Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition

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Objective: APOE ε4 status has been associated with greater cortical amyloid deposition, whereas exercise has been associated with less in cognitively normal adults. The primary objective here was to examine whether physical exercise moderates the association between APOE genotype and amyloid deposition in cognitively normal adults.

Design: APOE genotyping data and answers to a questionnaire on physical exercise engagement over the last decade were obtained in conjunction with cerebrospinal fluid (CSF) samples and amyloid imaging with carbon 11–labeled Pittsburgh Compound B ([11C]PiB) positron emission tomography. Participants were classified as either low or high exercisers based on exercise guidelines of the American Heart Association.

Setting: Knight Alzheimer’s Disease Research Center at Washington University, St Louis, Missouri.

Participants: A total of 201 cognitively normal adults (135 of whom were women) aged 45 to 88 years were recruited from the Knight Alzheimer’s Disease Research Center. Samples of CSF were collected from 165 participants. Amyloid imaging was performed for 163 participants.

Results: APOE ε4 carriers evidenced higher [11C]PiB binding (P < .001) and lower CSF Aβ42 levels (P < .001) than noncarriers. Our previous findings of higher [11C]PiB binding (P = .005) and lower CSF Aβ42 levels (P = .009) in more sedentary individuals were replicated. Most importantly, we observed a novel interaction between APOE status and exercise engagement for [11C]PiB binding (P = .008) such that a more sedentary lifestyle was significantly associated with higher [11C]PiB binding for ε4 carriers (P = .013) but not for noncarriers (P = .20). All findings remained significant after controlling for age; sex; educational level; body mass index; the presence or history of hypertension, diabetes mellitus, heart problems, or depression; and the interval between assessments.

Conclusion: Collectively, these results suggest that cognitively normal sedentary APOE ε4–positive individuals may be at augmented risk for cerebral amyloid deposition.

It has been suggested that APOE status may modify associations between lifestyle factors such as exercise engagement and risk of cognitive decline and dementia. Several examinations of potential interactive effects of APOE status and physical activity on cognitive decline have yielded mixed findings, with reports of greater beneficial effects of exercise for ε4 carriers, no difference between ε4 carriers and noncarriers in exercise effects, and greater benefits for noncarriers than ε4 carriers. By contrast, the interactive effects of APOE status and physical exercise on amyloid deposition have not been fully investigated. The goal of the present study was to assess whether exercise moderates the effects of APOE status on amyloid deposition in a cohort of cognitively normal older adults. The primary hypotheses were that (1) APOE ε4 status would be associated with greater amyloid deposition, (2) exercise engagement would be associated with lower amyloid deposition, and (3) a sedentary lifestyle would have a greater effect on amyloid deposition in APOE ε4–positive individuals.

MEASUREMENT OF PHYSICAL EXERCISE ENGAGEMENT

Validity

A validated questionnaire assessing history of walking, running, and jogging activity for the past 10 years was used to estimate exercise engagement. The measure was significantly correlated with cardiorespiratory fitness measured via a treadmill test in a sample of 5063 individuals aged 18 to 80 years. Stable correlations were observed between the retrospective self-report of activity for a particular year and the aerobic fitness for that year across 10 1-year assessment periods, suggesting that the participants across the examined age range were capable of a relatively accurate self-report over an extended time span. Correlations were similar with and without controlling for age, which suggests that age was not a significant contributor to the observed associations.

Procedure

The questionnaire was administered by telephone, and participants reported the number of months per year, the number of workouts per week, the average number of miles per workout, and average time per mile for each year in which they engaged in walking, running, and jogging activity for the preceding 10 years. A physical exercise engagement score was derived for each participant by estimating metabolic equivalent values using the compendium of physical activities. The index of exercise engagement was the average metabolic equivalent value in units of hours per week over the past 10 years.

