Neuropathology and Applied Neurobiology (2015), **41**, 858–881 doi: 10.1111/nan.12250

Review: An update on clinical, genetic and pathological aspects of frontotemporal lobar degenerations

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T. Lashley, J. D. Rohrer, S. Mead and T. Revesz (2015) *Neuropathology and Applied Neurobiology*
An update on clinical, genetic and pathological aspects of frontotemporal lobar degenerations

The development of our understanding of frontotemporal dementia (FTD) has gathered pace over the last 10 years. After taking a back seat to Alzheimer's disease for many years FTD has emerged as a significant group of heterogeneous diseases often affecting people under the age of 65. FTD has also been brought into the spotlight as the major disease entities of the group have clinical, genetic and pathological links to motor neuron disease/amyotrophic lateral sclerosis, indicating that they form a disease spectrum. In this review, we overview how the pathological concept of frontotemporal lobar degeneration (FTLD) and the clinical concept of FTD evolved and show that FTLD, once thought of as a single disorder, represents a heterogeneous group of diseases with overlapping clinical symptoms, multiple causative genes and varying underlying pathology. We also provide a brief summary of the clinical manifestations, summarize the major genetic aspects and describe the main pathological features seen in the different subtypes of FTLD. We also summarize the correlations that exist between clinical presentations and pathological variants. An overview of the main pathogenic mechanisms is also provided.

Keywords: classification, frontotemporal dementia, frontotemporal lobar degeneration, FUS, pathology, tau, TDP-43

Introduction

Frontotemporal lobar degeneration (FTLD) is a pathological term used for the description of a clinically, pathologically and genetically heterogeneous group of disorders, in which relatively selective degeneration of the frontal and temporal lobes is a prominent and common feature [1]. The clinical term frontotemporal dementia (FTD) is used for the description of a group of early onset dementias, which is the second most common dementing disorder among individuals under the age of 65 years [2]. However, in 25% of the cases FTD presents in old age [3]. The estimated prevalence of FTD is 15–22/100 000 and population studies indicate an equal gender distribution [3]. Clinically FTD patients can present with one of three canonical clinical syndromes: behavioural variant FTD (bvFTD) and two language variants, semantic dementia and progressive nonfluent aphasia (PNFA) (see later). FTD can overlap with motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) (FTD-MND), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) syndrome [4]. FTD is a highly heritable disorder with approximately 30–50% of cases reporting a positive family history [5]. Mutations in three genes microtubule-associated protein tau (*MAPT*), progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9orf72*) genes being responsible for most of the familial cases, and about 10–20% of all cases with FTD [5,6]. The current neuropathological classification of FTLDs recognizes five

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major subgroups, three of which are characterized by specific proteinaceous inclusions: tau in FTLD-tau, 43 kDa transactive response DNA-binding protein (TDP-43) in FTLD-TDP and fused in sarcoma (FUS) in FTLD-FUS. The protein nature of the ubiquitin-positive inclusions has not been identified in the fourth group and is currently classified as FTLD-UPS, represented mostly by cases of affected individuals of a Danish pedigree due to mutation in the charged multivesicular body protein 2B (*CHMP2B*) gene while no inclusions are found in a small minority of the cases designated as FTLD-ni. In this review, we also provide a summary of the evolution of the pathological and clinical concepts of FTD, and discuss the genetics and the main neuropathological findings of the FTLD subgroups and summarize issues related to the pathogenesis of the relevant disorders. The most recent classification is also provided in this review.

Evolution of the pathological concept of FTLDs

The concept of circumscribed cerebral cortical atrophy is over 120 years old (Figure 1). Between 1892 and 1906, Arnold Pick, the eminent Czech-Austrian neuropsychiatrist and head of the Department of Psychiatry at the Charles University in Prague, in a series of pioneering papers described a number of patients with such type of cortical atrophy. Pick, trained with Meynert in Vienna and Westphal in Berlin, is one of the forefathers of modern cognitive neurology, whose scientific ideas were greatly influenced by the work of John Hughlings Jackson in London [7–9]. The first of Pick's studies on circumscribed cerebral atrophy is his seminal paper, published in the Praguer Medizinische Wochenschrift in 1892, in which he described the case of August H, a 71-year-old male with progressive cognitive decline and prominent

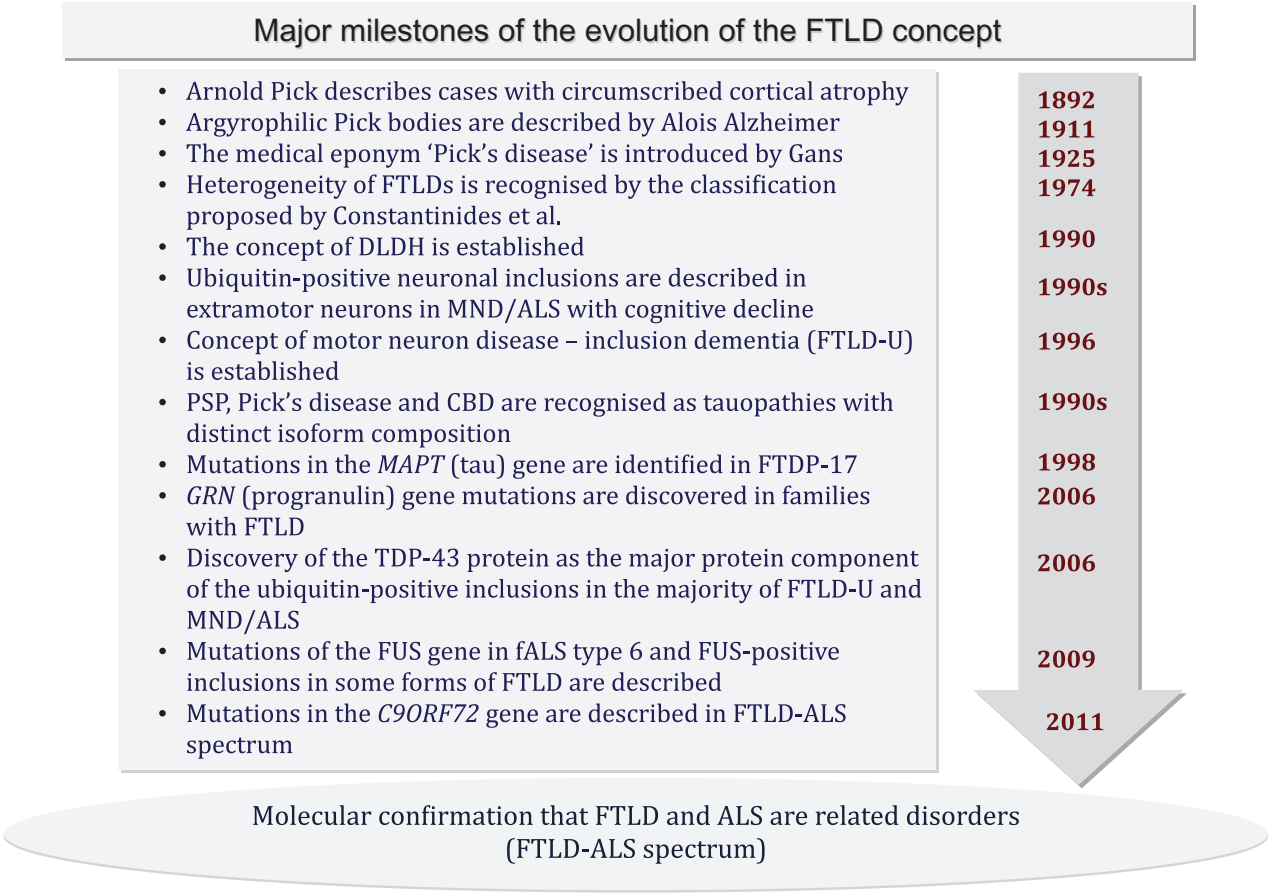

Figure 1. Major milestones of the development of the pathological concept of frontotemporal lobar degeneration (FTLD).

