



The landscape of autosomal-dominant Alzheimer's disease: global distribution and age of onset

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We present a comprehensive global analysis of genetic variants associated with autosomal-dominant Alzheimer's disease (ADAD). A total of 550 variants in the APP, PSEN1 and PSEN2 genes were identified, of which 279 were classified as pathogenic or likely pathogenic based on American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria, utilizing data from the Dominantly Inherited Alzheimer Network (DIAN), literature and public databases. Symptomatic age at onset (AAO) data were estimated for 227 of these variants, allowing detailed characterization of their frequency, pathogenicity and AAO.

Importantly, 226 variants met eligibility criteria for inclusion in disease-modifying clinical trials. Furthermore, we demonstrated the predictive value of mean variant AAO and parental AAO in predicting symptomatic AAO, validated against converters who became symptomatic during follow-up in the DIAN Observational Study. This dataset provides critical insights into the global landscape of ADAD and reveals the genetic and AAO heterogeneity of ADAD variants while refining variant trial eligibility criteria.

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Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by the accumulation of amyloid- β (A β) and tau protein aggregates in the brain, leading to neurodegeneration and progressive cognitive and functional decline.^{1,2} While the majority of AD cases are sporadic, a fraction (<1%) are caused by autosomal-dominant mutations in three key genes: APP, PSEN1 and PSEN2.^{1,3} These variants result in altered processing of amyloid precursor protein, accelerating the pathological aggregation of A β peptides.^{3–7} Unlike sporadic AD, patients with autosomal-dominant Alzheimer's disease (ADAD) typically experience an earlier symptomatic age at onset (AAO) that can be reasonably predicted using the specific variant AAO, enabling the estimation of years to

symptom onset (EYO) in asymptomatic family members.^{8,9} The study of patients with ADAD provides a valuable model for elucidating the early pathogenic events in AD progression, offering a crucial window for intervention that could inform therapeutic strategies targeting familial and sporadic forms of the disease.

Understanding the genetic mechanisms that underpin ADAD and influence AAO and the global distribution of ADAD variants is vital for clinical genetics, supporting affected families and informing public health strategies.¹⁰ Insights into population-level ADAD variants can facilitate early diagnosis, prompt intervention and optimize resource allocation, potentially improving outcomes.¹¹ Furthermore, identifying novel ADAD variants can propel the development of treatments for both ADAD and sporadic AD by enabling the identification of molecular targets and pathways that may

be amenable to pharmacological intervention. This approach serves as a critical bridge in translating genetic discoveries into actionable medical practices that could lead to more effective, personalized therapies, significantly delaying or even preventing the clinical onset of AD in susceptible populations.^{12–15}

While previous research has shed light on AAO of participants with ADAD and clinical characteristics, ongoing efforts by the Dominantly Inherited Alzheimer Network Observational Study (DIAN OBS), DIAN Trials Unit (DIAN-TU) and DIAN Expanded Registry (DIAN EXR) are uncovering new variants and evaluating their clinical significance and AAO.^{16–19} This study aims to provide a comprehensive analysis of ADAD by reviewing variant reports from the literature, public databases and DIAN prospective studies. We examined the global distribution of ADAD, including pathogenic variants and variants of uncertain significance (VUS), and estimated mean variant AAO. We further assessed the ability of variant and parental AAO to accurately predict symptomatic AAO.

Materials and methods

Data sources

To assess ADAD global distribution, AAO and variant pathogenicity, we reviewed data from: (i) a systematic literature review; (ii) existing DIAN data (an international research effort focused on ADAD); and (iii) the Alzheimer Research Forum Database (Alzforum).^{20–22} Details regarding data sources are provided below.

Systematic review and Alzforum

The published literature was searched for ADAD variants, clinical symptoms and reported AAO. The search strategies were created by a committee composed of a medical librarian, DIAN researchers and other stakeholders with expertise in AD genetics. The search strategies were established using a combination of standardized terms and keywords, including but not limited to (Alzheimer's disease) AND (autosomal dominant inheritance, OR presenilin 1 OR presenilin 2 OR amyloid precursor protein) AND (age of onset OR middle-aged). The search was run in December 2023 using a librarian-created filter for non-animal studies and a date restriction from 2014 (date of previous review by our group²³) to 2024 in the databases Ovid Medline (1946–present), Embase (1947–present), Scopus (1960–present), Cochrane Central and ClinicalTrials.gov. The final search yielded 4528 citations, which were imported into EndNote®. A total of 3343 duplicates were identified and excluded, leaving 1185 citations for further examination. These were assessed for relevance based on predetermined inclusion and exclusion criteria, as detailed in Fig. 1. Specifically, studies reporting on the clinical characteristics of ADAD families with variants in PSEN1, PSEN2 or APP were considered for inclusion. Following an initial screening of abstracts, 202 studies qualified for a full-text review to verify their relevance and validity. This detailed evaluation resulted in the selection of 184 peer-reviewed articles for comprehensive analysis (refer to Fig. 1). In addition to database searches, an exploratory review of Alzforum contributed five additional peer-reviewed studies to our final dataset.

DIAN OBS

The DIAN OBS is a longitudinal, observational study of individuals and families who carry genetic variants associated with ADAD. The DIAN OBS was established to inform ADAD natural history, biomarkers and clinical outcomes, and to identify intervention

strategies.²⁰ The study began in 2008 and has enrolled more than 600 participants across multiple sites in North America, Europe, Latin America, Australia and Asia.

DIAN-TU

The DIAN-TU is a global research effort established in 2012 to design and conduct clinical trials for the prevention or treatment of ADAD. The present analysis only included DIAN-TU participants enrolled in the placebo groups.

DIAN EXR

The DIAN EXR is an international registry that comprises more than 700 individuals from families affected by ADAD. The DIAN EXR was established in 2011 as a collaborative research effort to facilitate study referral to DIAN OBS and DIAN-TU and to support educational and outreach activities with ADAD family members (<https://dian.wustl.edu/our-research/registry/>).

