1-1-2022

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10.1002/alz.12684

Vöglein, J., Franzmeier, N., Morris, J. C., Dieterich, M., McDade, E., Simons, M., ... & Dominantly Inherited Alzheimer Network. (2022). Patterns and implications of neurological examination findings in autosomal dominant Alzheimer disease. *Alzheimer's & Dementia*. Advance online publication.

https://doi.org/10.1002/alz.12684

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Received: 21 September 2021 | Revised: 21 March 2022 | Accepted: 27 March 2022

DOI: 10.1002/alz.12684

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Pattern and implications of neurological examination findings in autosomal dominant Alzheimer disease

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Funding information
Dominantly Inherited Alzheimer Network, Grant/Award Number: UF1 AG032438; National Institute on Aging; German Center for Neurodegenerative Diseases; NIHR Queen Square Dementia Biomedical Research Centre and the MRC Dementias Platform UK, Grant/Award Numbers: MR/L023784/1, MR/009076/1; Deutsche Forschungsgemeinschaft

[Correction added on May 28, 2022, after first online publication: An extraneous letter that was accidentally introduced during file preparation was removed from the first word in the article title.]

Abstract

Introduction: As knowledge about neurological examination findings in autosomal dominant Alzheimer disease (ADAD) is incomplete, we aimed to determine the frequency and significance of neurological examination findings in ADAD.

Methods: Frequencies of neurological examination findings were compared between symptomatic mutation carriers and non mutation carriers from the Dominantly Inherited Alzheimer Network (DIAN) to define AD neurological examination findings. AD neurological examination findings were analyzed regarding frequency, association with and predictive value regarding cognitive decline, and association with brain atrophy in symptomatic mutation carriers.

Results: AD neurological examination findings included abnormal deep tendon reflexes, gait disturbance, pathological cranial nerve examination findings, tremor, abnormal finger to nose and heel to shin testing, and compromised motor strength. The frequency of AD neurological examination findings was 65.1%. Cross-sectionally, mutation carriers with AD neurological examination findings showed a more than two-fold faster cognitive decline and had greater parieto-temporal atrophy, including hippocampal atrophy. Longitudinally, AD neurological examination findings predicted a significantly greater decline over time.

Discussion: ADAD features a distinct pattern of neurological examination findings that is useful to estimate prognosis and may inform clinical care and therapeutic trial designs.

KEYWORDS
Alzheimer disease, autosomal dominant Alzheimer disease, differential diagnosis, neurological examination, neurological examination findings, predictive value, prognosis

1 | INTRODUCTION

The neurological examination has formed the basis for the evaluation of neurological patients for over a century.[1] It is highly standardized, and the attribution of pathological findings to distinct brain regions is well established.[2] The neurological examination guides the process of diagnostic investigations and informs treatment decisions in a non-invasive as well as time- and cost-effective manner.[3] Physical examination, in combination with medical history, determined the correct diagnosis in approximately 40% of patients without any further diagnostic procedures in outpatient cohorts.[4,5]

Autosomal dominant Alzheimer disease (ADAD) is a rare monogenic form of AD.[6] ADAD shows comprehensive overlap with sporadic AD. With respect to clinical manifestation, both ADAD and sporadic AD exhibit typical amnestic and atypical non-amnestic cognitive presentations[7-11] and non-cognitive clinical symptoms such as motor symptoms, seizures, and myoclonus.[8,9,12-16] Neuropsychological characteristics include memory disturbance, visuospatial deficits, executive dysfunction, and in later stages, generalized cognitive decline in both AD variants.[7,10] ADAD and sporadic AD share biomarker changes proposed by the amyloid hypothesis.[6,17-19] Neuropathological findings in both AD forms comprise amyloid beta plaques and tau tangles with a higher burden including higher Braak scores in ADAD. Lewy body disease was reported in about 30% to 50% in ADAD and sporadic AD. Cerebral amyloid angiopathy is common in both disorders, with a higher severity in some ADAD mutations.[20-22] Non AD co-pathologies such as TAR DNA-binding protein 43 (TDP-43) pathology, argyrophilic grain disease, hippocampal sclerosis, and infarcts are much more common in sporadic AD.[21] ADAD and sporadic AD differ in the mean age at clinical onset, since ADAD starts on average in the mid-40s and sporadic AD in the 70s.[23] As a result, individuals with ADAD usually lack the age-related comorbidities commonly seen in sporadic AD, for example peripheral neuropathy, orthopedic problems, falls and consecutive traumatic brain injury, and the aforementioned neuropathological non AD co-pathologies including infarcts.[21,24-26] Since neurological examination can be influenced substantially by age and age-related comorbidities,[27] ADAD provides an opportunity to determine an AD-specific pattern of neurological examination findings.

We hypothesized that ADAD holds a distinct pattern of neurological examination findings (NEF) that may inform cognitive prognosis and clinical decision-making. Therefore, the aims of this study were to (1) determine the frequency of NEF in ADAD, (2) reveal a potential change in frequency over the disease course, (3) test the capacity of NEF to distinguish between mutation carriers (MC) and mutation non carriers (non MC) among mildly cognitive impaired individuals at risk, (4) analyze associations between NEF in ADAD and both cognitive performance and brain atrophy as assessed by magnetic resonance imaging (MRI), and (5) investigate the possibility of predicting cognitive decline over time based on NEF.

RESEARCH IN CONTEXT

1. **Systematic Review**: A comprehensive literature review in PubMed regarding neurological examination findings (NEF) in Alzheimer disease (AD) including a wide range of neurological manifestations in AD on a symptom and diagnosis level was performed (PubMed terms: "Alzheimer disease"/"autosomal dominant Alzheimer disease"/"familial Alzheimer disease" and "neurological examination findings"/"neurological findings"/"neurological symptoms"/"neurological manifestations").
2. **Interpretation**: NEF in AD are frequent and indicative of a broader affection of brain areas beyond those involved in cognition. This is associated with a poorer prognosis.
3. **Future Directions**: The knowledge about the association between the presence of non-cognitive NEF and a worse cognitive course may inform future therapeutic AD trial designs.

HIGHLIGHTS

- Neurological examination findings in Alzheimer disease (AD-NEF) are frequent.
- AD-NEF are associated with a two-fold faster cognitive decline.
- Patients with AD-NEF exhibit greater parieto-temporal atrophy, including hippocampal atrophy.
- AD-NEF predict a greater cognitive decline.

2 | METHODS

2.1 | Participants

We analyzed data from the observational study of the Dominantly Inherited Alzheimer Network (DIAN) that aims to investigate the clinical and biomarker course in individuals at risk for or with ADAD over time. That is, the DIAN observational study includes data from asymptomatic and symptomatic MC for ADAD and mutation-negative family members of ADAD MC (non MC). For this study, all patients with early-onset AD from the DIAN observational study at the time of data freeze 14 (n = 118) were evaluated. As it is a prerequisite for entering the DIAN study to be member of a family with a known ADAD mutation, no individuals with early-onset AD without ADAD mutations were included. Hence, all of the patients with early-onset AD studied here carried a mutation in either *presenilin 1* (*PSEN1*), the gene encoding for amyloid precursor protein (*APP*), or *presenilin 2* (*PSEN2*). Data were gathered at 17 study sites around the world (United States, UK, Australia, Japan, South Korea, Argentina, Spain, and Germany) between January 2008 and February 2020. Clinical data of the DIAN study participants were collected using the Uniform Data Set version 2 from the National Alzheimer's Coordinating Center (NACC-UDS2).[28] Clinical raters were blinded to the mutation status of the participants. The protocol of the DIAN observational study was approved by the respective institutional review boards of the study sites. The DIAN study is conducted in accordance with the declaration of Helsinki. Each study participant provided written informed consent.

