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Brief Research Communication

Analysis of Alpha-1 Antichymotrypsin, Presenilin-1, Angiotensin-Converting Enzyme, and Methylenetetrahydrofolate Reductase Loci as Candidates for Dementia

Carolyn Tysoe,[1] Daliah Galinsky,[1] Damian Robinson,[2] Carol E. Brayne,[2] Douglas F. Easton,[2] Felicia A. Huppert,[3] Tom Dening,[3] Eugene S. Paykel,[3] and David C. Rubinsztein[1]*

[1]*East Anglian Medical Genetics Service Molecular Genetics Laboratory, Addenbrooke's Hospital, Cambridge, UK*
[2]*Institute of Public Health, University Forvie Site, Cambridge, UK*
[3]*Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK*

The genetic factors which predispose individuals to dementia in old age have not been fully defined. Although the apolipoprotein E4 allele accounts for a proportion of the genetic risk for late-onset Alzheimer disease (AD), it is neither necessary nor sufficient to cause this disease. Recent suggestions that other loci are involved in dementia risk have been supported by findings of associations of genotypes at the alpha-1 antichymotrypsin (ACT) and presenilin-1 (PS-1) loci with AD. We investigated these loci in two community-based aged Cambridgeshire populations: the rural Ely population (cohort 1) comprised 60 pairs of demented and nondemented elderly individuals, with a mean age of 84.2 years; and the Cambridge city population (cohort 2) comprised 81 pairs all over age 84, with a mean age of 87.3 years. Since vascular risk factors are likely to impact on dementia risk, we also examined the angiotensin-converting enzyme (ACE) and methylenetetrahydrofolate reductase (MTHFR) genes as candidates. ACE, ACT, PS-1, and MTHFR genotype and allele frequencies were not significantly different in cases and matched controls. These data support the doubts which have been raised about the involvement of the PS-1 and ACT polymorphisms in late-onset dementia. Am. J. Med. Genet. 74:207–212, 1997.

KEY WORDS: Alzheimer disease; dementia; alpha-1 antichymotrypsin; presenilin

*Correspondence to: D.C. Rubinsztein, East Anglian Medical Genetics Service Molecular Genetics Laboratory, Box 158, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.

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INTRODUCTION

Cognitive decline is a characteristic of human aging. Severe loss leads to the dementias, which are common and increase in prevalence with age [Heston, 1992]. Alzheimer disease (AD) and vascular dementia are thought to account for about 60% and 30% of dementias in the UK, respectively. However, overlap of these pathologies occurs. Genetic factors play a role in the etiology of both diseases [Heston, 1992; Rubinsztein, 1995].

AD is neuropathologically indistinguishable in the young and old, but has been arbitrarily divided into early- and late-onset disease, using an age cutoff of 65 years. Dominant mutations in the amyloid precursor protein and the recently identified presenilin 1 (PS-1) and presenilin 2 genes have been implicated in early-onset AD. Numerous studies have confirmed that AD risk after age 65 years is associated with allelic variation at the apo E locus. This locus has three alleles in the general population. Apo E4 is associated with increased risk of late-onset AD, and apo E2 is associated with decreased risk [reviewed by Sandbrink et al., 1996].

Apo E allelic variation only accounts for a proportion of the genetic risk for late-onset AD, and the apo E4 allele is neither necessary nor sufficient to cause dementia. For instance, Henderson et al. [1995] showed that homozygosity for apo E4 is only associated with the development of dementia in 50% of individuals by age 90, and Jarvik et al. [1996] demonstrated that other genetic or familial factors besides apo E play a role in late-onset dementia.

Vascular dementia is associated with multiple infarcts or hemorrhages in the brains of cases. This pathology is associated with atherosclerotic risk [Jarvik et al., 1995] and hypertension [Skoog et al., 1996]. Thus, we considered that additional candidates for dementia risk may be the angiotensin-converting enzyme (ACE), where an Alu insertion deletion polymorphism has been associated with cardiovascular and hyperten-

sion risk [Beohar et al., 1995], and the methylenetetrahydrofolate reductase (MTHFR) gene, where homozygotes for the common C to T mutation at position 677 have increased risk of myocardial infarction [Frosst et al., 1995]. MTHFR catalyzes the reduction of 5,10 methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which acts as a carbon donor for remethylation of homocysteine to methionine. MTHFR deficiency is characterized by homocysteinemia, which increases risk for atherosclerosis and thrombosis. It has been suggested that high levels of circulating homocysteine are associated with cognitive loss in depressed elderly patients [Bell et al., 1992]. Thus, it is possible that MTHFR deficiency is associated with dementia in general.

