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Maternal Family History is Associated with Alzheimer's Disease Biomarkers

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Abstract

A family history of Alzheimer's disease (AD) increases one's risk of developing late-onset AD (LOAD), and a maternal family history of LOAD influences risk more than a paternal family history. Accumulating evidence suggests that a family history of dementia associates with AD-typical biomarker changes. We analyzed cross-sectional data from non-demented, mild cognitive impairment (MCI), and LOAD participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with PET imaging using Pittsburgh Compound B (PiB, $n = 99$) and cerebrospinal fluid (CSF) analysis ($n = 403$) for amyloid-β peptide (Aβ) and total tau. We assessed the relationship of CSF and PiB biomarkers and family history of dementia, as well as parent gender effects. In the larger analysis of CSF biomarkers, we assessed diagnosis groups individually. In the overall sample, CSF Aβ, tau/Aβ ratio, and global PiB uptake were significantly different between family history positive and negative groups, with markers of increased AD burden associated with a positive maternal family history of dementia. Moreover, a maternal family history of dementia was associated with significantly greater PiB Aβ load in the brain in the parietal cortex, precuneus, and sensorimotor cortex. Individuals with MCI positive for a maternal family history of dementia had significantly more markers of AD pathophysiology than individuals with no family history of dementia. A family history of dementia is associated with AD-typical biomarker changes. These biomarker associations are most robust in individuals with a maternal family history, suggesting that a maternally inherited factor influences AD risk.

Keywords

Alzheimer's disease; cerebrospinal fluid; genetics; PET

Introduction

Identifying risk factors for late-onset Alzheimer's disease (LOAD) can provide diagnostic, mechanistic, and therapeutic insights into this common age-related disease. Although LOAD does not demonstrate recognizable Mendelian patterns, genetic inheritance is a known modifier of LOAD risk. Individuals with a family history of Alzheimer's disease (AD), specifically a parent, have a 4–10 times increased risk [1–3].

Even in the absence of cognitive decline, adult children of LOAD parents, and especially those with a maternal family history, show a variety of brain changes that are indicative of

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LOAD itself. We have shown that nondemented individuals with a maternal family history of AD have increased rates of brain atrophy in several regions of the cortex that are the first to atrophy in AD [4, 5]. Other longitudinal studies on individuals with a family history of LOAD have shown that individuals with a maternal family history have progressive reductions of brain glucose metabolism on 2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography (FDG-PET) compared to those with a paternal family history and to those with a negative family history in both parents [6,7]. Healthy adult children with a maternal family history of LOAD also have increased fibrillar amyloid-β (Aβ) deposition on PET imaging with Pittsburgh Compound B (PiB) compared to individuals with a paternal or no family history [8]. A recent cross-sectional study showed that subjects with a maternal family history have decreased cerebrospinal fluid (CSF) $A\beta_{42/40}$ ratio and increased CSF F_2-isoprostanes (a marker of oxidative stress) as compared to subjects with a paternal or no family history, even when controlling for apolipoprotein E genotype [9]. These data support the hypothesis that maternally transmitted genetic factors influence LOAD risk [10].

A limitation to these initial studies has been their small sample size; however, datasets such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) allow access to larger samples with clinical, imaging, and biomarker data. The ADNI dataset includes CSF and PiB biomarker data in individuals with ascertained family histories, which have not been looked at in light of family history. We sought to extend our prior observations of AD-like brain imaging endophenotypes in individuals positive for a family history, and study CSF and PiB markers of AD pathophysiology across family history groups in the ADNI sample. We predicted that markers of AD pathophysiology (higher PiB uptake, lower CSF Aβ, higher CSF tau, and higher tau/Aβ ratio) would be more prevalent in individuals with a maternal family history of dementia. We also predicted that individuals with a maternal family history would have increased PiB uptake in the precuneus and temporal cortices, regions reported to have greater atrophy, abnormal glucose metabolism, and PiB uptake in individuals at risk for AD [4, 8, 9].

Materials and Methods

Subjects

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD (PI: Michael W. Weiner, M.D., VA Medical Center and University of California-San Francisco). ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see http://www.adni-info.org. Data for the present analysis were downloaded from the ADNI web site in November 2010.

In order to be included in the current analysis, individuals had to have family history (FH) information defining the dementia status of both parents. A positive family historyofdementia (FH+) was considered if either parent had dementia. Of the 821 individuals that completed the questionnaire, 235 subjects had maternal but not paternal history of dementia (FHm), 76 subjects had paternal but not maternal history of dementia (FHp), 31 subjects had both maternal and paternal history of dementia (FHboth), and 465

had neither maternal nor paternal history of dementia (FH−). We did not include individuals with incomplete or uninformative family histories in these analyses (n = 14).

