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The molecular basis of frontotemporal dementia

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Frontotemporal dementia (FTD) is a clinical syndrome with a heterogeneous molecular basis. Familial FTD has been linked to mutations in several genes, including those encoding the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), valosin-containing protein (*VCP*) and charged multivescicular body protein 2B (*CHMP2B*). The associated neuropathology is characterised by selective degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration, FTLD), usually with the presence of abnormal intracellular protein accumulations. The current classification of FTLD neuropathology is based on the identity of the predominant protein abnormality, in the belief that this most closely reflects the underlying pathogenic process. Major subgroups include those characterised by the pathological tau, TDP-43, intermediate filaments and a group with cellular inclusions composed of an unidentified ubiquitinated protein. This review will focus on the current understanding of the molecular basis of each of the major FTLD subtypes. It is anticipated that this knowledge will provide the basis of future advances in the diagnosis and treatment of FTD.

The clinical syndrome of frontotemporal dementia (FTD) is characterised by progressive changes in behaviour, personality and/or language, with relative preservation of memory (Refs 1, 2, 3). Clinical subtypes include the frontal (behavioural) variant (fvFTD) and two forms of primary progressive aphasia (PPA): primary non-fluent aphasia (PNFA) and semantic dementia (SD) (Refs 1, 2). FTD is often associated with an extrapyramidal movement disorder (parkinsonism or corticobasal syndrome) or with motor neuron disease (MND) (Refs 4, 5). FTD accounts for 5–15% of all dementia and is the second commonest cause in the presenile age group (Refs 6, 7). A family history of similar disease is present in 25–50% of patients, indicating a significant genetic influence (Refs 8, 9, 10).

It should be noted that there are currently two conventions used for the nomenclature of this clinicopathological syndrome. Here, we use the one that is more popular in North America, in

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which FTD is used as the general term for the clinical syndrome (including all behavioural and language variants) and the term frontotemporal lobar degeneration (FTLD) is reserved for the associated pathology. However, in the UK, FTLD is often used as the general term for both the clinical and the pathological entities, whereas FTD refers only to the clinical subtype in which behavioural abnormalities predominate. We recognise that this situation is confusing; however, both terminologies are currently in wide use and there is no consensus as to which is more appropriate.

The molecular genetic basis of FTD is heterogeneous. Autosomal dominant FTD may be caused by mutations in several genes, including those encoding the microtubule-associated protein tau (*MAPT*) (Refs 11, 12, 13), progranulin (*GRN*) (Refs 14, 15), valosin-containing protein (*VCP*) (Ref. 16) and charged multivescicular body protein 2B (*CHMP2B*) (Ref. 17), and several families with FTD and MND have shown genetic linkage to a locus on chromosome 9p (Refs 18, 19, 20).

The neuropathology associated with clinical FTD is also heterogeneous (Ref. 21). Relatively selective degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration, FTLD) is a consistent feature, which correlates with the main clinical manifestations. As with many other neurodegenerative conditions, the pathology of most cases of FTD includes the presence of abnormal intracellular protein accumulations. Traditionally, these inclusion bodies were demonstrated with special histochemical staining techniques, such as silver impregnation methods. Eponymous and syndromic names were used for clinical syndromes associated with a specific morphology and anatomical distribution of cellular inclusions. However, in many cases, these clinicopathological correlations turned out to be imperfect. Modern laboratory techniques, such as immunohistochemistry, have allowed the biochemical composition of the pathological changes to be more readily determined. In recent years, it has become popular to classify FTLD pathology based on the presumed molecular defect, in the belief that this most closely reflects the underlying pathogenic process (Ref. 21).

In this review, we will use the molecular-based system of nosology and nomenclature recommended in a recent consensus paper (Ref. 22). The term FTLD will be used as the general terminology for pathological conditions that are commonly associated with clinical FTD, and major subdivisions will be designated by the protein abnormality that is presumed to be pathogenic or most characteristic (Table 1). Cases are further subclassified, using traditional terminology, to define specific patterns of pathology [i.e. FTLD-tau (PiD) for Pick disease]. Existing descriptive terms are retained for rare causes of FTD that have characteristic pathological features of unknown biochemistry (such as basophilic inclusion body disease, BIBD). Finally, cases with no inclusions visible with special histochemical stains or immunohistochemistry (formerly known as dementia lacking distinctive histopathology, DLDH), will be designated FTLD-ni (no inclusions).