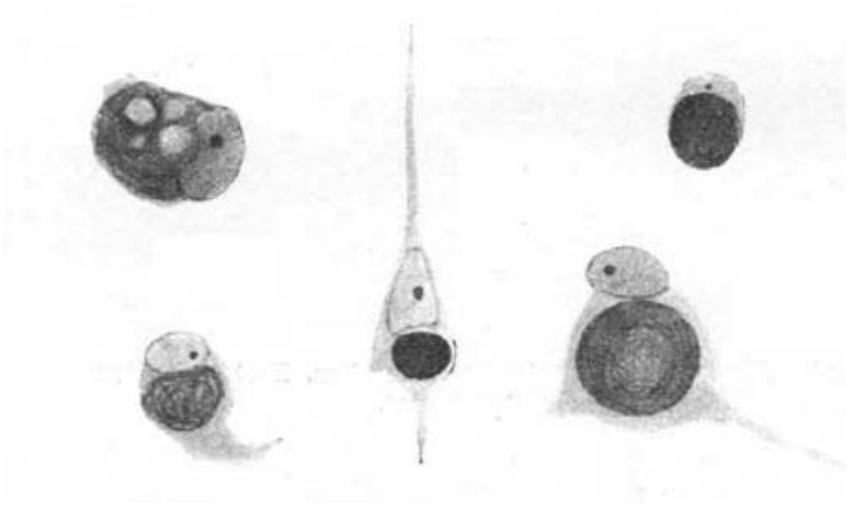

Figure 2. Illustration of argyrophilic Pick bodies by Alois Alzheimer. (Z *Gesamte Neurol Psychiatr* 1911; 4: 356–85).

speech disorder consisting of poor understanding of speech and written commands, paraphasias and partial preservation of repetition, for which Pick used Wernicke's term, 'transcortical sensory aphasia' [10]. *Post mortem* examination, performed by Pick's pathologist colleague Chiari, confirmed cerebral atrophy, which was more prominent in the left than in the right hemisphere and Pick postulated that the particularly severe atrophy of the left superior temporal gyrus ('*atrophia cerebri praecipue haemisphaerii sin. in regione gyri primi lobi sphenoidalis*') was responsible for his patient's aphasia [10]. Pick's original paper provided no detailed microscopic description and the argyrophilic globular neuronal cytoplasmic inclusions, subsequently named as Pick bodies and are considered pathognomonic of Pick's disease (PiD) today, were described and illustrated by Alois Alzheimer in 1911 (Figure 2) [11]. As a result of clinicopathological observations a new disease entity was gradually emerging, and in 1925 the medical eponym PiD was first introduced by A. Gans as 'Ziekte van Pick' in the Dutch [12], and a year later by Onari and Spatz, who were aware of Gans's work, as 'Picksche Krankheit' in the German medical literature [13].

In the following decades, the clinical and neuropathological heterogeneity of cases with frontotemporal lobar atrophy became apparent, which was also supported by findings indicating that argyrophilic Pick bodies were present only in about 20% of larger case series [14]. The neuropathological classification of PiD, put forward by Constantinidis and his colleagues in 1974 [15], was based on this notion of clinical and morphological heterogeneity of a disease for which the umbrella term PiD was still used. These authors distinguished three major categories of PiD on the basis of the distribution of the pathology and the presence or absence of swollen, achromatic neurons (Pick cells) and the argyrophilic Pick bodies. Cases with both Pick bodies and Pick cells were classified as group A, cases that only possessed swollen neurons belonged to group B, while both Pick cells and Pick bodies were absent in group C. The striking absence of either Pick bodies or Alzheimer-type pathological changes in the majority of cases with FTD was also emphasized in the subsequent pioneering studies of the research groups of Lund and Manchester Universities [16,17]. A pattern of pathological changes was also identified in such cases, which includes loss of neurons accompanied by gliosis and microvacuolation of the neuropil in superficial cortical laminae without amyloid plaques, neurofibrillary tangles or other 'silver positive' changes (for a review see [18]). In keeping with the 'nonspecific' nature of such pathology, the term 'dementia lacking distinctive histological features' (DLDH) was also coined and subsequently widely used [19]. During the 1990s, as a prelude to the molecular understanding of FTLDs, ubiquitin-positive inclusions were recognized in extramotor cerebral structures such as neurons of the dentate fascia or the frontal and temporal cortices in cases with MND/ALS with associated FTD [20,21]. The link between ubiquitin-immunoreactive extramotor neuronal cytoplasmic inclusions, initially described in MND/ALS, and FTLD was subsequently firmly established

by the recognition that such inclusions also occur in cases with progressive FTD, but without clinical evidence of either upper or lower motor neuron involvement, which resulted in the introduction of the FTLD with ubiquitin-positive inclusions (FTLD-U) concept [22], subsequently underpinned by several clinicopathological studies [23–26]. This knowledge gave the impetus for pathological studies to be performed, which demonstrated that ubiquitin-positive inclusions are characteristic perhaps in a majority of clinically well-documented FTD cases [23,26] and that the neuropathological diagnosis of DLDH is only rarely justified [26–28]. The following two decades witnessed several landmark discoveries. In the 1990s, the tau isoform composition of sporadic tauopathies, such as PiD, PSP and corticobasal degeneration (CBD) [29–31], which according to the currently used classification system are part of the FTLD-tau spectrum [32], was identified. Furthermore, in 1998, mutations in the microtubule-associated protein tau gene (*MAPT*) were reported, indicating that a significant proportion of hereditary FTDs, previously linked to chromosome 17 (17q21–22), is due to mutations in this gene [33,34]. Further landmark discoveries include the recognition that TDP-43 is the main component of the ubiquitin-positive inclusions in the majority of the FTLD-U cases and MND/ALS [35]. Involvement of TDP-43 in both FTLD-TDP and MND/ALS also provided a firm molecular link between FTLD and MND/ALS underpinning the notion that these two large groups of neurodegenerative disorders represent two, often overlapping ends of a disease spectrum. This is also supported by clinical data indicating that about 30% of patients with FTD develop clinical signs of MND/ALS and that 50% of MND/ALS patients show some evidence of cognitive deficits [36]. In addition to the *MAPT* gene, a number of further genes associated with different forms of familial FTD and/or MND/ALS was identified, including the progranulin (*GRN*) gene, whose mutations are responsible for Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). FTDP-17 in families without harbouring an *MAPT* mutation [37,38] or the much rarer mutations in the valosin-containing protein (*VCP*) gene in familial FTD [39] also associated with Paget's disease and inclusion body myositis [40], *TARDP* and *FUS* genes in MND/ALS [41,42], as well as the *CHMP2B* gene in familial FTD linked to chromosome 3 (FTD-3), described in a Danish pedigree [43]. The discovery in 2011 that intronic hexanucleotide (GGGGCC) repeat expansion in the *C9orf72* gene is a common genetic cause of ALS/MND and FTLD (C9FTD/ALS), is a recent addition to the list of genes whose mutations play an important role in FTLD [44,45]. This rapid increase in knowledge also allowed that a molecular classification of FTLDs has become available (Figures 1 and 3), which is now widely accepted and used [32,46].

Clinical concept of FTD

After the publication of Pick's original paper in the late 19th century, further publications documented that patients with circumscribed cerebral atrophy had both personality change and language impairment consistent with the modern day split of FTD into behavioural and language variants. However, despite these descriptions the early 20th century saw limited reports of such cases in the Western world, although in Japan the disorder Gogi aphasia (a progressive language disorder) was described in the 1940's [47].

The first modern accounts of the progressive language disorders in the Western literature were by Warrington [48] and Mesulam [49]. Warrington described the selective impairment of semantic memory in a group of patients, although she did not use the term semantic dementia, which was coined a number of years later [1,50]. Mesulam independently described a group of patients with progressive language problems initially calling them 'slowly progressive aphasia without generalized dementia' [49], and then later 'primary progressive aphasia' (PPA) [51], a term that has stuck to this present day. Around the same time period, in the late 1980s and early 1990s, a group of researchers came together to start to understand better the bvFTD. This led to the first International Conference of Frontal Lobe Degeneration of non-Alzheimer type in Lund, Sweden and subsequently a set of diagnostic criteria in 1994 [52].

