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RESEARCH ARTICLE

Plasma levels of an N-terminal tau fragment predict Alzheimer's and neurodegenerative disease biomarkers in autosomal dominant Alzheimer's disease

Stephanie A. Schultz[1,2] | Yiwen Rao[3] | Lei Liu[3,4] | Beth Ostaszewski[3,4] | Amirah K. Anderson[3,4] | Wai-Ying Wendy Yau[1,2,3] | Zahra Shirzadi[1,2] | Brian A. Gordon[5] | Jason Hassenstab[5] | John C. Morris[5] | Richard J. Perrin[5] | Ricardo F. Allegri[6] | Nicolas R. Barthélemy[5] | Nick Fox[7] | Gregory S. Day[8] | Mathias Jucker[9] | Allan I. Levey[10] | Johannes Levin[11,12,13] | Hiroshi Mori[14] | Stephen Salloway[15] | Peter Schofield[16] | Eric McDade[5] | Reisa A. Sperling[1,2,3] | Randall J. Bateman[5] | Dennis J. Selkoe[3,4] | Jasmeer P. Chhatwal[1,2,3,4] | and the Dominantly Inherited Alzheimer's Network

[1]Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

[2]Department of Neurology, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

[4]Division of Basic Neuroscience Research, Ann Romney Center for Neurologic Diseases, Boston, Massachusetts, USA

[5]Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA

[6]Department of Cognitive Neurology, Neuropsychiatry and Neuropsychology, Instituto Neurológico Fleni, Buenos Aires, Argentina

[7]Dementia Research Centre & UK Dementia Research Institute, UCL Institute of Neurology, London, UK

[8]Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

[9]Department of Cellular Neurology, German Center for Neurodegenerative Diseases, Tübingen, Germany

[10]Department of Neurology, Emory, Atlanta, Georgia, USA

[11]Department of Clinical Research, German Center for Neurodegenerative Diseases, Munich, Germany

[12]Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany

[13]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[14]Department of Clinical Neuroscience, Osaka Metropolitan University Medical School, Nagaoka Sutoku University, Osaka, Japan

[15]Department of Neurology, Butler Hospital, Providence, Rhode Island, USA

[16]Deparment of Medicine & Health, University of New South Wales, Sydney, Australia

Correspondence
Stephanie Schultz and Jasmeer Chhatwal, Massachusetts General Hospital, Boston, Massachusetts USA.
Email: saschultz@mgh.harvard.edu and chhatwal.jasmeer@mgh.harvard.edu

Abstract

INTRODUCTION: Tau species lacking truncation of the N-terminal region, including plasma N-terminal tau fragment 1 (NT1), have been previously associated with cognitive decline, neurodegeneration, and tau pathology in late-onset sporadic Alzheimer's disease (AD).

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METHODS: Here, we examined cross-sectional and longitudinal plasma NT1 as a possible predictor of cognitive, clinical, and core AD biomarker trajectories in autosomal dominant AD (ADAD).

RESULTS: NT1 levels in ADAD mutation carriers (MC; $n = 132$) increased across the disease continuum, compared to non-carriers (NC; $n = 75$), becoming elevated about a decade prior to estimated symptom onset. Cross-sectional and longitudinal NT1 levels in MC were associated with clinical, cognitive, and biomarker changes. NT1 increases continued in symptomatic phases of disease, a distinct trajectory from that seen with CSF p-tau217 and other phospho-tau species.

DISCUSSION: Together, our results suggest that plasma NT1—alone or combined with other tau measures—may be useful in studying AD-related clinical, cognitive, and biomarker outcomes.

KEYWORDS
ADAD, biomarker, neurodegeneration, tauopathy

Highlights

- Leveraging a deeply phenotyped cohort of individuals carrying a pathogenic variant for autosomal dominant Alzheimer's disease (ADAD) and their non-carrier family members, our results suggest that plasma N-terminal tau fragment 1 (NT1) levels mirrored changes in clinical, cognitive, and neurodegenerative measures in ADAD, particularly in late asymptomatic and early symptomatic phases of disease.
- NT1 levels correlated with cerebrospinal fluid (CSF) measures of tau pathology but less so with CSF or imaging measures of β-amyloid pathology.
- Together with previous supportive findings in preclinical and symptomatic sporadic AD, these results suggest that plasma NT1—alone or combined with other tau measures—may be useful in studying AD-related tau pathology and neurodegeneration across a wide spectrum of disease.

1 | BACKGROUND

The advent of cost-effective and accessible blood-based biomarkers for tau pathophysiology has transformed the Alzheimer's disease (AD) field. Blood-based biomarkers that predict cognitive decline and AD pathology have the potential to accelerate AD therapeutic development and improve clinical care.[1] Prior work[2–4] suggests that fluid biomarkers of tau pathology, particularly post-translational modifications of tau, may be highly useful in the diagnosis of and risk stratification for AD-related tauopathy, neurodegeneration, and cognitive decline, and better reflect tau tangle load than established fluid biomarkers of tau pathology. While the vast majority of studies have focused on phosphorylation of tau at specific threonine or serine residues, truncation of tau represents another type of important and disease-relevant tau post-translational modification. N-terminal intact forms of tau appear to be secreted in response to injury, including the presence of toxic Aβ species. Several of these N-terminal intact forms of tau (including N-terminal tau fragments 1, 2, A, and B—NT1, NT2, NTA, and NTB) have been measured in cerebrospinal fluid (CSF) and blood, and have previously been shown to be associated with increasing age[5,6] and cognition[6] in down syndrome and cognitive decline,[3,7] neurodegeneration,[3,8] and tau pathology[4,9] in preclinical and symptomatic late-onset AD.

