Original Investigation

Apolipoprotein E Genotype and the Diagnostic Accuracy of Cerebrospinal Fluid Biomarkers for Alzheimer Disease

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IMPORTANCE Several studies suggest that the apolipoprotein E (APOE) ε4 allele modulates cerebrospinal fluid (CSF) levels of β-amyloid 42 (Aβ42). Whether this effect is secondary to the association of the APOE ε4 allele with cortical Aβ deposition or whether APOE ε4 directly influences CSF levels of Aβ42 independently of Aβ pathology remains unknown.

OBJECTIVE To evaluate whether the APOE genotype affects the diagnostic accuracy of CSF biomarkers for Alzheimer disease (AD), in particular Aβ42 levels, and whether the association of APOE ε4 with CSF biomarkers depends on cortical Aβ status.

DESIGN, SETTING, AND PARTICIPANTS We collected data from 4 different centers in Sweden, Finland, and Germany. Cohort A consisted of 1345 individuals aged 23 to 99 years with baseline CSF samples, including 309 with AD, 287 with prodromal AD, 399 with stable mild cognitive impairment, 99 with dementias other than AD, and 251 controls. Cohort B included 105 nondemented younger individuals (aged 20-34 years) with CSF samples available. Cohort C included 118 patients aged 60 to 80 years with mild cognitive symptoms who underwent flutemetamol F 18 (t[18F]flumetamol) positron emission tomography amyloid imaging and CSF tap.

EXPOSURES Standard care.

MAIN OUTCOMES AND MEASURES Cerebrospinal fluid levels of Aβ42 and total and phosphorylated tau in relation to the APOE ε2/ε3/ε4 polymorphism in different diagnostic groups and in cases with or without cortical uptake of [18F]flutemetamol.

RESULTS The CSF levels of Aβ42 but not total and phosphorylated tau were lower in APOE ε4 carriers compared with noncarriers irrespective of diagnostic group (cohort A). Despite this, CSF levels of Aβ42 differed between participants with AD when compared with controls and those with stable mild cognitive impairment, even when stratifying for APOE genotype (P < .001 to P = .006). Multiple binary logistic regression revealed that CSF levels of Aβ42 and APOE ε4 genotype were independent predictors of AD diagnosis. In cohort B, APOE ε4 carrier status did not influence CSF levels of Aβ42. Moreover, when stratifying for cortical uptake of [18F]flutemetamol in cohort C, APOE ε4 genotype did not influence CSF levels of Aβ42. This result was replicated in a cohort with individuals from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) using carbon 11-labeled Pittsburgh Compound B scanning.

CONCLUSIONS AND RELEVANCE Cerebrospinal fluid levels of Aβ42 are strongly associated with the diagnosis of AD and cortical Aβ accumulation independent of APOE genotype. The clinical cutoff for CSF levels of Aβ42 should be the same for all APOE genotypes.

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The apolipoprotein E (APOE) genotype constitutes the most prominent susceptibility gene for late-onset Alzheimer disease (AD). Two polymorphisms (rs7412 and rs429358) make up 3 different alleles—ε2, ε3, and ε4—of the APOE gene (OMIM 107741). These polymorphisms lead to amino acid substitutions at positions 112 and 158 in the ApoE protein. The ε4 allele is known to increase the risk for and lower the age at onset of AD in a gene dose–dependent manner. Compared with individuals lacking the ε4 allele, individuals homozygous for the ε4 allele have an approximately 12-fold increased risk for AD and an age at onset of approximately 65 years, whereas heterozygous carriers have about a 3-fold increased risk and an age at onset of approximately 75 years. The exact pathophysiological mechanisms underlying this strong genetic association are yet to be revealed, but some data point toward an impaired clearance of β-amyloid (Aβ) from the brains of individuals with the APOE ε4 allele as a possible key factor.