DIAN OBS and DIAN-TU study assessments include detailed information on parental and participant AAO documented across partner sites using a standardized AAO form. In addition, DIAN-TU and DIAN OBS collect extensive data from participants, including clinical-cognitive data obtained through the Clinical Dementia Rating® score (CDR) as well as CSF, plasma and neuroimaging biomarkers. Details about DIAN OBS and DIAN-TU protocols have been described previously.^{18,21–23}

Information on sociodemographic characteristics, country reports and evidence of variant pathogenicity was extracted from each data source. Information on clinical features (AAO, age of death, disease duration, clinical presentation, atypical manifestations and neurological findings) was obtained when available. We considered each symptom or sign as present or absent when clearly stated in the reports. To avoid potential double reporting across DIAN studies and published literature, pedigrees for each ADAD variant were manually examined to identify and remove possible duplicates. The combined dataset included 387 pedigrees, including 3275 individuals, of whom 2110 had cognitive impairment attributed to ADAD with known AAO. Key definitions about AAO used in our study are provided in Box 1.

Variant pathogenicity assessment and DIAN trial eligible list

For the purpose of this review, we assessed variants using two approaches. First, we categorized variants as pathogenic, likely pathogenic, VUS, likely benign or benign according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) guidelines. This classification was informed by data from literature reports, Alzforum records and findings from DIAN studies. Second, we determined trial eligibility based on the DIAN-TU trial eligibility criteria (see Fig. 2), which evaluate variants for inclusion in disease-modifying clinical trials.

The inclusion of ADAD individuals in the DIAN-TU clinical trials requires rigorously validated evidence for variant pathogenicity. As a result, DIAN-TU utilizes stringent criteria for enrolling patients with pathogenic ADAD variants, as delineated by the DIAN-TU Clinical-Genetics Committee. ADAD variants eligible for trial inclusion must meet rigorous standards for evidence of pathogenicity. The DIAN-TU eligibility list is dynamic and regularly updated by assessing new variants as scientific evidence—such as new families, AD-related biomarkers, results from segregation studies and

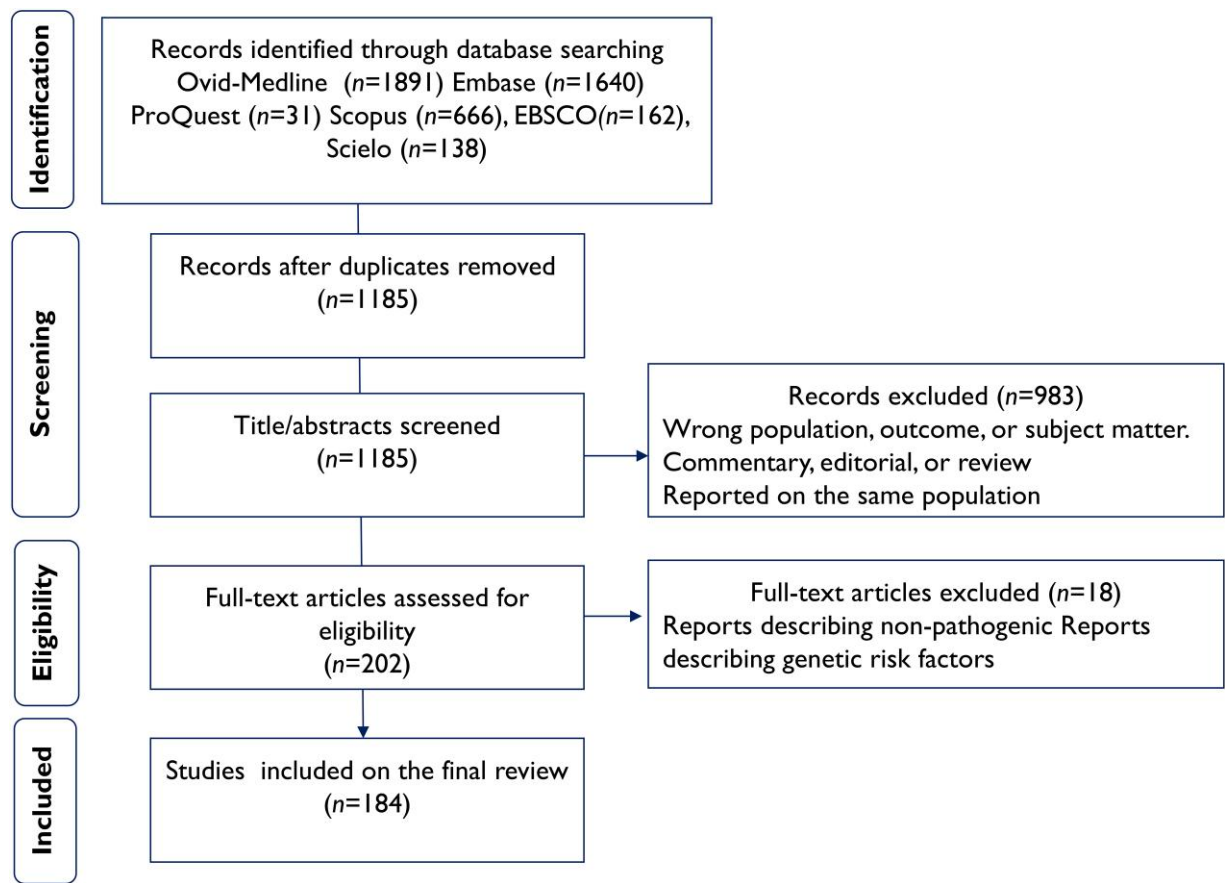


Figure 1 Systematic review flow chart. Flow chart outlines the sequential steps in the systematic literature review.

functional analyses—becomes available. This ensures that new variants are evaluated and added to the trial list.

The DIAN-TU eligibility algorithm integrates three key streams of information: (i) family history of dementia; (ii) evidence of AD; and (iii) genetic data suggesting a causal relationship between variant and AD. Corresponding supportive findings include: (i) a multigenerational family history of dementia suggesting an autosomal-dominant pattern of inheritance; (ii) clinical documentation of amnesic-predominant, progressive cognitive impairment leading to dementia due to AD, ideally with fluid or imaging biomarkers supportive of AD, and/or neuropathological confirmation of AD in at least one family member; and (iii) predictors of variant pathogenicity, including low frequency in a large population series (Genome Aggregation Database, gnomAD v.4.1.0), and evidence of variant segregation or functional analysis exploring A β isoform levels *in vitro* (A β_{42} and A β_{40} levels or the A $\beta_{42/40}$ ratio) relative to wild-type and known pathogenic variants.³⁰ Additional criteria supportive of variant eligibility include conservation of the variant amino acid residue between PSEN1 and PSEN2, presence of other ADAD pathogenic variants at the residue and *in silico* prediction of damaging effects. While the DIAN-TU pathogenicity algorithm incorporates several *in silico* predictions of damaging effects [Combined Annotation Dependent Depletion (CADD; GRCh37-v.1.6), rare exome variant ensemble learner (REVEL),³¹ Sorting Intolerant From Tolerant (SIFT; Ensembl 66), PolyPhen-2 (V13-3)], it predominantly relies on the CADD score. This score is an integrative approach used in genomics to assess the deleteriousness of single

nucleotide variants (SNVs) and insertion-deletion variants (indels) across the human genome. Developed to prioritize functional, deleterious, and disease causal variants in clinical genomics and genetic research, CADD integrates multiple annotations into a single metric by contrasting variants that survived natural selection with simulated variants to derive a score for each variant, reflecting its potential pathogenic impact.^{30,32} In this study, we provide additional evidence on the utility of CADD scores to predict pathogenicity. The DIAN-TU algorithm to assess eligibility for trial inclusion is shown in Fig. 2.

