

LETTER TO THE EDITOR

LATE to the PART-y

Keith A. Josephs,¹ Ian Mackenzie,² Matthew P. Frosch,³ Eileen H. Bigio,⁴ Manuela Neumann,⁵ Tetsuaki Arai,⁶ Brittany N. Dugger,⁷ Bernardino Ghetti,⁸ Murray Grossman,⁹ Masato Hasegawa,¹⁰ Karl Herrup,¹¹ Janice Holton,¹² Kurt Jellinger,¹³ Tammarny Lashley,¹² Kirsty E. McAleese,¹⁴ Joseph E. Parisi,¹⁵ Tamas Revesz,¹² Yuko Saito,¹⁶ Jean Paul Vonsattel,¹⁷ Jennifer L. Whitwell,¹⁸ Thomas Wisniewski¹⁹ and William Hu²⁰

- 1 Department of Neurology, Mayo Clinic, Rochester, MN, USA
- 2 Department of Pathology and Laboratory Medicine, University of British Columbia and Vancouver General Hospital, Vancouver, British Columbia, Canada
- 3 Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
- 4 Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
- 5 Center for Neuropathology and Prion Research, Munich, Germany
- 6 Department of Psychiatry, Division of Clinical Medicine, University of Tsukuba, Tsukuba, Japan
- 7 Department of Pathology and Laboratory Medicine, UC Davis, Sacramento, CA, USA
- 8 Pathology and Laboratory Medicine, Indiana University, Indiana, IL, USA
- 9 Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
- 10 Department of Dementia and Higher Brain Function, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- 11 Department of Neurology, Alzheimer's Disease Research Center, University of Pittsburgh, Pittsburgh, PA, USA
- 12 UCL Queen Square Institute of Neurology, University College London, London, UK
- 13 Institute of Clinical Neurobiology, Medical University of Vienna, Vienna, Austria
- 14 Institute of Neuroscience, Newcastle University, Newcastle, UK
- 15 Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
- 16 National Center of Neurology and Pathology Brain Bank, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan
- 17 Columbia University, New York, NY, USA
- 18 Department of Radiology, Mayo Clinic, Rochester, MN, USA
- 19 Alzheimer's Disease Center Research, New York University, NY, USA
- 20 Department of Neurology and Center for Neurodegenerative Diseases Research, Emory University, Atlanta, GA, USA

Correspondence to: Keith A. Josephs, MD, MST, MSc
 Professor of Neurology and Neuroscience
 Department of Neurology
 Behavioral Neurology and Movement Disorders
 Mayo Clinic, College of Science and Medicine
 200 1st Street SW
 Rochester, MN 55905, USA
 E-mail: josephs.keith@mayo.edu

Sir,

We wish to address the recent proposal of a disease entity newly titled 'limbic-predominant age-related TDP-43 encephalopathy (LATE)' (Nelson *et al.*, 2019) which, to our reading, is itself a derivative of the 2016 proposed term

cerebral age-related TDP-43 with sclerosis (CART) (Nelson *et al.*, 2016). The transactive response DNA binding protein of ~43 kD (TDP-43) was first reported in 2006 to be a main component of ubiquitinated inclusions in autopsy-confirmed cases of frontotemporal lobar

degeneration (FTLD) negative for tau immunoreactivity (Arai *et al.*, 2006; Neumann *et al.*, 2006). Over a decade of research into FTLD-TDP (and FTLD-U before it) has highlighted important phenotypic variability in TDP-43-immunoreactive lesions resulting in the identification of five different types of FTLD-TDP (Mackenzie *et al.*, 2006, 2011; Sampathu *et al.*, 2006; Josephs *et al.*, 2009; Lee *et al.*, 2011, 2017). There have also been important advances in the molecular and biochemical characterization of TDP-immunoreactive in FTLD-TDP (Sampathu *et al.*, 2006; Hasegawa *et al.*, 2008; Igaz *et al.*, 2008; Zhang *et al.*, 2009; Bigio *et al.*, 2013; Laferriere *et al.*, 2019). Soon after the initial characterization of TDP-immunoreactive lesions in FTLD and amyotrophic lateral sclerosis, TDP-immunoreactive lesions were identified in 25–33% of cases with pathologically confirmed Alzheimer's disease (Amador-Ortiz *et al.*, 2007; Higashi *et al.*, 2007). TDP-immunoreactive lesions related to Alzheimer's disease were initially thought to appear first in the hippocampus (Amador-Ortiz *et al.*, 2007), but more detailed morphological studies involving multiple anatomical regions revealed the amygdala to be the earliest affected region (Higashi *et al.*, 2007; Hu *et al.*, 2008; Arai *et al.*, 2009) followed by the entorhinal cortex and hippocampus, occipitotemporal cortex, insular and inferior temporal cortex, brainstem, and frontal neocortex and basal ganglia (Josephs *et al.*, 2014, 2016); a scheme that has been independently validated (Tan *et al.*, 2015). TDP-immunoreactive lesions have also been described in cognitively normal individuals (Wilson *et al.*, 2011; Arnold *et al.*, 2013; Uchino *et al.*, 2015; Wennberg *et al.*, 2019) including those with asymptomatic definite primary age related tauopathy (PART) (Josephs *et al.*, 2017; Zhang *et al.*, 2019), as well being associated with other well-defined clinic-pathological entities (Fig. 1) including Lewy body disease (with or without co-existing Alzheimer's disease) (Arai *et al.*, 2009; McAleese *et al.*, 2017), the amyotrophic lateral sclerosis/