With the emergence of biomarker-supported dementia diagnostics, interest in cerebrospinal fluid (CSF) biomarkers associated with AD, especially Aβ42 and tau proteins, is increasing. Low CSF levels of Aβ42 indicate ongoing AD, but several studies have also shown decreased CSF levels of Aβ42 in individuals with the APOE ε4 allele without clinical AD. Whether the effect of APOE ε4 on CSF levels of Aβ is secondary to the association of the APOE ε4 allele with cortical Aβ deposition or whether the allele directly influences CSF levels of Aβ42 independently of Aβ pathology remains unknown. Further, for optimal clinical use of genetic and CSF biomarkers, studies are needed to clarify to what extent the APOE genotype and CSF biomarkers correlate and provide overlapping vs complementing information for the diagnosis and prognosis of AD and whether different clinical cutoffs for CSF levels of Aβ42 should be used depending on the APOE genotype. Several studies have emphasized that the APOE ε4 allele could affect the diagnostic power of CSF Aβ42 and that the APOE genotype should be taken into account when using CSF levels of Aβ42 as a biomarker for AD. Herein, we approached these issues by evaluating the effects of the APOE ε2/ε3/ε4 polymorphism on the diagnostic accuracy of CSF levels of Aβ42, total tau (T-tau), and phosphorylated tau (P-tau) for AD in a cohort of 1345 individuals. We also assessed the association of CSF biomarker levels with the APOE genotype and/or cortical Aβ42 deposition in a cohort with younger individuals, in patients with mild cognitive symptoms with and without abnormal cortical Aβ42 uptake of flutemetamol F 18 ([18F]flutemetamol), and in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort among participants who had undergone CSF biomarker analyses and carbon 11-labeled Pittsburgh Compound B ([11C]-PIB) positron emission tomography (PET).

**Methods**

The study received approval from regional ethical committees and followed the tenets of the Helsinki declaration. Written informed consent was obtained from all participants. The study received approval from regional ethical committees and followed the tenets of the Helsinki declaration. Written informed consent was obtained from all participants.

**Cohorts**

**Cohort A**

Four memory clinics in Sweden, Finland, and Germany took part in the study. The total cohort consisted of 251 control subjects, 399 patients with stable mild cognitive impairment (MCI), 287 patients with prodromal AD (MCI-AD), 309 patients with dementia and AD (hereinafter referred to as AD patients), and 99 patients with dementias other than AD. Patients with stable MCI were followed up for at least 2 (median, 3 [range, 2-11]) years. All participants underwent assessment by physicians specializing in cognitive disorders who were blinded to all CSF results. Parts of this cohort, including 186 patients from the ongoing prospective clinical longitudinal Göteborg MCI Study, have been included in earlier publications.

**Cohort B**

We also included a separate cohort consisting of 105 individuals aged 20 to 34 (mean [SD], 27.7 [3.8]) years without neurodegenerative conditions (67 patients with bipolar disorder and 38 healthy controls). This cohort was used only to assess the association of the APOE ε4 allele with CSF biomarker levels but was not included in the studies of the diagnostic accuracy of the biomarkers owing to their relative youth.

**Cohort C**

These individuals were included from the larger Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BIOFINDER) study, which enrolls consecutive patients with mild cognitive symptoms but no dementia from 3 memory clinics in Sweden. More information regarding the BIOFINDER study is available at http://www.biofinder.se. From this study, we selected the first 118 patients who had undergone [18F]flutemetamol PET imaging and CSF tap. Based on an extensive neuropsychological battery and the clinical assessment of a neuropsychologist, 52.5% of these individuals were classified as having subjective cognitive decline and 47.5% as having MCI. Among those with MCI (56 patients), 43 (77%) had amnestic MCI (26 with single-domain and 17 with multidomain) and 13 (23%) had nonamnestic MCI.

**ADNI Cohort**

We obtained data for 53 individuals (9 with AD, 33 with MCI, and 11 healthy controls) with data on the CSF analysis and [11C]-PIB scans from the ADNI database (adni.loni.usc.edu). A more detailed description of the cohorts is given in eMethods 1 in the Supplement.