Clinical assessment

Standard clinical and neuropsychological evaluations were conducted at regular intervals and standardized across ADNI sites (ADNI protocol available at http://www.adni-info.org). All data records were reviewed by a Central Review Committee to insure the uniform application of eligibility and diagnostic criteria across sites (including conversion from MCI to AD). The evaluations included a Clinical Dementia Rating (CDR) [11], physical exam, laboratory procedures, a battery of cognitive screening instruments, and 9 neuropsychological tests. Collectively, these metrics comprise the Uniform Data Set defined by the National Alzheimer's Coordinating Committee [12]. We used the Mini-Mental State Exam (MMSE) [13] score and 11-item Alzheimer's Disease Assessment Scale-cognitive sub-scale (ADAS-cog) [14] as cognitive outcomes in our analyses.

Nondemented participants (ND) had MMSE scores between 24–30 (inclusive), a CDR of 0, and were non-depressed. Visits were schedule at baseline, 6, 12, 24, 36, and 48 months post-enrollment for those with cognitive impairment. Participants diagnosed with MCI had MMSE scores between 24–30 (inclusive), a memory complaint and objective memory loss measured by education-adjusted scores on WMS-R Logical Memory II, a CDR of 0.5, largely preserved activities of daily living, and an absence of dementia. Participants diagnosed with AD had MMSE scores between 20–26 (inclusive), a CDR of 0.5 or 1.0, and met NINCDS/ADRDA criteria for probable AD.

CSF biomarkers

The ADNI Biomarker Core has previously described the procedures for acquiring and processing CSF for biomarker analysis [15]. Briefly, all individuals provided CSF samples after overnight fasting. Aβ and tau were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with immunoassay kit-based, research use-only reagents (INNO-BIA AlzBio3; Innogenetics, Ghent, Belgium). We also assessed biomarkers as binary variables (i.e., positive or negative) corresponding to cut-points indicative of AD pathophysiology based on biomarker analyses in the ADNI sample [15]. Individuals whose CSF Aβ values were 192pg/mL or lower were considered “CSF Aβ-positive” [15]. Participants were classified as having an elevated CSF tau/A(3 ratio if it was >0.39 [16].

PiB PET imaging

PiB PET imaging was performed on a subset of ADNI participants at 14 sites. Procedures for acquisition and processing are available online (http://adni.loni.ucla.edu/research/protocols/pet-protocols/). In short, standard 4 × 1300 second frame dynamic PIB was acquired beginning approximately after 50 min of a tracer injection dose of 15+1.5 mCi (555 MBq) of PiB. Variations in ADNI PET acquisitions as well as a schematic of the acquisition time frame are available online (http://adni.loni.ucla.edu/wp-content/uploads/2010/09/PET_PIB_Tech_Procedures_Manual_Supplv1.3.pdf). Only PiB values from the first PiB imaging timepoint were used in the present analysis. PiB standardized uptake value ratios (SUVR) normalized to the cerebellum were averaged within 14 a priori regions of interest that have been processed and posted by the University of Pittsburgh (http://adni.loni.ucla.edu/wp-content/uploads/2011/03/UPitt_PIBPET_AD_ROI.pdf; details on processing here: http://www.loni.ucla.edu/twiki/pub/Trash/TrashAttachment/UPitt_PIBPET_Analysis.pdf). Global PiB uptake was calculated as the average of PiB SUVR from 7 gray matter regions that have been used in combination for a global PiB value by other publications in the ADNI sample [17] and included the anterior cingulate, anterior

ventral striatum, frontal cortex, lateral temporal cortex, occipital cortex, parietal cortex, and precuneus.

Statistical analyses

First, differences between FH− and FH+ (including FHm, FHp, or FHBoth individuals) groups were tested across all diagnostic groups using parametric analyses (ANOVA) or nonparametric analyses (Chi square, Kruskal-Wallis) when appropriate, controlling for age, gender, education, and diagnostic classification (global CDR) at baseline. Primary analyses did not focus on APOE4-controlled biomarker data to avoid variance inflation given its high correlation with CSF and PiB measures of Aβ [18]; however, results from secondary APOE4-controlled analyses are reported in the text. Post-hoc testing was performed to test for parent gender effects (FHm and FHp subgroups). Because we had a larger sample size of individuals with CSF measures, for those analyses we also did tests within diagnosis groups. As determined with Shapiro Wilks test, Global PiB, CSF $A\beta_{42}$, total tau, and tau/Aβ measures were not normally distributed (p <0.05) within one or both of the FH+ and FH− groups. For these variables, statistically significant results obtained from raw data were confirmed after applying a log transformation of the raw values.

Results

From the ADNI dataset, we identified 403 individuals for whom both CSF and family history data were available (n = 209 FH− and n = 194 FH+; FHp = 42, FHm = 130, and FHBoth = 22). Of these 403 individuals, 99 had at least one PiB-PET scan (n = 54 FH− and n = 45 FH+; FHp =10, FHm = 27, and FHBoth = 8). Descriptive information on the PiB-PET cohort is provided in Table 1. There were no significant differences in age, gender, education, distribution of APOE4 carriers, MMSE, ADAS-Cog, or breakdown of diagnoses per group in the PiB cohort. Demographics for the CSF cohort can be found in Table 3. In the CSF cohort, there were significant differences in age between FH groups, with FH+ individuals being significantly younger (p < 0.005). Otherwise, there were no significant differences in age, gender, education, distribution of APOE4 carriers, MMSE, ADAS-Cog, or breakdown of diagnoses per group.