2.2 | Genetic analyses

For identification of mutations in *PSEN1*, *PSEN2*, and *APP* the respective exons were amplified using polymerase chain reaction, followed by Sanger sequencing.[6]

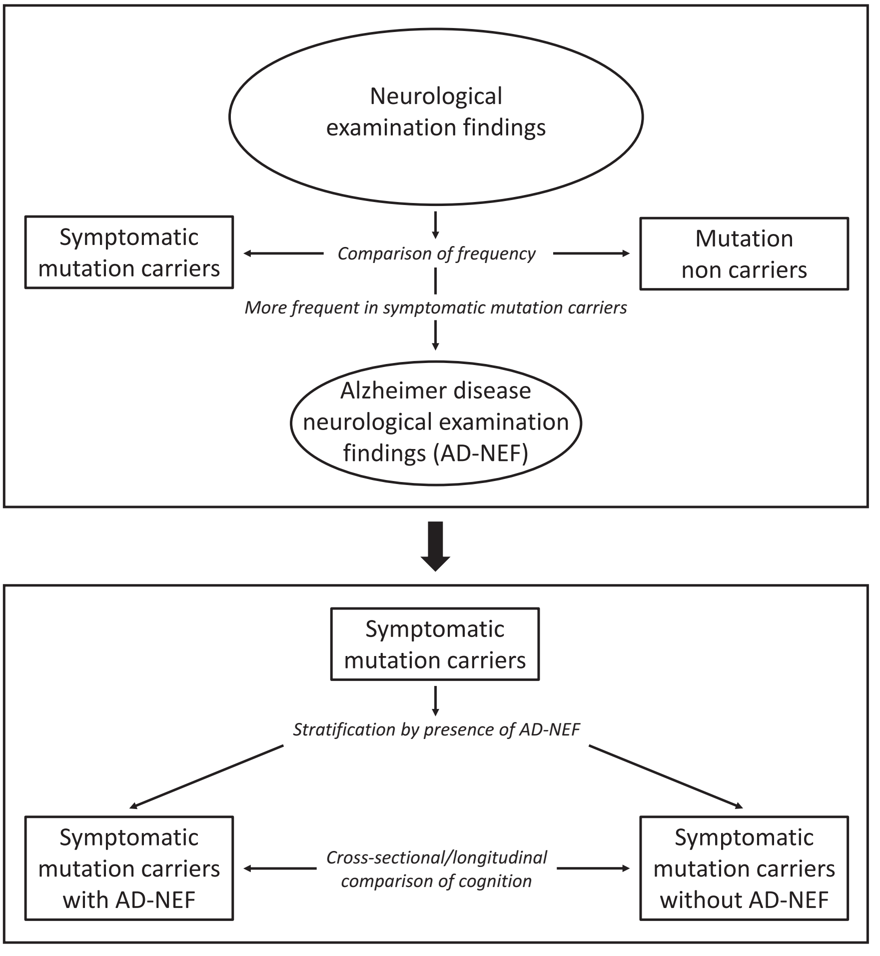

FIGURE 1 Flow chart depicting the processes to determine Alzheimer disease neurological examinations findings (AD-NEF), of group stratifications, and of analyses performed in this study

2.3 | Neurological examination

The DIAN observational study includes a comprehensive, structured neurological examination that is completed by a trained clinical rater at each visit. The neurological examination is subdivided into 13 domains including visual impairment, auditory impairment, tremor, consciousness, cranial nerve examination findings, motor strength, finger to nose testing, heel to shin testing, sensory testing, deep tendon reflexes, plantar reflexes, gait, and other findings. Each item is rated either as absent versus present or normal versus abnormal depending on whether the respective domain label represents a pathological condition. For each rating as abnormal or present in the case of pathological conditions the study clinician may provide further details.

2.4 | Definition and classification of symptomatic ADAD

In accordance with previous studies from the DIAN,[6,9,18] the clinical dementia rating (CDR) global score[29] was used to classify an individual as symptomatic (CDR global >0) or asymptomatic (CDR global = 0). For investigating the pattern of NEF across the course of ADAD, we stratified symptomatic MC by CDR global scores (groups for CDR global 0.5, 1, and 2 or 3). As numbers in the groups with CDR 2 ($n = 7$) and CDR 3 ($n = 5$) were small, these groups were taken together to form a group of MC with CDR scores of >1.

2.5 | Determination of Alzheimer disease neurological examination findings and group stratification procedures

The frequency of findings in the single subscale components of the neurological examination was compared between symptomatic MC and non MC. As both groups were relatively young (46.1 and 38.2 years, respectively) and difference in age was only 7.9 years, we did not perform statistical age matching that can cause bias itself.[30] For those neurological examination subscale findings that occurred more frequently in symptomatic MC than in non MC we introduced the term Alzheimer disease neurological examination findings (AD-NEF). Then, symptomatic MC were stratified by the presence of at least one AD-NEF into symptomatic MC with AD-NEF and symptomatic MC without AD-NEF. The latter stratification was done to form a cross-sectional population, that is, by the use of data from baseline visits, and a longitudinal population that included only symptomatic MC with at least the baseline visit and one follow-up visit (Figure 1).

2.6 | Calculation of disease duration

If a participant is rated as symptomatic in the DIAN observational study, the rating clinician determines the age at symptom onset by exploring the earliest progressive symptom from a predefined list of symptoms. Disease duration was calculated as the difference between the age of a participant at the time of evaluation minus her/his age at symptom onset.

2.7 | Relevant comorbidities

The data set was screened for relevant comorbidities that can influence NEF. Two participants had a history of stroke, one in the symptomatic MC group and one in the non MC group (0.8% vs 0.5%, $P = 1$). Three participants had a history of traumatic brain injury, one in the symptomatic MC group and two in the non MC group (0.8% vs 0.9%, $P = 1$). The one symptomatic mutation carrier with a history of stroke was also part of the longitudinal data set, in the symptomatic MC without AD-NEF group. The one symptomatic MC with traumatic brain injury was not part of the longitudinal data set. These participants were included in the analyses, as it was not determinable if these comorbidities actually affected NEF, were very rare, were equally distributed between groups, and in the case of stroke may be a consequence of AD-associated cerebral amyloid angiopathy.

2.8 | Magnetic resonance imaging

Structural MRI included a three-dimensional magnetization-prepared rapid acquisition with gradient echo (3D MPRAGE) sequence on 3T scanners with 1.1×1.1×1.2 mm voxel resolution. For the current analysis, we used FreeSurfer-processed (Version 6) region of interest (ROI) data (i.e., cortical thickness and subcortical volumes) in Desikan-Killiany Atlas space,[31] provided by the DIAN neuroimaging core.

2.9 | Statistical analysis

2.9.1 | Baseline comparisons

Baseline parameters were compared using Student *t*-test for continuous variables and chi-square test or Fisher exact test for categorical variables, where appropriate.

2.9.2 | Frequencies of neurological examination findings

We used chi-square test or Fisher exact test, as appropriate, for comparison of frequencies of NEF between groups. False discovery rate correction (via Benjamini-Hochberg method) was used to account for multiple comparisons.

