Increased CSF-BACE 1 activity is associated with ApoE-ε4 genotype in subjects with mild cognitive impairment and Alzheimer’s disease

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The Apolipoprotein (ApoE) ε4 allele is a major genetic risk factor of Alzheimer’s disease, and may affect the production of amyloid beta (Aβ1-42). Recently, we have shown that β-secretase (BACE 1) activity can be reliably detected within the brain and human CSF. Here, we have examined an association between the ApoE genotype and CSF-levels of BACE 1 activity in Alzheimer’s disease and mild cognitive impairment (MCI). A total of 148 subjects were included: 60 Alzheimer’s disease patients, 51 MCI subjects and 37 elderly healthy controls. The CSF-levels of Aβ1-42, BACE 1 activity and BACE protein were measured in all of these subjects. The differences between ApoE-ε4 carriers and ApoE-ε4 non-carriers in these CSF-based measures were determined controlling for gender, age and MMSE score. The ApoE-ε4 genotype was associated with increased BACE 1 activity in both Alzheimer’s disease (P = 0.03) and MCI (P = 0.04) subjects. Levels of Aβ1-42 were decreased in ApoE-ε4 carriers in MCI (P = 0.004) but not Alzheimer’s disease subjects. This study is the first to demonstrate the association between ApoE-ε4 and CSF-BACE 1 activity in MCI and Alzheimer’s disease subjects. The assessment of BACE 1 in CSF may provide a sensitive measure to detect in vivo alterations in the amyloidogenic processing potentially modified by the ApoE genotype.

Keywords: mild cognitive impairment; cerebrospinal fluid; Alzheimer’s disease; ApoEε4, β-amyloid.; biological marker; prediction; early detection; biological activity; cerebrospinal fluid; CSF

Abbreviations: ApoE = Apolipoprotein; APP = amyloid precursor protein; Aβ = beta-amyloid; CSF = cerebrospinal fluid; HC = healthy control; MCI = mild cognitive impairment


Introduction

The Apolipoprotein (ApoE) ε4 allele is a major risk factor of Alzheimer’s disease. ApoE ε4 genotype shows increased frequency in sporadic and familial late-onset Alzheimer’s disease, occurring in about 52% of all cases of familial Alzheimer’s disease compared to 16% in healthy controls (Strittmatter et al., 1993). In elderly people without dementia, the ApoE ε4 genotype is associated with over twice the risk for developing Alzheimer’s disease (Slooter et al., 1999). In subjects with amnestic mild cognitive impairment (MCI), the presence of the ApoE ε4 genotype has been demonstrated to be a strong predictor in the progression towards Alzheimer’s disease (Petersen et al., 1995; Tierney et al., 1996; Buerger et al., 2005).

Several lines of research suggest that the ApoE ε4 genotype may be associated with Alzheimer’s disease by its role in the development of amyloid pathology. Post-mortem studies have shown that the ApoE ε4 genotype
is associated with an increase in the production of beta-amyloid (Aβ) (Ye et al., 2005) and the formation of senile plaques in the cerebral cortex (Rebeck et al., 1993; Schmechel et al., 1993). Results from in vitro studies suggest that the ApoE protein of the ε4 isoform may regulate the generation of Aβ (Puglielli et al., 2003; Ye et al., 2005).

The Aβ peptide is generated from the transmembrane polypeptide called amyloid precursor protein (APP): APP is initially cleaved by β-secretase, which is pivotal for the subsequent cleavage of APP fragments by γ-secretase that results in the long fibrillar Aβ1–40 and Aβ1–42 peptides. In Alzheimer’s disease, these peptides aggregate into plaques within the brain (Selkoe, 1994). Thus, BACE 1 activity is pivotal for the amyloidogenic processing of APP (Sinha and Lieberburg, 1999; Vassar et al., 1999; Yan et al., 1999). Recently, we have demonstrated increased levels of BACE 1 protein and enzymatic activity within the brain homogenate of the frontal and temporal cortex in Alzheimer’s disease subjects (Yang et al., 2003; Li et al., 2004), further supporting the hypothesis that abnormal activity of BACE 1 is associated with Alzheimer’s disease. For in depth review on BACE 1 please see Hampel & Shen, in press.