The late 1990s and early 2000s saw a flowering of FTD research. One of the keys to this was the development of criteria for both the behavioural and language variants by a group of researchers in the field in 1998 [1]. These criteria coined the term FTLD and defined a behavioural variant (called FTD) and two variants of progressive aphasia: PNFA and semantic dementia. Arguments over the nosology of these language variants has continued over the years and in 2004, a third variant was described by Gorno-Tempini *et al.*, called logopenic aphasia (LPA) [53]. More recently, this variant was incorporated into a

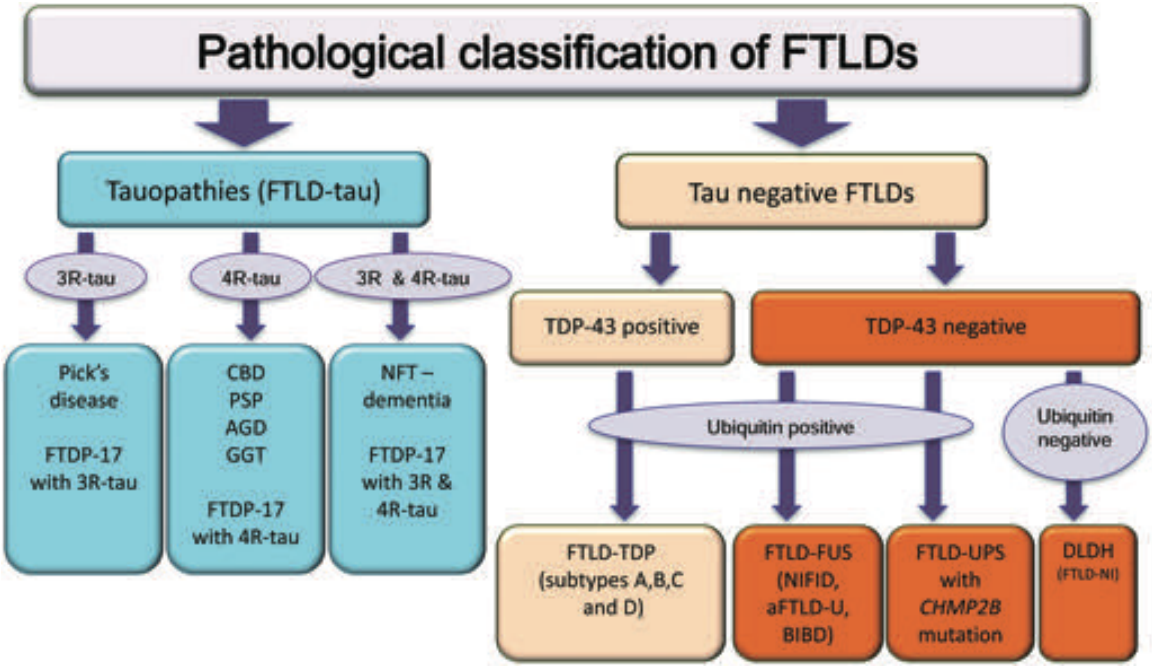

Figure 3. A schematic illustration of the pathological classification of frontotemporal lobar degenerations. Current classification is based on the molecular features of the disease-associated, inclusion forming proteins, morphological phenotypes and genetic data (for description of the different disease groups and individual diseases see text). 3R-tau, three-repeat tau; 4R-tau, four-repeat tau; aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin immunoreactive neuronal inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histology; FTLD, frontotemporal lobar degeneration; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; GGT, globular glial tauopathy, NFT-dementia, neurofibrillary tangle dementia; NIFID, neuronal intermediate filament inclusion disease.

new set of diagnostic criteria for the progressive language disorders (PPA), which were renamed, the nonfluent/agrammatic variant, the semantic variant and the logopenic variants of PPA [53]. Around the same time, an international consortium came together to update the diagnostic criteria for the behavioural variant, now known as bvFTD [54].

bvFTD is characterized by a set of behavioural symptoms including disinhibition, apathy, abnormal appetite (commonly a sweet tooth), loss of empathy and obsessive-compulsive behaviour. However, patients also develop cognitive impairment, usually executive dysfunction initially, but other cognitive domains also become involved as the disease progresses. Patients with nonfluent variant of PPA develop agrammatism and/or apraxia of speech, while those with the semantic variant develop anomia and impaired single word comprehension, later developing nonverbal semantic impairment as well; the LPA variant is characterized by word-finding pauses and impaired working memory.

Neither of the current diagnostic criteria describes the overlap of FTD with MND/ALS or the atypical parkinsonian disorders, CBS and PSP. The overlap with these disorders has been increasingly recognized in recent years with a substantial proportion of bvFTD patients (and a smaller number of nonfluent aphasia cases) developing MND/ALS or parkinsonism at some point during the disease process.

Genetics of FTD

A family history of a similar disease is common in FTD, typically in a pattern that suggests dominant inheritance [5]. In populations of European ancestry, there are three major FTD disease genes (*MAPT*, *GRN* and *C9orf72*) and many rarer disease genes. It is also recognized that mutations in genes more commonly associated with related neurodegenerative diseases such as Alzheimer's disease, MND/ALS, Parkinson's disease or prion disease can be found in patients with clinical diagnoses of FTD. The frequency of mutations in specific regions or clinical centres

varies according to population factors such as founder effects, drift and migration; however, typically, a clinic will find high single digit percentages of all FTD are explained by each of the three major genes individually. A substantial proportion of familial FTD, depending on how this is defined, remains unexplained [5]. A core clinical and pathological phenotype is recognized for each gene, although clinical distinction is imperfect, particularly in the early stages when gene testing is discussed with patients and their families. Gene panel technologies are now available to screen all known common and rare FTD genes simultaneously [55,56].

In pedigrees with several affected individuals, the location of the responsible gene can be narrowed by genetic linkage using markers across the genome. The region including the *MAPT* gene on chromosome 17 was first linked with familial FTD in 1994 [57], and mutations in this gene were first described in 1998 [33]. *MAPT* gene mutations are typically associated with bvFTD. Associated syndromes can include parkinsonism, aphasia, early amnesia and semantic problems. Over 50 different causal mutations are now known. They fall into two broad categories: missense mutations, which alter the amino acid code of the protein usually in or near to the fourth repeat region of the microtubule-binding domains (see later), and splice site mutations, which alter the inclusion of exon 10 [58]. Common genetic variation near to the *MAPT* gene is a risk factor in PSP and Parkinson's disease [59], but not FTD.

Mutations in the *GRN* gene, coincidentally near to *MAPT* on chromosome 17, were identified as causal of FTD in 2006 [37,38]. The protein product, progranulin, is a secreted glycoprotein, cleaved into granulin peptides and found in the brain and serum with roles in inflammatory diseases, diabetes and obesity [60]. Complete loss of progranulin protein is associated with neuronal ceroid lipofuscinosis [61]. Like *MAPT* mutations, they are most commonly associated with the bvFTD; however, nonfluent aphasia, CBS and other Parkinsonian syndromes have been reported. Over 150 variants of *GRN* have been reported in patients [62]. The large majority of mutations are premature stop codons, splice site, exon/gene deletions or frameshift mutations, which result in a hemi-loss of functional protein. Serum levels of progranulin are reduced by ~50% in mutation carriers. Most of the missense changes in *GRN*, aside from those in or near to the transcription initiation codon are classified as variants of unknown significance. Variants of *TMEM106b* modify the clinical phenotype of *GRN* mutation associated FTD [63].

The *C9orf72* gene on chromosome 9 has a hexanucleotide repeat region located in either in the promoter or intron 1 of the gene (depending on the transcript variant). When massively expanded, the mutation causes FTD, MND/ALS or the combined syndrome [44,45]. Particularly high frequencies of the *C9orf72* expansion mutation are found in Finland because of a founder effect [64]. Although the repeat region is variable in length in the healthy population (up to around 30 repeats), repeat expansions typically seen in patients are far more massively expanded, typically >400 repeats [44,65,66]. We still do not have certainty about the smallest hexanucleotide expansion that confers risk. The core clinical phenotype is the combination of FTD and MND/ALS; however, the expansion mutation is commonly associated with pure FTD, pure MND/ALS and may be reported in patients labelled with AD, movement disorders, ataxias and nonspecific neuropsychiatric/neurodegenerative syndromes (for a review see [67]). No other mutation types have been reported in the gene and the function of the C9orf72 protein is not well understood.

Mutations in several other genes have been uncommonly associated with FTD. These might best be classified as rare gene mutations, which typically cause FTD (*CHMP2B* and *VCP*, the latter in association with inclusion body myopathy and/or Paget's disease of bone), or more common gene mutations associated with neurodegeneration, but rarely the FTD phenotype (Alzheimer's disease genes: *PSEN1*, *APP*; prion disease gene: *PRNP*; ALS genes: *FUS*, *TARDBP*; others: *CSF1R*).

Neuropathology of FTLD – an overview of current classification

As a result of recent advances in the understanding of the molecular mechanisms associated with FTLDs, this heterogeneous group of diseases are now subdivided pathologically on the basis of the deposited abnormal intracellular protein aggregates [32,46,68] (Figure 3). In approximately 40% of all FTLD cases the microtubule-associated protein tau forms inclusions in neurons, and in some diseases, in both neurons and glial cells (both astrocytes and oligodendrocytes) (FTLD-tau). With the exception of a small minority of the cases, the tau-negative cases have neuronal inclusions, which were originally identified by their immunoreactivity for

ubiquitin (FTLD-U) [22,27,69]. The majority of the FTLD-U cases are associated with accumulation of TDP-43 [35], and the term FTLD-TDP is assigned to this group [32,46]. In a smaller group of the FTLD-U, the inclusions are positive for the FUS protein (FTLD-FUS) [32,70,71], and such cases are responsible for the majority of tau and TDP-43-negative FTLDs representing about 5–10% of ubiquitin-positive FTLDs. FTLD-FUS includes three diseases, neurofilament inclusion body disease (NIFID), atypical FTLD-U (aFTLD-U) and basophilic inclusions body disease (BIBD) [70–73]. Two neuropathological subtypes still remain elusive; one primarily representing familial FTLD with *CHMP2B* mutation (FTD-3) and with ubiquitin-positive inclusions, which are negative for tau, TDP-43 or FUS and is now termed FTLD-UPS, and a second group, termed FTLD-ni, which contains rare cases with no discernible pathological inclusions [32].

