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Research paper

Aldose reductase C-106T polymorphism is associated with the risk of essential hypertension

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ABSTRACT

Aldose Reductase (AR), encoded by *AKR1B1*, is a member of NADPH-dependent aldo-keto reductase superfamily. The C-106T polymorphism of *AKR1B1* is closely related to the diabetic complications. Our previous studies have indicated that the expression of AR was increased in spontaneously hypertensive rats, suggesting the effect of AR in hypertension. Here we investigated whether *AKR1B1* C-106T polymorphism was associated with essential hypertension (EH). *AKR1B1* C-106T polymorphism was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and the direct sequencing methods. 383 healthy subjects and 383 essential hypertensive patients were recruited in this study. The polymorphism of *AKR1B1* C-106T in EH and normal tensive (NT) groups was in agreement with Hardy-Weinberg equilibrium. -106T allele of *AKR1B1* C-106T variants was more frequent in EH patients compared with normal tensive subjects, indicating that -106T allele was a risk factor of EH (OR = 1.841, 95%CI = 1.366–2.481). In male patients, C-106T polymorphism was associated significantly with decreased serum high density lipoprotein cholesterol and higher systolic blood pressure levels. Our results suggest that -106T allele of *AKR1B1* C-106T polymorphism may be associated with increased risk for EH in Chinese Han population.

1. Introduction

Essential hypertension (EH) is an independent risk factor for cardiovascular diseases, such as myocardial infarction and stroke. Aldose reductase (AR), a member of the aldo-keto reductase superfamily, is the first rate-limiting enzyme of the polyol pathway and catalyzes the NADPH-dependent reduction of glucose to sorbitol (Wang et al., 1993). Our previous studies showed that the expression level of AR was increased in spontaneously hypertensive rat (SHR; Gu et al., 2011; Li et al., 2013), demonstrating that AR may be involved in the development and progression of hypertension.

Proinflammatory conditions and inflammation are associated with the pathophysiology of EH (González et al., 2014). AR is a redox-sensitive enzyme and acts as a key mediator in the oxidative and inflammatory signaling pathways that are associated with cardiovascular disease (Maccari et al., 2015). Previous studies have indicated that AR plays a role in causing glomerular fibrosis through mesangial cell proliferation and extracellular matrix biosynthesis (Li et al., 2014; Jing et al., 2015). Vascular fibrosis is the pathological basis for the development of hypertension. Therefore, we believe that AR plays an important role in EH by accelerating the inflammatory response and vascular fibrosis.

EH is considered to be a multifactorial disease resulting from a combination of environmental and genetic factors. Increasing evidence has shown the effects of genetics on the high prevalence of EH (Luo et al., 2014; Vimaleswaran et al., 2014). Human AR is a monomeric protein (36 kDa) comprising 315 amino acids that is encoded by *AKR1B1*, which maps to chromosome region 7q35. The C-106T (rs759853) single nucleotide polymorphism (SNP), which is located at the promoter of the *AKR1B1* gene, has been reported to be associated with the risk of diabetic complications, including nephropathy (Cui et al., 2015), retinopathy (dos Santos et al., 2006; Katakami et al., 2011) and macroangiopathy (Watarai et al., 2006). Our pre-experiment has explored the association between *AKR1B1* gene polymorphisms and EH, but we failed to obtain positive results that may be due to limited sample size. Therefore, we increased sample size to investigate the association between *AKR1B1* gene polymorphisms and EH in the present study.

Abbreviations: AR, aldose reductase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; EH, essential hypertension; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NT, normal tensive; OR, odds ratio; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride.

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2. Material and methods

2.1. Subject

This study protocol was approved the Independent Ethics Committee of the Institute of Clinical Pharmacology, Central South University (Hunan, China). Written informed consent was obtained from each participant.

From February 2014 to May 2014, a total of 766 Chinese Han volunteers, including 383 patients diagnosed with EH and 383 healthy subjects, were recruited by the Physical Examination Center of the Third Xiangya Hospital, Central South University. Blood pressures were measured twice at 5-minute intervals, according to the guidelines of the European Society of Hypertension (Mancia et al., 2007). Hypertension was diagnosed in participants exhibiting a mean clinic systolic blood pressure (SBP) ≥140 mm Hg and/or a mean clinic diastolic blood pressure (DBP) ≥90 mm Hg, as well as in participants receiving ongoing treatment for hypertension. Subjects with a history of secondary hypertension, diabetes mellitus, primary renal disease or other serious diseases were excluded from this study. Information regarding patient sex, age, height, weight, and family history, as well as triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and fasting blood glucose (FBG) levels, was collected.

2.2. Genotyping

Blood samples were placed in EDTA-containing containers and stored at −20 °C. Genomic DNA was extracted from peripheral whole blood using a Qiagen DNA Isolation Kit (Valencia, CA, USA). The C-106T polymorphism of *AKR1B1* was identified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using the primers and conditions described by Kao et al. (1999). PCR products were digested using the restriction enzyme Bfa I and fractionated via a 3% agarose gel. The amplified PCR product was 263 bp, and two fragments of 57 bp and 206 bp were generated after restriction digestion of the sequence corresponding to the CC genotype. Samples obtained from subjects who were heterozygous for the mutant allele were cut into four fragments (57, 59, 147 and 206 bp) due to the presence of an additional cutting site, while three fragments (57, 59 and 147 bp) were generated for samples obtained from subjects who were homozygous for the mutant allele, as shown in Fig. 1. To confirm PCR-RFLP genotyping results, 5% of the DNA samples were randomly selected to perform direct sequencing (Fig. 2), and we obtained consistent results using the two detection methods.