Statistical analysis

Participant symptomatic age at onset prediction analysis

We extracted the AAO for each ADAD-affected family member and determined the parental/family proxy AAO and variant AAO for those with the same ADAD variant. Next, we assessed the accuracy of the variant AAO and parental AAO in predicting participant symptomatic AAO. We identified participants who developed cognitive impairment, i.e. progressed from a cognitively normal state (CDR = 0) to impaired (CDR > 0) during the DIAN study and classified them as ‘converters’. Converters’ symptomatic AAO was considered the gold standard and compared with the predicted AAO according to the variant AAO present in the family and the parental AAO. If there were insufficient data to assess variant AAO (<3 known affected variant carriers), only parental AAO was used to

Box 1 Definitions and methods for calculating variant age at onset and estimated years to symptom onset in autosomal-dominant Alzheimer's disease participants

Participant symptomatic age at onset (AAO): the age at which progressive symptoms attributed to Alzheimer's disease (AD)²⁴ (e.g. cognitive, behavioural or motor) were first noticed by someone who knew the participant well (i.e. their collateral source).

Parental/family proxy AAO: the age at which progressive symptoms attributed to AD (e.g. cognitive, behavioural or motor) were first noted in the participant's parent or relative.²⁴

Variant AAO: the mean AAO for a specific ADAD variant calculated across all known symptomatic carriers with the same variant (e.g. mean age of onset for all participants known to carry PSEN1 E184D).^{17,22} For this analysis, variant AAO is reported only when the age at which first progressive symptoms attributed to AD was available for three or more carriers of the same variant.

Estimated years to symptom onset (EYO): calculated by subtracting the variant AAO or parental AAO from the age of the participant at the study visit (e.g. a participant of 25 years with a parental AAO at 37 will be at EYO –12). EYO serves as a variable of time along the disease stages of ADAD, centred on the individual participant's estimated AAO (EYO = 0). EYO < 0 refers to participants who are younger than their estimated AAO (i.e. those who have not yet reached their EYO). EYO > 0 refers to participants who are older than their estimated AAO (i.e. those who have exceeded their EYO).^{16,25–27}

calculate the EYO. Linear regression was used to explore the relationship between variant AAO, parental AAO and participant symptomatic AAO.

Pathogenicity prediction analysis

We further explored the validity and predictive ability of the DIAN-TU eligibility algorithm by producing a receiver operating characteristic (ROC) curve using the pROC R package (<https://cran.r-project.org/>). The results from the functional analysis exploring A β isoform levels *in vitro* relative to wild-type and known pathogenic variants were considered the gold standard. The DIAN-TU algorithm was validated using 71 variants encompassing diverse parameters such as gene and variant, protein-level effect, gnomAD exome/genome frequency, CADD score, SIFT prediction/score, PolyPhen-2 prediction/score, clinical phenotype, mean differences of A β ₄₂, A β ₄₀, and A β _{42/40} relative to wild-type variants and known pathogenic variants, and mean AAO. Our primary analytical focus was on assessing the potential of the AAO, AD biomarkers, population frequency, variant segregation and CADD scores to predict pathogenicity. Subsequent statistical analyses included maximum likelihood estimates with emphasis on the Wald Chi-squared test to deduce the association between the AAO and CADD score and the variant A β _{42/40} *in vitro* results. To measure the strength and direction of this association, we computed odds ratios. To validate further the diagnostic utility of the AAO and CADD scores in predicting pathogenicity, we conducted an ROC analysis.

All statistical analyses were conducted using either SAS software (version 9.4, SAS Institute Inc., Cary, NC) or R (version 4.3.1; <https://cran.r-project.org/>). A P-value threshold of <0.05 was considered statistically significant.

Results

Global distribution of variants

Global analysis of ADAD variant distribution revealed 550 variants across patients in 55 countries: 67.7% (372) in PSEN1, 16.5% (91) in PSEN2 and 15.8% (87) in APP. Variants were classified following ACMG-AMP criteria, using data derived from literature reports, Alzforum records and DIAN studies. Using ACMG-AMP criteria, 279/550 ADAD variants were classified as pathogenic/likely pathogenic,

27 as VUS and 50 as benign/likely benign [including one (APP p.A673T) as protective]. In addition, 194 variants were not classified due to insufficient evidence to support a pathogenic or benign designation. Additionally, variants co-occurring in individuals with other known pathogenic mutations or those with ambiguous application of ACMG-AMP criteria could not be conclusively classified.

The highest number of reported pathogenic variants were from the USA (74 variants: PSEN1 = 65, PSEN2 = 1, APP = 8), France (67 variants: PSEN1 = 54, PSEN2 = 4, APP = 9) and the UK (42 variants: PSEN1 = 39, APP = 3). Figure 3 provides a breakdown of pathogenic and likely pathogenic variants by gene, number of variants and country.

