Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to *APOE* ε4 haplotype status: a community-based cohort study

Hyun-Sik Yang, Lei Yu, Charles C White, Lori B Chibnik, Jasmeer P Chhatwal, Reisa A Sperling, David A Bennett, Julie A Schneider, Philip L De Jager**

Summary

Background Transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy in older adults frequently coexists with Alzheimer's disease pathology and hippocampal sclerosis. It is unclear whether there is a link between *APOE* ε4 and TDP-43 proteinopathy, and the role of *APOE* ε4 in the association of TDP-43 proteinopathy with hippocampal sclerosis remains to be examined. We investigated the relationships of TDP-43 proteinopathy and hippocampal sclerosis with *APOE* ε4.

Methods We used data from two community-based cohort studies of ageing and dementia: the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). A battery of cognitive tests examining multiple cognitive domains is given to ROS-MAP participants each year, and a measure of annual global cognitive function for each participant is derived by averaging *Z* scores of these tests. The final clinical diagnosis is assigned after death by a neurologist using all available clinical data without access to post-mortem pathology. Amyloid-β, paired helical filament tau, Lewy bodies, TDP-43, and hippocampal sclerosis were microscopically evaluated in the midbrain, medial temporal, and neocortical regions that capture the progression of each neuropathology. TDP-43 proteinopathy topographic stage was recorded as an ordinal variable, and TDP-43 burden was defined by averaging a semi-quantitative six-point scale across six brain regions. The relationships among *APOE* ε4, TDP-43 proteinopathy, and hippocampal sclerosis were tested with regression models controlled for sex and age at death, and they were further explored with a mediation analysis using the quasi-Bayesian Monte Carlo method.

Findings ROS began data collection in 1994, and MAP began data collection in 1997. The data included in this study were analysed from Jan 16, 2017, to July 12, 2017. When analysis began in January, 2017, a total of 1059 ROS-MAP participants who were deceased had *APOE* genotype and complete pathological measures for amyloid-β, paired helical filament tau, and TDP-43 proteinopathy stage. After excluding 15 participants with other pathological diagnoses, 1044 participants, 1042 of whom also had measures of Lewy body pathology, were included in this study (470 from ROS and 574 from MAP). *APOE* ε4 count was associated with higher TDP-43 proteinopathy stage (odds ratio [OR] 2·0, 95% CI 1·6–2·6; p=$1·9\times10^{-9}$) and TDP-43 burden (0·40, 0·28–0·52; p=$1·2\times10^{-10}$). Amyloid-β, paired helical filament tau, or Lewy body pathology did not fully explain this association. *APOE* ε4 increased the odds of hippocampal sclerosis (OR 2·1, 95% CI 1·4–3·0; p=$1·7\times10^{-4}$); this effect was largely mediated by TDP-43 burden (mediated effect p<$1·0\times10^{-4}$) but not directly by *APOE* ε4 (direct effect p=0·40). *APOE* ε4 was associated with worse global cognition proximate to death even after adjusting for amyloid-β and paired helical filament tau (estimated effect –0·18, 95% CI –0·31 to –0·04; p=0·010), but this association was attenuated by additionally adjusting for TDP-43 burden (–0·09, –0·22 to 0·04; p=0·18).

Interpretation *APOE* ε4 seems to increase TDP-43 burden, and this effect in turn was associated with higher odds of hippocampal sclerosis, a pathology potentially downstream of TDP-43 proteinopathy. TDP-43 proteinopathy contributes to the detrimental effect of *APOE* ε4 on late-life cognition through mechanisms independent of Alzheimer's disease pathology, and future research should consider that TDP-43 proteinopathy might be an integral component of *APOE*-related neurodegeneration.

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*Contributed equally

Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA (H-S Yang MD, Prof R A Sperling MD); **Department of Neurology, Massachusetts General Hospital, Boston, MA, USA** (H-S Yang, J P Chhatwal MD, Prof R A Sperling); **Department of Neurology, Harvard Medical School, Boston, MA, USA** (H-S Yang, J P Chhatwal, Prof R A Sperling); **The Broad Institute of MIT and Harvard, Cambridge, MA, USA** (H-S Yang, C C White PhD, L B Chibnik PhD, Prof P L De Jager MD); **Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA** (L Yu PhD, Prof D A Bennett MD, Prof J A Schneider MD); **Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA** (L Yu, Prof D A Bennett, Prof J A Schneider); **Harvard T H Chan School of Public Health, Boston, MA, USA** (L B Chibnik); **and Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA** (Prof P L De Jager)

Correspondence to:
Prof Philip L De Jager, Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY 10032-3784, USA
pld2115@cumc.columbia.edu

Introduction

Transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy is a core pathology of amyotrophic lateral sclerosis and frontotemporal lobar degeneration (FTLD) with TDP-43 (FTLD-TDP),[1] but it is also commonly observed in older adults without these diseases. TDP-43 proteinopathy in older adults has clinical and pathological characteristics distinct from that seen in FTLD-TDP[2–5] and commonly coexists with hippocampal sclerosis[3,6–8] and Alzheimer's disease pathology (amyloid-β and tau).[2,4,6,9] An association between hippocampal sclerosis and Alzheimer's disease pathology has also been reported, but

Research in context

Evidence before this study

We searched PubMed for articles published before May 1, 2018, with the search term "(TDP-43 OR hippocampal sclerosis) AND (genetic association OR *APOE*)", yielding 189 articles. We reviewed these studies to summarise previously identified genetic risk loci of transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy or hippocampal sclerosis, or both, and to outline the relationship between *APOE* and TDP-43 proteinopathy. A previous study reported that rs1990622 near *TMEM106B*, which is a risk variant for frontotemporal lobar degeneration (FTLD) with TDP-43 (FTLD-TDP), is also associated with TDP-43 proteinopathy in older adults without FTLD or amyotrophic lateral sclerosis. Two studies reported higher number of *APOE* ε4 carriers in participants with Alzheimer's disease pathology and comorbid TDP-43 proteinopathy than in people with Alzheimer's disease pathology without TDP-43 proteinopathy. For hippocampal sclerosis in older adults that is not from epilepsy or FTLD, genetic association studies have identified several risk variants: rs704178 within *ABCC9*, rs5848 near *GRN*, rs1990622 near *TMEM106B*, and rs9637454 within *KCNMB2*. By contrast, multiple studies have reported that *APOE* haplotypes are not associated with hippocampal sclerosis in older adults.