FTLD-tau

The natively unfolded tau protein with a suggested role in microtubule assembly and stabilization as well as regulation of axonal transport, is the most commonly misfolded protein forming intracellular inclusions in human neurodegenerative diseases [74]. Tauopathies are responsible for a major group of FTLDs, designated as FTLD-tau [32], which represents a clinically, biochemically, genetically and pathologically heterogeneous group of diseases with the overarching feature that all forms possess abundant neuronal, and in some variants, both neuronal and glial filamentous inclusions. These are composed of abnormally hyperphosphorylated form of tau in the absence of amyloid-β deposits [74,75]; hence, they are 'primary' tauopathies [76]. In addition to tau phosphorylation, which is an early event of tau aggregation, a number of other post-translational modifications of tau are also known. These include ubiquitination, acetylation, glycation, glycosylation with O-linked N-acetylglucosamine (O-GlcNAcylation), nitration, sumoylation, and truncation, which are also thought to be associated with the aggregation process [58]. It is widely accepted that the inclusions contribute to disease pathogenesis in tauopathies as they occur in specific brain regions whose functions are altered by the tau pathology [77]. In this regard, formation of tau aggregates and filaments, which possess a cross-β structure characteristic of amyloid fibrils, is a highly relevant process [58], which is also supported by experimental data indicating that tau aggregates can induce neurotoxicity [78] and are associated with nerve cell dysfunction [79].

The current molecular classification of FTLD-tau is based upon genetics and the biochemical composition of the inclusions. FTLD-tau includes patients with *MAPT* gene mutations (FTD and parkinsonism linked to chromosome 17 or FTDP-17 *MAPT*), PiD, PSP, corticobasal degeneration (CBD), argyrophilic grain disease (AGD), globular glial tauopathy (GGT) and NFT-dementia, which was recently redefined (somewhat controversially [80]) and designated as primary age-related tauopathy or PART (Figures 3 and 4) [32,81–84]. It should be noted that the clinical presentation is not that of FTD in the majority of AGD and PART cases. Although both PSP and CBD are clinically often referred to as atypical Parkinsonian disorders, they are now recognized as disorders of both movement and cognition [85–89]. It is well documented that both CBD and PSP patients may present with bvFTD [88–92] or language impairment (PSP-FTD variants) [89,92–94]. It is of note that the 'cortical' PSP variants, which, in addition to PSP-FTD also include PSP-CBS (PSP with CBS), are associated with increased neocortical tau load due to a shift of the tau burden from the basal ganglia towards the cerebral cortices [95–97]. An intriguing aspect of several protein folding neurodegenerative disorders is clinical disease progression, which is thought to be due to a stereotypic spatial, time dependent expansion of the underlying pathology. Data from Alzheimer's disease indicate that clinical progression is dependent on such an anatomical progression of the neurofibrillary tau pathology, described by the Braak and Braak staging system, which is widely used in neuropathological practice [98]. Recent experimental data indicate that tau can show prion-like propagation and spread, which is consistent with pathological disease progression in human disease [74]. However, apart from AGD [99], staging of tau pathology has not been established in other forms of FTLD-tau such as PiD, CBD and PSP despite significant advancement in recognizing disease subtypes.

FTLD-tau can be divided on the basis of the predominant tau species making up the inclusions. The six tau isoforms, which are expressed in the adult human brain, are produced by alternative mRNA splicing from the *MAPT* gene [100,101]. The isoforms differ from one another by whether they possess 0, 1 or 2 29-amino-acid-long N-terminal inserts, encoded by exons 2 and 3 and by the presence or absence of a fourth 31-amino-acid-long repeat

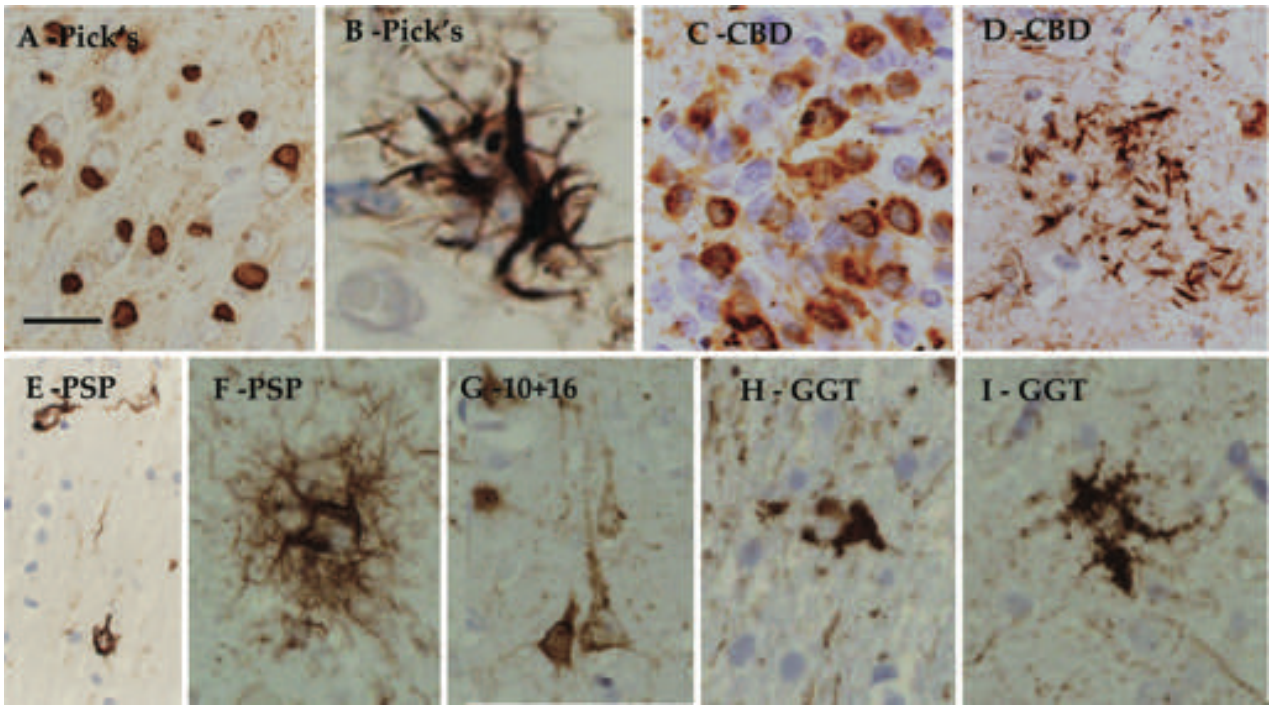

Figure 4. Examples of tau pathology in some of the diseases comprising frontotemporal lobar degeneration (FTLD-TAU). Tau immunohistochemistry demonstrates typical Pick bodies in the granular cell layer of the dentate fascia (A). The glial pathology in Pick's disease includes ramified astrocytes (B). Pretangles in the granular cell layer of the dentate fascia (C) together with a characteristic astrocytic plaque (D) in corticobasal degeneration (CBD). Four-repeat tau-positive coiled bodies in white matter (E) and tufted astrocytes in grey matter structures (F) are characteristic pathological features of progressive supranuclear palsy (PSP). FTDP-17 due to mutations of the microtubule-associated protein tau (*MAPT*) gene have a number of pathological variants, determined by the localization of the mutations; cases with an exon 10+16 intronic mutation also show extensive four-repeat tau-positive glial pathology and numerous pretangles and neurofibrillary tangles (G). Globular glial tauopathy (GGT) is characterized by the presence of globular glial inclusions, including globular oligodendroglial inclusions (H) and globular astrocytic inclusions (I). AT8 immunohistochemistry, bar on A represents 40 microns on A and E; 20 microns on C, D E–I and 5 microns on B.

in the microtubule-binding domain of tau, encoded by exon 10. Two major groups of the six tau isoforms, each group containing three isoforms, can be differentiated on the basis of whether the repeat encoded by exon 10 is present or absent. Isoforms with four-repeat sequences are designated as 4-repeat-tau (4R-tau) while those without this sequence are called 3-repeat tau (3R-tau) [100]. In PiD [30] and some forms of FTDP-17 *MAPT* [102] 3R-tau is the predominant protein species in the tau filaments making up the inclusions, whereas 4R-tau assembles into filaments in CBD, PSP, GGT, AGD and some FTDP-17 *MAPT* variants [102–105]. In a third group of diseases, which includes NFT-dementia and some FTDP-17 *MAPT* variants, both 3R-tau and 4R-tau are present in the inclusions (for a recent review see [102]). The differences in the tau isoform composition of the tau filaments are also reflected by characteristic differences in the ultrastructural morphologies of the filaments [106].