When assessing in vivo the CSF-concentration of BACE 1 activity, we have recently found increased levels of both BACE 1 measures in subjects with MCI when compared to healthy controls and Alzheimer’s disease patients, demonstrating the presence of abnormal BACE 1 concentration already present an at-risk group of Alzheimer’s disease (Zhong et al., 2007). Since the ApoE genotype has been linked to increased production and deposition of Aβ (Strittmatter et al., 1993, 1994), and BACE 1 is pivotal for the Aβ generation, we hypothesized that the ApoE ε4 genotype is associated with increased levels of BACE 1 activity. Here, we investigated the CSF-levels of BACE 1 and Aβ1–42 as a surrogate marker of Aβ within the brain samples of MCI and Alzheimer’s disease subjects recruited from two different centres with expertise in neurodegenerative diseases. Since decreased levels of Aβ1–42, as measured in CSF correlate with increased Aβ deposition within the brain (Strozyk et al., 2003), we further hypothesize that ApoE ε4 could be associated with decreased levels of Aβ1–42 in the CSF. We used CSF-based measurement of BACE 1 as a surrogate marker of BACE 1 within the brain, since previous studies have shown that CSF-based markers of Alzheimer’s disease-specific pathology, such as Aβ1–42 or hyperphosphorylated tau at threonine 231 (p-tau231), correlated well with brain pathology in Alzheimer’s disease (Strozyk et al., 2003; Buergel et al., 2006), and are accurate and reliable predictors of Alzheimer’s disease even when assessed within a multi-centre context (Ewers et al., 2007). In the current study, we examined whether BACE 1 and ApoE genotype could be also used as a surrogate marker in Alzheimer’s disease and MCI subjects. For detailed review of biological marker research in insipient AD see Blennow & Hampel, 2003.

### Methods

#### Patients

A total of 51 subjects with MCI, 60 patients with Alzheimer’s disease and 37 elderly healthy controls (HC) were included in the study. The diagnosis of Alzheimer’s disease was made according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria (McKhann et al., 1984). Amnestic MCI was diagnosed according to Mayo clinic criteria (Petersen et al., 2001), i.e. MCI patients had memory performance 1.5 SD below the age-adjusted normal average, as assessed by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) cognitive battery, (Morris et al., 1989) including verbal learning, recognition and recall tests. Global cognitive function and activities of daily living were unimpaired in the MCI subjects. CSF from cognitively normal controls was obtained as part of spinal anaesthesia for the primary purpose of surgery of the urinary tract or lower extremities. Psychiatric co-morbidity was excluded by history, clinical examination and Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). All controls were cognitively normal according to CERAD cognitive battery performance (within 1 SD in all subtests), and subjects had no complaints of cognitive impairment. To avoid spinal anaesthesia as a potential confounding factor when collecting CSF, CSF was obtained immediately after inserting the needle and just before application of the anaesthetic drug. Subjects were recruited at the department of psychiatry at the University of Munich, Germany, and the department of clinical neuroscience, at the University of Göteborg, Sahlgren’s University Hospital, Sweden. The subject group included here is a sub-sample of subjects examined in our previous study on the differences of CSF-concentration of BACE 1 protein and BACE 1 activity between Alzheimer’s disease, MCI and HC (Zhong et al., 2007). In that study, 80 patients with Alzheimer’s disease, 59 subjects with MCI and 69 HC were included. Mean levels of BACE 1 protein and activity in the CSF for each group were reported previously in that study (Zhong et al., 2007). The current sub-sample results from the availability of blood-samples for the ApoE-genotype analysis. All procedures are approved by the institutional review boards (IRBs) of the respective institutions, and consent forms were signed by the patients before sample withdrawals.

The mean age, MMSE and gender distribution split-up for different ApoE genotype groups (see below) are shown in Table 1.