Age at onset and estimated years to symptom onset

Data on AAO were available in 2110 individuals with 227 unique variants: 176 in PSEN1, 20 in PSEN2 and 31 in APP. The combined dataset revealed a mean AAO of 47.3 years (SD = 10.1), ranging from 21 to 90 years. The mean variant AAO was 44.9 \pm 9.4 years (range 22–90 years) for PSEN1 variants, 59.5 \pm 6.8 years (range 21–82 years) for PSEN2 variants and 52.1 \pm 8.1 years (range 30–88 years) for APP variants (Table 1). PSEN2 variants had a later AAO compared with other groups (PSEN2 versus PSEN1 P < 0.001; PSEN2 versus APP P = 0.01). Table 1 provides a summary of the AAO for each gene and according to variant pathogenicity. In addition, Supplementary Tables 1 and 2 provide the AAO for each independent variant. Figure 4 depicts the relationship between individual participants' symptomatic AAO and variant AAO by variant and gene (APP, PSEN1 or PSEN2). The scatter plot in Fig. 4 (top left) shows the association between individual AAO and mean variant AAO. The strong association between variant AAO and observed AAO (R^2 = 0.56) suggests that specific variants account for a substantial proportion (56%) of variability in individual AAO overall. The degree of association varied by gene (Fig. 4, top right), being strongest for PSEN1 (R^2 = 0.60), modest for APP (R^2 = 0.30) and weakest for PSEN2 (R^2 = 0.13). In addition, we explored whether there is a greater degree of variability in AAO across different genes (APP, PSEN1, PSEN2) and according to variant-level factors, including the codon location (PSEN1 <200 versus >200) and the affected protein domain (cytoplasmic versus transmembrane), as shown in Supplementary Tables 3 and 4. First, we examined potential variability in AAO at the individual level (Supplementary Table 3), and despite significant differences in mean AAO across genes [PSEN1 (45.7 years), APP (50.8 years) and

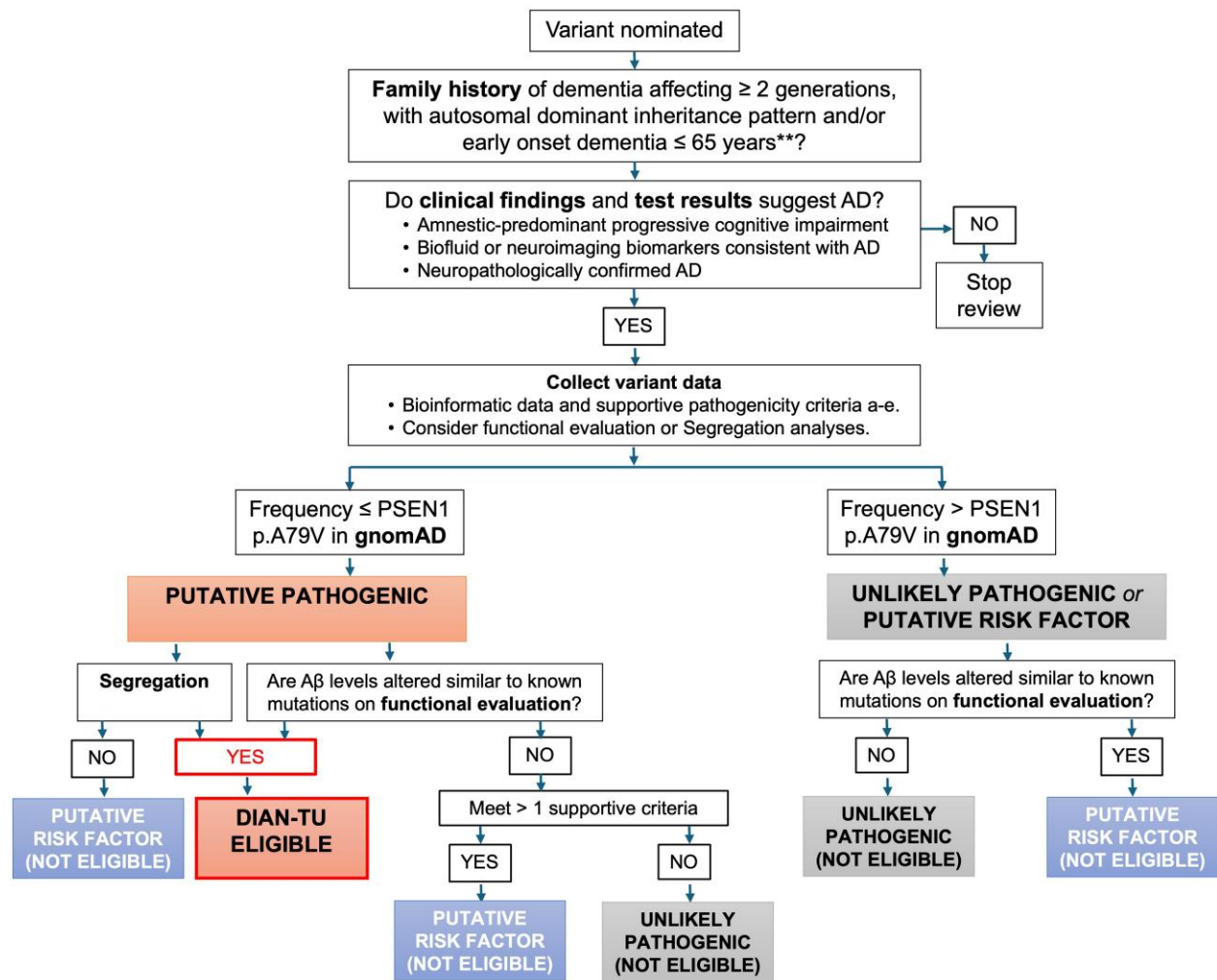


Figure 2 Dominantly Inherited Alzheimer Network–Trials Unit (DIAN-TU) algorithm to classify variant trial eligibility. Algorithm to assess eligibility for DIAN-TU trials. This model was modified from a previously proposed algorithm^{28,29} GnomAD frequency is used to determine whether APP, PSEN1 and PSEN2 variants represent rare or common polymorphisms. Autosomal-dominant Alzheimer’s disease (ADAD) pathogenic variant PSEN1 A79 V allele frequency is used as a cut-off reference to define rare variants. Additional supportive criteria include: (a) whether other variants at the same residue have previously been confirmed as pathogenic; (b) whether a given presenilin variant is at a residue conserved between PSEN1 and PSEN2; (c) the number of unrelated families in which the variant is present at a consistent age at onset and evidence of AD biomarkers; (d) the number of generations with early-onset AD (<65 years); and (e) *in silico* predictions (CADD, REVEL score or comparable computational score). **The presence of multiple affected family members is considered supportive evidence but not required for variant review or trial inclusion. APP, PSEN1 and PSEN2 *de novo* variants are also assessed for pathogenicity by the Clinical-Genetic Committee using the DIAN algorithm. Families that exhibit multigenerational incidences of biomarker-confirmed Alzheimer’s dementia and age of onset under 40 years are automatically deemed eligible for inclusion in the trial while additional evidence is systematically gathered. CADD = Combined Annotation Dependent Depletion; REVEL = rare exome variant ensemble learner; GnomAD = Genome Aggregation Database.