2.3. Statistical analysis

SPSS 19.0 software was used for data analysis. Comparisons between the groups regarding quantitative data were performed using an independent samples *t*-test, and a chi-square test was used to analyse categorical data. Differences in genotype and allele frequencies between groups and deviations from Hardy-Weinberg equilibrium were calculated by chi-square test. The associations between *AKR1B1* genetic variants and EH were analyzed via binary logistic regression analysis to calculate odds ratios (OR) and 95% confidence intervals (95%CI), which were adjusted for age and sex. Linear regression analysis and Bonferroni correction were used to analyse the relationships between *AKR1B1* genetic variants and EH-related phenotypes, which were adjusted for age and sex, while comparisons between males and females were adjusted for age only. PASS software 11.0 was used to calculate the power of the tests. A two-tailed p-value < 0.05 was considered statistically significant.

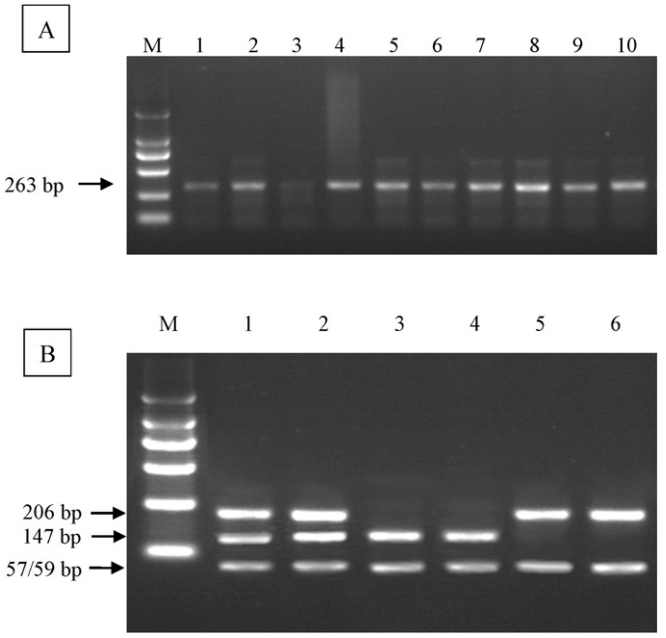

Fig. 1. A, the PCR results of the polymorphism of *AKR1B1* gene. M, DL2000 DNA marker (100, 250, 500, 750, 1000, 2000 bp). Lanes 1–10 are amplification products of samples obtained from subjects. B, the PCR-RFLP results of polymorphisms of *AKR1B1* gene. M, DL2000 DNA marker (100, 250, 500, 750, 1000, 2000 bp). Lanes 1 and 2 are CT genotype (57, 59, 147 and 206 bp); Lanes 3 and 4 are TT genotype (57, 59 and 147 bp); Lanes 5 and 6 are CC genotype (57 and 206 bp).

3. Results

3.1. Characteristics of the participants

The clinical and biochemical characteristics of all subjects are shown in Table 1. There were no differences in the distributions of age and

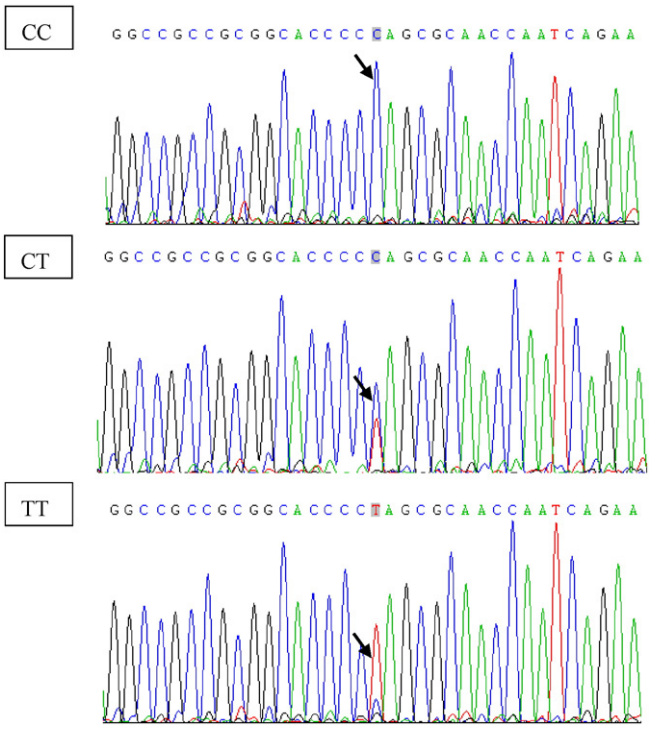

Fig. 2. Genotyping results according to direct sequencing methods. Arrows indicated the polymorphism loci.