FTLD-tau

Tau protein

Tau is a microtubule-associated phosphoprotein (MAP) that is abundantly expressed in both the central and peripheral nervous system. By promoting microtubule (MT) assembly and stability, tau plays a fundamental role in maintaining neuronal integrity and axoplasmic transport (Refs 23, 24). The tau gene (*MAPT*) is located on chromosome 17q21 and has two major haplotypes, H1 and H2, which are defined by a set of single nucleotide polymorphisms and a 238 base pair deletion in intron 9 (Ref. 25). The H2 haplotype is also associated with an inversion of a ~900 kb region that includes *MAPT* (Ref. 26). *MAPT* contains 16 exons, 11 of which encode the major tau protein isoforms (Ref. 27). Through alternative mRNA splicing of exons 2, 3 and 10, a set of six isoforms, ranging from 352 to 441 amino acids, are generated in the adult human brain. Exons 9 to 12 encode four microtubule-binding motifs, which are imperfect repeats of 31 or 32 amino acids, in the C-terminal half of the tau molecule. It is these binding domains that mediate the interaction between tau and MTs. Alternative splicing of exon 10 generates tau isoforms with either three (exon 10 missing) or four (exon 10 present) repeat domains, known as 3R and 4R tau, respectively (Fig. 1a) (Refs 28, 29). In Alzheimer disease (AD), abnormally hyperphosphorylated tau is the major component of the neurofibrillary lesions (known as neurofibrillary tangles, neuropil

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Table 1. Recommended nomenclature for frontotemporal lobar degenerations

Previous terminology		Recommended terminology (Ref. 13)	Major pathological subtypes[a]	Associated gene
Tau-positive FTLD		FTLD-tau	PiD CBD PSP AgD MSTD FTDP-17*T*[b]	 *MAPT*
Tau-negative FTLD	FTLD-U, TDP-43-positive	FTLD-TDP	Type 1[c] Type 2[c] Type 3[c] Type 4[c]	 Chrom. 9p *GRN* *VCP*
	FTLD-U, TDP-43-negative	FTLD-UPS	aFTLD-U FTD-3	 *CHMP2B*
	NIFID	FTLD-IF		
	DLDH	FTLD-ni		
	Other (BIBD)	BIBD		

[a]Characteristic pattern of pathology, not the clinical syndrome.
[b]FTDP-17*T* is not really a pathological subtype because the pathology varies between cases with different *MAPT* mutations.
[c]Based on classification system by Cairns et al. (Ref. 100).
Abbreviations: aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AgD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; CBD, corticobasal degeneration; *CHMP2B*, charged multivesicular body protein 2B gene; chrom. 9p, linked to locus on chromosome 9p; DLDH, dementia lacking distinctive histopathology; FTD-3, frontotemporal dementia linked to chromosome 3; FTLD, frontotemporal lobar degeneration; FTLD-U, FTLD with ubiquitinated inclusions; FTDP-17*T*, frontotemporal dementia and parkinsonism caused by mutations in the tau gene; *GRN*, progranulin gene; IF, intermediate filament; *MAPT*, microtubule-associated protein tau gene; MSTD, multiple system tauopathy with dementia; ni, no inclusions; NIFID, neuronal intermediate filament inclusion disease; NII, neuronal intranuclear inclusion; PiD, Pick disease; PSP, progressive supranuclear palsy; UPS, ubiquitin proteasome system; *VCP*, gene encoding valosin-containing protein.

threads and dystrophic neurites), whereas β-amyloid peptide is the major component of senile plaques. Abnormal intracellular accumulation of tau is also characteristic of a number of other neurodegenerative disorders, collectively known as 'tauopathies' (Refs 30, 31). Comparison of the tau aggregates in these disorders reveals differences in both phosphorylation and the content of different tau isoforms. Thus, tauopathies might be subdivided into disorders with inclusions made predominantly of 3R or 4R tau or an admixture of both (Ref. 32). A number of these tauopathies may be associated with clinical FTD (FTLD-tau), including Pick disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and hereditary frontotemporal dementia and parkinsonism linked to chromosome 17, as a result of *MAPT* mutations (FTDP-17*T*) (Ref. 21).