**Lumbar Puncture**

Samples of CSF were obtained by lumbar puncture in the L3/4 or L4/5 interspace without any reported serious adverse effects, collected in polypropylene tubes, centrifuged, and stored frozen at −80°C until analysis according to standard operating procedures. Most biomarker measurements were performed at the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital, but samples from Kuopio, Finland, and Munich, Germany, were analyzed locally.
Cerebrospinal Fluid Biomarkers for AD

Original Investigation Research

CSF Analyses
We measured CSF levels of T-tau using a sandwich enzyme-linked immunosorbent assay (Innotest hTau-Ag; Innogenetics), which detects all tau isoforms irrespective of phosphorylation status as previously described.²¹ We determined CSF levels of P-tau (at threonine 181) using another sandwich enzyme-linked immunosorbent assay (Innotest Phospho-Tau[181P]; Innogenetics) as previously described.²² The CSF concentration of Aβ42 was measured using a third sandwich enzyme-linked immunosorbent assay (Innotest β-amyloid[1-42]; Innogenetics) designed to detect the 1st and the 42nd amino acids in the Aβ protein as previously described.²³ A subset of the samples underwent analysis for T-tau, P-tau, and Aβ42 using a multiplex semiautomated assay platform (xMAP LumineX AlzBio3; Innogenetics) normalized to Innotest concentrations as previously described.²⁴ All analyses were performed by experienced laboratory technicians who were blinded to the study participants’ diagnosis and other clinical information.

To adjust for variation in biomarker levels between the different laboratories, data were normalized by defining 1 center cohort as the reference group and then calculating factors between the APOE ε4-negative controls from each participating center and the APOE ε4-negative controls in the reference group. These factors were then applied to all data, hence relating biomarker levels in all the different cohorts to those in the reference group. Cross-fertilization of standard samples in each assay was not used, which is a limitation of the study.

APOE Alleles
Genotyping for APOE (gene map locus 19q13.2) was performed using allelic discrimination technology (TaqMan; Applied Biosystems) or equivalent techniques. Genotypes were obtained for the 2 single-nucleotide polymorphisms that are used to define the ε2, ε3, and ε4 alleles unambiguously (rs7412 and rs429358).

[¹⁸F]Flutemetamol PET Acquisition and Analysis
[¹⁸F]Flutemetamol (GE Healthcare) injection²⁵ and PET/computed tomographic scanning of the whole brain were conducted at 2 sites (Malmö and Lund) in Sweden as described previously.²⁶ A detailed description of PET acquisition and analysis is provided in eMethods 2 in the Supplement.

Statistical Analysis
Pairwise comparisons of biomarker levels between and within the diagnostic groups were performed using a Mann-Whitney test for independent samples. Comparisons between more than 2 groups were performed using a Kruskal-Wallis test for several independent samples. The area under the receiver operating characteristic curve was calculated for all biomarkers and separately for each APOE ε4 carrier group in AD patients vs controls and for patients with stable MCI vs MCI-AD. Multiple backward stepwise binary logistic regression was performed to study the associations simultaneously between clinical diagnosis vs biomarker levels and age as continuous variables and sex and APOE genotype (carriers of 0, 1, or 2 APOE ε4 alleles) as nominal variables. We used general linear model (analysis of covariance) to examine the association between CSF levels of Aβ42 (independent variable) and APOE ε4 status (carriers of 0 or 1 to 2 APOE ε4 alleles) when adjusting for [¹⁸F]Flutemetamol uptake (dichotomized). We defined statistical significance at P < .05. All statistical calculations above were performed using a commercially available software package (SPSS, version 19; SPSS, Inc). All Figures were created using a graphics package (GraphPad Prism, version 5; GraphPad Software, Inc).

Results
Demographics and Genetic and Biochemical Data of Cohort A
As expected, most AD and MCI-AD patients carried 1 or 2 copies of the APOE ε4 allele, with fewer than 30% having no APOE ε4 allele (Table 1). Non-AD groups showed opposite results. Frequencies of different genotypes were similar between AD and MCI-AD patients. The AD and MCI-AD groups showed the lowest mean CSF levels of Aβ42 and the highest mean CSF levels of tau proteins (Table 1). Biomarker levels in the stable MCI group were similar to those in the control group.

CSF Levels of Aβ42 in Relation to APOE Genotype
Cerebrospinal fluid levels of Aβ42 were lower in APOE ε4 carriers than in noncarriers in a gene dose-dependent manner irrespective of diagnostic group (P < .001 in all groups) (Figure 1A). However, the levels of Aβ42 differed significantly between all participants with AD compared with controls and between MCI-AD compared with stable MCI patients, even when analyzing subgroups according to APOE ε4 carrier status separately (P < .001 to P = .006) (Figure 1A).