The distribution of exercise engagement scores was zero-inflated and heavily skewed. Transformations (eg, logarithmic) could not resolve these distributional issues. Therefore, rather than treating the exercise engagement score as a continuous variable, participants were categorized into low- and high-exercise engagement groups based on whether reported exercise levels were at or above 7.5 metabolic equivalent hours/week for moderate exercise 5 days/week) recommended by the American Heart Association (AHA).

CSF COLLECTION, PROCESSING, AND BIOMARKER MEASUREMENT

Samples of CSF free from blood contamination were collected by lumbar puncture in polypropylene tubes at 8:00 AM after overnight fasting, as described previously. Samples were gently inverted to avoid gradient effects, briefly centrifuged at low speed to pellet any cellular elements, and aliquoted (500 µL) into polypropylene tubes before freezing at −84°C. Analyses for Aβ42 were completed using a commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics). Samples were continuously kept on ice, with only a single thaw after initial freezing before assaying.

POSITRON EMISSION TOMOGRAPHIC PiB IMAGING

In vivo amyloid imaging via positron emission tomography (PET) with [11C]PiB was performed as described previously. Approximately 12 mCi of [11C]PiB was administrated intravenously simultaneously with the initiation of a 60-minute dynamic PET scan in 3-dimensional mode. Measured attenuation factors and a ramp filter were used to reconstruct dynamic PET images. Three-dimensional regions of interest were then created for each participant based on their individual magnetic resonance imaging scans (T1-weighted 1 × 1 × 1.25-mm magnetization-prepared rapid acquisition gradient-echo sequences). A binding potential for each region of interest was calculated to express regional binding values in a manner proportional to the number of binding sites. The binding potential values from the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions of interest were averaged to calculate a mean cortical binding potential (MCBP) value based
on brain regions known to have high [11C]PiB uptake among participants with AD.40 This derived MCBP value has been shown to correlate inversely with CSF Aβ42 level39 and exercise engagement,12 to predict progression from cognitively normal status to symptomatic AD,41 and to be associated with disrupted functional connectivity of the default mode.42

APOE GENOTYPING

TaqMan assays (Applied Biosystems) for both rs429358 (ABI#C_3084793_20) and rs7412 (ABI#C_904973_10) were used for APOE genotyping. Allele calling was performed using the allelic discrimination analysis module of ABI Sequence Detection Software. Positive controls for each of the 6 possible APOE genotypes were included on the genotyping plate. Individuals were then classified as being positive24,34,43 or negative22,23,33 for ε4.

TIMING OF ASSESSMENTS

The mean (SD) interval between the clinical assessment and the PET scan was ±6.0 (12.4) months. The mean (SD) interval between the clinical assessment and the CSF assessment was ±2.9 (3.9) months. The mean (SD) interval between clinical and exercise assessments was ±3.4 (7.7) months for the [11C]PiB sample and ±3.3 (7.6) months for the CSF sample. Individuals had a Clinical Dementia Rating of 0 at all assessments.

The mean (SD) interval between the exercise assessment and the PET scan was ±0.92 (1.3) years. For 105 of 163 individuals, the exercise assessment was subsequent to the PET scan and thus captured exercise behavior during the time of the PET scan. For the remaining 58 individuals, the exercise assessment was prior to the PET scan by a mean (SD) of −0.33 (0.33) years. Thus, for these individuals, the reported exercise behavior would have occurred almost exclusively during a time period prior to the PET scan.

The mean (SD) interval between the exercise assessment and the CSF assessment was ±1.6 (2.2) years. For 113 of 165 individuals, the exercise assessment was subsequent to the CSF assessment and thus captured exercise behavior during the time of the CSF assessment. For the remaining 52 individuals, the exercise assessment was prior to the CSF assessment by a mean (SD) of −0.28 (0.34) years. Thus, for these individuals, the reported exercise behavior would have occurred almost exclusively during a time period prior to the CSF assessment.

