Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease

Running title: Motor signs in familial Alzheimer's disease

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Abstract

Owing to an early and marked deposition of amyloid β in the basal ganglia, autosomal dominant Alzheimer's disease could distinctly involve motor symptoms. Therefore, we aimed to assess the prevalence and characteristics of motor signs in autosomal dominant Alzheimer's disease. Baseline Unified Parkinson Disease Rating Scale part three scores from 433 participants of the Dominantly Inherited Alzheimer's Network observational study were analyzed. Motor symptoms were scrutinized with respect to associations with mutation carrier status, mutation site within *presenilin 1*, basal ganglia amyloid β as measured by Pittsburgh compound B-positron emission tomography, estimated years to symptom onset and Clinical Dementia Rating Scale-Sum of Boxes. Motor findings in mutation carriers were compared to patients with sporadic Alzheimer's disease using data of the National Alzheimer's Coordination Center. Mutation carriers showed motor findings at a higher frequency (28.4% vs. 12.8%; $P<0.001$) and severity (mean Unified Parkinson Disease Rating Scale part three scores 2.0 vs. 0.4; $P<0.001$) compared to non-carriers. Eleven of the 27 Unified Parkinson Disease Rating Scale part three items were statistically more frequently affected in mutation carriers after adjustment for multiple comparisons. Ten of these 11 items were subscale components of bradykinesia. In cognitively asymptomatic mutation carriers, dysdiadochokinesia was more frequent compared to non-carriers (right hand: 3.8% vs. 0%; adjusted $P=0.023$; left: 4.4% vs. 0.6%; adjusted $P=0.031$). In this cohort, the positive predictive value for mutation carrier status in cognitively asymptomatic participants (50% *a priori* risk) of dysdiadochokinesia was 100% for the right and 87.5% for the left side. Mutation carriers with motor findings more frequently were basal ganglia amyloid β positive (84% vs. 63.3%; $P=0.006$) and showed more basal ganglia amyloid β deposition (Pittsburgh compound B-standardized uptake value ratio 2.472 vs. 1.928; $P=0.002$) than those without. Frequency and severity of motor findings were greater in post codon 200 *presenilin 1* mutations (36%; mean Unified Parkinson Disease Rating Scale part three score

3.03) compared to mutations pre codon 200 *presenilin 1* (19.3%, *P*=0.022; 0.91, *P*=0.013). In mutation carriers, motor symptom severity was significantly positively correlated with basal ganglia amyloid β deposition, Clinical Dementia Rating scores and estimated years to symptom onset. Mutation carriers with a Clinical Dementia Rating global score of 2 exhibited more pronounced motor symptoms than sporadic Alzheimer's disease patients with the same Clinical Dementia Rating global score (mean Unified Parkinson Disease Rating Scale part three scores 20.71 vs. 5.96; $P < 0.001$). With a prevalence of approximately 30% and increasing severity with progression of dementia, motor symptoms are proven as a clinically relevant finding in autosomal dominant Alzheimer's disease, in particular in advanced dementia stages, that correlates with deposition of amyloid β in the basal ganglia. In a very small percent of cognitively asymptomatic members of families with autosomal dominant Alzheimer's disease, dysdiadochokinesia may increase the chance of an individual´s status as mutation carrier.

Keywords

Alzheimer's disease, motor symptoms, amyloid β, genetics, Unified Parkinson Disease Rating Scale

Abbreviations

AD = Alzheimer's disease; ADAD = autosomal dominant Alzheimer's disease; UPDRS-III = Unified Parkinson Disease Rating Scale part three

Introduction

Autosomal dominant Alzheimer's disease (ADAD) is a monogenic neurodegenerative disease caused by pathogenic sequence variants in one of the three genes *presenilin 1*, *presenilin 2* or the gene encoding the amyloid precursor protein (Bateman *et al.*, 2011). Compared to sporadic Alzheimer's disease (AD), the average age of clinical onset is earlier, at a mean of 45 years (Ryman *et al.*, 2014; Masters *et al.*, 2015). Due to its predictable course, ADAD serves as a model to explore AD pathophysiology (Schindler and Fagan, 2015). Studies in ADAD have led to crucial insights on the temporal sequence of pathological events that result in the clinical manifestation of AD (Bateman *et al.*, 2012).

Beyond its typical cognitive manifestation, a subset of patients with ADAD display non-cognitive features such as parkinsonism, ataxia, or spasticity (Tang *et al.*, 2016). In single cases, an association of motor findings in ADAD with the presence of amyloid β plaques in the basal ganglia at autopsy has been reported, conceivably indicating a possible pathomechanism (Takao *et al.*, 2002). In sporadic AD, motor dysfunction is present in a substantial portion of patients and increases with cognitive impairment (Portet *et al.*, 2009). Motor impairment has been reported in early disease stages and may even precede cognitive decline in a small subset of patients (Albers *et al.*, 2015).

Different mutation sites within the *presenilin 1* gene, i.e. a location before or after codon 200, were reported to impact clinical course, neurological and neuropsychological manifestations, neuropathological features, and the extent of magnetic resonance imaging white matter hyperintensities in ADAD (Mann *et al.*, 2001; Ryan and Rossor, 2010; Ryan *et al.*, 2015; Ringman *et al.*, 2016; Shea *et al.*, 2016; Tang *et al.*, 2016).