For diagnosis *post mortem* microscopic investigation of the brain, including demonstration of the characteristic neuronal and if present glial inclusions, by tau, and if necessary, supplemented by 3R-tau and 4R-tau immunohistochemistry (Figure 4) together with documentation of the anatomical distribution of the tau lesions, is required. Microscopic studies may need to be supplemented with genetic and biochemical investigations in some cases, especially if a familial FTLD-tau variant is suspected. Although there is significant overlap between different forms of FTLD-tau, the presence of characteristic morphological features associated with the different tauopathies allows a specific diagnosis to be made in the majority of the cases. The presence of Pick bodies in PiD or other relevant neuronal and thread pathology in combination with characteristic glial inclusions, such as astrocytic plaques in CBD, tufted astrocytes in PSP, ramified astrocytes in PiD or numerous globular oligodendroglial

Table 1. Correlations between clinical presentation, genetics and pathology in different subtypes of frontotemporal lobar degeneration

Clinical presentation	*Brain pathology*		*Gene*	*References*
bvFTD	FTLD-tau	Pick's disease		[89,92,169,170]
		MAPT mutations	*MAPT*	[89,170]
		CBD		[89,92,170]
		GGT		[83,84]
	FTLD-TDP	Type A	*GRN, C9orf72*	[89,170]
	FTLD-TDP	Type B	*C9orf72*	[170]
	FTLD-TDP	Type C		[170]
	FTLD-TDP	Type D	*VCP*	[89]
	FTLD-FUS	NIFID		[89,158]
		aFTLD-U		[89,158]
Semantic dementia	FTLD-tau	Pick's disease		[89,169,170]
	FTLD-TDP	Type C		[89,170]
FTLD-MND	FTLD-tau	GGT		[83,84]
	FTLD-TDP	Type A		[89,170]
	FTLD-TDP	Type B	*C9orf72*	[89,170]
PNFA	FTLD-tau	Pick's disease		[89,92,169,170]
		CBD		[89,92,170]
		PSP		[170]
	FTLD-TDP	Type A	*GRN, C9orf72*	[89,170]
	FTLD-TDP	Type B	*C9orf72*	[170]
PSPS	FTLD-tau	*MAPT* mutations	*MAPT*	[171]
		CBD		[88,172]
		PSP		[89,92,170]
		GGT		[83,84]
	FTLD-FUS	NIFID		[158]
CBS	FTLD-tau	*MAPT* mutations	*MAPT*	[89]
		CBD		[88,89,92,170]
		PSP		[89,92,96,97,170]
		GGT		[83,84]
	FTLD-TDP	Type A		[89]
	FTLD-FUS	NIFID		[156,158]

aFTLD-U, atypical frontotemporal dementia with ubiquitin-positive inclusions; bvFTD, behavioural variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72; CBD, corticobasal degeneration; CBS, corticobasal syndrome; FUS, fused in sarcoma; GGT, globular glial tauopathy; GRN, progranulin; MAPT, microtubule-associated protein tau; MND, motor neurone disease; NIFID, neuronal intermediate filament inclusion disease; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; PSPS, progressive supranuclear palsy syndrome; TDP, transactive response DNA-binding protein; VCP, valosin containing protein.

and astrocytic inclusions in GGT are important helpers of the morphological diagnosis (Figure 4) (for a review see [107]). The FTDP-17 *MAPT* variants may show similarities to PiD, PSP, CBD, AGD or GGT and variability within the same family is also known [58]. For correlations between clinical presentation, genetics and pathology see Table 1.

FTLD-TDP

The discovery demonstrating the TDP-43 protein as the main component of the ubiquitin-positive inclusions in the majority of FTLD-U, designated as FTLD-TDP, and also in MND/ALS (ALS-TDP) resulted not only in a better understanding of the pathogenesis of these diseases, but this has also provided further support for a molecular classification of FTLDs [35]. TDP-43 is a highly conserved and ubiquitously expressed multifunctional, heterogeneous nuclear ribonucleoprotein (hnRNP), encoded by the *TARDBP* gene located on chromosome 1. TDP-43 possesses nuclear localization and nuclear export signals and it shuttles between the cell nucleus and cytoplasm. TDP-43 also has an N-terminal domain, two RNA-recognition motifs (RRMs) involved in RNA and DNA binding and its glycine-rich C-terminal region contains most of the mutations causing familial MND/ALS and rarely familial FTD [108,109]. The C-terminal region of TDP-43 contains a prion-like protease resistant domain [110]. TDP-43 protein expression is tightly controlled by

autoregulatory mechanisms and both over and under expression results in impaired neuronal function [111]. Cellular functions of TDP-43 include regulation of RNA splicing, translation, miRNA processes and mRNA transport and stability [112] with more than 6000 RNA targets. The aggregation of TDP-43 is associated with several post-translational modifications including phosphorylation of serine residues, ubiquitination, oxidation, lysine acetylation and C-terminal cleavage. Pathological examination, utilizing antibodies specific for phosphorylated TDP-43 (pTDP-43) confirms that the cellular TDP-43 aggregates contain phosphorylated epitopes [113]. In disease TDP-43 aggregates can accumulate in both the cytoplasm and nuclei of affected neurons and glia, which results in cellular dysfunction. There is now evidence to suggest that TDP-43 in inclusions, the majority of which have been shown to show amyloid features [114], has cellular prion-like properties, which could have relevance for the pathomechanism of FTLD-TDP [115]. The disease-associated TDP-43 making up the inclusions, is thought to exercise its deleterious effect via toxic gain of function due to overexpression or mutant forms, but given the number of its functions it is also likely that a loss of function effect also has a role in the pathogenesis of FTLD-TDP. FTLD-TDP has recently been reported to be associated with chronic traumatic encephalopathy [116]. TDP43-positive inclusions are also found in around 90% of patients with hippocampal sclerosis, which is also a feature in the majority of FTLD-TDP suggesting a special relationship between these two pathologies [117,118].

FTLD-TDP subtypes

Subtypes of FTLD-U were originally established, using findings of ubiquitin immunohistochemistry, and two major classification systems were in existence [69,119]. One of the strengths of these classifications is that they have been validated by clinical, genetic and pathological correlations. In order to eliminate competing classifications a single harmonized system was proposed in 2011, which has gained wide acceptance [120]. Accordingly, the four different subtypes of FTLD-TDP, which are recognized, are based on the predominant lesion type(s) and the distribution of the pathological inclusions. The TDP-43 immunoreactive inclusion types considered include neuronal cytoplasmic inclusions (NCIs), neuronal intranuclear inclusions (NIIs), oligodendroglial inclusions and dystrophic neurites (DNs). Neurons containing TDP-43-positive inclusions lose their normal nuclear TDP-43 staining that can be observed in neurons without an inclusion, which in every day neuropathological practice is a helper of identifying affected neurons (Figure 5). FTLD-TDP type A is characterized by numerous NCIs, DNs and variable numbers of NIIs and the TDP-43 immunoreactive lesions are most numerous in layer 2 of affected cortices. FTLD-TDP type B is characterized by numerous NCIs in both the superficial and deeper cortical layers, but this subtype can exhibit the occasional DNs. FTLD-TDP type C is associated with abundant long DNs often with a corkscrew appearance throughout the cortical layers. Some TDP-43 type C cases are associated with corticospinal tract degeneration [121]. FTLD-TDP type D is characterized by numerous NIIs, DNs and infrequent NCIs (Figure 5) [122,123]. It remains unclear whether differences in underlying pathophysiology or selective neuronal vulnerability determine the distinction between the FTLD-TDP subtypes via a single pathogenic mechanism or whether there are multiple mechanisms involved. For correlations between clinical presentation, genetics and pathology see Table 1.

FTLD-TDP in familial FTD

TDP-43 pathology is characteristic not only in sporadic, but also in some of the familial forms. In cases with mutations in the *GRN* gene FTLD-TDP type A is the characteristic morphology, while FTLD-TDP type D is restricted to cases with mutations in the *VCP* gene. The majority of the FTLD cases with *C9orf72* repeat expansion mutations show FTLD-TDP type B pathology, but a proportion of them have changes consistent with type A and rare cases with type C pathology have also been reported [121,124,125]. Families with pathogenic mutations in both the *GRN* and the *C9orf72* genes have been documented [126,127].

