RESEARCH ARTICLE

Pattern and degree of individual brain atrophy predicts dementia onset in dominantly inherited Alzheimer’s disease

Ophir Keret1 | Adam M. Staffaroni2 | John M. Ringman3 | Yann Cobigo2 | Sheng-Yang M. Goh2 | Amy Wolf2 | Isabel Elaine Allen1,4 | Stephen Salloway5 | Jasmeer Chhatwal6 | Adam M. Brickman7 | Dolly Reyes-Dumeyer7 | Randal J. Bateman8,9,10,11,12 | Tammie L.S. Benzinger,8,10 | John C. Morris8,9,10,11,12 | Beau M. Ances8,9,10,11,12 | Nelly Joseph-Mathurin8,9,10,11,12 | Richard J. Perrin8,9,10,11,12 | Brian A. Gordon8,9,10,11,12 | Johannes Levin13,14 | Jonathan Vöglein13,14 | Mathias Jucker15,16 | Christian la Fougère15,17 | Ralph N. Martins18,19,20,21,22 | Hamid R. Sohrabi18,19,20,21,22 | Kevin Taddei19,21 | Victor L. Villemagne23 | Peter R. Schofield24,25 | William S. Brooks24,26 | Michael Fulham27 | Colin L. Masters28 | Bernardino Ghetti29 | Andrew J. Saykin30,31 | Clifford R. Jack32 | Neill R. Graff-Radford33 | Michael Weiner34,35,36,37,38 | David M. Cash39,40 | Ricardo F. Allegri41 | Patricio Chrem41 | Su Yi42 | Bruce L. Miller1,2 | Gil D. Rabinovic1 | Howard J. Rosen1,2 | Dominantly Inherited Alzheimer Network

1 Global Brain Health Institute, University of California, San Francisco, California, USA
2 Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA
3 Alzheimer’s Disease Research Center, Keck School of Medicine, University of Southern California, Los Angeles, California, USA
4 Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA
5 Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
6 Massachusetts General Hospital, Harvard Medical School Boston, Boston, Massachusetts, USA
7 Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, Columbia University, New York, New York, USA
8 Charles F. and Joanne Knight Alzheimer Disease Research Center, Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA
9 Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA
10 Department of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA
11 Division of Neuropathology, Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, Missouri, USA
12 Division of Biostatistics, Department of Psychiatry, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA
13 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
14 German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
15 German Center for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
16 Institute for Nuclear Medicine and Clinical Molecular Imaging, Eberhard Karls University, Tübingen, Germany
17 Department of Biomedical Sciences, Macquarie University, North Ryde, New South Wales, Australia
18 Centre of Excellence for Alzheimer’s Disease Research and Care, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia

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Abstract

Introduction: Asymptomatic and mildly symptomatic dominantly inherited Alzheimer’s disease mutation carriers (DIAD-MC) are ideal candidates for preventative treatment trials aimed at delaying or preventing dementia onset. Brain atrophy is an early feature of DIAD-MC and could help predict risk for dementia during trial enrollment.

Methods: We created a dementia risk score by entering standardized gray-matter volumes from 231 DIAD-MC into a logistic regression to classify participants with and without dementia. The score’s predictive utility was assessed using Cox models and receiver operating curves on a separate group of 65 DIAD-MC followed longitudinally.

Results: Our risk score separated asymptomatic versus demented DIAD-MC with 96.4% (standard error = 0.02) and predicted conversion to dementia at next visit (hazard ratio = 1.32, 95% confidence interval [CI: 1.15, 1.49]) and within 2 years (area under the curve = 90.3%, 95% CI [82.3%–98.2%]) and improved prediction beyond established methods based on familial age of onset.

Discussion: Individualized risk scores based on brain atrophy could be useful for establishing enrollment criteria and stratifying DIAD-MC participants for prevention trials.

KEYWORDS
autosomal dominant Alzheimer’s disease, brain atrophy, Dominantly Inherited Alzheimer Network, preclinical Alzheimer’s disease
1 | INTRODUCTION

Alzheimer’s disease (AD) is a devastating progressive neurodegenerative disease with high worldwide prevalence. Recent drug trials for patients with dementia and underlying AD have failed to show meaningful benefit.1,2 One potential explanation for the failure to demonstrate efficacy is that the interventions were given at disease stages that are too late to alter clinical progression.2 Many ongoing trials are attempting treatment at an earlier stage, such as at the time of mild cognitive symptoms or before the onset of cognitive symptoms.3,4 To evaluate the ability of these interventions to prevent development of dementia, researchers need to recruit individuals with a very high risk of developing symptoms of dementia over the duration of a clinical trial (usually 1 or 2 years).3 Carriers of mutations in genes that cause dominantly inherited AD (DIAD), such as presenilin-1 (PSEN1), presenilin-2 (PSEN2), and amyloid precursor protein (APP), are certain to develop dementia, and thus are ideal candidates for AD prevention studies.

