Associations of α-Adducin and Angiotensin I-Converting Enzyme Genes with Essential Hypertension in Koreans

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ABSTRACT

The genes encoding α-adducin (ADD1, G460W polymorphism) and angiotensin I-converting enzyme (ACE, T2547C and I/D polymorphisms) have been implicated in essential hypertension (EH) and may regulate the blood pressure (BP) regulation through sodium homeostasis. In order to investigate whether the polymorphisms in these genes are associated with EH in Koreans, we carried out a case-control study of 449 hypertensive cases and age-/gender-matched 459 normotensive controls recruited from Cardiovascular Genome Center of Yonsei University in Korea. The genotypes for these polymorphisms were determined by polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), and the allelic-specific PCR for I/D, T2547C, and G460W, respectively. The genotype frequency of ACE T2547C polymorphism was significantly different between the hypertensive and the normotensive subjects, which was only present in females ($P = 0.019$). ACE 2547C homozygosity, in comparison with the other ACE genotypes, was strongly associated with increase in the incidence of hypertension (OR, 1.788; 95% CI, 1.139-2.809, $P = 0.011$) in single-gene analyses. The pairwise linkage disequilibrium (LD) test was found to be in significant LD ($D' = 0.958$) between ACE T2547C and I/D polymorphisms in our study population. In haplotype and logistic regression analyses, significant OR was also observed for ACE haplotype CD within the ADD1 460 T carriers in the female group (OR, 1.334; 95% CI, 1.004-1.772, $P = 0.047$). Interestingly in males, the group with ACE haplotype CD had significantly low incidence of hypertension in the presence of the ADD1 460 TT homozygosity in males (OR, 0.530; 95% CI, 0.328-0.859, $P = 0.010$). These findings suggest that the ACE gene polymorphisms may be associated with some determinants increasing BP, and imply an
interaction between ACE and ADD1 gene polymorphisms is a positive genetic risk factor for EH in females.

Key words: renin-angiotensin system, α-Adducin, angiotensin I-converting enzyme, essential hypertension, polymorphism, Koreans.

INTRODUCTION

Essential hypertension (EH) is a multifactorial and polygenic disease influenced by various genetic backgrounds and environmental factors. EH is an important risk factor for morbidity and mortality cardiovascular diseases (CVD) (Watt et al., 1992; Bae et al., 2001). Evidence for genetic influence on elevated blood pressure (BP) comes from the twins and population studies (Longini et al., 1984). Although the aetiology of EH is mostly unclear, 20-60% of variability in elevated BP among populations may be attributable to genetic factors (Ward et al., 1995). Many epidemiological reports suggest that genetic factors account for approximately 30% of the variation in BP in various populations (Luft, 2000; Beevers et al., 2001). Several lines of evidence suggest that many genetic loci are responsible for EH; however, the specific genetic mechanisms involved are not known (Harrap et al., 2000; Lifton et al., 2001). The renin-angiotensin system (RAS) influences the maintenance of vascular tone, and both salt and water homeostasis, consequently, components of RAS may be related to the regulation of BP (MacGregor et al., 1981; Tamura et al., 1995). Several genes that consist of RAS have been studied as the strong candidate genes associated with EH (Danser and Schunkert, 2000; Keavney, 2002). Angiotensin I-converting enzyme (ACE, dipeptidyl-carboxypeptidase I, EC.3.4.15.1) plays a central role in RAS, and acts on many substrates, primarily, angiotensin I to produce the potent vasoactive octapeptide angiotensin II and bradykinin, a vasodilator, to inactivate (Soubrier et al., 1993). Angiotensin II, the end product of RAS, has an effect on vasoconstriction, sodium-retaining activity and production of aldosterone (Morishita et al., 1994). Therefore, with its key role in these important cardiovascular hormonal regulatory systems, ACE has a great impact on cardiovascular structure and function (Baudin, 2000). In humans, the ACE gene is located on chromosome 17q23 (Mattei et al., 1989) and is composed of a 24,070 bp including 26 exons (Rieder et al., 1999). Association studies of population-based subjects with binary genetic markers can be helpful in indicating whether variation in a candidate gene may influence hypertension (Turner et al., 1999). Up to date, one of the most extensively studied polymorphisms in the RAS is the insertion/deletion polymorphism of the ACE gene. An I/D polymorphism of the ACE gene is characterized by either presence (insertion, I) or absence (deletion, D) of a 287 bp DNA fragment in an Alu repetitive sequence located near 3′ end in intron 16, resulting in three genotypes (II, DD homozygotes and ID heterozygotes) (Rigat et al., 1990, 1992). A population-based study of unrelated persons with the I/D polymorphism revealed an association between this polymorphism and plasma ACE levels, individuals with DD genotype displaying ACE levels nearly twice as high as those in individuals with II genotype and ID heterozygotes being associated with an intermediate level (Rigat et al., 1990). Accordingly, it is hypothesized that the I/D polymorphism is strongly associated with BP variations and hypertension. Efforts to establish an association between ACE I/D polymorphism and hypertension have been carried out and found conflicting results in different ethnic groups (Frossard et al., 1997; Zaman et al., 2001; Todoroki et al., 2003). Several studies demonstrated evidence of a significant association between I/D polymorphism and EH in males but not in females (Fornage et al., 1998; O’Donnell et al., 1998). However, it was also shown that this correlation in males was inconsistent, but was variable depending on age (Turner et al., 1999). These results suggest that the effects of I/D polymorphism in the aetiology of the elevated BP and EH may vary according to the surveyed hypertensive subjects as they are classified by gender, age and ethnicity. Many investigators reported that the strong candidate regions for an active portion affecting plasma ACE levels are the 5′-, 3′-untranslated region (5′-UTR; 3′-UTR) and the promoter region of ACE gene (Villard et al., 1996; Foy et al., 1997; Zhu et al., 2000; Bouzekri et al., 2004). In particular, the promoter region was found to contain