The characteristic aspect of the pathology of C9FTLD/ALS cases is the presence of star-like p62/sequestosome-1-positive, but TDP-43-negative NCIs in the hippocampus (granule cell layer and CA4 hippocampal subregion) and cerebellar cortex (cerebellar granule cells) (Figure 6) [44,125,128,129], which are also positive for ubiquitin and the ubiquitin-binding protein ubiquilin-2. The high frequency of *C9orf72* repeat expansion in both FTD and ALS has generated great interest in the underlying mechanisms in these diseases, of which several nonmutually

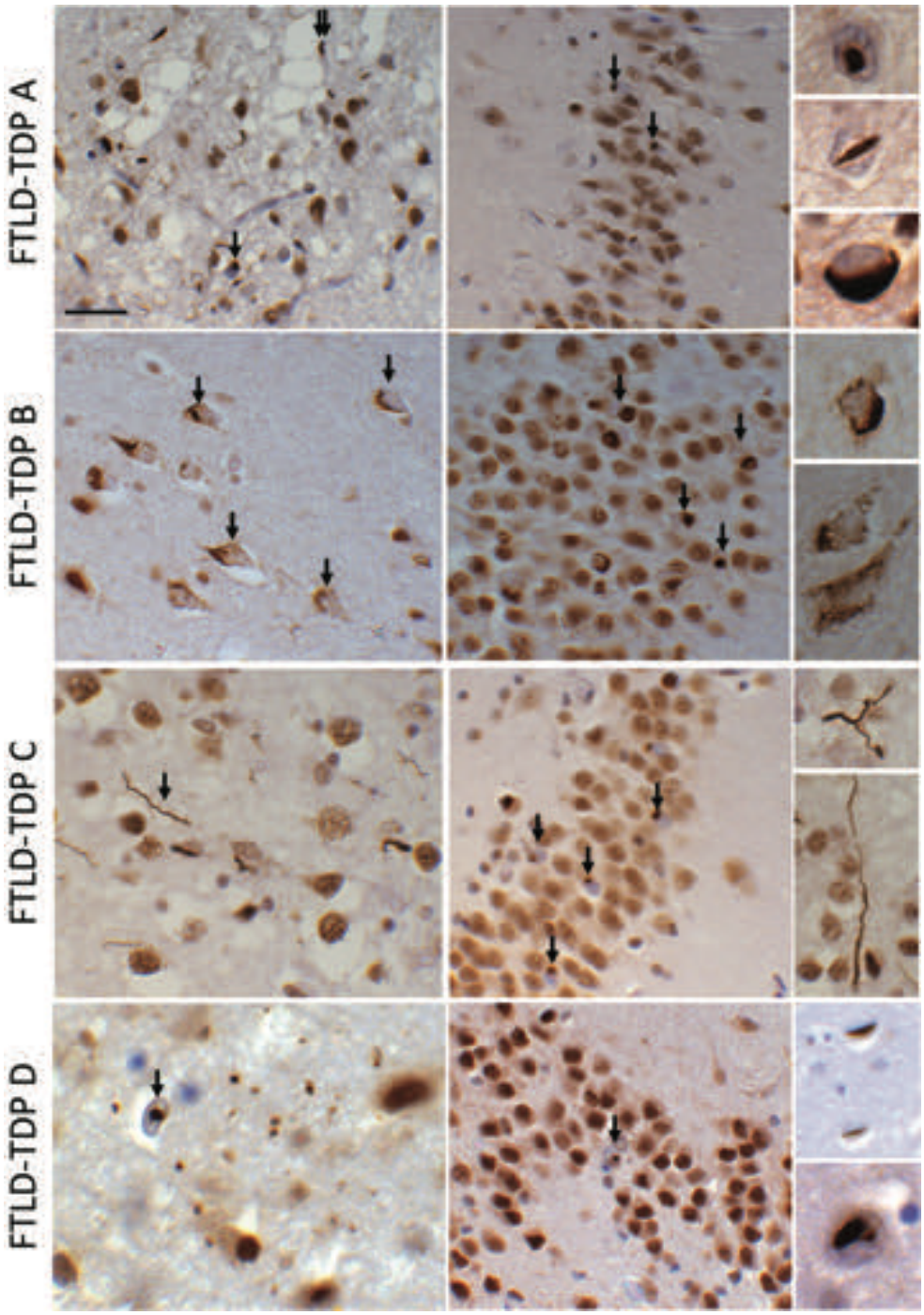

Figure 5. Morphological features of frontotemporal lobar degeneration-transactive response DNA-binding protein (FTLD-TDP) subtypes A, B, C and D. The separation of the different FTLD-TDP subtypes is based on the microscopic features of a number of different TDP-43-positive inclusion types. In FTLD-TDP type A neuronal cytoplasmic inclusions (arrows), short dystrophic neurites and neuronal intranuclear inclusions are characteristic. In FTLD-TDP type B neuronal cytoplasmic inclusions, often with somewhat granular appearances, are seen and the inclusions are present in all cortical layers. FTLD-TDP type C is characterized by unique, long corkscrew-type neurites (arrow). FTLD-TDP type D shows numerous neuronal intranuclear inclusions (arrow) and short neurites while neuronal cytoplasmic inclusions are rare. TDP-43 immunohistochemistry, bar on top panel represents 40 microns on all large panels and FTLD-TDPC inserts; 10 microns on all other inserts.

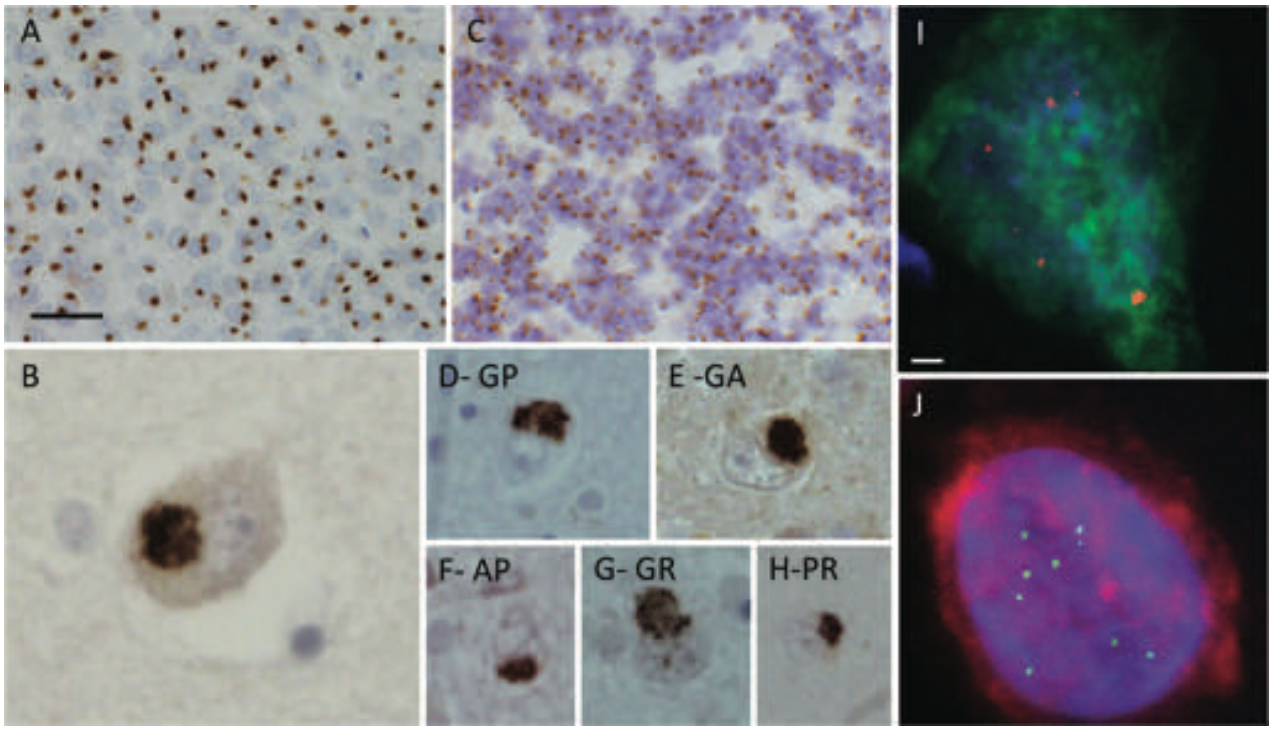

Figure 6. Dipeptide repeat pathology in chromosome 9 open reading frame 72 (*C9orf72*) repeat expansion cases. All cases carrying a *C9orf72* expansion repeat mutation contain additional p62-positive, transactive response DNA-binding protein (TDP)-43-negative neuronal cytoplasmic inclusions. These inclusions are composed of dipeptide repeat proteins, which are translated from the *C9orf72* expansion repeats. The p62-positive inclusions are numerous in the granule cell layer of the dentate gyrus (A) and are prominent in areas including the CA4 hippocampal subregion (B) and the cerebellar granule cells (C). Antibodies have also been raised against the 5 dipeptides [antisense: Pro-Arg (H), Pro-Ala (F); sense: Gly-Ala (E), Gly-Arg (G); antisense or sense Gly-Pro (D)], which show that all dipeptides are present in the p62 positive inclusions. Representative images of frontal cortex tissue from heterozygous *C9orf72* cases with RNA fluorescent in-situ hybridisation (FISH) for sense foci (*red, **I***) or antisense foci (*green, **J***) with immunostaining for neurons with NeuN (*green in **I**, red in **J***) and nuclear DNA staining with 4′,6-diamidino-2-phenylindole (DAPI) (*blue*). Bar on A represents 40 microns on A and C; 20 microns on D–H; 10 microns on B. Scale bar in I represents 2 μm on I and J.