Nearly all DIAD mutation carriers (DIAD-MC) develop dementia. Although the time until the onset of dementia can be estimated based on the age of symptom onset from individuals with the same type of mutation,6 variability of several years is frequently observed, and this can occur even within the same family.7

Another approach for approximating time to symptom onset is to use established biological markers of disease (biomarkers). Similar to sporadic AD, DIAD-MC undergo biological changes years before the onset of dementia.9,10 Such changes can be measured with magnetic resonance imaging (MRI);6,8,10–17 cerebrospinal fluid (CSF) levels of amyloid beta (Aβ) and phosphorylated tau and total tau;6,8,12,18 and positron emission tomography (PET) radiotracers that measure glucose metabolism,6,8,12 Aβ fibrils, and tau accumulation.19 Indeed, previous studies have shown that changes in many of these biomarkers precede cognitive decline in DIAD-MC.12 Some of the aforementioned imaging modalities are expensive, involve exposure to ionizing radiation, and are relatively scarce in many parts of the world. It is thus encouraging that baseline hippocampal volume and change in hippocampal volume over time, which can be measured from MRI, are both predictive of decline in DIAD-MC.12 Changes in volume in other brain regions are also predictive of cognitive decline in DIAD-MC.10,14 This would be expected given that cognition is dependent on many brain regions and that AD characteristically spreads through the brain as disease advances.20 Prior studies in sporadic AD have indicated that measurements of volume across the brain can predict likelihood of developing dementia.21,22 Together, these findings suggest that quantification of volume loss across the brain might provide a good predictor of time to onset of dementia. If such an estimate could be derived from a single measurement, it would further improve its value, for instance by allowing people who appear far from dementia to defer follow-up for a longer period compared to those in whom dementia is imminent.

Individualized atrophy-based risk scores have been previously reported to predict symptom onset in asymptomatic carriers of mutations that cause frontotemporal dementia.23 The risk score uses calculated atrophy in each brain region at a single time point to predict the individual’s risk for dementia at subsequent visits. The aim of the current study was to evaluate whether a similar method is useful in DIAD and to assess its added benefit beyond the estimated years to onset (EYO) that is calculated based on the reported age of onset for each specific DIAD mutation.

2 | METHODS

2.1 | Overview

Our analysis was conducted in two stages. The first stage used logistic regression in cognitively normal DIAD-MC participants and DIAD-MC patients with established dementia at study entry to identify a pattern of atrophy associated with the presence of dementia and to develop a dementia risk score that can be calculated based on the similarity of a given individual’s regional brain volumes to that pattern. In the second stage of the analysis, the risk score was applied to DIAD-MC participants who had not yet developed dementia at study entry and who were followed longitudinally, and the ability of the risk score to predict onset of dementia at follow-up was assessed.

2.2 | Subjects

We included 216 DIAD-MC enrolled in the Dominantly Inherited Alzheimer Network (DIAN; 12th data freeze, 2008 to 2017), and 15 DIAD-MC seen at the Alzheimer’s Disease Research Centers at the University of California Los Angeles (ADRC-UCLA) and University of Southern California (ADRC-USC), as well as 99 non-carrier family members enrolled in DIAN as controls for image analysis. We included the additional ADRC cohort patients because the DIAN dataset contained relatively few cases who had established dementia at study entry.

DIAN is a multicenter study of individuals from families with known causative mutations for AD. Enrolled family members undergo initial genotyping and clinical reassessment every one or more years, including neuroimaging. Subjects can be DIAD-MC or non-carrier family members. The DIAN study receives approval from the institutional review board (IRB) of each participating site. Written informed consent is obtained from all participants or their designated guardians.8

HIGHLIGHTS

- Brain atrophy precedes cognitive decline by years in dominantly inherited Alzheimer’s disease.
- Brain atrophy–based risk scores can predict dementia onset in mutation carriers.
- Risk score can help establish enrollment criteria for Alzheimer’s disease prevention trials.
The ADRC-UCLA and ADRC-USC are both National Institute on Aging–designated research centers that offer extensive clinical, neuroimaging, and molecular profiling of patients with dementia, including DIAD-MC. In the case of DIAD-MC evaluated in ADRC-UCLA or ADRC-USC, the study was approved by each institution’s IRB. Subjects or their proxies gave written approval for study participation.13

Our inclusion criteria included availability of the following data for each individual: age, sex, and functional status data as expressed in Clinical Dementia Rating Global Score (henceforth referred to as CDR), and one or more 3-Tesla T1 structural MRIs.