ADAD mutation carriers exhibit an increased burden of amyloid β in the basal ganglia earlier than 10 years before expected symptom onset (Bateman *et al.*, 2012). Therefore, we hypothesized that motor findings may play a significant role in ADAD. In particular with

respect to the cognitively asymptomatic disease stage, currently there is little comprehensive clinical data on motor function in ADAD and potential neuropathological correlations. In addition, the interaction between specific mutation effects and motor function is also unknown. We used data from the Dominantly Inherited Alzheimer Network observational study (Morris *et al.*, 2012) to fill this gap.

Materials and methods

Participants

To assess motor findings in ADAD we used data from the Dominantly Inherited Alzheimer Network observational study gathered at 15 sites in the United States of America, Australia, United Kingdom, Germany and Argentina between January 2009 and December 2015 (data freeze 10). Four hundred thirty-three participants, including 261 ADAD mutation carriers (*presenilin 1*, *presenilin 2* and the gene encoding the amyloid precursor protein) and 172 non-carriers were identified, the latter serving as a control group. In the Dominantly Inherited Alzheimer Network observational study, examiners are blinded to the mutation status of the participants. Baseline visit data of all participants were used. Clinical and demographic data were collected using the Uniform Data Set version 2 from the National Alzheimer's Coordinating Center (Morris *et al.*, 2006). The dataset analyzed included comprehensive clinical, demographic, genetic, and imaging data.

To analyze motor findings in sporadic AD we used data from the National Alzheimer's Coordination Center, gathered using the Uniform Data Set (Morris *et al.*, 2006) between September 2005 and March 2015 at 36 Alzheimer's Disease Centers. National Alzheimer's Coordination Center data has been described in detail before (Beekly *et al.*, 2004; Morris *et al.*, 2006; Beekly *et al.*, 2007; Weintraub *et al.*, 2009).

The protocol for the Dominantly Inherited Alzheimer Network observational study has received approval by the institutional review boards of all participating sites. The Dominantly Inherited Alzheimer Network observational study is performed in accordance with the declaration of Helsinki and written informed consent was obtained from each participant. Research utilizing the National Alzheimer's Coordination Center database was approved by the Institutional Review Board of the University of Washington. Informed consent from individuals that are part

of the National Alzheimer's Coordination Center dataset was obtained at the respective Alzheimer's Disease Centers.

Motor assessment

The motor examination in part three of the Unified Parkinson Disease Rating Scale (UPDRS-III) (Fahn and Elton, 1987), being a part of Uniform Data Set version 2 from the National Alzheimer's Coordinating Center, was used. UPDRS-III comprises 14 items and its scale ranges from 0 to 108, where greater numbers indicate increasing impairment. UPDRS-III scores were assessed by trained clinicians at all participating sites of the Dominantly Inherited Alzheimer Network observational study. All UPDRS-III raters were blinded to the mutation status of the participants. There was no blinding of UPDRS-III raters regarding the cognitive state of the participants.

For comparison of frequency of motor findings, mutation carriers and non-carriers were each divided into two groups: one with normal UPDRS-III results (0) and the other with suspicious values (>0), both for total scores as well as for each item separately. The positive predictive value, sensitivity and specificity regarding mutation carrier status of impaired rapid alternating hand movements in cognitively asymptomatic participants (defined by a Clinical Dementia Rating global score of 0) were calculated. Mean UPDRS-III scores were compared between mutation carriers and non-carriers. In mutation carriers, we investigated correlations between UPDRS-III score and estimated years to symptom onset and Clinical Dementia Rating - Sum of Boxes, respectively. Clinical Dementia Rating - Sum of Boxes is a global clinical cognitive assessment with a scale from 0 to 18 (none to severe impairment) (Morris *et al.*, 1997). Stratified by global Clinical Dementia Rating scores, frequencies of UPDRS-III scores greater 0 and mean UPDRS-III scores were compared between cognitively symptomatic ADAD mutation carriers from the Dominantly Inherited Alzheimer Network observational study and patients with a clinical diagnosis of AD from the National Alzheimer's Coordination Center. Participants from

the National Alzheimer's Coordination Center with an indicated ADAD mutation in their family or an ADAD mutation found post-mortem examination were excluded from analyses. Individuals with a Clinical Dementia Rating global score = 3 were not analyzed due to a very small number (n=4) in the ADAD group from the Dominantly Inherited Alzheimer Network cohort. Further, cognitively normal controls from the Dominantly Inherited Alzheimer Network cohort (non-carrier with a Clinical Dementia Rating global score = 0) were compared to cognitively normal controls from the National Alzheimer's Coordination Center cohort (individuals with a Clinical Dementia Rating global score = 0 that were additionally rated cognitively normal at baseline and all occurring follow-up visits).

Estimated years to symptom onset

Estimated years to symptom onset were calculated from the age of a participant at the time of the baseline visit minus his/her expected age of onset. Expected age of onset was determined using the mean onset of a respective mutation (deriving from combined data of the Dominantly Inherited Alzheimer Network and prior publications (Ryman *et al.*, 2014)) or, if unavailable, the age of onset of the participants´ affected family member. In symptomatic participants, the actual time of symptom onset was taken as the expected age of onset.