More recently, studies have shown, in sporadic AD populations, that elevations in NT1 may be amyloid-dependent.[7,10,11] To this end, several studies support the finding that NT1 may be actively secreted from neurons when exposed to amyloid-beta (Aβ),[12,13] suggesting NT1 may provide particular insight into Aβ-driven neurodegenerative processes. Autosomal dominant AD (ADAD) is caused by pathogenic mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) genes.[14] ADAD-causing pathogenic variants, by and large, lead to an overproduction of aggregation-prone amyloid-beta peptides.[15–18] While ADAD shares the neuropathological hallmarks of AD, including accumulation of amyloid-beta peptides-containing plaques and hyperphosphorylated tau-containing tangles, the deterministic and predictable onset of symptoms in ADAD mutation

carriers (MC) has also made ADAD an important model for sporadic AD.

Ongoing development of tau-directed therapies for the treatment of AD[19,20] (including in ADAD) and other neurodegenerative tauopathies is rapidly evolving and underscores the critical need for reliable biomarkers to measure and stage advancing tau pathology and assess response to therapy. Recently, fluid-based biomarkers have shown great promise in tracking AD progression.[21] In the setting of ADAD, rates of change in fluid-based phosphorylated-tau (p-tau) isoform levels appear dynamic across the disease course, showing a positive rate of change prior to symptom onset, then beginning to slow, with an eventual negative rate of change in p-tau levels observed after symptom onset.[22–24] This suggests that examining tau biomarkers beyond p-tau species may be helpful in staging and assessing treatment response, particularly in symptomatic individuals in whom p-tau measures may paradoxically decline over time. Here, we examined cross-sectional and longitudinal plasma NT1 as a possible predictor of cognitive, clinical, pathologic, and neurodegenerative trajectories across the entire ADAD continuum using data from the Dominantly Inherited Alzheimer Network Observational Study (DIAN-Obs).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Tau species lacking truncation of the N-terminal region, including cross-sectional levels of plasma N-terminal tau fragment 1 (NT1), have been previously associated with cognitive decline, neurodegeneration, and tau pathology in late-onset sporadic Alzheimer's disease (AD). These relevant citations are appropriately cited.
2. **Interpretation**: Our findings suggest that cross-sectionally and longitudinally, NT1 measured in plasma mirrors changes in clinical, cognitive, tau, and neurodegenerative measures in autosomal dominant AD.
3. **Future directions**: The manuscript highlights observed differences in the rates of change of NT1 from other tau species, suggesting that composite biomarkers considering different tau post-translational modifications may be useful in staging disease progression.

2 | METHODS

2.1 | Participants

The DIAN-Obs enrolls individuals who carry pathogenic variants in *PSEN1*, *PSEN2*, or *APP* (MC) and their non-mutation carrying family members (NC). A total of 288 plasma NT1 samples from 207 individuals (132 MC and 75 NC) with one or more concurrent plasma NT1 measures, Clinical Dementia Rating® (CDR) global score, CDR-Sum of Boxes (SB), Mini-Mental State Examination (MMSE), Pittsburgh Compound B (PiB)—positron emission tomography (PET) imaging, and structural magnetic resonance imaging (MRI) assessments were included in this study. Participants provided written informed consent prior to the completion of any study procedures, in accordance with Institutional Review Board policy at each participating site. Participants' most recent visit with available plasma NT1 was selected for cross-sectional analyses. A subset of 64 MC and 22 NC with two or more NT1 samples with concurrent longitudinal PiB-PET, MRI, and MMSE was included in longitudinal analyses.

2.2 | Plasma analyses

2.2.1 | NT1

For the current study, DIAN plasma samples (data freeze version 15) were shipped to the DIAN site in Boston, MA, USA. Prior to analysis, plasma samples were thawed on wet ice for 1 hour. Afterward, samples were centrifuged at 14,000 × g for 4 min and then diluted 1:4 with Tau 2.0 sample diluent reagent (Quanterix). Tau210 standard was diluted linearly with Tau 2.0 sample diluent to a concentration range of 540–0.02 pg/mL.

The NT1 Simoa assay utilized a 3-step protocol and was performed at ambient temperature on a single-molecule array (Simoa) HD-X analyzer (Quanterix). In step 1, 100 µL of standard, blank, or sample was added to beads coated with capture antibody and mixed for 30 min. The beads were then harvested and washed with the wash buffer. In step 2, biotinylated detection antibody (0.6 µg/mL) was added and incubated for 10 min 30 s, and the beads were then washed three times. In step 3, 150 pM streptavidin-β-galactosidase was added, and following a further wash step, enzyme substrate (resorufin β-D-galactopyranoside) was added. The bead-bearing complexes were resuspended and loaded into Simoa arrays, each containing 216,000 femtoliter-sized wells. The average enzyme unit per bead (AEB) was determined as described previously.[3] Standard curves of AEB versus Tau210 concentration were fitted to a five-parameter logistic function with 1/Y2 weighting. Samples were analyzed in triplicate. Samples with more than two runs below the lower limit of detection or CV > 20% (n = 21) and one extreme value (> 40 pg/L) were excluded from analyses. All samples were measured blinded to participant status.

2.2.2 | Neurofilament light chain

Measurement of neurofilament light chain (NfL) in plasma was performed on the Simoa HD-X platform (Quanterix) with commercially available assay kits. All samples were measured in duplicate using a two-step assay. Plasma samples were 1:4 auto-diluted with Simoa NfL sample diluent. Inter-assay variability was evaluated with three native

human CSF samples. All samples were measured blinded to participant status.

2.3 | Genotyping

The presence of ADAD pathogenic variants (Sanger sequencing) and apolipoprotein E (*APOE*) ε4 genotype (polymerase chain reaction [PCR]-based) was confirmed using lymphocyte-derived DNA at the DIAN Genetics Core (DGC; Mount Sinai School of Medicine) and the National Cell Repository for Alzheimer's Disease (NCRAD), as previously described.[25] Concordant results between DGC and NCRAD were required for inclusion in the present dataset. Individuals with a family Dutch-type CAA pathogenic variant (*APP* E693Q; $n = 19$) were excluded from the current study.

