and progression of AS and finally damage the target

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organs.<sup>[2]</sup> Therefore, early detecting AS and investigating the pathogenesis of AS are fundamental for preventing and managing EH and its complications.

Aldehyde dehydrogenase 2 (ALDH2) is a homotetramer enzyme located in the mitochondrial matrix. ALDH2 exists in multiple organs with active metabolism including heart, liver, and brain.<sup>[5]</sup> Changes of ALDH2 functions are associated with polymorphisms of the *ALDH2* genes. The G151 (Glu504Lys) point mutation of the *ALDH2* gene in exon 12 could result in ALDH2\*2, which will change the functional ALDH2 into nonfunctional ALDH2.<sup>[6]</sup> The decrease or loss of the ALDH2 enzyme function could severely decrease the anti-oxidative stress effects. Previous studies have shown that the mutation rate of the *ALDH2* gene is substantially different among different ethnicities. The ALDH2\*2 allele is relatively common in China, Japan, and Korea; however, this mutation is very rare in Africa and Europe. People carrying the mutations have a low tolerability to alcohol and are at higher risk of developing cardiovascular diseases and of elevated blood pressure.<sup>[7,8]</sup>

The pathogenesis of EH and AS is very complex and still poorly understood. Current opinions suggest that both EH and AS are the results of the interactions between genetic and environmental factors.<sup>[9,10]</sup> Previous studies have shown that oxidative stress participates in the development and progression of both EH and AS.<sup>[11,12]</sup> ALDH2 is not only one of the critical enzymes involved in the metabolism of ethanol but also an important factor against oxidative stress. Therefore, we hypothesized that ALDH2 could play an important role in the development and progression of AS in patients with EH. Previous studies have shown that ALDH2 deletion could increase oxidative stress and is a susceptibility factor for hypertension.<sup>[13]</sup> However, the associations between *ALDH2* gene polymorphisms and AS in EH patients have not been reported yet. Therefore, the present study first investigated the association between *ALDH2* gene Glu504Lys polymorphism and CIMT in Chinese Han patients with EH in Sichuan, China. The study aimed to provide evidence to help improving the early prevention and treatment of AS in patients with EH.

## METHODS

### Subjects

From April 2014 to July 2015, 410 patients with EH (220 males and 190 females) who received physical examinations at the Physical Examination Center of the People's Hospital of Sichuan Province, China, were included. Their mean age was  $56.6 \pm 11.6$  years (ranging from 30 to 70 years). All patients were diagnosed with EH according to the 2013 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension:<sup>[14]</sup> systolic blood pressure (SBP)  $\geq 140$  mmHg and/or diastolic blood pressure (DBP)  $\geq 90$  mmHg without antihypertensive drug, or the patient was using antihypertensive drugs. The patients

were diagnosed according to their disease history, clinical presentation, physical examination, laboratory results, chest images, electrocardiogram, abdominal ultrasonography, and echocardiography. Patients with diseases of the vital organs including heart, brain, liver, and kidneys due to endocrine system diseases, rheumatic or autoimmune systemic diseases, or other causes such as secondary hypertension, polyarthritis, peripheral vascular disease, congenital heart disease, rheumatic heart disease, valvular heart disease, cardiomyopathy, coronary heart disease, diabetes, hyper- or hypo-thyroidism, or hyperlipidemia were excluded. All patients had to be free of lipid-lowering or anti-oxidative drugs within the past 4 weeks. All included patients were unrelated Han Chinese living in Sichuan province, China. The present study was approved by the Ethics Committee of the People's Hospital of Sichuan Province, China. All patients voluntarily signed an informed consent form.

### Data collection

Data were collected using questionnaires. The patients were asked to answer the questions under the guidance of trained health professionals. The data collected were as follows: general characteristics (name, gender, ethnicity, age, and birthplace), medical history (smoking, drinking, and family histories; hypertension, diabetes, etc.), physical examination results (blood pressure, height, weight, waist circumference, and body mass index [BMI], which was calculated as  $\text{kg}/\text{m}^2$ ).