Amyloid β imaging

Amyloid β imaging was conducted after a bolus injection of about 15 mCi of Pittsburgh Compound B ([11C]PiB). Dynamic imaging acquisition began either at injection for 70 minutes or 40 minutes post-injection for 30 minutes. The data acquired between 40 to 70 minutes were used for further analysis. Each participant's Pittsburgh Compound B - positron emission tomography data underwent motion correction and were registered to his or her magnetic resonance imaging using established procedures (Eisenstein *et al.*, 2012). The Standardized Uptake Value Ratio was calculated with the cerebellum serving as the reference for each region

of interest (defined by FreeSurfer) (Benzinger *et al.*, 2013a). The mean of the Standardized Uptake Value Ratios of the caudate nucleus, of putamen, pallidum and the nucleus accumbens was calculated for each participant to obtain a mean basal ganglia Standardized Uptake Value Ratio. Amyloid β positivity was defined as Pittsburgh Compound B - Standardized Uptake Value Ratio > 1.3 (Dominantly Inherited Alzheimer Network Imaging Core Methods and Definitions; version 1.1; August 5, 2015). The rates of amyloid β positivity and the means of basal ganglia Standardized Uptake Value Ratios were compared among mutation carriers (with and without motor findings, respectively). Correlation of UPDRS-III scores and basal ganglia Standardized Uptake Value Ratios was analyzed. Pittsburgh Compound B - positron emission tomography data at baseline visits were available from 200 participants and had been acquired at the time of clinical assessment. *presenilin 1* and *presenilin 2* mutation carriers with dysdiadochokinesia were compared to those without dysdiadochokinesia regarding Pittsburgh Compound B - Standardized Uptake Value Ratios in the cerebellar cortex. Brainstem was used as the reference region.

Genetic analyses

To determine the presence or absence of an ADAD mutation and for characterization of apolipoprotein E genotypes the respective exons were amplified by polymerase chain reaction, followed by Sanger sequencing (Bateman *et al.*, 2012). Distributions of ADAD mutation types (*presenilin 1*, *presenilin 2* or the gene encoding the amyloid precursor protein) and apolipoprotein E genotypes were compared between mutation carriers with and without motor findings. *presenilin 1* mutations post codon 200 were compared to those pre codon 200 with respect to frequency and degree of motor findings, respectively. Four intronic *presenilin 1* mutations were excluded from the latter analysis, because mutations in introns were not part of the first description of a clustering relative to *presenilin 1* codon 200 with respect to phenotypic

features (Mann *et al.*, 2001) and their effects on the protein structure substantially differ from and are less predictable than in exonic mutations (Vaz-Drago *et al.*, 2017).

Statistical analysis

For statistical analysis the Statistical Package for the Social Sciences (IBM SPSS Statistics, Version 24) was used. Baseline clinical and demographic characteristics were analyzed using Student's t-tests and Fisher's exact tests. To compare frequencies of motor findings, amyloid β positivity, and distributions of genetic variants between groups, Fisher's exact tests or Pearson's chi-square tests were used. Benjamini-Hochberg procedure was performed to adjust for multiple testing with respect to 27 UPDRS-III subscale components. The positive predictive value, sensitivity and specificity were calculated using a two-dimensional contingency table. For group comparisons with respect to mean UPDRS-III scores and basal ganglia Pittsburgh Compound B - Standardized Uptake Value Ratios Student's t-tests or Mann-Whitney U tests were performed. Distribution patterns were analyzed with the Kolmogorov-Smirnov test. For correlation analyses, Spearman's rank correlation coefficient was calculated and tested for statistical significance. *P*-values below 0.05 were considered statistically significant. All tests were performed two-sided.

Results

Participants

The dataset consisted of comprehensive data from 433 members of 107 ADAD families, with 261 (60.3%) carrying a mutation in *presenilin 1*, *presenilin 2* or the gene encoding the amyloid precursor protein or an duplication of the gene encoding the amyloid precursor protein, respectively. 172 individuals did not carry an ADAD mutation. One hundred fifty-nine mutation carriers (60.9%) were cognitively asymptomatic (global Clinical Dementia Rating score = 0). Baseline clinical and demographic data are provided in Table 1.

Additionally, the dataset included data from 1120 patients with a clinical diagnosis of sporadic AD, and from 8185 cognitively normal controls from the National Alzheimer's Coordination Center dataset (Table 4).

Motor assessment

Motor findings, as illustrated in Fig. 1A, were present at a significantly higher frequency in mutation carriers (28.4% vs 12.8%; $P < 0.001$; with 74/261 mutation carriers and 22/172 non-carriers affected). Comparing each of the 27 UPDRS-III items between the carrier and non-carrier groups, we found 13 items statistically more frequently abnormal in mutation carriers of which seven remained statistically significantly different after correction for multiple testing. Scores greater than 0 on assessing rigidity of the right lower extremity (7.3% vs. 1.7%; $P = 0.030$), right and left hand finger taps (6.9% vs. 0%; $P < 0.001$; 6.5% vs. 1.2%; $P=0.025$, respectively), right and left hand movements (5.7% vs. 0%; $P = 0.004$; 6.1% vs. 0.6%; $P = 0.016$, respectively), right and left hand rapid alternating movements (7.7% vs. 0%; $P < 0.001$; 9.6% vs. 0.6%; $P < 0.001$, respectively), right and left leg agility (4.6% vs. 0%; $P = 0.013$; 5.0% vs. 0.6%; $P = 0.030$), gait (4.2% vs. 0%; $P = 0.016$), as well as posture stability (6.1% vs. 1.2%; $P = 0.030$) (given P-values are adjusted for multiple comparisons) occurred significantly more

often in mutation carriers as compared to non-carriers (Table 2). No UPDRS-III item was scored > 0 more frequently in non-carriers than in carriers.