2.4 | Clinical evaluation

Each DIAN participant's estimated years to symptom onset (EYO) was calculated based on the participant's age subtracted from the expected age of symptom onset (AOO). As previously described, the AOO was determined through a combination of structured interviews to determine the age at onset of progressive cognitive decline for the participant's first-degree relative(s) and, if available, prior literature on the AOO for the participant's pathogenic variant.[26] Clinical evaluators were blind to the mutation status of participants. CDR-SB and MMSE scores were measured for each participant using structured interviews, as previously described.[27] Two individuals missing MMSE scores were excluded from this study. Data from NC with a CDR > 0 (i.e., 0.5 in all the cases, $n = 8$) either within all visits available or at least the latest visit were excluded.

2.5 | Imaging analyses

2.5.1 | Aβ PET

PET imaging was performed after a bolus injection of PiB. Acquisition consisted of a 70-min scan starting at injection or a 30-min scan beginning 40 min post-injection. Data in the 40–70 min post-injection window were converted to regional standardized uptake value ratios (SUVRs) relative to the cerebellar gray matter using FreeSurfer-derived regions of interest (ROIs) (PET Unified Pipeline, https://github.com/ysu001/PUP). Partial volume correction using a regional spread function technique was employed.[28] Scanner-specific spatial filters were applied to achieve a common resolution (8 mm) across PET scanners. MRI and PET data acquisition and processing have been described in detail in previous studies.[27,29] As previously described, a composite measure for mean cortical Aβ deposition was generated using the average across the left and right lateral orbitofrontal, medial orbitofrontal, rostral middle frontal, superior frontal, superior temporal, middle temporal, and precuneus regions.[30,31]

2.5.2 | MRI

DIAN Imaging data were screened for protocol compliance and artifacts. All sites used a 3T scanner qualified for use at study initiation and required to pass regular quality control assessments. Volumetric T1-weighted images were acquired for all participants and were processed using FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/)[32,33] and the Desikan–Killany atlas to produce regional estimates of gray-matter volume within brain regions. Analyses focused on the hippocampus as the a priori ROI. Hippocampal volume was averaged across left and right hemispheres and adjusted for total intracranial volume prior to statistical analysis.

2.6 | CSF analyses

CSF was obtained using procedures consistent with the biofluid protocol of the Alzheimer's Disease Neuroimaging Initiative (ADNI). Briefly, CSF was drawn using 21–22 g Sprotte or Quincke spinal needles into polypropylene tubes, followed by placement on dry ice and shipment to the DIAN Biomarker Core at Washington University. Frozen samples were then thawed, aliquoted, and stored at −84 degrees C until assayed. CSF assays for Aβ 40, Aβ 42, and p-tau 181 were performed at the DIAN Biomarker Core using an automated immunoassay system (LUMIPULSE G1200, Fujirebio, Malvern, PA) according to the manufacturer's specifications. All samples were measured blinded to participant status.

As previously described,[24] a subset of thawed CSF samples was additionally analyzed by nano liquid chromatography coupled to high-resolution tandem mass spectrometry (HRMS/MS) using parallel reaction monitoring and higher-energy collisional dissociation (HCD) fragmentation. Phosphorylation ratios on T181, S202, T205, and T217 were measured using the ratio of the HRMS/MS transitions from phosphorylated peptides and the corresponding non-phosphorylated peptides. Each phosphorylated/non-phosphorylated peptide endogenous ratio was normalized using the ratio measured on the HRMS/MS transitions of the corresponding phosphorylated/non-phosphorylated peptide internal standards. CSF %p-tau181, CSF %p-tau202, CSF %p-tau205, and CSF %p-tau217 were analyzed in a subset of 90 MC in the current study. All samples were measured blinded to participant status.

2.7 | Statistical analyses

To examine whether NT1 levels differed by mutation status (MC vs. NC), we performed a t-test. Next, the MC group was further subdivided into four groups based on CDR global and PiB-PET amyloid status (CDR = 0 and Aβ- [$n = 30$], CDR = 0 and Aβ+ [$n = 51$], CDR = 0.5 [$n = 34$], and CDR > 0.5 [$n = 17$]). We performed multiple comparison corrected (Tukey) linear regression to compare NT1 levels between the MC sub-groups as well as the NC group, adjusting for age, sex, and body mass index (BMI). BMI was included as a covariate in all

models due to its potential influence on blood-based biomarkers of tau and neurodegeneration[34,35]. Details of PiB-PET amyloid status in the cross-sectional NC and MC subgroups are provided in Table S1.

The extent to which NT1 levels change in MC and NC across the disease course (EYO), was estimated using a linear regression model with an EYO*Mutation group (MC vs NC) interaction term and NT1 as the dependent variable of interest. Covariates included age, sex, and BMI. Model parameters were estimated using an open-source package for Hamiltonian Markov chain Monte Carlo analyses, Stan (http://mc-stan.org/). This resampling approach leads to a distribution of parameter estimates across 10,000 iterations. We estimate the 90% credible intervals of the model fits at every EYO for NC and MC across the iterations, and the distribution from all iterations of the difference between NC and MC. The first EYO where NC and MC groups differed was determined to be the first point where the 90% credible intervals around the differences distribution between NC and MC did not overlap 0.

Linear and linear mixed-effects models assessed cross-sectional and longitudinal relationships between NT1 and cognitive, clinical, fluid, and imaging measures. Primary analyses included age, BMI, and sex as covariates. Longitudinal analyses included these covariates both alone and including interactions with time, in addition to terms for random slope and intercept. Intracranial volume (ICV) was accounted for in structural MRI analyses, with ICV regressed out of hippocampal volume prior to study entry.