FTLD-tau (PiD)

PiD is the clinicopathological prototype of FTD (Refs 33, 34, 35). The most distinctive gross pathological feature is marked atrophy of the frontal and anterior temporal lobes, also known as 'knife-edge' lobar atrophy (Fig. 2a). The main histological features consist of severe neuronal loss, ballooned neurons (Pick cells) and pathognomonic spherical argyrophilic neuronal inclusions, called Pick bodies (PBs) (Fig. 2b). PBs are found mainly in

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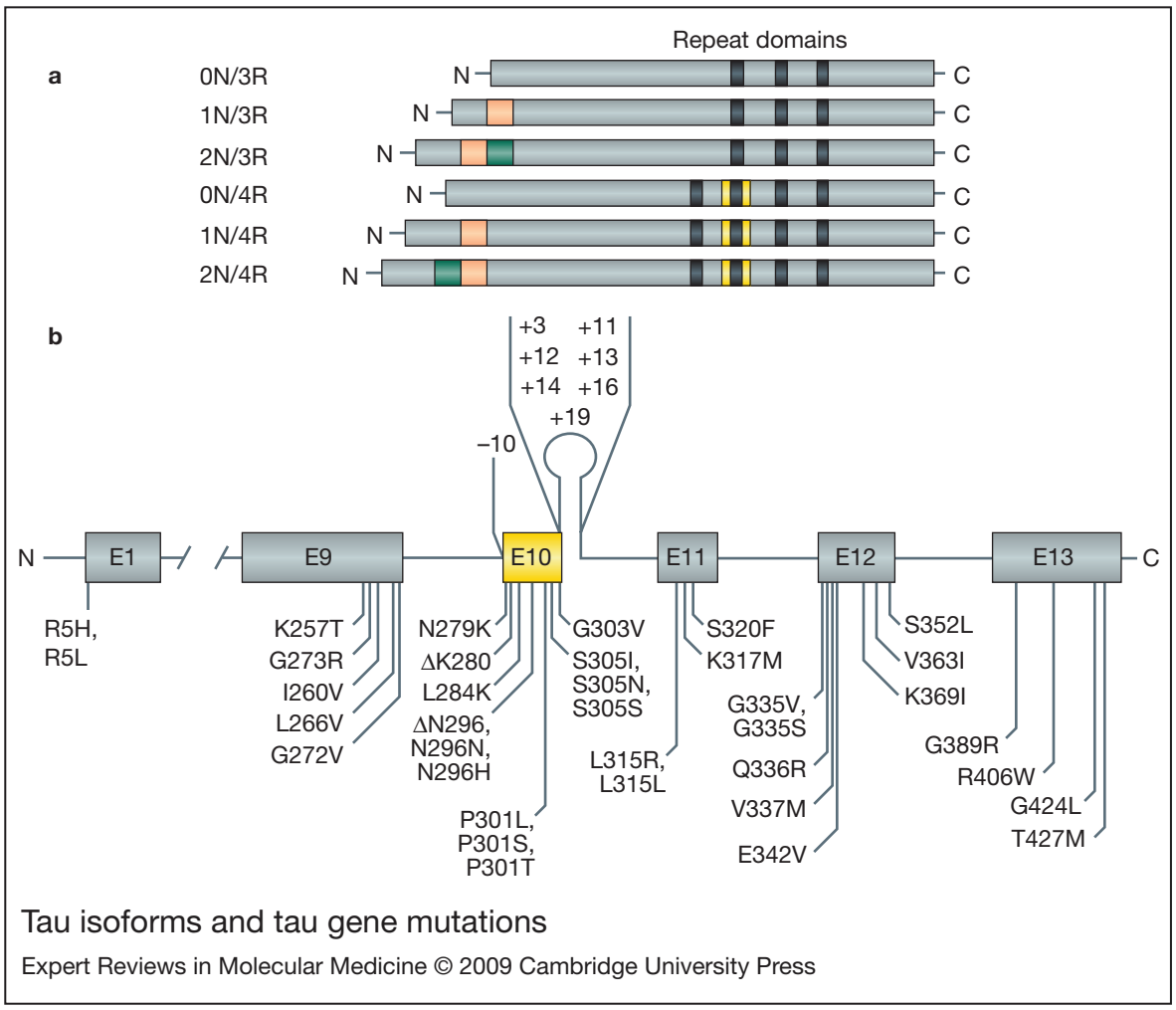