The alpha-1 antichymotrypsin (ACT) and presenilin-1 (PS-1) genes are important candidates to examine for late-onset dementia. Alpha-1 antichymotrypsin is associated with apo E in senile plaques, and mutations in the PS-1 gene are associated with most cases of early-onset AD [Sandbrink et al., 1996]. Furthermore, polymorphisms at these loci have been associated with risk for AD [Kamboh et al., 1995; Wragg et al., 1996; Higuchi et al., 1996; Kehoe et al., 1996]. However, these data have not been consistently replicated [Haines et al., 1996; Scott et al., 1996; Perez-Tur et al., 1996].

MATERIALS AND METHODS

In this study we examined ACE, ACT, PS-1, and MTHFR as candidates for dementia. Allele and genotype frequencies were compared at these loci for community-based demented cases and controls in two aged populations from Cambridgeshire.

The Ely Population

Subjects were enrolled in the Cambridge Centre of the Medical Research Council Multicentre Study of Cognitive Function and Aging (MRC CFA Study) [Chadwick, 1992]. In this study, the cognitive functioning of a random sample of 2,500 individuals age 65 years and over from Ely, a city 14 miles from Cambridge, and surrounding rural areas, was assessed on at least two occasions, separated by an interval of 2 years. In addition, a subset of the sample was assessed in more detail approximately 1 month after the initial screen. This subset included all those respondents with evidence of cognitive impairment and a comparable number of noncognitively-impaired individuals.

At each screening and assessment interview, two composite measures of dementia status and cognitive state were obtained. The AGECAT organicity score was derived from the Geriatric Mental State (GMS) examination, a standardized interview developed to detect psychiatric morbidity in epidemiological studies [Copeland et al., 1976, 1986]. The range of possible scores is from 0–6; a score of 0 indicates a low probability of cognitive impairment, while increasing scores correspond to increasing likelihood of a diagnosis of dementia being made by a clinician. In this study, a score of 3 or above was taken to indicate the likely presence of dementia.

The second measure of cognitive state was the Mini-Mental State Examination (MMSE) test score [Folstein et al., 1975]. The maximum score is 30, and lower scores indicate some degree of cognitive impairment. Various cutoffs were used to indicate dementia.

In the Cambridge component of the CFA study, the second wave of screening at 2 years was modified to incorporate a nested case-control study. All respondents who had an AGECAT organicity score of 3 or above at baseline or follow-up were entered into the nested case-control study as cases. Each case was paired with a single age- and sex-matched control selected from the nonimpaired respondents. These respondents were interviewed at home by an experienced psychiatrist using the full GMS examination, augmented with the Cambridge Cognitive Examination (CAMCOG), a neuropsychological battery which forms part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) diagnostic interview [Roth et al., 1986, 1988] and additional cognitive items. In addition to obtaining the AGECAT organicity score and MMSE score, the psychiatrist made a clinical diagnosis of dementia using DSM-IIIR criteria [American Psychiatric Association, 1987].

Cases and controls were age-matched within a maximum of 5 years of each other. Three hundred and forty-six respondents were eligible for entry into the case-control study, from whom 277 interviews were completed and 174 mouthwash samples were collected. Some respondents died before mouthwash samples were obtained, and some cases with severe dementia could not provide samples; thus, samples from 60 age- and sex-matched pairs were analyzed. All cases and controls investigated in this study were older than age 70 years.

