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Review article

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Limbic-predominant age-related TDP43 encephalopathy (LATE) neuropathological change in neurodegenerative diseases

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Abstracts

TAR DNA-binding protein 43 (TDP43) is a focus of research in late-onset dementias. TDP43 pathology in the brain was initially identified in amyotrophic lateral sclerosis and frontotemporal lobar degeneration, and later in Alzheimer disease (AD), other neurodegenerative diseases and ageing. Limbic-predominant age-related TDP43 encephalopathy (LATE), recognized as a clinical entity in 2019, is characterized by amnestic dementia resembling AD dementia and occurring most commonly in adults over 80 years of age. Neuropathological findings in LATE, referred to as LATE neuropathological change (LATE-NC), consist of neuronal and glial cytoplasmic TDP43 localized predominantly in limbic areas with or without coexisting hippocampal sclerosis and/or AD neuropathological change and without frontotemporal lobar degeneration or amyotrophic lateral sclerosis pathology. LATE-NC is frequently associated with one or more coexisting pathologies, mainly AD neuropathological change. The focus of this Review is the pathology, genetic risk factors and nature of the cognitive impairments and dementia in pure LATE-NC and in LATE-NC associated with coexisting pathologies. As the clinical and cognitive profile of LATE is currently not easily distinguishable from AD dementia, it is important to develop biomarkers to aid in the diagnosis of this condition in the clinic. The pathogenesis of LATE-NC should be a focus of future research to form the basis for the development of preventive and therapeutic strategies.

Sections

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Key points

- In the two decades since the localization of TAR DNA-binding protein (TDP43) pathology in amyotrophic lateral sclerosis and frontotemporal lobar degeneration, much information has become available regarding the tissue localization of TDP43 pathology in Alzheimer disease (AD) and other neurodegenerative disorders as well as in ageing.
- Characterization of limbic-predominant age-related TDP43 encephalopathy (LATE, the clinical disease) and LATE neuropathological change (LATE-NC) is a relatively recent development and its importance lies in the finding that LATE-NC is a common pathology underlying amnestic dementia, especially in individuals aged 80 years or more.
- LATE-NC can coexist with a variety of clinical and pathological conditions.
- As the clinical and cognitive profile of LATE is not yet easily distinguishable from AD dementia, it is important to develop biomarkers to aid in the diagnosis of this condition in the clinic.
- Future research needs to focus on the pathogenesis of LATE-NC to form the basis for the development of preventive and therapeutic strategies.

Introduction

TAR DNA-binding protein 43 (TDP43), initially identified as a transcriptional repressor of HIV type 1 gene expression[1], is a research focus in late-onset dementias following its detection in the brain and spinal cord of 97% of individuals with amyotrophic lateral sclerosis (ALS) and in the brain of 50% of individuals with frontotemporal lobar degeneration (FTLD)[2,3]. TDP43 pathology has also been reported in other FTLD-tau degenerations such as progressive supranuclear palsy and corticobasal degeneration[4] (Box 1).

Localization of TDP43 pathology predominantly in the limbic areas, with or without coexisting hippocampal sclerosis and/or Alzheimer disease (AD) neuropathological change (ADNC) and occurring in older adults (>80 years of age) without FTLD or ALS, has been a specific focus of attention, especially as many of these individuals have an amnestic dementia syndrome that mimics AD dementia[5]. Following extensive discussion among members of a multidisciplinary consensus group[6], this clinical syndrome was named limbic-predominant age-related TDP43 encephalopathy (LATE) in 2019. Because the term 'encephalopathy' as used in current neurological practice can imply a clinically active process, it was recommended that LATE be used to describe the clinical disease, which remains to be better defined by further studies, and that the neuropathological findings be referred to as LATE neuropathological change (LATE-NC)[6]. The term LATE is intended to describe a process that can be easily understood by patients, clinicians and researchers. Although this terminology seems to be still evolving, the terms LATE and LATE-NC, as defined above, are used in this Review.

Many were opposed to adoption of the LATE and LATE-NC terminology and felt that broad usage of these terms should be deferred "until (and only if) the science is mature"[7], and that the available data were insufficient to separate LATE as a distinct clinical entity[8]. The consensus group strongly disagreed with these recommendations because they would result in the lack of a common terminology for the TDP43 proteinopathy predominantly in limbic brain regions in older individuals[9].

LATE-NC with or without concomitant ADNC is estimated to be around 100-fold more prevalent than FTLD among older individuals with and without dementia[6], underscoring the magnitude of the health problem that this condition presents. LATE-NC coexists with other pathologies in neurological diseases (Box 1), notable among which is the pathological diagnosis of AD, which in the recent literature is described as intermediate or high ADNC according to the National Institute on Aging and Alzheimer's Association staging scheme[10]. In this Review, we use the term AD to refer to the pathological diagnosis of AD, as this term is widely recognized in the scientific community. Other neurodegenerative diseases, such as chronic traumatic encephalopathy[11] and Huntington disease[12], have distinct and different patterns of TDP43 pathology from those observed in LATE-NC, and these are best grouped as diseases with TDP43 proteinopathy and not LATE-NC (Box 1).

This Review summarizes the structure and cellular functions of TDP43 and provides a brief overview of ALS and FTLD with TDP43-immunoreactive pathology (FTLD-TDP). Although the TDP43 pathology in these diseases is not included in the term LATE-NC, they are the most researched of the TDP43 proteinopathies. The focus of this Review is the ongoing studies of the pathology, genetic risk factors and nature of the cognitive impairment and dementia associated with pure LATE-NC, as well as the clinical and pathological features of LATE-NC associated with coexisting pathologies such as AD, hippocampal sclerosis, Lewy bodies, arteriolosclerosis and primary age-related tauopathy (PART). As there are no definite biomarkers or treatment for LATE-NC, the therapeutic strategies being developed for other TDP43 proteinopathies, such as for ALS and FTLD, are briefly discussed.

Structure and function of TDP43

TDP43 is a 414-amino acid RNA-binding protein belonging to the heterogeneous nuclear ribonucleoprotein (hnRNP) family and encoded by the *TARDBP* gene on chromosome 1.p36.22, an essential gene that is ubiquitously expressed in mammals, zebrafish and flies. TDP43 is expressed throughout CNS development and into adulthood, the expression pattern being ubiquitous and mostly nuclear[13]. Prominent expression of TDP43 is present in neural stem cells of the neuroepithelium, which eventually differentiate into multiple cell types, including neurons, astrocytes and other glial cells, that comprise the adult CNS. In terms of protein structure, TDP43 comprises an N-terminal region, nuclear localization signal, two RNA-recognition motifs (RRMs) – RRM1 (amino acids 105–169) and RRM2 (amino acids 193–253)[14] – and a C-terminal region encompassing a glycine-rich region and a prion-like domain rich in glutamine and asparagine[15,16] (Fig. 1). The C-terminal region is implicated in TDP43 pathogenesis because it regulates protein solubility and mediates pathological aggregation[17]. TDP43 is also present in mitochondria, where it associates with the mitochondrial genome, thus having an important role in the respiratory chain pathways[18].

Further information about the known functions of TDP43 in the nucleus and cytoplasm can be obtained from refs. 18–21. In brief, in the nucleus, TDP43 performs several important functions, such as engaging promoter regions of genes to repress transcription[22], and physically interacts with various proteins involved in splicing and translation[23]. At the RNA level, TDP43 performs diverse functions in the nucleus, which include splicing and inhibition of exon recognition,

long intron binding and stabilization, microRNA biogenesis, co-transcriptional limitation of double-stranded RNA formation, inhibition of specific RNA editing events, and binding of long non-coding RNA[14,24]. TDP43 also performs crucial RNA-binding functions in the cytoplasm related to RNA transport and translation and stress granule formation[25,26]. These collective nuclear and cytoplasmic functions are facilitated by the RNA-binding activity of TDP43 coupled with interactions with numerous hnRNPs (hnRNPA1 and hnRNPA2), microprocessor proteins (dicer and drosha), and splicing factors (PSE, splicing factor 3a and PTBP2)[23,27,28]. In the brain, TDP43 affects the splicing of ≥950 mRNAs and engages the 3′ untranslated region (UTR) of >1,000 mRNAs[29,30]. TDP43 also engages and stabilizes very long introns in various pre-mRNAs and is estimated to affect the levels of >600 mRNAs in the mammalian nervous system[29,30].

TDP43 pathology

Under normal conditions, nuclear TDP43 shuttles to and from the cytoplasm[31,32]. In some neurodegenerative diseases, neurons and glia (astrocytes and microglia) show loss of normal nuclear TDP43 associated with translocation of TDP43 into the cytoplasm and neurites in the form of inclusions – findings that are referred to as TDP43 pathology or proteinopathy[33–35] (Fig. 2). TDP43 inclusions can also occur in nuclei of affected neurons and glia, resulting in cellular dysfunction[2,3]. The aggregation of cytoplasmic TDP43 is associated with several post-translational modifications, including phosphorylation of serine residues, ubiquitination, oxidation, lysine acetylation and C-terminal cleavage[36]. TDP43 is detected using immunohistochemistry or western blots[2,36] with polyclonal antibodies such as MC2085, which recognizes a peptide sequence in the 25-kDa C-terminal fragment of TDP43 (ref. 37), or monoclonal antibodies against phosphorylated S409–410 of TDP43 (refs. 36,38). The latter antibody detects pathological inclusions in all sporadic and familial forms of TDP43 proteinopathy[38] but does not detect physiological nuclear TDP43. Double immunostaining of brain samples from individuals with AD for TDP43 and phospho-tau showed that the TDP43-immunoreactive inclusions are usually distinct from neurofibrillary tangles[39]. Most studies report qualitative dichotomous (present versus absent) TDP43 data. However, in the Religious Orders Study and Memory and Aging Project (ROSMAP) (Box 2), a semiquantitative estimate of TDP43 cytoplasmic inclusions in neurons and glia found that, as more brain regions become affected by TDP43 pathology, the mean number of TDP43 inclusions in each region increases[34] (Fig. 3).