### Genomic DNA extraction

All patients were fasted for 12 h, and then 9 ml of peripheral venous blood were collected in the morning: 4 ml in ethylenediaminetetraacetic acid-anticoagulated tubes and 5 ml in nonanti-coagulated tubes. The anti-coagulated sample was separated into two parts: bidirectional sequencing was performed for the DNA from the first part of the sample to detect the Glu504Lys polymorphism of the *ALDH2* gene, while the second part was used for the microarray chip detection. Genomic DNA was extracted using the BaiO ALDH2 gene detection kit (BaiO Technology Co., Ltd., Shanghai, China) according to the manufacturer's protocol.<sup>[15]</sup> The purity and concentration of the DNA were measured using an ultraviolet spectrophotometer. All DNA samples had to have a concentration of at least 10 ng/ $\mu\text{l}$ , and purity of  $A_{260}/A_{280} \geq 1.8$ . The other sample part of the sample (nonanti-coagulated) was used for the separation of the serum for biochemical examinations. Total cholesterol (TC) and triglycerides (TGs) were measured with enzymatic methods, high-density lipoprotein cholesterol (HDL-C) was measured with the magnesium/phosphotungstic acid precipitation method, and low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation ( $\text{LDL-C} = \text{TC} - \text{TG}/2.2 - \text{HDL-C}$ ).

### Genotyping the aldehyde dehydrogenase 2 gene

The DNA microarray chip method was used for the genotyping of *ALDH2* gene.<sup>[15]</sup> In brief, 1  $\mu\text{l}$  of DNA was added into the amplification solution (BaiO Technology Co., Ltd., Shanghai, China) and then amplified using

polymerase chain reaction (PCR) in a 25 µl reaction system, using the following conditions: 50°C for 5 min, followed by 94°C for 5 min, 94°C for 25 s, 60°C for 25 s, and 72°C for 30 s for 35 cycles, then at 72°C for 5 min to end the PCR reaction. PCR products (5 µl) were separated by 1.5% agarose gel electrophoresis and observed under ultraviolet light. The band size was 360 bp. The genotypes of the *ALDH2* gene were determined with a gene chip technique, as previously described.<sup>[16]</sup> In brief, 10 µl of PCR product were processed using the BaiO hybridization kit (BaiO Technology Co., Ltd.) according to the manufacturer's protocols. The chip was read using the BaiO gene chip analysis system (BaiO Technology Co., Ltd.), and the BaiO gene chip image analysis software was used to scan the images, analyze the data, and present the results to identify the genotypes of the *ALDH2* gene.

### Doppler ultrasonography of the carotid artery

A trained sonographer who was blind to the conditions of the patients and the research contents of the present study was asked to perform the Doppler ultrasonography of the carotid arteries of all the patients using Siemens Sequoia 512 Color Doppler Ultrasound Diagnostic System (Siemens, Erlangen, Germany). The frequency of the probe was 7.5 MHz. The patients were placed in the supine position; the head was slightly turned to the contralateral side of the examined carotid artery to fully expose the neck. The bilateral carotid arteries were examined, and the CIMT was measured at the common carotid artery and internal carotid artery along the long axis of the blood vessel. The vertical distance from the tunica intima to the interface between the tunica media and adventitia was recorded as the CIMT. The measure was repeated 3 times at this site as well as 1 cm proximal and distal, and the mean value was calculated as the CIMT of the patient.<sup>[17]</sup> Quality control included repeated scans on a subset of 20 subjects on two separate occasions 7–10 days apart. The coefficient of variability for CIMT was 3.1%.

### Statistical analysis

A *post hoc* power analysis was performed, based on the CIMT between the two genotype groups. The power was 100% ( $n = 241$  and  $n = 169$ , respectively,  $\alpha = 5\%$ ). Therefore, the sample size was adequate. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative data are described with means and standard deviations. The Student's *t*-test was used for comparisons between two groups. One-way analysis of variance (ANOVA) followed by the LSD test was used for comparisons among three or more groups. The Chi-square test was used for the comparisons of qualitative data, Hardy-Weinberg equilibrium (HWE) test, and the comparisons of the genotype distributions among different groups. Multivariate nonconditional logistic regression was used to analyze the factors affecting the CIMT. All statistical analyses were two-sided, and a value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### General characteristics of the patients

The general characteristics (including gender, age, BMI, waist-to-hip ratio [WHR], family history of hypertension, smoking, drinking, heart rate, SBP, DBP, pulse pressure, fasting plasma glucose [FPG], serum creatinine [SCr], serum urea nitrogen, TC, TG, LDL-C, and HDL-C) and the CIMT of the patients are shown in Table 1. A total of 410 patients with EH (including 220 males and 190 females) were included, the mean age of the patients was  $56.6 \pm 11.6$  years, and the mean CIMT was  $0.88 \pm 0.29$  mm.

