Neurobiology of Aging 76 (2019) 215.e9–215.e14

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

HTT gene intermediate alleles in neurodegeneration: evidence for association with Alzheimer's disease

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ARTICLE INFO

Article history:
Received 14 May 2018
Received in revised form 14 November 2018
Accepted 14 November 2018
Available online 28 November 2018

Keywords:
Huntington's disease
Neurodegeneration
HTT gene
Intermediate alleles
Cognitive decline

ABSTRACT

Huntington's disease (HD) is an autosomal progressive neurodegenerative disorder caused by the expansion of CAG repeats in the *HTT* gene. Intermediate alleles (IAs) are in the range of 27–35 repeats and have been associated to a normal phenotype. The aim of this work was to analyze the association between intermediate huntingtin CAG-repeat alleles (IAs) and neurodegenerative diseases, other than HD. We screened the *HTT* CAG repeats in patients with Alzheimer's disease (AD) (n = 1126), Parkinson's disease (PD) (n = 610), and frontotemporal lobar degeneration (FTLD) (n = 225). We also studied 509 healthy controls (HCs). The relative frequency of IAs for each group was 6.03% in AD, 5.3% in FTLD, 3.5% in PD, and 2.9% in HCs. The frequency of IA was significantly higher among patients with AD when compared to HCs ($p = 0.011$, OR = 2.11, 95% CI = 1.19–3.74); no significant difference was observed in FTLD ($p = 0.17$; OR = 1.88, 95% CI = 0.85–4.03) and PD ($p = 0.69$; OR = 1.21; 95% CI (0.61–2.37) versus HCs. No atypical symptoms or clinical features distinctive of HD were found among carriers of IAs. We found 3 cases with CAG expansions within the pathological range, one diagnosed with AD, one with PD, and one with FTD. Results suggest that IAs might have a role in the pathogenesis of AD. In addition, HD patients might be misdiagnosed with other neurodegenerative diseases, particularly when CAG repeats are in the lower pathological range.

1. Introduction

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder clinically characterized by movement disorders, cognitive impairment, and neuropsychiatric symptoms in variable combinations. Even when there is a substantial heterogeneity in the intensity of the symptoms and the age at onset, the disease always progresses over time. Although chorea is the most representative feature of the disease and one of the most common onset symptom, it is well known that HD can also present with cognitive impairment decades before the movement symptoms are noted (Cardoso, 2017; Paulsen, 2011).

HD is caused by the expansion of the CAG trinucleotide repeat (>35 repeats) resulting in an expanded polyglutamine tract in the huntingtin protein. Intermediate alleles (IAs) are defined as CAG repeats between 27 and 35 and are considered to be genetically unstable and prone to expansion in offspring (Semaka et al., 2006). It is questioned whether IA carriers may manifest HD symptoms with age or not (Andrich et al., 2008; Groen et al., 2010; Ha and Jankovic, 2011; Herinashu et al., 2009).

The prevalence of IAs varies from 0.45% to 8.7% in the general population (Apolinario et al., 2017). However, a large study using data from the European Huntington's Disease Registry database described an 11.6% frequency for IAs and showed that elderly IAs carriers had more chorea and faster cognitive decline than controls after a 1-year

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https://doi.org/10.1016/j.neurobiolaging.2018.11.014

follow-up but otherwise there is little clinical difference when assessed on other motor or behavioral scores. However, carriers with larger IAs (34–35 repeats) may develop a much milder HD-like phenotype in later life (Cubo et al., 2016). In addition, a population-based study found that IAs carriers have a higher risk of manifesting apathy and suicidal ideation (Killoran et al., 2013), while a "U relationship" has been found between the number of repeats and the risk of suffering depression: lifetime depression risk is higher with both relatively short and relatively large huntingtin (HTT) CAG repeat sizes in the normal range (Gardiner et al., 2017). Similarly, an "inverted U relationship" was described between size of CAG repeats and intelligence: increasing repeats are beneficial to a certain point and then becomes detrimental to intelligence (Lee et al., 2018).