PiB-PET measures

Cerebral amyloid load as measured by PiB-PET (mean global PiB uptake) was higher in the FH+ group than it was in the FH− group (p = 0.009, Table 1). This difference remained significant when accounting for non-normal distribution by assessing log-transformed values (p = 0.015) and when controlling for age, gender, education, and diagnostic classification. Our post-hoc analysis of global PiB uptake between family history subgroups showed that the FHm group had significantly higher global PiB uptake with both raw and log-transformed measures compared to the FH− group (p < 0.05). The FHp group did not have significantly different global PiB uptake when compared to the FHm and FH− groups.

In our analysis of mean PiB uptake within specific regions of interest, we found that FH+ individuals had significantly greater cerebral amyloid load in the parietal cortex (p < 0.05), precuneus (p < 0.05), and sensorimotor cortex (p = 0.005) (Table 2), even when controlling for age, gender, education, and diagnostic classification. Controlling for APOE4 did not alter the results, thus data in Table 2 is adjusted for age, gender, education, diagnostic classification, and APOE4. Our post-hoc analysis of regional PiB uptake between family history subgroups showed that the FHm group had significantly more cerebral amyloid load in the parietal cortex, precuneus, and the sensorimotor cortex compared to FH− individuals (p = 0.003). The FHp group did not have significantly higher regional PiB uptake compared to the FHm and FH− groups.

CSF biomarkers

In the overall group, the CSF Aβ levels were significantly lower ($p = 0.006$) and the tau/Aβ ratios were higher ($p = 0.05$) in the FH+ group (Table 3). There were no significant differences between FH− and FH+ groups in total tau. In our assessment of CSF biomarkers as binary variables, we found that CSF Aβ-positive (CSF Aβ ≤ 192) participants were most common in the FH+ group compared the FH−. Post hoc analyses of CSF measures within FH subgroups showed that FHm individuals had significantly lower CSF Aβ levels and higher tau/Aβ ratios than FH−, with a trend for differences compared to the FHp group. CSF Aβ-positive (CSF Aβ ≤ 192) participants were most common in the FHm group compared the FH− group.

Analyses within diagnostic groups revealed that FH+ individuals with MCI had significantly lower Aβ levels ($p < 0.05$), and a trend for higher tau/Aβ ratios ($p = 0.058$), and no significant difference in total tau compared to MCI FH− individuals ($p = 0.101$) (Table 4). MCI FH+ individuals also had a significantly higher proportion of AD-like Aβ levels compared to MCI FH− individuals ($p < 0.05$). There was no significant effect of FH on CSF biomarkers in ND or AD individuals. Our post-hoc analysis of family history subgroups revealed that FHm individuals with MCI had significantly decreased CSF Aβ levels, increased total tau, and increased tau/Aβ ratio compared to FH− and FHp individuals ($p < 0.05$). CSF Aβ-positive (CSF Aβ ≤ 192) participants were most common in the FHm MCI group compared the FH− ($p < 0.05$) and FHp individuals ($p < 0.01$). In other words, the FHp group had CSF measures that were more like the FH− group than the FHm group. Results remained significant when using log-transformed values for CSF measures (Table 5). All analyses were controlled for age, gender, and education. Controlling for APOE attenuated the differences in CSF measures between FH+ and FH− groups, most likely because ApoE is highly correlated with Aβ levels in CSF [18]. The effects of APOE4 on CSF biomarkers in the ADNI sample have been reported in a prior publication [19].

Discussion

Overall, we found that a family history of dementia is associated with AD-typical biomarker changes. More specifically, we found that a maternal family history of AD is associated with increased global PiB uptake, specifically in the parietal, precuneus, and sensorimotor cortices, as well as decreased CSF Aβ levels and increased tau/Aβ ratio. When analyzing diagnostic group separately, this family history relationship with CSF measures was only significant in individuals with MCI, a heterogeneous pathological state. These data complement and extend reports of increases in Aβ burden on PiB-PET scans in FHm subjects in these same parietal and association cortex regions, and another report of increases in an AD-like CSF biomarker signature in individuals with a maternal family history of AD [20].

Our findings suggest that a maternal family history of dementia may be associated with increased fibrillar Aβ deposition in the brain in posterior parietal and association cortex regions, a hallmark of AD pathophysiology. Increased brain Aβ levels in individuals with MCI have been associated with accelerated gray matter atrophy within temporal and parietal brain regions, and increased risk for progression to AD [21]. Interestingly, increased Aβ deposition on PiB PET scans has recently been shown in healthy individuals with a maternal family history of LOAD in the interior and posterior cingulate cortex, precuneus, and parietal regions among others [8]. Thus, impairment of the posterior cingulate and precuneus may be a marker to distinguish early stage AD from healthy aging [22]. For instance, otherwise healthy individuals at genetic risk for AD have abnormal default mode activity in the precuneus and parietal cortex [23]. Longitudinal studies in nondemented individuals with FHm have also shown a progressive decline in posterior cortical glucose uptake [7],