STATISTICAL ANALYSES

All analyses were conducted using SPSS/PASW version 17.0 (SPSS Inc). We first tested for group differences (ie, exercise group and APOE status) in demographic and health variables using the Student t test for continuous variables and the Fisher exact test for dichotomous variables (Tables 1 and 2).

We used hierarchical multiple regression (using ordinary least squares method) to examine the unique variance accounted for by the exercise group × APOE status interaction above and beyond the main effects (ie, exercise group and APOE status) for each of the separate estimates of amyloid deposi-
There were separate regression models for each complete cohort (i.e., MCBP and CSF Aβ42 level) with no missing data points. The main effects of exercise group and APOE status were entered in one step, and the exercise group × APOE status interaction term was entered in the next step. Importantly, a significant interaction indicates that exercise group exerts a moderating effect on the influence of APOE status on amyloid deposition above and beyond the influence of either exercise group or APOE status alone. All statistical significance tests were 1-tailed because we had a priori directional hypotheses regarding the main and interactive effects, and α = .05.

RESULTS

MCBP COHORT

There were significant APOE group differences in age (P = .03) and a nonsignificant trend for a group difference in presence or history hypertension (P = .07). In addition, there were significant exercise group differences in educational level (P = .04) and presence or history of hypertension (P = .04) and a nonsignificant trend for BMI (P = .09). Lastly, there was a significant correlation between MCBP and age (P = .02). No other associations with demographic or health variables reached or approached significance (all P > .15). Thus, age, educational level, BMI, and presence or history of hypertension were included as covariates in the first step in the model examining MCBP. Because there was evidence of mild-to-moderate heteroscedasticity in the initial ordinary least squares model (White's test = 43.20; P = .03), robust regression was conducted and is reported (results were equivalent for ordinary least squares and robust regression).

In the regression model examining MCBP (Table 3), there were significant exercise group (P < .001) and APOE status (P < .001) differences. High-exercise individuals had lower MCBP compared with low-exercise individuals (mean difference, −0.079 [95% CI, −0.124 to −0.034]), and ε4-positive individuals had higher MCBP compared with ε4-negative individuals (mean difference, 0.141 [95% CI, 0.071–0.211]). There was a significant exercise group × APOE status interaction (P = .002; Figure 1) that reflected a greater exercise effect on MCBP in ε4-positive individuals (mean difference between exercise groups, 0.183 [95% CI, −0.308 to 0.059]) compared with ε4-negative individuals (mean difference between exercise groups, −0.019 [95% CI, −0.052 to 0.014]). Notably, results were similar when other potentially confounding demographic and health variables (i.e., sex and the presence or history of diabetes, heart problems, or depression) and the delay between the PET scan and exercise assessment were additionally included as covariates (exercise