Recently, several studies focused on establishing the association between CAG expansions and susceptibility to neurodegenerative diseases other than the disease known to be caused by expansions in that particular gene. Expansions of the CAG repeat in the *ATXN2* gene, which cause spinocerebellar ataxia type 2, have been associated with increased risk of amyotrophic lateral sclerosis (Sproviero et al., 2017), but no significant association was found with HTT CAG repeats (Ramos et al., 2012). Intermediate *ATXN1* alleles have been suggested as a risk factor in amyotrophic lateral sclerosis, mostly in *C9ORF72* expansion carriers (Lattante et al., 2018).

However, the role of IAs in other neurodegenerative disorders has not been fully assessed. Our aim was to determine the frequency of IA in patients with Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), and a cohort of healthy controls.

2. Materials and methods

2.1. Study design

This is a genetic study based on samples from patient's biobanks; therefore, the clinical data were retrospectively collected from medical records.

2.2. Subjects and medical records

All patients were Caucasian. The Alzheimer cohort consisted of 1126 unrelated patients clinically diagnosed according to National Institute of Aging and Alzheimer's Association criteria (McKhann et al., 2011). The FTLD cohort included 225 unrelated patients diagnosed with behavioural variant frontotemporal dementia or primary progressive aphasia according to the Frontotemporal Dementia Consortium (Rascovsky et al., 2011) and Consensus Criteria (Gorno-Tempini et al., 2011), respectively. A total of 610 unrelated patients were clinically diagnosed with PD according to the Movement Disorder Society criteria (Postuma et al., 2015).

All the patients were ascertained at the Hospital Universitario de Cabueñes, Hospital Universitario Central de Asturias and Hospital Santa Creu and Sant Pau. In those cases where we found IAs, we examined the medical records to retrieve the demographic and clinical data. For patients with AD or FTLD, we collected age at onset, main cognitive domains affected (memory, language, praxias and visuospatial and executive functions), motor symptoms (gait abnormalities, extrapyramidal signs, chorea, tremor or other involuntary movements), neuropsychiatric symptoms (psychotic, depressive, anxiety, impulse control disorder), structural neuroimaging findings (computed tomography [CT] and magnetic resonance imaging [MRI] scans) at onset, when available. For patients with PD, we collected age at onset, motor phenotype (tremoric, rigid-akinetic, mixed, or postural instability gait disorder), cognitive status at the latest follow-up (no cognitive impairment, mild cognitive impairment, dementia), neuropsychiatric symptoms (psychotic, depressive, anxiety, impulse control disorder) and structural neuroimaging findings (based in CT and MRI scans) at onset, when available. Functional neuroimaging was also recorded for FTLD [^{18}F-labeled fluoro-2-deoxyglucose- positron emission tomography (18-FDG-PET)] and PD (DaTSPECT), whereas CSF biomarkers were recorded for AD, when available.

The control group was a cohort of unrelated Caucasian individuals (n = 509) free of neurodegenerative disease. They were recruited through the Health Community Service (elderly subjects who agreed to participate).

All the patients and controls gave informed consent to participate in the study which was approved by the Ethical Committees of Hospital Universitario Central de Asturias and Hospital Santa Creu i Sant Pau.

2.3. Genetic testing

Genomic DNA was extracted from peripheral blood samples following standard procedures. *HTT* CAG repeat genotyping was determined by a polymerase chain reaction with 5′-fluorescence–labeled primers (Jama et al., 2013). The number of repeats was determined by capillary electrophoresis using an ABI 3130X automated DNA sequencer and the GeneMapper version 4.0 software (Applied Biosystems). To provide size standards, we sequenced several samples with different *HTT* CAG alleles. As previously reported, high IAs were classified as 34-35 CAG repeats and moderate IAs as 27-33 CAG repeats.

All the patients and controls were also genotyped for the apolipoprotein E (APOE) alleles (E2, E3, and E4) by real-time polymerase chain reaction using commercially available Taqman assays (Applied Biosystems).

2.4. Statistical analyses

The χ^2 and Fisher's exact tests, with the Bonferroni adjustment, were used to compare the frequency of HTT IAs between patient's groups and controls. The HTT CAG repeats distribution among different groups was analyzed using the Kruskal-Wallis test because the samples did not display a normal distribution, followed by the Dunn's post hoc test whenever appropriate. A parametric test (Student t-test) was performed to analyze the correlation between IAs and age at onset. The statistical analysis was performed using R Statistical Software (version 3.4.4) and SPSS (version 17).