2.9.3 | Cross-sectional analyses

To analyze the association between the presence of AD-NEF and cognition over time, we fitted a linear mixed effects model including random intercepts with the main effects disease duration and presence/absence of AD-NEF and a disease duration*presence/absence of AD-NEF interaction term using CDR – Sum of Boxes (CDR-SB) as the outcome measure. The CDR-SB score ranges from 0 to 18, with higher values indicating worse cognitive performance. CDR-SB was chosen based on its advantages as an outcome parameter including a comprehensive assessment of cognitive performance and an almost linear decline in AD.[32]

In symptomatic MC, exploratory cross-sectional structural MRI analyses were performed to determine whether the presence of AD-NEF was associated with increased gray matter atrophy determined via analyses of cortical thickness and subcortical volumes, using analyses of covariance (ANCOVA) controlling for disease duration and global Pittsburgh compound B–positron emission tomography standardized uptake value ratio (PiB-PET SUVR). Details with respect to the acquisition of PiB-PET in the DIAN observational study were described before.[6]

In addition, exploratory analyses were performed to determine whether the single AD-NEF, ataxia, or saccadic smooth pursuit eye movement were associated with specific patterns of gray matter atrophy determined via analyses of cortical thickness and subcortical volumes, using ANCOVA controlling for disease duration, PiB-PET SUVR, and for all other AD-NEF. As an indicator of ataxia, a pathological finding in either finger to nose or heel to shin testing was used.

2.9.4 | Longitudinal analyses

For investigation of a longitudinal association between AD-NEF and cognitive decline over time, that is, the rate of change in CDR-SB, a linear mixed effects model that included disease duration and presence/absence of AD-NEF at each visit as the main effects and a disease duration*presence/absence of AD-NEF interaction term with CDR-SB as the outcome parameter was used. To investigate the predictive capacity of AD-NEF regarding a future cognitive decline over time, a linear mixed effects model that included disease duration and presence/absence of AD-NEF at baseline as the main effects and a disease duration*presence/absence of AD-NEF at baseline interaction term with CDR-SB as the outcome parameter was used. The models included random slopes for each individual with variance components as the covariance matrix across random effects. For selection of the best fitting model the goodness-of-fit Akaike information criterion was used for the linear mixed effects models in this study. Linear mixed effects models were chosen for analyses because of several benefits including the ability to increase statistical power and to deal with unequal numbers of measurements or intervals.[33]

Missing data were considered missing at random. All tests were performed two-sided. *P* values less than .05 were considered statistically

TABLE 1 Comparison of baseline characteristics between symptomatic mutation carriers and mutation non carriers

	Symptomatic mutation carriers (*n* = 118, 35.9%)	Mutation non carriers (*n* = 211, 64.1%)	*P* value
Age (years), mean (SD)	46.1 (10.0)	38.2 (11.4)	*<.001*
Sex (female), *n* (%)	56 (47.5)	87 (41.2)	.27
Education (years), mean (SD)	13.5 (3.4)	14.7 (2.9)	*.001*
At least one NEF, *n* (%)	69 (65.1)	47 (25.3)	*<.001*
Age at onset (years), mean (SD)	42.6 (8.8)	na	na
Disease duration (years), mean (SD)	3.7 (2.9)	na	na
CDR global, *n* (%)	0.5, 78 (66.1) : 1, 28 (23.7) : 2, 7 (5.9) : 3, 5 (4.2)	0, 196 (92.9) : 0.5, 15 (7.1)	*<.001*
CDR-SB, mean (SD)	3.8 (4.0)	0.07 (0.27)	*<.001*
MMSE, mean (SD)	22.5 (7.0)	29.0 (1.3)	*<.001*
Mutated gene, *n* (%)	*PSEN1*, 97 (82.2) : *APP*, 19 (16.1) : *PSEN2*, 2 (1.7)	na	na
APOE ε4 carrier, *n* (%)	34 (29.3)	59 (29.1)	.96

P values below .05 are italicized.
Abbreviations: SD, standard deviation; NEF, neurological examination finding; CDR, Clinical Dementia Rating; SB, Sum of Boxes; MMSE, Mini-Mental State Examination; *APOE, apolipoprotein E*.

significant. IBM SPSS Statistics Version 25 and R statistical software (Version 3.6.1) were used for statistical analyses.

2.10 | Role of the funding source

The funding source had no role in study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

3 | RESULTS

3.1 | AD-NEF

Baseline data regarding AD-NEF were available for 118 symptomatic MC and 211 non MC. Clinical and genetic parameters at baseline are listed and compared between groups in Table 1.

An abnormal neurological examination result, defined by the presence of at least one NEF, occurred more frequently in symptomatic MC compared to non MC (65.1% vs 25.3%, $P < .001$). Symptomatic MC exhibited more frequently abnormal findings in nine subdomains of the neurological examination. The highest frequency of abnormal findings showed the subdomain deep tendon reflexes (35.9% in symptomatic MC vs 3.3% in non MC, $P < .001$), followed by other findings (22.4% vs 2.7%, $P < .001$), gait (17.8% vs 2.8%, $P < .001$), cranial nerve examination findings (14.4% vs 4.7%, $P = .002$), tremor (12.7% vs 4.7%, $P = .009$), finger to nose testing (11.0% vs 0%, $P < .001$), heel to shin testing (7.7% vs 0.5%, $P = .001$), plantar reflexes (6.8% vs 1.4%, $P = .02$), and motor strength (5.1% vs 0.9%, $P = .027$). Abnormal findings in these nine subdomains of the neurological examination are referred to as AD-NEF in this article. All of these differences remained statistically significant after correction for multiple comparisons. There were no subdomains in which abnormal neurological examination findings occurred more frequently in non MC than in symptomatic MC (Figure 2). No statistically significant differences in frequencies of AD-NEF were observed between MC with a global CDR score of 0 or in non MC (11.1% vs 14.6%; $P = .33$).

For the five most frequent AD-NEF pathological deep tendon reflexes, gait disturbance, abnormal cranial nerve examination findings, tremor, and other findings, specifications provided by the respective clinical raters were available. The most frequent findings within the respective AD-NEF were asymmetrical brisk deep tendon reflexes, reduced arm swing while walking, saccadic smooth pursuit eye movement, postural tremor, and increased muscle tone. Further specifications are depicted in Figure 3.

The ADAD MC in this study had 46 different mutations (49 *PSEN1*, 1 *PSEN2*, and 6 *APP* mutations). The single AD-NEF were compared regarding their respective frequency between single mutations using chi-square test and false discovery rate correction (via Benjamini-Hochberg method) to account for multiple comparisons. There was no difference in frequency of any AD-NEF between the single ADAD mutations.

3.2 | AD-NEFs in symptomatic MC stratified by disease stage

The frequencies of AD-NEF in symptomatic MC were analyzed by disease stage determined by CDR global scores (Figure 4). The frequency of all AD-NEF increased over the whole disease course. In all disease stages abnormal deep tendon reflexes were the most frequent finding among AD-NEF. Frequency was 33.3% at CDR 0.5, remained stable at CDR 1, and rose to 58.3% at CDR >1. Gait disturbance was present in 9.0% at CDR 0.5 and rose steadily to 28.6% at CDR 1 and to 50.0% at CDR >1. Frequency of abnormal cranial nerve examination findings