The Cambridge Population

The second, distinct, study group came from a 10-year longitudinal study of cognitive function and aging [Paykel et al., 1994]. Participants were originally age 75 years and over, identified from population registers for family practitioners in Cambridge city. The participants had taken part in at least three further screening interviews since baseline: at 2.4 years, 6 years, and 10 years. These interviews included the MMSE. In this 10-year follow-up, of the original 1,968, 546 who had taken part in the previous follow-ups were available for interview. Of these, 83% (446) agreed to be seen, and successful venepuncture was carried out on 63% of these: 182 females and 100 males. (The "unsuccessful" venepuncture resulted either from difficulty in venepuncture in the elderly individuals, or when individuals and relatives decided against venepuncture.) These individuals represent a sample who were all age 84 or older at time of venepuncture. Age matching was within 5 years except for 2 cases, who were matched within 7 years of their controls' ages.

All Cambridge cases and controls were older than age 84 years. The mean (±SD) of ages of cases and controls in the Ely population was 84.6 (±6.42) and 83.8 (±5.81) years, and in the Cambridge population was 87.3 (±3.05) and 87.3 (±2.6) years, respectively. The Ely sample was significantly younger than the Cambridge

TABLE I. MTHFR Allele and Genotype Frequencies*

Allele	Ely: DSM-IIIR and AGECAT (n = 116) Demented	Ely: DSM-IIIR and AGECAT (n = 116) Non demented	Cambridge: MMSE (n = 152) <22	Cambridge: MMSE (n = 152) >23	Total: MMSE (n = 258) <22	Total: MMSE (n = 258) >23
C	65 (56%)	75 (65%)	100 (66%)	99 (65%)	165 (64%)	171 (66%)
T	51 (44%)	41 (35%)	52 (34%)	53 (35%)	93 (36%)	87 (34%)
Genotype	**Ely: DSM-IIIR and AGECAT (n = 58) Demented**	**Ely: DSM-IIIR and AGECAT (n = 58) Non demented**	**Cambridge: MMSE (n = 76) <22**	**Cambridge: MMSE (n = 76) >23**	**Total: MMSE (n = 129) <22**	**Total: MMSE (n = 129) >23**
C/C	17 (29%)	28 (48%)	35 (46%)	33 (43%)	54 (42%)	58 (45%)
C/T	31 (54%)	19 (33%)	30 (39.5%)	33 (43%)	57 (44%)	55 (43%)
T/T	10 (17%)	11 (19%)	11 (14.5%)	10 (14%)	18 (14%)	16 (12%)

*There was no significant association between dementia and the MTHFR 2/2 risk genotype when compared to the two other combined MTHFR genotypes. Allele and genotype frequencies were not significant different in the cases and controls in the Ely, Cambridge, or combined populations ($P > 0.05$).

sample ($P < 0.001$). In these studies, controls and cases were well-matched for ethnicity and geographical origin.

Cases and controls from the Ely cohort were defined by both DSM-IIIR and AGECAT criteria. In the Cambridge cohort, cases were defined as individuals with MMSE scores of 21 or less, while controls had MMSE scores of 24 or more. MMSE scores were also obtained in the Ely cohort. Thus, when we pooled data from the Ely and Cambridge samples, we adopted the MMSE cutoffs as an additional criteria on top of DSM-IIIR and AGECAT diagnoses for the Ely group, since the MMSE was a diagnostic measure shared with the Cambridge group. Tables I–IV show genotype and allele frequencies for the Ely sample (defined by AGECAT and DSM-IIIR), the Cambridge sample (defined by MMSE), and the combined total sample (defined by MMSE). MMSE data for the Ely group can be obtained by subtracting the Cambridge data from the combined data. The combined sample of about 125 cases and controls gives power to reveal an odds ratio of 2.5, where 10% of the control group have the genotype in question and an odds ratio of 2.0 when 30% of the controls have the genotype (5% significance and 80% power) [Breslow and Day, 1987]. Thus, if our sample consisted only of AD patients, it should be large enough to reveal effects of the size described for the PS-1 intronic polymorphism, where the 1/1 genotype is found in about 30% of controls and was associated with a doubling of AD risk (Wragg et al., 1996). Although the overwhelming majority of demented cases in this age range have AD pathology [Heston, 1992], many will also have changes associated with vascular dementia. The presence of individuals with vascular dementia and other dementias distinct from AD in our cases will diminish the power to detect effects of loci which are specific to AD.