The 231 DIAD-MC were divided into two groups. A training group (n = 166) was created to identify the atrophy pattern associated with dementia and develop a dementia risk score. This group consisted of 123 participants with CDR = 0 and 43 patients with CDR ≥1 at their first visit. To maximize the likelihood that the images from the CDR = 0 group represented the asymptomatic phase of disease, we only included individuals with a CDR = 0 rating for two consecutive visits. The first study image from each participant was used for training. The testing group consisted of 65 DIAD-MC who did not have dementia at study entry and who were followed longitudinally, and whose images were used to test the risk score. Table 1 summarizes the groups and the amount of DIAD-MC in each.

2.3 Clinical and genetic assessment

Functional status was determined using the CDR. Each individual’s CDR represents a weighted average of six functional domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care). The scale categorizes individuals as asymptomatic (CDR = 0), having very mild symptoms that do not impair independent functioning (CDR = 0.5), or clear symptoms of dementia (CDR ≥ 1). Genotyping methods have been previously described.8,13

The mutation-EYO is a variable that estimates the time until symptom onset and is calculated at each visit by subtracting the participant’s age from the mean age of symptom onset for their specific mutation7 (i.e., negative values indicate conversion is expected to occur in the future).

2.4 Image acquisition

Participants in the DIAN study underwent 3-Tesla volumetric T1-weighted MRI according to the Alzheimer’s Disease Neuroimaging Initiative (ADNI)–defined sequences.25 Matching between scanners and image quality control were performed according to the ADNI protocol by the study imaging core.12 Participants of the ADRC-UCLA and ADRC-USC underwent similar MRI acquisition protocols (see Table S1 in supporting information).

2.5 Image processing

For this study we only analyzed T1-weighted images. We excluded all images with excessive motion and imaging artifacts, as determined by visual inspection. We corrected for magnetic field bias using the N3 algorithm.26 We segmented the remaining images using the unified segmentation procedure in Statistical Parametric Mapping (SPM) version 12 into gray matter (GM), white matter, and CSF.27

The next steps in image processing depended on whether the participant contributed an image from a single observation or multiple longitudinal observations. For the training group, a study-specific template representative of all participants was generated from T1 GM images using diffeomorphic anatomical registration using exponentiated lie algebra.28 The images were subsequently normalized and modulated in the study-specific template space using linear and non-linear registration.

For the testing group, an additional step included creation of an intraparticipant template using nonlinear diffeomorphic and rigid body registration implemented with SPM.29 This process minimizes bias in

| TABLE 1 | Participant demographics and genotype (of three mutated genes causing dominantly inherited Alzheimer’s disease) |
| Control group | Training group | Testing group |
|----------------|----------------|---------------|
| Cohort         |                  |               |
| N (visits)     | 99 (99)         | 123 (123)     | 15 (15)       |
| Follow up Mean ± SD (years) | 2.9 ± 3.4 | 2.79 ± 1.09 | 1.56 ± 1.36 | NA |
| PSEN1          | NA              | 87            | 22            | 15 |
| PSEN2          | NA              | 15            | 0             | 0  |
| APP            | NA              | 21            | 6             | 0  |
| Age Mean ± SD (years) | 38 ± 11.3 | 33.6 ± 9.5 | 48.7 ± 8.8 | 43 ± 6.1 |
| Male %         | 41 (41%)        | 56 (45.5%)    | 14 (50%)      | 9 (60.0%) |
|                |                | 4 (26.6%)     | 5 (25%)       | 11 (36.6%) |
| Abbreviations: ADRC, Alzheimer’s Disease Research Center; APP, amyloid precursor protein; CDR, Clinical Dementia Rating; DIAN, Dominantly Inherited Alzheimer Network; PSEN, presenilin; SD, standard deviation; UCLA, University of California Los Angeles; USC, University of Southern California. |
| aRefers to subjects from the ADRC-UCLA and ARDC-USC. |
| bConverters refers to subject who converted from CDR 0 or from CDR 0.5 to CDR 1, 2, or 3, and to subjects who converted from CDR 0 to CDR 0.5. |
estimating change in volume over time. The group template for this group was generated from the within-participant averaged GM, white matter, and CSF tissue maps by nonlinear and rigid-body registration. All images were then warped into a group template space and smoothed with a 4 mm isotropic Gaussian kernel. We calculated total intracranial volume (TIV) for each participant in group template space.