Impaired rapid alternating hand movements (dysdiadochokinesia) occurred more often in cognitively asymptomatic mutation carriers (right: 6/159, 3.8%; left: 7/159, 4.4%) than in non-carriers (right: 0/172; 0%; left: 1/172, 0.6%) (adjusted P = 0.023 and 0.031, respectively). In cognitively asymptomatic mutation carriers with a value > 0 in rapid alternating hand movements, they were scored "2" (moderately impaired; definite and early fatiguing; may have occasional arrests in movement) or "1" (mild slowing and/or reduction in amplitude) (Fahn and Elton, 1987), whereas the one non-carrier with a value > 0 in this item was scored "1" with respect to the left side. The positive predictive value of dysdiadochokinesia for presence of a pathogenic mutation in cognitively asymptomatic first-degree relatives of individuals with symptomatic ADAD was 100% for the right and 87.5% for the left side. While specificity was high (right: 100%; left: 99.4%), sensitivity was low (right: 3.8%; left: 4.4%). For both sides, the negative predictive value was 52.9%.

Overall motor findings were more pronounced in mutation carriers (mean UPDRS-III score 2.0) than in non-carriers (mean UPDRS-III score 0.4) ($P < 0.001$) (Fig. 1D). The extent of motor findings (UPDRS-III scores) in mutation carriers was positively correlated both with disease duration (r_s=0.409; $P < 0.001$), as estimated via estimated years to symptom onset (Fig. 2A), and with cognitive decline (r_s=0.420; $P < 0.001$) as assessed with Clinical Dementia Rating - Sum of Boxes (Fig. 2B). Frequencies of abnormal UPDRS-III values increased with global Clinical Dementia Rating scores (0 : 14.5%; 0.5 : 43.1%; ≥ 1 : 62.2%) and with estimated years to symptom onset (-30 to -20 : 2.8%; -20 to -10 : 18.3%; -10 to 0 : 26.1%; 0 to 10 : 52.6%; 10 to 20 : 75.0%) in mutations carriers.

Cognitively symptomatic ADAD mutation carriers with a Clinical Dementia Rating global score of 2 showed more pronounced motor symptoms than patients with sporadic AD with the same Clinical Dementia Rating global score (mean UPDRS-III scores 20.71 vs. 5.96; $P <$

0.001). Frequencies of abnormal UPDRS-III scores were 71.4% for ADAD mutations carriers and 62.2% for sporadic AD patients in the Clinical Dementia Rating global score = 2 group (*P* =0.71). Frequencies of abnormal UPDRS-III scores and mean UPDRS-III scores were 43.1% vs. 43.1% (*P* = 1) and 2.15 vs. 2.32 (*P* = 0.76) in the group with global Clinical Dementia Rating scores of 0.5, and 61.5 vs. 51.5 (*P* = 0.31) and 5.38 vs. 3.86 (*P* = 0.27) in the group with global Clinical Dementia Rating scores of 1 (Table 4).

Cognitively normal controls from the National Alzheimer's Coordination Center database were significantly older, and a higher percentage of individuals showed abnormal UPDRS-III scores as well as had higher mean UPDRS-III scores compared to cognitively normal non-carrier controls from the Dominantly Inherited Alzheimer Network cohort (69.32 years vs. 39.04 years, *P* < 0.001; 27.1% vs. 10.1%, *P* < 0.001; 1.49 vs. 0.33, *P* < 0.001) (Table 4).

Amyloid β imaging

84% of the mutation carriers with motor findings that had undergone Pittsburgh Compound B - positron emission tomography were amyloid β positive in the basal ganglia (42 of 50), in contrast to 63.3% (95/150) of mutation carriers without motor findings (*P* = 0.006) (Fig. 1C). Mean basal ganglia Pittsburgh Compound B - Standardized Uptake Value Ratio was significantly higher in carriers with motor findings as opposed to those without (2.472 and 1.928 respectively, *P* = 0.002) (Fig. 1F). Overall motor dysfunction as assessed by UPDRS-III scores was positively correlated with basal ganglia amyloid β burden (r_s=0.233; *P* = 0.001) (Fig. 2C). All analyses that included basal ganglia amyloid burden measured by Pittsburgh Compound B - positron emission tomography were repeated using the brainstem as the reference region. All results were consistent with the results of the analyses that used the cerebellar reference. Details are shown in the supplementary table.

There was no statistically significant difference between *presenilin 1* and *presenilin 2* mutation carriers with dysdiachokinesia (n=15) and those without (n=154) regarding cerebellar cortex Pittsburgh Compound B - Standardized Uptake Value Ratios (0.59 vs. 0.56; P = 0.23).

