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PharmGKB summary: very important pharmacogene information for angiotensin-converting enzyme

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Overview

Angiotensin-converting enzyme (ACE) plays an important role in two pathways which contribute to the regulation of blood pressure, the renin-angiotensin-aldosterone system (RAAS) and the kinin–kallikrein cascade (see the RAAS-acting drug pathways at PharmGKB for a simplified view of the candidate genes involved). ACE converts the inactive angiotensin I peptide (also known as Ang I or Ang 1–10) to the active angiotensin II (Ang II or Ang 1–8). Angiotensin II has a variety of functions including vasoconstriction and stimulating release of aldosterone, which in turn causes resorption of sodium and water from urine and increases blood pressure (reviewed in Ref. [1]). ACE also inactivates the vasodilator bradykinin, a component of the kinin–kallikrein cascade, preventing it from stimulating its receptor (BDKRB2) and the subsequent downstream release of nitric oxide, which relaxes vascular smooth muscle and lowers blood pressure [2]. In addition, ACE has also been shown to have a variety of other interesting substrates and interactions including amyloid precursor protein, a major component of plaques in Alzheimer’s disease (AD) [3,4].

ACE is the target of the ACE inhibitor family of drugs making it a potential pharmacodynamic pharmacogene. However, most evidence to date on polymorphisms in *ACE* have been with respect to their impact on disease and clinical outcomes rather than drug response (described extensively in OMIM 106180 and various reviews including [3,5–7]). More than 300 studies have examined over 100 different conditions including cardiovascular disease, renal disease, diabetes, and AD but only about half of the studies found significant association [3]. ACE inhibitors are standard treatment for hypertension, heart failure, and renal disease [8] but there is also discussion about potential use for treatment of AD [9].

The *ACE* gene has been resequenced in African–American and European–American individuals from the Coriell DNA repository, and 78 variants and 13 haplotypes were identified [10]. The most well-known variant in the *ACE* gene is the insertion/deletion in

intron 16, ACE:I/D (insertion/deletion) described in more detail later [5,11]. Other single nucleotide polymorphisms in *ACE* have been significantly associated with AD, including rs1800764, rs4267385, and rs4291, and are catalogued in an online repository at <http://www.alzgene.org> [12] [accessed on 9 September 2009]. Variants rs4290 and rs7213516 in the *ACE* promoter have been shown to reduce transcription and have been associated with adverse cardiovascular outcomes [13].

The *ACE* gene comprises 26 exons that are alternately spliced to give two isoforms. The predominant isoform contains exons 1–12 and 14–26 and when translated results in a 1306 amino acid protein with two zinc-binding catalytic domains (N and C terminal sites). It is expressed in many tissues including kidney, intestine, and lung in endothelial, epithelial, and neuroepithelial cell types [1,14]. This is referred to as somatic ACE or sACE. There is a truncated isoform expressed only in testis, tACE, or gACE/germinal ACE, which contains only the C-terminal catalytic site comprised of exons 13–26 [1,10]. One report mentions a third splice variant, which starts at the same place as tACE but extends through several additional exons; however, no additional data was found to support this [3].

ACE gene product, ACE, is predominantly found attached to the plasma membrane (tissue-bound ACE). ACE can be released into plasma (soluble ACE); however, this form is not considered to catalyze the cleavage of Ang I to Ang II [15,16]. ACE is an M2 zinc metalloprotease and the active sites have the zinc binding motif HEXXH [14]. ACE inhibitor drugs were designed using a rational approach, but at that time a structure was not available and they were instead designed on the basis of an assumed mechanistic homology with carboxypeptidase A. A three-dimensional structure for tACE (1o8a) was elucidated in 2003 and also with the ACE inhibitor lisinopril bound (1o86) [17]. These structures showed that rather than resembling carboxypeptidase A, it looked more similar to neurolysin and may allow for structure-based design of more efficient ACE inhibitors with fewer side effects. Many other crystal structures are currently available in the pdb, several cocrystallized with inhibitors (including 1uze, 1uzf, 2iux).

Adverse drug responses to ACE inhibitors include mild side effects such as cough and serious side effects such as angioedema. These adverse drug responses occur at different frequencies in different racial and ethnic groups, with an increased risk for cough in Asians and women and an increased risk for angioedema in black individuals [18]. ACE inhibition is also associated with birth defects, particularly cardiovascular and renal abnormalities, and ACE inhibitors are contraindicated for women who are or may become pregnant [19,20].

Important variant: ACE:I/D

The ACE:I/D allele is a large insertion/deletion in intron 16. It was first reported by Rigat *et al.* [11], in 1990 and since then has been associated with a large variety of phenotypes in over 800 published articles, many with conflicting results. These phenotypes include plasma ACE levels, blood pressure status, atherosclerosis, coronary heart disease, stroke, diabetic nephropathy, muscle performance, Alzheimer's disease, and early mortality (reviewed in Sayed-Tabatabaei *et al.* [5]). Differences in the allele frequencies have been observed in different racial groups, with the D allele less frequent in Asians [21]. In addition, it has been reported that although ACE activity is related to ACE:I/D genotype in white individuals, it is unrelated in black individuals [22].