Within each diagnostic group, the subjects were split up into groups of ApoE-ε4 carriers (ApoE ε3/4 and ApoE ε4/4) and respectively ApoE-ε4 non-carriers (ApoE ε2/3 and ApoE ε3/3) in order to yield sufficiently large sample sizes for a statistical group comparison with regard to the ApoE-ε4 genotype (Table 1). The ApoE groups within MCI or Alzheimer’s disease subjects did not differ significantly in age or MMSE (P > 0.05) scores. For the gender distribution between ApoE genotype groups, there were relatively more female than male patients within the ApoE-ε4 carriers compared to ApoE-ε4 non-carriers in the Alzheimer’s disease patient group (P=0.02, Table 1). Therefore, gender differences were controlled for in the statistical analysis of the ApoE genotype effect.

A minimum ApoE-genotype-related effect size of f=0.33 (in Alzheimer’s disease) and f=0.4 (in MCI) could be detected with a power of 0.8 at a significance level of 0.05.
Table 1 Demographic and clinical data for subjects with MCI or Alzheimer’s disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Measure</th>
<th>Genotype</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>ApoE-ε4</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>35</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Gender (f/m)*</td>
<td>25/10</td>
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<tr>
<td></td>
<td>Mean age in years (SD)</td>
<td>68.3 (8.6)</td>
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<tr>
<td></td>
<td>Mean MMSE (SD)</td>
<td>19.7 (4.1)</td>
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<tr>
<td>MCI</td>
<td>Sample size</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Gender (f/m)</td>
<td>17/14</td>
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<tr>
<td></td>
<td>Mean age in years (SD)</td>
<td>69.7 (6.8)</td>
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<tr>
<td></td>
<td>Mean MMSE (SD)</td>
<td>26.5 (2.3)</td>
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<tr>
<td>HC</td>
<td>Sample size</td>
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<td>Gender (f/m)</td>
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<td></td>
<td>Mean age in years (SD)</td>
<td>63.3 (78)</td>
</tr>
<tr>
<td></td>
<td>Mean MMSE (SD)</td>
<td>293.8 (8.1)</td>
</tr>
</tbody>
</table>

f = female, m = male, *Gender distribution differed between genotype groups: χ² = 7.5, P = 0.02.

ApoE genotyping

ApoE genotyping was performed according to standard procedures using a polymerase chain reaction (PCR) kit for the Light Cycler (Roche Diagnostics, Mannheim, Germany).

For the Alzheimer’s disease group, the frequency of the different ApoE genotypes was as follows: ApoE e2/2 (n = 1), ApoE e2/3 (n = 3), ApoE e3/3 (n = 21), ApoE e3/4 (n = 28) and ApoE e4/4 (n = 7). For the MCI group, the frequency of the different ApoE genotypes was as follows: ApoE e2/2 genotype (n = 1), ApoE e3/3 (n = 19), ApoE e3/4 (n = 24) and ApoE e4/4 (n = 7 patients). For the analysis of the ApoE genotype effect, groups were binarized into ApoE e4 carriers and ApoE e4 non-carriers. Thus, the Alzheimer’s disease group included a total of 35 ApoE e4 carriers and 25 ApoE 4 non-carriers; the MCI group included 31 ApoE e4 carriers and 20 ApoE e4 non-carriers. The HC group included: ApoE e2/2 (n = 1), ApoE e2/3 (n = 3), ApoE e3/3 (n = 27), ApoE e3/4 (n = 6).

BACE 1 protein level analysis

Two BACE 1 protein sandwich-ELISAs were established as we recently published (Zhong et al., 2007): one used a combination of anti-BACE 1 polyclonal antibody SECB2 as a capture antibody, and biotinylated anti-BACE 1 polyclonal antibody SECB1 as a detection antibody. The other ELISA was established by using the anti-BACE 1 polyclonal antibody, B280, as a capture antibody, and anti-BACE 1 monoclonal antibody, (R&D), as a detection antibody. Recombinant BACE 1 from Amgen was used as the standard, and all were assayed under the same conditions. BACE 1 concentration was calculated from the standard curve and expressed as micrograms per millilitre. Previously, we have described this method in great detail (Zhong et al., 2007).