Genetic analyses

Among the 261 mutation carriers, 197 carried *presenilin 1* (75.5%), 20 *presenilin 2* (7.7%) and 44 mutations or duplications in or of the gene encoding the amyloid precursor protein (16.9%). No significant differences regarding the distribution of the three affected ADAD genes between mutation carriers with and without motor findings were found (P = 0.259). Neither did distribution of apolipoprotein E genotypes differ between the groups (P = 0.554). Carriers of *presenilin 1* mutations that were localized after codon 200 more commonly showed motor findings that were also more pronounced (36%; mean UPDRS-III score 3.03) (Fig. 1B and E) in comparison to participants with *presenilin 1* mutations before codon 200 (19.3%, P = 0.022; mean UPDRS-III score 0.91, P = 0.013) (Table 3).

Discussion

In the Dominantly Inherited Alzheimer Network observational study, motor signs were found to be present in about 30 % of ADAD mutation carriers, with their severity increasing as the disease progresses (Fig. 1A and 2A). Motor function was abnormal in nearly a fifth of mutation carriers between estimated years to symptom onset -20 and -10, and in more than half of those between estimated years to symptom onset 0 and 10. As reflected by the mean age of mutation carriers of around 39 years, the study subjects were young in comparison to cohorts with sporadic AD. Hence, this population is more unlikely to have relevant comorbidities that might contribute to the occurrence of motor findings. Our analysis therefore may indicate that early motor findings, before the onset of cognitive symptoms, could be a distinct feature of ADAD in a very small subset of individuals. The early occurrence of motor symptoms in this small subgroup could possibly relate to the early basal ganglia pattern of amyloid β in ADAD that is not typically seen in sporadic AD (Bateman *et al.*, 2012; Benzinger *et al.*, 2013b; Villemagne *et al.*, 2013; McDade *et al.*, 2014; Fleisher *et al.*, 2015). Motor signs in ADAD can be assessed and scored using the Unified Parkinson Disease Rating Scale, which has great strengths in reliability and validity (Goetz *et al.*, 2003), due to precisely defined subscale components (Fahn and Elton, 1987). Hereby even slight differences in Unified Parkinson Disease Rating Scale scores are distinguishable for trained clinicians.

UPDRS-III allows to measure a range of distinct motor phenotypes. Compared to non-carriers, ADAD mutation carriers showed motor abnormalities in 41% (11/27) of the UPDRS-III items. Interestingly, the majority (91%) of the abnormalities were found in subscale components that focus on the detection of bradykinesia, not of tremor or rigidity (Table 2). This suggests that motor symptoms in ADAD primarily manifest with a bradykinetic profile.

With an UPDRS-III score of 2 on average, motor symptoms were rather mildly pronounced in ADAD mutations carriers. This is also reflected by only one mutation carrier with motor findings who was treated with levodopa at the time of his baseline visit. However, 61% of the studied mutation carriers were cognitively asymptomatic, with a mean estimated years to symptom onset of approximately -8.

Our suggestion of motor symptoms as a distinct feature of ADAD is consistent with associations between the presence, respectively the amount of fibrillar amyloid β in the basal ganglia and the manifestation of motor findings in mutation carriers (Fig. 1C and F, Fig. 2C). This association of ADAD pathology with motor symptoms, that can be caused by basal ganglia dysfunction (Nelson and Kreitzer, 2014), accords with the concept that the anatomical distribution of pathology determines the clinical phenotype (Weintraub and Mesulam, 2009).
The significant increase of the prevalence of motor signs reaching almost 20 percent between estimated years to symptom onset -20 and -10, compared to a proportion of about 3 percent between estimated years to symptom onset -30 and -20, also complies with a potential association between amyloid β pathology and motor symptoms in ADAD, as it coincides with the proposed starting point of amyloid β accumulation in the timeline of ADAD (Bateman *et al.*, 2012). However, motor symptoms were solely more pronounced in ADAD than in sporadic AD at the stage of moderately severe dementia, and not at earlier stages.
Also other conditions with different neuroanatomical substrates such as cerebellar pathologies, corticospinal dysfunction or cognitive dysfunction, i.e. apraxia, may influence motor function as measured by UPDRS-III. Therefore, the results of our study do not warrant to link motor dysfunction specifically to amyloid β in the basal ganglia. Regarding cerebellar amyloid β deposition, no difference between *presenilin 1* and *presenilin 2* mutation carriers with and without dysdiadochokinesia was found.

Potential basic premises for the association of subcortical amyloid β with basal ganglia symptoms include a directly induced neuronal dysfunction, as well as a mediation of regional neurodegeneration through tau pathology (Nelson *et al.*, 2012; Shinohara *et al.*, 2014). Further, a potential impact of Lewy body pathology, that is frequently present in ADAD (Lippa *et al.*, 1998; Leverenz *et al.*, 2006; Cairns *et al.*, 2015; Ringman *et al.*, 2016), on the manifestation of motor symptoms has to be considered (Chung *et al.*, 2015). To investigate the conceivable influence of these and other non-amyloid β pathologies on motor function in ADAD tau imaging and clinicopathologic correlation studies are required in the future.