and increased regional gray matter atrophy in posterior parietal cortices [24]. Furthermore, reduced precuneus choline acetyltrans-ferase enzyme activity postmortem has been associated with increased [(3)H]PiB binding, increased soluble $A\beta_{42}$, lower MMSE score, genetic risk, and more advanced AD pathophysiology [25]. We found a significant effect of FH on CSF biomarkers in MCI, as opposed to ND individuals, similar to another ADNI report of differences in hippocampal atrophy rates between FH groups [26]. This could be because of the stringency of clinical criteria for ND in the ADNI sample, a difference of parental history grouping, or differences in the CSF assay or processing. Overall, our results support these prior findings and demonstrate that individuals with a maternal family history of dementia have significantly increased fibrillar Aβ deposition in the precuneus, parietal cortex, and sensorimotor cortices. To our knowledge, this is the first report of parental history of dementia affecting PiB uptake in AD-vulnerable regions in MCI subjects.

CSF measures of $A\beta_{1\text{-}42}$ and tau have shown prognostic value in discriminating MCI patients that will develop AD [27–29]. We found that a maternal family history of AD is associated with decreased Aβ levels and increased tau/$A\beta_{42}$ ratio in CSF, adding to a growing literature showing increased AD-associated biomarkers in individuals with a family history of AD. A recent report from the Washington University Adult-Children Study found that among cognitively normal middle- to older-aged individuals, age-related changes in brain $A\beta_{42}$ amounts were influenced by FH of AD [20]. In addition, Mosconi et al. recently reported reduced $A\beta_{40/42}$ ratio levels in CSF of nondemented FHm individuals [9]. Concurrently, we report that FHm individuals with MCI had the only significant reductions in CSF $A\beta_{42}$. Studies have shown that reduced $A\beta_{42}$ levels in CSF are predictive of AD and reflect increased brain Aβ load [27]. Population-based CSF studies have found that reduced Aβ levels were related to AD risk in elderly individuals more than CSF total tau or phosphorylated tau [30]. Thus, ours and other studies show that individuals with a maternal family history of AD may have greater AD pathophysiology.

While the genetic basis for the transmission of imaging and CSF phenotypes of AD pathophysiology are unknown, studies of maternal inheritance, mitochondrial DNA (mtDNA) mutations, and cytochrome oxidase deficits in AD provide converging evidence for the role of mitochondria in risk for LOAD [5, 7, 8, 31–33]. Mitochondria supply energy from aerobic metabolism and play an important regulatory role in apoptosis, and produce and detoxify free radicals. Mitochondrial DNA is exclusively maternally inherited in humans, and may differ between persons with and without AD [34]. Studies of cytoplasmic hybrids (cybrids) demonstrate that AD mtDNA has decreased cytochrome oxidase activity and increased oxidative stress, among other abnormalities [35, 36]. Moreover, a recent study connected mitochondrial malfunction with a family history of AD by demonstrating that otherwise healthy FHm individuals have reduced cytochrome oxidase activity in platelet mitochondria compared to those with a paternal or no family history of AD, suggesting that mtDNA may influence AD risk [37]. Thus, converging evidence of platelet mitochondrial malfunction [37], AD-like brain imaging phenotypes [5–8,24], and CSF biomarkers of AD pathophysiology contribute to our hypothesis that increased risk for LOAD in FHm individuals may be due to mutations in mtDNA.

This study has several important limitations. In ADNI, parental history of dementia is provided by subject self-report, which, while practical to obtain, does not provide a neuropathologic diagnosis. Similar to a recent ADNI study on family history and structural imaging markers [26], we chose to use a parental history of dementia as opposed to a parental history of AD, as in many instances the suspected etiology of parental dementia was never recorded. The rationale for using “family history of dementia” was based on the number of available subjects with a positive parental history with PiB PET data. This likely led to the inclusion of some subjects with parental non-AD dementia, such as vascular

dementia, Parkinson's disease dementia, or dementia with Lewy bodies. Both limitations may have influenced our analyses by reducing our power to detect the presence or true extent of family history effect in AD. We did not observe a consistent relationship of FH with CSF measures in the AD group although we suspect the restricted variance in these measures reduce the power to detect a significant relationship. Moreover, there was an imbalance of individuals with a paternal versus a maternal family history in both PiB and CSF analysis, possibly limiting our power to find more significant relationships of FHp with AD biomarkers. We also had limitations in our small sample size of individuals with PiB data, with samples too small to perform analyses within clinical groups. Thus there was an imbalance within this sample of proportions of FHm versus FHp individuals in the ND and AD groups (all AD FH+ individuals were FHm, and the ND group had only 1 FHp individual). To address this, we corrected for clinical status as a covariate while examining PiB measures across all diagnostic groups. However, despite these statistical corrections, analysis of a combined diagnostic sample may have limited our ability to interpret our findings in terms of the role of PiB in risk for AD, since increased PiB in FHm may be due to a higher proportion of AD patients in the FHm group. Additionally, our findings were confined to associations between AD biomarkers and FH at baseline, and follow-up time in the ADNI study is warranted to investigate the causal relationship between FH and change in biomarkers, as well as progression to AD.