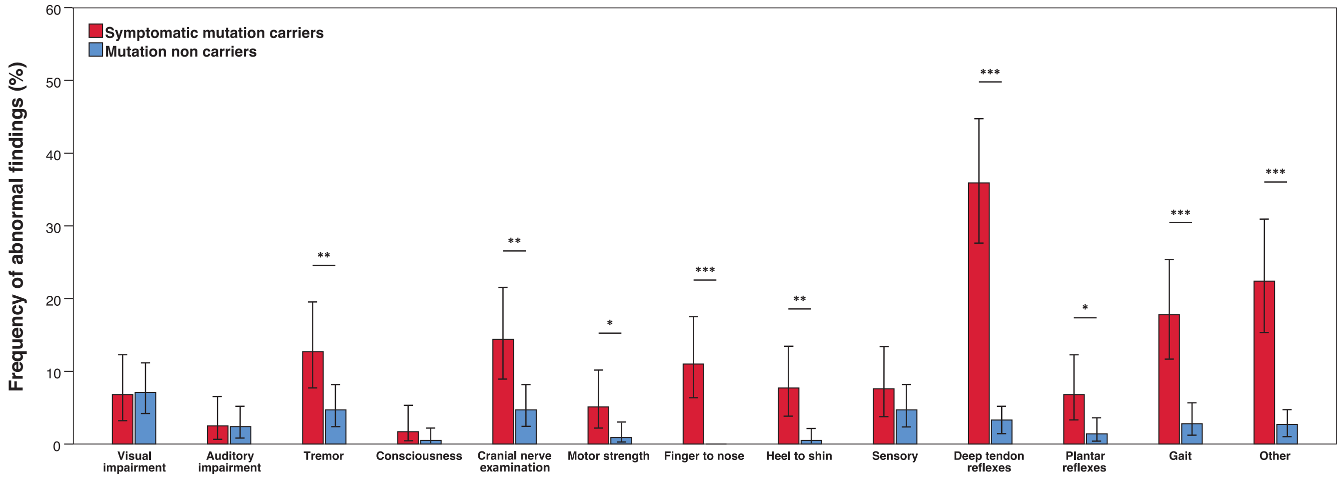

FIGURE 2 Comparisons of frequencies of neurological examinations findings between symptomatic mutation carriers and mutation non carriers. Tremor, abnormal cranial nerve examination findings, compromised motor strength, abnormal findings on finger to nose testing and heel to shin testing, pathological deep tendon reflexes, abnormal plantar reflexes, gait disturbance, and other findings were more frequent in symptomatic mutation carriers. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$. Error bars represent 95% confidence intervals

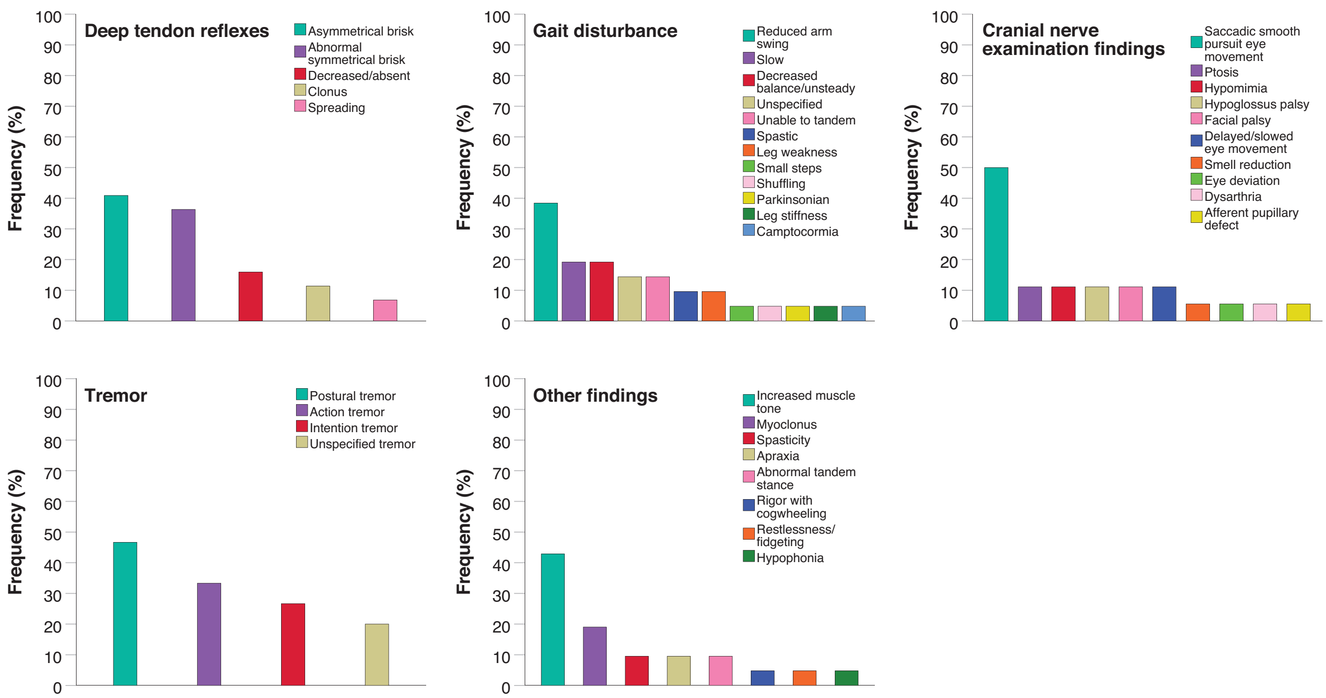

FIGURE 3 Particular signs and their frequencies within the group of the five most frequent Alzheimer disease neurological examination findings pathological deep tendon reflexes, gait disturbance, abnormal cranial nerve examination findings, tremor, and other findings. The most frequent particular signs of each of the five Alzheimer disease neurological examination findings were asymmetrical brisk deep tendon reflexes, reduced arm swing while walking, saccadic smooth pursuit eye movement, postural tremor, and increased muscle tone

was in the medium range of frequencies across disease stages: 11.5% at CDR 0.5, stayed roughly stable at CDR 1 (10.7%), and increased to 41.7% at CDR >1. Tremor occurred in 9.0% at CDR 0.5, its frequency rose slightly to 14.3% at CDR 1 and then more steeply to 33.3% at CDR >1. Abnormal finger to nose testing was found in a relatively small percentage of 2.6% at CDR 0.5, its frequency increased steeply to 28.6% at CDR 1, and then decreased slightly to 25.0% at CDR >1. Abnormalities in heel to shin testing exhibited the lowest frequency at CDR 0.5 (1.3%), and rose relatively steadily to 17.9% at CDR 1, and to 27.3% at CDR >1, in the medium range of frequencies of AD-NEF in the CDR 1 and

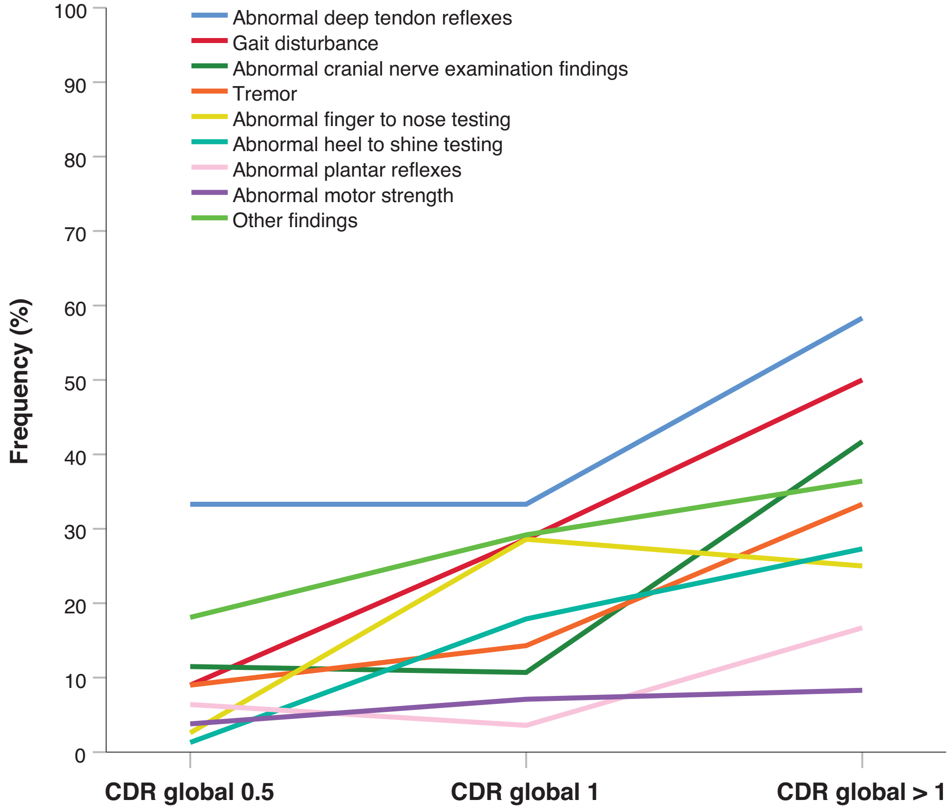

FIGURE 4 Frequencies of Alzheimer disease neurological examination findings stratified by global CDR scores. All Alzheimer disease neurological examination findings increased in frequency with CDR global stages. Abnormal deep tendon reflexes were the most frequent finding in all disease phases. Gait disturbance exhibited the steepest increase in frequency with autosomal dominant Alzheimer disease progression. Abbreviations: CDR, Clinical Dementia Rating

