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ACE genotype and cognitive decline in an African-Caribbean population

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Abstract

The insertion/deletion (I/D) polymorphism of the angiotensin I converting enzyme (ACE) gene is believed to influence risk of cerebrovascular disease. However, associations with cognitive outcomes remain controversial. As far as we are aware, all studies to date have been carried out in white American or European populations. African-Caribbean populations have high prevalence rates of hypertension, diabetes and cerebrovascular disease but risk factors for cognitive outcomes remain under-researched. In a UK community sample of 148 African-Caribbean people aged 55–75 years, we investigated the association between ACE genotype and cognitive decline over 3 years using a battery of repeated tests. No direct association was found between ACE genotype and decline. However, the association between increased age and cognitive decline was significantly stronger in people with the ACE DD genotype (odds ratio 3.6 per 5-year increase, 95% CI: 1.9–6.7) compared to those with ID/II genotype (odds ratio 0.7, 95% CI 0.4–1.2). This interaction was particularly strong for decline in verbal memory and was not apparently mediated by vascular risk factors measured at baseline.

Keywords: ACE genotype; Cognitive decline; Polymorphism; African-Caribbean

1. Background

The insertion/deletion (I/D) polymorphism of the angiotensin I converting enzyme (ACE; dipeptidyl carboxypeptidase 1; DCP1) gene is believed to influence risk for cerebrovascular disease. The DD genotype is associated with increased ACE activity and with stroke [41]. It has also been found to be associated with subclinical white matter disease [18,42]. Associations with cognitive decline and dementia remain controversial. One large study of two samples found associations between Alzheimer's disease and the ACE D allele [12]. However, several other studies have found an association between the ACE I allele and Alzheimer's disease [1,9,11,20,22,50], associations with both II and DD genotypes compared to ID [21,30] or no association with either allele [6,7,10,27,29,39,52]. For 'dementia' as an outcome, one case control study in two samples found an association with the ACE D allele [35] although other studies have found no associations [3,7,39,52] including a large community survey [51].

Some of this variation may be artefact arising from standard diagnostic criteria for Alzheimer's disease which exclude people with higher levels of cerebrovascular disease (potentially associated with ACE genotype) from case groups [25]. For dementia as an outcome, differential mortality might also influence associations with ACE genotype and differential rates of admission to institutional care (associated with cerebrovascular disease) might influence findings in community samples. Studies which have investigated associations with cognitive function or decline in younger age groups are less subject to these sources of bias and may help to clarify the effects of this polymorphism. Several studies have found associations between the DD genotype and worse cognitive function [2,4,5,34], although one found no association [15]. Fewer studies have investigated prospective associations with cognitive decline. One study of twins aged 73 years and above found no association between ACE polymorphism and change in Mini Mental State Examination (MMSE) score over a 2-year period [15]. Furthermore, in a community sample of people aged 65 years and over, no association was found between ACE genotype and mean change in MMSE score over a 6-year period [51]. On the other hand, in a sample of healthy volunteers aged 59–71 years, a three-point decline in MMSE score over a 4-year period was approximately 50% more likely in people with DD compared to ID genotype [34].

As far as we are aware, the association between ACE genotype and cognitive outcomes have only been

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investigated in white European, American and East Asian samples. These do not necessarily apply to other populations since gene–environment interactions may differ. African-Caribbean populations have a high risk of cerebrovascular disease [43] due in part to high prevalence rates of hypertension and diabetes [8,47]. Increased carotid intima-media thickness has also been found in this group [24]. These have all been identified as important potential risk factors for cognitive decline and dementia in European and American populations [19,23,31], but cognitive outcomes have received little research in African-Caribbean groups. Hypertension and diabetes were associated with cognitive impairment in British African-Caribbean elders [45], and diabetes was associated with an increased risk of age-associated cognitive decline over a 3-year period [44]. The ACE DD genotype is slightly more common in African- compared to European-origin populations [37] and has been found to be associated with increased angiotensin converting enzyme activity [14] and hypertension [38] in African-Caribbean samples. Associations with cognitive outcomes have not been investigated. In 1997–1998, a community sample of older African-Caribbean people participated in an investigation of vascular risk and cognitive function and were subsequently followed over 3 years. ACE genotype was assayed from blood taken at baseline. We hypothesised that the DD genotype would be associated with cognitive decline over 3 years, but that this would be mediated by increased vascular risk at baseline.

2. Method

2.1. Study population

The study was designed to investigate the association between vascular risk factors and cognitive impairment in an African-Caribbean community population and an inclusion age range of 55–75 years was chosen. The lower age limit was chosen considering the likely point at which subtle cognitive impairment would be detectable. The upper age limit was chosen considering the age range of this migrant population. Most members of this group migrated from Caribbean nations to the UK as young working adults in the 1950s and 1960s. At the time of recruitment therefore there were few people from this population aged more than 75 years. Recruitment of the baseline sample has been described in detail previously [45]. Registration lists for seven primary care services in south London were used as a sampling frame, practice staff identified all potentially eligible registered patients (regarding ethnic group) within the inclusion age range and 290 people were interviewed (60% response rate). All participants were aged 55–75 years, were of Caribbean birth and ancestry (78% Jamaican-born) and were living in community accommodation. There were no other inclusion or exclusion criteria. In 2000–2001, participants were contacted and re-interviewed.

2.2. Baseline measurements

Medical and cognitive examinations at baseline were carried out by different interviewers and cognitive tests administered blind to health status. Self-reported previous diagnoses of stroke, hypertension or diabetes were recorded at interview and coded as binary present/absent variables. The following were also carried out: a resting electrocardiogram (EKG, Minnesota coding), resting blood pressure, and Multistix urinalysis for glucose and protein. Hypertension was categorised as ‘complicated’ if EKG hypertrophy and/or proteinuria was present. Diabetes was categorised as poorly controlled if glycosuria was detected.

2.3. Genotype assays

DNA was extracted from anticoagulated blood samples taken at baseline. ACE I/D genotype was detected by a PCR according to the presence of the intron 16 specific insertion and deletion fragments using primers CTGGAGACCACTCCCATCCTTTCT and GATGTGGCCATCACATTCGTCAGAT. PCR products were separated on 1% agarose gel by electrophoresis and were visualised using ethidium bromide and ultraviolet light. A second intron 16 insertion specific amplification was carried out on all samples to confirm the ID and DD genotypes using primers TGGGACCACAGCGCCCGCCACTAC and CGGCAGCCCTCCCATGCCCATAA [36,40]. Typing was carried out blind to case characteristics.

2.4. Cognitive assessments

Cognitive tests were drawn predominantly from the CERAD battery [28], which has been evaluated in other cross-cultural settings [46]. The following five tests were administered in identical format at both interviews: orientation (MMSE [13]), immediate word list recall (CERAD), delayed word list recall (CERAD), delayed word list recognition (CERAD), visual attention/motor speed (Trail A test [33]). As in other analyses on this cohort, our strategy was to investigate initially a composite measure of cognitive decline as a dependent variable [44]. Because of the nature of the tests administered, analyses on this cohort have focused on defining a declining subgroup rather than quantifying change as a continuous variable. A single binary category for cognitive decline was generated in the following way:

(i) ‘Change’ variables were calculated for each of the five repeated tests.
(ii) A factor analysis was carried out for these change variables and a single factor extracted and generated as a variable. This had an Eigen value of 2.1, and explained 42% of the variance. Loadings of individual test change scores on this factor were satisfactory, ranging from 0.51 (orientation) to 0.73 (Trail A).
(iii) Cognitive decline was defined as a score on this variable below the 20th percentile so that participants with