BACE 1 enzymatic activity assay

Activity assays of BACE 1 were performed by using synthetic peptide substrates containing the BACE 1 cleavage site (MCA-Glu-Val-Lys-Met-Asp-Ala-Glu-Phe-(Lys-DNP)-OH) at 50 mM concentration in reaction buffer (50 mM acetic acid pH 4.1, 100 mM NaCl) (Zhong et al., 2007). To examine the BACE 1 activity, we used 10 μl of CSF from each sample. The fluorescence was observed by the fluorescent microplate reader with excitation wavelength at 320 nm and emission wavelength at 383 nm. CSF-BACE 1 activity was tested in the presence of the BACE 1 inhibitor (Calbiochem), which revealed about 80% inhibition of the CSF-BACE 1 activity.

Regarding the pH condition, the best range of pH for detection of BACE 1 activity has been found to be between 4 and 5 acidic conditions; for our substrate the best pH ranged from 4.0 to 4.5 (Vassar et al., 1999). The condition we chose was within this range (pH 4.1), in which BACE 1 showed over 95% activity. The substrate and pH range chosen enabled the detection of BACE 1 activity regardless of its form, as long as it had the ability to cleave the substrate. Therefore, the BACE 1 activity measured here should best be regarded as total BACE 1 activity.

Aβ₁₋₄₂ concentration

Aβ₁₋₄₂ ELISA concentration was determined by INNOTEST β-amyloid (1–42) (Innogenetics, Ghent, Belgium). The assay and its characteristics have been described in detail previously (Vanderstichele et al., 2000).

Statistics

Differences in CSF-levels of BACE 1 activity, BACE 1 protein and Aβ₁₋₄₂ between Alzheimer’s disease, MCI and HC were analysed through separate analyses of covariance (ANCOVAs) with diagnosis, gender and ApoE genotype as fixed factors, and age as covariate. A significant main effect of diagnosis (P<0.05) was followed up by pair-wise comparisons of the groups.

Differences between ApoE-ε4 carriers and ApoE-ε4 non-carriers in levels of BACE 1 activity and Aβ₁₋₄₂ were computed, using ANCOVA models with ApoE group and gender as independent variables, and MMSE and age as covariates. In order to control for the influence of possible outliers and the accumulation of Type I error due to multiple comparisons, bootstrapping, within a multiple regression model including ApoE group, gender, MMSE and age, was conducted for each group comparison (Efron and Tibshirani, 1986). The asymptotic 95% confidence intervals (95% CI) of the beta-regression weight (B) of the factor ‘ApoE genotype’ estimated upon a basis of 999 iterations of samplings are reported. An effect is statistically significant at significance level of the α = 0.05, if the 95% CI does not include the value zero, i.e. the regression weight is significantly different from zero. The HC group was included here to test whether the concentration of BACE 1 activity and Aβ₁₋₄₂ was abnormal in the MCI and Alzheimer’s disease groups. Since there were only six ApoE-ε4 carriers in the HC sample in comparison to 31 ApoE-ε4 carriers, ApoE genotype difference was not calculated within the HC group, rather only the MCI and Alzheimer’s disease groups. All analyses were conducted using SPSS 13.01 (SPSS Inc., Chicago, USA).

Results

CSF-levels of BACE 1 activity, BACE 1 protein and Aβ₁₋₄₂ in MCI and Alzheimer’s disease

Consistent with our previous results (Zhong et al., 2007), BACE 1 activity in CSF was significantly increased in subjects with MCI when compared to Alzheimer’s disease
Association ApoE versus BACE

For Alzheimer’s disease patients, the CSF-level of BACE 1 activity revealed a statistically significant increase in ApoE-e4 carriers \( F(1,54) = 5.22, P = 0.03, \) Fig. 1A, Table 2, and was confirmed in the bootstrap analysis \( (B = 0.078, 95\% CI = 0.73–0.84). \) Neither gender nor the interaction between ApoE genotype and gender were significant. For BACE protein levels, no significant group differences were detected \( (F < 1, \) Table 2).

For MCI patients, BACE 1 activity showed a significant increase in ApoE-e4 carriers \( (F(1,45) = 4.48, P = 0.04). \)

Bootstrapping of the main effect of the ApoE genotype confirmed a statistically significant effect \( (B = 0.111, 95\% CI = 0.104–0.116). \) However, the interaction between the ApoE genotype and gender did not reach statistical significance \( (P = 0.07). \) BACE 1 protein levels did not differ between ApoE genotype groups \( (F < 1, \) Table 2). Since the sample size of ApoE-e4 carriers in HC was too small \( (n=6) \) no statistical test on the effect of APoE genotype on BACE 1 was computed for the HC group. For descriptive comparison, the mean values of BACE 1 activity and BACE 1 protein for ApoE-e4 carriers and ApoE-e4 non-carriers for each group are displayed in Table 2.