exclusive possibilities exist (for a review, see [130]). One of the mechanisms is RNA-related toxicity, based on evidence from microsatellite expansion diseases with large repeat expansions. In these disorders, the transcribed repeat RNA aggregates in the nucleus in discrete structures termed RNA foci, which sequester select RNA-binding proteins resulting in loss of their function, ultimately leading to disease. RNA foci have also been identified in C9FTD/ALS neurons [44] and, as the GGGGCC repeat expansions are bidirectionally transcribed, the RNA foci are formed of both sense and antisense transcripts, typically found in separate cells, but they can also co-localize in the same nucleus [131,132]. The possibility between high RNA foci burden and early age of disease onset has been raised [131,133]. Although the precise function of the C9orf72 protein is not known, it has been shown to be structurally related to a class of GDP/GTP exchange factors that activate Rab-GTPases, suggesting that it may have a role in vesicular trafficking [134]. The possibility that toxicity is, at least partly due to a decrease/loss of the function of the C9orf72 protein is considered and such a hypothesis is supported by findings of decreased levels of GGGGCC repeat-containing transcripts in C9FTD brains [44,135]. A third mechanistic option is that both the sense and antisense transcripts of the GGGGCC expansion repeats are translated via the mechanism of RAN (repeat-associated non-ATG) translation into C9RANT (RAN-translated) protein aggregates (antisense: Pro-Arg, Pro-Ala, Pro-Gly; and sense: Gly-Ala, Gly-Arg, Gly-Pro), which form the dipeptide repeat proteins found in the p62-positive inclusions and thought to contribute to disease pathogenesis (Figure 6) [132,136,137]. The topographical distribution of these dipeptide repeat proteins is similar regardless of the clinical phenotype [138,139]. RAN translation is ‘unconven-

tional' mode of translation with unknown mechanism, which occurs across expanded repeat tracts in the absence of an initiating codon [140]. This mechanism has been shown in several microsatellite expansion disorders such as myotonic dystrophy, type 1 (DM1), spinocerebellar ataxia, type 8 (SCA8) and fragile X-associated tremor/ataxia syndrome (FXTAS) and data suggest that RAN translation may be a significant mechanism in C9FTD/ALS [130,132,141]. Experimental data indicate that both arginine-rich proteins and repeat RNA contribute to C9orf72-mediated neurotoxicity [131].

Disease staging and progression

There have been attempts for establishing stages of disease progression in FTLDs, which initially were based on progression of clinical signs [142] or macroscopic brain atrophy [143]. A recent study using pTDP-43 immunohistochemistry aimed to establish microscopic patterns of disease progression in bvFTD cases [144]. Four stereotypical patterns of pTDP-43 pathology suggestive of potentially sequential spreading of the TDP-43 aggregates along a fronto-occipital gradient could be established; cases with 'pattern I' had widespread pTDP-43 lesions in the orbital gyri, gyrus rectus and amygdala. In 'pattern II' there was evidence for increased pTDP-43 burden with lesions emerging in middle frontal and anterior cingulate gyrus, anteromedial temporal structures, superior and middle temporal gyri, striatum, red nucleus, thalamus and precerebellar nuclei. Cases with more advanced pathology were labelled as showing 'pattern III' with involvement of the motor cortex, bulbar somatomotor neurons and the spinal cord anterior horn while cases with 'pattern IV' pTDP-43 lesions were present in the visual cortex [144]. A previous study by the same research group suggested that in MND/ALS pTDP-43 aggregates may spread via axonal transport, initially spreading from the motor cortex towards the brainstem and spinal cord followed by cortical areas and finally towards anteromedial temporal lobe structures [145] (for a recent see review [146]).

FTLD-FUS

Introduction and FTLD-FUS subtypes

The recognition that mutations in the *FUS* gene are associated with familial MND/ALS type 6 (ALS-FUS), and that the ubiquitin-positive NCIs in motor neurons are positive for the 526-amino-acid-long, 53 kDa nucleoprotein FUS [41,42] gave the impetus for the investigation of a possible role in FTLDs.

FUS is a member of the FET family of multifunctional DNA/RNA-binding proteins and is encoded by the *FUS* gene located on chromosome 16 [147–149]. FUS is ubiquitously expressed multifunctional hnRNP, also known as hnRNP P2 [150,151]. Different regions of the protein are involved in different functions; its N-terminus is involved in transcription activation [152] while the C-terminal region contains multiple domains involved in RNA-protein interactions and contains the nuclear localization signal, which is targeted by transportin1 (TRN1) and is essential for the nuclear transport of FUS [153]. The majority of the mutations causing familial MND/ALS affects the region of the nuclear localization signal, which decrease the binding affinities of FUS for TRN1 [154]. The subcellular localization of the FUS protein is cell type dependent, for example FUS is present in proportionally larger amounts in the nucleus than in the cytoplasm of neurons while FUS expression is exclusively nuclear in glia [155]. Under normal physiological conditions the FUS protein continuously shuttles between the cytoplasm and the nucleus [150].

Neuropathological features of FTLD-FUS

The discovery that *FUS* mutations are the cause of a subgroup of familial MND/ALS gave the impetus for investigating the role of the FUS protein in sporadic, tau and TDP-43-negative, ubiquitin-positive FTLD-U cases. These studies showed that, indeed, the FUS protein is a major component of the pathological lesions in such cases comprising about 5–10% of all FTLD-U [70,71,73]. This finding gave the basis for the introduction of a third smaller FTLD group, appropriately termed FTLD-FUS, which at present includes three conditions: NIFID [71,156], aFTLD-U [70] and BIBD [73].

All three diseases classified under the umbrella term FTLD-FUS contain FUS-positive inclusions and show morphological similarities, but the differences in the inclusions types and their locations in the different brain regions is sufficient for a specific diagnosis to be made [157,158]. There are considerably more FUS-positive inclusions in NIFID compared with aFTLD-U in many