These studies have been approved by the Addenbrooke's Hospital ethics committee. Informed consent was given by all cases or caregivers. These individuals were all formally evaluated prior to DNA testing.

DNA Analysis

DNA was extracted from mouthwash cell pellets by phenol extraction (population 1) or from venous blood (population 2). Apo E, ACE, MTHFR, ACT, and PS-1 genotypes were determined using the polymerase chain reaction (PCR) primers and conditions described

TABLE II. ACE Allele and Genotype Frequencies*

Allele	Ely: DSM-IIIR and AGECAT (n = 110) Demented	Ely: DSM-IIIR and AGECAT (n = 110) Non demented	Cambridge: MMSE (n = 146) <22	Cambridge: MMSE (n = 146) >23	Total: MMSE (n = 232) <22	Total: MMSE (n = 232) >23
1	50 (45%)	41 (37%)	56 (38%)	69 (47%)	95 (41%)	107 (46%)
2	60 (55%)	69 (63%)	90 (62%)	77 (53%)	137 (59%)	125 (54%)
Genotype	**Ely: DSM-IIIR and AGECAT (n = 55) Demented**	**Ely: DSM-IIIR and AGECAT (n = 55) Non demented**	**Cambridge: MMSE (n = 73) <22**	**Cambridge: MMSE (n = 73) >23**	**Total: MMSE (n = 116) <22**	**Total: MMSE (n = 116) >23**
1/1	11 (20%)	8 (15%)	11 (15%)	17 (23%)	21 (18%)	26 (22%)
1/2	27 (49%)	25 (45%)	34 (47%)	35 (48%)	53 (46%)	55 (47%)
2/2	17 (31%)	22 (40%)	28 (38%)	21 (29%)	42 (36%)	35 (30%)

*Allele and genotype frequencies were not significantly different in the cases and controls in the Ely, Cambridge, or combined populations ($P > 0.05$).

TABLE III. α1ACT Allele and Genotype Frequencies*

	Ely: DSM-IIIR and AGECAT (n = 116)		Cambridge: MMSE (n = 152)		Total: MMSE (n = 248)	
Allele	Demented	Non demented	<22	>23	<22	>23
T	61 (53%)	64 (55%)	73 (48%)	62 (41%)	118 (48%)	105 (42%)
A	55 (47%)	52 (45%)	79 (52%)	90 (59%)	130 (52%)	143 (58%)
	Ely: DSM-IIIR and AGECAT (n = 58)		Cambridge: MMSE (n = 76)		Total: MMSE (n = 124)	
Genotype	Demented	Non demented	<22	>23	<22	>23
T/T	16 (28%)	19 (33%)	15 (20%)	10 (13%)	26 (21%)	22 (18%)
T/A	29 (50%)	26 (45%)	43 (56%)	42 (55%)	66 (53%)	61 (49%)
A/A	13 (22%)	13 (22%)	18 (24%)	24 (32%)	32 (26%)	41 (33%)

*Allele and genotype frequencies were not significantly different in the cases and controls in the Ely, Cambridge, or combined populations ($P > 0.05$).

by Hixson and Vernier [1990], Rigat et al. [1992], Frosst et al. [1995], Kamboh et al. [1995], and Wragg et al. [1996], respectively. In short, ACE insertion and deletion alleles were resolved on 2% agarose/1% Nusieve (Flowgen, Sittingbourne, UK) gels. Apo E, MTHFR, ACT, and PS-1 alleles were characterized by restriction digestion of PCR products with *Hha*I, *Hinf*I, *Bst*NI, and *Bam*HI, respectively. The Ely (mouthwash) samples were resolved on 10% (Apo E, MTHFR) and 8% (ACT, PS-1) nondenaturing polyacrylamide gels and silver-stained, while the samples of the Cambridge cohort were analyzed on 2% agarose/1% Nusieve (Flowgen) gels stained with ethidium bromide.

RESULTS AND DISCUSSION

Allele and genotype frequencies were compared for the alpha-1 antichymotrypsin, presenilin-1, angiotensin-converting enzyme, and methylenetetrahydrofolate reductase loci in demented cases and controls using chi-square tests. In addition, the proportions of cases and controls homozygous for the C-T mutation at position 677 in the MTHFR gene were assessed.