Figure 1. Tau isoforms and tau gene mutations. (a) Six isoforms of the tau protein found in the adult human brain result from alternative splicing of exons 2 (red), 3 (green) and 10 (yellow). Exons 9–12 encode imperfectly repeated microtubule-binding repeats (shown in black). (b) Mutations in the tau gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17*T*). Thirty-six coding region mutations in exons (E) 1 and 9–13 and eight intronic mutations flanking exon 10 are shown.

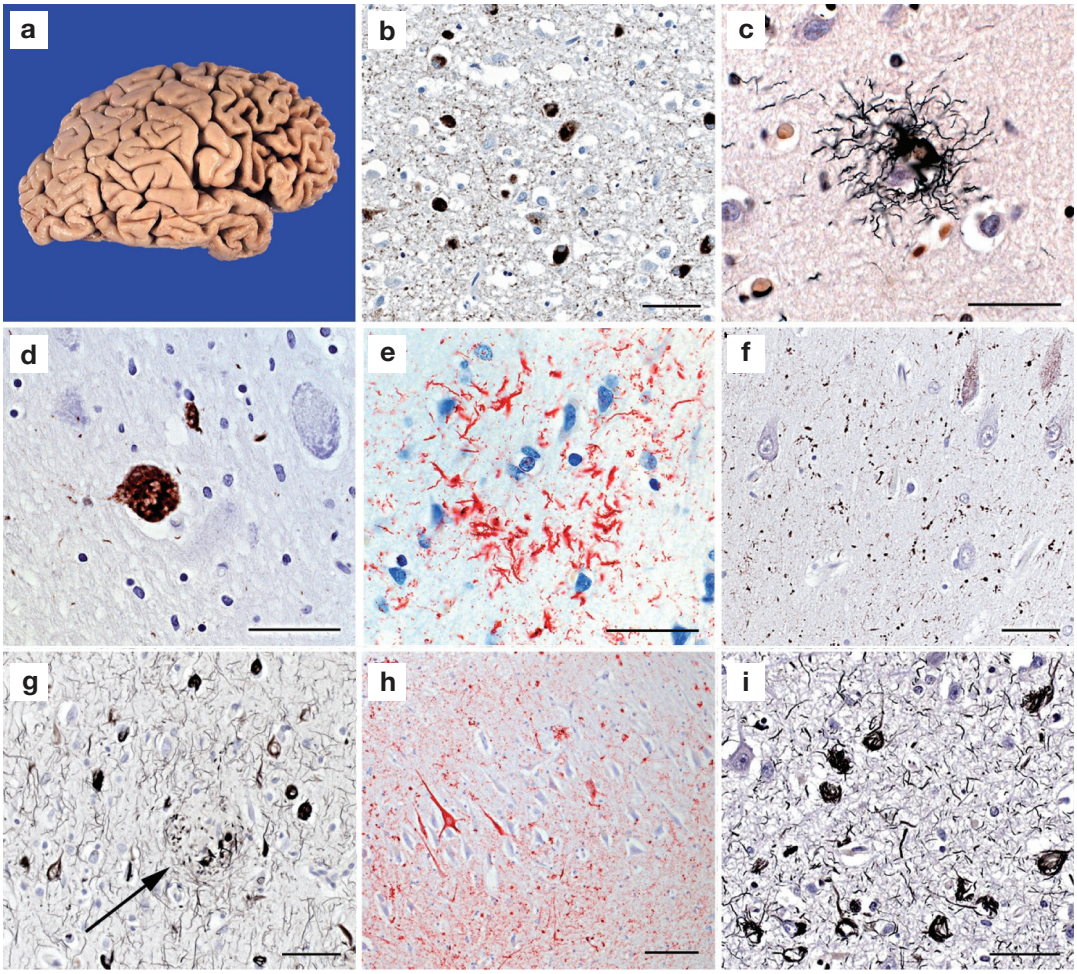
neocortical neurons of layers II–IV, the granule cells of the dentate gyrus, pyramidal cells of the hippocampus, subiculum and entorhinal cortex, and subcortical nerve cell populations. PBs are composed predominantly of 3R tau isoforms (Ref. 32), whereas 4R tau deposits might be present in glia in a subset of cases (Refs 36, 37).