Added value of this study

To our knowledge, this study is the first to report the independent association of *APOE* ε4 with the presence and severity of TDP-43 proteinopathy, taking into account other *APOE* ε4-related proteinopathies (Alzheimer's disease pathology and Lewy body pathology), in large community-based cohorts of older adults. We also report that the independent *APOE* ε4–TDP-43 proteinopathy association is not moderated by other *APOE* ε4-related proteinopathies. Our results indicate that the association of *APOE* ε4 with hippocampal sclerosis is largely mediated through TDP-43 burden, reinforcing previous literature that suggests TDP-43 proteinopathy is a central component in the pathological cascade leading to hippocampal sclerosis. Finally, we observed that TDP-43 proteinopathy could contribute to the detrimental effect of *APOE* ε4 on late-life cognition, beyond Alzheimer's disease pathology.

Implications of all the available evidence

Multiple neurodegenerative pathologies commonly coexist in the ageing brain and synergistically contribute to cognitive decline and dementia. *APOE* ε4 is associated with an increased risk of multiple major neurodegenerative proteinopathies associated with cognitive decline in older adults (amyloid-β, paired helical filament tau, α-synuclein, and TDP-43). Also, accumulating evidence suggests that hippocampal sclerosis is a pathological condition downstream of TDP-43 proteinopathy. Thus, beyond their common coexistence, major neurodegenerative proteinopathies in older adults might share common pathogenic pathways, a potentially important point to consider in future clinical trials and translational research.

this association was no longer significant when TDP-43 proteinopathy was concurrently considered.[3] Because TDP-43 proteinopathy has a large effect on hippocampal atrophy, cognitive decline, and the risk of Alzheimer's disease dementia beyond what can be explained by Alzheimer's disease pathology alone,[4,9–12] it is important to understand the relationship of TDP-43 proteinopathy with other neurodegenerative pathologies in older adults.

Genetic risk factors are not subject to reverse causation, because the random assignment of parental genotypes to an individual during conception cannot be affected by post-natal phenotypes; this property is referred to as Mendelian randomisation.[13] Thus, genetic association studies can provide a unique opportunity in examining the relationship between different post-mortem neuropathologies by assessing shared genetic associations between two pathologies. Notably, two previous studies showed that among participants with autopsy-confirmed Alzheimer's disease pathology, *APOE* ε4 was associated with the presence of comorbid TDP-43 proteinopathy.[10,12] However, it is unclear whether the link between *APOE* ε4 and TDP-43 proteinopathy is independent from other *APOE*-ε4-related pathologies, and the role of the *APOE* ε4 haplotype in the association of TDP-43 proteinopathy with hippocampal sclerosis remains to be examined.

Therefore, we aimed to investigate the relationship among *APOE* ε4, TDP-43 proteinopathy, and other *APOE*-ε4-related proteinopathies, such as amyloid-β, paired helical filament tau, and Lewy body pathology.[14] Subsequently, leveraging Mendelian randomisation of *APOE* ε4, we aimed to investigate whether the relationship between TDP-43 proteinopathy and hippocampal sclerosis was causal. Finally, we aimed to examine the clinical implications of the *APOE* ε4–TDP-43 proteinopathy association.

For the **Resource Sharing Hub** see https://www.radc.rush.edu/

Methods

Study design and participants

We did a community-based cohort study using the Religious Orders Study[15] (ROS) and the Rush Memory and Aging Project[16] (MAP). Both ROS and MAP are longitudinal cohort studies of ageing and dementia that enrol older adults without known dementia and collect annual clinical and post-mortem pathological data. ROS launched in 1994, and enrols Catholic priests, brothers, and nuns from more than 40 religious communities across the USA. MAP started in 1997, and targets participants from diverse backgrounds, including continuous-care retirement communities throughout northeastern Illinois and individual homes across the Chicago metropolitan area of the USA. Further details about the participants are available in previous publications[15,16] and the Rush Alzheimer's Disease Center Research Resource Sharing Hub. Each participant has

signed a written informed consent and a written Anatomical Gift Act document at the time of enrolment, and the data collection and usage protocols of ROS and MAP have been approved by the Rush University Medical Center Institutional Review Board.

Procedures

To determine cognitive phenotypes, a battery of cognitive tests including the Mini-Mental State Examination and 19 other tests examining multiple cognitive domains was given to ROS-MAP participants each year (appendix),[15–17] and an annual global cognitive function for each participant was derived by averaging *Z* scores of these tests, excluding the Mini-Mental State Examination.[15–17] Subsequently, the random slope of global cognition was derived from linear mixed models with annual global cognitive function as the longitudinal outcome, adjusting for age at baseline, sex, and years of education.[18] The final clinical diagnosis was assigned after death by a neurologist using all available clinical data without access to post-mortem pathology,[15,16] and individuals with probable Alzheimer's disease dementia (ie, Alzheimer's disease with no other cause of cognitive impairment) or possible Alzheimer's disease dementia (ie, Alzheimer's disease with other cause contributing to cognitive impairment) were considered to have Alzheimer's disease dementia.

Codons 112 and 158 from *APOE* exon 4 were sequenced to derive *APOE* haplotypes (ε2, ε3, or ε4).[19] We derived genotype dosage of *TMEM106B* rs1990622[A], a known TDP-43 proteinopathy risk allele,[5,20] as previously reported (appendix).[21,22] Neuropathological evaluation was done as previously reported.[15,16] Pathological diagnosis of Alzheimer's disease was assigned for individuals with high or intermediate likelihood according to the modified National Institute on Aging–Reagan Institute criteria. Amyloid-β was quantified as the mean percentage area of cortex occupied by amyloid-β, assessed with immunohistochemistry (one of three monoclonal antibodies: 4G8 [Covance Labs, Madison, WI, USA; 1:9000 dilution], 6F/3D [Dako North America, Carpinteria, CA, USA; 1:50 dilution], or 10D5 [Elan Pharmaceuticals, San Francisco, CA, USA; 1:600 dilution]) in eight regions (hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal cortex, angular gyrus, calcarine cortex, anterior cingulate cortex, and superior frontal cortex), generating a continuous variable.[15,16] Paired helical filament tau was detected with an anti-phosphotau antibody (AT8, targeting Ser202/Thr205 [Thermo Fisher Scientific, Rockford, IL, USA; 1:2000 dilution]) in the same eight regions and quantified with mean cortical density (per mm²), generating a continuous variable.[15,16]