Association between ApoE genotype and \( \text{A}_{\beta_{1-42}} \)

For Alzheimer’s disease patients, no group differences between ApoE genotypes were observed \( (p = 0.63, \) Fig. 1B).

In MCI, levels of \( \text{A}_{\beta_{1-42}} \) were decreased in ApoE-e4 carriers when compared to ApoE-e4 non-carriers. This significant difference \( (P = 0.004, \) Fig. 1B, Table 2) was confirmed by bootstrapping \( (95\% CI = –357.76 \text{ to } –96.37); \) however, the interaction between the ApoE genotype and gender was not significant \( (P = 0.94). \)

For a descriptive comparison, the mean values of \( \text{A}_{\beta_{1-42}} \) for ApoE-e4 carriers and ApoE-e4 non-carriers are displayed in Table 2.
The expression of the ApoE-e4 allele has been associated with increased production of Aβ pathology (Ye et al., 2005). We have recently developed a CSF-based assay for the in vivo detection of BACE 1 protein and BACE 1 activity (Zhong et al., 2007), a secretase which has been implicated in the generation Aβ1-42. Here we examined the effect of BACE 1 activity and protein levels in CSF. Although there was no change in BACE 1 protein CSF-levels, we found that BACE 1 activity was increased within ApoE-e4 carriers when compared to ApoE-e4 non-carriers in both MCI and Alzheimer’s disease as confirmed by bootstrapping. These results show, for the first time, an association between the ApoE genotype and BACE 1 activity as measured in CSF of Alzheimer’s disease and MCI subjects.

Consistent with the findings in our previous study, the concentration of BACE 1 activity and BACE 1 protein was significantly increased in MCI subjects when compared to HC and Alzheimer’s disease, thus replicating our previous findings in the overall sample (Zhong et al., 2007). For Aβ1-42, we found a decrease in both MCI and Alzheimer’s disease subjects when compared to HC, which is consistent with previous findings (Hampel et al., 2004; Herukka et al., 2007).

For the ApoE-e4 genotype, the current results suggest an enhancement of CSF-BACE 1 activity in association with MCI and Alzheimer’s disease subjects. Since previous studies have shown that CSF-levels of biomarkers, such as Aβ1-42 and p-tau231, correlate with the deposition of Aβ and neurofibrillary pathology found within the brain (Strozyk et al., 2003; Buerger et al., 2006), CSF-based measures may provide a excellent way to assess in vivo Alzheimer’s disease-specific pathology in the brain. Thus, the current findings of elevated BACE 1 activity in CSF may suggest that the ApoE genotype is associated with higher cerebral BACE 1 activity within the brain in both MCI and Alzheimer’s disease subjects. However, it is not clear how the expression of the ApoE genotype may lead to increased BACE 1 activity and Aβ generation within the brain. One possibility is that ApoE influences the production of Aβ via modulation of cholesterol levels. Studies in patients with Alzheimer’s disease have shown that the ApoE-e4 genotype is associated with increased cholesterol levels in both blood (Corder et al., 1993; Notkola et al., 1998) and CSF as measured by the metabolite 24S-hydroxycholesterol (Papassotiropoulos et al., 2002; Leoni et al., 2006). In vitro and in vivo experiments have shown that increased levels of cholesterol are associated with enhanced activity of α, β and γ-secretases (Fassbender et al., 2001; Kojro et al., 2001; Runz et al., 2002). Thus, ApoE may lead to increased levels of cholesterol and thereby BACE 1 activity (Puglielli et al., 2003; Lahiri et al., 2004). Alternatively, ApoE-e4 expression may increase BACE 1 activity via increased APP endocytosis in a cholesterol-independent way (Ye et al., 2005), and may lead to an increased exposure of BACE 1 to APP within the cell compartments such as endosomes, which eventually enhances the amyloidogenic processing of APP (Koo and Squazzo, 1994). If accumulated within the neuron, however, it is currently not clear how BACE 1 would escape into CSF, leading to increased CSF-levels of BACE 1 activity. Potentially, BACE 1 may be released either by active transport, degeneration of the membrane or neuronal death. However, such a link has not been described yet, and thus remains unclear.