CDR >1 groups. Frequencies of abnormal plantar reflexes were in the lower range of frequencies through all disease stages. They were present in 6.4% at CDR 0.5, slightly declined in frequency to 3.6% at CDR 1, and rose relatively steeply to 16.7% at CDR >1. Also in the lower frequency range through all disease stages were abnormalities in motor strength. They occurred in 3.8% at CDR 0.5 and increased slightly to 7.1% at CDR 1 and to 8.3% at CDR >1.

3.3 | Association between AD-NEF and cognition

To analyze the associations between AD-NEF and cognitive performance, symptomatic MC were stratified in groups by the presence ($n = 64$) or absence ($n = 42$) of AD-NEF. Baseline clinical and genetic parameters are shown in Table 2. Symptomatic MC with AD-NEF exhibited a worse cognitive performance as assessed by CDR-SB than symptomatic MC without AD-NEF (mean CDR-SB scores: 4.32 vs 2.59, $P = .007$) while being at the same disease phase as determined by disease duration (mean disease duration: 3.9 vs 3.6 years, $P = .53$). A linear mixed effects model revealed a significant effect of the presence of AD-NEF on cognitive performance as measured by CDR-SB towards abnormal over disease duration (disease duration: estimate = 0.406, standard error = 0.186, $P = .031$; disease duration*presence of AD-NEF interaction: estimate = 0.572, standard error = 0.221, $P = .011$). In this cross-sectional model, the decline in CDR-SB per year was 0.41 points in symptomatic MC without AD-NEF and 0.98 points in MC with AD-NEF. Symptomatic MC with AD-NEF declined significantly more, by 0.57 points on CDR-SB per year (Figure 5A).

3.4 | Association between AD-NEF and gray matter atrophy in MC

In symptomatic MC, we found that the presence of AD-NEF was associated with greater gray matter atrophy in the temporo-parietal cortex (left precuneus, left posterior cingulate, left entorhinal cortex, right superior temporal gyrus) and bilateral hippocampus at an exploratory ROI-wise alpha threshold of 0.05, controlling for disease duration and global PiB-PET SUVR (Figure 5B). At a Bonferroni-corrected alpha threshold accounting for 82 ROIs ($P < .0006$), only the left hippocampus remained significant.

The results of the exploratory analyses to determine whether the single AD-NEF, ataxia, or saccadic smooth pursuit eye movement were associated with specific patterns of gray matter atrophy are summarized in the supplementary figure. In summary, most of the single AD-NEF, ataxia, and saccadic smooth pursuit eye movement were

TABLE 2 Comparison of baseline characteristics between symptomatic mutation carriers with and without Alzheimer disease neurological examination findings

	Symptomatic MC with AD-NEF (*n* = 64, 60.4%)	Symptomatic MC without AD-NEF (*n* = 42, 39.6%)	*P* value
Age (years), mean (SD)	45.9 (10.3)	46.2 (8.7)	.90
Sex (female), *n* (%)	30 (46.9)	25 (59.5)	.20
Education (years), mean (SD)	12.9 (3.8)	14.0 (2.6)	.12
Age at onset (years), mean (SD)	42.0 (8.9)	43.1 (8.1)	.54
Disease duration (years), mean (SD)	3.98 (3.18)	3.46 (2.58)	.39
CDR global, *n* (%)	0.5, 40 (62.5) : 1, 15 (23.4) : 2, 5 (7.8) : 3, 4 (6.3)	0.5, 32 (76.2) : 1, 9 (21.4) : 2, 1 (2.4) : 3, 0 (0)	.20
CDR-SB, mean (SD)	4.32 (4.60)	2.62 (2.10)	*.012*
MMSE, mean (SD)	21.45 (7.36)	24.76 (5.22)	*.008*
Mutated gene, *n* (%)	*PSEN1*, 52 (81.3) : *APP*, 11 (17.2) : *PSEN2*[a]	*PSEN1*, 33 (78.6) : *APP*, 8 (19.0) : *PSEN2*[a]	.92
APOE ε4 carrier, *n* (%)	20 (31.3)	9 (21.4)	.27

P values below .05 are italicized.
Abbreviations: MC, mutation carriers; AD-NEF, Alzheimer disease neurological examination findings; SD, standard deviation; CDR, Clinical Dementia Rating; SB, Sum of Boxes; MMSE, Mini-Mental State Examination; *APOE*, *apolipoprotein E*.
[a]As there were fewer than three *PSEN2* mutation carriers in the study, no figures are shown.

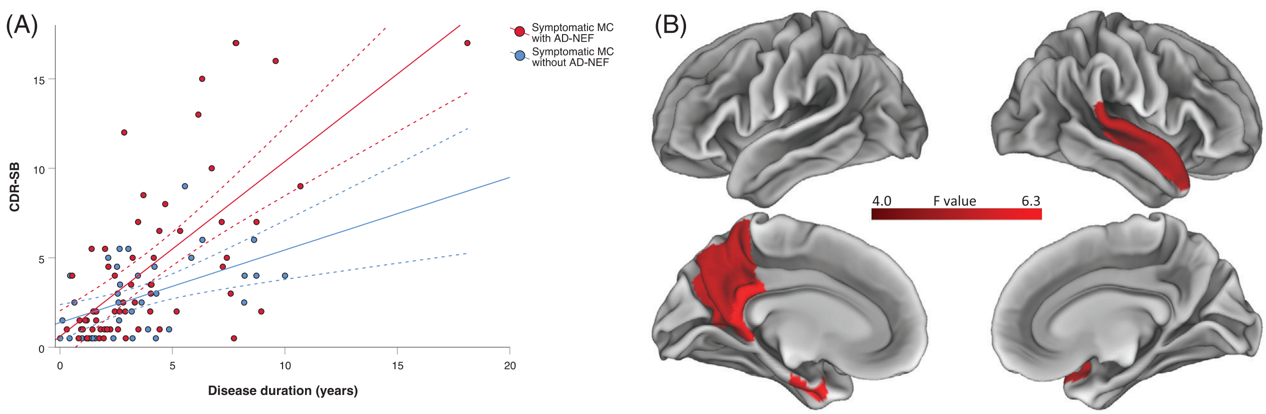

FIGURE 5 Cross-sectional associations between AD-NEF and (A) cognitive performance and (B) brain atrophy. (A) Grouped scatter plot depicting the cross-sectional relationship between CDR – Sum of Boxes scores and disease duration in symptomatic MC with and without Alzheimer disease neurological examination findings. Symptomatic MC with AD-NEF showed a significantly more pronounced decline in CDR – Sum of Boxes over the disease duration compared to symptomatic MC without AD-NEF. Dashed lines represent 95% confidence intervals. (B) Differences in brain atrophy between MC with and without AD-NEF. MC with AD-NEF showed a greater atrophy in temporo-parietal brain regions and greater bilateral hippocampal atrophy in an exploratory analysis with an alpha threshold of 0.05. After adjusting for 82 regions of interest using the Bonferroni method (resulting alpha threshold <0.0006), only the left hippocampal volume remained significantly different. Abbreviations: CDR-SB, Clinical Dementia Rating–Sum of Boxes; MC, mutation carriers; AD-NEF, Alzheimer disease neurological examination findings

associated with a fronto-temporo-parietal pattern of atrophy. There were no significant associations between any AD-NEF, ataxia, or saccadic smooth pursuit eye movement and atrophy in any subcortical region. At a Bonferroni-corrected alpha threshold accounting for 82 ROIs ($P < .0006$), no brain region remained significant.