### Glu504Lys genotypes of the aldehyde dehydrogenase 2 gene

Results showed that there were 3 Glu504Lys genotypes of the *ALDH2* gene: wild type homozygote GG (ALDH2\*1/\*1, Glu504Glu), mutant heterozygote AG (ALDH2\*1/\*2, Glu504Lys), and mutant homozygote AA (ALDH2\*2/\*2, Lys504Lys). Among all patients, 41.22% (169/410) were carrying the Glu504Lys GG genotype and 58.78% (241/410) were carrying the AG and AA genotypes. The results obtained from the chip analysis were in agreement with the sequencing results. The distribution of the genotypes was in accordance with the HWE, suggesting that the patients were from the same population, and the sample was with good representativeness [Table 2].

### Comparisons of the general characteristics and carotid intima-media thickness among patients with different genotypes

No significant difference was found in gender, age, BMI, WHR, family history of hypertension, smoking, drinking,

**Table 1: Characteristics of the EH patients (N = 410)**

Variables	Value
Gender (male/female), <i>n</i>	220/190
Age (years)	56.6 ± 11.6
BMI (kg/m <sup>2</sup> )	25.9 ± 4.1
WHR	0.84 ± 0.08
Family history, <i>n</i> (%)	128 (31.22)
Smoking, <i>n</i> (%)	122 (29.76)
Drinking, <i>n</i> (%)	139 (33.90)
Heart rate (beats/min)	78.9 ± 9.3
Systolic pressure (mmHg)	155.8 ± 18.3
Diastolic pressure (mmHg)	94.6 ± 11.0
Pulse pressure (mmHg)	58.6 ± 13.1
Fasting plasma glucose (mmol/L)	5.39 ± 0.64
Serum creatinine (µmol/L)	74.22 ± 19.89
Serum urea nitrogen (mmol/L)	5.14 ± 1.69
Total cholesterol (mmol/L)	4.51 ± 0.46
Triglycerides (mmol/L)	1.25 ± 0.35
Low-density lipoprotein cholesterol (mmol/L)	2.34 ± 0.62
High-density lipoprotein cholesterol (mmol/L)	1.31 ± 0.35
CIMT (mm)	0.88 ± 0.29

Data are presented as mean ± SD unless otherwise indicated. BMI: Body mass index, WHR: Waist-to-hip ratio, CIMT: Carotid intima-media thickness; SD: Standard deviation; EH: Essential hypertension.



heart rate, SBP, DBP, pulse pressure, FPG, SCr, serum urea nitrogen, TC, TG, LDL-C, and HDL-C between the patients carrying the AG/AA and GG genotypes (all  $P > 0.05$ ). CIMT was significantly higher in the patients carrying the AG/AA genotypes compared with the ones carrying the wild-type GG genotype ( $1.02 \pm 0.31$  mm vs.  $0.78 \pm 0.28$  mm;  $P < 0.001$ ) [Table 2].

### Multivariate nonconditional logistic regression

Multivariate nonconditional logistic regression was performed using the changes of the CIMT as the dependent variable, and the Glu504Lys genotypes of the *ALDH2* gene as the independent variable. Results showed that age (odds ratio [OR] = 2.987, 95% confidence interval [CI] = 1.641–3.744,  $P = 0.004$ ), BMI (OR = 3.426, 95% CI = 1.445–6.397,  $P = 0.010$ ), TG (OR = 2.412, 95% CI = 0.701–4.866,  $P = 0.002$ ), HDL-C (OR = 1.842, 95% CI = 1.346–7.739,  $P = 0.009$ ), and the Glu504Lys AA/AG genotype of the *ALDH2* gene (OR = 3.731, 95% CI = 1.589–8.124,  $P = 0.001$ ) were the major factors influencing the CIMT in patients with EH [Table 3].

### DISCUSSION

The *ALDH2* gene contains 13 exons and is located on chromosome 12. The mutation at position 609 in exon 12 (from G to A) will cause an amino substitution from Glu to Lys in codon 504 (Glu504Lys [rs671]). Therefore, people could carry three different rs671 *ALDH2* genotypes as follows: wild type homozygote GG (*ALDH2*\*1/\*1, Glu504Glu), mutant heterozygote AG (*ALDH2*\*1/\*2, Glu504Lys), and mutant homozygote AA (*ALDH2*\*2/\*2, Lys504Lys).<sup>[18]</sup> The individuals with the AG genotype have an *ALDH2* enzyme activity of about 6%, while the activity is almost absent among the ones carrying the AA genotype.<sup>[18]</sup> The loss of *ALDH2* activity will substantially reduce the anti-oxidative stress effects, increase the oxidative stress, and aggravate the endothelial cell damages.<sup>[19]</sup> This polymorphism is of especially important clinical significance for Asians since these populations have high frequencies of *ALDH2* gene mutations.