FTLD-tau (PSP)

Also known as Steele-Richardson-Olszewski syndrome (Ref. 38), PSP is the second most-common parkinsonian disorder, after classical Parkinson disease. Clinical features typically include early postural instability, axial dystonia, supranuclear vertical gaze palsy, pseudobulbar palsy and parkinsonism that is resistant to levodopa therapy. Although cognitive dysfunction is often mild, some cases of PSP present with dementia and only mild motor features (Ref. 39). The pathology of PSP is characterised by gross atrophy of the midbrain (especially the pretectal region), superior cerebellar peduncles, subthalamic nucleus and substantia nigra. Fibrillar tau pathology occurs in both neurons and glia. Glial inclusions include tufted astrocytes (Fig. 2c), which are fairly specific for PSP, as well as thorn-shaped astrocytes, coiled bodies in oligodendrocytes and neuropil threads, all of which are also

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Pathological features in FTLD-tau

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Figure 2. Pathological features in FTLD-tau. (a) Severe atrophy of the frontal and temporal lobes and (b) Pick bodies in the temporal cortex of a patient with Pick disease. (c) Tufted astrocyte and (d) a globose tangle in a case with progressive supranuclear palsy. (e) Astrocytic plaque as a hallmark lesion of corticobasal degeneration. (f) Abundant argyrophilic grains in the hippocampus of a patient with argyrophilic grain disease. (g) Neurofibrillary tangles and neuropil threads in the frontal cortex of a case with frontal variant Alzheimer disease. Arrow indicates a neuritic plaque. (h) Tau pathology in sector CA2 of the hippocampus in hippocampal sclerosis dementia. (i) Neuronal and glial tau pathology in the frontal cortex of a patient with an intron 10 +3 splice-site mutation in the tau gene. b, d, e, f, h, tau immunohistochemistry; c, g, i, Gallyas-Braak silver stain. Scale bars: 50 μm.

found in other tauopathies. Neurofibrillary tangles typically have a round or globose appearance (Fig. 2d). Many subcortical regions are affected, including the striatum, pallidum, subthalamic nucleus, substantia nigra, oculomotor complex, periaqueductal grey, superior colliculi, basis pontis and dentate nucleus. Cases of PSP with dementia are also found to have significant tau pathology in the cerebral cortex (Ref. 40). Biochemically, the inclusions in PSP consist predominantly of 4R tau isoforms (Ref. 41). Inheritance of the H1 tau gene haplotype predisposes to the sporadic 4R tauopathies, PSP and CBD (Refs 42, 43).

FTLD-tau (CBD)

CBD is an increasingly recognised neurodegenerative disease with both motor and

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cognitive dysfunction (Ref. 44). The initial motor symptoms are akinesia, rigidity and apraxia. There is often parkinsonism, which is resistant to dopaminergic drugs. Recent studies have found that FTD is also a common clinical presentation of CBD (Refs 39, 45). Gross examination typically shows depigmentation of the substantia nigra and frontoparietal atrophy that is most severe in the pre- and post-central areas and often asymmetrical. Swollen, achromatic neurons were initially thought to be the most characteristic histological change (Ref. 44); however, it is now recognised that the affected cortex and subcortical regions have abundant glial and neuronal intracytoplasmic tau pathology. In addition to various neuronal inclusions, abundant thread pathology, coiled bodies and thorn-shaped astrocytes, a particularly characteristic feature of CBD is the presence of circular rings of short tau-positive cell processes, referred to as 'astrocytic plaques' (Fig. 2e) (Ref. 46). The biochemical profile of the pathological tau in CBD is similar to that in PSP, and consists predominantly of 4R tau isoforms (Refs 30, 31).

