Genetic association of an *LBP-1c/CP2/LSF* gene polymorphism with late onset Alzheimer's disease

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Abstract

***Objectives*—The only locus unequivocally associated with late onset Alzheimer's disease (AD) risk is *APOE*. However, this locus accounts for less than half the genetic variance. A recent study suggested that the A allele of the 3'UTR biallelic polymorphism in the *LBP-1c/CP2/LSF* gene was associated with reduced AD risk. Samples were diagnosed predominantly by clinical rather than pathological criteria. We have sought to replicate this finding in a series of necropsy confirmed, late onset AD cases and non-demented controls.**

***Methods*—The 3'UTR polymorphism in the *LBP-1c/CP2/LSF* gene was typed in 216 necropsy confirmed AD cases and 301 non-demented controls aged >73 years.**

***Results*—We found different *LBP-1c/CP2/LSF* allele distributions in our AD cases and controls (p=0.048); the A allele was associated with reduced AD risk. The allele and genotype frequencies observed in our cases and controls were similar to those previously reported. No significant effects emerged when the data were adjusted for age, sex, or apoE ε4 carrier status.**

***Conclusions*—Our data support *LBP-1c/CP2/LSF* as a candidate gene/risk factor for AD and provide justification for future studies to investigate the role of this gene in Alzheimer's disease.**

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Keywords: Alzheimer's disease; *LBP-1c/CP2/LSF*; dementia; MRC/CFAS study

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Alzheimer's disease (AD) is characterised clinically by dementia and neuropathologically by the presence of β amyloid plaques and neurofibrillary tangles. Although the pathological changes are similar at all ages of onset, AD is often divided into early and late onset disease using an arbitrary age at onset of 65 years. Most AD cases are late onset.

Mutations in the amyloid precursor protein, presenilin 1 and presenilin 2, can cause autosomal dominant forms of early onset AD. The only locus unequivocally associated with late onset AD risk is *APOE*. However, this locus accounts for less than half the genetic variance.[1 2]

In a previous study Lambert *et al*[3] sequenced the transcription factor *LBP-1c/CP2/LSF* gene, which lies within the chromosome 12 AD locus, in order to identify any genetic variants that may modify the risk of developing AD. They found that the A allele of a G/A polymorphism located in the 3'UTR was associated with sporadic AD in samples diagnosed predominantly by clinical, rather than pathological, criteria. In this study we have typed for the 3'UTR polymorphism in a series of necropsy confirmed AD cases and age matched non-demented controls to see if we could confirm an association between this polymorphism and sporadic AD, and thus give further support for the role of this genetic variant as a risk factor in AD.

Methods

CLINICAL SAMPLES

Anonymised cases (n=239) with necropsy confirmed AD with an onset after 65 years (using CERAD criteria) were obtained from brain banks in Cambridge, Oxford, and London. Cases were of white English origin and comprised 86 males and 153 females; mean age at death was 81.2 years (SD 7.8). Our white, English, non-demented controls aged 73 years and older with MiniMental State Examination (MMSE) scores of 24 or more were collected around Oxford and Cambridge (n=342) as part of ongoing community based studies, the MRC Multicentre Study of Cognitive Function and Ageing and Cambridge City Study.[4 5] Controls comprised 140 males and 202 females and had a mean age of 82.1 years (SD 3.8). There was no significant difference in the sex distributions in the two groups or the age at death of the cases compared to the age of examination of the controls. These studies have been approved by the Addenbrooke's Hospital local ethics committee. A total of 216 AD cases and 301 controls were successfully genotyped for both *LBP-1c/CP2/LSF* and *APOE*.

POLYMORPHISM DETECTION

The 3'UTR polymorphism was typed in necropsy confirmed AD cases and controls, as described by Lambert *et al*.[3] Apo E data on these samples are described in Narain *et al*.[6] Calculations of odds ratios with 95% confidence intervals were determined using Stata 6.0 software.

Results

The 3'UTR polymorphism of the *LBP-1c/CP2/LSF* gene was typed in a series of necropsy confirmed AD cases and age matched non-demented controls (table 1). The genotypes of the control samples were in Hardy-Weinburg equilibrium (χ^2_1=2.69, p=0.10). The frequency of the A allele was reduced in the AD cases compared to the controls (odds ratio=0.59,

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Table 1 Allele and genotype frequencies of LBP-1c/CP2/LSF gene 3'UTR polymorphism in AD cases and controls. Odds ratios and 95% confidence intervals are shown. Alleles: χ^2_1=3.91, p=0.048; genotypes: χ^2_2=3.60, p=0.16

	AD	Controls	Odds ratio	95% CI
Alleles				
G	411 (0.95)	554 (0.92)	1.00	
A	21 (0.05)	48 (0.08)	0.59	0.35–1.00
Genotypes				
G, G	196 (0.91)	257 (0.85)	1.00	
G, A	19 (0.09)	40 (0.13)	0.62	0.35–1.11
A, A	1 (0.005)	4 (0.01)	0.33	0.04–2.97

95% CI 0.35-1.00) (χ^2_1=3.91, p=0.048). However, the genotype frequencies of the AD cases when compared to the controls were not significantly different. No significant effects/interactions emerged when the genotypic data were adjusted for age, sex, or the presence of the apoE ε4 allele (p>0.05 Mantel-Haenszel test).

Discussion

Our data comparing late onset, necropsy confirmed AD cases to non-demented controls (matched for age and sex) are consistent with those of Lambert *et al*,[3] in that the A allele of the 3'UTR polymorphism was associated with a reduction in the risk of AD. The rare A allele, found in 8% of controls, appears to confer a protective effect. The magnitude of this effect (OR=0.59 for A allele) is similar to that described in the combined samples of Lambert *et al*[3] (OR=0.60). It is also reassuring that the allele and genotype frequencies in our cases and controls were similar to those reported by Lambert *et al*.[3] For instance, the A allele was found in 4% of the pooled cases and 7% of the pooled controls described previously,[3] and in 5% of our cases and 8% of our controls. We observed no significant differences between the genotype frequencies in the cases and controls. This is probably because there are twice as many alleles as genotypes, which therefore results in a greater power to detect an effect. Indeed, the phenomenon of significantly different allele frequencies but not significantly different genotype frequencies was also observed in some of the populations studied by Lambert *et al*.[3] However, the mean odds ratios we obtained for A allele heterozygotes and homozygotes were 0.62 and 0.33, respectively, consistent with an effect for this locus.

While Lambert *et al*[3] suggested that the effect of this polymorphism was greatest in younger cases (<70 years), it was notable that we observed an effect in our samples where the cases had a mean age of death of 81 years (SD 7.8) and the mean age of our controls was 82.1 years (SD 3.8). It is possible that the selection of necropsy confirmed cases in our study reduced the possible confounding interference of other forms of dementia. Like Lambert *et al*,[3] we observed no interactions between *LBP-1c/CP2/LSF* genotypes and gender or apoE ε4 carrier status in relation to AD risk.

In conclusion, our data support *LBP-1c/CP2/LSF* as a candidate gene/risk factor for AD. It is intriguing that the protective A allele gene product has decreased binding to nuclear protein(s) and that the absence of the A allele is associated with a tendency towards decreased *LBP-1c/CP2/LSF* mRNA expression.[3] As Lambert *et al*[3] postulated, *LBP-1c/CP2/LSF* may be involved in AD pathogenesis by regulating the expression of proteins of interest, such as GSK3β and serum amyloid A3, or by interacting with the APP binding protein FE65. Thus, we believe further studies are justified to investigate the role of the *LBP-1c/CP2/LSF* gene in Alzheimer's disease.

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