2.6 Calculation of atrophy burden

For every processed image, we estimated atrophy in each GM voxel by regional voxel estimates of volume relative to a control group of 99 non-carrier asymptomatic family members from the DIAN study. This was done to create a W-score, which is similar to a z-score and represents a standardized estimate of atrophy at that voxel after accounting for age and TIV. We summed the voxel-wise W-scores within 179 regions of interest (ROI), as defined by the Desikan brain atlas, to create a measure of atrophy burden for each ROI.

2.7 Generation of DIAD atrophy-based dementia risk score

The concept and method for generating an atrophy-based dementia risk score (henceforth risk score) from w-scores has been described in detail previously. Briefly, we created w-score based regional measures of atrophy burden, as described above, from the earliest images obtained from individuals in the training group. The regional atrophy burden estimates from the asymptomatic and CDR ≥ 1 cases in the training group were entered into an L2-regularized logistic regression algorithm, with diagnosis as the categorical outcome. The algorithm was implemented in a machine learning Python package using the fast incremental gradient method. The probability distribution formula and method of optimizing the empirical log-logistic have been previously described. To estimate model performance a five-fold cross-validation scheme was used, as previously described. The predicted outcome from the fitted logistic regression equation is a risk score that ranges from 0 to 1 and represents the probability of either being demented or asymptomatic. To test the accuracy of our risk in separating asymptomatic from DIAD-MC with dementia we dichotomized individual scores above 0.5 as approximating dementia and below 0.5 approximating asymptomatic individuals. We compared risk score-based approximation of symptoms to actual symptoms in each individual. The risk score accuracy was calculated as the proportion of patients correctly classified.

2.8 Testing the utility of the risk score

We next assessed the utility of the risk score and mutation-EYO for predicting dementia onset in the testing group using two methods: a Cox regression model and a receiver operating characteristic (ROC) curve. Risk scores were calculated from all images in the testing group, which included carriers who started at a CDR 0 or 0.5 and were followed longitudinally.

We used a Cox regression model with atrophy risk score and mutation-EYO as time-varying predictors and conversion from CDR = 0 or CDR = 0.5 to CDR ≥ 1 as the outcome. Sex was added as a covariate in these models. To quantify the relationship between risk score and outcome, we estimated the effect of a 10% increase in the risk score (increase in value of 0.1). A Kaplan–Meier curve was constructed for this model with individual scores dichotomized above and below risk score value 0.5; this value was chosen for illustrative purposes. We also tested an interaction effect of risk score by mutation-EYO in a second model.

In addition, we evaluated and compared the risk scores and mutation-EYO performance in identifying DIAD-MC who converted from either CDR 0 or 0.5 to CDR ≥ 1 within 25 months of their baseline visit using a ROC curve. This time frame was chosen to approximate duration of some disease-modifying drug trials that might target prevention of dementia. For this analysis, we included the same individuals as in the Cox regression model. We dichotomized the risk scores above 0.5 and the mutation-EYO value higher than negative 25 months as predicting change from CDR = 0 or 0.5 to CDR ≥ 1. This technique fits a maximum likelihood ROC model using a binormal distribution of the true state of the observation (progressed vs. not progressed). The ROC models were fitted using Stata v16.1.

3 RESULTS

3.1 Participants

The study group included 231 DIAD-MC and 99 non-carrier family members. Of these, 166 DIAD-MC were included in the training group for generating the logistic model risk score (124 PSEN1, 15 PSEN2, and 27 APP) and 65 in the testing group for survival analysis (45 PSEN1, 3 PSEN2, and 17 APP). Table 1 summarizes the age and sex by symptom severity for each analysis used, including the control group.