<table>
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<tr>
<th>Characteristic</th>
<th>PIB-PET Sample (n = 38)</th>
<th>Nonexercisers (n = 125)</th>
<th>CSF Aβ42 Sample (n = 35)</th>
<th>Nonexercisers (n = 130)</th>
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<td>Age, mean (SD), y</td>
<td>65 (9)</td>
<td>67 (10)</td>
<td>66 (9)</td>
<td>67 (10)</td>
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<td>Sex, No.</td>
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<tr>
<td>Male</td>
<td>13</td>
<td>39</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>86</td>
<td>22</td>
<td>90</td>
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<td>Education, mean (SD), y</td>
<td>17 (3)</td>
<td>16 (3)(^a)</td>
<td>16 (3)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27 (5)</td>
<td>29 (6)(^a)</td>
<td>26 (4)</td>
<td>29 (6)(^b)</td>
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<td>MMSE, mean (SD), score</td>
<td>29.4 (0.9)</td>
<td>29.1 (1.2)</td>
<td>29.3 (1.0)</td>
<td>29.2 (1.2)</td>
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<td>2</td>
<td>12</td>
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<td>15</td>
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<td></td>
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<tr>
<td>No</td>
<td>27</td>
<td>69(^a)</td>
<td>26</td>
<td>72(^a)</td>
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<tr>
<td>Yes</td>
<td>11</td>
<td>56(^a)</td>
<td>9</td>
<td>58(^a)</td>
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<td>113</td>
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<td>14</td>
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<td>17</td>
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<td>106</td>
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<td>Yes</td>
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<td>5</td>
<td>17</td>
</tr>
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<td>GDS, mean (SD), score</td>
<td>1.1 (1.6)</td>
<td>1.1 (1.5)</td>
<td>1.3 (1.8)</td>
<td>1.0 (1.5)</td>
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<td>APOE ε4 carrier, No.</td>
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<td></td>
<td></td>
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<td>86</td>
<td>22</td>
<td>87</td>
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<tr>
<td>Yes</td>
<td>13</td>
<td>39</td>
<td>13</td>
<td>43</td>
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<tr>
<td>Exercise, mean (SD), MET h/wk</td>
<td>14.95 (8.83)</td>
<td>2.12 (2.28)(^b)</td>
<td>13.88 (7.97)</td>
<td>2.14 (2.17)(^b)</td>
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<td>MCBP, mean (SD)</td>
<td>0.01 (0.06)</td>
<td>0.09 (0.29)(^b)</td>
<td></td>
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<td>Aβ42 level, mean (SD), pg/mL</td>
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</table>
Table 3. Regression Results for MCBP Cohort

<table>
<thead>
<tr>
<th>Effect</th>
<th>( \Delta R^2 )</th>
<th>( F ) Value</th>
<th>Unstandardized Coefficient (95% CI)</th>
<th>Standardized Coefficient</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effects step</td>
<td>0.167</td>
<td>( F_{158} = 16.707 )</td>
<td>-0.079 (-0.124 to -0.034)</td>
<td>-0.188</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.141 (0.071-0.211)</td>
<td>0.371</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.029</td>
<td>( F_{155} = 6.021 )</td>
<td>-0.154 (-0.257 to -0.050)</td>
<td>-0.236</td>
<td>.002</td>
</tr>
<tr>
<td>AHA exercise group ( \times ) APOE status</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: AHA, American Heart Association; MCBP, mean cortical binding potential.

Figure 1. Association between APOE status and exercise engagement for the mean cortical binding potential (MCBP). There was a significant APOE status \( \times \) exercise engagement interaction such that a more sedentary lifestyle was significantly associated with higher carbon 11-labeled Pittsburgh Compound B uptake for \( \varepsilon 4 \) carriers but not for noncarriers. Error bars represent standard error of measurement.

CSF A\( \beta 42 \) COHORT

There were significant APOE group differences in age (\( P = .02 \)), BMI (\( P = .014 \)), and presence or history of hypertension (\( P = .012 \)) and significant exercise group differences in BMI (\( P < .001 \)) and presence or history of hypertension (\( P = .02 \)). No other associations approached or reached significance. Thus, age, BMI, and presence or history of hypertension were included as covariates in the first step in the model examining CSF A\( \beta 42 \) levels. There was no evidence of heteroscedasticity (White’s test = 21.11; \( P = .39 \)), so the ordinary least squares regression results are reported.

In the regression model examining CSF A\( \beta 42 \) levels (Table 4), there were significant exercise group (\( P = .005 \)) and APOE status (\( P < .001 \)) differences (Figure 2). Low-exercise individuals had lower CSF A\( \beta 42 \) compared with high-exercise individuals (mean difference, 96.08 [95% CI, 17.21-174.95]), and \( \varepsilon 4 \)-positive individuals also had lower CSF A\( \beta 42 \) compared with \( \varepsilon 4 \)-negative individuals (mean difference, -159.18 [95% CI, -227.90 to -90.45]). However, the exercise group \( \times \) APOE status interaction was not significant (\( P = .41 \)). Thus, the exercise effect on CSF A\( \beta 42 \) level did not differ between \( \varepsilon 4 \)-positive individuals (mean difference between exercise groups, 80.11 [95% CI, -41.37 to 201.58]) and \( \varepsilon 4 \)-negative individuals (mean difference between exercise groups, 102.48 [95% CI, -2.35 to 207.32]). Notably, results were similar when other potentially confounding demographic and health variables (ie, sex; educational level; and presence or history of diabetes, heart problems, or depression) and the delay between lumbar puncture and exercise assessment were included as covariates (exercise group, \( P = .011 \); APOE status, \( P < .001 \); exercise group \( \times \) APOE status interaction, \( P = .37 \)).

