High Striatal Amyloid β-Peptide Deposition Across Different Autosomal Alzheimer Disease Mutation Types

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Background: Supported by compelling genetic data regarding early-onset familial Alzheimer disease (AD), the amyloid β-peptide (Aβ)–centric theory holds that Aβ is involved in the pathogenesis of sporadic AD. Mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes lead to increased Aβ levels before symptoms arise.

Objectives: To evaluate the pattern of Pittsburgh Compound B (PiB) retention in subjects with different autosomal dominant mutations associated with familial AD vs that in healthy age-matched control subjects and subjects with probable sporadic AD, to correlate Aβ burden as measured by PiB with available clinical and cognitive data, and to compare the regional brain patterns of PiB retention and fluorodeoxyglucose F 18 (FDG) uptake.

Design: Correlation analysis of positron emission tomography (PET) imaging studies.

Setting: Academic research.

Participants: Seven PSEN1 mutation carriers and 1 APP mutation carrier underwent PiB and FDG PET imaging.

Amyloid β-peptide burden and FDG uptake were established using standardized uptake values normalized to pons.

Main Outcome Measure: Primary outcomes were PET results, which were compared with those of a well-characterized cohort of 30 healthy control subjects and 30 subjects with probable sporadic AD.

Results: All mutation carriers had high PiB retention in the striatum, with some also having cortical PiB retention in ventrofrontal and posterior cingulate/precuneus areas. The striatal pattern of PiB retention was similar in the PSEN1 and APP mutation carriers. Neither striatal nor cortical Aβ burden was related to cognitive status.

Conclusions: Consistent with previous studies, the pattern of Aβ deposition in familial AD differs from that in sporadic AD, with higher striatal and somewhat lower cortical PiB retention in familial AD. The pattern and degree of Aβ deposition were not associated with mutation type nor cognitive status.

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ALZHEIMER DISEASE (AD), the leading cause of dementia in older persons, is an irreversible progressive neurodegenerative disorder that is clinically characterized by memory loss and cognitive decline. It leads invariably to death, usually within 7 to 10 years after diagnosis.

To date, evidence supports the notion that amyloid β-peptide (Aβ) is central to AD pathogenesis. Amyloid β-peptide is a 4-kDa 39– to 43–amino acid metalloprotein derived from the proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases. The presence of extracellular Aβ in highly specialized cortical brain regions implicated in memory and cognition indicates that increases in Aβ are involved in early presymptomatic stages of the disease. Compelling genetic data further support the Aβ-centric theory. Although it is probable that additional genes are involved, the following 4 genes associated with Aβ production or clearance have been implicated in the pathogenesis of AD: mutation of the APP gene on chromosome 21, polymorphism of the apolipoprotein E gene (APOE) on chromosome 19, and mutations in the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes on chromosomes 14 and 1, respectively. Three of them (PSEN1, PSEN2, and APP) have a clear-cut autosomal dominant pattern with a penetrance above 85%, while the fourth (APOE) is a weaker susceptibility factor, despite being the most prevalent of these.
risk factors for AD.\textsuperscript{6,7} The main feature of APP, \textit{PSEN1}, and \textit{PSEN2} mutations (involved in different steps of the APP processing pathway) is increased production and deposition of A\textbeta{}, especially A\textbeta{}\textsubscript{42}.\textsuperscript{6,8} Despite some clinical heterogeneity associated with \textit{PSEN1} mutations,\textsuperscript{10,11} these various genetic mutations lead to increased levels of A\textbeta{} in the brain before symptoms arise.\textsuperscript{11}

Amyloid B-peptide imaging with positron emission tomography (PET) allows early and accurate diagnosis of AD.\textsuperscript{12,13} Pittsburgh Compound B (PiB), the most widely used amyloid tracer, provides quantitative insights on A\textbeta{} burden in vivo, which has led to new insights on A\textbeta{} deposition in the brain. The use of this technique has shown a robust difference in PiB retention between healthy control subjects (HCs) and subjects with AD,\textsuperscript{12,13} and has demonstrated inverse correlations of A\textbeta{} burden with glucose hypometabolism in some brain regions,\textsuperscript{14} cerebrospinal fluid A\textbeta{}\textsubscript{42},\textsuperscript{15} and rate of cerebral atrophy.\textsuperscript{16} About 25% to 35% of asymptomatic age-matched HCs present with cortical PiB retention and greater risk of cognitive decline, likely representing preclinical AD.\textsuperscript{17-19} Two previous studies\textsuperscript{20,21} reported high striatal PiB retention in \textit{PSEN1} mutation carriers, while a third study\textsuperscript{22} reported a novel APP mutation in which A\textbeta{} remains in an oligomeric form showing mild cortical PiB retention. From these few studies, it is difficult to infer the significance of PiB retention in asymptomatic mutation carriers. Therefore, it is crucial to examine more patients with familial AD (FAD) having early-onset or variable mutations to better define the role of A\textbeta{} in this population and its association with cognitive status.