3. Results

3.1. Frequency of IA in neurodegenerative patients

Table 1 displays the demographic data of patients and controls and intermediate carrier frequencies. As expected, the frequency of the APOE-ε4 allele was significantly higher in patients with AD compared with controls (0.26 vs. 0.089 $p < 0.0001$; OR = 3.73, 95% CI = 2.83–4.41). The risk of AD was significantly increased in patients with E4/E4 genotype ($p < 0.0009$; OR = 13.011). In the FTLD and PD groups, the *APOE* allele and genotype frequencies were similar to the control population (data not shown).

In all groups, *HTT* alleles with 17 and 18 CAG repeats were the most frequent. In the IA group, the most frequent was 27 CAG repeats and the longest repeat was 34, found in one individual (Fig. 1). Using the Kruskal-Wallis test, no differences were found in the distribution of normal alleles (8-26 CAG-repeats) between groups of patients and controls. In addition, for IAs (27–35), no difference in the allele distribution was detected likely due to the small number of patient carriers of IAs.

In the PD cohort, the frequency of IAs did not differ from the frequency found in the controls (3.5% vs. 2.9%). In the AD cohort, the

Table 1
Demographic data of patient's cohorts and frequencies of HTT intermediate alleles

Group	N	Male (%)	Age at last examination/age at onset	Carriers of IAs (%)	*p*-value	OR (95% CI)	Bonferroni
Controls	509	234 (46%)	71.14 ± 6.42	15 (2.9%)			
AD	1126	337 (30%)	74.32 ± 9.67	68 (6.03%)	0.011[a] 0.038[b]	2.11 (1.19–3.74)[a] 1.71 (1.05–2.8)[b]	$p = 0.029$[a] $p = 0.13$
FTLD	225	79 (35%)	60.84 ± 11.9	12 (5.3%)	0.17	1.88 (0.85–4.03)	$p = 0.87$
PD	610	315 (52%)	59.85 ± 13.6	22 (3.5%)	0.69	1.21 (0.61–2.37)	$p = 1$

Key: AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; HTT, huntingtin; IA, intermediate alleles; PD, Parkinson's disease.
[a] AD cohort versus control cohort.
[b] AD cohort versus PD cohort.

frequency of IAs carriers was 6.03%, significantly higher than the observed in controls and PD ($p = 0.011$ and $p = 0.038$, respectively). In the FTLD cohort, although the association was not statistically significant there was an increased frequency of IAs (5.3% vs. 2.9% in controls).

We did not find differences in the mean age of onset between carriers and noncarriers of IAs (AD: 75.30 ± 8.60 years in non-carriers vs. 73.92 ± 9.3 years in carries; FTLD: 64.23 ± 10.96 years in noncarriers vs. 64.20 ± 14 years in carriers). Moreover, in the patients with AD, the frequency of IAs and age at onset did not differ between *APOE*-ε4 carriers and noncarriers.

3.2. *Clinical features of intermediate* HTT *carriers*

The clinical features, biomarkers, and neuroimaging findings of all carriers of IAs are shown as Supplementary Material, Table 1. We found no atypical clinical features in carriers of IAs. Particularly, chorea was not found in any subject. Other movement disorders such as tremor or gait imbalance were considered not atypical for the respective diagnoses or attributable to the pharmacological treatment. The domains affected in carriers of IAs diagnosed with AD or FTLD were the domains expected to be affected in these diseases. Psychiatric symptoms were frequent, especially in FTLD. Regarding structural and functional neuroimaging studies, we found no relevant findings in any of the diagnostic groups.

Among AD only, one case had IAs in the higher intermediate range (allele with 34 or 35 CAG repeats) (1.5%), compared to 8.3% (1/12) in FTLD and 6.6% (1/15) in the controls (Fisher exact test, $p = 0.29$ and $p = 0.25$, respectively). No IAs in the higher intermediate range were detected among the patients with PD. None of the carriers with IAs in the higher intermediate range has an abnormal motor phenotype. Within the FTLD cohort, 2 IAs carriers also presented a *C9ORF72* hexanucleotide expansion. One patient with AD has 2 IAs of 27 and 31 repeats but no HD-like signs were observed.