Immunoelectron microscopic studies of brain sections from people with ALS or FTLD with ubiquitin-positive inclusions have detected bundles of TDP43-positive and ubiquitin-positive straight filaments in neurons[40–42]. These filaments were 10–20 nm in diameter. Although amyloid-like filaments 10–15 nm in diameter were also observed by electron microscopy of insoluble fractions extracted from brains from people with ALS or FTLD[36,43], TDP43 inclusions do not demonstrate the properties of amyloid[44] nor do they stain with amyloid-specific dyes such as thioflavin T or Congo red[3,45]. Electron cryomicroscopy of aggregated TDP43 in the frontal cortices of two individuals with either ALS or FTLD showed an identical amyloid-like filament structure comprising a single protofilament that adopted a double-spiral-shaped fold[46]. An abundance of glycine and neutral polar residues facilitated numerous turns and restricted β-strand length, resulting in an absence of the β-sheet stacking that is associated with cross-β amyloid structure. Thus, the TDP43 filaments in ALS and FTLD are structurally distinct from the amyloid filaments observed in other neurodegenerative diseases.

Box 1

TDP43 localization in neurodegenerative diseases

Diseases with primary TDP43 pathological change

- ALS[2,3,62]
- Guam ALS[208]
- FTLD-TDP, types A–E[105,205,206]
- LATE[6]
- Perry syndrome[209,210]

Diseases that can have coexisting LATE-NC

- AD (intermediate-to-high grades of AD neuropathological change)[39,53,113,143,144]
- Down syndrome with early-onset AD[211,212]
- Age-related hippocampal sclerosis[49,148,157]
- Lewy body diseases[113,143,166,167]
- Primary age-related tauopathy[138,175,176]

Diseases that can have coexisting TDP43 proteinopathy

- FTLD-tau
  - Pick disease[213]
  - Progressive supranuclear palsy[4]
  - Corticobasal degeneration[4]
  - Argyrophilic grain disease[51,214]
- Chronic traumatic encephalopathy[11]
- Guam parkinsonism–dementia complex[208,215]
- Huntington disease[12]
- Machado–Joseph disease[216]
- Spinocerebellar ataxia 2 (ref. 217)
- Cockayne syndrome[218]

Diseases with only astrocytic TDP43

- Alexander disease[219]

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; FTLD-TDP, frontotemporal lobar degeneration with TDP43-immunoreactive pathology; LATE, limbic-predominant age-related TDP43 encephalopathy; LATE-NC, LATE neuropathological change; TDP43, TAR DNA-binding protein 43.

TDP43 staging schemes

Several cumulative staging schemes have been used to characterize the regional distribution of TDP43 in neurodegenerative diseases.

Three-stage schemes. In 2017, three stages of regional TDP43 distribution were observed in a ROSMAP study (n = 343) of community-dwelling older individuals with pure LATE-NC (without coexisting AD or FTLD) and with and without dementia at the time of death[47]. In stage 1, LATE-NC was localized to the amygdala; in stage 2 LATE-NC extended to the hippocampus and/or entorhinal cortex; and in stage 3 there was further extension to neocortical areas such as the midtemporal or midfrontal cortices. Among individuals with pure LATE-NC, the frequencies of stages 1–3 were 43.7%, 40.0% and 16.3%, respectively.

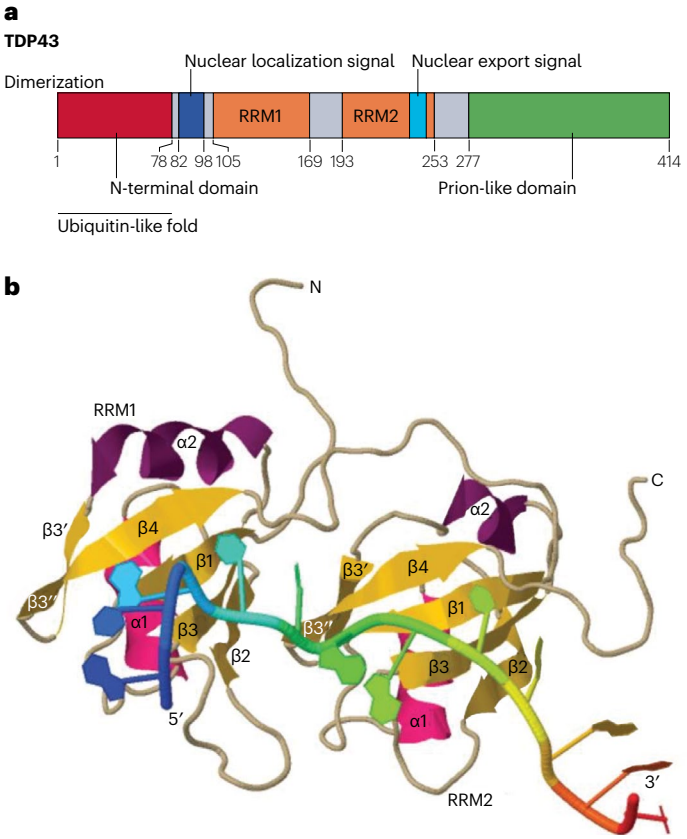

Fig. 1 | TDP43 structure. a, Domain architecture of TAR DNA-binding protein 43 (TDP43). Domain boundaries are numbered according to the full-length protein sequence[19]. **b**, Ribbon representation of the structure of the TDP43 RNA-recognition motif (RRM) construct (amino acids 102–269) in complex with *AUG12* RNA (Protein Data Bank ID code 4BS2)[207]. Parts **a** and **b** reprinted with permission from ref. 19, Cold Spring Harbour Laboratory Press.

Most studies of mixed LATE-NC and AD in the ROSMAP cohort used this three-stage scheme to assess the distribution of LATE-NC[35,48,49].

In 2019, this ROSMAP three-stage scheme was further simplified by the LATE consensus group to include the assessment of only three regions, which are examined during routine neuropathological brain assessment by most neuropathology centres[6]. In this scheme, presence of TDP43 in the amygdala was stage 1, additional involvement of the hippocampus was stage 2 and additional involvement of the midfrontal cortex was stage 3. Over the years, it became evident that not all cases of LATE-NC are readily classifiable using the consensus group LATE-NC scheme, as phosphorylated TDP43 positivity in neurites with fewer cytoplasmic inclusions (reported in 36.4% of cognitively healthy older individuals[50]) and TDP43 positivity restricted to neurites (observed in 40% of cognitively healthy older Japanese individuals[51]) were not included. This observation led to revision of the three-stage consensus group scheme to include cases with only neurite positivity in either the hippocampus or amygdala[52].

ROSMAP five-stage scheme. In another ROSMAP study (n = 1,160) published in 2018, LATE-NC was identified in additional regions such as the anterior temporal pole cortex (ATPC), which is at the interface of limbic structures, on the one hand, and neocortical areas on the other, and the orbitofrontal cortex, which is involved early in FTLD[34]. Correlation between the pathology and clinical findings led to the description of a five-stage scheme of LATE-NC distribution in ageing and AD. In this new scheme, stages 1 and 2 were similar to those in the ROSMAP three-stage scheme referred to above whereas, in stage 3, there was additional involvement of the ATPC, a neocortical area (Fig. 4). In stage 4, there was additional involvement of other neocortical areas, such as the midtemporal and orbitofrontal cortices, and, in stage 5, in addition to all the other areas listed, the midfrontal cortex was affected. The ATPC was the most frequently involved neocortical area; therefore, adding this region to the TDP43 staging protocol allows more cases with early neocortical involvement to be classified[34]. The importance of the five-stage LATE-NC staging scheme is that specific clinical findings are associated with each stage, as discussed below.

TDP43 in AD staging scheme. The progression of TDP43 in AD has been reported to be stereotypical and, in 2014, a five-stage scheme describing the distribution of TDP43 across eight brain regions in AD was published[53]. This scheme — the TDP43 in AD (TAD) scheme — was expanded in 2016, on the basis of conditional probability analyses, to a 6-stage distribution across 14 brain regions[54]. In this scheme, TDP43 deposition begins in the amygdala (stage 1), followed by the entorhinal cortex and subiculum (stage 2), the dentate gyrus of the hippocampus and occipitotemporal cortex (stage 3), the insular cortex, ventral striatum, basal forebrain and inferior temporal cortex (stage 4), the substantia nigra, inferior olive and midbrain tectum (stage 5) and, finally, involvement of the basal ganglia and middle frontal cortex (stage 6). This updated scheme allowed the staging of 100% of AD cases. Not included in this staging scheme is TDP43 localization in the olfactory bulb, which is observed in around 15% of cases of AD[55].

TDP43 and neurodegenerative diseases

TDP43 dysfunction has an important role in neurodegeneration in both ALS and FTLD, and a large body of literature is available regarding the pathogenesis of and therapeutic strategies for both of these diseases. Therefore, a brief overview of the salient characteristics of ALS and FTLD is given below.