The objectives of the study were as follows: (1) to evaluate the pattern of PiB retention in subjects with distinct but different autosomal dominant mutations associated with FAD vs that in age-matched HCs and subjects with probable sporadic AD (SAD), and (2) to correlate A\textbeta{} burden as measured by PiB with available clinical and cognitive data, and (3) to compare the regional brain patterns of PiB retention and fluorodeoxyglucose F 18 (FDG) uptake.

## METHODS

### PARTICIPANTS

Written informed consent for participation in this study was obtained from all subjects or caregivers before imaging. The study was approved by the Austin Health (Melbourne, Australia) human research ethics committee and by the Osaka City University Medical School (Osaka, Japan) institutional ethics committee.

Eight subjects who were carriers of APP or \textit{PSEN1} mutations were studied using PiB and FDG PET imaging. All subjects were aware that they were carrying a mutation linked to AD. Specific mutations are listed in Table 1.

PiB and FDG PET studies of mutation carriers were compared with those of a well-characterized cohort of 30 HCs and 30 subjects with probable SAD. The latter subjects met the criteria for probable AD as outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.\textsuperscript{23}

Subjects underwent a neurologic examination. In addition to the Clinical Dementia Rating (CDR) and the Mini-Mental State Examination (MMSE), subjects without complete impairment underwent various neuropsychological tasks designed to assess a broad range of cognitive domains, although no specific test to assess striatal function was administered.

### IMAGING PROCEDURES

All subjects underwent T1-weighted magnetic resonance (MR) imaging for screening and subsequent coregistration with PET images. Each subject received approximately 370 megabecquerels (MBq) of PiB by intravenous injection over 1 minute.

Imaging was performed in Melbourne for the \textit{PSEN1}\textsubscript{E} mutation carriers (Eminence-B PET imaging system; Phillips, Amsterdam, the Netherlands) and in Osaka for the \textit{PSEN1}\textsubscript{E} mutation carriers (Allegro PET camera; Allegro PET imaging system; Phillips, Osaka, Japan). PET imaging for screening and subsequent coregistration with MR images were obtained in all subjects. All subjects underwent T1-weighted magnetic resonance (MR) imaging for screening and subsequent coregistration with PET images. Each subject received approximately 370 megabecquerels (MBq) of PiB by intravenous injection over 1 minute. Imaging was performed in Melbourne for the \textit{PSEN1}\textsubscript{E} mutation carriers (Eminence-B PET imaging system; Phillips, Amsterdam, the Netherlands) and in Osaka for the \textit{PSEN1}\textsubscript{E} mutation carriers (Allegro PET camera; Allegro PET imaging system; Phillips, Osaka, Japan).
Shimadzu, Osaka, Japan). A 20- to 30-minute emission acquisition was then performed in 3-dimensional mode starting 40 minutes after injection of PiB. In 7 of 8 subjects, static FDG images were obtained 45 minutes after injection of approximately 250 MBq of FDG.

**IMAGE ANALYSIS**

Coregistration of PET images was performed using a computer program (SPM5; Statistical Parametric Mapping 5; Medical Research Council Cognition and Brain Sciences Unit, Cambridge, England), and an MR imaging-defined region-of-interest template was then applied to PET images. The mean standardized uptake value (SUV) was obtained from the region of interest for cortical, subcortical, and cerebellar regions.

Because of the reported presence of plaques in the cerebellar cortex of patients with FAD, PiB retention and FDG uptake were normalized to pons radioactivity to generate standardized uptake value ratio pons (SUVRpons). Regional PiB and FDG PET imaging SUVRpons of mutation carriers were then compared with those of a well-characterized (although significantly older) cohort of 30 HCs without evidence of Aβ deposition in the brain (PiB negative) and 30 subjects with probable SAD.

**STATISTICAL ANALYSIS**

$z$ Scores exceeding 2 were considered significantly different from HCs or subjects with probable SAD. Correlations were assessed using Pearson product moment correlation analyses. Group data are expressed as the mean (SD).