3.3. *Carriers of pathological CAG expansions in the* HTT *gene*

We found 3 cases with expansions within the pathological range.

Case 1 was a 55-year-old male with cognitive impairment and unbalanced gait. His mother and 2 maternal uncles suffered from

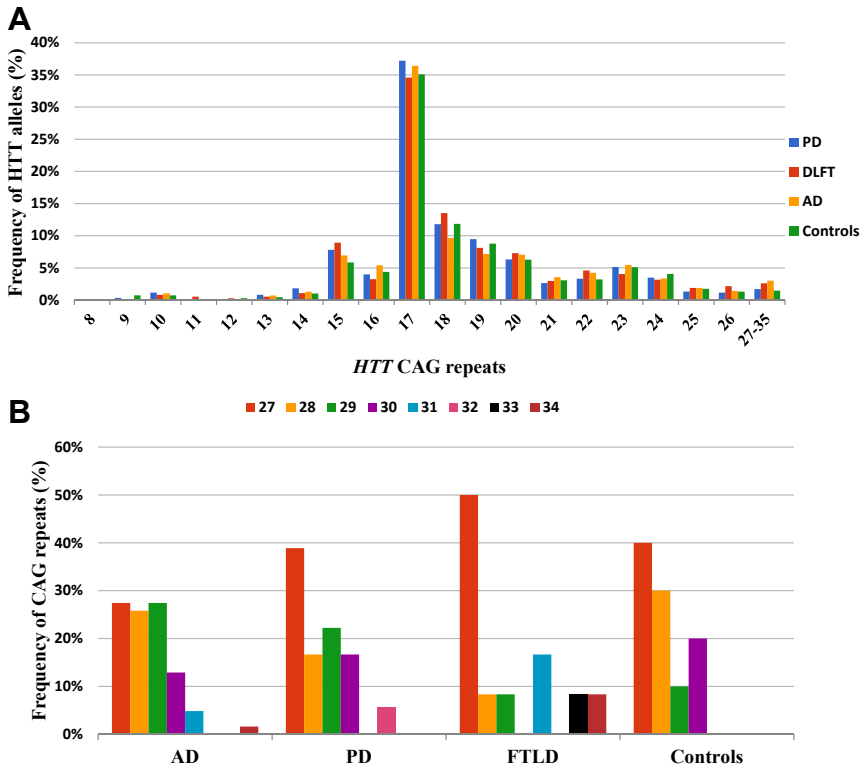

Fig. 1. (A) Frequency of HTT CAG repeats in patients and controls. (B) Distribution of HTT intermediate CAG alleles in patients groups and controls. Abbreviations: AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; HTT, huntingtin; PD, Parkinson's disease.

cognitive impairment. Baseline motor examination was normal. Follow-up motor examination 18 months later showed mild bilateral bradykinesia, motor impersistence, and impaired postural reflex without tremor or hyperkinetic movements. Neuropsychological assessment showed a marked slowing in the performance of all tests and poor attention. Short-term auditory-verbal memory and working memory were impaired, as well as long-term memory, both verbal and visuospatial. In the executive functions, there is a reduction in nonverbal fluency and sequencing tasks, as well as in inhibition of automatized responses. Altogether, neuropsychological performance is suggestive of a diffuse corticosubcortical dysfunction, more marked on the right hemisphere. Genetic testing did not identify mutations on *PSEN1, PSEN2, APP,* and *GRN* genes, *APOE* genotype was 3/4 and biomarkers in the CSF were negative for probable AD diagnosis. MRI found no pathological changes other than slight and diffuse cortical atrophy (Fig. 2A). 18F-FDG-PET showed hypometabolism in the anterior cinguli and left frontal cortex involving the superior frontal gyrus and the frontoparietal junction (Fig. 2B). There was also hypometabolism on the left parietal lobe. We found a pathological expansion of 36 repeats confirmed by Sanger sequencing.