Analysis of the receiver operating characteristic curve showed that Aβ42 levels had high diagnostic accuracy for AD patients vs controls in individuals with 0 or 1 APOE ε4 allele (Figure 1B). The diagnostic accuracy of Aβ42 levels in individuals with 2 alleles was lower than in the other APOE groups, but the uncertainty was largely owing to the relatively small number of APOE ε4 homozygous controls. A similar pattern was seen for the MCI-AD vs stable MCI patients (Figure 1C). The 95% confidence interval of the different areas under the receiver operating characteristic curve clearly overlapped (Figure 1B-C), indicating no real difference between them.

To determine the extent to which CSF levels of Aβ42 and APOE genotype contributed to distinguishing between AD patients and controls and between MCI-AD and stable MCI patients, we performed multiple binary logistic regression models that revealed that the CSF concentration of Aβ42 and the APOE genotype were independent statistical predictors of AD diagnosis. Table 2 shows logistic regression using a backward stepwise conditional method. We entered APOE genotype, CSF level of Aβ42, age, and sex in the first step. Sex was nonsignificant and removed from the model. Analysis used AD patients vs controls and revealed that CSF levels of Aβ42, APOE genotype, and age were independent statistical predictors of

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AD diagnosis. Results were similar in the MCI cohort but with a somewhat smaller contribution from APOE genotype (data not shown).

**CSF Levels of Tau Proteins in Relation to APOE Genotype**

Cerebrospinal fluid levels of T-tau were similar in all APOE genotype subgroups across the diagnostic spectrum and did not show the same dose-dependent differences as CSF levels of Aβ42 within the diagnostic groups (Figure 2A). Statistical differences were only observed within the stable MCI and MCI-AD groups ($P = .005$ and $P = .02$, respectively), which could be attributed to differences between having 0 and 1 ε4 alleles. However, as expected, CSF levels of T-tau differed significantly between AD patients and controls ($P < .001$ to $P = .01$) as well as between MCI-AD and stable MCI patients ($P < .001$) irrespective of the APOE genotype group (Figure 2A).

As far as the diagnostic performance is concerned, receiver operating characteristic curve analyses showed that the APOE genotype did not affect the diagnostic accuracy of CSF levels of T-tau (Figure 2B-C). As shown for Aβ42 levels, the diagnostic accuracy for T-tau among homozygous APOE ε4 carriers was somewhat lower than in the other APOE genotype subgroups when comparing AD patients vs controls (Figure 2B). When comparing MCI-AD vs stable MCI patients, the diagnostic performance of CSF levels of T-tau showed high accuracy across all APOE ε4 subgroups (Figure 2C). Relating the CSF levels of P-tau to the different APOE genotypes revealed the same pattern as for CSF levels of T-tau (data not shown).

**No Effect of APOE ε4 Genotype on CSF Levels of Aβ42 in Patients With Mild Cognitive Symptoms by Cortical [18F]Flutometamol Uptake**

Next we analyzed a cohort of 118 individuals with CSF tap and [18F]Flutometamol PET imaging (cohort C). Participants with positive cortical [18F]Flutometamol uptake (standardized uptake value ratio [SUVR], >1.42) had lower CSF levels of Aβ42 (Figure 4A). When the patients with positive or negative findings on [18F]Flutometamol PET scans underwent separate analysis, we found no difference in CSF levels of Aβ42 between those with 0 or 1 to 2 APOE ε4 alleles (Figure 4A). Moreover, when adjusting for cortical [18F]Flutometamol uptake status, we found no association between CSF levels of Aβ42 and APOE ε4 carrier status ($P = .77$). Similar results were obtained for CSF levels of T-tau and P-tau (data not shown). We next aimed to replicate the results in the ADNI cohort. Because [18F]Flutometamol scans were not performed, we instead examined data from scans with the similar PET tracer [11C]-PiB. Twenty-five participants with results of CSF analysis and [11C]-PiB scans were located in the ADNI database, including 9 with AD, 33 with MCI, and 11 healthy controls. The cutoff to identify an abnormal mean [11C]-PiB SUVR was established with mixture modeling (SUVR, >1.63). The results were very similar to those of our study (Figure 4B), that is, no differences were
Apolipoprotein E (APOE) Genotype and the Diagnostic Accuracy of Cerebrospinal Fluid (CSF) Levels of β-Amyloid 42 (Aβ42)