Demographic data for mutation carriers and for the HC and probable SAD cohorts are given in Table 1. All symptomatic mutation carriers had onset of cognitive decline within the expected range of their respective pedigrees. At the time of PET imaging, 3 subjects had severe impairment, and it was impossible to obtain MMSE scores.

The pattern of PiB retention in all mutation carriers, independent of mutation type, differed from that in subjects with probable SAD, with higher PiB retention in the striatum among the mutation carriers (Figure 1). Older mutation carriers had higher striatal PiB retention. Table 2 gives the regional SUVRpons of mutation carriers vs HCs and subjects with probable SAD. Another common feature was high PiB retention in the prefrontal, orbitofrontal, and gyrus rectus regions in most (6 of 8) mutation carriers (Figure 1). Despite their sharing the same PSEN1 mutation (L219P) (Table 1), the degree of PiB retention was higher and more widespread in the 62-year-old subject closer to the age at onset for his pedigree, while PiB retention was restricted to the caudate nuclei in the 36-year-old subject (18 years away from the age at onset for her pedigree). A cortical PiB retention pattern similar to that usually seen in SAD was observed in 2 women with dementia (the 45-year-old PSEN1 mutation carrier and the 52-year-old PSEN1 mutation carrier) and in 2 men without dementia (the 48-year-old APP...
mutation carrier and the 62-year-old PSEN1c mutation carrier). Half of the mutation carriers demonstrated significantly higher cerebellar PiB retention than that in HCs (Table 2).

Although global and regional FDG uptake was lower in most symptomatic mutation carriers (Table 3), there was no common pattern of FDG uptake among the subjects studied (Figure 1). Three subjects (the PSEN1c, PSEN1f, and PSEN1e mutation carriers) showed marked global glucose hypometabolism in which reduced FDG uptake was associated with severe brain atrophy, while the PSEN1g mutation carrier demonstrated asymmetric FDG uptake but less atrophy on MR imaging than that in the other 2 subjects. Three other subjects (the PSEN1b, APP, and PSEN1e mutation carriers) showed an almost normal pattern of FDG uptake. The PSEN1g mutation carrier had lower FDG uptake than that among HCs in the parietal cortex, as is usually observed in SAD, and had high FDG uptake in the anterior cingulate, lateral temporal, and striatum (Table 3).

Striatal and cortical PiB retention was not associated with mutation type, disease severity, or cognitive impairment (Figure 2). In contrast to PiB findings, the FDG posterior cortical index correlated with MMSE score ($r=0.85$, $P<.02$), CDR ($r=-0.84$, $P=.02$), and years from onset for the respective families ($r=-0.78$, $P=.04$). There was no regional or global correlation between PiB retention and FDG uptake. Given the dichotomy of the CDR and the MMSE score, mutation carriers were separated into 2 subgroups according to their disease severity (MMSE score $>20$ or $\leq20$ and CDR $>2$ or $\leq2$) for further comparison. There was no significant difference between the subgroups in striatal or neocortical PiB retention, while the most cognitively impaired subgroup (MMSE score $\leq20$ and CDR $>2$) had significantly lower striatal FDG uptake ($P=.03$) and FDG posterior cortical index ($P=.01$).

In vivo amyloid PET imaging has allowed new insights on Aβ deposition in the brain, facilitating research into the causes, diagnosis, and future treatment of dementia in which Aβ may have a role.12,13,26 We examined the pattern and degree of PiB retention in familial cases with PSEN1 and APP mutations. All mutation carriers showed some degree of increased PiB retention. Although the degree of cortical retention was generally lower than that usually observed in SAD, the striatal retention was remarkably high. Early onset and rapid progression of the disease indicate that other factors besides Aβ deposition have a role in the cognitive impairment process in FAD, in which Aβ upregulation and deposition represent an early and necessary but not sufficient immediate cause of cognitive decline.

The pattern of PiB retention was similar to that reported in 2 previous studies20,21 of PSEN1 mutation carriers. Postmortem studies21,27 of patients with FAD had shown Aβ deposits in the striatum. The high PiB retention in the striatum is difficult to reconcile with the clinical phenotype given the similar symptoms in SAD, in which this pattern of retention is not observed. However, this pattern is constant across different mutation types, and it has been proposed that Aβ deposition in FAD starts in the striata.20 High striatal PiB retention was accompanied by significant retention in the frontal regions, although the retention was not as high as that observed in SAD. As in a high percentage of HCs, PiB retention is observed in the frontal and posterior cingu-