Amyotrophic lateral sclerosis. Among adult-onset motor neuron diseases, ALS is the most common, with an incidence of 2 per 100,000 persons and a prevalence of 5.4 per 100,000 persons[56]. Peak age at onset is 58–63 years for the sporadic disease and 47–52 years for the familial disease[57]. Upper and lower motor neuron degeneration leads to rapidly progressive paresis, with a mean survival of approximately 3 years[57]. In addition to motor dysfunction, cognitive and behavioural changes are now recognized in 35–50% of individuals with ALS[58,59], and up to half of individuals with ALS show additional clinical signs of frontotemporal dementia (FTD) — most commonly the behavioural variant — resulting from coexisting FTLD[60]. Approximately 90% of ALS cases are sporadic while 10% are familial[61]. ALS-associated variants in more than 40 genes have been identified, which vary in frequency, mode of inheritance (mostly dominant, rarely recessive) and penetrance[62]. Hexanucleotide repeat expansions in the *C9orf72* gene are the most frequent (40%), followed by missense mutations in *SOD1* (20%), *FUS* (1–5%) and *TARDBP* (1–5%)[63,64]. More than 50 mutations in *TARDBP* have now been connected to sporadic and familial ALS as well as to FTLD-TDP[65]. Among cases of sporadic ALS, 40–60% are thought to be genetic, with repeat expansions being observed in several

genes (*ATXN1*, *ATXN2* and *NIPA1*) and multiple single-nucleotide polymorphisms (SNPs).

Brain and spinal motor neurons of individuals with ALS have abnormal neuronal and oligodendroglial cytoplasmic inclusions of aggregated TDP43, which appear as compact, round Lewy body-like or skein-like inclusions. Olfactory impairment[66] and olfactory TDP43 inclusions occur in 50% of individuals with ALS[67], and phosphorylated TDP43 has also been observed outside the CNS in skeletal muscle[68,69] and the myocardium[69].

Studies of the pathogenesis of ALS follow two main hypotheses: toxic gain of function of TDP43 owing to cytoplasmic expression or mutant forms, or nuclear loss of normal TDP43 function in degenerating neurons leading to impaired RNA-binding capacity and splicing dysfunction[70–72]. However, previous studies have shown that nuclear depletion is not a requirement for neuronal toxicity induced by ALS-associated mutant TDP43 (refs. 73,74), and that cytoplasmic mutant TDP43 is sufficient to cause neurodegeneration[75]. Another group performed genetic studies in several species and reported that loss of normal function of TDP43, rather than the toxic properties of aggregates, is the key factor in TDP43-mediated neurodegeneration[76]. The authors further proposed that the formation of aggregates triggered by TDP43 mutations or mutations in other known and still unknown genes upstream in the pathogenic cascade leads to nuclear depletion, which eventually results in loss of the normal nuclear function of TDP43.

In post-mortem brain samples from individuals with ALS or FTLD, phosphorylated TDP43 was reported to co-localize with the stress granule markers TIA1, PABP1 and eIF3 (refs. 77,78), leading to the hypothesis that stress granules have an important role in the formation of TDP43 inclusions. This hypothesis is supported by the finding that the formation of TDP43 inclusions in cell cultures can be suppressed by the inhibition of stress granule formation using translational inhibitors[79]. More recently, use of an optogenetic-based method to induce controlled TDP43 proteinopathy in live cells demonstrated that pathological inclusions are also present outside stress granules[80]. The authors reported that aberrant phase transitions of cytoplasmic TDP43 were neurotoxic and that treatment with oligonucleotides composed of TDP43 target sequences prevented inclusion formation and rescued neurotoxicity.

TDP43 accumulates in neuronal mitochondria of individuals with ALS or FTD, and disease-associated mutations increase TDP43 mitochondrial localization[81], leading to mitochondrial dysfunction, which exacerbates TDP43 toxicity and amplifies the degree of oxidative stress[21]. Evidence from mouse models indicates that inhibition of TDP43 mitochondrial localization is sufficient to alleviate mitochondrial dynamic abnormalities, neuronal loss and behavioural deficits in different lines of mutant TDP43 transgenic mice[81,82]. The available data suggest that the pathogenesis of ALS is multifactorial and implicates numerous factors, including excitotoxicity, oxidative stress, mitochondrial dysfunction, defective autophagy, neuroinflammation, apoptosis, defective nucleocytoplasmic transport, DNA damage, misregulation of RNA splicing and metabolism, abnormal stress granule dynamics, and disruption of cytoskeletal integrity and axonal trafficking[18,20,63,83–85]. Further details about ALS and its pathogenesis are beyond the scope of this Review and have been reviewed elsewhere[18–21,57,62,63,83,85–89].

Frontotemporal lobar degeneration. The pathological term FTLD refers to selective atrophy of the frontal and temporal lobes in a group of disorders that are heterogeneous in their clinical, pathological and genetic features and can have concomitant features of motor neuron disease or parkinsonism[90,91]. Pathologically, five main groups of FTLD are recognized, three of which are characterized by specific proteinaceous inclusions: tau in FTLD-tau, TDP43 in FTLD-TDP, and fused in sarcoma (FUS) in FTLD-FUS. The protein nature of the ubiquitin-positive inclusions in the fourth group has not yet been identified. In a small minority of cases, no inclusions are found; these cases are designated as FTLD-ni[92–94]. The clinical term FTD refers to a group of early-onset dementias that are the second most common dementing disorder among individuals under the age of 65 years[95]. The estimated prevalence of FTD is 15–22 per 100,000 persons, and population studies indicate an equal sex distribution[96]. Most commonly, individuals with FTD present with a change in personal and social conduct, often associated with disinhibition, and with gradual and progressive changes in language[97]. Recognized FTD clinical syndromes include behavioural variant FTD[98] and primary progressive aphasia, which has three variants — non-fluent or agrammatic, semantic, and logopenic[99]. In the later stages of these syndromes, both behavioural and language dysfunction can be present. Parkinsonism and clinical ALS or motor neuron disease are present in a proportion of cases[2,3,91,100]. In the behavioural variant of FTLD, four patterns of TDP43 distribution have been reported[101], which are characterized by different levels of TDP43 burden, from involvement of just the orbital and inferior frontal gyri and anteromedial temporal structures early in the disease to widespread cortical TDP43 pathology in late-stage disease.

FTLD-TDP, in which TDP43 is the main component of the ubiquitin-positive inclusions, accounts for around 50% of FTLD cases[102]. Individuals with FTLD-TDP show a striking degree of frontotemporal atrophy on MRI[103,104]. The harmonized classification system recognizes four types of FTLD-TDP based on the distribution and morphology of the TDP43 inclusions, which are designated as types A–D, with A being the most common[105] (Table 1). A more recent addition to this group is FTLD-TDP type E[106]; some evidence suggests that types E

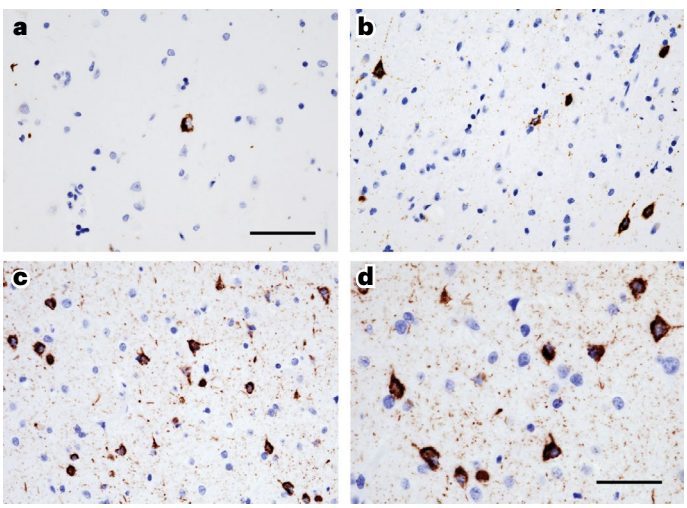

Fig. 2 | TDP43 pathology. Sparse (part **a**), moderate (part **b**) and frequent (part **c**) intracytoplasmic neuronal TAR DNA-binding protein 43 (TDP43) inclusions and neurite immunostaining in the anterior temporal pole cortex. The areas depicted in parts **a**–**c** are smaller than the 0.25 mm^2 counting frame used to quantify the inclusions. Cytoplasmic TDP43 in neurons and prominent neurite immunostaining shown at high magnification (part **d**)[34]. Scale bars: 25 μm in parts **a**–**c** and 50 μm in part **d**. Reprinted with permission from ref. 34, BioMed Central Ltd.

Box 2

Characteristics of four longitudinal studies of ageing and dementia

Studies

Four studies from the Rush Alzheimer's Disease Center — the Rush Memory and Aging Project (Rush MAP), the Religious Orders Study (ROS), the Minority Aging Research Study (MARS) and the African American core — are discussed prominently in this Review. Additional information about the participants is included here to provide the reader with helpful context.

Participants

- Enrolled at 65 years of age with no dementia.
- Signed informed consent for annual clinical evaluations at baseline and annually thereafter to include the following:
  - Neurological examination, 21 cognitive tests, olfactory testing, the modified Unified Parkinson's Disease Rating Scale for parkinsonism, BMI, actigraphy, DynaPort, sleep and nutrition studies.
  - Behavioural economics, decision-making and related behaviours in MAP, including risk aversion and temporal discounting, health and financial decision-making, health and financial literacy, and susceptibility to scams[220].
- Signed an Anatomical Gift Act form for brain donation, which was added to MARS in 2010 and was optional.