Figure 1. Cerebrospinal fluid levels of Aβ42 show gene dose–dependent differences within the diagnostic groups, with lower levels in individuals with 1 and 2 APOE ε4 alleles (−/+ and +/+) (P < .001 in all groups). The CSF levels of Aβ42 differ significantly between patients with Alzheimer disease (AD) and control subjects (Mann-Whitney test, P < .001 to P = .006) and between patients with stable mild cognitive impairment (MCI) and prodromal AD (MCI-AD) (Mann-Whitney test; P < .001 to P = .001) irrespective of APOE genotype. B, Receiver operating characteristic curve analysis for AD patients vs controls. The diagnostic performance of CSF levels of Aβ42 is high irrespective of APOE genotype. Among individuals homozygous for the APOE ε4 allele, the diagnostic accuracy is lower with a large uncertainty owing to the limited number of controls with 2 (+/+) APOE ε4 alleles (n = 7). C, Receiver operating characteristic curve analysis for MCI-AD vs stable MCI patients. The diagnostic performance of CSF levels of Aβ42 is similar to that in the comparison of AD patients vs controls, with a somewhat lower diagnostic accuracy among individuals with 2 APOE ε4 alleles. AUC indicates area under the curve; −/−, 0 ε4 alleles.

Table 2. AD Patients vs Controls in Logistic Regression Using a Backward Stepwise Conditional Method

<table>
<thead>
<tr>
<th>Variable</th>
<th>B Intercept (SE)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE ε4 −/−</td>
<td>NA</td>
<td>.01</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>APOE ε4 +/−</td>
<td>−0.79 (0.31)</td>
<td>.01</td>
<td>2.20 (1.20–4.03)</td>
</tr>
<tr>
<td>APOE ε4 +/+</td>
<td>−1.22 (0.55)</td>
<td>.03</td>
<td>3.40 (1.16–10.01)</td>
</tr>
<tr>
<td>CSF level of Aβ42</td>
<td>−0.01 (0.001)</td>
<td>&lt;.001</td>
<td>0.99 (0.99–0.99)</td>
</tr>
<tr>
<td>Age</td>
<td>0.14 (0.02)</td>
<td>&lt;.001</td>
<td>1.15 (1.11–1.19)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ42, β-amyloid 42; AD, Alzheimer disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; NA, not applicable; OR, odds ratio; −, absent; +, present.

found in Aβ42 levels between patients with no APOE ε4 alleles and those with 1 to 2 alleles when the patients with positive or negative results of [11C]-PiB PET scans underwent separate analysis. Further, we found no association between APOE ε4 status and Aβ42 levels (P = .36) when adjusting for [11C]-PiB amyloid status. Even when using a previously defined [11C]-PiB cutoff by Jagust et al28 (SUVR, >1.46), the results were similar (data not shown).
Discussion

Distribution of APOE Genotypes Across the Diagnostic Spectrum

In cohort A, we conducted a large study with data from 4 specialized memory clinics to assess the effect of the APOE ε2/ε3/ε4 polymorphism on the diagnostic accuracy of CSF biomarkers for AD (Aβ42, T-tau, and P-tau). The memory clinics were not prospectively harmonized against each other regarding the details of the diagnostic algorithms, but all used the same clinical criteria. Likewise, the laboratory procedures for the measurement of CSF biomarkers were not harmonized, which necessitated a normalization approach (described in detail in the Methods section). Finally, the median follow-up time of patients with stable MCI was 3 years, which may be considered somewhat short to rule out MCI-AD in the light of recent studies.29 We consider these 3 major limitations of our study all unlikely to influence the interpretability of the data.