parkinsonism-dementia complex of Guam (Hasegawa *et al.*, 2007; Geser *et al.*, 2008), Pick's disease (Freeman *et al.*, 2008), progressive supranuclear palsy (Yokota *et al.*, 2010; Koga *et al.*, 2017), corticobasal degeneration (Uryu *et al.*, 2008; Koga *et al.*, 2018), polyglutamine diseases such as Huntington's disease (Schwab *et al.*, 2008), Machado-Joseph disease (Tan *et al.*, 2009) and spinocerebellar ataxia type 2 (Toyoshima *et al.*, 2011), Perry syndrome (Wider *et al.*, 2009), and chronic traumatic encephalopathy (McKee *et al.*, 2010).

The term LATE is proposed as a catchy acronym to describe the presence of TDP-immunoreactive lesions in Alzheimer's disease, as well as in older adults. The review manuscript describing LATE, of which many of the authors of this response are cited in, provides a thorough appraisal of an important topic and is meritorious in promoting recognition of TDP-43 and encouraging future research, as well as the development of neuroimaging and molecular biomarkers. However, we question the term's novelty and nosology, the framework that seemingly separates LATE from FTLD-TDP and other diseases, and the proposed guidelines provided for assessing LATE and LATE-NC. As the authors identify, the term LATE is new, although there is an extensive literature on the relationship between TDP-immunoreactive inclusions and clinical and imaging features, both in isolation and in association with Alzheimer's disease. LATE is used to rebrand already characterized features, yet identifies no new TDP-43 pathological subtype, no link between TDP-immunoreactive pathology with new cognitive symptoms (other than likelihood of dementia diagnosis) according to known brain-behaviour relationship, and no biochemical demonstration that TDP-immunoreactive lesions in older adults with and without Alzheimer's disease are equivalent to each other or distinct from those in FTLD-TDP and other neurodegenerative diseases. Critically, using the term encephalopathy ('E' of LATE) presumes causation of functional impairment