A third possibility is the influence of ApoE on Aβ generation within the cerebral microvasculature. Neuropathological studies have shown that damage of the endothelium of the cerebral capillary microvasculature is a frequently observed brain abnormality in Alzheimer’s disease subjects (Bailey et al., 2004) and has been associated with Aβ (Thomas et al., 1996; Deane et al., 2003; de la Torre, 2004; Zlokovic, 2005). The ApoE e4 genotype may especially affect the amyloidosis within the cerebral vasculature, serving both as a chaperone of Aβ and potentially increasing the production of Aβ. Smooth muscle cells of cerebral vessels have been shown to produce Aβ in situ (Frackowiak et al., 1995), where the presence of ApoE e4 leads to the increase of amyloidogenic processing of APP, possibly linked to increased oxidative stress (Mazur-Kolecka et al., 2004). Thus, increased BACE 1 activity in ApoE e4 carrier may partially reflect ApoE-e4 regulated Aβ production within the vasculature. Alternatively, ApoE may have a role in the accumulation and clearance of Aβ at the blood–brain barrier (Holtzman et al., 2000). Future studies will need to address the
mechanism that may underlie the ApoE-associated increase in BACE 1 activity.

Note that BACE 1 activity but not BACE 1 protein level in CSF was associated with the ApoE genotype. We previously reported a relatively low correlation between BACE 1 activity and BACE 1 protein levels (Zhong et al., 2007). One explanation of the lack of the correlation may be that activation of BACE 1 may occur only in the glycolysation-dependent mature form of the BACE 1 protein, whereas the current assay detects both the mature and immature forms of BACE 1 protein (Zhong et al., 2007). Thus, it is possible that despite the lack of an association between total BACE 1 protein levels and the ApoE genotype, the mature sub-form of BACE 1 protein, which we found to be highly correlated with BACE 1 activity (Zhong et al., 2007), may still be affected by the ApoE genotype.

Parallel to the differences in BACE 1 activity, we found a difference in the CSF-levels of Aβ1–42 between ApoE-ε4 carriers and non-carriers in MCI. The ApoE-ε4 carriers show a decrease in levels of Aβ1–42 in MCI subjects, which suggests an increase of cerebral Aβ deposition within the brain of ApoE-ε4 carriers (Strozyk et al., 2003). In contrast, we did not detect a difference between genotype groups in Alzheimer’s disease subjects. Previous studies in Alzheimer’s disease have shown inconsistent results, with some studies reporting a decrease (Tapiola et al., 1997; Galasko et al., 1998) in CSF-levels Aβ1–42, while others did not find such an effect of the ApoE genotype (Motter et al., 1995; Nitsch et al., 1995). Discrepancies between the findings may partially be due to the methodological aspects, such as varying sample size, where those studies that did not find an association between the ApoE genotype and CSF-levels Aβ1–42 were relatively small. In addition to methodological differences, ApoE-ε4 allele frequency may be relevant, as the number of ApoE-ε4 is linearly correlated with a decrease in Aβ1–42 (Galasko et al., 1998). In the present study, the frequency of homozygous ApoE-ε4 genotype was with 11.7% substantially lower than in Galasko et al.’s (1998) study (21.1%) that found a significant decrease in Aβ1–42 associated with ApoE-ε4.

It should be noted that in the current study, amnestic MCI subjects were included. Although amnestic MCI subjects have been reported to convert to Alzheimer’s disease at a mean rate of 10–15% annually, some may return to normal or remain stable for several years. Thus, the current sample of amnestic MCI patients may include a diversity of pathology or even an absence of any neuropathology. Follow-up assessment of the MCI subjects is warranted in order to determine whether the subjects progress to Alzheimer’s disease.

A follow-up study is underway to determine whether the BACE 1 activity levels measured in CSF are predictive of the conversion of from MCI to Alzheimer’s disease.

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