As expected, the APOE ε4 allele was more prevalent in AD and MCI-AD patients than in controls and stable MCI patients. However, stable MCI patients also had higher APOE ε4 prevalence compared with controls, especially patients with low CSF levels of Aβ42. One possible explanation for this somewhat skewed distribution might be that some of these indi-
individuals, despite being nondemented at the time of sampling, actually had MCI-AD. To fully verify that an MCI case is non-progressive, a follow-up time of 5 to 10 years is probably needed.\textsuperscript{29,30} The short clinical follow-up time of MCI patients and the lack of autopsy data are also major limitations of our study.

**Diagnostic Accuracy of CSF Biomarker Levels Does Not Depend on APOE Genotype**

We clearly verified that APOE ε4 genotype is associated with lower CSF levels of Aβ42 but not T-tau and P-tau in a gene dose-dependent manner, which is in agreement with earlier studies.\textsuperscript{9-13} However, all 3 biomarkers showed significant differences between AD patients and controls and between MCI-AD and stable MCI patients irrespective of APOE genotype. Even the high diagnostic accuracy of CSF levels of Aβ42, T-tau, and P-tau was shown to be independent of APOE genotype (with the exception of a somewhat lower diagnostic performance in APOE ε4-homozygous individuals, which is owing to the low number of observations in this subgroup) and further underlines the biomarkers’ strength in discriminating between the diagnostic groups. Finally, multiple logistic regression analysis confirmed that CSF levels of Aβ42 and APOE genotype are in fact independently associated with AD diagnosis. This result is in line with earlier findings, including those of the North American multicenter ADNI study.\textsuperscript{9,13}

**APOE Genotype Does Not Modulate CSF Levels of Aβ42 in Younger Individuals**

The underlying mechanism of the association between APOE and CSF concentrations of Aβ42 is not fully understood but might be partly linked to the hypothesis that the ε4-encoded ApoE isoform is less effective at clearing Aβ from the brain, thus resulting in accelerated Aβ deposition and lower Aβ42 levels in the CSF in APOE ε4 carriers.\textsuperscript{3-4} Although our study is observational and therefore cannot address molecular mechanisms, we decided to explore the APOE-Aβ42 association in young individuals who were likely to be amyloid free to test the hypothesis that a primary effect (not amyloid mediated) of different ApoE isoforms on CSF levels of Aβ42 may exist. In this group of individuals, the gene dose–dependent effect on CSF levels of Aβ42 was absent. Thus, in the absence of Aβ pathology, the APOE ε4 allele is not associated with CSF levels of Aβ42. Earlier results showing a gene dose–dependent effect on CSF levels of Aβ42 in cognitively normal elderly individuals\textsuperscript{9-13} may thus be interpreted as driven by APOE ε4-
associated preclinical Aβ pathology and not a direct effect of APOE ε4 on CSF levels of Aβ42.

**CSF Aβ42 in Relation to Amyloid PET**

It has been suggested that different cutoff levels should be used for CSF Aβ42 based on APOE ε4 status. Our data show a strong association between CSF levels of Aβ42 and cortical [18F]flutemetamol uptake but no effect of the APOE ε4 genotype on CSF levels of Aβ42 when stratifying patients into those with positive or negative findings of [18F]flutemetamol PET scans (Figure 4A). This result was also replicated in the ADNI database using the almost identical PET tracer [11C]-PIB (Figure 4B). These data strongly suggest that CSF levels of Aβ42 reflect cortical Aβ deposition and not the APOE ε4 genotype per se. Consequently, the cutoff level for CSF Aβ42 should be the same for all APOE genotypes.

**Conclusions**

Our data confirm that the APOE ε4 allele is associated with lower CSF levels of Aβ42 but not T-tau or P-tau in age groups in whom amyloid pathology is prevalent and also in the absence of manifest AD. We extend these data by showing that CSF levels of Aβ42 are not associated with the APOE ε4 genotype when stratifying for cortical uptake of [18F]flutemetamol, suggesting that CSF levels of Aβ42 reflect cortical Aβ deposition in an APOE ε4-independent manner. Consequently, the clinical cutoff level for CSF Aβ42 should be the same for all APOE genotypes. Finally, CSF biomarkers are strongly associated with AD diagnosis and cortical Aβ deposition independently of APOE ε4 genotype.
Cerebrospinal Fluid Biomarkers for AD

Original Investigation Research