3.2 Atrophy-based dementia risk score generation

The training group consisted of 43 DIAD-MC with CDR ≥ 1 and 123 with CDR = 0 for two consecutive visits, and a mean time on CDR = 0 of 2.79 ± 1.09 years. Figure 1 shows the optimal weight each brain region is given as a covariate in the logistic regression formula for the risk score. An ROI’s weight indicates its reliability in separating CDR = 0 and CDR ≥ 1. As expected, subregions of the medial temporal, precuneus, temporoparietal, and dorsolateral frontal regions comprised most of the list and showed the largest degree of atrophy, but high weights for prediction were also observed in subcortical regions such as the cerebellar cortices, globus pallidus, and caudate nuclei. Our model achieved good
FIGURE 1  Brain map displaying the relative weight (color coded) each region of interest (ROI) is given in the atrophy-based dementia risk score. Individual ROI weights were the result of the optimization of the logistic regression model. These weights were subsequently used to calculate prediction scores for the survival analysis. The weight indicates the degree of reliability of an ROI in separating presymptomatic and demented dominantly inherited Alzheimer’s disease mutation carriers. An ROI with a high positive or negative weight increases the probability that a given individual with atrophy in this region is Clinical Dementia Rating (CDR) scale $\geq 1$ or CDR $= 0$ respectively, whereas a weight closer to zero or zero indicates the ROI is less relevant for separating between these two outcomes. A and D, Left lateral and medial views, respectively. C and F, Right lateral and medial views, respectively. B and E, Hippocampal and basal ganglia level coronal slices, respectively.

3.3 Predicting symptom onset

The hazard ratio (HR) for our Cox model was 1.31 (95% confidence interval [CI] 1.14–1.49, $P < .001$), indicating higher risk and shorter time to conversion with increasing risk score. Results of Kaplan–Meier curve for the Cox model, after dichotomizing the risk score using a threshold of 0.5, can be seen in Figure 2. The HR for mutation-EYO was 1.18 (95% CI 1.03–1.35, $P = .017$). Sex was not a statistically significant predictor of survival (HR = 0.41, 95% CI 0.15–1.16, $P = .093$), but was in the direction of greater risk for males. There was no significant interaction between mutation-EYO and risk score ($P = .88$). The ROC area under the curve (AUC) was 0.903 (0.823–0.982) for the risk score, 0.825 (0.724–0.927) for the EYO, and 0.910 (0.830–0.990) for both (Figure 3).

4 DISCUSSION

Our aim was to determine whether individualized atrophy-based risk scores from a single observation could predict onset of dementia in DIAD-MC. Our developed risk score separated asymptomatic DIAD-MC from those with dementia with an accuracy of 96.4%. Moreover, in an independent subset of asymptomatic and mildly symptomatic DIAD-MC with longitudinal observations, every 0.1 unit increase in our risk score (a 10% increase) translated to roughly 1.3-fold increased likelihood of converting to dementia. Last, the risk score was useful in identifying asymptomatic DIAD-MC that converted to dementia within 2 years with 90.3% accuracy, and achieved 91% accuracy when combined with the EYO.

These findings are consistent with and extend prior work. In particular, previous studies have shown that hippocampal volumes and decline in hippocampal and whole brain cortical volumes, as well as other biomarkers, predict decline in DIAD-MC. To our knowledge...
this is the first study demonstrating the utility of single measurements of cerebral GM for predicting dementia onset, a critical event in the evolution of disease, in DIAD-MC.

Our results suggest that individualized atrophy-based dementia risk scores could help address several challenges in developing treatments for AD. The age of symptom onset can vary by many years in DIAD-MC even within carriers of the same type of DIAD mutation. Trials seeking to delay dementia onset must identify individuals that will develop symptoms within a short, defined time frame. An atrophy-based risk score may be useful for selecting mutation carriers that are closest to dementia conversion. This can help avoid unnecessary inclusion of individuals at low risk for dementia within 2 to 3 years in studies of DIAD-MC and increase trial power. Moreover, individual atrophy maps and risk scores can theoretically be used to follow recruited subjects for progression throughout trials. Proximity to dementia onset may also be used to inform clinical care of DIAD-MC.