Case 2 was an 80-year-old woman with 39 CAG repeats and APOE 3/3 genotype. There was no family history of neurodegenerative diseases. High blood pressure was the only relevant finding in her medical records. She lived in a nursing home for 3 years before the first visit when relatives found her unable to live alone. Memory difficulties were the main cognitive impairment in the patient and other family members. Indeed, memory was markedly affected in neuropsychological screening tests and verbal fluency. No motor signs were noted on examination. Blood tests were normal and the brain CT scan showed diffuse cortical atrophy and a defect in the parietal bone of unknown etiology.

Case 3 was a 37-year-old woman with 39 CAG repeats and APOE 3/3 genotype, without a family history of neurodegenerative diseases. She presented with asymmetric rest tremor. A diagnosis of PD was stablished after clinical assessment and positive DaTSPECT (Fig. 2C). No cognitive impairment or psychiatric symptoms were present. Genetic analysis identified a *PARK2* homozygous pathogenic variant, c.155delA (p.N52MfsX2) and *HTT* alleles of 17 and 39 CAG repeats.

4. Discussion

In this study, we examined the frequency of intermediate *HTT* alleles in 3 groups of neurodegenerative diseases and identified a significant association with disease risk for AD (OR = 2.11, 95% CI = 1.19–3.74), while the increase of frequency in our FTLD cohort (5.3% FTLD vs. 2.9% control population) was not significant but suggestive of some association. To our knowledge, this is the first report of an association of IAs of the *HTT* gene with neurodegenerative diseases other than HD. The main interest of this finding is the possibility of elucidating new potential common pathways in some neurodegenerative diseases. However, the lack of association with PD suggests that IAs do no play a significant role in all the neurodegenerative processes. The mechanism by which the *HTT* IAs might contribute to neuronal degeneration in AD is unclear. However, an important evidence supporting the association of the *HTT* gene with AD is the reported neuropathological study of 15 elderly HD subjects that found evidence of co-occurring AD neuropathology in 82% of the cases (n = 11) with prominent dementia (Davis et al., 2014).

It would be interesting to find clinical, neuropsychological, or neuroimaging features that may help us to identify cases where IAs are involved. In our series, all diagnoses were consistent with current clinical criteria for AD, PD, and FTLD. None of the IAs carriers have distinctive HD phenotype and we did not find any significant difference in the age at onset, clinical features, or neuroimaging findings. Some reports claimed that IAs might produce HD phenotypes, even when no solid neuropathological evidences have been obtained in humans (other than that single case reports), animal models, or in vitro studies. The only report with autopsy-confirmed diagnosis was a case with 29 CAG repeats (Kenney et al., 2007) with some neuropathological changes compatible with HD but no huntingtin intranuclear inclusions. The challenge to know whether IAs *HTT* produce HD pathology will be solved as soon as we have more pathological studies from these cases and we can definitively confirm or rule out the presence of huntingtin deposits.

When HD onsets late, movement disorders are usually less severe and cognitive complains may be the reason for consultation. Then, late-onset HD might be easily misdiagnosed with other neurodegenerative diseases especially when diagnoses are not supported by biomarkers (Burger,2002). In this study, we identified 3 patients with pathological expansion in the *HTT* gene. One of these patients was a middle-aged male with cognitive impairment and neuroimaging findings compatible with FTLD, but it could also be suggestive of HD without basal ganglia involvement. Other case was an old woman with cognitive impairment and a clinical diagnosis of AD, with no biomarkers available. The third case was a young woman with autosomal recessive juvenile PD and homozygous carrier of a mutation in the *Park2* gene and a pathological