PSEN2 (55.8 years)], we found a similar degree of individual-level variability in AAO across genes ($P=0.13$). Similarly, variant-level factors like protein domain location (cytoplasmic versus trans-membrane) and variant location (PSEN1 pre- or post-codon 200) showed no significant effect on AAO variability ($P=0.07$ and $P=0.19$, respectively). In summary, our analysis suggested that gene- or variant-level factors do not significantly influence the degree of AAO variability at the individual or family level.

To assess the accuracy of variant and parental AAO in predicting individual symptomatic AAO, we performed a comparative analysis of estimated and participant symptomatic AAO in 53 participants within the DIAN-TU placebo arm and DIAN OBS study who developed cognitive impairment during follow-up (‘converters’). Table 1 shows the distribution of the converter AAO relative to mean variant AAO and parental AAO. The analysis revealed an

average discrepancy between participant symptomatic AAO and expected parental AAO of -1.1 years (SD = 5.6; 95% CI: -2.6 to 0.5), with an R^2 of 0.52; meaning that observed AAO occurred, on average, 1.1 years earlier than reported in a participant’s parent. Similarly, the difference between participant symptomatic AAO and variant-specific AAO, was -0.9 years (SD = 5.2; 95% CI: -2.3 to 0.5), with an R^2 of 0.56 ($P < 0.0001$). Figure 4 (bottom) demonstrates the predictive validity of both parental and variant-specific AAO for observed AAO, highlighting the substantial association between observed AAO and EYO in ADAD.

DIAN-TU trial eligibility

Application of the DIAN-TU eligibility algorithm (Fig. 2) determined that 226 of the 551 identified ADAD variants qualified for inclusion

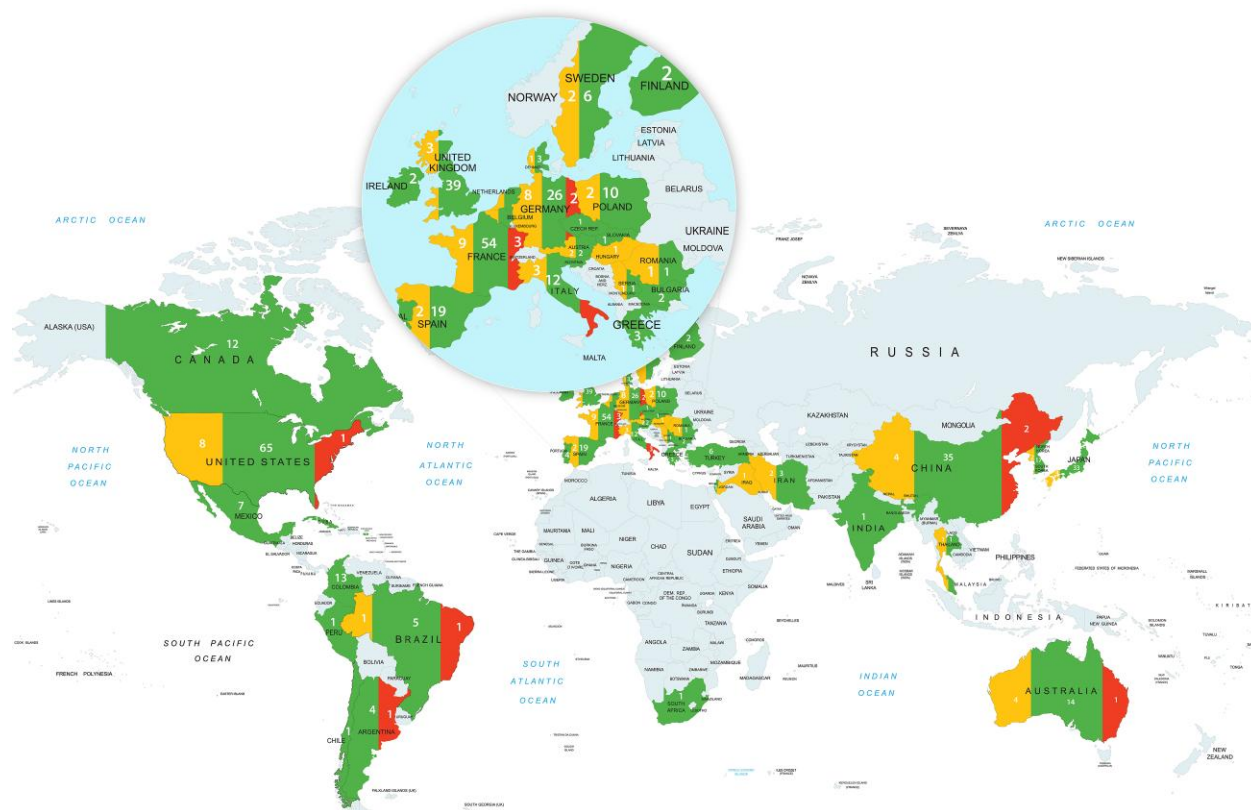


Figure 3 Global distribution of pathogenic autosomal-dominant Alzheimer's disease variants. Number of pathogenic variants in APP, PSEN1 or PSEN2 by country. The map displays PSEN1 variants in green, APP variants in yellow and PSEN2 variants in red. The colours indicate the presence of different genetic variants among various countries but not the distribution within each country. The count of variants within individual genes is represented numerically.

in the DIAN-TU (see [Supplementary Table 1](#)). Remarkably, 35 eligible variants were previously categorized as VUS based on literature reports, with an additional 21 not documented in existing variant databases. The eligibility of VUS for inclusion in the DIAN-TU was re-assessed based on AD-specific biomarkers and neuropathology reports, which were primarily obtained through the DIAN OBS and contributions from DIAN site investigators.

A total of 195/226 of DIAN-TU eligible variants were in PSEN1, 23 in APP and 8 in PSEN2. The mean AAO for DIAN-TU eligible variants was 43.3 years (SD = 8.3, range 26–63), and the average CADD score was 27.3 (SD = 2.7). Gene-specific analyses revealed PSEN1 variants with an AAO of 43.2 years (SD = 8.2, range 26–60) and a CADD score of 27.4 (SD = 2.8), PSEN2 variants had an AAO of 53.5 years (SD = 7.0, range 46–56) and a CADD score of 26.0 (SD = 1.5), and APP variants were noted for an AAO of 47.5 years (SD = 7.2, range 34–58) and a CADD score of 27.1 (SD = 2.3). For an in-depth review of each variant, including country report, mean AAO, clinical phenotype and other details, see [Supplementary Tables 1](#) and [2](#).