A series of linear regression models was used to assess (1) %p-tau217 alone, (2) NT1 alone, and (3) NT1 and %p-tau217 together, and their associations with cognitive (MMSE) and neurodegeneration (hippocampal volume) outcomes. Akaike information criterion (AIC) and adjusted r-squared were evaluated.

Analyses in which cognitive variables were modeled also included years of education as a covariate. Analyses were implemented using R version 3.4.4 (R Foundation for Statistical Computing). A two-tailed $p < 0.05$ was considered statistically significant unless otherwise noted.

3 | RESULTS

3.1 | Participant characteristics

Cross-sectional participant characteristics are reported in Table 1.

3.2 | Plasma NT1 increases with disease severity

First, we examined the associations between NT1 and potential confounders, including age, sex, and BMI. Univariate analyses revealed that, cross-sectionally, higher plasma NT1 is associated with higher BMI (r [73] = 0.27, $p = 0.018$) and higher age (r [73] = 0.30, $p = 0.009$) in NC, but not MC (p's > 0.05). Plasma NT1 was not associated ($p > 0.05$) with sex in either the MC or NC groups. We next examined whether NT1 levels differed by mutation status (MC vs. NC). Plasma NT1 levels were higher in MC compared to NC (t[170.9] = -2.4, $p = 0.016$; Figure 1A), specifically between NC and MC with dementia (CDR1+; B[SE] = 4.00[0.7], $p < 0.001$; Figure 1B and Table S2). Within MC, plasma NT1 levels were higher within the CDR1+ group compared to the CDR0 groups (CDR0 Aβ- group: B[SE] = 4.01 [0.8], $p < 0.001$; CDR0 Aβ+ group: B[SE] = 3.68 [0.7], $p < 0.001$) and CDR0.5 group (B[SE] = 2.61 [0.8], $p = 0.006$; Figure 1B and Table S2). To determine the extent to which NT1 levels change in MC and NC across the disease course, we evaluated the pseudo-trajectories of NT1 as a function of EYO. Cross-sectional plasma NT1 levels were higher in MC compared to NC as a function of EYO (B[SE] = 0.07 [0.03], $p = 0.042$) and became abnormal starting approximately 10 years before estimated symptom onset (Figure 1C and Figure S1).

3.3 | Plasma NT1 is associated with cognitive and neurodegenerative measures

Cross-sectionally within the entire MC group, plasma NT1 most strongly correlated with CSF tau hyperphosphorylation measured with %p-tau205 ($r = 0.49$) and %p-tau217 ($r = 0.48$; Figure S2).

Adjusting for age, sex, BMI, and years of education, NT1 levels were associated with measures of cognition (MMSE: B[SE] = -0.53 [0.12], $p = 3.56 \times 10^{-5}$ and CDR-SB: B[SE] = 0.33 [0.07], $p = 1.52 \times 10^{-5}$; Figure 2A,B and Figure S3A).

Adjusting for age, sex, and BMI, NT1 levels were associated with measures of neurodegeneration ($\log_{10}$(NfL): B[SE] = 0.05 [0.01], $p = 2.38 \times 10^{-13}$ and ICV-adjusted Hippocampal volume: B[SE] = -90.49 [16.12], $p = 1.19 \times 10^{-7}$; Figure 2C,D and Figure S3A).

Additionally, we observed associations between plasma NT1 and other tau proteoforms ($\log_{10}$(p-tau181): B[SE] = 0.05 [0.01], $p = 3.33 \times 10^{-8}$; %p-tau202: B[SE] = 0.07 [0.03], $p = 0.009$; %p-tau181: B[SE] = 0.97 [0.24], $p = 8.43 \times 10^{-5}$; %p-tau205 B[SE] = 0.07 [0.01], $p = 2.89 \times 10^{-10}$; and %p-tau217: B[SE] = 0.73 [0.11], $p = 3.04 \times 10^{-10}$; Figure 2E–H and Figure S3A) and total tau ($\log_{10}$(total tau): B[SE] = 0.04 [0.01], $p = 3.46 \times 10^{-6}$; Figure 2J and Figure S3A). To a lesser degree, NT1 was also associated with CSF and brain amyloid levels (CSF Aβ 42/40: B[SE] = -0.003 [0.001], $p = 0.001$; PiB-PET: B[SE] = 0.11 [0.03], $p = 0.001$; Figure 2K, L, and Figure S3A).

In an exploratory analysis, we included an additional term for NT1*CDR grouping to examine the impact of disease stage (asymptomatic MC vs symptomatic MC) on the observed associations. As expected, there were differences in the relationship between NT1 and clinical (CDR-SB; B[SE] for NT1*CDR grouping term: 0.40 [0.14], $p = 0.004$) and cognitive (MMSE; B[SE] for NT1*CDR grouping term: -0.43 [0.15], $p = 0.004$). The relationship between NT1 and biomarker outcomes was not moderated by CDR group, except in the case of plasma NfL (B[SE] for NT1*CDR grouping term: 0.30 [0.13], $p = 0.022$; Figure S4).

TABLE 1 Background characteristics of cross-sectional sample.