FTLD-tau (AGD)

AGD is a sporadic late-onset dementia that accounts for approximately 5% of all cases of dementia (Refs 47, 48). The clinical features are still poorly understood, and it can be difficult to distinguish from AD (Refs 49, 50). However, a subset of AGD patients present with clinical features of FTD (Refs 51, 52). The hallmark lesions are abundant argyrophilic grains (AGs) in neuronal processes (Fig. 2f) and coiled bodies in oligodendrocytes. AGs are abundant in various limbic structures, including the CA1 sector of the hippocampus, layers II and III of the entorhinal and transentorhinal cortices, the amygdala and the hypothalamic lateral tuberal nuclei (Ref. 47). Recent biochemical studies have revealed that AGD is also a 4R tauopathy (Refs 53, 54, 55). At present, there is controversy over whether the H1 tau haplotype is also a risk factor for AGD (Ref. 47).

Other sporadic tauopathies

Some additional rare forms or variants of tauopathies may be associated with clinical FTD and/or demonstrate a frontotemporal lobar distribution of tau pathology. These include the frontal variant of AD (fvAD) (Fig. 2g) (Refs 56, 57), neurofibrillary tangle dementia (reviewed in Ref. 58), sporadic multiple system tauopathy with dementia (MSTD) (Ref. 59), and white matter tauopathy with globular inclusions (Ref. 60). Although insoluble tau in fvAD and neurofibrillary tangle dementia contains both 3R and 4R tau isoforms, sporadic MSTD and white matter tauopathy with globular glial inclusions are 4R tauopathies. Hippocampal sclerosis (HS) is a descriptive term for near-complete, selective loss of pyramidal neurons in the CA1 sector of the hippocampus and subiculum. HS can be the primary pathology in some cases of late-onset dementia (Ref. 61), but it more frequently occurs in association with tauopathies (Fig. 2h) (Ref. 62) or FTLD-TDP (see below) (reviewed in Ref. 63).

FTDP-17*T*

In 1994, a familial form of FTD and parkinsonism was linked to chromosome 17q21-22 (Ref. 64). Over the following years, other families with autosomal dominant FTD were identified with linkage to the same region and, based on similarities in the clinical, neuropathological, and genetic findings, these were grouped under the umbrella of FTD and parkinsonism linked to chromosome 17 (FTDP-17) (Ref. 65). About half of the original FTDP-17 families were found to have *MAPT* mutations (FTDP-17*T*) (Refs 11, 12, 13), whereas the genetic cause in the others remained unknown until recently (see section on FTLD-TDP). At present, 44 *MAPT* mutations have been described in 131 families (Fig. 1b) (AD&FTD Mutation database: http://www.molgen.ua.ac.be/FTDMutations). Clinically, FTDP-17*T* is typically characterised by personality changes, motor symptoms and cognitive decline. The earliest symptoms are usually disinhibition, loss of initiative, obsessive-compulsive behaviour, and/or psychosis, followed by cognitive decline leading to profound dementia (Ref. 66). However, some *MAPT* mutations result in a clinical phenotype that more closely resembles PiD, CBD, PSP, AGD or AD. In all cases of FTDP-17*T*, the neuropathology includes various types of fibrillar tau pathology. Some mutations are associated with inclusions in both neurons and glia (Fig. 2i), whereas others lead to a predominance of neuronal tau pathology. Depending on the mutation site, tau aggregates can be composed predominantly of 3R or 4R

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tau isoforms, or a mixture of both. *MAPT* mutations are located in the coding region or in the intron flanking the alternatively spliced exon 10 (Fig. 1b) and fall into two main functional categories: those that affect the alternative splicing of tau pre-mRNA, and those whose primary effect is at the protein level. The mechanisms by which the various *MAPT* mutations impair tau functions and generate filamentous tau inclusions are beyond the scope of this review, but they have recently been reviewed elsewhere (Refs 28, 66, 67).