Lewy bodies, another pathology that has been linked with *APOE* ε4,[14] were assessed with α-synuclein immunostain (one of two monoclonal antibodies: LB509 [Zymed Labs, Invitrogen, Carlsbad, CA, USA; 1:150 or 1:100 dilution] or pSyn#64 [Wako Chemicals, Richmond, VA, USA; 1:20,000 dilution]) and each participant was assigned a previously described topographic stage (stage 0=not present; stage 1=nigral-predominant; stage 2=limbic; and stage 3=neocortical), generating an ordinal variable.[19,23] TDP-43 proteinopathy was assessed with monoclonal antibodies to phosphorylated TDP-43 (TAR5P-1D3, targeting Ser409/Ser410 [Ascenion, Munich, Germany; 1:100 dilution]), and its topographic stage was recorded as an ordinal variable (stage 0=none; stage 1=amygdala only; stage 2=amygdala and limbic [entorhinal or hippocampus]; stage 3=amygdala, limbic, and neocortical).[3,5] TDP-43 cytoplasmic inclusion burden was defined by averaging a semi-quantitative six-point scale (0–5; treated as a continuous variable in our analyses) across six brain regions (amygdala, hippocampus CA1 or subiculum, dentate gyrus, entorhinal cortex, midfrontal cortex, and middle temporal cortex) that captures topographic progression of TDP-43 proteinopathy.[4] Each region was graded for severity of TDP-43 cytoplasmic inclusions on a 0–5 scale (0=none; 1=sparse [1–2 inclusions in a 0·25 mm² area of greatest density within that region]; 2=sparse to moderate [3–5 inclusions]; 3=moderate [6–12 inclusions]; 4=moderate to severe [13–19 inclusions]; 5=severe [≥20 inclusions]), and the scores from the six regions was averaged to yield the semi-quantitative TDP-43 burden. TDP-43 dystrophic neurite (thread) burden was quantified separately, using the same scale and regions as the TDP-43 cytoplasmic inclusions.

Hippocampal sclerosis was evaluated in a coronal section of the mid-hippocampus at the level of the lateral geniculate body, and was recorded as present if there was a severe neuronal loss and gliosis in the CA1 sector or subiculum, or both, generating a binary variable.[3] Hippocampal sclerosis was diagnosed independent of coexisting Alzheimer's disease pathology or TDP-43 proteinopathy, but the diagnosis was not considered in the cases with hippocampal changes related to FTLD or gross or microscopic infarcts. Presence of one or more gross chronic cerebral infarcts was recorded as a binary variable (ie, present or absent).[15,16]

Statistical analysis

ROS and MAP were combined in our analyses, because both cohorts capture common clinical and pathological measures and are managed by the same team of investigators, who designed both studies.[15,16] All regression analyses were controlled for sex and age at death. We excluded participants with missing values.

After observing a correlation between two semi-quantitative measures of TDP-43 burden (cytoplasmic inclusion and dystrophic neurites; Spearman's $\rho=0\cdot96$; $p<2\cdot2\times10^{-16}$), we chose to use the TDP-43 cytoplasmic inclusion burden for the TDP-43 burden analyses. We estimated the general population prevalence of *APOE* ε4 haplotype in individuals of European descent

See Online for appendix

	APOE ε4 non-carrier (n=774)	*APOE* ε4 heterozygote (n=251)	*APOE* ε4 homozygote (n=19)	All study participants (n=1044)	All deceased ROS-MAP participants (n=1624)
Age at enrolment (years)	80·6 (7·1)	79·8 (6·4)	74·5 (7·3)	80·3 (7·0)	80·8 (6·9)
Age at death (years)	89·5 (6·6)	88·9 (6·1)	83·8 (5·9)	89·2 (6·5)	88·7 (6·6)
Sex					
Women	532 (69%)	172 (69%)	13 (68%)	717 (69%)	1077 (66%)
Men	242 (31%)	79 (31%)	6 (32%)	327 (31%)	547 (34%)
Education (years)	16·0 (3·6)	16·6 (3·7)	17·3 (4·6)	16·1 (3·6)	16·1 (3·7)
MMSE score proximate to death*	21·7 (8·6)	17·6 (10·4)	14·9 (10·4)	20·6 (9·3)	21·1 (9·0)
Global cognitive function proximate to death†	−0·82 (1·11)	−1·34 (1·29)	−1·78 (1·19)	−0·96 (1·19)	−0·94 (1·16)
Random slope of global cognition‡	−0·006 (0·088)	−0·053 (0·109)	−0·098 (0·096)	−0·019 (0·096)	−0·023 (0·099)
Diagnosis of Alzheimer's disease dementia§	284 (37%)	139 (55%)	14 (74%)	437 (42%)	634 (39%)
Pathological diagnosis of Alzheimer's disease	447 (58%)	209 (83%)	16 (84%)	672 (64%)	NA¶
Amyloid-β burden	3·8 (4·2)	6·4 (4·2)	8·0 (4·9)	4·5 (4·3)	NA¶
Paired helical filament tau burden	5·6 (6·6)	10·0 (9·9)	15·4 (12·6)	6·9 (8·0)	NA¶
Presence of TDP-43 proteinopathy	370 (48%)	154 (61%)	14 (74%)	538 (52%)	NA¶
Lewy body pathology	173 (22%)	71 (28%)	4 (21%)	248 (24%)	NA¶
Diagnosis of hippocampal sclerosis‖	59 (8%)	37 (15%)	3 (16%)	99 (9%)	NA¶

Data are mean (SD) or n (%). ROS-MAP=Religious Orders Study and the Rush Memory and Aging Project. MMSE=Mini-Mental State Examination. TDP-43=transactive response DNA-binding protein of 43 kDa. NA=not available. *Data missing for two participants. †Data missing for six participants. ‡Data missing for 52 participants. §Data missing for 11 participants. ¶Data missing for more than 10% of participants. ‖Data missing for two participants.