CIMT is the vertical distance from the tunica intima to the interface between the tunica media and adventitia. When AS occurs, lipids deposit in the subintimal space and thus increase the IMT. CIMT is the most commonly used index to evaluate early peripheral blood vessel damages and early AS severity in hypertension patients. Changes of CIMT could reflect the changes of the risk factors of cardiovascular events in patients with hypertension to a certain extent.<sup>[20]</sup> Ghiadoni *et al.*<sup>[21]</sup> suggested that long-term hypertension could result in a high-stress to the carotid artery, endothelial dysfunction, and thus cause damage to the intimal functions and increase the intima-media thickness, which is an early marker of AS. The increase of the intima-media thickness will increase the risk of developing cardiovascular and cerebrovascular diseases. The European hypertension guidelines<sup>[14]</sup> and the Chinese hypertension management guidelines (2010) both

**Table 2: Relationships between the clinical parameters and *ALDH2* genotypes**

Items	Genotype		P
	AA/AG (n = 241)	GG (n = 169)	
Gender (male/female), n	126/115	94/75	0.452
Age (years)	57.3 ± 12.0	55.9 ± 11.2	0.714
BMI (kg/m <sup>2</sup> )	26.1 ± 4.1	25.4 ± 4.1	0.641
WHR	0.87 ± 0.09	0.82 ± 0.07	0.512
Family history, n (%)	79 (32.78)	49 (28.99)	0.264
Smoking, n (%)	77 (31.95)	45 (26.63)	0.097
Drinking, n (%)	73 (30.29)	66 (39.05)	0.089
Heart rate (beats/min)	80.5 ± 9.3	77.4 ± 8.1	0.510
Systolic pressure (mmHg)	159.2 ± 18.3	150.9 ± 18.1	0.069
Diastolic pressure (mmHg)	97.6 ± 11.6	90.9 ± 10.7	0.081
Pulse pressure (mmHg)	59.2 ± 13.4	59.8 ± 13.1	0.794
Fasting plasma glucose (mmol/L)	5.42 ± 0.66	5.37 ± 0.59	0.472
Serum creatinine (μmol/L)	75.47 ± 20.21	72.11 ± 19.64	0.321
Serum urea nitrogen (mmol/L)	5.01 ± 1.62	5.14 ± 1.69	0.136
Total cholesterol (mmol/L)	4.55 ± 0.48	4.40 ± 0.42	0.109
Triglycerides (mmol/L)	1.28 ± 0.37	1.22 ± 0.34	0.413
Low-density lipoprotein cholesterol (mmol/L)	2.38 ± 0.60	2.23 ± 0.64	0.242
High-density lipoprotein cholesterol (mmol/L)	1.27 ± 0.33	1.36 ± 0.37	0.335
CIMT (mm)	1.02 ± 0.31	0.78 ± 0.28	<0.001

Data are presented as mean ± SD unless otherwise indicated. BMI: Body mass index, WHR: Waist- to-hip ratio, CIMT: Carotid intima-media thickness; SD: Standard deviation; *ALDH2*: Aldehyde dehydrogenase 2.

**Table 3: Logistic regression analysis of the various risk factors for CIMT in patients with EH**

Items	OR	95% CI	P
Age	2.987	1.641–3.744	0.004
BMI	3.426	1.445–6.397	0.010
Triglycerides	2.412	1.701–4.866	0.002
High-density lipoprotein cholesterol (mmol/L)	1.842	1.346–7.739	0.009
AA/AG genotype of <i>ALDH2</i> Glu504Lys	3.731	1.589–8.124	0.001

BMI: Body mass index; *ALDH2*: Aldehyde dehydrogenase 2; CI: Confidence interval; OR: Odds ratio; CIMT: Carotid intima-media thickness; EH: Essential hypertension.

recommended using the CIMT to evaluate the subclinical damages of the target organs caused by hypertension. The rapid development of ultrasound technologies in recent years makes the early diagnosis of AS by high-resolution sonography possible. To measure the CIMT of hypertension patients with an ultrasound examination, early evaluating and predicting the risk of developing AS, and applying prophylactic treatments are of important significances.