Other investigations

- Neuropathological assessment for macroinfarcts and microinfarcts and haemorrhages, Alzheimer disease pathology (amyloid-β and neurofibrillary tangles), hippocampal sclerosis, limbic-predominant age-related TAR DNA-binding protein 43 (TDP43) encephalopathy neuropathological change, Lewy bodies and vascular pathologies (atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy)[34].
- Structural and functional neuroimaging in a subset of participants: antemortem 3D magnetization-prepared rapid acquisition with gradient echo, diffusion-weighted imaging, 2D fast spin echo, 2D fluid-attenuated inversion recovery, quantitative susceptibility mapping, resting-state functional MRI and ex vivo imaging[149,221,222].
- Multi-level omics studies of the dorsolateral prefrontal cortex, including DNA methylation, H3K9Ac, microRNA and RNA sequencing.
- Establishment of 50 human induced pluripotent stem cell lines.

and B represent a continuum[107]. Molecular genetic studies have identified five FTLD-associated genes, of which the gene encoding tau protein (*MAPT*), the growth factor precursor gene *GRN* (encoding progranulin) and *C9orf72* (with unknown function) are most frequently mutated[91,108]. Rare mutations have also been identified in the genes encoding valosin-containing protein and charged multivesicular body protein 2B. The search for genetic risk factors for FTLD-TDP led to the discovery of three SNPs within a 68-kb region on chromosome 7p21.3 (ref. 109). The three SNPs, rs6966915, rs1020004 and rs1990622 (the top marker SNP), were in a genomic region encoding the transmembrane protein 106B (TMEM106B). TDP43 pathology in FTLD-TDP type A or, less commonly, type B can resemble that observed in LATE-NC, and the features that differentiate these two conditions are discussed below. TDP43 in FTLD is not the focus of this Review and further information on this subject can be obtained elsewhere[91,92,94,102,107,110,111].

LATE-NC

Epidemiology and genetics

Healthy individuals and individuals with severe mental illness have some degree of TDP43 immunostaining in dystrophic cellular processes or granular cytoplasmic immunostaining in subpial, subependymal and white matter perivascular locations[112]. The frequency of pure LATE-NC (absence of coexisting AD or FTLD) is reported to vary from 17.9%[113] to 39.4%[47] in community-dwelling older individuals and was 29% in a study of individuals with chronic severe mental illness, mainly schizophrenia[112]. Multiple studies found age to be a significant risk factor for LATE-NC[6,51,112,113] and, in a ROSMAP study, pure LATE-NC was more common in those >90 years of age than in those <90 years of age[47]. Sex seems to have no influence on susceptibility to LATE-NC[5,47,114]. In multiple independent datasets, LATE was more common in individuals with moderate to severe arteriolosclerosis than in those with no or mild arteriolosclerosis[115,116].

Several genes and single nucleotide variants are linked to LATE-NC. Five genes — *GRN*, *TREM106B*, *ABCC9*, *KCNMB2* and *APOE* (encoding apolipoprotein E) — are known to have risk alleles for LATE-NC. The nature of these risk genes indicates that LATE shares pathogenetic mechanisms with both FTLD and AD but also suggests disease-specific underlying mechanisms[6]. The rs1990622A allele of *TREM106B* is associated with susceptibility to FTLD-TDP[109] and increases the risk of LATE-NC, independent of AD or hippocampal sclerosis[117]. Another study confirmed the association of *TMEM106B* rs1990622 with LATE-NC and identified an association of the rs5848 allele of *GRN* with LATE-NC[118]. *APOE* ε4 was associated with increased risk of LATE-NC in older adults in the ROSMAP cohort[119] and the National Alzheimer's Coordinating Center (NACC) study[118] as well as in individuals with AD (in whom the association was independent of amyloid-β (Aβ))[120]. *APOE* ε4 was reported to be a strong genetic predictor of the presence and severity of LATE-NC in older adults, an association not fully explained or significantly moderated by other *APOE* ε4-related proteinopathies (Aβ, tau paired helical filaments and Lewy bodies)[119]. Furthermore, LATE-NC contributed to worse cognitive impairment and increased odds of dementia associated with *APOE* ε4 independently of the effects of Aβ and hyperphosphorylated tau. These findings suggest that, in addition to Aβ, hyperphosphorylated tau and Lewy bodies[121], LATE-NC 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[122,123].

Differentiation of LATE-NC from FTLD-TDP

TDP43 pathology in LATE-NC can be similar to that observed in FTLD-TDP type A or, less commonly, type B; therefore, it is important to differentiate between these two conditions[52]. Age can be helpful in this differentiation as individuals with FTLD are usually, although not always, <65 years of age[95], whereas the frequency of LATE is higher in those >90 years of age[47]. About one-third of individuals with FTLD-TDP have disease-associated genetic mutations (Table 1) that are not present

in LATE. LATE is associated with deficits in episodic memory[47], as opposed to the prominent language or behavioural disturbances that are typical of the FTLDs[98,99]. Regional distribution of TDP43 in FTLD differs from that of pure LATE-NC as early involvement of the orbital gyri is reported in behavioural variant FTLD[101], whereas this region is involved late (stage 4) in LATE-NC[34]. LATE-NC can be reliably differentiated from FTLD-TDP by assessment of the density of phosphorylated TDP43-immunoreactive neuronal cytoplasmic inclusions and ropy dystrophic neurites in anterior cingulate and midfrontal cortices[111]. The presence of more than 15 TDP43-immunoreactive structures per 40× high-power field favours a diagnosis of FTLD-TDP.

Pathogenesis

The precise mechanisms underlying neurodegeneration in LATE-NC remain uncertain. As LATE-NC coexists with many pathologies, one hypothesis is that TDP43 interacts with other proteins, such as tau or Aβ, to induce neurodegeneration. Several studies have analysed data gathered in large autopsy series to test hypotheses about the progression of LATE. Multivariable regression-based assessment was used to generate models to test whether cross-sectional data align with proposed sequential pathways of neuropathological changes[6,124]. The results of one such pathway analysis of a ROSMAP autopsy cohort (n = 1,309)[6] are compatible with at least three hypotheses. First, a subset of individuals with LATE-NC might develop hippocampal sclerosis that is caused or exacerbated by overlapping processes that promote TDP43 proteinopathy or directly by LATE-NC itself. Second, LATE-NC might be independently associated with dementia, even in individuals lacking hippocampal sclerosis. Last, pathogenetic mechanisms associated with ADNC (neuritic Aβ plaques) might also be associated with increased LATE-NC[6]. Further studies are required to unravel the pathogenesis of LATE-NC, which might be multifactorial, as observed in ALS.

Clinical features of LATE-NC

Cognitive impairment. Pure LATE-NC is strongly associated with cognitive impairment independent of AD[6,47,125]. In the ROSMAP cohort[47], pure LATE-NC was associated with a lower level of global cognitive function, predominantly in the domain of episodic memory with less effect on semantic memory and other domains, than in people without LATE-NC. These associations remained when the model controlled for hippocampal sclerosis. In the five-stage TDP43 distribution scheme (described above), impairment of episodic memory was present in stages 2–5 (ref. 34). Significantly lower Mini-Mental State Examination (MMSE) scores and additional impairment of semantic memory and perceptual speed only occurred when the midfrontal cortex was involved (stage 5). In two other studies, impairment of episodic memory and cognitive decline was a consistent finding in individuals with and without AD when LATE-NC was present beyond the amygdala[35,49]. In a study of the combined ROSMAP–MARS cohort, global cognition and episodic

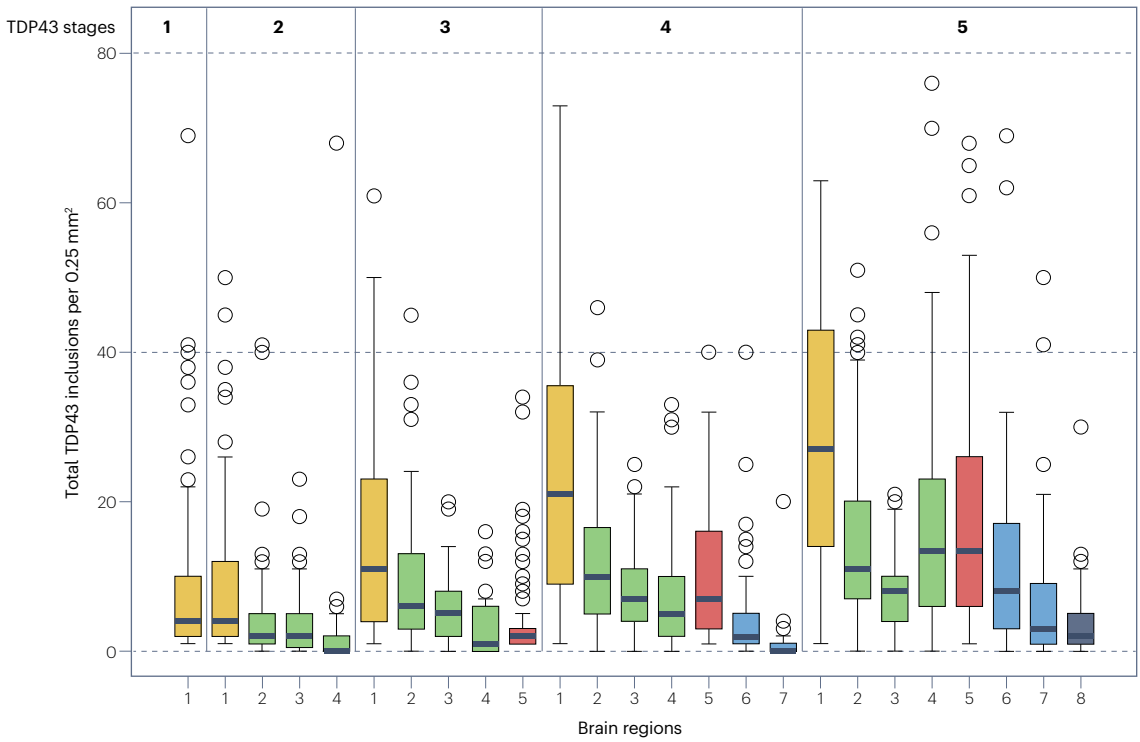

Fig. 3 | Numbers of TDP43 inclusions by TDP43 stage. Box-and-whisker plots show the total number of TAR DNA-binding protein 43 (TDP43) inclusions per 0.25 mm² in eight brain regions (as shown in Fig. 4) by TDP43 stage in 1,160 individuals. Data were obtained at a total magnification of 200× from an area showing the highest density of inclusions in the stated regions. TDP43 inclusions increase progressively in the amygdala by stage. Inclusions in all regions including the anterior temporal pole cortex are maximal in stage 5. Outlier values are indicated by circles. The numbers on the x-axis denote the brain regions: 1, amygdala; 2, entorhinal cortex; 3, CA1 sector of the hippocampus; 4, dentate neurons of the hippocampus; 5, anterior temporal pole cortex; 6, midtemporal cortex; 7, orbitofrontal cortex; 8, midfrontal cortex. Centre line, median; box limits, lower and upper quartiles; whiskers, data range; circles, outliers. Reprinted with permission from ref. 34, BioMed Central Ltd.

