Genetic evidence for protective effects of angiotensin converting enzyme against Alzheimer's disease but not other neurodegenerative diseases

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Abstract

Genetic evidence has supported a protective effect of cerebral angiotensin converting enzyme (ACE) against Alzheimer's disease (AD). However, it is unclear whether this is mediated through blood pressure and extends to other neurodegenerative diseases. We performed genetic colocalization investigating an effect of cortical ACE expression on AD risk. We further investigated whether any effect of ACE expression is mediated through changes in blood pressure, and whether effects extend to Parkinson's disease, small vessel disease or cognitive function. There was genetic evidence supporting a protective effect of cortical ACE expression on AD risk. Although higher cortical ACE expression was associated with higher blood pressure, there was no strong evidence to support that its association with AD was mediated through blood pressure, nor that ACE expression affected risk of other neurodegenerative traits. Genetic evidence supports protective effects of cerebral ACE expression on AD, but not other neurodegenerative outcomes.

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Abstract

Genetic evidence has supported a protective effect of cerebral angiotensin converting enzyme (ACE) against Alzheimer's disease (AD). However, it is unclear whether this is mediated through blood pressure and extends to other neurodegenerative diseases. We performed genetic colocalization investigating an effect of cortical *ACE* expression on AD risk. We further investigated whether any effect of *ACE*expression is mediated through changes in blood pressure, and whether effects extend to Parkinson's disease, small vessel disease or cognitive function. There was genetic evidence supporting a protective effect of cortical *ACE* expression on AD risk. Although higher cortical*ACE* expression was associated with higher blood pressure, there was no strong evidence to support that its association with AD was mediated through blood pressure, nor that *ACE* expression affected risk of other neurodegenerative traits. Genetic evidence supports protective effects of cerebral ACE expression on AD, but not other neurodegenerative outcomes.

What is already known about this subject

ACE inhibitors are a commonly prescribed class of medication used to treat heart failure, hypertension and chronic kidney disease.

However, previous observational studies have shown conflicting directions of associations between ACE inhibitors and risk of Alzheimer's disease.

What this study adds

In this study, we provide genetic evidence to support that cerebral cortex *ACE* expression protects against Alzheimer's disease but not other neurodegenerative traits, with this effect being independent of systolic blood pressure.

Further work is required to investigate whether therapeutic inhibition of ACE increases risk of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a leading cause of morbidity worldwide and its prevalence is projected to increase in line with the aging global population[1]. Several pre-clinical and observational studies have implicated the role of central nervous system angiotensin converting enzyme (ACE) levels in the pathogenesis of AD. Cerebral ACE, and downstream product angiotensin II, are increased in patients with AD and promote neuroinflammatory cytokines, reduce acetylcholine release and attenuate cerebral blood flow – all factors implicated in the development of AD[2]. Animal models have shown that hypertensive rats treated with centrally acting ACE inhibitors (e.g. captopril, perindopril), but not hydralazine, have significantly lower age-related impairment in learning and memory, regardless of changes in blood pressure[3]. Observational data also supports the neuroprotective role of central-acting ACE-inhibitors compared to predominantly peripherally acting ACE-inhibitors[2,4].

On the contrary, there is also some evidence that ACE may serve in preventing AD. For example, *in vitro* studies have supported that ACE degrades amyloid-β plaques, a pathological hallmark of AD[5]. Animal AD models with heterozygous deletion of the *ACE* gene demonstrated that a decrease in ACE levels promoted amyloid-β deposition and increased the number of apoptotic neurons[4]. At present, there is therefore uncertainty surrounding the role of ACE-inhibitors in the pathogenesis of AD.

Recent genetic evidence has identified the *ACE* gene as a locus of interest in the development of AD[6]. Bivariate GWAS and colocalisation studies suggest that the *ACE* gene may mediate an association between blood pressure traits and AD risk, with the allele associated with lower SBP also associated with higher AD risk. Tissue-specific expression has demonstrated that higher cerebellar *ACE* expression has a positive association with AD risk[7]. By extension, this implicates a possible detrimental effect of centrally acting pharmacological ACE inhibition on AD risk. This is of direct clinical relevance as ACE inhibitors are one of the most commonly prescribed anti-hypertensive agents and are oftentimes commenced as a first-line medication in younger patients. Therefore, it is imperative to understand any potential long-term effect of ACE modulation on risk of later life neurodegenerative diseases.