CADD score and predictor of pathogenicity

CADD scores are widely used to interpret whole-genome sequencing data, providing a high-resolution view of pathogenicity across the human genome.³³ We evaluated the CADD score as a predictor of clinical classification, specifically targeting variants likely to be detrimental and potentially pathogenic. CADD scores were available for 520 of 551 variants, and the average scores for variants classified as pathogenic or likely pathogenic were 26.9 and 25,

respectively, for VUS. Variants identified as benign had an average CADD score of 14.4. There was a significant difference in the average CADD score among different groups (Pathogenic versus VUS, Pathogenic versus Benign, VUS versus Benign; $P < 0.0001$). All 226 DIAN-TU trial eligible variants with an available CADD score registered scores exceeding 21.

We also evaluated the utility of the CADD score to predict variant functional analysis results. Variants that led to a significant rise in A β isoform levels (or A $\beta_{42/40}$ ratio) had higher CADD scores (mean = 26.2, SD = 3.0) than variants that did not alter A β_{40} or A β_{42} levels (mean = 22.1, SD = 5.1) ($P = 0.002$). *In vitro* functional assays revealed that a one-unit increase in the CADD score was associated with a 25% increase in the odds of changes in A β isoform levels (OR = 1.25, 95% CI = 1.1–1.5). The predictive utility of the CADD score is further substantiated by the ROC analyses, with an AUC of 0.68 ([Supplementary Fig. 4](#)). The use of the CADD score to predict variant functional analysis results was further enriched by including the variant genomAD frequency in the model (AUC = 0.75). Additional analysis on the utility of CADD scores in identifying potential damaging variants is provided in [Supplementary Figs 1–3](#) and [Supplementary Table 5](#).

Discussion

This study represents a substantial advancement in our understanding of ADAD epidemiology through the systematic analysis of 550 genetic variants across APP, PSEN1 and PSEN2. We have

Table 1 Distribution and characteristics of variants with available age at onset across PSEN1, PSEN2 and APP

	PSEN1	PSEN2	APP	Total
Affected family members, n (%)	1591 (75.4)	117 (5.5)	402 (19.1)	2110
ADAD variants with known AAO, n (%)	176 (77.5)	20 (8.8)	31 (13.7)	227
AAO, mean ± SD, years	44.9 ± 9.4	59.5 ± 6.8	52.1 ± 8.1	47.3 ± 10.1
DIAN-TU trial eligible variants				
DIAN-TU trial eligible variants, n (%)	195 (86.3)	8 (3.5)	23 (10.2)	226
DIAN-TU trial eligible variants with known AAO, mean ± SD, years	43.2 ± 8.2	53.5 ± 7.0	47.5 ± 7.2	43.9 ± 8.3
DIAN converters ^a				
DIAN converters, mean ± SD, years	42.8 ± 4.6	48.6 ^b	48.2 ± 6.1	43.4 ± 7.7
Parental AAO, mean ± SD, years	43.6 ± 5.7	47.0 ^b	48.1 ± 4.9	44.5 ± 7.3
Mean variant AAO, mean ± SD, years	43.9 ± 4.7	50.2 ^b	48.4 ± 4.6	44.3 ± 6.5
DIAN converter AAO – parental AAO, mean ± SD, years	–1.3 ± 3.5	1.6 ^b	–0.4 ± 7.0	–1.1 ± 5.6
DIAN converter AAO – variant AAO, mean ± SD, years	–1.1 ± 2.8	–1.6 ^b	–0.4 ± 7.1	–0.9 ± 5.2

Autosomal-dominant Alzheimer’s disease (ADAD) variants and affected family members summarized by gene (PSEN1, PSEN2 and APP), along with their respective mean age at onset (AAO). The total number and percentage of known affected individuals; the number of variants with known AAO; and the mean AAO for each gene (all variants combined accordingly by gene) are listed. The number of Dominantly Inherited Alzheimer Network-Trial Unit (DIAN-TU) trial eligible variants by gene are given, reporting the number and percentage of eligible variants within each gene and mean AAO. DIAN converters are reported, comparing their mean AAO to parental and variant-specific AAOs to assess potential shifts in disease onset. The mean difference between DIAN converter AAO and expected parental and variant AAOs are reported. SD = standard deviation.

^aDIAN converters: participants who transitioned from asymptomatic to symptomatic during the DIAN observational (OBS) study.

^bSince only one PSEN2 carrier transitioned from asymptomatic to symptomatic during the DIAN-OBS study, we report a point estimate rather than a mean or standard deviation.

