

**Review**

## **Angiotensin-Converting Enzyme Gene in Alzheimer's Disease**

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Dementia has been increasing exponentially in recent years, especially in Asia. This increasing prevalence calls for the necessity of antecedent biomarkers. The angiotensin-converting enzyme (ACE) gene, located on chromosome 17q23, has been regarded as a candidate susceptibility gene for Alzheimer's disease (AD), because ACE could degrade  $\beta$ -amyloid, the pathological hallmark of AD, thereby inhibiting its aggregation. The level and activity of ACE, in part, may be modulated by the insertion or deletion (indel) polymorphism of ACE gene. The indel polymorphism, consisting of the presence or absence of a 287-bp DNA fragment, has been considered the biomarker of AD, although its validity varies with race. In the Japanese, seemingly different results have been reported. One report shows significant association of insertion homozygote with AD, whereas other shows no association of indel polymorphism with AD. In the Taiwanese, the significant association of deletion homozygote with AD was found. Moreover, clinical studies have shown that using ACE inhibitors could slow the deterioration of cognitive function in AD patients, despite that ACE can degrade  $\beta$ -amyloid. These heterogeneous results on the association of ACE gene with AD and clinical significance of using ACE inhibitor in AD highlight the necessity of exploring detailed mechanisms from the ACE gene to the development of AD. These detailed mechanisms and findings may serve as the basis for further study. ——— Angiotensin Converting Enzyme; Alzheimer's disease; Japanese; Taiwanese;  $\beta$ -amyloid.

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Dementia will increase exponentially in coming years especially in Asia, and the number of patients suffering from dementia is predicted to double every 20 years to 81.1 million by 2040 in the world (Ferri et al. 2005). This increasing prevalence underlines the necessity for antecedent biomarkers in order to have more accurate diagnosis and treatment.

Genetic factors that predispose individuals to Alzheimer's disease (AD) remain unresolved. Presenilin-1, presenilin-2, amyloid precursor protein, and apolipoprotein E (APOE) genes are acknowledged to be associated with AD, but their contributions to AD are estimated at approximately 30% (Richard et al. 2001) and vary with race (Tang et al. 1998).

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The angiotensin-converting enzyme (ACE) gene is located on chromosome 17q23 (Rigat et al. 1992; Mattila et al. 2000), and is regarded as a plausible biological susceptibility gene for AD, because it can degrade  $\beta$ -amyloid (Hu et al. 2001; Hemming et al. 2005; Oba et al. 2005). Individuals diagnosed with AD have higher ACE activity in the hippocampus, parahippocampus, and temporal cortex than non-demented individuals (Arregui et al. 1982; Barenès et al. 1991; Savaskan et al. 2001). AD patients also have decreased ACE activity and ACE levels in cerebrospinal fluid when compared to age and sex-matched non-demented individuals (Zubenko et al. 1985). Moreover, the presence or absence of a 287-bp DNA fragment in ACE gene results in the insertion (I)/deletion (D) polymorphism (indel), which is associated with the ACE level and activity related to AD (Rigat et al. 1992; Mattila et al. 2000). Two meta-analyses addressing the relationships between the ACE indel polymorphism and AD indicate that the D/D genotype is associated with a reduced risk (Lehmann et al. 2005), but the I allele shows increased risk of AD (Elkins et al. 2004).

#### ACE gene insertion/deletion polymorphism in AD

The meta-analyses addressing the relationship between ACE indel polymorphism and AD have shown that I allele and I/D genotype are associated with an increased risk of AD, and D/D genotype with reduced risk of AD (Rigat et al. 1992; Mattila et al. 2000). However, these findings are not consistent within different subgroups of Caucasians, north Europeans and south Caucasians (Mediterranean and Middle East) and within Asians (Lehmann et al. 2005). Published

studies reported no association (Seripa et al. 2003), or association with a particular age group (Farrer et al. 2000) for the relationships between ACE indel polymorphism and AD in Caucasian-Americans. Even in Asians, such associations between ACE indel polymorphism and AD were not consistently detected among Japanese and Taiwanese. For Japanese, the ACE I homozygote was associated with the increased prevalence of AD (Hu et al. 1999); however, the result could not be duplicated in another study (Wakutami et al. 2002). For Taiwanese, the D homozygote and D allele were significantly associated with the increased prevalence of AD (Wang et al. 2006), which is different from the results in the Japanese study (Table 1). The detailed and definite relationships between ACE indel polymorphism and AD are therefore still to be determined.

#### ACE in AD

Several studies have examined the association of ACE I/D polymorphism and ACE plasma concentration and have determined that the D allele (Tiret et al. 1992) or D/D homozygote (Rigat et al. 1990; Danser et al. 1995) is associated with increased plasma ACE level. These findings in part imply that the increased ACE level may lead to cerebral infarction (Ohrui et al. 2004; Oba et al. 2005) or other cardiovascular disorder (Samani et al. 1996; Doi et al. 1997) to be associated with subsequent AD (Snowdown et al. 1997; Vermeer et al. 2003).

Other studies have explored the association of ACE activity with AD. Individuals diagnosed with AD have higher ACE activity in the hippocampal, parahippocampal, and temporal cortex than individuals without AD (Arregui et al. 1982; Barenès et al. 1991). AD patients have decreased

TABLE 1. Associations between ACE insertion/deletion polymorphism and Alzheimer's disease in Taiwanese and Japanese.

Authors	Race	Association with increased risk of Alzheimer's Disease
Hu et al. (1997)	Japanese	I homozygote
Wakutami et al. (2002)	Japanese	No association
Wang et al. (2006)	Taiwanese	D homozygote

ACE activity and level in their cerebrospinal fluid than those in age and sex-matched non-demented individuals (Zubenko et al. 1985). Moreover, some in vitro studies have shown that ACE can degrade  $\beta$ -amyloid and inhibit its aggregation (Hu et al. 2001; Hemming et al. 2005; Oba et al. 2005), and ACE inhibitors would inhibit these functions of ACE (Hemming et al. 2005). These findings highlight the necessity to explore the detailed mechanisms connecting the ACE gene to the development of AD.

### ACE Inhibitors in Cognitive Function

On the contrary, ACE inhibitors seem to provide protection of cognitive function in AD patients. A clinical study assessed the using of brain-penetrating ACE inhibitors in treating AD patients with hypertension has found that using brain-penetrating ACE inhibitors could slow the deterioration of cognitive function of these patients (Ohrui et al. 2004), because ACE inhibitors may enhance the release of acetylcholine in human and rat entorhinal cortex slices (Barnes et al. 1992). The improved cognition with ACE inhibitors was shown in another study (Tzourio et al. 2003). ACE inhibitors can increase cerebral blood perfusion and vasomotor reactivity (Hatazawa et al. 2004; Walters et al. 2004).

### COMMENTS

It is still unclear whether ACE indel polymorphism can be a biomarker of AD in Japanese and in Taiwanese. However, it is important to clarify this point not only for the biomarker itself, but also for the emerging alternative therapy provided by the ACE protein. They appear to conflict over the point that using ACE inhibitors can slow the decline of cognitive function of AD patients and in in vitro study, ACE can directly degrade  $\beta$ -amyloid. The possible benefits of using ACE inhibitors to slow cognitive function may depend on the ACE genotype of the patient, although this lacks definite evidence. These current conflicts and possible benefits of using ACE inhibitors to AD should be clarified in future research.

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