Our approach is similar to prior analyses that used baseline atrophy patterns to predict dementia in sporadic AD. Many of these studies were conducted using data from the ADNI. This database comprises individuals with sporadic AD that are on average 30 to 40 years older than most DIAD-MC. Brain atrophy in DIAD-MC can occur in areas not typically associated with sporadic AD, such as the putamen and thalamus. Thus, models relying on atrophy in sporadic AD, particularly in predetermined ROI, might not be generalizable to DIAD populations. This justified an empirical approach to identify the most valuable regions for predicting dementia in DIAD. Our method is designed to identify regions that predict onset of dementia without reliance on a priori ROI. Indeed, although our analysis showed that the temporal, parietal, and frontal regions showed the highest degree of atrophy and predicted onset of dementia, as would be expected based on sporadic AD (Figure 1, Table 2), regions not typically atrophic in sporadic AD, such as the cerebellar cortices, globus pallidi, and caudate nuclei also contributed to prediction. The highest contribution of atypical ROI was from the cerebellar cortices, although it should be noted that the combined contributions of atypical subcortical regions was smaller than for the typical AD regions taken together. While cerebellar GM volume in DIAD-MC with dementia was reliably lower than that of asymptomatic DIAD-MC, regions typical of sporadic AD were on average more atrophic and together contributed more to the risk score (Table 2). Cerebellar atrophy is generally understudied in AD and DIAD. It has been previously described in some studies of DIAD-MC, but many studies have relied on surface-based methods that exclude the cerebellum from analysis.

Our current methods have several limitations that could be addressed in future analyses to improve utility. Accuracy of the risk score can be increased by using a larger sample size. To generate our risk score we pooled three different DIAD genes (with 67 different mutations) to maximize our sample size. Building this model in each gene separately would likely increase risk score accuracy but would require a larger sample size. Furthermore, the relative value of imaging-based predictors compared to mutation-EYO may vary by mutation. The risk score was generated from neuroimaging data of 43 DIAD-MC with dementia; of these 12 had a CDR of 2 or 3. Using neuroimaging data from DIAD carriers at earliest conversion to CDR
### TABLE 2 (Continued)

| Gray matter regions of interest (Desikan-Killiany Atlas) | Weight   | W-scores in CDR ≥ 1 (mean ± SD) |
|---------------------------------------------------------|----------|---------------------------------|
| Caudal middle frontal left                              | 0.2593   | -1.18 ± 0.71                    |
| Superior parietal left                                 | 0.2573   | -1.02 ± 0.51                    |
| Rostral middle frontal right                           | 0.2422   | -0.74 ± 0.65                    |
| Precentral right                                        | 0.2267   | -1.09 ± 0.81                    |
| Pars opercularis right                                 | 0.2245   | -0.58 ± 0.71                    |
| Supramarginal left                                     | 0.2237   | -1.3 ± 0.82                     |
| Lateral orbital frontal left                            | 0.2145   | -0.6 ± 0.77                     |
| Lateral occipital left                                 | 0.2127   | -1.29 ± 0.62                    |
| Lingual left                                            | 0.2106   | -1.27 ± 0.77                    |
| Insula left                                             | 0.2096   | -0.94 ± 0.91                    |
| Superior temporal left                                 | 0.2081   | -1.17 ± 0.78                    |
| Cuneus left                                             | 0.2072   | -1.44 ± 0.78                    |
| Caudate left                                            | 0.2061   | -0.73 ± 0.94                    |
| Cuneus right                                            | 0.1955   | -1.68 ± 0.71                    |
| Superior temporal right                                | 0.1879   | -1.21 ± 0.88                    |
| Lingual right                                           | 0.1814   | -1.34 ± 0.72                    |
| Hippocampus left                                        | 0.1767   | -1.81 ± 1.17                    |
| Superior frontal right                                 | 0.1754   | -0.55 ± 0.67                    |
| Lateral occipital right                                | 0.155    | -1.2 ± 0.7                      |
| Amygdala right                                          | 0.1542   | -2.04 ± 1.69                    |
| Isthmus cingulate left                                 | 0.1541   | -1.64 ± 0.83                    |
| Rostral anterior cingulate right                       | 0.1454   | -0.78 ± 0.82                    |
| Posterior-cingulate left                               | 0.1433   | -1.53 ± 0.72                    |
| Parahippocampal right                                  | 0.1428   | -0.88 ± 1.04                    |

Note: Individual ROI weights were the result of the optimization of the logistic regression model. The weight indicates the degree of reliability of an ROI in separating presymptomatic and demented DIAD mutation carriers and does not necessarily correlate with the degree of atrophy. An ROI with a high positive or negative weight increases the probability that a given individual with atrophy in this region is CDR ≥ 1 or CDR = 0, respectively, whereas a weight closer to zero or zero indicates the ROI is less relevant for separating these two outcomes.
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CONFLICTS OF INTEREST
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Additional supporting information may be found online in the Supporting Information section at the end of the article.