In conclusion, our results support and extend previous studies of FH and AD biomarkers, which demonstrate a relationship between FH, and particularly FHm status, and AD pathophysiology in the earliest stages of AD. These results are consistent with the view that in the earliest stages of AD, changesinthe brain associated with the disease process are influenced by a maternally inherited genetic factor.

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References

1. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. Ann Neurol. 1989; 25:485–493. [PubMed: 2774490]

2. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: The REVEAL study. Genet Med. 2004; 6:192–196. [PubMed: 15266206]
3. Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA. Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA. 2002; 287:329–336. [PubMed: 11790212]
4. Honea RA, Swerdlow RH, Vidoni ED, Burns JM. Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease. Neurology. 2011; 76:822–829. [PubMed: 21357834]
5. Honea RA, Swerdlow RH, Vidoni ED, Goodwin J, Burns JM. Reduced gray matter volume in normal adults with a maternal family history of Alzheimer disease. Neurology. 2010; 74:113–120. [PubMed: 20065246]
6. Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proc Natl Acad Sci U S A. 2007; 104:19067–19072. [PubMed: 18003925]
7. Mosconi L, Mistur R, Switalski R, Brys M, Glodzik L, Rich K, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer disease. Neurology. 2009; 72:513–520. [PubMed: 19005175]
8. Mosconi L, Rinne JO, Tsui WH, Berti V, Li Y, Wang H, Murray J, Scheinin N, Nagren K, Williams S, Glodzik L, De Santi S, Vallabhajosula S, de Leon MJ. Increased fibrillar amyloid-{beta} burden in normal individuals with a family history of late-onset Alzheimer's. Proc Natl Acad Sci U S A. 2010; 107:5949–5954. [PubMed: 20231448]
9. Mosconi L, Glodzik L, Mistur R, McHugh P, Rich KE, Javier E, Williams S, Pirraglia E, De Santi S, Mehta PD, Zinkowski R, Blennow K, Pratico D, de Leon MJ. Oxidative stress and amyloid-beta pathology in normal individuals with a maternal history of Alzheimer's. Biol Psychiatry. 2010; 68:913–921. [PubMed: 20817151]
10. Mosconi L, Berti V, Swerdlow RH, Pupi A, Duara R, de Leon M. Maternal transmission of Alzheimer's disease: Prodromal metabolic phenotype and the search for genes. Hum Genomics. 2010; 4:170–193. [PubMed: 20368139]
11. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993; 43:2412b–2414. [PubMed: 8232972]
12. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21:249–258. [PubMed: 17804958]
13. Folstein MF, Folstein SE, McHugh PR. Mini-mental State: A practical method for grading the cognitive state of patients for the clinicians. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
14. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984; 141:1356–1364. [PubMed: 6496779]
15. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009; 65:403–413. [PubMed: 19296504]
16. Shaw LM, Vanderstichele H, Knapik-Czajka M, Figurski M, Coart E, Blennow K, Soares H, Simon AJ, Lewczuk P, Dean RA, Siemers E, Potter W, Lee VM, Trojanowski JQ. Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. Acta Neuropathol. 2011; 121:597–609. [PubMed: 21311900]
17. Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boeve BF, Kemp BJ, Weiner M, Petersen RC. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: Implications for sequence of pathological events in Alzheimer's disease. Brain. 2009; 132:1355–1365. [PubMed: 19339253]
18. Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol. 67:122–131. [PubMed: 20186853]

19. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, Shaw LM, Trojanowski JQ, Potkin SG, Huentelman MJ, Craig DW, DeChairo BM, Aisen PS, Petersen RC, Weiner MW, Saykin AJ. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology. 2011; 76:69–79. [PubMed: 21123754]
20. Xiong CJ, Roe CM, Buckles V, Fagan A, Holtzman D, Balota D, Duchek J, Storandt M, Mintun M, Grant E, Snyder AZ, Head D, Benzinger TLS, Mettenburg J, Csernansky J, Morris JC. Role of family history for Alzheimer biomarker abnormalities in the adult children study. Arch Neurol. 2011; 68:1311–1317.
21. Ewers M, Insel P, Jagust WJ, Shaw L, Trojanowski JJ, Aisen P, Petersen RC, Schuff N, Weiner MW. CSF biomarker and PIB-PET-derived beta-amyloid signature predicts metabolic, gray matter, and cognitive changes in nondemented subjects. Cereb Cortex. 201110.1093/cer-cor/bhr271
22. Bai F, Zhang Z, Yu H, Shi Y, Yuan Y, Zhu W, Zhang X, Qian Y. Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. Neurosci Lett. 2008; 438:111–115. [PubMed: 18455308]
23. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A. 2009; 106:7209–7214. [PubMed: 19357304]
24. Honea RA, Swerdlow RH, Vidoni ED, Burns JM. Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease. Neurology. 2010; 76:822–829. [PubMed: 21357834]
25. Ikonomovic MD, Klunk WE, Abrahamson EE, Wuu J, Mathis CA, Scheff SW, Mufson EJ, DeKosky ST. Precuneus amyloid burden is associated with reduced cholinergic activity in Alzheimer disease. Neurology. 2011; 77:39–47. [PubMed: 21700583]
26. Andrawis JP, Hwang KS, Green AE, Kotlerman J, Elashoff D, Morra JH, Cummings JL, Toga AW, Thompson PM, Apos-tolova LG. Effects of ApoE4 and maternal history of dementia on hippocampal atrophy. Neurobiol Aging. 2010; 33:856–866. [PubMed: 20833446]
27. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010; 6:131–144. [PubMed: 20157306]
28. Buerger K, Ewers M, Andreasen N, Zinkowski R, Ishiguro K, Vanmechelen E, Teipel SJ, Graz C, Blennow K, Hampel H. Phosphorylated tau predicts rate of cognitive decline in MCI subjects: A comparative CSF study. Neurology. 2005; 65:1502–1503. [PubMed: 16275849]
29. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: A follow-up study. Lancet Neurol. 2006; 5:228–234. [PubMed: 16488378]
30. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebrospinal fluid beta-amyloid 1-42 concentration may predict cognitive decline in older women. J Neurol Neurosurg Psychiatry. 2007; 78:461–464. [PubMed: 17098843]
31. Bonilla E, Tanji K, Hirano M, Vu TH, DiMauro S, Schon EA. Mitochondrial involvement in Alzheimer's disease. Biochim Biophys Acta. 1999; 1410:171–182. [PubMed: 10076025]
32. Orth M, Schapira AH. Mitochondria and degenerative disorders. Am J Med Genet. 2001; 106:27–36. [PubMed: 11579422]
33. Cardoso SM, Santana I, Swerdlow RH, Oliveira CR. Mitochondria dysfunction of Alzheimer's disease cybrids enhances Abeta toxicity. J Neurochem. 2004; 89:1417–1426. [PubMed: 15189344]
34. Parker WD Jr, Filley CM, Parks JK. Cytochrome oxidase deficiency in Alzheimer's disease. Neurology. 1990; 40:1302–1303. [PubMed: 2166249]
35. Swerdlow RH. Mitochondria in cybrids containing mtDNA from persons with mitochondriopathies. J Neurosci Res. 2007; 85:3416–3428. [PubMed: 17243174]
36. Swerdlow RH, Parks JK, Cassarino DS, Maguire DJ, Maguire RS, Bennett JP Jr, Davis RE, Parker WD Jr. Cybrids in Alzheimer's disease: A cellular model of the disease? Neurology. 1997; 49:918–925. [PubMed: 9339668]
37. Mosconi L, de Leon M, Murray EL, Lu J, Javier E, McHugh P, Swerdlow RH. Reduced mitochondria cytochrome oxidase activity in adult children of mothers with Alzheimer's disease. J Alzheimers Dis. 2011; 27:483–490. [PubMed: 21841246]

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Table 1

Demographic and biomarker measures of ADNI participants with PiB-PET data

	FH−	FH+	FH+ subgroups			*p* value
			FHp	FHm	FHBoth	FH− versus FH+
PiB subsample	(*n* = 54)	(*n* = 45)	(*n* = 10)	(*n* = 27)	(*n* = 8)	
Age, y	76.5(7.8)	74.4(7.8)	72.9(9.9)	74.6(7.8)	75.9(4.6)	0.193
% Female	33.3	37.8	30.0	40.7	37.5	0.401
Education, y	15.7 (2.9)	16.1 (2.9)	16.8 (2.6)	15.5 (2.9)	17.1 (3.4)	0.535
APOE ε4 carrier, %	40.7	53.3	50.0	48.1	75.0	0.147
MMSE	26.9 (2.4)	27.1 (2.1)	27.4 (1.7)	27 (2.3)	27.3 (2.1)	0.559
ADAS-Cog	10.9 (6.6)	10.7 (5.5)	10.6 (4.0)	11.2 (6.0)	9.1 (5.3)	0.846
Diagnostic breakdown, % (*n*)						
ND	24% (13)	13% (6)	10% (1)	15% (4)	13% (1)	0.196
MCI	59% (32)	64% (29)	90% (9)	55% (15)	62% (5)	
AD	17% (9)	22% (10)	0% (0)	30% (8)	25% (2)	
Global PiB uptake	1.6 (0.29)	1.8 (0.34)	1.8 (0.35)	1.8 (0.31)	1.9 (0.34)	**0.009°**
Log-transformed global PiB uptake	0.18 (0.08)	0.24 (0.09)	0.24 (0.09)	0.24 (0.08)	0.26 (0.11)	**0.015°**

All values are means (SD). *p* values <0.05 (in bold) represent a significant difference present between FH− and FH+ groups (in the last 2 rows we controlled for age, gender, education, and diagnostic classification). Percentages in the diagnostic breakdown reflect percentage of total for column, representing each FH group. When FH− versus FH+ group differences were present, we identified specific group differences using post hoc contrasts, ° = FH− > FHm ($p < 0.05$). AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; FH−, negative family history of dementia; FH+, positive family history of dementia; FHp, paternal only family history of dementia; FHm, maternal only family history of dementia; FHBoth, Both parents family history of dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ND, no dementia.