To further explore the relationship between ACE and neurodegenerative diseases, we advance previous work by performing three-way colocalization analyses for *ACE* gene expression in the cortex, systolic blood pressure (SBP) and AD risk. This approach enables us to identify a genetic proxy for the effect of ACE inhibitors that cross the blood-brain barrier, and explore its association with risk of AD and other neurodegenerative diseases. Finally, we assess whether any association could be mediated by effects of SBP on AD risk. In this way, we elucidate the complex interplay between ACE and AD, and assess the potential effect of ACE-inhibition on neurodegenerative disease risk more widely.

Methods

Data sources

For both colocalization and Mendelian randomization (MR) analyses, data were obtained from publicly available summary statistics of genome-wide association studies (GWAS) outlined in Table 1. We selected Parkinson's disease, cognitive performance, lacunar stroke and MRI quantified white matter hyperintensity as outcomes to represent common neurodegenerative conditions. Lacunar stroke and MRI-quantified white matter hyperintensity, both which are well-recognised features of vascular dementia, were used as surrogate outcomes in the absence of available GWAS for vascular dementia.

Statistical analysis

We conducted colocalization analysis of genetic associations for *ACE* gene expression in brain cortex tissue and AD liability within +/-20kb of the *ACE* gene using coloc,[8] a Bayesian method for colocalization. We also assessed for three-way colocalization with SBP using the HyPrColoc method[9](Hypothesis Prioritisation for multi-trait Colocalization), to investigate whereby AD risk, cortical *ACE* expression and blood pressure share a common causal variant. The single-nucleotide polymorphism (SNP) with the greatest posterior probability from colocalization analysis of cortical *ACE* expression and AD risk represents the genetic proxy most likely to simulate the effect of cerebral cortex ACE modulation on AD risk. We then employ a MR paradigm to explore whether this variant is associated with other neurodegenerative traits. Finally, the effect of SBP on AD risk was explored in an MR analysis using an instrument comprising of genetic variants from across the genome. Full details are given in Supplementary Methods**.**

Results

Genetic colocalization

Colocalization analysis provided evidence for a shared causal variant for each pairwise combination (PP for colocalization of cortical*ACE* gene expression and AD liability = 0.98; PP for colocalization of cortical *ACE* expression and SBP = 0.97; PP for SBP and AD liability = 0.98). In three-way colocalization by HyPrColoc, the estimated PP of full colocalization = 0.83. The variant rs4291 was the most likely shared causal variant for all traits (figure 1). Similar results were obtained when only considering AD cases and not also AD-by-proxy (Supplementary Results).

Mendelian randomization

The A allele of rs4291 that associated with lower cortical *ACE*expression was negatively associated with SBP (effect estimate per increase -0.28mmHg, 95% confidence interval -0.35 to -0.22). This same variant was positively associated with AD risk (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.04 to 1.08, figure 2). However, strong associations were not identified for the other neurodegenerative traits as outlined in figure 2 (OR for lacunar stroke 0.97 (95% CI 0.93 to 1.01); OR for Parkinson's disease 0.99 (95% CI 0.96 to 1.03); beta estimate for cognitive function 0.01 (95% CI -0.001 to 0.01); beta estimate for white matter hyperintensity -0.02 (95% CI -0.11 to 0.07; Supplementary Table 2). Genetically predicted SBP was not associated with AD risk (OR 1.01, 95% confidence interval 1.0 to 1.01) using a genome-wide instrument, suggesting that while SBP colocalizes with cortical *ACE* expression at the *ACE* gene, reduction in SBP more generally is not directly associated with AD risk. These findings was consistent in sensitivity analysis (Supplementary Table 3).

Discussion

This study leveraged genetic data to identify support for ACE in prevention of AD, with no strong evidence identified supporting effects of ACE on other neurodegenerative traits. While increased cortical*ACE* expression associated with lower AD risk, there was no MR evidence supporting that genetically predicted SBP affects risk of AD.