APOE status is associated with increased risk of cognitive decline and elevated amyloid deposition.\(^6,10-13\) In contrast, exercise engagement has been associated with reduced risk of cognitive decline\(^19,20\) and lower levels of amyloid deposition.\(^12\) In the present investigation, we sought to replicate the effects of APOE genotype and exercise engagement on amyloid deposition and to further examine whether exercise moderates the effects of APOE genotype on amyloid deposition.

Consistent with several past findings,\(^12-15\) the presence of an APOE \( \varepsilon 4 \) allele was associated with elevated amyloid deposition as assessed with a [\(^{11}\)C]PiB-PET scan. In addition, we observed lower [\(^{11}\)C]PiB binding for individuals who exercised at or above levels recommended by the AHA, similar to our previous study\(^12\) of 69 individuals. However, herein we report the novel finding of a significant interaction between APOE and exercise engagement for cerebral amyloid burden. Specifically, a significant effect of exercise engagement was present for APOE \( \varepsilon 4 \) carriers but not for noncarriers, with sedentary \( \varepsilon 4 \)-positive individuals having greater MCBP values compared with active \( \varepsilon 4 \)-positive individuals. In fact, post hoc analyses indicate that the magnitude of MCBP was equivalent between active \( \varepsilon 4 \)-positive individuals and all \( \varepsilon 4 \)-negative individuals (\( t = 0.07; P = .41 \)) and between active \( \varepsilon 4 \)-positive individuals and all \( \varepsilon 4 \)-negative individuals (\( t = -0.722; P = .24 \)). Collectively, these findings suggest that the combination of \( \varepsilon 4 \)-positive status and a sedentary lifestyle may place individuals at augmented risk for amyloid deposition, as assessed via [\(^{11}\)C]PiB PET. This result remained robust after controlling for significant group differences in demographic and health variables, and after controlling for additional health variables that did not differ between groups but may have potentially contributed to the observed findings.
A greater effect of exercise engagement in APOE ε4 carriers is consistent with and extends existing data demonstrating increased risk of cognitive decline and dementia in sedentary ε4-positive individuals.26-33 Greater exercise-related improvements in cognitive performance and markers of hippocampal plasticity in APOE ε4 transgenic mice is also supportive of the differential benefits for ε4 carriers.34 The APOE ε4 allele appears to be associated with reduced neuronal plasticity,35,36 and it has been argued that this inherent neurophysiological disadvantage makes beneficial lifestyle factors, such as exercise, preferentially important for ε4 carriers.28,37 The MCBP findings support the idea that a physically active lifestyle may allow ε4 carriers to experience brain amyloid levels equivalent to ε4-negative individuals. Although the mechanisms through which exercise may influence amyloid deposition remain unclear, there may be both relatively direct effects on amyloid precursor protein metabolism21,40,47 and indirect effects through influences on neurotrophic factors, neuroinflammation, cerebrovascular functioning, or glucose metabolism.46-48

In terms of CSF Aβ42, we again observed that the APOE ε4 allele had a negative influence, with ε4-positive individuals having lower CSF Aβ42 levels, consistent with past reports.12-15 Exercise engagement was again associated with a more beneficial profile such that those who met AHA recommendations had higher CSF Aβ42 levels. However, there was no interaction between APOE status and exercise engagement for CSF Aβ42 level. Unlike for MCBP, sedentary ε4-positive individuals did not have a significantly greater effect of exercise engagement on CSF Aβ42 level compared with active ε4-positive individuals.