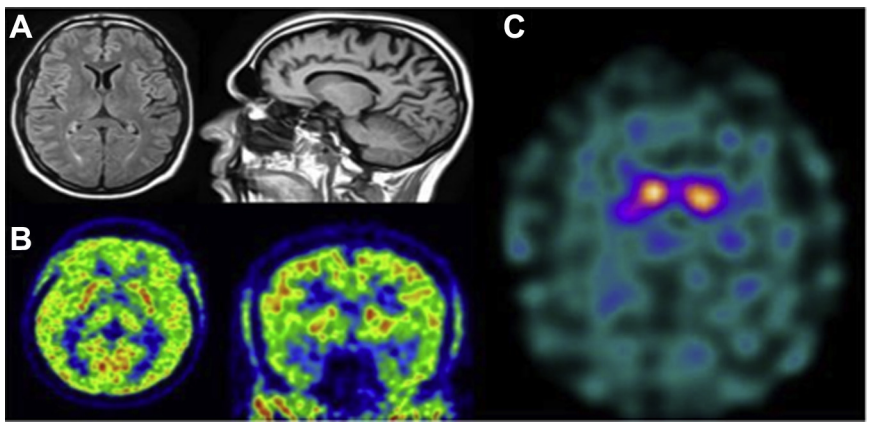

Fig. 2. (A) T1 MRI of case 1 showing slight and diffuse cortical atrophy. (B) FDG-PET scan of case 1 showing hypometabolism in the anterior cinguli and left frontal cortex involving the superior frontal gyrus and the frontoparietal junction as well as in the left parietal lobe. Metabolism in the basal ganglia is normal. (C) DaTSPECT of case 3 showing very low density of dopamine presynaptic transporters in both putamen nuclei, especially on the left. Abbreviation: MRI, magnetic resonance imaging.

expansion (39 repeats) in the *HTT* gene. DaTSPECT was positive and the most affected nuclei were the putamen, instead of the caudate which is the most frequently involved in HD (Kawabe, 2016). The potential pathogenicity of the *HTT* gene in these cases should be interpreted with caution because it is well known that the size of the CAG repeat correlates with the age of onset, and CAG repeats in the range of 36–39 were associated with a late onset of the disease and age-dependent penetrance. However, the number of *HTT CAG* repeats accounts for 50%–70% of the variance in age of onset, and the remaining frequency was attributed to other modifying gene and environmental risk factors. Moreover, it has been showed that a striking mosaicism is present in the brain, and the size of CAG repeats in blood does not necessarily replicate the length and toxicity of CAG repeats in the striatum (Groen et al., 2010; Sun et al., 2017). Although the clinical features of cases 1 and 2 are plausible due to the *HTT* gene expansion, the current symptoms of case 3 are most likely due to the mutation in the *Park2* gene as suggested by the clinical phenotype and the DaTSPECT.

The main limitation of this study is the variability of the available data because they were collected retrospectively. The diagnosis accuracy is also variable because some diagnoses were supported by biomarkers, whereas others did not. However, this study supports a genetic link between AD and the *HTT* gene. Although not statistically significant, results also suggest a link between FTLD and the *HTT* gene; therefore, IAs in *HTT* might act as a risk factor for cognitive impairment and IAs in *HTT* should be studied in other neurodegenerative diseases such as dementia with Lewy bodies or in patients diagnosed with neuropsychiatric disorders.

Finally, although our AD cohort is relatively large, our FTLD cohort is relatively small, and it is possible that the real frequency of IAs in FTLD is not accurately represented. To further assess the results, these findings need replication in other cohorts. The potential coinfluence of other variants and haplotypes should also be assessed because it is well known that CAG stability is related to other single nucleotide polymorphisms in *HTT* gene (Warby et al., 2009).

5. Conclusions

The frequency of IAs was higher in AD compared to healthy controls. IAs might play a role in the pathogenesis of AD and perhaps in other neurodegenerative diseases. No atypical signs or symptoms were found among carriers of IA in our cohort. Patients with HD might be misdiagnosed with other neurodegenerative diseases, particularly when CAG repeats are in the lower pathological range. More studies are needed to replicate these findings.

Disclosure

The authors report no conflicts of interest related with this work.

Acknowledgements

The authors are indebted to all the patients and their families for their participation. The authors wish to thank Fundación Parkinson Asturias-Obra Social Cajastur for their support. This study is supported by grant PI 15/00878 (Fondos Feder) to VA. OD-I is funded by Departament de Salut de la Generalitat de Catalunya, Pla strategic de recerca i innovació en salut (PERIS) 2016-2020 (SLT002/16/00040). IIG is supported by the Rio Hortega grant (CM17/00074) from "Acción Estratégica en Salud 2013-2016" and the European Social Fund. JC and VA research's groups are members of Dementia Genetics Spanish Consortium (DEGESCO. Irene Rosas is supported by a grant from Fundación JOse Luis Castaño-SEQC).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.11.014.

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