Table 1: **Demographic characteristics of the study participants**

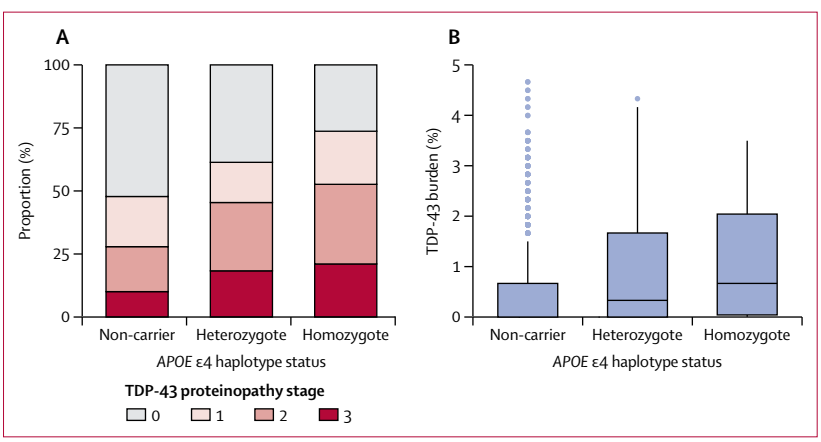

Figure 1: ***APOE* ε4 haplotype status and TDP-43 proteinopathy stage and burden**
(A) *APOE* ε4 haplotype status and TDP-43 proteinopathy stage (0–3). (B) *APOE* ε4 haplotype status and semi-quantitative TDP-43 burden (0–5). The middle horizontal lines of the boxes are medians, the upper edges are the 75th percentiles, and the lower edges are the 25th percentiles. The whiskers extend from the box to the largest and smallest values, but no further than 1·5 × IQR from the hinge. Datapoints beyond the end of the whiskers (outliers) are plotted individually. TDP-43=transactive response DNA-binding protein of 43 kDa.

from the allele frequency of rs429358[T] in the 1000 Genome Project European population.[24] The association of *APOE* ε4 count (continuous ordinal variable values of 0, 1, or 2; independent variable) with TDP-43 proteinopathy stage (outcome variable) was examined with multivariate ordinal logistic regression (R MASS package), and the association of *APOE* ε4 count (independent variable) with TDP-43 burden (outcome variable) was assessed with multivariate linear regression. Effect of each *APOE* genotype (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4) on TDP-43 burden was compared with the reference *APOE* ε3/ε3 homozygotes, as detailed in the appendix. Additional analyses controlling for amyloid-β, paired helical filament tau, and Lewy bodies were done, and we also assessed whether age at death or other proteinopathies modified the *APOE* ε4–TDP-43 proteinopathy association by including interaction terms. We used square-root transformed values of the quantitative amyloid-β and paired helical filament tau variables to account for their positively skewed distributions. *APOE* ε4 count and rs1990622[A] dosage were analysed for their statistical interaction in increasing TDP-43 proteinopathy. The association between *APOE* ε4 and hippocampal sclerosis was assessed with logistic regression without and with adjustment of TDP-43 proteinopathy to examine whether TDP-43 proteinopathy explains this association.

We also did a mediation analysis with *APOE* ε4 carrier status as an independent causal variable, TDP-43 burden as a mediator, and hippocampal sclerosis as a binary outcome, and the mediated effect and direct effect were estimated with the default quasi-Bayesian Monte Carlo method and bootstrap simulation from the R mediation package.[25]

Finally, the residual association of *APOE* ε4 count with global cognitive function proximate to death (continuous variable; linear regression) or Alzheimer's disease dementia (binary variable; logistic regression) was evaluated after controlling for amyloid-β, paired helical filament tau, age at death, sex, and years of education; we added TDP-43 proteinopathy to these models as a

covariate to assess whether TDP-43 proteinopathy explains this residual effect of *APOE* ε4 on cognition and dementia. To assess clinical characteristics of each subgroup defined by TDP-43 proteinopathy stage, hippocampal sclerosis, and *APOE* ε4 carrier status, we defined advanced TDP-43 proteinopathy as stages 2 and 3, the stages that are associated with increased odds of dementia.[9] Residual global cognitive decline (or residual global cognitive function) was defined as the residual from a linear model having the random slope of global cognition (or global cognitive function proximate to death adjusted for sex, age at death, and years of education) as the outcome and amyloid-β and paired helical filament tau as predictors. Further details on the covariate selection procedure, power calculation for subgroup analyses, and mediation analyses are described in the appendix.

We did all statistical analyses using R (version 3.3).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. The first and corresponding authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit this manuscript for publication.

Results

ROS began data collection in 1994, and MAP began data collection in 1997. The data included in this study were analysed from Jan 16, 2017, to July 12, 2017. At the time of analysis in January 2017, a total of 3225 ROS-MAP participants had completed baseline evaluation (1349 from ROS and 1876 from MAP). Among these participants, 1396 (86%) of 1624 deceased participants had an autopsy (691 (91%) of 760 from ROS and 705 (82%) of 864 from MAP). A total of 1059 deceased participants had *APOE* genotype data and complete pathological measures for amyloid-β, paired helical filament tau, and TDP-43 proteinopathy stage. Most of these participants also had measures of Lewy body pathology (n=1042). After excluding 15 participants with pathological diagnoses of FTLD, amyotrophic lateral sclerosis, progressive supranuclear palsy, or corticobasal degeneration, 1044 participants were included in our study (470 from ROS and 574 from MAP). The characteristics of the 1044 ROS-MAP participants included in our study were similar to all deceased ROS-MAP participants (table 1). 1010 (97%) participants self-reported their race to be white, and 270 (26%) participants were *APOE* ε4 carriers (251 heterozygotes and 19 homozygotes), similar to the estimated general population prevalence in individuals of European descent (26%). Data for ROS and MAP participants are compared in the appendix.

APOE ε4 count showed a dose-response relationship with TDP-43 proteinopathy stage and burden (figure 1).