From a mechanistic perspective, ACE has been shown to breakdown neurotoxic amyloid-beta isoform (Aβ42) to a less toxic form (Aβ40). Administration of a clinical dose of ACE inhibitor to human amyloid precursor protein transgenic mice was associated with increased brain amyloid deposition[4]. In humans, patients with AD have lower Aβ42-to-Aβ40–converting activity compared with sera from age-matched healthy individuals[4]. Our current findings support that ACE protects against AD, although further work is required to investigate whether this is attributable to reduced amyloid aggregation or other unrelated mechanisms.

An observational study among 406 participants with mild-to-moderate AD demonstrated a reduction in cognitive decline for people receiving a centrally-acting ACE inhibitor (perindopril) compared to peripherally-acting ACE inhibitor[18]. Other studies have shown increased risk of incident dementia and disability associated with peripherally-acting ACE inhibitors compared to other anti-hypertensive medication[19]. Conflicting findings between genetic and observational studies could be explained by MR being less liable to environmental confounding and reverse causality[20], due to the random allocation of genetic variants at conception.

Our current work is consistent with other genetic studies supporting a role of ACE in preventing AD and has several additional strengths. Firstly, obtaining association estimates from the MetaBrain consortium (n = 6,601 participants)[10], we investigate cortical*ACE* expression and AD risk. This dataset is significantly larger than the GTEx resource (n = 205) that has been utilised in previous work[7]. Secondly, we investigate whether SBP mediates the relationship between ACE and AD risk, and do not find evidence that supports this. Finally, we explore the associations of genetically proxied cortical *ACE* expression with other traits and do not find evidence to support that this association applies across other neurodegenerative traits.

This work also has several limitations. Clinical diagnosis of AD is challenging as there is significant overlap in symptoms with other forms of dementia, limiting the specificity of case definitions in GWAS. To explore for this, we also assessed several other neurocognitive traits. Given the absence of strong evidence of ACE effects for these outcomes, it seems likely that our findings are specific for AD risk, rather than a generic effect on dementia or cognition. As with all studies leveraging genetic data, there remains the possibility of biological pleiotropy introducing confounding. It is also not possible to extrapolate the magnitude of clinical effect or required drug exposure for ACE inhibitors to represent a real-world risk for AD. Factors such as the ability of an ACE inhibitor to cross the blood-brain-barrier may also shape AD risk and should be further studied. Furthermore, our work was based on data obtained from individuals of European genetic ancestry, and it is unclear whether these findings extend to other ethnic groups.

In summary, while ACE inhibitors have numerous indications and are the cornerstone of hypertension, chronic kidney disease and heart failure management, this study finds evidence for a beneficial effect of cerebral cortex ACE in preventing AD. It would be premature to alter current clinical practice based on this evidence, and rather these findings should encourage further research into the effect of ACE inhibitors on AD risk.

Conflicts of interest statement

DG and TGR are employed part-time by Novo Nordisk.

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Data availability statement

All data used in this study are publicly available. The statistical code used in this work is available from the corresponding author upon reasonable request.

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Table 1: Sources for genetic data

Data	**Data source**	Population
Cortex *ACE* gene expression	MetaBrain cortical eQTL GWAS 2021 [10]	6,518 individuals of European ancestry

Data	Data source	Population
Systolic blood pressure	Evangelou et al 2018[11]	757,601 individuals of European ancestry
Alzheimer's disease	De Rojas et al 2020[13]	GWAS meta-analysis of up to (i) 36,675 cas
Parkinson's disease	Nalls et al 2019[14]	GWAS meta-analysis of 37,688 cases and 18
Lacunar stroke	Traylor et al 2021[15]	GWAS of 6,030 Cases, 219,389 controls in i
White matter hyperintensity	Persyn et al 2020[16]	GWAS of 17,663 individuals of European an
Cognitive function	Lee et al 2018[17]	Meta-analysis of UK Biobank (n = 222,543)

Table 1: Details genome-wide association studies used in the present study. COGENT consortium: Cognitive Genomic Consortium, eQTL: expression quantitative trait loci, GWAS: genome-wide association study, MRI: magnetic resonance imaging, PC: principal component, RNA-seq: RNA sequencing