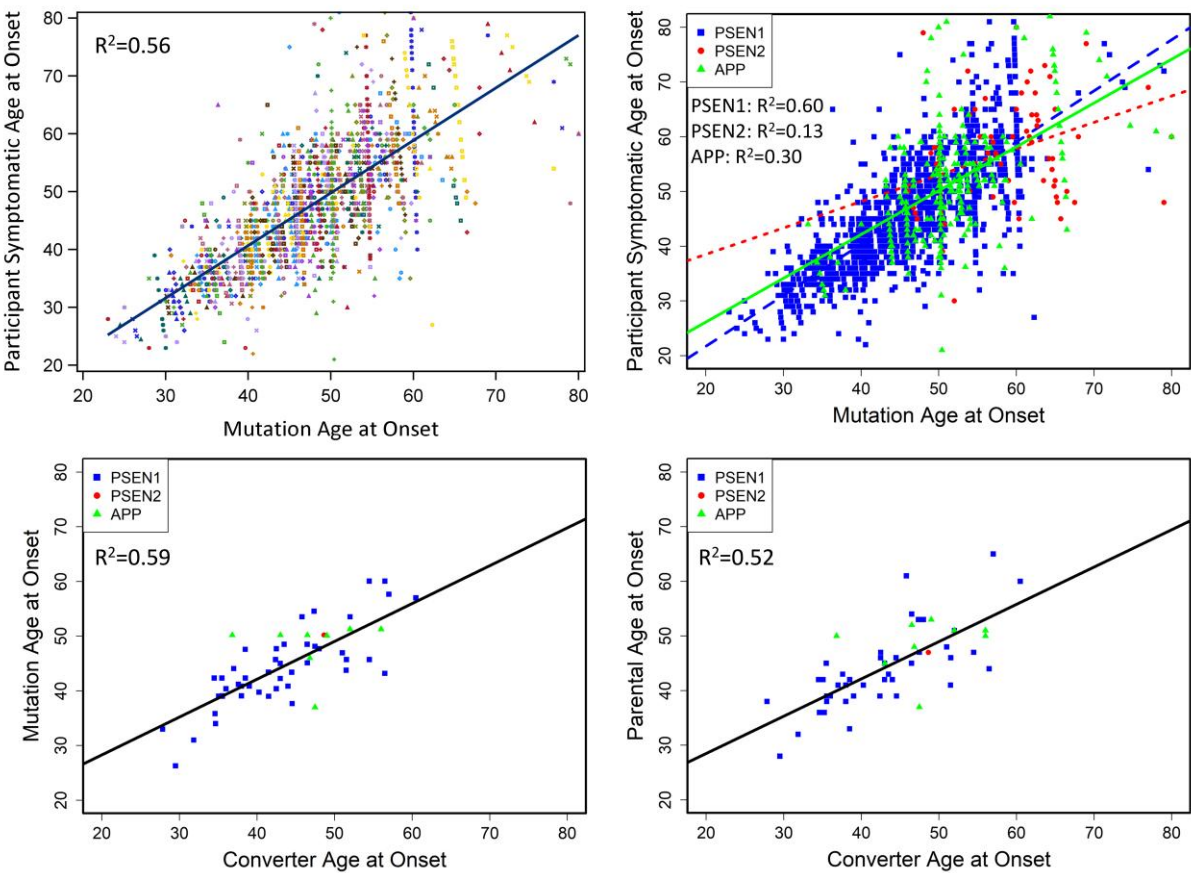


Figure 4 Individual symptomatic age at onset (AAO) versus variant AAO and accuracy assessment of AAO. Top: Each affected individual participant’s symptomatic AAO (n = 2110) on the y-axis, plotted against values predicted from variant AAO on the x-axis. Top left: All individuals combined, regardless of gene type. Data points are coloured/shaped according to each variant for autosomal-dominant Alzheimer’s disease. Top right: All individuals according to gene (PSEN1, PSEN2, APP). Bottom left: Relationship between converter and variant AAO, and (bottom right) between converter and parental AAO. Blue filled squares = PSEN1; red filled circles = PSEN2; green filled triangles = APP. Regression lines and adjusted R² values show the strength of the association between individual AAO and variant AAO. Converters are participants who transitioned from being asymptomatic to symptomatic during follow-up in the Dominantly Inherited Alzheimer Network observational study.

demonstrated a notable global distribution of these variants, provided variant-specific AAO and validated the predictive accuracy of variant and parental AAO in forecasting symptomatic onset (EYO). Our investigations identified 550 ADAD variants, with 226 considered eligible for DIAN-TU trial eligibility. The DIAN OBS and DIAN-TU studies offered deep phenotype data, which included clinical, cognitive, fluid and neuroimaging biomarkers for 109 variants spanning *PSEN1*, *PSEN2* and *APP*, which supported the classification of several VUS or those not previously reported in the literature. Overall, our findings not only enhance the genetic and clinical understanding of ADAD but will also inform future ADAD prevention trials.

The occurrence of ADAD varied across different countries, with the USA, France and UK documenting the highest number of ADAD variants. This observation is consistent with previous studies that have reported a higher frequency of ADAD in developed countries.^{30–32,34} However, the observed variation in ADAD frequency is in part due to unequal access to diagnostic testing, including genetic testing. Similarly, the lack of reporting on ADAD variants from some countries might be related to limited access to healthcare, lack of awareness and resource limitations. DIAN is attempting to mitigate these issues through comprehensive outreach programmes and the support of genetic counselling and testing via a growing number of increasingly distributed study sites in regions with fewer resources.^{14,15}

Relative to a previous analysis,²² we have expanded the number of ADAD variants with variant AAOs and included a larger number of mutation carriers with known age at symptom onset ($n = 2110$), which will enhance the accuracy of the predicted AAO in ADAD patients. Our study also supports using variant and parental AAOs to predict an individual's AAO (EYO). In assessing the predictive accuracy of AAO in DIAN converters, a comparison between the observed AAO and the expected AAO derived from parental data revealed an average discrepancy of -1.1 years (95% CI: -2.6 to 0.5), indicating the strength of parental AAO to predict symptomatic AAO at preclinical stages. A similar analysis comparing observed to variant AAOs showed a slightly smaller discrepancy of -0.9 years (95% CI: -2.3 to 0.5). Despite the high correlation between variant AAO and participant symptomatic AAO, our findings also highlight variability in AAO across individuals within families and within variants. This variability suggests that additional factors may either confer resilience or pose risks, thereby significantly influencing the clinical presentation and progression of the disease.³⁵ Variability across different variants is likely explained by the differential effects of each variant on γ -secretase activity and A β production. A previous analysis in the DIAN OBS study indicated that variants in the 3rd transmembrane domain of *PSEN1* were associated with pronounced Pittsburgh Compound B (PIB) accumulation and steep cognitive declines. In contrast, variants in the 8th transmembrane domain showed only modest PIB accumulation. Distinctions were more pronounced when comparing variants based on their location relative to codon 200.¹⁹ In addition, carriers of transmembrane-affecting variants exhibited more severe cognitive impairment, reduced hippocampal volume and higher phosphorylated tau levels compared with cytoplasmic variant carriers and non-carriers.³⁶

These variant-level effects primarily capture the initial stage in the AD cascade, leading to tau aggregation, neurodegeneration and cognitive decline. Consequently, variability in the AAO within families carrying the same variant is likely due to differences in additional genetic, environmental or lifestyle factors that modulate these downstream processes.

Variability in this study and others underscores the need to further refine predictive models to enhance clinical utility.^{37,38} Current models are based only on familial data, which may not account for environmental factors or interactions between multiple genetic loci that could influence AAO in a broader population. It is also important to recognize that study findings apply to participants at the group level. For individuals carrying such variants, it is crucial to understand that the development of the disease within 1 year of EYO is not assured. Lifestyle factors and other risk factors can significantly influence the onset and progression of the disease.^{39,40} Such insights emphasize the importance of a current comprehensive dataset in improving the accuracy of predictive models for AAO in ADAD patients.

In our evaluation, 226 of the 550 ADAD variants analysed met the eligibility criteria for the DIAN-TU trial. The robustness and reliability of the DIAN-TU algorithm are enriched by the integration of clinical, cognitive and biomarker data from the DIAN studies, which allowed the inclusion of variants previously categorized as VUS and the identification of 21 novel pathogenic variants to be eligible for trial inclusion. These outcomes support the need for ongoing updates and reassessments in genetic variant databases to enhance their clinical relevance and accuracy. Moreover, the demonstrated precision of the DIAN-TU algorithm in evaluating trial-worthy variants suggests its potential for wider application in clinical and research settings.