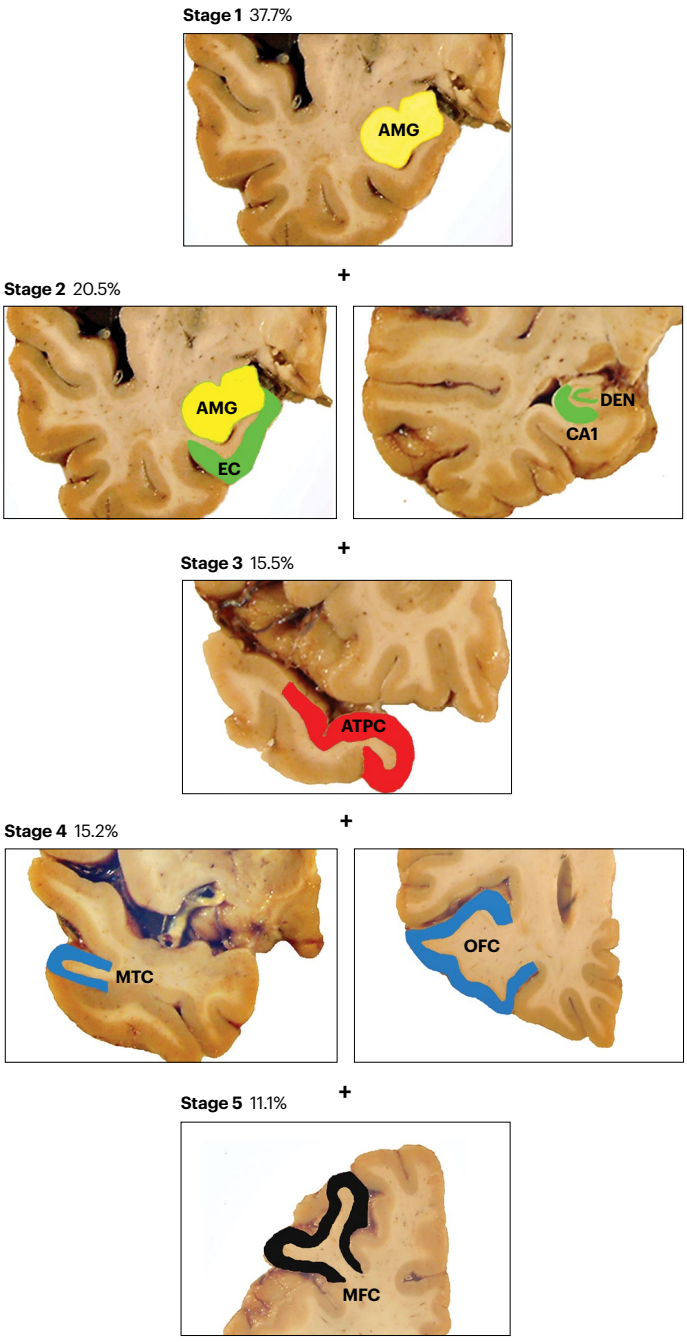

Fig. 4 | The ROSMAP five-stage LATE-NC scheme. Coronal brain sections showing the regional distribution of phosphorylated TAR DNA-binding protein 43 (TDP43) cytoplasmic inclusions and the percentage of cases showing inclusions at stages 1–5 of the Religious Orders Study and Memory and Aging Project (ROSMAP). This is a cumulative staging system such that any stage from 2 to 5 is rated as positive only if the preceding stage or stages are positive. AMG, amygdala; ATPC, anterior temporal pole cortex; CA1, CA1 sector of the hippocampus; DEN, dentate gyrus; EC, entorhinal cortex; MFC, midfrontal cortex; MTC, midtemporal cortex; OFC, orbitofrontal cortex. Adapted from ref. 34, BioMed Central Ltd.

memory declined faster in older individuals with pure LATE-NC than in a reference group that had neither LATE-NC nor AD[126]. However, the rate of decline in individuals with pure LATE was slower than in those with pure AD. Importantly, individuals with mixed LATE-NC and AD had the most rapid decline.

Dementia. In a ROSMAP study, individuals with pure LATE-NC, especially those >90 years of age, had a higher frequency of dementia and lower mean MMSE scores than individuals without LATE-NC[47]. In this study, of those with dementia, 67.7% had a clinical diagnosis of probable AD, 23.1% had a diagnosis of possible AD and 9.2% were diagnosed with other dementias. Pathological examination of those with dementia showed that half of the participants had LATE-NC.

In a ROSMAP cohort (n = 946) consisting of individuals with and without dementia[48], the overall frequency of LATE-NC was 52%. In this study, the frequency of LATE-NC was higher (64.6%) in individuals with AD dementia than in individuals without dementia (43.6%). LATE-NC was independently associated with dementia in older individuals from the ROSMAP cohort[35,48,49] and in the oldest old (>90 years of age) from other cohorts[127,128], even after controlling for ADNC. LATE-NC was present in almost two-thirds of ROSMAP older individuals with AD dementia (n = 1,000) and was, thus, the second most common neurodegenerative pathology after a pathological diagnosis of AD[129]. LATE-NC was associated with AD dementia (OR 1.51, 95% CI 1.11–2.05) independently of pathological AD or other age-related pathologies such as infarcts, arteriolosclerosis, Lewy bodies and hippocampal sclerosis[129]. Mixed LATE-NC and AD were associated with higher odds of AD dementia than pathological AD alone. Using the ROSMAP five-stage scheme, higher odds of dementia were observed independently of coexisting age-related pathologies when LATE-NC was present in the ATPC and other neocortices (stages 3–5), suggesting that the progression of LATE-NC from the mesial temporal lobe to the ATPC is likely to mark the onset of more severe functional changes[34].

Most of the LATE-NC studies described here were performed in cohorts consisting of mainly white individuals. To the best of our knowledge, the cohort for the ROSMAP–MARS–African American Core study (n = 76) is the largest group of community-dwelling Black individuals in whom the frequency and distribution of LATE-NC and its association with cognition and odds of dementia have been documented in the literature[130]. Black individuals with moderate-to-severe LATE-NC were older, had significantly lower global cognition scores (particularly in memory domains), and had a higher frequency of AD, hippocampal sclerosis and cerebral amyloid angiopathy (CAA) than Black individuals with no or mild LATE-NC. LATE-NC in Black individuals was independently associated with impaired global cognition, episodic and semantic memory, and visuospatial abilities. The overall frequency of LATE-NC was similar in Black (40.8%) and white (45.4%) individuals matched on key demographics, dementia and follow-up time[130]. In this study, no racial differences in cognitive function test scores or the pathological distribution of LATE-NC were observed except for a significant increase in the mean number of cytoplasmic TDP43 inclusions in the entorhinal and midtemporal cortices in white compared with Black individuals. In addition, no racial differences in cognitive profiles or the odds of dementia were observed in Black versus white individuals.

LATE-NC and literacy. Financial and health literacy could represent a high-order neurobehavioural function that extends beyond traditional aspects of cognition and is particularly sensitive to neurodegeneration.

Although LATE-NC is common in the ageing population, there are few data on its association with health and financial literacy in older individuals. Many older individuals have low levels of health and financial literacy, which are crucial for the many complex and influential health and financial decisions they face, for example, end-of-life health-care choices, retirement planning or distribution of accumulated wealth[131,132]. A previous ROSMAP study reported that lower levels of health and financial literacy predict subsequent age-related cognitive decline[133], the development of mild cognitive impairment[134,135] and AD dementia[136]. One study of individuals in the ROSMAP cohort aged >65 years (n = 293) reported that LATE-NC was associated with lower literacy even when demographics and AD pathology were accounted for, and this association persisted even when the model was also adjusted for global cognition[137]. Lower levels of literacy were observed in individuals with neocortical LATE-NC than in individuals without LATE-NC, suggesting that older individuals with an advanced LATE-NC stage are at a disadvantage when confronted by complex medical and financial matters.

Comorbidities associated with LATE-NC

LATE-NC is best understood as a pathology associated with cognitive impairment, cognitive decline and dementia, as noted above. Other clinical conditions are emerging as possible risk factors, protective factors or diseases associated with LATE-NC. For example, a preliminary study reported a negative association between congestive heart failure and LATE-NC, and controlling for medications commonly used to treat oedema and heart failure did not change these findings[138].

LATE-NC and diabetes mellitus. Both LATE-NC and type 2 diabetes mellitus are associated with cognitive impairment and, in type 2 diabetes, semantic memory and perceptual speed are impaired[139]. In 2020, a study reported that neither diabetes mellitus nor the medications used to treat diabetes were associated with LATE-NC[138]. However, a prior study reported that diabetes was associated with a decreased risk of ALS. Other studies have reported an inverse association between diabetes mellitus and ALS among individuals aged >65 years[140,141] — the age range when LATE-NC is common — suggesting that an inverse association could also exist between diabetes mellitus and LATE-NC. A ROSMAP study that included individuals with an average age of 90 years (n = 817) used the haemoglobin A1C test — a marker of average blood sugar levels over the previous 2 or 3 months — to investigate the association of diabetes mellitus with semiquantitative scores of cytoplasmic TDP43 inclusions[142]. In this study, a high haemoglobin A1C value was associated with decreased severity of LATE-NC, and this association was not confounded or modified by age, *APOE* ε4, vascular risk factors, stroke, or the use of medications for diabetes. However, survival bias in this association cannot be excluded, and further studies are required to uncover the molecular mechanisms underlying this association.