Variable	Overall $n = 207$[1]	Non-carrier $n = 75$[1]	Carrier $n = 132$[1]	p-value[2]
Age (yr)	40.6 (11.1)	41.9 (12.2)	39.9 (10.4)	0.4
Sex				0.091
Male	82 (40%)	24 (32%)	58 (44%)	
Female	125 (60%)	51 (68%)	74 (56%)	
APOE4				0.7
APOE4-	150 (72%)	53 (71%)	97 (73%)	
APOE4+	57 (28%)	22 (29%)	35 (27%)	
Education (yr)	14.7 (2.8)	14.9 (2.3)	14.6 (3.0)	0.2
BMI	28.5 (6.0)	28.9 (6.5)	28.2 (5.7)	0.6
EYO (yrs)	−6.7 (11.0)	−5.9 (12.4)	−7.1 (10.2)	0.6
CDR Global				<0.001
CDR 0	156 (75%)	75 (100%)	81 (61%)	
CDR 0.5	34 (16%)	0 (0%)	34 (26%)	
CDR 1+	17 (8.2%)	0 (0%)	17 (13%)	
Plasma NT1 (pg/mL)	8.4 (2.8)	7.8 (2.5)	8.8 (2.9)	0.022

Abbreviations: APOE4, apolipoprotein E4; BMI, body mass index; CDR, Clinical Dementia Rating scale; EYO, estimated years to symptom onset; NT1, N-terminal tau fragment 1.
[1]Mean (SD); *n* (%).
[2]Wilcoxon rank sum test; Pearson's chi-squared test.

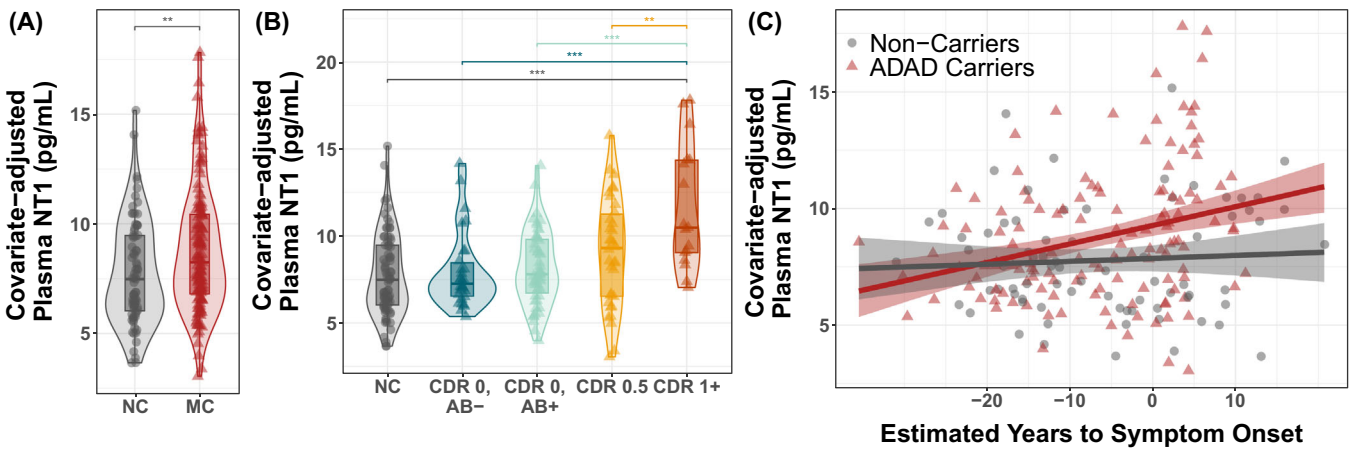

FIGURE 1 **Plasma NT1 increases with disease severity.** (A) Plasma NT1 levels were higher in MC (all CDR groups) compared to NC. (B) Between-group analyses show plasma NT1 levels were higher in severely cognitively impaired MC groups (see Table S2). Within MC, NT1 levels were higher within the CDR1+ group compared to the CDR0 groups and CDR0.5 group. Aβ positivity (AB+) was defined as cortical PiB-PET SUVR ≥ 1.25 SUVR. Between-group estimates of NT1 from models covariate-adjusted for BMI, sex, and age are provided in Table S2. (C) NT1 levels increase in MC (red) compared to NC (grey) as a function of EYO, adjusting for age, sex, and BMI, and become abnormal starting approximately 10 years before estimated symptom onset (Figure S1). Significant pairwise comparisons are depicted as * for $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$. Aβ, amyloid-beta; BMI, body mass index; CDR, Clinical Dementia Rating; EYO, estimated years to symptom onset; MC, mutation carrier; NT1, N-terminal tau fragment 1; PET, positron emission tomography; PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio.

3.4 | NT1 is a complementary biomarker for assessing cognition and neurodegeneration

Next, we examined whether the combination of NT1 and %p-tau217 improves the prediction of MMSE and hippocampal volume compared to NT1 or %p-tau217 alone. Comparing three models (%p-tau217 alone, NT1 alone, and NT1 + %p-tau217), the combined model with NT1 + %p-tau217, adjusting for relevant covariates, resulted in the best fit compared to models with NT1 or %p-tau217 alone, when examining both cognitive (MMSE) and neurodegeneration (hippocampal