The reason for the discrepancy between MCBP and CSF Aβ42 is uncertain. The 2 largely reflect complimentary estimates of the same process of amyloid plaque development in the brain and are strongly associated.38,49 However, [11C]PiB PET identifies only fibrillar Aβ, whereas CSF Aβ42 levels may reflect nonfibrillar Aβ species as well.30-32 In addition, although CSF Aβ42 estimates could conceivably reflect amyloid deposition in various regions of the brain, the MCBP estimate represents select regions of high amyloid deposition, and this difference may contribute to our findings. It is also possible that our sample size was insufficient to detect differences in exercise effects on APOE groups in terms of CSF Aβ42.

The present investigation provides support for an association between exercise engagement and amyloid deposition, with stronger associations in ε4-positive individuals in terms of MCBP. However, several limitations must be considered. It is conceivable that some confounding factors not assessed here (eg, socioeconomic status, ability to engage in physical exercise, and personality) may have influenced our results and are thus relevant to examine in future investigations. Inferences about causal flow between exercise and amyloid deposition are not possible given the cross-sectional design. Although it is possible that subclinical dementia may have subtly influenced exercise engagement or reporting of exercise in ε4-positive individuals, neither the proportion of individuals meeting AHA-recommended levels nor the mean exercise levels differed between APOE groups. Another potential concern is the use of a self-report measure of exercise engagement and the administration of the questionnaire by telephone in contrast to the in-person interview used in the validation study.37 Furthermore, the measure is significantly, but not perfectly, correlated with cardiorespiratory fitness. Although the validation sample included older adults and although the magnitudes of association with cardiorespiratory fitness were similar with and without controlling for age, the measure may still be limited by older adults’ ability to accurately recall and report their exercise behavior over an extended period of time.

In summary, our findings suggest that exercise at levels recommended by the AHA may be particularly ben-
eficial in reducing the risk of brain amyloid deposition in cognitively normal ε4-positive individuals. Longitudinal investigations and intervention studies that incorporate measures through which exercise may influence amyloid deposition are warranted to address causality and mechanisms.

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Author Contributions: Study concept and design: Head and Bugg. Acquisition of data: Head, Bugg, Goate, Fagan, Mintun, Benzinger, and Morris. Analysis and interpretation of data: Head, Bugg, Mintun, and Holtzman. Drafting of the manuscript: Head and Bugg. Critical revision of the manuscript for important intellectual content: Head, Bugg, Goate, Fagan, Mintun, Benzinger, Holtzman, and Morris. Obtained funding: Goate, Holtzman, and Morris. Administrative, technical, and material support: Head, Fagan, Mintun, Benzinger, and Morris. Study supervision: Goate, Holtzman, and Morris.

Financial Disclosure: Dr Goate reports that she has received consultancy fees from AstraZeneca, has provided expert testimony to Howrey & Associates, and has received payment for lectures, including service on speakers bureaus, from Pfizer, AstraZeneca, and Genentech and royalties from Taconic, and that her institution has received grants from AstraZeneca, Genentech, and Pfizer. Dr Holtzman reports that he has consulted for Pfizer, Bristol-Myers Squibb, Innogenetics, and Medtronic and is on the scientific advisory boards of EnVivo, Satori, and C2N Diagnostics and that he has received research grants from AstraZeneca, Eli Lilly, and C2N Diagnostics.

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REFERENCES


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Correction

Error in Figure. In the article titled “Archetypal and New Families With Alexander Disease and Novel Mutations in GFAP” by Messing et al published in the February issue of the Archives (2012;69[2]:208-214), 2 of the symbols in Figure 1 are incorrect. In Figure 1B, the symbol for patient V.C should not have the slash. In Figure 1C, the symbol for patient III.1 should be filled in, with a slash, and with a plus sign at the upper left.