### Table 2. Individual Cerebral Regional Pittsburgh Compound B Retention SUVRpons in Familial AD, 30 HCs and 30 Subjects With Probable Sporadic AD

<table>
<thead>
<tr>
<th>Location</th>
<th>PSEN1L219P</th>
<th>PSEN1E9</th>
<th>APPV717L</th>
<th>PSEN1Y115C</th>
<th>PSEN1E206</th>
<th>PSEN1C236T</th>
<th>PSEN1L173</th>
<th>PSEN1L173S</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>0.53</td>
<td>0.91a</td>
<td>1.32a</td>
<td>1.04a</td>
<td>1.50a</td>
<td>0.84a</td>
<td>0.63</td>
<td>0.87a</td>
<td>0.59 (0.10)</td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td>0.57</td>
<td>0.82a</td>
<td>1.34a</td>
<td>1.01a</td>
<td>1.40a</td>
<td>0.88a</td>
<td>0.68</td>
<td>0.89a</td>
<td>0.61 (0.09)</td>
</tr>
<tr>
<td>Gyrus rectus</td>
<td>0.70</td>
<td>0.92a</td>
<td>1.31a</td>
<td>1.17a</td>
<td>1.65a</td>
<td>0.93a</td>
<td>0.57</td>
<td>1.01a</td>
<td>0.62 (0.09)</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>0.62</td>
<td>0.91a</td>
<td>1.31a</td>
<td>1.17a</td>
<td>1.53a</td>
<td>0.77</td>
<td>0.76</td>
<td>1.02a</td>
<td>0.63 (0.11)</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>0.58</td>
<td>0.81</td>
<td>1.65a</td>
<td>1.17a</td>
<td>1.65a</td>
<td>0.73</td>
<td>0.82a</td>
<td>0.95a</td>
<td>0.62 (0.09)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.54</td>
<td>0.81a</td>
<td>1.00a</td>
<td>0.81a</td>
<td>1.34a</td>
<td>0.68</td>
<td>0.73</td>
<td>1.00a</td>
<td>0.55 (0.09)</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.47</td>
<td>0.72</td>
<td>0.91a</td>
<td>0.68</td>
<td>1.14a</td>
<td>0.74</td>
<td>0.74</td>
<td>0.96a</td>
<td>0.64 (0.07)</td>
</tr>
<tr>
<td>Lateral temporal</td>
<td>0.51</td>
<td>0.68</td>
<td>1.24a</td>
<td>0.94a</td>
<td>1.34a</td>
<td>0.66</td>
<td>0.66</td>
<td>0.95a</td>
<td>0.59 (0.08)</td>
</tr>
<tr>
<td>Mesial temporal</td>
<td>0.56</td>
<td>0.60</td>
<td>0.80a</td>
<td>0.69</td>
<td>0.83a</td>
<td>0.50</td>
<td>0.55</td>
<td>0.42a</td>
<td>0.61 (0.07)</td>
</tr>
<tr>
<td>Caudate nuclei</td>
<td>1.04a</td>
<td>1.37a</td>
<td>1.76a</td>
<td>1.46a</td>
<td>1.97a</td>
<td>0.70b</td>
<td>1.19a</td>
<td>1.59a</td>
<td>0.64 (0.10)</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.76</td>
<td>1.15a</td>
<td>1.25a</td>
<td>1.34a</td>
<td>1.57a</td>
<td>0.96a</td>
<td>1.15a</td>
<td>1.38a</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.63</td>
<td>0.82</td>
<td>1.19a</td>
<td>1.06a</td>
<td>1.28a</td>
<td>0.82</td>
<td>0.72</td>
<td>1.04a</td>
<td>0.72 (0.07)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.88</td>
<td>0.95</td>
<td>0.96a</td>
<td>0.88</td>
<td>0.98</td>
<td>0.90</td>
<td>0.80</td>
<td>0.92</td>
<td>0.87 (0.10)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.47</td>
<td>0.47</td>
<td>0.63a</td>
<td>0.65a</td>
<td>0.59</td>
<td>0.62a</td>
<td>0.65a</td>
<td>0.51</td>
<td>0.48 (0.06)</td>
</tr>
<tr>
<td>Striatal</td>
<td>0.90a</td>
<td>1.26a</td>
<td>1.50a</td>
<td>1.40a</td>
<td>1.77a</td>
<td>0.83a</td>
<td>1.17a</td>
<td>1.49a</td>
<td>0.63 (0.09)</td>
</tr>
<tr>
<td>Neocortex</td>
<td>0.54</td>
<td>0.80a</td>
<td>1.24a</td>
<td>0.96a</td>
<td>1.39a</td>
<td>0.76</td>
<td>0.72</td>
<td>0.93a</td>
<td>0.60 (0.08)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; HCs, healthy control subjects; SUVR, standardized uptake value ratio.

aSignificantly different from HCs ($t$ score, $>2$).
bSevere caudate nuclei atrophy.
cThe mean of the SUVRpons for frontal, cingulate, parietal, lateral temporal, and occipital cortex.