	TDP-43 proteinopathy stage		TDP-43 burden	
	Odds ratio (95% CI)	p value	Estimated effect (95% CI)	p value
Model 1*				
APOE ε4	2·0 (1·6–2·6)	$1·9\times10^{-9}$	0·40 (0·28 to 0·52)	$1·2\times10^{-10}$
Model 2*				
APOE ε4 (adjusted for amyloid-β and paired helical filament tau)	1·5 (1·2–2·0)	$7·4\times10^{-4}$	0·23 (0·10 to 0·35)	$4·2\times10^{-4}$
Amyloid-β	1·1 (1·0–1·2)	0·13	0·08 (0·02 to 0·13)	$9·5\times10^{-3}$
Paired helical filament tau	1·3 (1·2–1·5)	$7·6\times10^{-9}$	0·14 (0·09 to 0·19)	$2·5\times10^{-8}$
Model 3†				
APOE ε4 (adjusted for amyloid-β, paired helical filament tau, and Lewy body pathology)	1·5 (1·2–2·0)	$9·9\times10^{-4}$	0·22 (0·09 to 0·35)	$6·1\times10^{-4}$
Amyloid-β	1·1 (1·0–1·2)	0·13	0·08 (0·02 to 0·13)	$9·7\times10^{-3}$
Paired helical filament tau	1·3 (1·2–1·5)	$3·2\times10^{-8}$	0·14 (0·09 to 0·19)	$1·4\times10^{-7}$
Lewy body pathology	1·1 (1·0–1·2)	0·10	0·06 (0·01 to 0·12)	0·015
Model 4*				
APOE ε4 × pathological diagnosis of Alzheimer's disease	1·5 (0·8–2·8)	0·20	0·21 (–0·09 to 0·51)	0·18
APOE ε4	1·3 (0·7–2·3)	0·33	0·16 (–0·10 to 0·43)	0·23
Pathological diagnosis of Alzheimer's disease	1·6 (1·2–2·1)	$1·3\times10^{-3}$	0·27 (0·13 to 0·41)	$1·2\times10^{-4}$
Model 5†				
APOE ε4 × amyloid-β	0·9 (0·7–1·2)	0·56	0·03 (–0·10 to 0·17)	0·61
APOE ε4 × paired helical filament tau	1·1 (0·9–1·3)	0·47	0·03 (–0·06 to 0·12)	0·50
APOE ε4 × Lewy body pathology	1·0 (0·9–1·3)	0·66	0·04 (–0·07 to 0·15)	0·45
APOE ε4	1·5 (0·8–2·8)	0·26	0·03 (–0·28 to 0·35)	0·83
Amyloid-β	1·1 (1·0–1·3)	0·10	0·07 (0·01 to 0·14)	0·027
Paired helical filament tau	1·3 (1·1–1·5)	$4·2\times10^{-5}$	0·12 (0·06 to 0·18)	$1·2\times10^{-4}$
Lewy body pathology	1·1 (0·9–1·2)	0·27	0·05 (–0·01 to 0·11)	0·096

Odds ratios of higher TDP-43 proteinopathy stage as *APOE* ε4 count increased were reported from ordinal logistic regressions with TDP-43 proteinopathy stage (0–3) as an outcome, and estimated effects (adjusted increase in TDP-43 burden as *APOE* ε4 count increased) were reported from linear regressions with a semi-quantitative TDP-43 burden (range 0–5) as an outcome. Model 1 is the primary analysis, and has *APOE* ε4 count as the independent variable and TDP-43 proteinopathy stage or burden as the outcome. Models 2 and 3 also have *APOE* ε4 count as the independent variable, and adjust for other *APOE* ε4-related proteinopathies. Model 4 tests whether the interaction term between *APOE* ε4 count and the pathological diagnosis of Alzheimer's disease is associated with TDP-43 proteinopathy stage or burden. Model 5 tests whether any of the interaction terms between *APOE* ε4 count and amyloid-β, paired helical filament tau, or Lewy body pathology stage is associated with TDP-43 proteinopathy stage or burden. All analyses were adjusted for sex and age at death. TDP-43=transactive response DNA-binding protein of 43 kDa. *n=1044 for TDP-43 proteinopathy stage as the outcome, and n=1027 for TDP-43 burden as the outcome. †n=1042 for TDP-43 proteinopathy stage as the outcome, and n=1025 for TDP-43 burden as the outcome (two participants had missing values for Lewy body pathology).

Table 2: **Association of TDP-43 proteinopathy with *APOE* ε4 count and other neurodegenerative proteinopathies**

Higher *APOE* ε4 count was associated with higher TDP-43 proteinopathy stage (odds ratio [OR] 2·0, 95% CI 1·6–2·6; $p=1·9\times10^{-9}$) and TDP-43 burden (0·40, 0·28–0·52; $p=1·2\times10^{-10}$) in the regression models (table 2), and this association was significant in both ROS and MAP (appendix). Age at death did not moderate the *APOE* ε4–TDP-43 proteinopathy association and the presence of *APOE* ε2 did not significantly affect TDP-43 burden (appendix). The effect of *APOE* ε4 was much stronger than that of *TMEM106B* rs1990622[A] (appendix). There was no significant interaction between *APOE* ε4

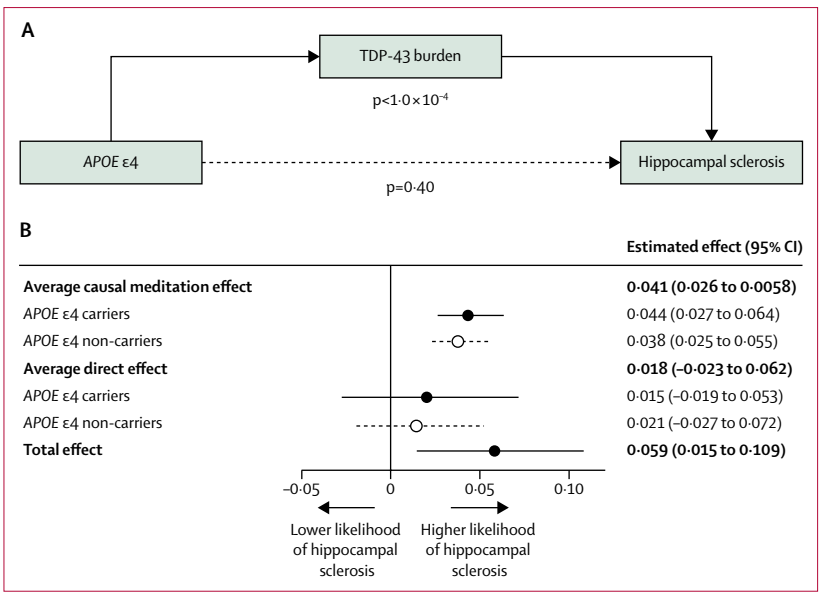

Figure 2: **Mediation models of the relationships among *APOE* ε4 carrier status, TDP-43 burden, and hippocampal sclerosis**