Table 1 | Clinical, pathological and genetic features of the FTLD-TDP types

FTLD-TDP type	Common phenotype	TDP43 pathology in sporadic and familial forms	Associated gene defect in familial forms
Type A	bvFTD progressive non-fluent aphasia	Greater in cortical layer 2 than in deeper layers; many compact NCIs, short thick dystrophic neurites and variable numbers of lentiform NIIs	Mutation in progranulin gene (*GRN*)
Type B	bvFTD motor neuron disease with FTD	All cortical layers; many diffuse granular NCIs, few dystrophic neurites; abundant wispy thread and dot pathology	*C9orf72* repeat expansion mutations; some cases have type A or C pathology
Type C	Semantic dementia bvFTD	All cortical layers, mainly in layer 2; many long, thick dystrophic neurites, few NCIs	–
Type D	Familial inclusion body myopathy with Paget disease of bone and FTD	All cortical layers; many lentiform NIIs, short dystrophic neurites and infrequent NCIs	Mutations in the gene encoding valosin-containing protein (*VCP*)
Type E	Motor neuron involvement and rapid clinical course (1–3 years)	All cortical layers; granulofilamentous NCIs on a background of fine grain-like deposits	–

bvFTD, behavioural variant frontotemporal dementia; FTLD-TDP, frontotemporal lobar degeneration with TDP43-immunoreactive pathology; NCIs, neuronal cytoplasmic inclusions; NIIs, neuronal intranuclear inclusions; TDP43, TAR DNA-binding protein 43. For more information see refs. 105,107,205,206.

LATE-NC and coexisting pathologies

More prevalent than pure LATE-NC in the brains of older individuals is the association of LATE-NC with heterogeneous pathologies such as AD, hippocampal sclerosis, Lewy bodies, arteriolosclerosis and PART, and the specific pathological and clinical features in these cases are influenced by the comorbid pathology present.

LATE-NC and AD. Several studies[39,116,138,143,144] have reported LATE-NC in the brains of individuals with AD, and a more recent study reported the frequency of the coexistence of both pathologies to be 74%[113]. The distribution of TDP43 in the brains of individuals with AD has been described in this Review in the section on the TAD staging scheme. In a study of 616 individuals aged >75 years at death, only half of the samples with Braak neurofibrillary tangle stage VI (high ADNC) had comorbid LATE-NC, indicating that LATE-NC is not an inevitable sequela of severe ADNC[138].

Pathological subtyping of AD cases by neurofibrillary tangle distribution into typical, limbic and those with hippocampal sparing showed TDP43 frequencies of 59%, 67% and 21%, respectively[145]. Furthermore, the authors of the study reported that clinical presentation in these cases, whether amnestic or atypical, was driven by the pathological AD subtype and not by TDP43. In another study, after accounting for age, APOE ε4 and other pathologies, TDP43 had a strong effect on cognition, memory loss and medial temporal atrophy in AD[146]. Individuals positive for TDP43 and with AD were ten times more likely to have cognitive impairment at death than those negative for TDP43 and with AD. Greater cognitive impairment and medial temporal atrophy were associated with greater TDP43 burden and more extensive TDP43 distribution. In a study of 84 individuals with a pathological diagnosis of AD, those positive for TDP43 had a different clinicopathological and radiological phenotype from that of individuals negative for TDP43 (ref. 144). This phenotype included greater age of disease onset and death and worse performance on the Clinical Dementia Rating Scale, MMSE and the Boston Naming Test. Although individuals with AD positive for TDP43 and those with AD negative for TDP43 both had reduced

medial temporal and temporoparietal grey matter on T1-weighted volumetric MRI compared with controls, those positive for TDP43 had a greater reduction in grey matter volume in the hippocampus.

Heterogeneity in TDP43 distribution was reported in the brains of older individuals (n = 553) with Braak neurofibrillary tangle stages 0–VI and an absence of FTLD[147]. The authors of the study defined two distinct TDP43 types — α and β. In type α, typical TDP43-immunoreactive inclusions were present, whereas in type β, TDP43 immunoreactivity was adjacent to and/or associated with neurofibrillary tangles in the same neuron. In the study cohort, type α had a frequency of 54% and type β a frequency of 46%. Individuals with type α cases were older than those with type β at death (median 89 years versus 87 years), and individuals with type α had lower amygdala and hippocampal volumes than those with type β on pre-mortem MRI, although both groups had lower amygdala and hippocampal volumes than individuals negative for TDP43. The pattern of TDP43 distribution was more widespread in individuals with type α — 85% had temporal, frontal and brainstem (TAD stages 4–6) involvement — whereas, in approximately 85% of the type β group, TDP43 deposition was predominantly limbic, with the amygdala, entorhinal cortex and the hippocampal subiculum (TAD stages 1–3) being involved. The frequency of hippocampal sclerosis was different in the two types: 60% in type α and 15% in type β. Significant differences in the frequency of protective (GG) and risk (CC) *TMEM106B* haplotypes were also observed between the two types. Another study applied the proposed subtype scheme to cases with amygdala TDP43 deposition but reported poor inter-rater reliability among neuropathologists[111]. Whether TDP43 in the α or β types is biologically similar to or different from TDP43 in FTLD-TDP remains to be determined.

LATE-NC and hippocampal sclerosis. Hippocampal sclerosis refers to severe neuronal loss and gliosis in the hippocampal CA1 region and/or subiculum that is out of proportion to the amount of ADNC present[39,49,148]. In advanced stages of LATE-NC, hippocampal volume loss has been documented by ex vivo MRI[149,150]. When both hemispheres were evaluated, hippocampal sclerosis was found to be bilateral in 45%, left-sided in 32% and right-sided in 23% of cases[151]. Hippocampal sclerosis represents the end stage of a diverse range of pathologies, including epilepsy, hypoxia–ischaemia, hypoglycaemia, specific infections and many neurodegenerative diseases, and has a high frequency in LATE and in FTLD[152–155]. Hippocampal sclerosis is increasingly identified in older individuals, particularly in the oldest old, with or without AD, and these cases are referred to as hippocampal sclerosis of ageing (hippocampal sclerosis–ageing)[127,156–158]. In a ROSMAP study (n = 636), hippocampal sclerosis was reported to be twice as common in individuals aged >90 years (18.0%) as in individuals aged <90 years (9.2%)[49]. Prior studies reported the prevalence of hippocampal sclerosis in individuals aged >80 years to be 10–25%[148,156,157]. Compared with individuals with LATE-NC and no hippocampal sclerosis, individuals with LATE-NC and hippocampal sclerosis (LATE-NC–hippocampal sclerosis) have a greater frequency of arteriolosclerosis[47,156,158,159] and tend to have more severe atherosclerosis in the circle of Willis[159]. In the NACC data set, none of the upstream vascular risk factors, such as diabetes, hypertension, hypercholesterolaemia or cardiac disease, showed a positive association with LATE-NC–hippocampal sclerosis[158].

A high frequency of LATE-NC among individuals with hippocampal sclerosis was observed in a study published in 2007 (ref. 39) and was replicated in more recent studies, which reported frequencies varying from 86.0%[49] to 89.9%[148,160]. Brain TDP43 pathology was not identified in young individuals with epilepsy and pathologically confirmed hippocampal sclerosis[148]. Therefore, hippocampal sclerosis without LATE-NC does not represent LATE and these individuals are more likely to have stroke[159]. Among individuals with LATE-NC, the stages are more advanced and the burden of TDP43 inclusions is greater — not only in the hippocampus but also in the amygdala, entorhinal and neocortices — in individuals with hippocampal sclerosis than in individuals without hippocampal sclerosis[49,159]. Although hippocampal sclerosis commonly coexists with AD and Lewy bodies, only LATE-NC increases the odds of hippocampal sclerosis (odds ratio (OR) 2.63, 95% confidence interval (CI) 2.07–3.34). In logistic regression models accounting for age, LATE-NC and other common age-related pathologies, individuals with hippocampal sclerosis had higher odds of dementia (OR 3.71, 95% CI 1.93–7.16), mild cognitive impairment and probable AD (OR 3.75, 95% CI 2.01–7.02) than individuals without hippocampal sclerosis[49]. In linear regression models that included an interaction term for hippocampal sclerosis and LATE-NC, LATE-NC–hippocampal sclerosis was associated with lower function in multiple cognitive domains whereas hippocampal sclerosis without LATE-NC did not have statistically significant associations except for an association with lower episodic memory[49]. Among individuals with LATE-NC, those with hippocampal sclerosis had worse cognitive status — scoring lower on the 'personal care' and 'orientation' domains — than those without hippocampal sclerosis[159]. The combined role of hippocampal sclerosis and LATE-NC is an important factor underlying global cognitive impairment and AD dementia in older individuals.

The relationship between *APOE* ε4 and LATE-NC–hippocampal sclerosis was studied using Mendelian randomization in the ROSMAP cohort (n = 1,044). This analysis indicated that TDP43 was likely to be upstream of hippocampal sclerosis in the pathogenic pathway connecting *APOE* ε4 and hippocampal sclerosis[119]. The authors of this study, along with others[6,118], suggest that TDP43 in older adults is on a pathogenic continuum with hippocampal sclerosis; therefore, most cases of hippocampal sclerosis might represent downstream consequences of TDP43-mediated neurodegeneration. One hypothesis proposes that *APOE* ε4 and AD predispose to LATE-NC, which then drives an individual towards severe LATE-NC–hippocampal sclerosis[118].