Recent advancements in the study of ADAD underscore the need to understand the pre-symptomatic stages of AD and implement early disease-modifying trials.^{41,42} Knowledge concerning the duration of the pre-symptomatic stages of AD and the ability to accurately define EYO are central to efforts to improve early detection and management of AD, and to the design of clinical trials aimed at preventing the symptomatic onset of AD.^{43,44} Our findings highlight the utility of using AAO and EYO as screening tools to enhance selection of participants with ADAD for clinical trials, minimize confounding variables and improve the likelihood of successful outcomes through more accurate EYO estimation. These measures can inform the design of prevention trials and the implementation of stringent inclusion and exclusion criteria, ensuring that suitable candidates are enrolled at appropriate ages, thus enhancing trial reliability. Furthermore, our study extends beyond conventional uses of AAO and EYO by incorporating a globally representative dataset, which allows for the discovery of novel ADAD variants. This broadens our understanding of ADAD's genetic and clinical diversity, enabling healthcare professionals to utilize our comprehensive data for more precise outcome forecasting, informed treatment planning and prognostication in patients with ADAD. Collectively, these findings have the potential to impact patient care and advance the development of treatments for AD.

The use of the CADD score in this study underscores its value as a robust tool for predicting the pathogenicity of genetic variants in ADAD. Higher CADD scores were associated with variants classified as pathogenic, affirming the score's effectiveness in distinguishing likely pathogenic variants from benign variations in a clinical context. However, the reliance on CADD scores also presents certain limitations. CADD has limitations in classifying large structural or splice-site variants and is influenced by reported clinical observations, allele frequencies and molecular data. While the CADD approach is evolving, factors such as variant spectrum, penetrance, resilience mechanisms, genetic background, disorder heterogeneity, variant classification quality and inheritance patterns must be considered to enhance its clinical utility. Therefore, while

CADD scores are instrumental in enhancing the predictive accuracy of our pathogenicity assessments, they should be interpreted with caution and supplemented with disease-specific functional assays and clinical data when available.

This manuscript presents several distinct strengths that contribute to the field of neurogenetics and the ongoing study of ADAD. First, we offer a comprehensive analysis of 550 genetic variants in the *PSEN1*, *PSEN2* and *APP* genes, which allows for a detailed examination of the genetic landscape of ADAD, offering a richer understanding of its global prevalence and genetic diversity that may inform public health strategies and resource allocation for AD care and prevention globally. Second, a substantial contribution of this study is the innovative use of the DIAN-TU pathogenicity algorithm, which integrates clinical, biomarker and genetic data to enhance the accuracy of variant eligibility for clinical trials. Additionally, our approach validates the predictive accuracy of the estimated AAO models and supports its application in clinical trials aimed at prevention. Overall, these findings have direct implications for the design and execution of clinical trials aimed at preventing or delaying the onset of AD symptoms in at-risk populations.

However, this study is also subject to certain limitations. First, it is possible that pertinent studies may have been overlooked despite a systematic literature review. Additionally, our systemic review was limited to variants with sufficient information to accurately determine an AAO (227/550). Second, the use of AAO instead of age at diagnosis was intended to account for differences in delay to diagnosis. However, this method is subject to its own limitations. In many cases, the AAO is reported by participants with mild cognitive impairment or their caregivers, which may result in recall bias. Furthermore, the estimation of AAO relied on clinical data that may have variability in diagnostic accuracy and criteria across different research sites, which could affect the consistency of the symptomatic AAO data and the classification of variants. Third, although the study covers a large number of genetic variants, the geographic distribution of the studied population may not fully represent global diversity. Certain regions are underrepresented due to limited access to genetic testing, potentially impeding the generalization of study findings across ethnic and racial groups. Additionally, reports of new variants are more likely to occur in regions with active ADAD research programmes. While healthcare institutions with clinical genetic diagnostic capabilities might conduct testing for *APP*, *PSEN1* and *PSEN2*, routine clinical findings might not be documented in the scientific literature without an active research programme.

Finally, the field of genetic research in AD is rapidly advancing. As the landscape of genomic data expands and new ADAD variants and families are described, interpretations and conclusions drawn in this study will need to be revisited and revised.

Data availability

Data supporting the findings of this study are available on request according to the policies of the DIAN (<https://dian.wustl.edu>), which comply with the guidelines established by the Collaboration for Alzheimer's Prevention.³⁴ To protect the privacy of participants some data are not publicly accessible.

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Competing interests

J.C.M. is the Friedman Distinguished Professor of Neurology, Director, Knight ADRC; Associate Director of DIAN and Founding Principal Investigator of DIAN. He is funded by NIH grants P30 AG066444; P01 AG003991; P01 AG026276; U19 AG032438 and U19 AG024904. Neither J.C.M. nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. J.H. is a paid consultant for F. Hoffmann-La Roche, Ltd., Takeda and Lundbeck, and is on the Data Safety and Monitoring Board for Eisai. C.C. receives research support from: Biogen, Eisai, Alector and Parabon. The funders of the study had no role in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. C.C. is a member of the advisory board of Vivid Genetics, Halia Therapeutics and Adx Healthcare. R.J.B. is the Director of the DIAN-TU and Principal Investigator of the DIAN-TU-001. He receives research support from the NIH-NIA, DIAN-TU Trial Pharmaceutical Partners (Eli Lilly and Company, F. Hoffman-La Roche, Ltd. and Avid Radiopharmaceuticals), Alzheimer's Association, GHR Foundation, Anonymous Organization, DIAN-TU Pharma Consortium (active: Biogen, Eisai, Eli Lilly and Company, Janssen, F. Hoffmann-La Roche, Ltd./Genentech, United Neuroscience. Previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi). He has been an invited speaker and consultant for AC Immune, F. Hoffman La Roche, Ltd., and Janssen and a consultant for Amgen and Eisai. A.E.D. reports no competing interests. He receives research support for this work from the NIA (R01AG053267, U19AG032438). T.I. reports no competing interests. He received research support for this work from Agency for Medical Research and Development (AMED) (JP23dk0207066 and JP23dk0207060). G.S.D. reports no competing interests that are directly relevant to this work. His research is supported by NIH (K23AG064029, U01AG057195, U01NS120901, U19AG032438) and

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Supplementary material

Supplementary material is available at Brain online.

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