No significant associations were detected at any of the other loci in these groups (Tables I–IV). In addition, no significant association was observed between the presence of the MTHFR 2/2 risk genotype and dementia when compared to a combination of the two other MTHFR genotypes (Table I). In contrast to an earlier report, there was no overrepresentation of the ACT A allele in the total demented population (Table III). A previous study suggested an interaction between the ACT A allele and apo E4. However, we did not detect such an interaction using the same analytical procedures that were used previously [Kamboh et al., 1995]: the apo E4 allele combined with the ACT A allele did not confer a significant increase in dementia risk in this population (data not shown). ACT genotype frequencies did not differ significantly between demented and nondemented individuals, when classified by apo E4 carrier status (data not shown).

Some of the Cambridge cohort could not complete their MMSE because they were either too demented, or had visual or motor impairment. Although these individuals were included in the analyses, they only accounted for 23 case-control pairs. No differences in results were obtained when these individuals were deleted from the analyses (data not shown). An MMSE cutoff score of 21 for defining cases may have resulted in the inclusion of some nondemented individuals in

TABLE IV. PS-1 Allele and Genotype Frequencies*

	Ely: DSM-IIIR and AGECAT (n = 122)		Cambridge: MMSE (n = 154)		Total: MMSE (n = 266)	
Allele	Demented	Non demented	<22	>23	<22	>23
1	74 (61%)	68 (56%)	85 (55%)	93 (60%)	151 (57%)	160 (60%)
2	48 (39%)	54 (44%)	69 (45%)	61 (40%)	115 (43%)	106 (40%)
	Ely: DSM-IIIR and AGECAT (n = 61)		Cambridge: MMSE (n = 77)		Total: MMSE (n = 133)	
Genotype	Demented	Non demented	<22	>23	<22	>23
I/I	21 (34%)	18 (30%)	23 (30%)	26 (34%)	41 (31%)	44 (33%)
1/2	32 (52%)	32 (52%)	39 (51%)	41 (53%)	69 (52%)	72 (54%)
2/2	8 (14%)	11 (18%)	15 (19%)	10 (13%)	23 (17%)	17 (13%)

*Allele and genotype frequencies were not significantly different in the cases and controls in the Ely, Cambridge, or combined populations ($P > 0.05$).

the Cambridge case group. Accordingly, this population was reanalyzed using more stringent criteria, by defining cases as having MMSE scores of 17 or less and controls as having scores of 24 or more. Thirty-five case-control pairs remained and showed no significant differences at any of the loci, either in the Cambridge sample alone, or when these cases and controls were pooled with the Ely sample (data not shown).

The diagnosis of dementia was made on clinical grounds only in this study. The Ely cohort was diagnosed according to DSM-IIIR and AGECAT diagnoses, which are sensitive and relatively specific indicators for dementia [Roth et al., 1986, 1988; Copeland et al., 1976]. The Cambridge cohort was assessed using the MMSE, and cutoff scores of 21 and 17 were used to categorize demented cases, while controls had scores of 24 and more. While the reduction of the cutoff to 17 would have reduced the proportion of nondemented individuals in this case group, this was accompanied by a reduction in sample size. Our failure to replicate previous associations at the PS-1 and alpha-1 antichymotrypsin loci may have been affected by the size of our sample or because the demented group included too many individuals with conditions other than AD. Although the overwhelming majority of these cases will have AD pathology [Heston, 1992], many of these will also have the changes associated with vascular dementia. Alternatively, these genetic effects may be most influential in dementia in younger late-onset cases, since our sample is an old population, where the majority of individuals were older than age 84. This would be compatible with the model that these loci are not the primary cause of the disease but merely accelerate the pathogenic process resulting from distinct genes which cause dementia between age 65–85 years. Despite these caveats, our data are consistent with those of Haines et al. [1996], who could not replicate the alpha-1 antichymotrypsin findings. Although this group and others could not replicate the PS-1 association in their large set of cases and controls [Scott et al., 1996; Perez-Tur et al., 1996], others have presented supporting replication studies [Higuchi et al., 1996; Kehoe et al., 1996]. Further careful studies are needed to assess the contribution of these loci to late-onset dementia.

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