The Golden Path genomic sequence (hg17) has the deletion allele. The insertion allele has an additional 287 bases that resembles an incomplete Alu type sequence. Comparison with the chimpanzee genome, which has no Alu element at that location, suggests that the D allele is the ancestral allele. On account of different methods and formats for defining the location of insertion/deletion polymorphisms, there are multiple entries in dbSNP at

different golden path genomic positions, but that are all referred to as the ACE I/D (rs4340, rs1799752, rs13447447, rs4646994). The D variant has been associated with increased plasma levels of ACE in several studies [11,23], but the closely linked ACE:4656(CT)2/3 (rs# not found) has also been suggested as causative for this phenotype [24]. The marker CSH1.01, in the growth hormone-chorionic somatomammotropin hormone gene cluster is also in linkage with ACE:I/D and has been proposed as a potential causative variant for some of the phenotypes observed as associated with ACE:I/D [25]. The relationship among *ACE* gene variation, ACE plasma concentrations, and ACE activity is not fully understood; although early studies sometimes referred to ACE activity and concentration interchangeably, there is some evidence that the two are not always correlated. In AD, studies have shown increased ACE activity while protein levels were the same as controls, and the II genotype (which is associated with lower plasma levels of ACE) has been associated with increased risk of AD [26].

ACE:I/D and drug response

Angiotensin-converting enzyme inhibitors

The GenHAT study, a large study of a subset of over 35 000 individuals from the AllHAT study of hypertension, found no influence of ACE:I/D on response to the ACE inhibitor lisinopril (This study also looked at the calcium channel blocker amlodipine, the diuretic chlorthalidone, and alpha 1 adrenergic blocker doxazosin and found no association). However, there was limited evidence for differences in the risk of fatal and nonfatal coronary heart disease across sex–gene–drug subgroups [27]. The PROGRESS study also found no evidence that ACE genotype influenced response to the ACE inhibitor perindopril [21]. Previous smaller studies had been contradictory, with some suggesting that the DD genotype was associated with a greater response to ACE inhibitors [28,29] and others reporting a better response for II genotypes [30,31] (also reviewed by Scharplatz *et al.* [32], and Kitsios and Zintzaras [6]).

Similarly, studies of diabetic neuropathy have shown conflicting influence of ACE:I/D genotypes on responses to ACE inhibitors, with some showing greater renoprotection for the II genotype [33] and others for the DD genotype [34]. Conflicting results have also been observed for the association of ACE:I/D and response to treatments for renal disease (reviewed in Ref. [7]).

In healthy Japanese volunteers challenged with capsaicin and treated with cilazapril, the cough threshold was reduced in those with the II genotype [35]. However, in patients with a history of cough induced by ACE inhibitor, there was no difference in percentage of ACE: I/D variants between cases and controls [36]. In addition, no associations were found between the interaction of ACE:I/D and α -adducin ADD1:Gly460Trp polymorphisms on blood pressure response to benazepril treatment of 954 Chinese hypertensive patients [37].

Angiotensin receptor blocking drugs

In irbesartan-treated Swedish hypertensives in the SILVHIA study, the II genotype was associated with a greater reduction in diastolic blood pressure than the D allele carriers [38]. These findings were not confirmed in 116 hypertensive patients treated with candesartan [39].

Beta blockers

In atenolol-treated Swedish hypertensives in the SILVHIA study, there was no observable effect of the ACE:I/D variant [38]. Smaller studies have confirmed the lack of association between ACE:I/D genotype and either metoprolol [40] or atenolol [41] responsiveness.

Thiazide diuretics

An interaction between sex and ACE genotype has been reported in the relationship between the ACE:I/D polymorphism and hydrochlorothiazide response as II homozygotes had the greatest response in females, whereas DD homozygotes had the greater reductions in blood pressure in males [42]. Italian hypertensives with at least one copy of the ACE I allele and one copy of the α -adducin (ADD1:Gly460Trp) Trp allele had greater blood pressure lowering with hydrochlorothiazide treatment than any other genotype combinations [43]. The GenHAT study showed no association of ACE I/D with chlorthalidone [27].

Statins

In the Cholesterol And Recurrent Events trial of myocardial infarction survivors, pravastatin reduced the risk of coronary disease death and recurrent myocardial infarction in the patients with the glycoprotein IIIa ITGB3: PI(A1,A2) genotype. The ACE D allele seemed to have modestly additive effects on the ITGB3: PI(A1,A2) risk [44]. In the Lipoprotein and Coronary Atherosclerosis Study population, response to fluvastatin was greater in patients with DD, compared with those with ID and II genotypes, with greater reductions in total cholesterol, LDL cholesterol, and apolipoprotein B and a greater chance of regression [45]. The Regression Growth Evaluation Statin Study trial of pravastatin-treated male patients with stable coronary found no difference in the lipid-lowering effects of pravastatin across ACE:I/D genotypes. However, there was a variant–variant interaction as individuals with the ACE:I/D, DD genotype, and AGTR1:1166A>C (polymorphism in the angiotensin II type 1 receptor, also known as rs5186). CC genotype had significantly more ischemic events than any other genotype combination [46].

Fibrates

In hyperlipidemic obese males treated with gemfibrozil, those with the DD genotype saw increased HDL cholesterol levels compared with I allele carriers [47].

Antipsychotics

Finnish schizophrenics with the COMT:Val108/158Met variant low-activity Met allele, plus the ACE:I/D variant DD genotype, were more likely to have a poor treatment response with conventional neuroleptic drugs. ACE:I/D genotype alone did not influence likelihood of response [48].

Conclusion

Most of the studies that have looked at *ACE* and drug effects have been underpowered to detect complex interactions and focused solely on ACE:I/D. In order for testing of *ACE* to be informative for prescribing, it will probably need to be as part of a panel of variants and haplotypes in *ACE* as well as several other genes in the RAAS and related pathways. There also remains the need to clarify the molecular mechanisms by which *ACE* variation controls plasma levels of ACE and ACE activity and how these are modulated by other genes, diseases, and drugs.

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