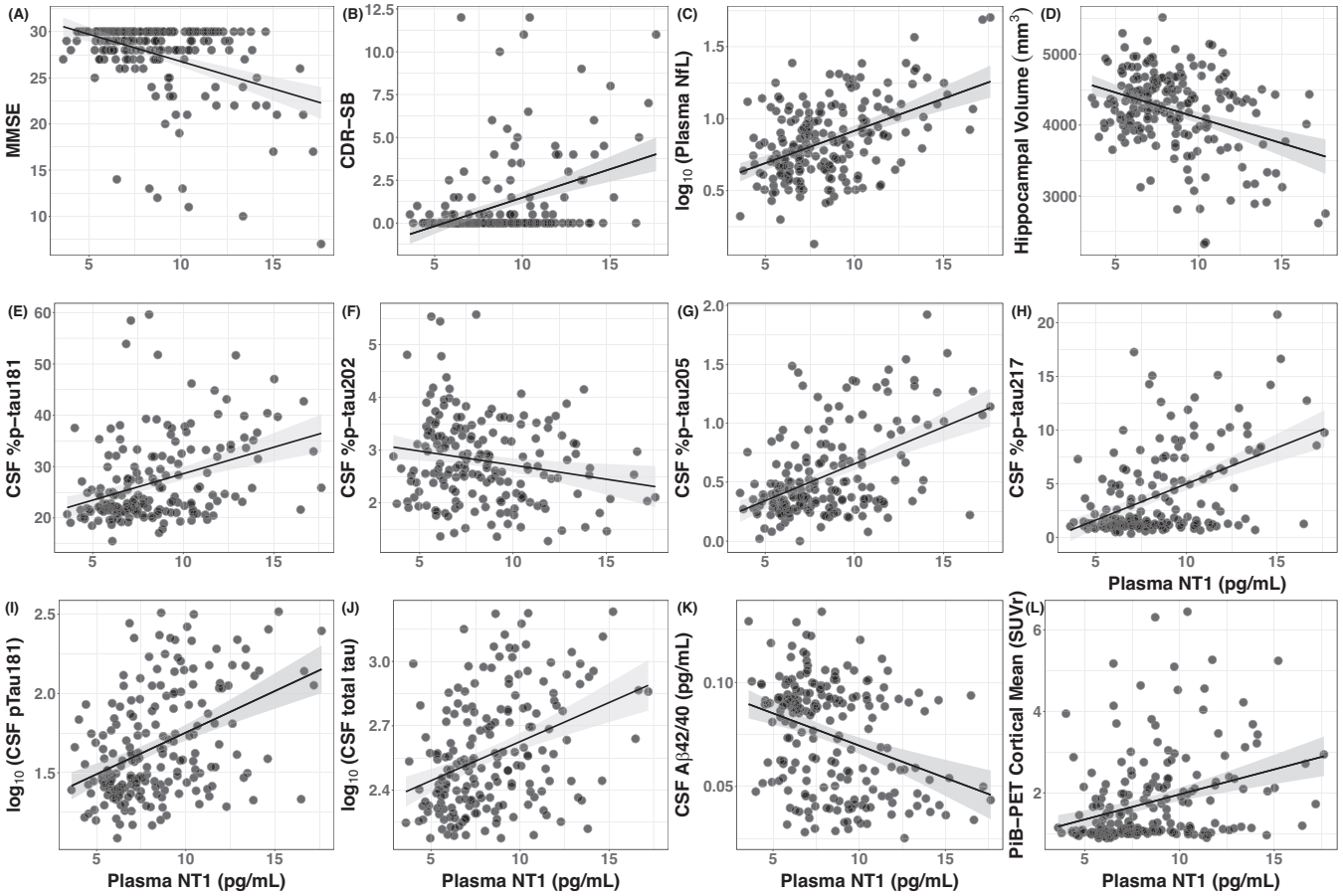

FIGURE 2 Plasma NT1 levels are associated with cognition, tau, and neurodegeneration in ADAD mutation carriers. Cross-sectional associations between plasma NT1 levels and MMSE (A; $n = 132$), CDR-SB (B; $n = 132$), plasma $\log_{10}$ (NfL) (C; $n = 131$) hippocampal volume (D; $n = 132$), CSF %p-tau181 (E; $n = 116$), CSF %p-tau202 (F; $n = 116$), CSF %p-tau205 (G; $n = 116$), CSF %p-tau217 (H; $n = 116$), CSF $\log_{10}$(p-tau181) (I; $n = 130$), CSF $\log_{10}$(total tau) (J; $n = 130$), Aβ42/40 (K; $n = 132$), and PiB-PET (L; $n = 132$) in MC. Standardized coefficients and 95% CI from linear regression models, adjusting for age, sex, and BMI are reported in Figure S3A. ADAD, autosomal dominant Alzheimer's disease; BMI, body mass index; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CSF, cerebrospinal fluid; MC, mutation carriers; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; NT1, N-terminal tau fragment 1; PET, positron emission tomography; PiB, Pittsburgh Compound B.

volume) outcomes (Table S3). Furthermore, when NT1 and %p-tau217 were entered into the same model, they account for unique variance (Table S4). Together, these results suggest that NT1 can be used in combination with and is complementary to other biomarkers, such as %p-tau217, for assessing neurodegeneration and cognition.

3.5 | Rate of change in plasma NT1 increases as a function of estimated years to symptom onset

Extending our cross-sectional findings to longitudinal measures in a subset of individuals with available data ($n = 86$; 64 MC and 22 NC; Figure S5A and Table S5) we explored the extent to which within-person rate of change in NT1 levels change in MC and NC across the disease course, we evaluated the trajectories of rate of change in NT1 as a function of baseline EYO. Adjusting for sex, baseline age, and baseline BMI, the rate of change in NT1 levels was increased in MC compared to NC as a function of EYO (B[SE] = 0.01 [0.003], $p = 0.018$) and became abnormal starting approximately 5 years before estimated symptom onset (Figure S5B,C).

3.6 | Rate of change in plasma NT1 is associated with rate of change in cognition and AD biomarkers

Within the MC group with longitudinal measures, rate of change in plasma NT1 in MC was associated with decreases in MMSE ($p = 7.77 \times 10^{-4}$; Figure 3A and Figure S3B), increases in CDR-SB ($p = 1.52 \times 10^{-4}$; Figure 3B and Figure S3B), increases in NfL ($p = 3.02 \times 10^{-8}$; Figure 3C and Figure S3B), hippocampal atrophy ($p = 5.64 \times 10^{-7}$; Figure 3D and Figure S3B), and decreases in rate of change in some CSF measures of tau pathology (%p-tau205: $p = 3.01 \times 10^{-9}$; and %p-tau217: $p = 1.77 \times 10^{-6}$; %p-tau181: $p = 0.007$; Figure 3E–G and Figure S3B). Rate of change in plasma NT1 was also associated with rate of change in CSF Aβ 42/40: $p = 0.016$ and in PiB-PET: $p = 0.008$, Figure 3H, I and Figure S3B).