Genomic data from three North American data bases support an association of *TMEM106B* rs1990622A, *GRN* rs5848 and *APOE* ε4 with LATE-NC–hippocampal sclerosis[118]. A study of three European population-based cohorts replicated the association between *TMEM106B* and *GRN* and LATE-NC–hippocampal sclerosis[161]. This study found no difference in *ABCC9* rs704178 genotype or allele frequency between individuals with LATE-NC–hippocampal sclerosis and individuals with hippocampal sclerosis and no LATE-NC, which meant that *ABCC9* was not confirmed as a genetic risk factor for LATE-NC–hippocampal sclerosis. However, other studies observed that an SNP in *ABCC9* was associated with the risk of hippocampal sclerosis–ageing[118,162,163] and hypothesized that *ABCC9* might be the driver that predisposes individuals with LATE-NC to developing hippocampal sclerosis[118]. The human *ABCC9* gene and its polypeptide product, SUR2, are involved in regulating arteriolar smooth muscle tone and participating in pathways implicated in neurodegenerative diseases, for example, hypoxia–ischaemia, neuroinflammation and injury responses, implicating these processes in the pathogenesis of hippocampal sclerosis–ageing[163].

Other genetic factors that contribute to the risk of developing hippocampal sclerosis–ageing or LATE-NC–hippocampal sclerosis are factors that modulate brain thyroid hormone. A study of triiodothyronine (T3) and thyroxine (T4) levels in the cerebellar parenchyma in individuals with LATE-NC and comorbid AD pathology (n = 136) reported

reduced T3:T4 ratios among individuals with *ABCC9* or *SLCO1A2/IAPP* (but not *GRN* or *TMEM106B*) risk-associated genotypes[164]. This observation suggests that these gene variants alter thyroid hormone processing and that individuals with low T3:T4 ratios have a relatively high likelihood of manifesting hippocampal sclerosis–ageing. *ABCC9* and *SLCO1A2/IAPP* risk-associated genotypes were also associated with altered expression of the astrocytic thyroid hormone receptor[165], suggesting that dysregulation of thyroid hormone signalling could have a role in the pathogenesis of LATE-NC–hippocampal sclerosis[164].

LATE-NC and Lewy bodies. LATE-NC has been reported to coexist with Lewy body disorders in some individuals, and the frequencies of LATE-NC among individuals with Parkinson disease, dementia with Lewy bodies (DLB) with AD, or Parkinson disease with dementia were reported to be 7.2%, 31.3% and 19.0%, respectively[166]. Another group reported a higher frequency (52.6%) of LATE-NC in individuals with both AD and DLB[113], and the frequency of LATE-NC in individuals with DLB varied among studies from 56%[143] to 72.7%[51]. A study of individuals with DLB ($n = 11$) observed LATE-NC in 45% of cases, with distribution of LATE-NC in the amygdala, hippocampus, dentate gyrus, and entorhinal, occipitotemporal and inferior temporal cortices[167]. In this study, no substantial differences in clinical data or neuropathological stages between individuals with or without LATE-NC were observed. Interestingly, in a subset of cases, Lewy bodies and TDP43 inclusions were present in the same neurons. Another study reported that individuals with LATE-NC had a higher frequency of amygdala-predominant or limbic-predominant Lewy body types (but not other types) than individuals without LATE-NC[138]. The hippocampal distribution of LATE-NC was reported to differ between individuals with LATE-NC plus DLB and individuals with LATE-NC plus AD[168]. Neuronal cytoplasmic TDP43 inclusions in the CA3 were more frequent in individuals with LATE-NC plus DLB than in individuals with LATE-NC plus AD. In addition, abundant fine neurites composed of C-terminal-truncated TDP43 protein were found mainly in CA2 to subiculum in LATE-NC plus DLB and were not as numerous in LATE-NC plus AD. Some of these fine neurites colocalized with phosphorylated α-synuclein. The authors also reported that *TMEM106B13* rs1990622 and *GRN* rs5848 are risk factors for the spread of LATE-NC in DLB, which might represent one of the neuropathological substrates for cognitive decline in DLB.

A larger ROSMAP–MARS study ($n = 1,670$) of older individuals reported an overall Lewy body frequency of 25.6% and LATE-NC frequency of 51.7%; the frequency of individuals with both Lewy bodies and LATE-NC was 15% in the whole cohort and 25% in individuals with AD dementia[169]. This study provided a better understanding of the relationship between the three Lewy body types and LATE-NC and their combined roles in cognitive impairment and AD dementia. The neocortical Lewy body type, but not the brainstem-predominant or limbic Lewy body types, increased the odds of moderate-to-severe LATE-NC in a model that controlled for demographics, AD pathology and *APOE* ε4, and this association was strongest in individuals aged <90 years and in women. LATE-NC and neocortical Lewy body type, separately, were associated with lower global cognition and lower function in each of the cognitive domains of episodic, semantic and working memory, perceptual speed, and visuospatial ability. In addition, both pathologies separately increased the odds of AD dementia more than was observed with ADNC alone. The presence of the limbic Lewy body type also increased the odds of LATE-NC but to a smaller degree than the neocortical Lewy body type. Furthermore, in individuals with the limbic Lewy body type and LATE-NC, impairment was only observed in three of the five cognitive domains (episodic, semantic and working memory). No interaction between limbic or neocortical Lewy body types and LATE-NC on cognitive function, cognitive domains or AD dementia was observed, indicating that the effects of both pathologies additively lowered global cognition and the function of five specific cognitive domains, and further increased the odds of AD dementia.

LATE-NC and arteriolosclerosis. The frequency of arteriolosclerosis is higher among individuals with LATE-NC[6,116,127] than among individuals without LATE-NC. The frequency of arteriolosclerosis increases with age, and the results of several studies agree that, among individuals >80 years of age, >80% have identifiable arteriolosclerosis[170,171]. Therefore, it is not surprising that the frequency of arteriosclerosis is higher among individuals with LATE-NC who are >80 years of age than in those aged <80 years. A study published in 2020 reported a decrease in α-smooth muscle actin and the pericyte markers PDGFRβ and CD13 in brain homogenates from individuals with AD and comorbid LATE-NC[172] compared with individuals without AD or LATE-NC. How arteriolosclerosis and LATE-NC, which are both independently associated with dementia, interact to contribute to dementia is unknown. A study that used the neuropathology data set from NACC found that LATE-NC, particularly in the entorhinal cortex, amygdala and inferior temporal cortex, was associated with comorbid moderate-to-severe arteriolosclerosis, particularly among individuals without *APOE* ε4 (ref. 116). This association was relatively specific, as a different study reported no association between LATE-NC and other brain pathologies related to vessels such as microinfarcts, macroinfarcts or lacunar infarcts[138]. Among individuals >90 years of age with LATE-NC, arteriolosclerosis was more frequent in the amygdala, hippocampus and frontal lobe than in those aged <90 years[127].

In our large ROSMAP–MARS study ($n = 749$), the frequency of LATE-NC was 54.6%, and 86.5% of individuals with LATE-NC had one or more microvascular pathologies. Among these individuals with microvascular pathologies, the frequency of moderate-to-severe arteriolosclerosis was 32.3% in the basal ganglia, 47.6% in the anterior watershed region and 32.5% in the posterior watershed region[173], supporting the concept of heterogeneity in arteriolosclerosis distribution across the brain. Individuals with arteriolosclerosis in the posterior watershed region had higher odds of advanced LATE-NC than those with arteriolosclerosis in the other regions, and this association persisted after adjusting for age and age-related neurodegenerative pathologies (such as AD, Lewy body disorders and other vascular pathologies) or after controlling for potential confounders (such as vascular risk, vascular disease burdens or *APOE* ε4). We suggested that reduced cerebral blood flow and lower perfusion across the posterior watershed regions (precuneus and posterior cingulate gyrus) compared with other brain regions could predispose to neuronal dysfunction rostrally in limbic and temporal regions where LATE-NC preferentially accumulates. However, further studies are warranted to examine the factors and mechanisms underlying the severity of posterior watershed arteriolosclerosis. In this study, CAA specific to capillaries but not CAA severity was also related to LATE-NC burden. The basis for this association is unclear and warrants further work to promote our understanding of capillary CAA and its role in the pathophysiology of LATE-NC.

LATE-NC in primary age-related tauopathy. PART is characterized by neurofibrillary tangles and a Braak stage of ≤IV, and is designated as definite in the absence of Aβ plaques and possible when few Aβ plaques are present[174]. In a study of individuals with definite PART ($n = 52$), 15 (29%)

were positive for TDP43 and, of these individuals, 75% were graded as TDP stage 1 as inclusions, when present, were rare and predominantly perivascular[175]. A smaller study (n = 16) of individuals with definite PART and a median age of 78.9 ± 7.2 years reported LATE-NC positivity in all individuals[176]. The authors of the study described a four-stage TDP43 distribution: stages 1–3 were similar to the consensus group LATE-NC scheme[6] whereas, in stage 4 (n = 2), TDP43 was present in the pallidum, putamen and insular cortex. LATE-NC distribution correlated with Braak neurofibrillary tangle stage: the density of TDP43 inclusions was low in individuals in Braak stages I and II, moderate in stage III, and high in stage IV. Another study using data from the NACC (n = 616) reported that the overall frequency of LATE-NC was low in individuals with or without PART, although the percentage of individuals with PART was higher among those without LATE-NC (8%) than among those with LATE-NC (2%). In an adjusted model, an association was observed between definite PART and LATE-NC, although this association was not as strong as that of ADNC or hippocampal sclerosis with LATE-NC[138].