Colocalisation plots

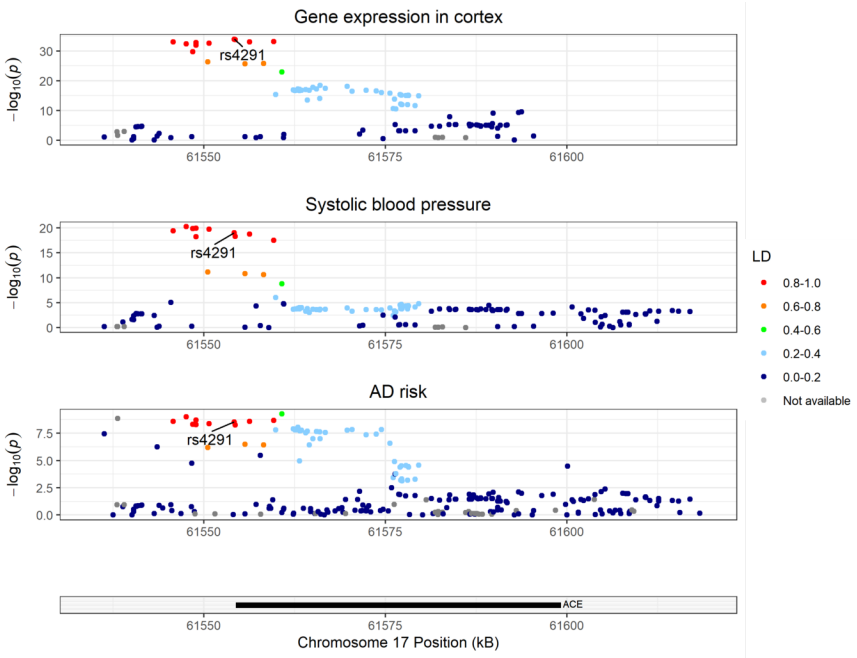

Figure 1: Colocalization plots depicting the association of single nucleotide polymorphisms (SNPs) with cortical ACE gene expression, systolic blood pressure and Alzheimer's disease (AD) risk. The X axis shows position within the genome (build Hg19) and Y axis denotes the -$\log_{10}$(p-value) for the association. Colour denotes the linkage disequilibrium (LD) between different variants (see legend). The results support that rs4291 is the most likely candidate SNP underlying all these traits, therefore, representing a common causal SNP for these traits.

Associations between genetically proxied ACE inhibition and neurodegenerative traits

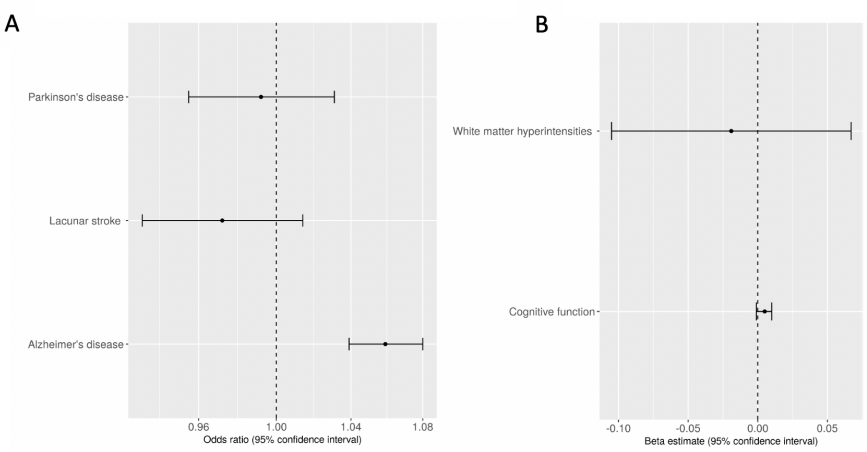

Figure 2: Forest plot showing associations between genetically proxied ACE inhibition (rs4291 effect allele A) with (A) disease outcomes and (B) continuous traits. In graph A, results reported as odds ratio per effect allele with 95% confidence interval. The x-axis is presented on the log10 scale. For graph B, results reported as beta estimate per effect allele with 95% confidence interval.

Figure legends

1. Sources for genetic data
2. Colocalisation plots
3. Associations between genetically proxied ACE inhibition and neurodegenerative traits