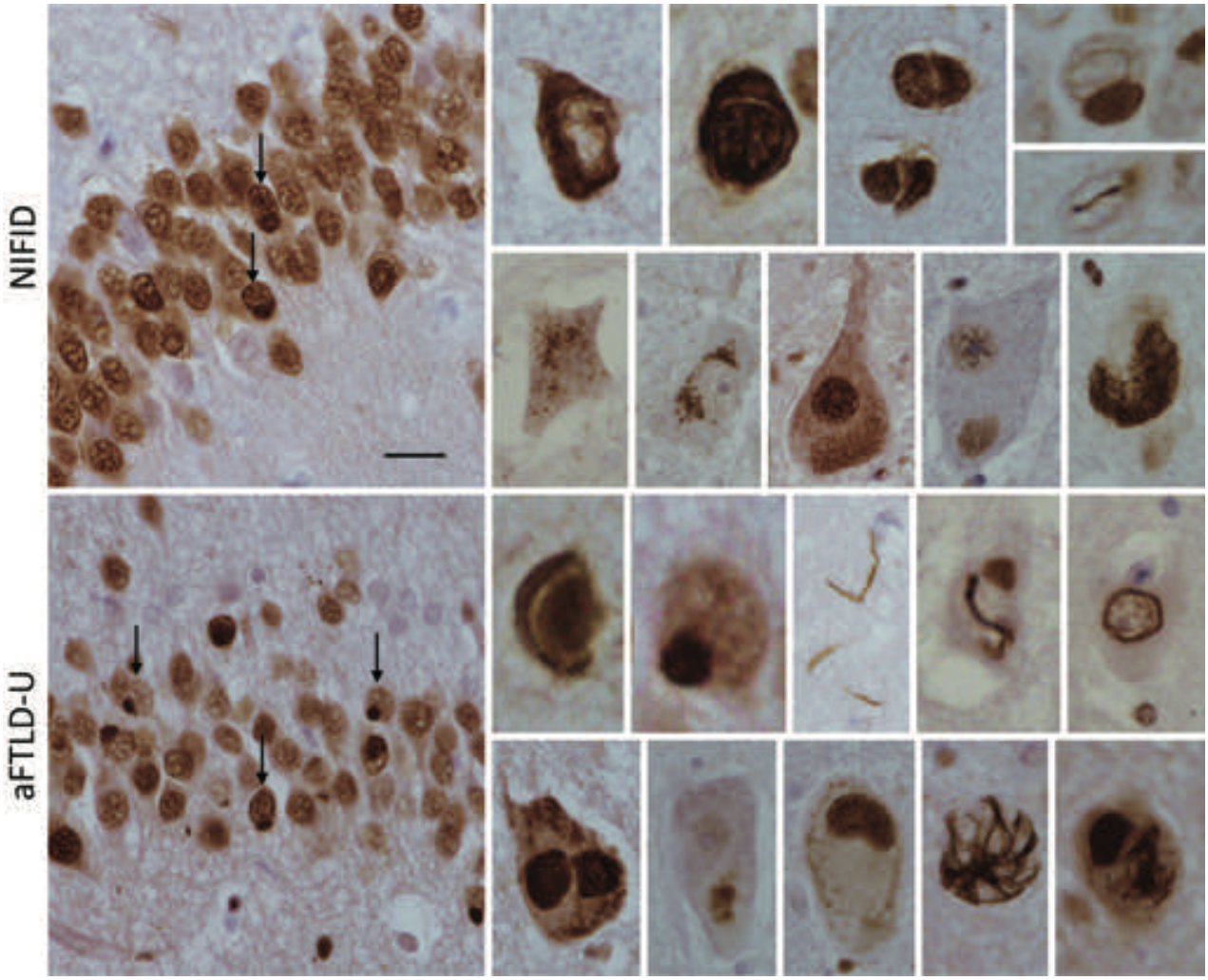

Figure 7. Fused in sarcoma (FUS) pathology demonstrated in two diseases of frontotemporal lobar degeneration (FTLD)-FUS, neuronal intermediate inclusion disease (NIFID) and atypical FTLD-U (aFTLD-U). The pathological inclusions found in FTLD-FUS are varied and diverse. Neuronal cytoplasmic inclusions of different morphological types are seen in the granule cell layer of the hippocampus in both the NIFID and aFTLD-U (arrows). FUS immunohistochemistry, bar on A represents 40 microns on granule cell layer panels and between 10 and 20 microns on the smaller panels.

anatomical regions including the cerebral cortex, medial temporal lobe structures, such as subiculum, entorhinal cortex and fusiform gyrus (but not in the granule cell layer of the dentate fascia), subcortical and brainstem nuclei [158]. It is of note that a greater cell loss has been found in these anatomical regions in aFTLD-U, which may account for the lower numbers of inclusions in these areas. Hippocampal sclerosis has been described to be a prominent feature of aFTLD-U, but only occasionally seen in NIFID [72,157–159]. Different inclusion types have been documented in all three subtypes of FTLD-FUS [70,71,157,158,160]. In NIFID, the morphology of the FUS immunoreactive NCIs is heterogeneous varying from small bean-shaped to larger annular shapes (Figure 7) [158], whereas NII were only occasionally found in NIFID cases. α-Internexin-positive inclusions are a prominent feature of all NIFID cases, although far less abundant than FUS-positive inclusions, whereas these are absent in both aFTLD-U and BIBD [157]. The FUS-immunoreactive NCIs in aFTLD-U are often compact, round or bean-shaped and vermiform NII, described previously [159], and found throughout the neocortex, granule cells of the dentate gyrus and striatum [158]. The third FTLD-FUS subtype, BIBD

shows basophilic NCIs on the haematoxylin and eosin-stained histological sections of cerebral cortices and FUS immunohistochemistry highlights widespread NCIs seen not only in cerebral cortices, but also in the basal ganglia and brainstem [73,157]. In all three FTLD-FUS subtypes, the cerebellar cortex remain unaffected. FUS-positive neuronal intranuclear inclusions have also been described in polyQ inclusions in Huntington's disease, spinocerebellar ataxia types 1, 2, 3 and dentatorubro-pallidoluysian atrophy [161,162].

The FUS-positive inclusion of NIFID, aFTLD-U and BIBD consistently contain the TATA-binding protein-associated factor 15 protein (TAF15) and variably contain the Ewing's sarcoma protein (EWS), which are other members of the FET family of proteins [163,164]. TRN1, responsible for the transport of FUS from the cytoplasm to the cell nucleus, has also been shown to be present in the NCIs and NIIs in all FTLD-FUS subgroups suggesting a role in the pathogenesis of these diseases [165]. However, TAF15 and EWS and TRN1 are not present in the inclusions in familial MND/ALS with mutations of the *FUS* gene [163,166]. For correlations between clinical presentation, genetics and pathology see Table 1.

FTLD-UPS

Mutations of the *CHMP2B* gene, located on chromosome 3, are a rare cause of hereditary FTLD. The first mutation, affecting the splice acceptor site of the sixth (last) exon, was described in affected members of a Danish kindred with FTD-3 followed by the discovery of a Q165X mutation in a Belgian FTD family. Both mutations appear to have a common mechanism; deletion of the C-terminus of the CHMP2B protein (for a review, see [167]). The CHMP2B protein is a component of the ESCRT-III complex (endosomal sorting complex required for transport-III), which has a role in protein degradation pathways.

Brains of affected individuals show marked fronto-temporal atrophy, but the parietal lobe can also be affected. There is cortical microvacuolation of the neuropil accompanied by nerve cell loss and astrogliosis. Remaining cortical neurons show enlarged vacuoles, which are thought to represent aberrant large, late endosomes [167]. Ubiquitin and p62-positive NCIs, which are tau, TDP-43 and FUS-negative, have been identified in the granule cells of the hippocampal dentate gyrus and in neurons of the frontal cortex [167,168].

Conclusions and future directions

The last 10 years witnessed the discovery of two major FTD genes, the *GRN* and *C9orf72* genes and proteins such as TDP-43 and FUS together with the recognition of the role of other FET proteins and TRN1 in the FUS inclusions in FTLD-FUS. Recognition of *C9orf72* as a major gene in both FTD and MND/ALS trigged major research into the disease mechanisms of C9FTD-MND/ALS, which has provided significant results in a relatively short period of time. This remarkable increase in knowledge has resulted in a better understanding of the pathogenesis of several FTLD subgroups, firmly established a molecular link between FTD and MND/ALS, and also facilitated the introduction of a molecular classification, which has been widely accepted and followed in everyday diagnostic practice of neuropathologists. As in other neurodegenerative diseases, the concept of cell-to-cell propagation of disease-associated proteins underlying disease spread and progression has been studied in an FTLD-TDP subgroup with bvFTD, although this is still awaited in all forms of FTLD-TDP, tauopathies such as PSP and CBD, and in the different disease entities of FTLD-FUS.

Despite the advances several fundamentally important questions related to pathogenesis remain unanswered and we only enlist here a few. Is there a common pathogenic mechanism determining selective neuronal vulnerability and linking all forms of FTLDs or, as it seems more likely, multiple mechanisms exist? What are the downstream mechanisms driving the TDP-43 pathology to different cell types and/or different neuronal compartments in the four pathological subtypes of FTLD-TDP? Detailed pathological investigation of larger cohorts with *c9orf72* repeat expansions is also required. The landmark findings of the past 20 years together with future discoveries, one may trust, will facilitate the translation of this knowledge into disease biomarkers, allowing precise clinical diagnosis and ultimately leading to the establishment of effective disease modifying therapies.

Acknowledgements

We would like to thank Dr Adrian Isaacs and Dr Sarah Mizielinska for providing the DPR antibodies and the RNA foci images. TL is supported by an Alzheimer's Research UK fellowship. TR is supported by a research grant from CBD Solutions. JDR is an NIHR Rare Disease Translational Research Collaboration (TRC) Postdoctoral Fellow. SM is

funded by the Medical Research Council. The Queen Square Brain Bank is supported by the Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology. This research was partly supported by the National Institute for Health Research (NIHR) Queen Square Biomedical Research Unit in Dementia based at University College London Hospitals (UCLH), University College London (UCL). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Author contributions

TL, JDR, SM and TR undertook a literature review and drafted the initial paper and prepared the figures. All authors were involved in editing the paper. TR did the final editing.

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Received 25 March 2015
Accepted after revision 27 May 2015
Published online Article Accepted on 4 Jun 2015