In the context of the various current and ongoing observational and treatment trials, in particular those with a focus on very early AD stages (Bateman *et al.*, 2012; Bateman *et al.*, 2017) as well as in terms of clinical diagnosis and care of AD, early and easy to assess clinical signs could become important for the identification of individuals in initial disease stages. Dysdiadochokinesia appears to be such an indicator and can be rapidly evaluated in clinical routine settings. In distinction from seizures, which we have also shown to be an early feature of ADAD in a subset of individuals and a predictor of mutation status in persons at risk for ADAD (Vöglein *et al.*, 2018), dysdiadochokinesia is independent from the individual´s history but is assessed in a standardized manner, also to be reevaluated as deemed necessary. However, given that only a very small percent (< 5%) manifest this symptom, its general utility is clearly limited.

In our investigation of effects of mutation position in *presenilin 1*, we concur with Mann and colleagues who first described a mutation clustering within the gene in relation to distinct neuropathological findings in the frontal cortex and cerebellum of *presenilin 1* mutation carriers. The first cluster, comprising mutations that affect codons 1 to 200, was associated with an amyloid plaque profile similar to sporadic AD. The second mutation cluster, after *presenilin*

1 codon 200, was associated with severe cerebral amyloid angiopathy (Mann *et al.*, 2001). This finding was subsequently corroborated (Ryan *et al.*, 2015; Ringman *et al.*, 2016). More extensive cerebral amyloid angiopathy could contribute to the greater extent of motor findings that we found in *presenilin 1* post codon 200 mutation carriers. This is of particular interest in the light of a marginally higher burden of cerebellar amyloid angiopathy in *presenilin 1* post codon 200 mutation carriers compared to pre codon 200 mutations (Ryan *et al.*, 2015). Findings of an increased amount of magnetic resonance imaging white matter hyperintensities, more severe neurofibrillary pathology and an increased likelihood for ischemic, hemorrhagic, or vascular pathology in *presenilin 1* post codon 200 mutation carriers (Ryan *et al.*, 2015; Ringman *et al.*, 2016) might also account for the more pronounced motor signs that we found in this subpopulation.

Regarding clinical manifestation, *presenilin 1* mutations after codon 200 were reported to be more frequently associated with spasticity, spastic paraparesis and visuospatial impairment, whereas mutations before codon 200 more frequently with seizures and myoclonus (Shea *et al.*, 2016; Tang *et al.*, 2016). Broadening the clinical characterization of *presenilin 1* mutation carriers and adding to the evidence that their exact mutation site influences the clinical phenotype, we found motor symptoms more common and even more severe with *presenilin 1* mutations after codon 200 (Fig. 1B and E). There have been interpretations regarding the impact of the mutation site in *presenilin 1* with respect to codon 200 on neuropathological and clinical manifestations of ADAD (Mann *et al.*, 2001; Ryan and Rossor, 2010). However, the underlying mechanisms remain unclear and deserve further study.

Our results indicate that ADAD patients with a Clinical Dementia Rating global score of 2 show more pronounced motor findings than sporadic AD patients with the same Clinical Dementia Rating global score. Prevalence and degree of motor symptoms did not differ between ADAD and sporadic AD patients with global Clinical Dementia Rating scores of 0.5 and 1,

respectively. This indicates that progressing dementia is the most significant factor that leads to more severe motor symptoms. Additionally, these findings might be in accordance with the delay of up to 20 years between deposition of amyloid β and manifestation of symptoms that is already known for cortical amyloid deposition and cognitive impairment in ADAD and sporadic AD (Mintun *et al.*, 2006; Bateman *et al.*, 2012). In ADAD, accumulation of amyloid β in the basal ganglia is more pronounced at early disease stages than in sporadic AD (Bateman *et al.*, 2012). Therefore, subsequent motor symptoms may occur at the stage of moderately severe dementia in ADAD, while patients with sporadic AD may manifest motor symptoms at the stage of severe dementia, if at all in their lifetime. Hence, the findings of this study would be in accordance with a common, while yet unknown, mechanism of substantially delayed functional impairment by amyloid β in cortex and basal ganglia. Of note, a limitation could be that clinical assessment could be more challenging at the stage of severe dementia.

Cognitively symptomatic mutation carriers from the Dominantly Inherited Alzheimer Network observational study, in average approximately 47 years old, were equally affected by motor symptoms (at Clinical Dementia Rating global score 0.5 and 1) or worse (at Clinical Dementia Rating global score 2) compared to patients with sporadic AD from the National Alzheimer's Coordination Center database who were in average approximately 72 years old, while normal controls from the National Alzheimer's Coordination Center database (mean age about 70 years) exhibited more pronounced motor symptoms than non-carriers from the Dominantly Inherited Alzheimer Network cohort (mean age about 40 years). This could be explained in two different ways. First, symptomatic mutations carriers develop more pronounced motor symptoms if age is factored out. Second, because motor symptoms are usually rare in healthy controls who are at an age similar to the mean age of mutation carriers studied here, motor symptoms could be recognized as an irregular symptom of ADAD at a young age. Therefore, an alternative interpretation may be that it could be the early age of manifestation but not the early phase of ADAD that is associated with the increase notion of motor symptoms.