In vivo amyloid PET imaging has allowed new insights on Aβ deposition in the brain, facilitating research into the causes, diagnosis, and future treatment of dementia in which Aβ may have a role.12,13,26 We examined the pattern and degree of PiB retention in familial cases with PSEN1 and APP mutations. All mutation carriers showed some degree of increased PiB retention. Although the degree of cortical retention was generally lower than that usually observed in SAD, the striatal retention was remarkably high. Early onset and rapid progression of the disease indicate that other factors besides Aβ deposition have a role in the cognitive impairment process in FAD, in which Aβ upregulation and deposition represent an early and necessary but not sufficient immediate cause of cognitive decline.

The pattern of PiB retention was similar to that reported in 2 previous studies20,21 of PSEN1 mutation carriers. Postmortem studies21,27 of patients with FAD had shown Aβ deposits in the striatum. The high PiB retention in the striatum is difficult to reconcile with the clinical phenotype given the similar symptoms in SAD, in which this pattern of retention is not observed. However, this pattern is constant across different mutation types, and it has been proposed that Aβ deposition in FAD starts in the striata.20 High striatal PiB retention was accompanied by significant retention in the frontal regions, although the retention was not as high as that observed in SAD. As in a high percentage of HCs, PiB retention is observed in the frontal and posterior cingu-
late regions of a significant proportion of cognitively unimpaired or minimally impaired mutation carriers. These findings in mutation carriers are in agreement with postmortem findings showing that a high percentage of non-demented older individuals have amyloid plaques (with deposits occurring well before the onset of dementia) and with evidence indicating that neuropathologic changes precede the clinical phenotype by many years.

At least 3 of 8 mutation carriers in our study demonstrated marked atrophy on MR imaging. Most extrastriatal PiB retention was confined to the ventrofrontal regions, with 4 mutation carriers showing a pattern of cortical PiB retention similar to the pattern observed in SAD.

Semiquantitative measures of Aβ burden are usually generated by normalizing the regional SUV to the cerebellum, a region unaffected by senile plaque deposition in SAD.

In contrast, mutation carriers in our study showed a pattern of Aβ deposition different from that of subjects with probable SAD, with higher PiB retention in the cerebellum of mutation carriers reflecting cerebellar Aβ deposition (Table 2).

Postmortem measurements of the distribution and density of diffuse and neuritic Aβ plaques have not consistently correlated with the degree of cognitive impairment in AD. The best correlation has been observed with neurofibrillary tangles and soluble levels of Aβ.

While the exact mechanism by which Aβ might produce synaptic loss and neuronal death is controversial, it is likely that PiB retention in non-demented individuals and in cognitively unimpaired or minimally impaired mutation carriers reflects preclinical AD in a classic neuropathologic view. This “delay” in the manifestation of the phenotype may be attributed to different idiosyncratic or cellular susceptibility or vulnerability to Aβ, variations in Aβ conformation affecting toxicity or PiB binding, or both. There is also the issue of mutation type, whereby some PSEN1 mutations are more aggressive and evolve faster than others, while others are associated with movement disorders such as spastic paraparesis or extrapyramidal signs. Larner and Doran have reviewed the phenotypic manifestations of some of the PSEN1 mutations discussed herein. These hypotheses would justify early involvement of the striatum and would help explain why some older individuals with significant Aβ burden are cognitively unimpaired, while others with genetic predisposing factors (despite lower Aβ burden) have already developed the full clinical AD phenotype.

Regarding PiB binding to different Aβ species with or without posttranslational modification or in a fibrillar oligomer or monomer form, it has been reported that PiB binds with higher affinity to one kind of N-terminally truncated Aβ1-42 species in senile plaques, specifically that truncated at position 3 (Aβ3[pE]), displaying a 5-fold higher affinity for Aβ3[pE] than for Aβ1-42. This is relevant to PiB binding because, besides the usual senile and diffuse plaques observed in SAD, cotton wool plaques are observed in the brains of PSEN1 mutation carriers. Cotton wool plaques are generally large with a clear rim and are composed mainly of neurofilament and Aβ12 species, ubiquitously located in the cortex and basal ganglia. Cotton wool plaques are particularly important not only because of their distribution in the striatum and cortex but also because they are mildly stained with thioflavin S, in contrast to conventional Aβ plaques seen in SAD or normal aging. Cotton wool plaques should be studied more extensively to explain their etiologic mechanism and how they might contribute to the different patterns of PiB retention among FAD.