3.5 | Longitudinal analysis and predictive value of AD-NEF regarding individual rate of cognitive decline

Longitudinal data, that is, data from the baseline visit and at least one follow-up visit of the same individual, were present for 73 symptomatic MC with a total of 222 visits (≥2 visits: $n = 73$; ≥3 visits: $n = 39$; ≥4 visits: $n = 21$; ≥5 visits: $n = 12$; ≥6 visits: $n = 3$; 7 visits: $n = 1$). Mean number of visits was 3.04 (standard deviation = 1.25) and mean follow-up time 2.49 years (standard deviation = 1.63; range = 0.96–7.03 years). There was a significant difference in slopes as a function of the presence of AD-NEF at each visit and disease duration with CDR-SB as the outcome parameter (disease duration: estimate = 0.981, standard error = 0.099, $P < .001$; disease duration*presence of AD-NEF at each visit interaction: estimate = 0.343, standard error = 0.136, $P = .012$). The rate of yearly decline estimated by the model was 0.98 points on the CDR-SB score in symptomatic MC without AD-NEF compared to 1.32 points in symptomatic MC with AD-NEF. That is, symptomatic

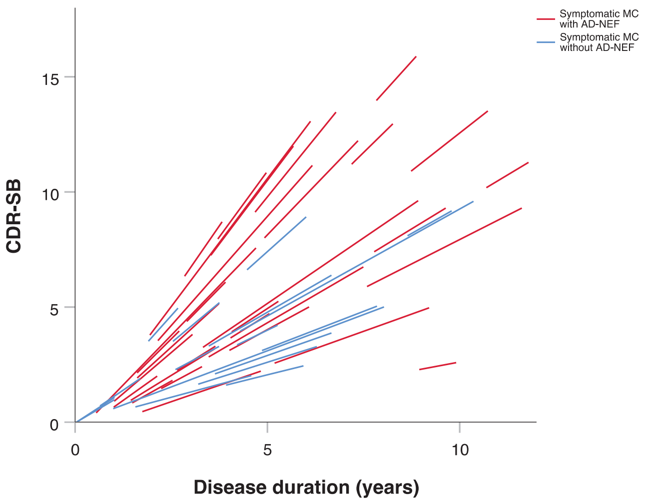

FIGURE 6 Individual linear estimates of change in Clinical Dementia Rating–Sum of Boxes (CDR-SB) score over time in symptomatic mutation carriers (MC) with and without Alzheimer disease neurological examination findings (AD-NEF). Description: Individual decline in CDR-SB score over time was significantly more pronounced in symptomatic MC with AD-NEF compared to those without. The individual linear changes in CDR-SB score were predicted by a linear mixed effects model based on longitudinal data, that is, data from symptomatic MC with at least the baseline visit and one follow-up visit. Abbreviations: MC, mutation carriers; CDR-SB, Clinical Dementia Rating–Sum of Boxes; AD-NEF, Alzheimer disease neurological examination findings

mutation carriers with AD-NEF declined significantly more, by 0.34 points per year, than symptomatic mutation carriers without AD-NEF (Figure 6). There was also a significant difference in slopes as a function of the presence of AD-NEF at baseline and disease duration with CDR-SB as the outcome parameter (disease duration: estimate = 1.020, standard error = 0.120, $P < .001$; disease duration*presence of AD-NEF at baseline interaction: estimate = 0.494, standard error = 0.211, $P = .022$). The rate of yearly decline estimated by the model was 1.02 points on the CDR-SB score in symptomatic MC without AD-NEF at baseline compared to 1.51 points in symptomatic MC with AD-NEF at baseline. That is, symptomatic mutation carriers with AD-NEF at baseline showed a significantly increased future cognitive decline, by 0.49 points on CDR-SB per year, than symptomatic mutation carriers without AD-NEF at baseline.

3.6 | Differential diagnostic significance of AD-NEF

Among individuals at risk for ADAD with a CDR global score of 0.5, that is, very mild cognitive impairment, AD-NEF were significantly more frequent in MC than in non MC (55.6% vs 26.7%; $P = .042$). The positive predictive value of AD-NEF to predict a MC status was 91%. Sensitivity was 56% and specificity was 73%.

4 | DISCUSSION

Two recently published studies, one using a European case series and the other comparing DIAN and literature data, provided insights about non-amnestic manifestations of ADAD on a symptom and diagnosis level.[8,9] Relatively frequent symptoms were seizures, myoclonus, and behavioral or personality changes. Compared to symptoms and diagnoses, findings are less based on inductive generalization and provide the least abstract level of categorization, and therefore may provide more objective information and a high degree of cue validity.[34,35] In the current study, a systematic investigation of single neurological findings as subscale components of a structured clinical neurological examination was performed, an approach that has not been pursued previously. Neurological examination findings in ADAD encompass pathological deep tendon reflexes, gait disturbance, cranial nerve examination findings, tremor, abnormal finger to nose and heel to shin test findings, pathological plantar reflexes, as well as compromised motor strength. Neurological examination findings in ADAD were associated with a two-fold faster cognitive decline and ADAD patients with neurological examination findings exhibited a greater parieto-temporal atrophy independent of disease duration. The presence of AD-NEF at baseline predicted an increased rate of future cognitive decline.

Knowledge about these examination findings may help clinicians to corroborate a suspected ADAD diagnosis and to distinguish from differential diagnoses of ADAD. Taking illustratively the five most frequent AD-NEF and their respective most frequent subitem (Figure 3) as the basis, a typical ADAD patient may present with asymmetrical brisk deep tendon reflexes, increased muscle tone, reduced arm swing while walking, saccadic smooth pursuit eye movements, and postural tremor.

A profile of motor symptoms measured by the Unified Parkinson Disease Rating Scale Part III was described recently in ADAD. This profile indicates that bradykinetic symptoms are the primary motor manifestation in ADAD.[14] The insights about clinical neurological examination findings of this study may add further to a sharper and more comprehensive clinical picture of ADAD.

The term Alzheimer disease neurological examination findings (or AD-NEF) was introduced for those findings that were more frequent in symptomatic mutation carriers than in non mutation carriers. The frequency of AD-NEF increased with the disease stage of ADAD. This finding is in accordance with the disease phase–dependent build-up of non-cognitive symptoms in AD such as for example seizures and motor symptoms.[9,14,15]

In at-risk individuals with mild cognitive symptoms in this study, the presence of AD-NEF was highly indicative of ADAD mutation carrier status. Since the presence of AD-NEF predicts a worse outcome in symptomatic ADAD, identifying this group early might facilitate earlier intervention and perhaps help to provide haste in confirming genetic results. The integration of knowledge of the predictive value of seizures and impaired rapid alternating hand movements regarding mutation carrier status in the cognitively presymptomatic phase of ADAD[13,14] and of AD-NEF in cognitively symptomatic at-risk persons may help to aid patient evaluation and care throughout disease phases.