Motor symptoms affect a relevant proportion of ADAD mutation carriers (Table 1) as well as of patients with sporadic AD and worsen along withprogression of cognitive impairment in AD. In particular, ADAD and AD patients at the stage of moderately severe dementia are affected by motor symptoms (Figure 2, Table 4) (Albers *et al.*, 2015). Identification of motor dysfunction is relevant for clinical care and for patient and family/caregiver interaction, as it is associated with disability (Murray *et al.*, 2004) and predictive of AD mortality (Bennett *et al.*, 1998; Zhou *et al.*, 2010).

In summary, our study describes motor symptoms in ADAD that are associated with disease stage and cognitive symptoms, particularly affecting patients in advanced dementia stages. In a very small percent of cognitively asymptomatic individuals motor signs can predict mutation carrier status. Further, the prevalence of motor findings is increased in *presenilin 1* mutations after codon 200.

Motor assessment is therefore proposed as an integral component in the clinical work-up of individuals from ADAD families. Evaluation of motor function should be considered to be comprehensively included in current and future observational and therapeutic trials of ADAD.

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Figures

Figure 1: Heading: Prevalence and degree of motor findings, as assessed by Unified Parkinson Disease Rating Scale part three, in autosomal dominant Alzheimer's disease mutation carriers compared to non-carriers (A,D) and in *presenilin 1* post codon 200 mutation carriers compared to *presenilin 1* pre codon 200 (B,E). Percentage of amyloid β positive basal ganglia, defined by a Pittsburgh Compound B - Standardized Uptake Value Ratio >1,3, and mean Pittsburgh Compound B - Standardized Uptake Value Ratios in the basal ganglia in mutations carriers with motor findings compared to those without (C,F). Legend: In D, E, and F single data points are shown. Bars indicate medians and interquartile intervals. *P*-values: * < 0.05 / ** < 0.01 / *** < 0.001. Abbreviations: Aβ = Amyloid β. UPDRS-III = Unified Parkinson Disease Rating Scale part three. PiB-SUVR = Pittsburgh Compound B - Standardized Uptake Value Ratio. Find. = Findings.

Figure 2: Heading: Correlations between Unified Parkinson Disease Rating Scale part three score and (A) estimated years to symptom onset (r_s=0.409; $P < 0.001$), (B) Clinical Dementia Rating-Sum of Boxes (r_s=0.420; $P < 0.001$) and (C) the basal ganglia Pittsburgh Compound B - Standardized Uptake Value Ratio (r_s=0.233; $P = 0.001$) in autosomal dominant Alzheimer's disease mutation carriers. Legend: Dashed lines represent 95% confidence intervals. Abbreviations: UPDRS-III = Unified Parkinson Disease Rating Scale part three. PiB-SUVR = Pittsburgh Compound B - Standardized Uptake Value Ratio.

Tables

	Mutation Carriers (n = 261)	**Non-Carriers (n = 172)**	**Total (n = 433)**	***P*-Value**
Mean Age, years	39.3	39.6	39.4	0.789
Females, n (%)	146 (56%)	102 (59%)	248 (57%)	0.551
Mean Years of Education	14.1	14.6	14.3	0.145
Mean EAO, years	47.2	N/A	N/A	N/A
Mean EYO	-7.9	N/A	N/A	N/A
Mean global CDR Score	0.32	0.04	0.21	**< 0.001**
Mean CDR-SB Score	1.55	0.07	0.96	**< 0.001**
Participants with UPDRS-III Score > 0, n (%)	74 (28.4%)	22 (12.8%)	96 (22.2%)	**< 0.001**

Table 1: Title: Comparison of population characteristics between autosomal dominant Alzheimer's disease mutation carriers and non-carriers. Legend: Bold indicates *P*-values below 0.05. Abbreviations: EAO = Expected Age of Onset. EYO = Estimated Years to Symptom Onset. CDR = Clinical Dementia Rating. CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes. UPDRS-III = Unified Parkinson Disease Rating Scale part three. N/A = not applicable.

UPDRS-III Items		**Mutation Carriers (n = 261)**	**Non-Carriers (n = 172)**	***P*-Value**
Speech		4.2%	1.2%	0.129
Facial expression		5.4%	1.7%	0.128
Tremor at rest	*Face, lips, chin*	0.8%	0.6%	1
	Right hand	0.8%	0%	0.585
	Left hand	0.8%	0%	0.585
	Right foot	0.4%	0%	1
	Left foot	0%	0%	1
Action or postural tremor of hands	*Right hand*	7.3%	2.9%	0.101
	Left hand	8.0%	2.9%	0.077
Rigidity	*Neck*	2.3%	0%	0.129
	Right upper extremity	8.8%	4.7%	0.181
	Left upper extremity	8.4%	5.2%	0.312

	Right lower extremity	7.3%	1.7%	**0.030**
	Left lower extremity	6.1%	1.7%	0.070
Finger taps	*Right hand*	6.9%	0%	**< 0.001**
	Left hand	6.5%	1.2%	**0.025**
Hand movements	*Right hand*	5.7%	0%	**0.004**
	Left hand	6.1%	0.6%	**0.016**
Rapid alternating movements of hands	*Right hand*	7.7%	0%	**< 0.001**
	Left hand	9.6%	0%	**< 0.001**
Leg agility	*Right leg*	4.6%	0%	**0.013**
	Left leg	5.0%	0.6%	**0.030**
Arising from chair		1.5%	0%	0.209
Posture		2.3%	0.6%	0.312
Gait		4.2%	0%	**0.016**
Posture stability		6.1%	1.2%	**0.030**