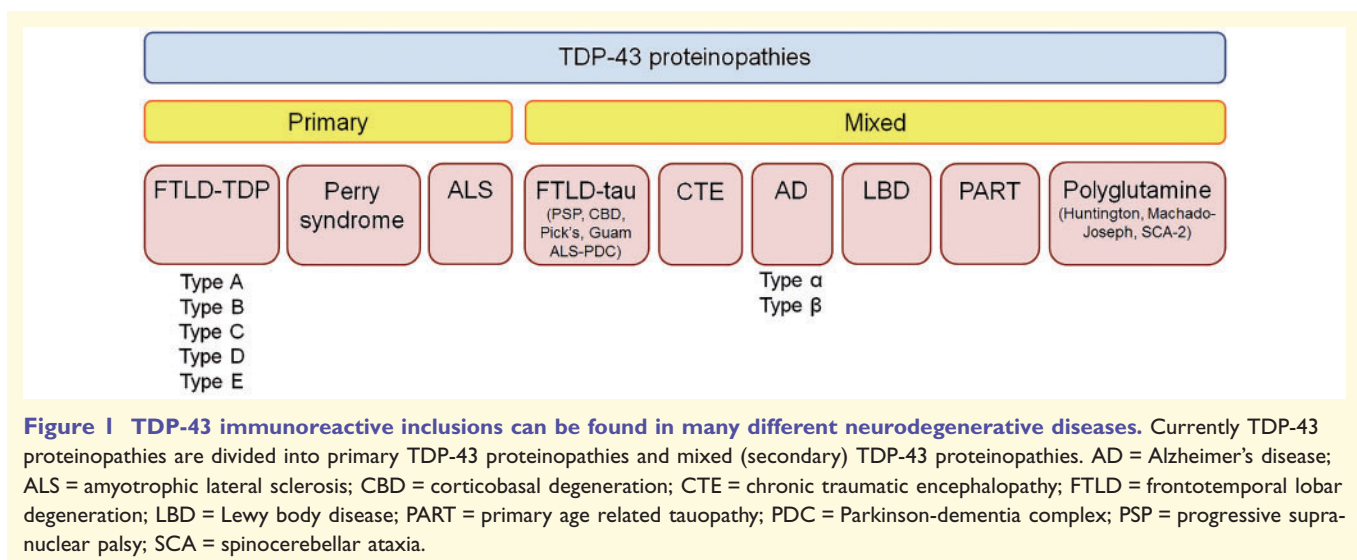


Figure 1 TDP-43 immunoreactive inclusions can be found in many different neurodegenerative diseases. Currently TDP-43 proteinopathies are divided into primary TDP-43 proteinopathies and mixed (secondary) TDP-43 proteinopathies. AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; CBD = corticobasal degeneration; CTE = chronic traumatic encephalopathy; FTLD = frontotemporal lobar degeneration; LBD = Lewy body disease; PART = primary age related tauopathy; PDC = Parkinson-dementia complex; PSP = progressive supranuclear palsy; SCA = spinocerebellar ataxia.

in the cerebrum and by incorporating the term encephalopathy, LATE implies a clinicopathological entity, when in reality LATE is only describing the pathology LATE-NC; similar to pathologies such as argyrophilic grains disease (Braak and Braak, 1987), primary age-related tauopathy (Crary *et al.*, 2014), ageing-related tau astroglialopathy (Kovacs *et al.*, 2016) and amygdala Lewy bodies (Uchikado *et al.*, 2006), which are not considered clinicopathological entities. Akin to the dichotomy of language between frontotemporal dementia and FTLT, LATE is something that, by definition, cannot be diagnosed under the microscope (i.e. encephalopathy). And as these lesions can be observed in the absence of cognitive alterations, rendering a diagnosis of an encephalopathy in a cognitively normal individual is an oxymoron (normal cognition with limbic associated TDP-43 encephalopathy).

Proposing that LATE is a distinct clinicopathological entity also overlooks the possibility that TDP-immunoreactive lesions in Alzheimer's disease could reflect impaired cellular function in end-stage neurodegeneration, and ignores the fact that the statistical association between TDP-immunoreactive pathology and a dementia diagnosis in old age is likely both not independent from Alzheimer's disease and other pathologies, and, in all likelihood, a reflection of competing relative risks of various degrees as one ages. In addition, the term limbic-predominant is an over simplification of the distribution of pathology. In fact, it has been demonstrated that there are different subtypes of TDP immunoreactivity that have different regional associations, with only one specific subtype of neurofibrillary tangle-associated TDP proving to be truly limbic-predominant (Amador-Ortiz *et al.*, 2007; Josephs *et al.*, 2019; Zhang *et al.*, 2019). The other subtype is associated with TDP-43 involving cortical and subcortical and brainstem regions identical to those affected in FTLT-TDP (Josephs *et al.*, 2019). This is akin to Lewy body disease, which can also have a limbic-predominance, but to label it as such would ignore the brainstem and diffuse distributions of the pathology. Different subtypes of TDP-immunoreactive also have different genetic and pathological associations, including with hippocampal sclerosis; important differences that would be lost when grouping subtypes together (Murray *et al.*, 2014; Josephs *et al.*, 2019).

Third, this paper does not consider how LATE can be distinguished from FTLT-TDP or the fact that LATE depends on a relative selection bias towards Alzheimer's disease-related diseases while ignoring the fact that TDP-43 has been identified in many other neurodegenerative diseases (Fig. 1) making teasing apart coincident versus associated processes a challenge. Of importance is the fact that a proportion of cases of Alzheimer's disease and ageing have TDP-immunoreactive lesions present in frontotemporal neocortex (Arai *et al.*, 2009; Josephs *et al.*, 2014, 2016; Nag *et al.*, 2018). It has been shown that such cases are strongly associated with single nucleotide polymorphisms in the *TMEM106B* gene (Josephs *et al.*, 2019), which is similar to the observed associations in FTLT-TDP (Van

Deerlin *et al.*, 2010). It is, therefore, unclear whether it is appropriate to make a diagnosis of LATE in the presence of a TDP-43 stage >3 (Josephs *et al.*, 2014, 2016), as opposed to a diagnosis of FTLT-TDP. The description of LATE also does not square with evidence that FTLT-TDP can occur in old age (Jellinger, 2006; Pao *et al.*, 2011), and that age itself may modify the clinical phenomenology of neuropathology due to the brain's structural and functional reorganization.