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Table 3. Individual Cerebral Regional Fluorodeoxyglucose F 18 Uptake SUVRpons, in Familial AD, 30 HCs, and 30 Subjects With Probable Sporadic AD

<table>
<thead>
<tr>
<th>Location</th>
<th>Mean (SD)</th>
<th>Location</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; L219P*</td>
<td>1.32</td>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; dE9</td>
<td>1.40</td>
</tr>
<tr>
<td>APP V717L</td>
<td>1.30</td>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; Y115C</td>
<td>1.43</td>
</tr>
<tr>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; C236T</td>
<td>1.23</td>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; L85P</td>
<td>0.80(*)</td>
</tr>
<tr>
<td>PSEN1&lt;sub&gt;1&lt;/sub&gt; L737S</td>
<td>0.89(*)</td>
<td>HCs</td>
<td>1.43(0.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sporadic AD</td>
<td>1.20(0.16)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; HCs, healthy control subjects; NA, not applicable; SUVR, standardized uptake value ratio.

*Significantly different from HCs (z score, >2).

**Severe caudate nuclei atrophy.

*The mean of the SUVRpons for posterior cingulate, parietal, and lateral temporal cortex.
SAD, and normal aging. Longitudinal studies combined with postmortem assessment of Aβ are needed to elucidate this point.

Although PiB investigations (in accord with previous studies) showed higher Aβ burden in the striata of all of the mutation carriers studied herein, there was no clear pattern of FDG hypometabolism, neither the typical temporoparietal hypometabolism observed in SAD nor the more restricted temporoparietal hypometabolism reported in asymptomatic at-risk subjects with known APP or chromosome 14–linked mutations and in subjects with a strong family history of AD. Despite their having generally lower FDG uptake than HCs, most mutation carriers did not show significant regional differences vs HCs or subjects with probable SAD. The reason may be the variance of FDG uptake among HCs and subjects with probable SAD, a variance that precluded achieving higher z scores among the mutation carriers. The 2 subjects with extremely low FDG uptake (the PSEN1 and PSEN1, mutation carriers) also have the most severe brain atrophy and the most severe cognitive impairment. The third subject with atrophy and marked cognitive impairment (the PSEN1 mutation carrier) showed an asymmetric pattern of FDG uptake. In FAD as in SAD, PiB seems to be a more sensitive and accurate biomarker than FDG for early detection of disease. This might be because Aβ deposition starts approximately 10 years before any cognitive or memory decline is noted and much earlier than the synaptic and neuronal loss that is reflected in regional glucose hypometabolism. Conversely, FDG uptake correlates with MMSE score and might prove to be a better marker of disease progression than PiB. Evaluation of more familial mutation cases with PiB and longitudinal follow-up are warranted to establish the usefulness of PiB as an early and reliable method of detecting Aβ deposition and assessing its prognostic accuracy. An international consortium, the Dominantly Inherited Alzheimer Network (http://www.dian-info.org/), has been organized to

Figure 2. Correlational analysis. Pearson product moment correlation linear correlation analysis shows lack of association between striatal or neocortical Pittsburgh Compound B (PiB) retention and disease severity data or years from onset for the respective pedigrees. Conversely, there are strong correlations between the same variables and fluorodeoxyglucose F 18 (FDG) posterolateral uptake. CDR indicates Clinical Dementia Rating; MMSE, Mini-Mental State Examination; and SUVR, standardized uptake value ratio.
comprehensively assess the origin of AD through FAD and to evaluate the usefulness of different biomarkers such as amyloid imaging. This kind of multidisciplinary approach should define the role of amyloid imaging in the evaluation of asymptomatic mutation carriers at risk of developing FAD.

In conclusion, although Aβ deposition (as in SAD) seems to precede the clinical manifestation of dementia, the pattern of Aβ deposition in FAD is not related to disease severity (irrespective of mutation type) differs from that observed in SAD. When disease-specific therapies aimed at preventing or slowing AD progression become available, amyloid imaging studies will have an important role in the identification of Aβ deposits in at-risk mutation carriers before the development of symptoms.

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