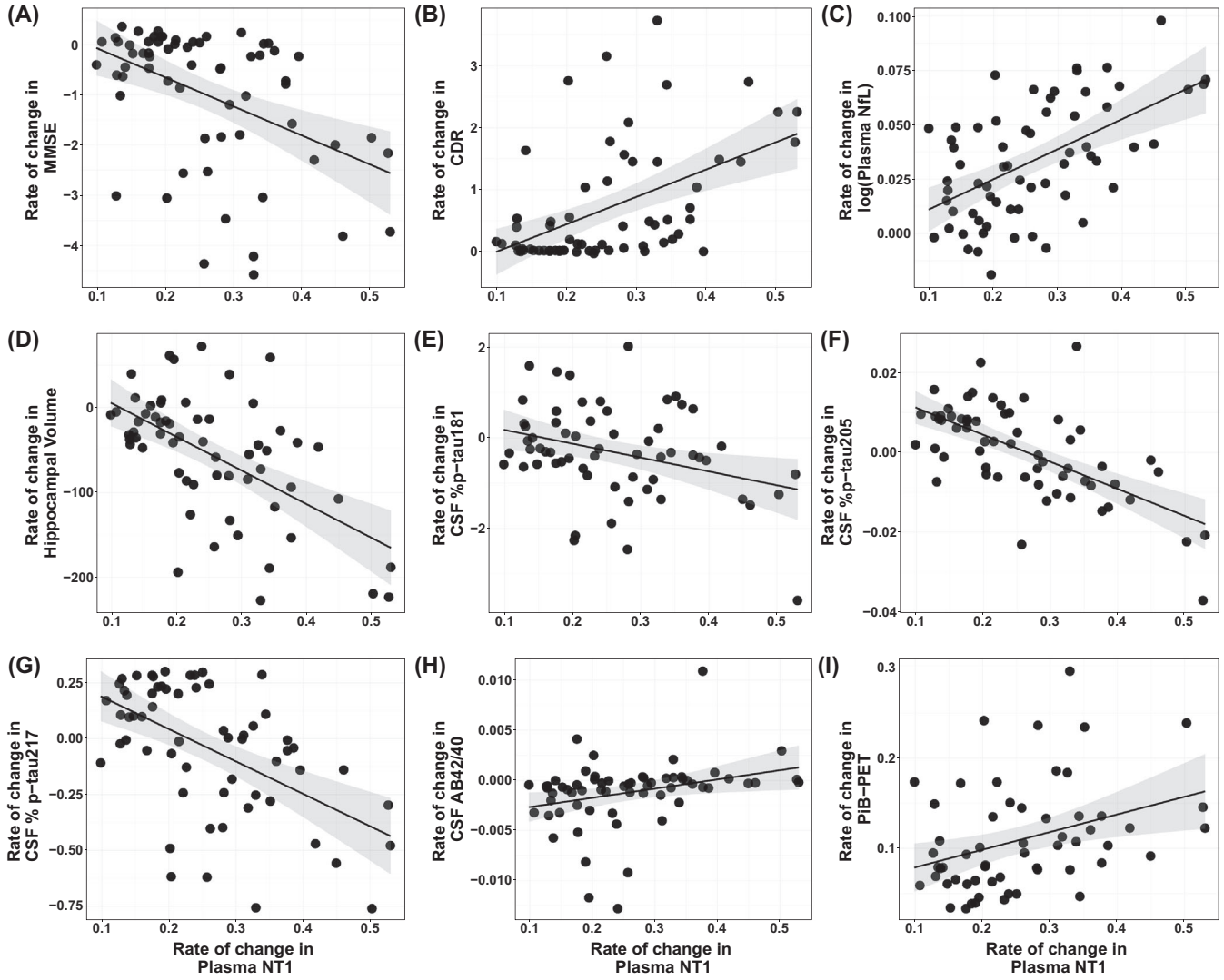

FIGURE 3 Rate of change in NT1 is associated with rate of change in cognitive, pathologic, and neurodegeneration measures. Associations between annualized rates of change for plasma NT1 and MMSE (A; $n = 64$), CDR-SB (B; $n = 64$), log10(plasma NfL)(C; $n = 64$), hippocampal volume (D; $n = 60$), CSF %pT181 (E; $n = 61$), CSF %pT205 (F; $n = 61$), CSF %pT217 (G; $n = 61$), CSF Aβ42/40 (H; $n = 64$), and PiB-PET (I; $n = 58$). Standardized coefficients and 95% CI are reported in Figure S3B. CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CSF, cerebrospinal fluid; MC, mutation carrier; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; NT1, N-terminal tau fragment 1; PET, positron emission tomography; PiB, Pittsburgh Compound B.

4 | DISCUSSION

Here, we investigated NT1 measured in plasma as a potential early AD biomarker that may provide complementary information to the more heavily studied p-tau species that are increasingly coming into use as core AD biomarkers. Both cross-sectionally and longitudinally, plasma NT1 levels correlated with changes in clinical, cognitive, and neurodegenerative measures in ADAD. While plasma NT1 levels were correlated with CSF tau species (including p-tau217), we observed that including NT1 in our models along with p-tau217 improved the prediction of cognition and neurodegeneration, suggesting that NT1 can be used in combination with and is complementary to other biomarkers, such as p-tau217, for assessing AD-related outcomes. Still, NT1 was less strongly associated with measures of β-amyloid burden, unlike what has been described with some measures of p-tau in DIAN.[23] Notably, longitudinal rates of change in plasma NT1 remained positive in symptomatic phases of ADAD. This contrasts with previously measured p-tau species in CSF, several of which show slowing or plateauing rates of change in symptomatic phases of disease.[24,36] Together with previous supportive findings in sporadic AD, these results suggest that plasma NT1 may be a valuable biomarker of AD-related tau pathology and neurodegeneration that may provide complementary information to widely used biomarkers based on tau phosphorylation.