The authors provide guidelines on how to assess LATE-NC neuropathologically and suggest analysing a few specific regions of the brain with the intent to have a limited number of TDP-43 stages. While this simplifies neuropathological analysis and is touted as being cost effective, it collapses data-driven staging schemes but without the requisite scientific evidence for doing so. This proposal mirrors the NIA-AA neuropathological guidelines for the pathological diagnosis of Alzheimer's disease, which collapse the Braak (Braak and Braak, 1991), Thal (Thal *et al.*, 2002) and CERAD (Mirra *et al.*, 1991) staging schemes. However, collapsing the TDP-43 staging scheme at such an early point in time when it was only published in the past few years, stifles the field's ability to understand the implications of the distribution of TDP-43 deposition and goes against the drive by many neuropathologists to include more comprehensive and quantitative assessment methods to unravel currently hidden relationships of pathologies.

The branding of clinical trials since the 1990s—especially names such as EPIC or EXCITE—is said to promote reference to such trials (Berkwits, 2000), but can compete with the understanding of the main message (Berlin, 2013; Narod *et al.*, 2016; Wittman *et al.*, 2018). Whether an acronym such as LATE is needed for diagnostic accuracy and communication between neuropathologists, neurologists, and other investigators is not clear. Therefore, we urge researchers to focus on defining the pathological processes and their biochemical differences underlying TDP-immunoreactive lesions in FTLT and non-FTLT disorders, particularly in diverse populations, and defer broad usage of LATE until (and only if) the science is mature.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Competing interests

The authors report no competing interests.

References

Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, *et al.* TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol* 2007; 61: 435–45.

- Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Commun* 2006; 351: 602–11.
- Arai T, Mackenzie IR, Hasegawa M, Nonaka T, Niizato K, Tsuchiya K, et al. Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies. *Acta Neuropathol* 2009; 117: 125–36.
- Arnold SJ, Dugger BN, Beach TG. TDP-43 deposition in prospectively followed, cognitively normal elderly individuals: correlation with argyrophilic grains but not other concomitant pathologies. *Acta Neuropathol* 2013; 126: 51–7.
- Berkwits M. Capture! Shock! Excite! Clinical trial acronyms and the “branding” of clinical research. *Ann Intern Med* 2000; 133: 755–62.
- Berlin L. TAC: AOITROMJA? (the acronym conundrum: advancing or impeding the readability of medical journal articles?). *Radiology* 2013; 266: 383–7.
- Bigio EH, Wu JY, Deng HX, Bit-Ivan EN, Mao Q, Ganti R, et al. Inclusions in frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP) and amyotrophic lateral sclerosis (ALS), but not FTLD with FUS proteinopathy (FTLD-FUS), have properties of amyloid. *Acta Neuropathol* 2013; 125: 463–5.
- Braak H, Braak E. Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. *Neurosci Lett* 1987; 76: 124–7.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991; 82: 239–59.
- Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* 2014; 128: 755–66.
- Freeman SH, Spire-Jones T, Hyman BT, Growdon JH, Frosch MP. TAR-DNA binding protein 43 in Pick disease. *J Neuropathol Exp Neurol* 2008; 67: 62–7.
- Geser F, Winton MJ, Kwong LK, Xu Y, Xie SX, Igaz LM, et al. Pathological TDP-43 in parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. *Acta Neuropathol* 2008; 115: 133–45.
- Hasegawa M, Arai T, Akiyama H, Nonaka T, Mori H, Hashimoto T, et al. TDP-43 is deposited in the Guam Parkinsonism-dementia complex brains. *Brain* 2007; 130: 1386–94.
- Hasegawa M, Arai T, Nonaka T, Kametani F, Yoshida M, Hashizume Y, et al. Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Ann Neurol* 2008; 64: 60–70.
- Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, Fujisawa K, et al. Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. *Brain Res* 2007; 1184: 284–94.
- Hu WT, Josephs KA, Knopman DS, Boeve BF, Dickson DW, Petersen RC, et al. Temporal lobar predominance of TDP-43 neuronal cytoplasmic inclusions in Alzheimer disease. *Acta Neuropathol* 2008; 116: 215–20.
- Igaz LM, Kwong LK, Xu Y, Truax AC, Uryu K, Neumann M, et al. Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Am J Pathol* 2008; 173: 182–94.
- Jellinger KA. Clinicopathological analysis of dementia disorders in the elderly: an update. *J Alzheimers Dis* 2006; 9: 61–70.
- Josephs KA, Murray ME, Tosakulwong N, Weigand SD, Serie AM, Perkerson RB, et al. Pathological, imaging and genetic characteristics support the existence of distinct TDP-43 types in non-FTLD brains. *Acta Neuropathol* 2019; 137: 227–38.
- Josephs KA, Murray ME, Tosakulwong N, Whitwell JL, Knopman DS, Machulda MM, et al. Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: a clinico-imaging-pathological study of primary age-related tauopathy (PART). *Acta Neuropathol* 2017; 133: 705–15.
- Josephs KA, Murray ME, Whitwell JL, Parisi JE, Petrucelli L, Jack CR, et al. Staging TDP-43 pathology in Alzheimer's disease. *Acta Neuropathol* 2014; 127: 441–50.
- Josephs KA, Murray ME, Whitwell JL, Tosakulwong N, Weigand SD, Petrucelli L, et al. Updated TDP-43 in Alzheimer's disease staging scheme. *Acta Neuropathol* 2016; 131: 571–85.
- Josephs KA, Stroh A, Dugger B, Dickson DW. Evaluation of subcortical pathology and clinical correlations in FTLD-U subtypes. *Acta Neuropathol* 2009; 118: 349–58.
- Koga S, Kouri N, Walton RL, Ebbert MTW, Josephs KA, Litvan I, et al. Corticobasal degeneration with TDP-43 pathology presenting with progressive supranuclear palsy syndrome: a distinct clinicopathologic subtype. *Acta Neuropathol* 2018; 136: 389–404.
- Koga S, Sanchez-Conteras M, Josephs KA, Uitti RJ, Graff-Radford N, van Gerpen JA, et al. Distribution and characteristics of transactive response DNA binding protein 43 kDa pathology in progressive supranuclear palsy. *Mov Disord* 2017; 32: 246–55.
- Kovacs GG, Ferrer I, Grinberg LT, Alafuzoff I, Attems J, Budka H, et al. Aging-related tau astroglialopathy (ARTAG): harmonized evaluation strategy. *Acta Neuropathol* 2016; 131: 87–102.
- Laferrriere F, Maniecka Z, Perez-Berlanga M, Hruska-Plochan M, Gilhespy L, Hock EM, et al. TDP-43 extracted from frontotemporal lobar degeneration subject brains displays distinct aggregate assemblies and neurotoxic effects reflecting disease progression rates. *Nat Neurosci* 2019; 22: 65–77.
- Lee EB, Lee VM, Trojanowski JQ. Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nat Rev Neurosci* 2011; 13: 38–50.
- Lee EB, Porta S, Michael Baer G, Xu Y, Suh E, Kwong LK, et al. Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration. *Acta Neuropathol* 2017; 134: 65–78.
- Mackenzie IR, Baborie A, Pickering-Brown S, Du Plessis D, Jaros E, Perry RH, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. *Acta Neuropathol* 2006; 112: 539–49.
- Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, et al. A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol* 2011; 122: 111–3.
- McAleese KE, Walker L, Erskine D, Thomas AJ, McKeith IG, Attems J. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. *Brain Pathol* 2017; 27: 472–9.
- McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 2010; 69: 918–29.
- Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; 41: 479–86.
- Murray ME, Cannon A, Graff-Radford NR, Liesinger AM, Rutherford NJ, Ross OA, et al. Differential clinicopathologic and genetic features of late-onset amnesic dementias. *Acta Neuropathol* 2014; 128: 411–21.
- Nag S, Yu L, Boyle PA, Leurgans SE, Bennett DA, Schneider JA. TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease. *Acta Neuropathol Commun* 2018; 6: 33.
- Narod SA, Ahmed H, Akbari MR. Do acronyms belong in the medical literature? A countercurrants series. *Curr Oncol* 2016; 23: 295–6.
- Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle P, Arfanakis K. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain* 2019; 142: 1503–27.
- Nelson PT, Trojanowski JQ, Abner EL, Al-Janabi OM, Jicha GA, Schmitt FA, et al. New old pathologies: AD, PART, and cerebral age-related TDP-43 with sclerosis (CARTS). *J Neuropathol Exp Neurol* 2016; 75: 482–98.

- Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006; 314: 130–3.
- Pao WC, Dickson DW, Crook JE, Finch NA, Rademakers R, Graff-Radford NR. Hippocampal sclerosis in the elderly: genetic and pathologic findings, some mimicking Alzheimer disease clinically. *Alzheimer Dis Assoc Disord* 2011; 25: 364–8.
- Sampathu DM, Neumann M, Kwong LK, Chou TT, Micsenyi M, Truax A, et al. Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. *Am J Pathol* 2006; 169: 1343–52.
- Schwab C, Arai T, Hasegawa M, Yu S, McGeer PL. Colocalization of transactivation-responsive DNA-binding protein 43 and huntingtin in inclusions of Huntington disease. *J Neuropathol Exp Neurol* 2008; 67: 1159–65.
- Tan RH, Kril JJ, Fatima M, McGeachie A, McCann H, Shepherd C, et al. TDP-43 proteinopathies: pathological identification of brain regions differentiating clinical phenotypes. *Brain* 2015; 138: 3110–22.
- Tan CF, Yamada M, Toyoshima Y, Yokoseki A, Miki Y, Hoshi Y, et al. Selective occurrence of TDP-43-immunoreactive inclusions in the lower motor neurons in Machado-Joseph disease. *Acta Neuropathol* 2009; 118: 553–60.
- Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 2002; 58: 1791–800.
- Toyoshima Y, Tanaka H, Shimohata M, Kimura K, Morita T, Kakita A, et al. Spinocerebellar ataxia type 2 (SCA2) is associated with TDP-43 pathology. *Acta Neuropathol* 2011; 122: 375–8.
- Uchikado H, Lin WL, DeLucia MW, Dickson DW. Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. *J Neuropathol Exp Neurol* 2006; 65: 685–97.
- Uchino A, Takao M, Hatsuta H, Sumikura H, Nakano Y, Nogami A, et al. Incidence and extent of TDP-43 accumulation in aging human brain. *Acta Neuropathol Commun* 2015; 3: 35.
- Uryu K, Nakashima-Yasuda H, Forman MS, Kwong LK, Clark CM, Grossman M, et al. Concomitant TAR-DNA-binding protein 43 pathology is present in Alzheimer disease and corticobasal degeneration but not in other tauopathies. *J Neuropathol Exp Neurol* 2008; 67: 555–64.
- Van Deerlin VM, Sleiman PM, Martinez-Lage M, Chen-Plotkin A, Wang LS, Graff-Radford NR, et al. Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nat Genet* 2010; 42: 234–9.
- Wennberg AM, Whitwell JL, Tosakulwong N, Weigand SD, Murray ME, Machulda MM, et al. The influence of tau, amyloid, alpha-synuclein, TDP-43, and vascular pathology in clinically normal elderly individuals. *Neurobiol Aging* 2019; 77: 26–36.
- Wider C, Dickson DW, Stoessl AJ, Tsuboi Y, Chapon F, Gutmann L, et al. Pallidonigral TDP-43 pathology in Perry syndrome. *Parkinsonism Relat Disord* 2009; 15: 281–6.
- Wilson AC, Dugger BN, Dickson DW, Wang DS. TDP-43 in aging and Alzheimer's disease: a review. *Int J Clin Exp Pathol* 2011; 4: 147–55.
- Witteman HO, Chipenda Dansokho S, Colquhoun H, Fagerlin A, Giguere AMC, Glouberman S, et al. Twelve lessons learned for effective research partnerships between patients, caregivers, clinicians, academic researchers, and other stakeholders. *J Gen Intern Med* 2018; 33: 558–62.
- Yokota O, Davidson Y, Bigio EH, Ishizu H, Terada S, Arai T, et al. Phosphorylated TDP-43 pathology and hippocampal sclerosis in progressive supranuclear palsy. *Acta Neuropathol* 2010; 120: 55–66.
- Zhang X, Sun B, Wang X, Lu H, Shao F, Rozemuller AJM, et al. Phosphorylated TDP-43 staging of primary age-related tauopathy. *Neurosci Bull* 2019; 35: 183–92.
- Zhang YJ, Xu YF, Cook C, Gendron TF, Roettges P, Link CD, et al. Aberrant cleavage of TDP-43 enhances aggregation and cellular toxicity. *Proc Natl Acad Sci U S A* 2009; 106: 7607–12.