AS is a multifactorial disease, in which both oxidative stress and reactive oxygen species (ROS) play critical roles in the development and progression of AS. ROS could increase the production of active aldehydes (such as 4-hydroxynonenal [4-HNE]), further aggravate oxidative

stress to cause vascular endothelial dysfunction, and thus promote the development of AS.<sup>[22]</sup> ALDH2 is an important aldehyde oxidase that participates in the metabolism of 4-HNE and exerts the functions of apoptosis inhibition, anti-oxidative damages of the myocardium, and promote metabolism of nitroglycerin into exogenous nitric oxide (NO). Therefore, ALDH2 plays an important role in the development and progression of cardiovascular diseases.<sup>[22,23]</sup> However, the results about the association between the *ALDH2* gene and AS are still controversial. Murph *et al.*<sup>[24]</sup> suggested that ALDH2 could exert its anti-AS effects via the detoxification of acetaldehyde and other aliphatic aldehydes (such as 4-HNE). Takagi *et al.*<sup>[25]</sup> showed that the AA genotype of the *ALDH2* gene was a risk factor of coronary atherosclerotic heart disease. However, Narita *et al.*<sup>[26]</sup> investigated 304 Japanese patients with carotid artery AS and found that the plaque scores in the patients carrying the ALDH2\*2/\*2 ( $2.7 \pm 1.2$ ,  $n = 21$ ) and ALDH2\*1/\*2 ( $4.5 \pm 0.5$ ,  $n = 116$ ) genotypes were lower than the ones carrying the ALDH2\*2/\*2 genotype ( $5.7 \pm 0.4$ ,  $n = 167$ ), and thus suggested that the mutant allele of the *ALDH2* gene could be a protective factor for AS. These data suggest that further studies are needed to investigate the association between the *ALDH2* gene and AS.

Gene chip is also known as DNA chip or DNA microarray. Gene chip is a novel biological technology that developed very fast in recent years and using gene chip could provide highly sensitive and high-resolution measurement of gene polymorphisms.<sup>[27]</sup> The present study used a DNA microarray method to measure the 504Lys polymorphism of the *ALDH2* gene, and the results were in agreement with the sequencing results. As most of the Chinese individuals are carrying the *ALDH2* AG genotype, while only <4% are carrying the AA genotype, the present study combined the patients carrying the AG and AA genotypes into one group for the statistical analyses. The present study showed that the CIMT of the patients with EH and carrying the Glu504Lys AG/AA genotypes was significantly higher than the ones carrying the GG genotype ( $1.02 \pm 0.31$  mm vs.  $0.78 \pm 0.28$  mm,  $P < 0.001$ ), suggesting that the Glu504Lys polymorphism of the *ALDH2* gene could be associated with the increase of CIMT in patients with EH. Further multivariate nonlogistic regression showed that age, BMI, TG, HDL-C, and the Glu504Lys AA/AG genotypes ( $OR = 3.731$ , 95%  $CI = 1.589-8.124$ ,  $P = 0.001$ ) were the major factors affecting the changes of CIMT in Han patients with EH in Sichuan, China. The ones carrying the Glu504Lys AA/AG genotypes were at higher risk of CIMT increasing. Oxidative stress is a major regulator for multiple signal transduction systems in the vascular inflammations of AS and plays an important role in the development and progression of AS. 4-HNE is the most representative aldehyde product of lipid peroxidation and can damage mitochondrial functions and induce AS vascular damages.<sup>[25]</sup> ALDH2 could exert anti-AS effects via metabolizing the acetaldehyde and 4-HNE. ALDH2 could prevent the lipid peroxidation of acetaldehyde, reduce the cellular oxidative damages, and thus exert anti-oxidation

effects. In addition, ALDH2 could catalyze the aldehyde group at the end of 4-HNE to finally metabolize into inactive 1,4-di-hydroxyl-2-nonylene,<sup>[22]</sup> thus exert protective effects for cells and tissues, reduce the risk of developing AS, and delay the progression of AS. Furthermore, ALDH2 is also a nitrate reductase which could affect the production of endogenous NO, promote the increase of oxidative stress, increase the endothelial function change, and thus elevate the incidence of AS.<sup>[25]</sup>

There were several limitations in the present study. First, as a case-control study, the mechanisms involved in the association between the Glu504Lys polymorphism of the *ALDH2* gene and CIMT of the EH patients could not be investigated. Second, the sample size was relatively small, and more studies with larger sample sizes are needed. Finally, the findings were not validated in another independent sample.

In summary, the present study showed that the Glu504Lys polymorphism of the *ALDH2* gene is associated with the CIMT in patients with EH and that the Glu504Lys variation of the *ALDH2* gene could be an independent genetic risk factor of increased CIMT in Chinese Han people with EH residing in Sichuan, China. The findings of the present study provide theoretical evidence for the early diagnosis and prevention of AS in patients with EH.

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### Conflicts of interest

There are no conflicts of interest.

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