Biomarkers of pathological TDP43

There are currently no generally accepted biomarkers for TDP43; therefore, LATE cannot be distinguished from AD clinically or radiologically, making it imperative to develop biomarkers for a definitive clinical diagnosis.

Imaging studies

Structural MRI studies have detected differences in brains between individuals with LATE and individuals with AD. For example, hippocampal atrophy was greater in individuals with LATE-NC than in those with pure AD[151], and atrophy and deformation of the hippocampus were considerably greater in individuals with LATE-NC–hippocampal sclerosis than in individuals with only ADNC[151]. In an antemortem study, ^{18}F-fluorodeoxyglucose (FDG)-PET was performed in individuals with amnestic dementia who, at subsequent autopsy, were diagnosed with LATE-NC (n = 7) or AD (n = 25)[177]. The FDG-PET signal showed distinct temporolimbic and temporoparietal patterns in individuals with LATE-NC and individuals with AD, respectively. Compared with individuals with the AD FDG-PET pattern, individuals with the LATE-NC FDG-PET pattern were significantly older, showed less abnormal AD biomarker levels, were less likely to have *APOE* ε4 and had a higher *TMEM106B* risk allele load, all of which are characteristic of LATE. Clinically, they exhibited a more memory-predominant profile and a generally slower disease course, which fits the clinical profile of LATE. This identification of a LATE-associated FDG-PET pattern is an important stride in the diagnosis of pure LATE in amnestic dementia in ageing individuals. A ROSMAP ex vivo MRI study of individuals with LATE-NC (n = 198) reported a negative correlation between LATE-NC and amygdala volume — independent of the effects of other age-related neuropathologies — and identified a unique pattern of inward deformation of the amygdala surface that was different from the patterns reported in AD or hippocampal sclerosis[178]. These findings might enhance future MRI-based biomarker studies.

Biofluid studies

TDP43 antibodies bind to the epitopes aa1–260, aa205–222 or aa256–296 of TDP43 (ref. 179) and, therefore, have the potential to detect full-length TDP43, longer C-terminal fragments or full-length phosphorylated TDP43. None of these antibodies binds to the extreme C-terminus of TDP43; hence, detection of the shorter C-terminal fragments described in the human brain is unlikely[180]. LATE-NC has been observed in subpial, subependymal or perivascular locations, which might result in increased levels of TDP43 in the cerebrospinal fluid (CSF) and blood through mechanisms that remain to be determined[112]. According to a meta-analysis of seven studies, individuals with ALS have a statistically significantly higher level of TDP43 in CSF than individuals without ALS[181]. This observation suggests that CSF TDP43 could be a biomarker for ALS. Thus far, it has not been possible to detect an immunoreaction with a phosphorylation-dependent antibody for TDP43 in CSF[180].

The first study to quantify the full-length TDP43 isoform in plasma reported elevated plasma levels in individuals with FTD and a subset of individuals with AD compared with controls[182]. This observation suggests the presence of comorbid LATE-NC in these individuals. In a subsequent study, levels of phosphorylated TDP43 in plasma correlated with the severity of TDP43 pathology in FTD but not in clinical AD with LATE-NC[183]. Overall, wide interindividual variations in plasma TDP43 levels were observed in the two groups.

Therapeutic strategies

Therapeutic strategies for TDP43 proteinopathies are still in the experimental phase and have been studied mainly in the context of ALS and FTD. These strategies focus on clearing TDP43 cytoplasmic aggregations, modulating some of the pathogenetic mechanisms stated above, restoring nuclear TDP43 by inhibiting TDP43 nuclear export or stimulating TDP43 import, and correcting disease-associated genetic alterations.

TDP43 co-localizes with stress granules; therefore, agents that promote stress granule disassembly or inhibit their initial assembly could have therapeutic potential[15,184]. Small-molecule inhibitors of TDP43 aggregation have been shown to prevent cellular toxicity[185], inhibit the accumulation of TDP43 into stress granules, reduce C-terminal fragment aggregation and enhance caspase-mediated cleavage in SH-SY5Y cells[186]. As autophagy pathways have an important role in the clearance of misfolded and aggregated proteins, enhancement of autophagy pathways could be of therapeutic importance in TDP43 proteinopathies. Induction of autophagy by rapamycin enhanced protein degradation, improved memory, rescued motor dysfunction and reduced cytoplasmic inclusions in a mouse model with TDP43 proteinopathy[187].

There is strong evidence that nuclear import defects contribute to the nuclear loss and cytoplasmic accumulation of TDP43 and FUS and thus to ALS and FTD pathogenesis, respectively[188–190]. Inhibition of nuclear export of TDP43 and FUS to compensate for poor nuclear import has already been tested in preclinical experimental models of C9orf72-associated and TDP43-associated ALS and FTD. KPT-276 and KPT-335, which are specific inhibitors of the nuclear export receptor exportin 1 (Xpo1), alleviated *C9orf72* repeat-mediated neurodegeneration in the *Drosophila* eye[191] and reduced TDP43 overexpression-induced cell death in cortical neurons[192], respectively. In an interspecies heterokaryon assay, predicted nuclear export signals in TDP43 or FUS were non-functional and both proteins were exported independently of the export receptor, indicating that Xpo1 inhibitors are likely to exert their neuroprotective effects independently of TDP43 or FUS[193].

Several genetic therapeutic approaches for ALS and FTLD have been tested in preclinical and clinical studies. Such approaches include antisense oligonucleotides, which can downregulate the expression of target genes; interference of RNA pathways through short interfering RNA; the bait RNA approach, which modulates protein

solubility through reversible binding; gene delivery techniques; and antibody-mediated reduction of protein aggregation[83,85,194]. The *SOD1* antisense oligonucleotide tofersen has been tested in clinical trials in ALS[195,196] as have antisense oligonucleotides that target other autosomal dominant gain-of-function mutations such as those in *C9orf72*, *FUS* and *ATXN2* (ref. 195). Several preclinical investigations have tested the use of short interfering RNA to target ALS-associated genes; however, none have reached clinical trials[197,198]. Patient-derived stem cell models used in ALS research include human induced pluripotent stem cell-derived motor neurons, fully differentiated somatic cells reprogrammed into neurons, and stem cells derived from the human olfactory mucosa[85]. Although trials of adult stem cells in individuals with ALS showed the treatment to be safe and well tolerated, long-lasting efficacy was not observed[199].

Another potential experimental therapeutic strategy is the use of engineered potentiated disaggregases, which reverse protein misfolding and restore proteins to their native structure, function and localization. Disaggregases could mitigate neurodegeneration by simultaneously reversing toxic gain of function of the misfolded form as well as any loss of function owing to misfolding[200]. Potentiated variants of heat shock protein 104, a protein disaggregase from yeast, were able to robustly disaggregate TDP43 or FUS in yeast models of TDP43 proteinopathy[200–202], suggesting that engineering potentiated human protein disaggregases or isolating small-molecule enhancers of their activity have the potential to provide neuroprotection in diverse neurodegenerative diseases.

The clinical and pathogenic heterogeneity of diseases such as ALS precludes a single therapeutic approach from being effective for all individuals with the disease. Instead, a personalized approach, based on the specific clinical and biological characteristics of patient subgroups, is more likely to be the avenue for effective targeted treatments.

Conclusions

In the two decades following the identification of TDP43 pathology in ALS and FTLD, much information has become available regarding the brain distribution of TDP43 pathology in AD, other neurodegenerative disorders and ageing. A relatively recent development is the characterization of LATE (the clinical disease) and LATE-NC (the neuropathological change), which affect older individuals, especially those aged ≥80 years, and underlie an amnestic dementia that is currently difficult to distinguish from AD dementia, hence the urgency to develop biomarkers for the diagnosis of LATE in the clinic and to convince those who are sceptical[203] that LATE is distinct from AD.

The frequency of pure LATE-NC might be as high as 40% in community-dwelling older individuals, and age is recognized as a significant risk factor, especially in individuals ≥90 years of age[47]. Pure LATE-NC is strongly associated with a lower level of global cognitive function, predominantly in the domain of episodic memory, with a smaller effect on semantic memory. Other memory domains are affected in the late stages when LATE-NC involves the midfrontal cortex. These associations are independent of coexisting AD. Individuals with pure LATE-NC, especially those aged ≥90 years, have an increased frequency of dementia. Thus far, the frequency of LATE-NC is similar in Black versus white individuals, and no differences in the cognitive profiles or the odds of dementia have been observed between these two groups. The *TMEM106B* rs1990622A genotype, which is associated with susceptibility to FTLD-TDP, also increases the risk of LATE-NC independently of AD and hippocampal sclerosis. Other studies have confirmed the association of *TMEM106B* rs1990622A and *GRN* rs5848 genotypes with LATE-NC and the association of *GRN* and *ABCC9* with LATE-NC–hippocampal sclerosis. A single hypothesis suggests that *TMEM106B, GRN* and *APOE* ε4 single nucleotide variants predispose individuals to LATE-NC and that *ABCC9* is the driver for development of hippocampal sclerosis in severe LATE-NC.

Despite ongoing research, the pathogenesis of LATE-NC is largely unknown and should be a focus of future research to develop strategies for the diagnosis, prevention and treatment of this condition, which might become a future public health problem given the projected increase in the worldwide population aged ≥65 years from 562 million in 2012 to 1.6 billion by 2050 (ref. 204). In addition to animal models, the significance of TDP43 could be investigated at the single-cell or brain-specific level in diseased tissue to identify new or early disease-specific changes that might be missed in whole-tissue analysis or cell culture overexpression models. The continual development of new research techniques, such as human induced pluripotent stem cells and genetic engineering, offers hope for unravelling the mysteries of LATE-NC and the other TDP43 proteinopathies, ultimately leading to disease-modifying therapies.

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