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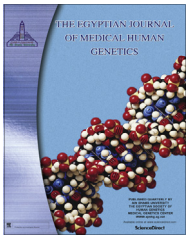

ORIGINAL ARTICLE

Association of insertion–deletion polymorphism of ACE gene and Alzheimer's disease in Egyptian patients

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KEYWORDS

ACE I/D polymorphism;
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Abstract *Introduction:* Alzheimer's disease (AD) is a progressive, neurodegenerative disease. Many studies proposed an association of the insertion (I)/deletion (D) polymorphism (indel) in intron 16 of the gene for angiotensin I-converting enzyme (ACE) on chromosome 17q23 with Alzheimer's disease. *ACE* indel and related haplotypes associated with AD risk have reduced plasma ACE whereas protective genotypes have elevated ACE.

Object: To investigate whether there is a correlation between polymorphisms of the ACE I/D locus gene and AD in Egyptian patients and to determine whether there is a difference in ACE activity in the plasma of clinically diagnosed AD patients.

Methods: Subjects of this study are 84 dementia patients diagnosed as having Alzheimer's disease, 45 males and 39 females aged 65 ± 7 years from the Geriatric Department at Ain-Shams University Hospitals and 86 individuals as non dementia controls, 44 males and 42 females aged 63 ± 6 years.

All subjects were genotyped for the common insertion/deletion polymorphisms for ACE gene locus, and ACE plasma activity assay was measured for AD patients.

Results: There was statistically significant difference in the frequency of the ACE insertion/deletion alleles between the cases and controls where the I allele distribution in AD cases and controls was 74% vs. 15%, and the I/I genotype frequency was 60% vs. 5%, respectively. They both reached a statistical significance range (I allele frequency: OR = 3.714, 95% CI 1.311–10.523, $p < 0.01$; I/I

Abbreviations: AD, Alzheimer's disease; ACE, angiotensin converting enzyme; I/D, insertion/deletion; Aβ, amyloid β; LOAD, late-onset Alzheimer's disease

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genotype frequency: OR = 3.18 95% CI 2.33–4.33, $p < 0.01$). But no significant difference in ACE plasma level was found between different genotypes in our AD patients.

Conclusions: Our present study supports the hypothesis of implication (I allele) of ACE gene polymorphism in the development of AD. On the other hand, we did not find significant difference in plasma ACE activities when compared with different studied genotypes.

1. Introduction

Dementia will increase exponentially in coming years, and the number of patients suffering from dementia is predicted to double every 20 years to 81.1 million by 2040 in the world [1]. This increasing prevalence underlines the necessity for antecedent biomarkers in order to have more accurate diagnosis and treatment [2].

Alzheimer's disease (AD) is the most over diagnosed and misdiagnosed disorder of mental functioning in older adults. Part of the problem, is that many other disorders show symptoms that resemble those of AD. The crucial difference, however, is that many of these disorders – unlike AD – may be stopped, reversed, or cured. Based on these findings, clinical diagnosis of AD has been referred to as "a diagnosis by exclusion", and one that can only be made in the face of clinical deterioration over time. There is no specific clinical test or finding that is unique to AD. Hence, all disorders that can bring on similar symptoms must be systematically excluded. The "classical" senile plaques and the neurofibrillary tangles seen in an AD brain at autopsy typically are the only definitive diagnosis of the disease [3].

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized clinically by gradual loss of memory and pathologically by neurofibrillary tangles and amyloid plaques in the brain. Currently, the apolipoprotein E ε4 allele is the only broadly recognized genetic risk factor for late-onset AD (LOAD) in most populations. Much attention has been focused on the connection between angiotensin I converting enzyme and AD [4].

Angiotensin-converting enzyme (ACE) is an endopeptidase that consists of two catalytic domains and is normally expressed by endothelial, epithelial and neuronal cells [5]. It exists in both membrane-bound (ACE) and soluble (sACE) forms, the latter is produced by the action of an as yet unidentified zinc metalloprotease ('ACE secretase') which cleaves mature, membrane-bound ACE at a juxtamembranous extracellular domain to release the large extracellular part of the enzyme [6,7]. The traditional view of the function of ACE relates to the renin-angiotensin system (RAS) pathway, within which ACE catalyzes the formation of the vasoconstrictor octapeptide angiotensin II (Ang II) from its non-vasoactive precursor angiotensin I (Ang I) and is also responsible for cleavage and inactivation of the vasodilator bradykinin [8]. The net result is vasopressor activity, which can be blocked by ACE inhibitors – a standard treatment for hypertension [9]. More recently ACE has been shown to cleave amyloid-β (Aβ), the accumulation of which is central to the pathogenesis of Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). ACE-mediated cleavage of Aβ has been demonstrated in vitro [10], ex vivo [11] and in some [12] but not in all [13] recently studied animal models of AD.

Several studies show that an insertion/deletion (I/D) polymorphism in the ACE gene is associated with increased plasma level of ACE. Studies showing association between the I/D polymorphism and cardiovascular disease risk, and evidence suggesting cardiovascular risk factors promote AD are consistent with the idea that ACE might play a role in AD via a cardiovascular mechanism [14].

Angiotensin converting enzyme (ACE) plays a key role in the renin-angiotensin system (RAS) pathway. The actions of the RAS have been extensively studied in the periphery, particularly the role of Ang II in hypertension. However, it is now recognized that nearly all organs of the body have their own local paracrine-like RAS, with organ-specific actions [15]. The actions of Ang II within the central nervous system are of increasing interest in the context of Alzheimer's disease (AD). Ang II inhibits the release of acetylcholine (ACh) and has a pro-inflammatory effect [16].

A polymorphism in the gene coding for angiotensin I-converting enzyme (ACE) was identified by Rigat et al. in 1990 [17]. The polymorphism is due to a 287 bp fragment in the ACE gene in chromosome 17. The fragment is present in the insertion (I variant) and absent in the deletion (D variant), which results in the three genotypes: Homozygotes II and DD and heterozygotes DI. The genotype accounts for approximately half of the variance in the circulating ACE level and from the II to the DD genotype the presence of each D allele is associated with an additive effect on ACE activity (50% higher in the DD compared with the II genotype) [18].

The relationship between ACE genotypes, in particular DD, and the occurrence of cardiovascular and renal diseases has therefore been the focus of several studies in the past decade [19].

In 1999, Kehoe et al. [20], proposed the first study that reported an association between Alzheimer's disease and the insertion (I)/deletion (D) polymorphism (indel) in intron 16 of the gene for angiotensin I-converting enzyme (ACE), and the D allele is associated with raised plasma levels of the enzyme [21]. While Lehmann et al. [22], found that I positives, that is, DI and II, were at increased risk of Alzheimer's disease.

The ACE gene (*ACE*) has been featured now as one of the top susceptibility genes for AD [20,22]. According to the meta-analysis database of AD candidate genes listed on Alzgene (www.Alzgene.org), *ACE* indel and related haplotypes associated with AD risk have reduced plasma ACE whereas protective genotypes have elevated ACE [23]. Other studies have observed reduced ACE activity in CSF from AD patients [16].

Indeed after *APOE*, the only widely accepted susceptibility gene for late-onset AD [24], *ACE1* is probably the strongest candidate susceptibility gene for AD. The Aβ degradation hypothesis would explain this on the basis that differences in *ACE1* genotype influence ACE levels and activity and these, in turn, affect Aβ accumulation and toxicity. In most