Consistent with recent evidence linking plasma NT1 to tau accumulation[3,4,9] in sporadic AD populations, we observed that higher plasma NT1 levels and increased longitudinal rate of change were associated with greater cognitive impairment and cognitive decline.

NT1 levels were most closely associated with markers of neurodegeneration (especially hippocampal volume) and levels of %p-tau205, %p-tau217, and total tau from the CSF. The correlation of plasma NT1 with measures of neurodegeneration in ADAD is consistent with what has previously been observed in sporadic and preclinical AD, where prior work suggests that NT1 levels may capture aspects of tau pathology and progressive neuronal and synaptic loss. Our results support this notion, showing that cross-sectional increases in plasma NT1 are strongly associated with increased plasma NfL and CSF %p-tau205 levels.

Prior work in ADAD indicates that the rate of change in several phospho-tau species is positive prior to symptom onset, then rates of change begin to slow and eventually become negative in the peri-symptomatic and symptomatic phases of the disease.[22–24] This declining rate of change in p-tau in later stages of ADAD creates a challenge for implementing these biomarkers in clinical trial settings, as well as evaluating treatment effects on tau pathology. In contrast, we observed a steady increase in NT1 levels across the ADAD disease course, mirroring increases in plasma NfL and CDR-SB and decreases in hippocampal volume, MMSE, and CSF %p-tau205 and %p-tau217. The striking inverse relationships between the rate of change in plasma NT1 and those of CSF p-tau205 and p-tau217 highlight the differential changes in NT1 and phospho-tau measures, and, in turn, suggest that consideration of multiple biomarkers of tau may be needed to comprehensively reflect ADAD progression in early versus late stages of disease.

Similar to other plasma biomarkers,[35,37–39] NT1 was associated with age and BMI. NT1 levels were elevated in individuals with an ADAD-causing pathogenic variant compared to non-carriers. They began to increase in late presymptomatic phases of the disease, around 10 years before estimated symptom onset. The observed elevation in NT1 in MC compared to NC coincides with previously reported increases in fluid and imaging markers of neurodegeneration, including NfL and gray-matter volume, in ADAD.[35,40–43]

Lastly, we showed cross-sectionally and longitudinally that NT1 had the strongest relationship with multiple measures of neurodegeneration and tau pathology, while having comparatively weak associations with amyloid measures, including CSF Aβ 42/40 and PiB-PET. These findings add to the growing evidence that plasma NT1 better reflects increasing pathological tau accumulation rather than early β-amyloid deposition.[44–46]

A limitation of the current study is the lack of sufficient tau-PET data available to directly assess correlations between NT1 and tau-PET and to determine if NT1 is more strongly associated with tau-PET levels than p-tau isoforms. As the DIAN-Obs study continues to collect tau-PET data in this cohort, we will be poised to evaluate this in the future. Additionally, our longitudinal findings should be interpreted with some caution, given the relatively small sample size, particularly in comparing the rate of change in NT1 and the rate of change in CSF p-tau isoforms. While our study focused on examining plasma NT1 as a suitable biomarker of tau pathology in ADAD and comparisons to established AD biomarkers, future studies incorporating other emerging fluid-based tau biomarkers (e.g., MTBR -au, brain-derived tau species) across multiple platforms will add to our understanding of NT1 as a biomarker of tau pathology in ADAD.

Leveraging a deeply phenotyped cohort of individuals carrying a pathogenic variant for ADAD and their non-carrier family members, our results suggest that plasma NT1 levels mirrored changes in clinical, cognitive, and neurodegenerative measures in ADAD, particularly in late asymptomatic and early symptomatic phases of disease. NT1 levels correlated with CSF measures of tau pathology but less so with CSF or PET measures of β-amyloid pathology. Together with previous supportive findings in preclinical and symptomatic sporadic AD, these results suggest that plasma NT1—alone or combined with other fluid-based tau measures—may be useful in studying AD-related tau pathology and neurodegeneration.

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CONFLICT OF INTEREST STATEMENT

D.J.S. is a director and consultant of Prothena Biosciences. L.L. is a consultant of KorroBio, Inc. J.P.C. has served on medical advisory boards for ExpertConnect. S.S. reports research support from Butler Hospital for conducting clinical trials through grants or contracts from Biogen, Eisai, Genentech, Roche, Lilly, and Johnson and Johnson; S.S. has received consulting fees from Abbvie, Acumen, Biogen, Cognition, Eisai, Genentech, Kisbee, Labcorp, Lilly, Neurophet, NovoNordisk, Prothena and Roche. A.I.L. is a director and consultant of EmTheraPro, and an advisor for Cognition Therapeutics, Asha Therapeutics, NextSense, and Cognito. N.R.B. and R.J.B. are coinventors on the following US patent applications: 'Methods to detect novel tau species in CSF and use thereof to track tau neuropathology in Alzheimer's disease and other tauopathies' (PCT/US2020/046224,

N.R.B. and R.J.B.); 'CSF phosphorylated tau and amyloid beta profiles as biomarkers of tauopathies' (PCT/US2022/022906, N.R.B. and R.J.B.); 'Plasma based methods for detecting CNS amyloid deposition' (PCT/UC2018/030518, R.J.B.); and 'Methods of diagnosing and treating based on site-specific tau phosphorylation' (PCT/US2019/030725, N.R.B. and R.J.B.). N.R.B. and R.J.B. may receive a royalty income based on technology licensed by Washington University to C2N Diagnostics.

All other authors (S.A.S., Y.R., B.O., A.K.A., W.Y., B.A.G., J.H., J.C.M., R.J.P., R.F.A., N.F., G.S.D., M.J., J.L., H.M., P.S., E.M., and R.S.) have nothing to disclose.

CONSENT STATEMENT

Participants provided written informed consent prior to the completion of any study procedures, in accordance with Institutional Review Board policy at each participating site.

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