(A) A causal mediation analysis using quasi-Bayesian Monte Carlo method with 10 000 simulations; 1025 participants with non-missing values were used for this analysis. The average causal mediation effect estimate (ie, the effect of the independent variable to the outcome through the mediator, solid arrows) was significant. By contrast, the average direct effect estimate (ie, the effect of the independent variable to the outcome that is independent from the mediator, dotted arrows) was not significant. (B) The x-axis denotes the size of effect measured by increased probability of the outcome (hippocampal sclerosis), expressed in a relative scale. A filled circle and solid line indicate the effect and 95% CI in the treatment group (ie, *APOE* ε4 carriers), and an empty circle and dotted line indicate the effect and 95% CI in the control group (ie, *APOE* ε4 non-carriers). Estimated average causal mediation effect and average direct effect were reported separately for *APOE* ε4 carriers and non-carriers in this simulation, as the outcome model was non-linear. The plot shows no significant difference between *APOE* ε4 carriers and non-carriers in their estimated average causal mediation effect or average direct effect. About 70% of the total effect is through the average causal mediation effect. All models were adjusted for sex and age at death.

and rs1990622[A] in predicting TDP-43 proteinopathy (appendix).

The *APOE* ε4–TDP-43 proteinopathy association was only partially attenuated after controlling for amyloid-β, paired helical filament tau, and Lewy body pathology (table 2). Conversely, the associations of *APOE* ε4 with other proteinopathies were not fully explained by TDP-43 proteinopathy (appendix). A logistic regression analysis confirmed the independent association between TDP-43 proteinopathy and *APOE* ε4 (appendix). Furthermore, diagnosis of Alzheimer's disease pathology or Lewy body pathology burden did not show significant interaction with the *APOE* ε4 count (table 2), suggesting no strong evidence that the effect of *APOE* ε4 count on TDP-43 proteinopathy varies with Alzheimer's disease or Lewy body pathological burden. We did not observe a significant association between *APOE* ε4 and TDP-43 proteinopathy when we limited our analysis to the subgroup of individuals without a pathological diagnosis of Alzheimer's disease (n=372, with 45 *APOE* ε4 carriers; appendix). However, this subgroup analysis is underpowered because the *APOE* ε4 haplotype frequency is lower than in the overall study population: we would need approximately 1100 participants without a pathological diagnosis of Alzheimer's disease (appendix) to show the same *APOE* ε4–TDP-43 proteinopathy association that was observed in the subgroup with a pathological diagnosis of Alzheimer's disease. Clinical and pathological characteristics of these subgroups are shown in the appendix.

In the logistic regression models, *APOE* ε4 count was associated with hippocampal sclerosis (OR 2·1 as *APOE* ε4 count increased, 95% CI 1·4–3·0, p=1·7×10⁻⁴), even when amyloid-β, paired helical filament tau, and Lewy body pathology were adjusted for, but this association was no longer significant when TDP-43 proteinopathy was considered (appendix). Because there are strong associations between *APOE* ε4 and TDP-43 proteinopathy, and TDP-43 proteinopathy and hippocampal sclerosis, TDP-43 proteinopathy could be a mediator of the association between *APOE* ε4 and hippocampal sclerosis (appendix). By contrast, hippocampal sclerosis is unlikely to be a strong mediator of the *APOE* ε4–TDP-43 proteinopathy association, because the association between *APOE* ε4 count and TDP-43 proteinopathy was still strong after controlling for hippocampal sclerosis (appendix). On the basis of a causal mediation analysis with the quasi-Bayesian Monte Carlo method, the effect of *APOE* ε4 carrier status on hippocampal sclerosis was largely mediated by TDP-43 burden (mediated effect p<1·0×10⁻⁴), whereas the direct effect of *APOE* ε4 on hippocampal sclerosis independent from TDP-43 burden was not significant (direct effect p=0·40; figure 2). A non-parametric bootstrap method yielded a similar result, and a sensitivity analysis further supported validity of our result (appendix).

APOE ε4 count was associated with worse global cognitive function proximate to death and higher odds of Alzheimer's disease dementia, and nominal residual associations were observed even after adjusting for Alzheimer's disease pathology (amyloid-β and paired helical filament tau; estimated effect –0·18, 95% CI –0·31 to –0·04; p=0·010; table 3). TDP-43 proteinopathy stage (estimated effect –0·13, 95% CI –0·27 to –0·001; p=0·048) and TDP-43 burden (–0·09, –0·22 to 0·04; p=0·18) attenuated this residual association (table 3). Adjusted global cognitive decline and adjusted global cognition proximate to death for each subgroups defined by the presence of advanced TDP-43 proteinopathy (stage 2 or 3), hippocampal sclerosis, and *APOE* ε4 carrier status are shown in table 4. We noted that the subgroup with both advanced TDP-43 proteinopathy and hippocampal sclerosis had the highest proportion of *APOE* ε4 carriers, highest TDP-43 burden, and the worst cognitive trajectory (adjusted for amyloid-β, paired helical filament tau, and sex, age at death, and years of education; the appendix shows cognitive measures in each subgroup only adjusted for sex, age at death, and years of education).

Discussion

In this study of more than 1000 well characterised older adults from community-based cohorts, we found that

APOE ε4 is a strong genetic predictor of the presence and severity of TDP-43 proteinopathy. This association was not fully explained or significantly moderated by other *APOE* ε4-related proteinopathies (amyloid-β, paired helical filament tau, and Lewy body pathology). Furthermore, TDP-43 proteinopathy contributed to poor cognition and increased odds of dementia associated with *APOE* ε4, which was beyond what could be explained by amyloid-β and paired helical filament tau. Therefore, in addition to amyloid-β, paired helical filament tau, and Lewy body pathology,[14] our results indicate that TDP-43 is another major neurodegenerative proteinopathy linked to *APOE* ε4, and has an independent contribution to the pleiotropic role of *APOE* ε4 in late-life dementia.[19,26]

The association between *APOE* ε4 and TDP-43 proteinopathy adds important insights into the relationship between TDP-43 proteinopathy and Alzheimer's disease: they not only coexist but also share a common genetic risk factor. However, the association between TDP-43 proteinopathy and Alzheimer's disease was not fully explained by *APOE* ε4 alone. Thus, multiple linking points other than *APOE* might underlie the intricate relationship among the neurodegenerative proteinopathies in older adults. We note that TDP-43 proteinopathy in older adults is unlikely to be a simple downstream or upstream pathology of Alzheimer's disease, because *APOE* ε4 had an independent association with TDP-43 proteinopathy or Alzheimer's disease even when the other condition was controlled for.