In the current study, an association between the presence of AD-NEF and poorer cognitive performance independent of the disease stage was found in ADAD patients. The exploratory MRI analysis revealed an increased temporo-parietal including hippocampal atrophy in MC with AD-NEF compared to MC without AD-NEF. A similar pattern was seen in a recent study of the spatial distribution of atrophy in ADAD patients.[33] Therefore, a potential pathophysiological explanation for the worse cognitive performance associated with AD-NEF may be a greater burden of AD-related atrophy in ADAD patients with AD-NEF independent of the disease stage.

Beyond the cross-sectional association of AD-NEF with poorer cognitive performance in ADAD patients, our intra-individual longitudinal analyses showed an association between the presence of AD-NEF and a significantly higher rate of cognitive decline over time, by approximately 35% per year on CDR-SB. Moreover, the longitudinal analysis showed that the presence of AD-NEF at baseline predicted a significantly higher rate of future decline in CDR-SB, by approximately 50% per year. The predictive capability of AD-NEF offers the opportunity to estimate prognosis and thus may add substance to patient counseling as well as to diagnostic and therapeutic strategies. Taking the stage of very mild dementia (CDR-SB 3.0-4.0) as an assumptive starting point, after 5 years patients without AD-NEF would arrive at the stage of mild dementia (CDR-SB 4.5-9.0), whereas patients with AD-NEF would be at the stage of moderate dementia (CDR-SB 9.5-15.5). After 10 years, ADAD patients without AD-NEF would exhibit moderate dementia and those with AD-NEF would suffer from severe dementia (CDR-SB 16.0-18.0).[36] The predictive nature of AD-NEF regarding cognitive decline over time could be explained through a potential capability of the neurological examination to detect subtle and localized AD-associated brain changes that did not yet extend to brain regions that cause cognitive decline when damaged.

Since a population with ADAD formed the basis for the analyses in this study, it is a crucial question how our findings may translate to sporadic AD. In literature, spastic paraparesis is more frequently described in ADAD than in sporadic AD. Nine of the 97 *PSEN1* mutation carriers in this study had mutations that were reported to be possibly associated with spastic paraparesis (Val261Phe, Pro264Leu, Leu271Val).[37] Only in one of these nine patients a bilateral spastic increase in lower limb tone was reported. Importantly, the higher age and frequency of age-related comorbidities in patients with sporadic AD that can cause abnormal NEF could challenge translatability.[27] Exploring for those comorbidities by thorough medical history taking including third-party anamnesis and analyses of medical files may account for these challenges and warrant translatability of the study findings to sporadic AD. However, this requires further study.

In summary, the results of our study may leverage differential diagnostic considerations by revealing neurological examination findings in symptomatic ADAD including their stage-dependent frequencies. The presence of these findings indicates mutation status in mildly cognitive impaired at-risk persons with accuracy. The association of neurological findings typical for ADAD with poor cognitive performance and their predictive value regarding increased cognitive deterioration over time may render the neurological examination suitable to contribute to estimation of prognosis, to improve patient consultation, and to inform treatment decisions and future therapeutic trial designs.

ACKNOWLEDGMENTS

This project was supported by the Dominantly Inherited Alzheimer Network (DIAN; UF1 AG032438) funded by the National Institute on Aging (NIA), the German Center for Neurodegenerative Diseases (DZNE), the NIHR Queen Square Dementia Biomedical Research Centre and the MRC Dementias Platform UK (MR/L023784/1 and MR/009076/1), and AMED JP21dk0207049. This work was supported by the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) (FOR2290) and was funded by the Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy - ID 390857198). G.H. acknowledges support by Niedersächsisches Ministerium für Wissenschaft und Kunst, VolkswagenStiftung (Niedersächsisches Vorab) and Petermax-Müller Foundation (Etiology and Therapy of Synucleinopathies and Tauopathies). This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families as well as the contributions of the DIAN research and support staff at each of the participating sites. Funding sources: German Center for Neurodegenerative Diseases (DZNE).

Open access funding enabled and organized by Projekt DEAL.