Body bradykinesia and hypokinesia	3.8%	0.6%	0.101

Table 2: Title: Prevalence of abnormality in each Unified Parkinson Disease Rating Scale part three item (i.e. item score > 0) in mutation carriers and non-carriers. Legend: All *P*-values are derived from Fisher's exact tests and are adjusted for 27 comparisons with Benjamini-Hochberg procedure. Bold indicates *P*-values below 0.05. Abbreviation: UPDRS-III = Unified Parkinson Disease Rating Scale part three.

ADAD Mutation	***PSEN1***	***PSEN2***	***APP***	***P*-Value**
Participants with Motor Findings, n (%)	61 (31%)	4 (20%)	9 (20.5%)	0.259
Total Participant Number, n	197	20	44	N/A

1

Mutation Site	***PSEN1* Post Codon 200**	***PSEN1* Pre Codon 200**	***P*-Value**
Participants with Motor Findings, n (%)	49 (36%)	11 (19.3%)	***0.022***
Different Mutations in Participants with Motor Findings, n	19	10	N/A
Total Participant Number, n	136	57	N/A
Mean UPDRS-III Score	3.03	0.91	***0.013***
Mean EYO	-5.9	-8.7	0.090

2

APOE Genotype	**e2e2**	**e2e3**	**e2e4**	**e3e3**	**e3e4**	**e4/e4**	***P*-Value**
Participants with Motor Findings, n (%)	0 (0%)	5 (19.2%)	2 (28.6%)	47 (29.9%)	16 (26.7%)	4 (50%)	0.554
Total Participant Number, n	2	26	7	157	60	8	N/A

Table 3: Title: Extent of motor symptoms in mutation carriers of autosomal dominant Alzheimer's disease, analyzed separately regarding affected gene (i.e. *presenilin 1*, *presenilin 2* or the gene encoding the amyloid precursor protein) (top), mutation site within *presenilin 1* (middle), and apolipoprotein E genotype (bottom). Legend: Percentages in brackets refer to affected gene, mutation site or apolipoprotein E genotype, respectively. The apolipoprotein E genotype was not available in one mutation carrier. Bold indicates *P*-values below 0.05. Abbreviations: ADAD = Autosomal Dominant Alzheimer's Disease. *PSEN1 = presenilin 1*. *PSEN2 = presenilin 2*. *APP* = the gene encoding the amyloid precursor protein. UPDRS-III = Unified Parkinson Disease Rating Scale part three. EYO = Estimated Years to Symptom Onset. APOE = Apolipoprotein E. N/A = not applicable.

CDR global score = 0.5			
	ADAD (n = 65)	**sAD (n = 1869)**	***P*-Value**
Mean UPDRS-III Score	2.15	2.32	0.76
Participants with Motor Findings, n (%)	28 (43.1)	805 (43.1)	1
Mean Age, years	43.88	72.35	***< 0.001***

CDR global score = 1			
	ADAD (n = 26)	**sAD (n = 947)**	***P*-Value**
Mean UPDRS-III Score	5.38	3.86	0.27
Participants with Motor Findings, n (%)	16 (61.5)	488 (51.5)	0.31
Mean Age, years	46.96	72.19	*< 0.001*

CDR global score = 2			
	ADAD (n = 7)	**sAD (n = 209)**	***P*-Value**
Mean UPDRS-III Score	20.71	5.96	***< 0.001***
Participants with Motor Findings, n (%)	5 (71.4)	130 (62.2)	0.71

Mean Age, years	52.14	73.88	< ***0.001***

	Non-carrier Controls (DIAN-OBS) (n = 159)	**Controls (NACC) (n = 8185)**	***P*-Value**
Mean UPDRS-III Score	0.33	1.49	< ***0.001***
Participants with Motor Findings, n (%)	16 (10.1)	2217 (27.1)	< ***0.001***
Mean Age, years	39.04	69.32	< ***0.001***

Table 4: Title: Comparison of motor symptoms between cognitively symptomatic mutation carriers for autosomal dominant Alzheimer's disease and patients with sporadic Alzheimer's disease, stratified for Clinical Dementia Rating global scores, and between non-carriers controls from the Dominantly Inherited Alzheimer Network cohort and controls from the National Alzheimer's Coordination Center cohort. Legend: Controls from the Dominantly Inherited Alzheimer Network cohort are non-carrier with a Clinical Dementia Rating global score = 0. Controls from the National Alzheimer's Coordination Center cohort are individuals with a Clinical Dementia Rating global score = 0 that were additionally rated cognitively normal at baseline and all occurring follow-up visits. Abbreviations: CDR = Clinical Dementia Rating. ADAD = Autosomal Dominant Alzheimer's Disease. sAD = sporadic Alzheimer's Disease. UPDRS-III = Unified Parkinson Disease Rating Scale part three. DIAN-OBS = Dominantly Inherited Alzheimer Network Observational Study. NACC = National Alzheimer's Coordinating Center.