Notably, the effect of *APOE* ε4 on TDP-43 proteinopathy was independent of and stronger than that of *TMEM106B* rs1990622[A], a previously reported genetic risk factor of TDP-43 proteinopathy in older adults and FTLD-TDP.[5,20] Thus, although TDP-43 proteinopathy in older adults shares the *TMEM106B*-related pathogenic pathway with FTLD-TDP, our result shows that the pathway downstream of *APOE* might play an independent and more important role in TDP-43 proteinopathy in older adults, supporting that TDP-43 proteinopathy in older adults is a process distinct from FTLD-TDP. Larger studies would be required to confirm these genetic associations, but the association between *APOE* ε4 and TDP-43 proteinopathy was statistically robust, and exceeded the significance threshold ($p<5\cdot0\times10^{-8}$) of an unbiased genome-wide association study.

Our results also provided an important insight into the relationship between TDP-43 proteinopathy and hippocampal sclerosis. TDP-43 proteinopathy might be pathogenically upstream of, or at least precede, most cases of hippocampal sclerosis in older adults,[8] but the causal relationship between two cross-sectional neuropathological measures has remained elusive. We leveraged Mendelian randomisation[13] to show that TDP-43 proteinopathy is likely to be pathogenically upstream of hippocampal sclerosis in the pathway connecting *APOE* and hippocampal sclerosis. Therefore, we suggest that TDP-43 proteinopathy in older adults is on a pathogenic continuum with hippocampal sclerosis: most cases of hippocampal sclerosis might represent downstream consequences of TDP-43 proteinopathy-mediated neurodegeneration.

Of note, the association between *APOE* ε4 and hippocampal sclerosis was not present in multiple previous studies.[7,14,27] Although ROS and MAP are volunteer cohorts whose participants do not have dementia at baseline, agreed to future autopsy at study entry, and have sociodemographic differences from the general population, they are community-based cohort studies that have very high rates of follow-up participation and autopsy, minimising biases that affect many large longitudinal studies. These features of the ROS-MAP population might have resulted in a more genetically representative sampling in our study, as shown by the number of participants with an *APOE* ε4 carrier status that is very close to the estimated general population prevalence, a condition that might have been important to capture the relatively weak association between *APOE* ε4 and hippocampal sclerosis.

The mechanism of the *APOE* ε4–TDP-43 proteinopathy association is currently unclear. Besides its well characterised effect on amyloid-β aggregation and clearance, *APOE* might also affect transport and clearance of other misfolded proteins. There is a

	Global cognitive function		Alzheimer's disease dementia	
	Estimated effect (95% CI)	p value	Odds ratio (95% CI)	p value
Model 1*				
APOE ε4	−0·57 (−0·71 to −0·42)	$1\cdot3\times10^{-14}$	2·4 (1·8–3·1)	$9\cdot6\times10^{-12}$
Model 2*				
APOE ε4 (adjusted for amyloid-β and paired helical filament tau)	−0·18 (−0·31 to −0·04)	0·010	1·4 (1·01–1·9)	0·042
Model 3†				
APOE ε4 (adjusted for amyloid-β, paired helical filament tau, and Lewy body pathology)	−0·17 (−0·31 to −0·04)	0·010	1·4 (1·004–1·9)	0·047
Model 4*				
APOE ε4 (adjusted for amyloid-β, paired helical filament tau, and TDP-43 proteinopathy stage)	−0·13 (−0·27 to −0·001)	0·048	1·2 (0·9–1·7)	0·19
Model 5‡				
APOE ε4 (adjusted for amyloid-β, paired helical filament tau, and TDP-43 burden)	−0·09 (−0·22 to 0·04)	0·18	1·2 (0·9–1·7)	0·29

Estimated effects (adjusted difference in global cognitive function as *APOE* ε4 count increased) were reported from linear regressions with global cognitive function proximate to death as the outcome, and odds ratio of Alzheimer's disease dementia as *APOE* ε4 count increased were reported from logistic regressions with Alzheimer's disease dementia as the outcome. In model 1, *APOE* ε4 count was the independent variable and sex, age at death, and years of education were controlled. Amyloid-β and paired helical filament tau were additionally controlled in model 2, and Lewy body pathology stage was also controlled in model 3. TDP-43 proteinopathy stage or TDP-43 burden was adjusted in addition to sex, age at death, years of education, amyloid-β, and paired helical filament tau in models 4 and 5, respectively. TDP-43=transactive response DNA-binding protein of 43 kDa. *n=1038 for global cognitive function and n=1033 for Alzheimer's disease dementia. †n=1036 for global cognitive function and n=1031 for Alzheimer's disease dementia. ‡n=1021 for global cognitive function and n=1016 for Alzheimer's disease dementia.

***Table* 3: Association of *APOE* ε4 count with cognition**

	n	TDP-43 burden	Unadjusted MMSE proximate to death	Adjusted global cognitive decline per year*	Adjusted global cognition proximate to death†
APOE ε4 non-carrier, no advanced TDP-43 proteinopathy, no hippocampal sclerosis	516	0·11 (0·21)	23·0 (7·8)	0·006 (0·079)	0·10 (0·92)
APOE ε4 carrier, no advanced TDP-43 proteinopathy, no hippocampal sclerosis	137	0·12 (0·22)	20·8 (9·0)	–0·005 (0·097)	0·10 (1·05)
APOE ε4 non-carrier, advanced TDP-43 proteinopathy, no hippocampal sclerosis	154	1·43 (0·81)	19·5 (9·0)	0·016 (0·075)	0·07 (0·90)
APOE ε4 carrier, advanced TDP-43 proteinopathy, no hippocampal sclerosis	77	1·65 (1·00)	15·8 (10·6)	–0·013 (0·089)	–0·20 (1·12)
APOE ε4 non-carrier, advanced TDP-43 proteinopathy, hippocampal sclerosis	42	2·56 (0·82)	14·0 (9·8)	–0·047 (0·090)	–0·86 (1·04)
APOE ε4 carrier, advanced TDP-43 proteinopathy, hippocampal sclerosis	35	2·64 (0·84)	11·9 (9·7)	–0·052 (0·094)	–0·60 (1·06)