CONFLICTS OF INTEREST

Jonathan Vöglein has nothing to disclose. Nicolai Franzmeier has received a research grant from Bright Focus Foundation. John C. Morris has received National Institutes of Health (NIH) grants, royalties or licenses for clinical dementia rating (CDR) registration, consulting fees from Barcelona BetaBrain Research Center and from Centre for Brain Research, Bangalore, India. He has received payment or honoraria from Montefiore, New York Grand Rounds. He has received support for attending meetings and/or travel from TS Srinavasan 40th Oration, India; World Congress of Neurology; Cure Alzheimer Board meeting; and CBR International Advisory Board. He has held a leadership or fiduciary role in Cure Alzheimer Board Meeting. Marianne Dieterich has received grants from the German Research Foundation and the German Foundation for Neurology. She has received support for attending meetings and/or travel from the European Academy of Neurology for the annual congress in 2019. Eric McDade has received grants or contracts from National Institutes of Health; Janssen; Eli Lilly; and Roche. He has received royalties or licenses from UpToDate. He has received personal consulting fees from: DSMB Eli Lilly, DSMB Alzamend, and Fondation Alzheimer. He has received payment or honoraria from Eisai (personal payment). He has received personal support for attending meetings and/or travel from Fondation Alzheimer Association. He has had any patents planned, issued, or pending: Novel Tau isoforms to predict onset of symptoms and dementia in Alzheimer's disease. He has participated on a Data Safety Monitoring Board or Advisory Board: see above. Mikael Simons has nothing to disclose. Oliver Preische has nothing to disclose. Anna Hofmann has nothing to disclose. Jason Hassenstab has received several NIH grants, payments to institution from BrightFocus foundation and personal consulting fees from Roche. He has participated on a Data Safety Monitoring Board or Advisory Boardfor Eisai. Payments were made to him. Tammie L. Benzinger has grants to her institution from NIH, and received personal payments from Biogen and Eisai. She has participated on a Data Safety Monitoring Board or Advisory Board for Biogen (payments made to her). She has received Precursor for flortaucipir from Avid Radiopharmaceuticals. Anne Fagan has received many grants from the NIH/National Institute of Aging (NIA), paid to her institution. She also received a research grant from Centene, paid to her institution. She is on the scientific advisory boards for Roche Diagnostics/Genentech and also a consultant for Diadem, DiamiR, and Siemens Healthcare Diagnostics Inc; payments were made to her. James M. Noble has received grants from NIH (all by his institution). He has any patents planned, issued, or pending: US20190298262A1 (does not relate to this manuscript). Sarah B. Berman has received grants or contracts from Michael J Fox Foundation to her institution. Neill R. Graff-Radford has nothing to disclose. Bernardino Ghetti has received NIH grants to Indiana University and two honoraria from University of Utah Northwestern University. He has held a leadership or fiduciary role in the International Society for Frontotemporal Dementias. Martin R. Farlow is a coinventor for US Patent No. 6184435 (does not relate to this manuscript). He has received consulting fees from Avanir, Biogen, Eli Lilly & Company, Cognition Therapeutics, Longeveron, Otsuka Proclara Therapeutics, Lexeo, Ionis, McClena and Athira. He has received payment for expert testimony: confidential. Jasmeer P. Chhatwal has received grants or contracts from NIH and Doris Duke Charitable Foundation Career Dev Award to his institution. He has received support for attending meetings and/or travel from NIH and Doris Duke Charitable Foundation. Stephen Salloway has received grants or contracts from Biogen. He has received consulting fees from Bolden Therapeutics, Ono, Genentech, Biogen, Prothena, Alnylam, ATRI, Roche, and Mayo, with payments to him. He has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Grand Rounds, PlatformQ, Biogen. He has received support for attending meetings and/or travel from RSNA symposium, Biogen, AMGEN, GEMVAX, and AVID. He has participated on a Data Safety Monitoring Board or Advisory Board for Acumen, Genentech. Chengjie Xiong has received grants or contracts from NIH and consulting fees from DIADEM. He participated on a Data Safety Monitoring Board or Advisory Board for the FDA Medical Imaging Drug Advisory Committee. He also serves on the External advisory Committee for University of Wisconsin Alzheimer disease research center. Celeste M. Karch has nothing to disclose. Nigel Cairns has nothing to disclose. Richard J. Perrin has received grants or contracts from NIH. Gregory Day has received grants to institution: K23AG064029 (NIH/NIA), Chan Zuckerberg Initiative (Neurodegeneration Challenge Network; WU-20-421), Alzheimer's Association (LDRFP-21-824473). He has received personal payments: DynaMED (Topic Editor, Dementia), Parabon Nanolabs (Consulting for NIA SBAR Grant) Texas Neurological Institute, Continuing Education Company, Barrow Law. He has held a leadership or fiduciary role in Anti-NMDA Receptor Encephalitis Foundation, Inc. Ralph Martins has nothing to disclose. Raquel Sanchez-Valle has received support for the present manuscript: ISCIII, Spain (grant number PI20/00448). She received grants or contracts from ISCIII, Sage Ph, and Biogen, payments were made to her institution. She reports personal fees from Wave pharmaceuticals and Ionis Pharmaceuticals for attending Advisory board meetings, and personal fees from Roche diagnostics, Janssen, and Neuraxpharm for educational activities. Hiroshi Mori reports a grant for DIAN-J by AMED (Japanese Government). Takeshi Ikeuchi has received grants by AMED. He has received honoraria for lectures from Eisai, Daiichi-Sankyo, Ono, Takeda, and Ajinomoto. Kazushi Suzuki has nothing to disclose. Peter R. Schofield has received support for the present manuscript: US National Institutes of Health, National Institute of Aging, Grant No UF1AG032438. He has received grants or contracts from: NSW Health Project, NHMRC Investigator Grant, NHMRC NNIDR Boosting Dementia Research Grants, MRFF Mental Health Pharmacogenomics 2020 Grant, Spanish Internationalisation Network I-Link Grant. He has held a leadership or fiduciary role in Neuroscience Research Australia, Neuroscience Research Australia Foundation, The Health-Science Alliance, Schizophrenia Research Institute, Australian Association of Medical Research Institutes, Australian Dementia Network, StandingTall Pty Ltd, Australasian Neuroscience Society, Maridulu Budyari Gumal - Sydney Partnership for Health Education, Research and Enterprise (SPHERE), The Judith Jane Mason & Harold Stannett Williams Memorial Foundation, Business Events Sydney. Colin L. Master has nothing to disclose. Alison Goate has received NIH grants and grants or contracts from Rainwater Charitable Foundation, Picower Foundation, Neurodegeneration Consortium. She has received royalties or licenses from Taconic, Athena Diagnostics. She has received consulting fees from Genentech, UK DRI, VIB centers in Antwerp and Leuven. She has received personal honoraria for presentations from Eisai, GSK, AbbVie. Virginia Buckles has received personal consulting fees from Washington University in St. Louis. Nick Fox: His institution has received payments from Ixico for the use of the Boundary Shift Intergral. He has provided consultancy for Eli Lilly and for Ionis - payments were to his institution. He has participated in advisory boards for Roche and Biogen - payment was to his institution. He has served on a DSMB for Biogen - payment was to him. Patricio Chrem has nothing to disclose. Ricardo Allegri has nothing to disclose. John M. Ringman has received support for the present manuscript from NIH. Dr. Ringman is also supported by Cure PSP. He has received consulting fees from Innosense, LLC. He has participated on a Data Safety Monitoring Board or Advisory Board for Renew, Inc.. Igor Yakushev has received grants or contracts from Federal Ministry of Education and Research Germany (BMBF). He has received payment or honoraria from Piramal. He has held a leadership or fiduciary role in Brain Imaging Council. Christoph Laske has nothing to disclose. Mathias Jucker has received grants or contracts from DFG, IMI2, AluCure. He has received payment or honoraria from Roche, Synapsis. Günter Höglinger has nothing to disclose. Randall J. Bateman has received support for the present manuscript from NIA. He has received grants or contracts from Avid Radiopharmaceuticals, Janssen, Eisai, Genentech, Abbvie, Biogen, Centene, United Neuroscience, Eli Lilly & Co, Hoffman-LaRoche. He has equity ownership interest in C2N Diagnostics and receive royalty income based on technology (stable isotope labeling kinetics and blood plasma assay) licensed by Washington University to C2N Diagnostics. He has received consulting fees from Janssen, Eisai, C2N Diagnostics, AC Immune, Amgen, Hoffman-LaRoche, and Pfizer. He has received support for attending meetings and/or travel from AC Immune, Hoffman-LaRoche. He has participated on a Data Safety Monitoring Board or Advisory Board for C2N Diagnostics, Hoffman-LaRoche, and Pfizer. He has held stock or stock options in entities related to the current manuscript and/or area of research included in this manuscript or related area of research: C2N Diagnostics- Equity ownership interests. Adrian Danek has received grants or contracts from Advocacy for Neuroacanthocytosis Patients. He has received payment or honoraria from three hospitals in Switzerland. He has received payment for expert testimony from Munich court of law. He has held a leadership or fiduciary role in Advocacy for Neuroacanthocytosis Patients. Johannes Levin reports speaker fees from Bayer Vital, Biogen, and Roche, consulting fees from Axon Neuroscience and Biogen, author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers, non-financial support from Abbvie and compensation for duty as part-time CMO from MODAG, outside the submitted work.

AUTHOR CONTRIBUTIONS

Jonathan Vöglein designed the study, wrote the manuscript, acquired, analyzed and interpreted the data, and generated the figures. Johannes Levin guided study design and concept, acquired, analyzed, and interpreted the data. Nicolai Franzmeier analyzed and visualized MRI data. Adrian Danek, John C. Morris, Marianne Dieterich, Eric McDade, Mikael Simons, Oliver Preische, Anna Hofmann, Jason Hassenstab, Tammie L. Benzinger, Anne Fagan, James M. Noble, Sarah B. Berman, Neill R. Graff-Radford, Bernardino Ghetti, Martin R. Farlow, Jasmeer P. Chhatwal, Stephen Salloway, Chengjie Xiong, Celeste M. Karch, Nigel Cairns, Richard J. Perrin, Gregory Day, Ralph Martins, Raquel Sanchez-Valle, Hiroshi Mori, Hiroyuki Shimada, Takeshi Ikeuchi, Kazushi Suzuki, Peter R. Schofield, Colin L. Masters, Alison Goate, Virginia Buckles, Nick C. Fox, Martin R. Farlow, Patricio Chrem, Ricardo Allegri, John M. Ringman, Igor Yakushev, Christoph Laske, Mathias Jucker, Günter Höglinger, and Randall J. Bateman were involved in study implementation and data collection at the respective study sites. All authors critically reviewed and revised the manuscript and figures for intellectual content.

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SUPPORTING INFORMATION

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How to cite this article: Vöglein J, Franzmeier N, Morris JC, et al. Pattern and implications of neurological examination findings in autosomal dominant Alzheimer disease. *Alzheimer's Dement*. 2022;1-14. https://doi.org/10.1002/alz.12684