HHS Public Access

Author manuscript

Lancet Neurol. Author manuscript; available in PMC 2018 October 24.

Published in final edited form as:

Lancet Neurol. 2018 September ; 17(9): 735–737. doi:10.1016/S1474-4422(18)30288-6.

Fitting TDP-43 into the *APOE* ε4 and neurodegeneration story

Keith A. Josephs, MD, MST, MSc [Professor of Neuroscience & Neurology]

Department of Neurology, Mayo Clinic, Rochester, MN 55905

The TAR DNA binding protein of 43 kDa (TDP-43) has recently been placed onto the neurodegenerative center court, next to the other key neurodegenerative proteins, beta-amyloid (Aβ), paired helical filament (PHF) tau and alpha-synuclein. TDP-43 was first reported to be a key biological component of frontotemporal lobar degeneration and amyotrophic lateral sclerosis in 2006[1]. Subsequently, it was demonstrated that TDP-43 immunoreactive lesions was also frequently present in the brains of patients with pathologically confirmed Alzheimer's disease (AD)[2]. TDP-43 has recently been implicated to contribute to memory loss, hippocampal volusme loss and rate of hippocampal atrophy in Alzheimer's disease (AD)[3, 4] and in broader cohorts of community-based older adults[5]. These findings have catapulted TDP-43 into the lime light. Unfortunately, even with strong evidence supporting TDP-43 being an integral part of late life neurodegeneration, many investigators continue to focus only, or predominantly, on Aβ and PHF-tau, and make comments like "TDP-43 is not an AD-spectrum proteinopathy", or "TDP-43 is only an age-associated phenomena". One of the reasons for these opinions is that TDP-43 has not been strongly linked with key genetic mechanisms underlying AD. The genetic Godfather of AD is undoubtedly the apolipoprotein (APOE) ε4 allele[6].

We first reported a potential link between TDP-43 and APOE ε4 in 2014[4] when we observed a higher proportion of APOE ε4 carriers in autopsy confirmed AD patients with TDP-43, compared to those without TDP-43, even after accounting for PHF-tau. Yet, even with this finding, TDP-43 continued to be overlooked; the naysayers argument being "the association was confounded by other neurodegenerative proteins and pathologies". In the *Lancet Neurology*, Yang and colleagues[7] conducted a genetic-pathological study to further investigate the relationship between APOE ε4 and TDP-43. The study was powered by a large autopsy cohort of 1044 community-based older adults recruited from the Religious Orders Study and Rush Memory and Aging Project. The authors performed regression analyses assessing the relationship between TDP-43 and APOE ε4 dose (no ε4, one ε4, two ε4) accounting for confounders, including Aβ, PHF-tau, alpha-synuclein, and age. They also assessed whether TDP-43 altered the relationship between APOE ε4 and hippocampal sclerosis, a common neurodegenerative pathology associated with TDP-43 and dementia[8]. They found a strong association between APOE ε4 and TDP-43, which persisted even after accounting for the other neurodegenerative proteins. The association between APOE ε4 and

Corresponding Author: Keith A. Josephs, MD, MST, MSc, Professor of Neuroscience & Neurology, Executive Director of Mayo Clinic Movement Disorders Enterprise, Behavioral Neurology & Movement Disorders, Mayo Clinic, College of Medicine & Graduate School, 200 1st Street S.W, Rochester, MN, 55905, Tele: (507)-538-1038, Fax: (507)-538-6012, josephs.keith@mayo.edu.

Conflict of Interest Statement

I have received funding from the National Institute of Health.

TDP-43 was, in fact, stronger than the association between TDP-43 and *TMEM106B* rs1990622[A] genotype; a known risk allele for TDP-43[9]. It was also found that TDP-43 mediated the relationship between APOE ε4 and hippocampal sclerosis, suggesting that hippocampal sclerosis is more likely a downstream consequence of TDP-43 neurodegeneration.

The strengths of the study are the large sample size, the assessment of multiple different pathologies and that Aβ and PHF-tau were assessed quantitatively. In addition, the association between TDP-43 and APOE ε4 was observed when TDP-43 was assessed as a semi-quantitative burden, as well as when TDP-43 distribution was assessed. There are some caveats to the study, although these do not detract from the main findings and cannot be used as ammunition against the findings. One caveat is the fact that the association was only identified in the subset of cases that met intermediate-high probability AD at autopsy (n=672), but not in those that did not meet AD criteria (n=372) where the frequency of APOE ε4 carriers was low (12%). The investigators argued that the lack of the association in the latter group was likely due to limited power with such a low APOE ε4 frequency. However, it is also possible that the relationship between APOE ε4 and TDP-43 is specific to AD. In fact, we did not find any effects of TDP-43 on clinical or neuroimaging outcomes in cognitively normal people with primary age related tauopathy[10]. The findings by Yang and colleagues[7] are also limited to this population and may not necessarily generalize to other populations, particularly since only 34 patients (3%) self-reported their race to be non-white.

The findings from this study[7] provide further support for TDP-43 to be considered as important as amyloid-β and paired helical filament tau in neurodegenerative cognitive impairment. Not only is TDP-43 present in a high proportion of cases with Alzheimer's disease and associated with key clinical and imaging outcomes, but now more evidence is supporting that a link between TDP-43 proteinopathy and APOE ε4 exists. Hence, although the Alzheimer's research establishment focuses predominantly on amyloid-β and paired helical filament tau, those who believe in the relevance of TDP-43 need to consider the next important steps. Future studies should focus on validating the APOE ε4 and TDP-43 proteinopathy association in other cohorts, as well as taking the analysis one step further by simultaneously modelling the direct and indirect relationships of APOE ε4 on TDP-43, amyloid-β, and paired helical filament tau to better appreciate the overall complex genetic–neuropathological relationships between these proteins.

Acknowledgement

National Institute of Health R01 AG37491 (PI, Josephs)

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