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

Alison E Taylor, Agustin Yip, Carol Brayne, Douglas Easton, John Grimley Evans, John Xuereb, Nigel Cairns, Margaret M Esiri, David C Rubinsztein

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.

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

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.

In a previous study Lambert et al 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. 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. Apo E data on these samples are described in Narain et al.

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 (χ²=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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et al described in the combined samples of Lambert (OR=0.59 for A allele) is similar to that found in 8% of controls, appears to confer a reduction in the risk of AD. The rare A allele, which was adjusted for age, sex, or the presence of 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, 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 (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. For instance, the A allele was found in 4% of the pooled cases and 7% of the pooled controls described previously, 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. 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 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, 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. As Lambert et al 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 F665. Thus, we believe further studies are justified to investigate the role of the LBP-1c/CP2/LSF gene in Alzheimer’s disease.

This work was supported by the Medical Research Council. AY is grateful to the Cambridge Overseas Trust and the European Dana Alliance for the Brain and JGE is grateful to the Clothworkers’ Foundation for funding. DCR is a Glaxo Wellcome Research Fellow.

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doi: 10.1136/jmg.38.4.232

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