Table 2

PiB regions by family history group

	FH−	FH+	FH+ subgroups		*p* value
			FHp	FHm	FH− versus FH+
PiB subsample	(*n* = 54)	(*n* = 45)	(*n* = 10)	(*n* = 27)	
Frontal cortex	1.69 (0.36)	1.93 (0.42)	1.89 (0.40)	1.89 (0.38)	0.075
Anterior cingulate cortex	1.63 (0.41)	1.76 (0.47)	1.90 (0.49)	1.80 (0.47)	0.801
Lateral temporal cortex	1.53 (0.29)	1.76 (0.37)	1.71 (0.37)	1.75 (0.36)	0.060
Parietal cortex	1.60 (0.35)	1.89 (0.39)	1.81 (0.36)	**1.91 (0.38)°**	**0.024**
Precuneus	1.69 (0.41)	2.03 (0.47)	2.01 (0.51)	**2.01 (0.45)°**	**0.026**
Medial temporal cortex	1.13 (0.13)	1.14 (0.13)	1.19 (0.17)	1.13 (0.10)	0.935
Occipital cortex	1.37 (0.19)	1.45 (0.20)	1.47 (0.24)	1.44 (0.20)	0.328
Occipital pole	1.49 (0.22)	1.52 (0.19)	1.51 (0.22)	1.51 (0.16)	0.924
Pons	1.81 (0.29)	1.74 (0.19)	1.71 (0.19)	1.72 (0.19)	0.481
Anterior ventral striatum	1.61 (0.36)	1.83 (0.40)	1.77 (0.39)	1.79 (0.35)	0.180
Sensorimotor cortex	1.32 (0.18)	1.49 (0.23)	1.48 (0.25)	**1.47 (0.22)°**	**0.005**
Sub-cortical white matter	1.79 (0.25)	1.75 (0.19)	1.75 (0.19)	1.72 (0.21)	0.429
Thalamus	1.42 (0.21)	1.46 (0.19)	1.42 (0.18)	1.45 (0.17)	0.956

All values are means (SD), controlling for age, gender, education, diagnostic classification, and ApoE4 carrier status. *p* values <0.05 (in bold) represent a significant difference present between groups, When FH− versus FH+ group differences were present, we identified specific group differences using post hoc contrasts, ° = FH− > FHm (*p* <0.01). FH−, negative family history of dementia; FH+, positive family history of dementia; FHp, paternal only family history of dementia; FHm, maternal only family history of dementia.

Table 3

Demographic and biomarker measures of ADNI participants with CSF data

CSF subsample	FH−	FH+	*p* value	FHp	FHm	Post hoc *p* value		
	(*n* = 209)	*n* = (194)	FH− versus FH+	(*n* = 42)	(*n* = 130)	FH− versus FHp	FH− versus FHm	FHp versus FHm
Age, y	75.9 (7.3)	73.9 (6.7)	**0.005**	74.1 (7.2)	73.9 (6.5)		**0.013**	
% Female	37.3	42.8	0.115	45.2	42.3			
Education, y	15.5 (3.2)	15.8 (2.8)	0.272	15.2 (2.6)	16.1 (2.8)			
APOE *ε4* carrier, %	46.4	53.1	0.107	45.2	56.2			
MMSE	26.7 (2.6)	26.6 (2.6)	0.777	27.1 (2.5)	26.5 (2.6)			
ADAS-Cog	11.8 (6.5)	12.2 (6.4)	0.441	11.3 (5.8)	12.4 (6.7)			
Diagnostic breakdown, % (*n*)								
ND	29% (61)	26% (51)	0.779	33% (14)	26% (34)			
MCI	46% (96)	48% (95)		50% (21)	48% (62)			
AD	25% (52)	26% (48)		17% (7)	26% (34)			
Total tau, pg/mL	94.5 (51)	102.1 (59)	0.168	86.5 (39)	104.3 (64)			
Aβ, pg/mL	177.7 (58)	162.0 (54)	**0.009**	177.8 (58)	159.9 (54)		**0.007**	0.060
Aβ positivity (<192pg/mL), %	62.2	74.7	**0.005**	64.3	76.2		**0.004**	
Tau/Aβ ratio	0.63 (0.46)	0.74 (0.58)	**0.05**	0.57 (0.36)	0.77 (0.65)		**0.027**	0.070
Elevated tau/Aβ ratio (>0.39), %	60.3	69.1	**0.041**	57.1	70.8		**0.032**	0.075

All values are means (SD). *p* values <0.05 (in bold) represent a significant difference present between FH− and FH+ groups while controlling for age, gender, diagnostic classification, and education. When FH− versus FH+ group differences were present, we identified specific group differences using post hoc contrasts described in the column post hoc results. Standard cut-points were used to classify individuals as “positive” CSF Aβ (≤192pg/mL) and as having an elevated tau/Aβ ratio (>0.39). Percentages in the diagnostic breakdown reflect percentage of total for column, representing each FH group. Aβ, amyloid-β; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CSF, cerebrospinal fluid; FH−, negative family history of dementia; FH+, positive family history of dementia; FHp, paternal only family history of dementia; FHm, maternal only family history of dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ND, no dementia.