Data are mean (SD). Advanced TDP-43 proteinopathy was defined as stage 2 or 3. We aimed to capture the cognitive trajectory not explained by Alzheimer's disease pathology (amyloid-β and paired helical filament tau), sex, age, and years of education with adjusted global cognitive decline per year and adjusted global cognition proximate to death. Data shown here are from a subset of participants with non-missing data for all variables displayed. Only 15 participants (four *APOE* ε4 carriers) had hippocampal sclerosis but did not have advanced TDP-43 proteinopathy, and this small subgroup (not displayed in this table) had the following characteristics: mean TDP-43 burden 0·11 (SD 0·17), mean unadjusted MMSE proximate to death 17·7 (SD 12·4), mean adjusted global cognitive decline –0·013 (SD 0·061), and mean adjusted global cognition proximate to death –0·10 (SD 0·80). TDP-43=transactive response DNA-binding protein of 43 kDa. MMSE=Mini-Mental State Examination *Random slope of global cognition additionally adjusted for amyloid-β and paired helical filament tau. †Global cognition proximate to death adjusted for amyloid-β, paired helical filament tau, sex, age at death, and years of education.

Table 4: **Adjusted cognitive decline in subgroups according to TDP-43 proteinopathy, hippocampal sclerosis, and *APOE* ε4**

suggestion that *APOE* and TDP-43 form complexes in vivo, thereby aggravating TDP-43 proteinopathy and related neurodegeneration.[28] However, we cannot rule out that toxic amyloid-β or tau oligomers could explain the link between *APOE* and TDP-43, as neuropathological evaluation through microscopic examination cannot quantify the oligomers present in the tissue.

Our study has several limitations. It is mainly based on highly educated volunteers who were healthy at study entry, and their average age at death was close to 90 years. Although age did not significantly moderate the *APOE* ε4–TDP-43 proteinopathy association, our findings might not apply to younger individuals or people from other socioeconomic backgrounds. Additionally, the majority of participants from both cohorts were of European descent, so our findings cannot be easily extrapolated to other racial groups. We combined ROS and MAP in our analyses, but these two cohorts consist of participants from different social backgrounds. The difference between the two cohorts did not significantly confound the association between *APOE* ε4 and TDP-43 proteinopathy in our study, but given the larger effect size of *APOE* ε4 on TDP-43 proteinopathy in MAP compared with ROS, further studies in independent cohorts are required for a better estimation of the effect size. Finally, we have evaluated only a subset of brain regions known to harbour TDP-43 proteinopathy.[2] Hippocampal sclerosis was evaluated on only a single coronal section of mid-hippocampus from each participant, whereas hippocampal sclerosis can be segmental in appearance;[29] therefore, we might have misclassified some cases of hippocampal sclerosis, underestimating the strength of association between TDP-43 proteinopathy and hippocampal sclerosis.

Despite these limitations, our study leveraged the largest TDP-43 proteinopathy dataset reported to date to add important insights to the relationships among Alzheimer's disease, TDP-43 proteinopathy, and hippocampal sclerosis through a shared genetic risk factor, *APOE* ε4. Beyond classic one-to-one clinical–pathological correlations, it has been well known that coexistence of multiple neuropathologies is the rule rather than an exception in late-onset dementia.[9] Our results suggest that such coexistence is not a coincidence: Alzheimer's disease and TDP-43 proteinopathy share *APOE* as a common risk gene, which implies further mechanistic link between them. Therefore, future clinical trials and translational investigations should consider TDP-43 proteinopathy as an integral component of *APOE*-related neurodegeneration, and assess TDP-43 proteinopathy whenever possible.

Contributors

H-SY conceptualised and designed the study, analysed and interpreted the data, and drafted and critically revised the manuscript for the intellectual content. LY conceptualised and designed the study, analysed and interpreted the data, and critically revised the manuscript for the intellectual content. CCW, LBC, JPC, and RAS interpreted the data and critically revised the manuscript for the intellectual content. DAB, JAS, and PLDJ conceptualised and designed the study, collected and interpreted the data, and critically revised the manuscript for the intellectual content.

Declaration of interests

H-SY reports grants from Alzheimer's Association, during the conduct of the study; and grants from Biogen, Eli Lilly, Eisai, and Merck Sharp & Dohme, outside the submitted work, for his duty as a clinical trial site study physician at Brigham and Women's Hospital. RAS reports grants from Eli Lilly, Janssen, US National Institutes of Health/National Institute on Aging (NIH/NIA), and Alzheimer's Association, during the conduct of the study; and personal fees from Biogen, Roche, Lundbeck, Merck, Pfizer, General Electric, Insightec, AC Immune, and Eisai, outside the submitted work. JAS reports grants from NIH/NIA, during

the conduct of the study; service on scientific advisory boards for Alzheimer's Association, Fondation Plan Alzheimer, The Dutch CAA Foundation, University of Washington/Group Health Alzheimer's Disease Patient Registry/Adult Changes in Thought study, New York University, Avid Radiopharmaceuticals, Genentech, Grifols, and Eli Lilly, outside the submitted work; personal fees from Avid Radiopharmaceuticals, Navidea Biopharmaceutical, The Michael J Fox Foundation, National Football League, National Hockey League, outside the submitted work; grants from AVID Radiopharmaceuticals and NIH/NIA, outside the submitted work; participation in legal proceedings involving the National Football League, National Hockey League, and World Wrestling Entertainment, outside the submitted work; and service on the editorial boards for the *Journal of Histochemistry* and *Cytochemistry* and *Journal of Neuropathology* and *Experimental Neurology*, outside the submitted work. PLDJ reports grants from NIH/NIA, during the conduct of the study; service on scientific advisory boards for from Teva Neuroscience, Genzyme/Sanofi, and Celgene; personal fees from Biogen, Source Healthcare Analytics, Pfizer, and Teva Neuroscience; service on the editorial boards for the *Journal of Neuroimmunology*, *Neuroepigenetics*, and *Multiple Sclerosis*; and grants from Biogen, Eisai, UCB, Pfizer, Sanofi/Genzyme, and National MS Society, outside the submitted work. All other authors declare no competing interests.

Data sharing

Researchers can apply for data access at Rush Alzheimer's Disease Center Research Resource Sharing Hub to access all ROS-MAP data.

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