Table 4

CSF Biomarker data between FH groups, within diagnosis groups

CSF Subsample	FH+	FH+	*p* value	FHp	FHm	*Post hoc p* value		
			FH− versus FH+			FH− versus FHp	FH− versus Fhm	FHp versus FHm
ND	*n* = 61	*n* =51		*n* =14	*n* = 34			
Total tau, pg/mL	68.5 (30)	71.8 (31)	0.474	71.5 (30)	67.1 (25)			
Aβ, pg/mL	211 (53)	199 (56)	0.204	209 (56)	201 (56)			
Aβ positivity (<192pg/mL), %	32.8	43.1	0.230	28.6	44.1			
Tau/Aβ ratio	0.37 (0.26)	0.41 (0.27)	0.319	0.39 (0.26)	0.37 (0.19)			
Elevated tau/Aβ ratio (>0.39), %	31.1	39.2	0.245	28.6	38.2			
MCI	*n* = 96	*n* =95		*n* =21	*n* = 62			
Total tau, pg/mL	95.4 (47)	109.6 (67)	0.101	88 (41)	116 (74)		**0.039**	
Aβ, pg/mL	172 (57)	155 (51)	**0.037**	173 (54)	148 (50)		**0.013**	**0.042**
Aβ positivity (<192pg/mL), %	67.7	81.1	**0.038**	76.2	83.9		**0.021**	**0.006**
Tau/Aβ ratio	0.65 (0.47)	0.82 (0.66)	**0.058**	0.57 (0.32)	0.91 (0.76)		**0.015**	**0.041**
Elevated tau/Aβ ratio (>0.39), %	64.6	74.7	0.155	61.9	79.0			
AD	*n* = 52	*n* =48		*n* =7	*n* =34			
Total tau, pg/mL	123 (62)	120 (52)	0.732	112 (43)	120 (56)			
Aβ, pg/mL	149 (47)	137 (32)	0.296	129 (37)	139 (33)			
Aβ positivity (<192pg/mL), %	86.5	95.8	0.221	100.0	94.1			
Tau/Aβ ratio	0.89 (0.45)	0.94 (0.52)	0.755	0.92 (0.41)	0.94 (0.56)			
Elevated tau/Aβ ratio (>0.39), %	86.5	89.6	0.438	100.0	88.2			

All values are means (SD) controlling for age, gender, and education. *p* values <0.05 (in bold) represent a significant difference present between groups. When FH− versus FH+ group differences were present, we identified specific group differences using post hoc contrasts described in the column post hoc results. Standard cut-points were used to classify individuals as "positive" CSF Aβ (≤ 192 pg/mL) and as having an elevated tau/Aβ ratio (>0.39). Aβ, amyloid-β; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CSF, cerebrospinal fluid; FH−, negative family history of dementia; FH+, positive family history of dementia; FHp, paternal only family history of dementia; FHm, maternal only family history of dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ND, no dementia.

Table 5

Log-transformed, covariate adjusted CSF biomarker data between FH groups, within diagnosis

	FH−	FH+	FH+ subgroups	
			FHp	FHm
Diagnosis at baseline				
ND	*n* = 61	*n* =51	*n* =14	*n* = 34
Log-transformed total tau, pg/mL	1.79 (0.17)	1.82 (0.17)	1.82 (0.18)	1.80 (0.15)
Log-transformed Aβ, pg/mL	2.31 (0.13)	2.28 (0.13)	2.30 (0.13)	2.28 (0.13)
Log-transformed tau/Aβ ratio	−0.51 (0.24)	−0.45 (0.24)	−0.48 (0.24)	−0.48 (0.21)
MCI	*n* = 96	*n* =95	*n* =21	*n* = 62
Log-transformed total tau, pg/mL	1.93 (0.21)	2.0 (0.22)	1.90 (0.19)	1.99 (0.24)°
Log-transformed Aβ, pg/mL	2.21 (0.14)	2.16 (0.13)°	2.22 (0.14)	2.15 (0.13)°
Log-transformed tau/Aβ ratio	−0.28 (0.29)	−0.19 (0.31)°	−0.31 (0.26)	−0.15 (0.31)[1°2]
AD	*n* = 52	*n* =48	*n* =7	*n* = 34
Log-transformed total tau, pg/mL	2.03 (0.23)	2.0 (0.20)	2.02 (0.23)	2.03 (0.21)
Log-transformed Aβ, pg/mL	2.15 (0.12)	2.1 (0.11)	2.09 (0.13)	2.13 (0.11)
Log-transformed tau/Aβ ratio	−0.12 (0.28)	−0.09 (0.25)	−0.07 (0.17)	−0.09 (0.25)

Values are means (SD). [1]Significant while covarying for age, gender, and education, °$p < 0.05$, *$p < 0.01$, p-values are for FH+, FHp, or FHm versus FH−, except for cells marked with a[2], where FHp <FHm. Aβ, amyloid-β; AD, Alzheimer's disease; FH−, negative family history of dementia; FH+, positive family history of dementia; FHp, paternal only family history of dementia; FHm, maternal only family history of dementia; MCI, mild cognitive impairment; ND, no dementia.