FTLD-tau due to other gene abnormalities

In addition to FTDP-17*T*, there remain many familial FTLD-tau cases for which no *MAPT* mutation has been discovered. Recently, an interesting association has been described between familial FTLD-tau and presenilin 1 (PS-1). Mutations in the genes encoding PS-1 and PS-2 (*PSEN1* and *PSEN2*) account for the majority of early-onset familial AD (Ref. 68). However, *PSEN1* mutations have also been identified in patients with an FTD presentation (Ref. 69). In one patient with familial FTD caused by the G183V *PSEN1* mutation, the neuropathology was found to be consistent with PiD in the absence of β-amyloid deposits (Ref. 70), whereas another FTD family with the M146L mutation had both PBs and AD pathology (Ref. 71). However, some FTD patients with *PSEN1* mutations have turned out to have typical AD pathology (Refs 72, 73). Finally, a family with FTD that was originally attributed to the PS-1 insR352 change was recently shown to have a *GRN* mutation and characteristic FTLD-TDP pathology (Refs 74, 75). Currently, the mechanisms by which *PSEN1* mutations contribute to neurodegeneration in a subset of FTD subjects are still elusive (Refs 76, 77).

FTLD-TDP

Until recently, most cases of tau-negative FTLD were thought to have no cellular inclusions and were classified as DLDH (Ref. 78). However, in the early 1990s, a novel pattern of pathology was first identified in patients with MND and dementia (MND-dementia), characterised by neuronal cytoplasmic inclusions (NCIs) and dystrophic neurites (DNs), in the superficial layers of frontotemporal neocortex and dentate granule cells of the hippocampus, that are immunoreactive for ubiquitin (ub-ir) but negative for tau and α-synuclein (Refs 79, 80). Subsequently, similar ub-ir pathology was identified in a subgroup of patients with clinically pure FTD without motor symptoms (FTD-MND type or MND inclusion dementia) (Ref. 81). The pathology in cases of MND-dementia and FTD-MND type was found to be similar, regardless of the clinical phenotype (Ref. 82), and became known as FTLD with ubiquitinated inclusions (FTLD-U) (Ref. 83). With growing knowledge of this entity amongst neuropathologists and improvements in immunohistochemical techniques, FTLD-U became appreciated as the most common neuropathological subtype of FTLD (Refs 84, 85). The recognition of distinct patterns of FTLD-U pathology, raised the possibility that this might actually be a heterogeneous group of disorders, each with a different ubiquitinated protein (Refs 86, 87). However, this issue was largely resolved in 2006, when the transactive response (TAR) DNA-binding protein with a mass of 43 kDa (TDP-43) was identified as the pathological protein in the vast majority of clinical and pathological FTLD-U subtypes as well as sporadic amyotrophic lateral sclerosis (ALS) (Refs 88, 89). The pathological group, now referred to as FTLD-TDP (Ref. 22), includes sporadic cases and three autosomal dominant familial forms of FTLD (Table 1).

Normal function of TDP-43

TDP-43 is a protein comprising 414 amino acids, which is encoded by the *TARDBP* gene on chromosome 1 (Fig. 3a). It was first cloned as a human protein capable of binding to the transactive response DNA of human immunodeficiency virus Type 1 (Ref. 90), and later identified as part of a complex involved in splicing of the cystic fibrosis transmembrane conductance regulator gene (Ref. 91) and the apolipoprotein-A-II gene (Ref. 92). TDP-43 is highly conserved, ubiquitously expressed and predominantly localised to the nucleus. It consists of two RNA-recognition motifs and a glycine-rich C-terminal region (Fig. 3a). Recent studies have shown that TDP-43 continuously shuttles between the nucleus and cytoplasm – a process partially regulated by nuclear localisation signal (NLS) and nuclear export signal (NES) motifs (Refs 93, 94). In addition to its well-characterised role in regulation of

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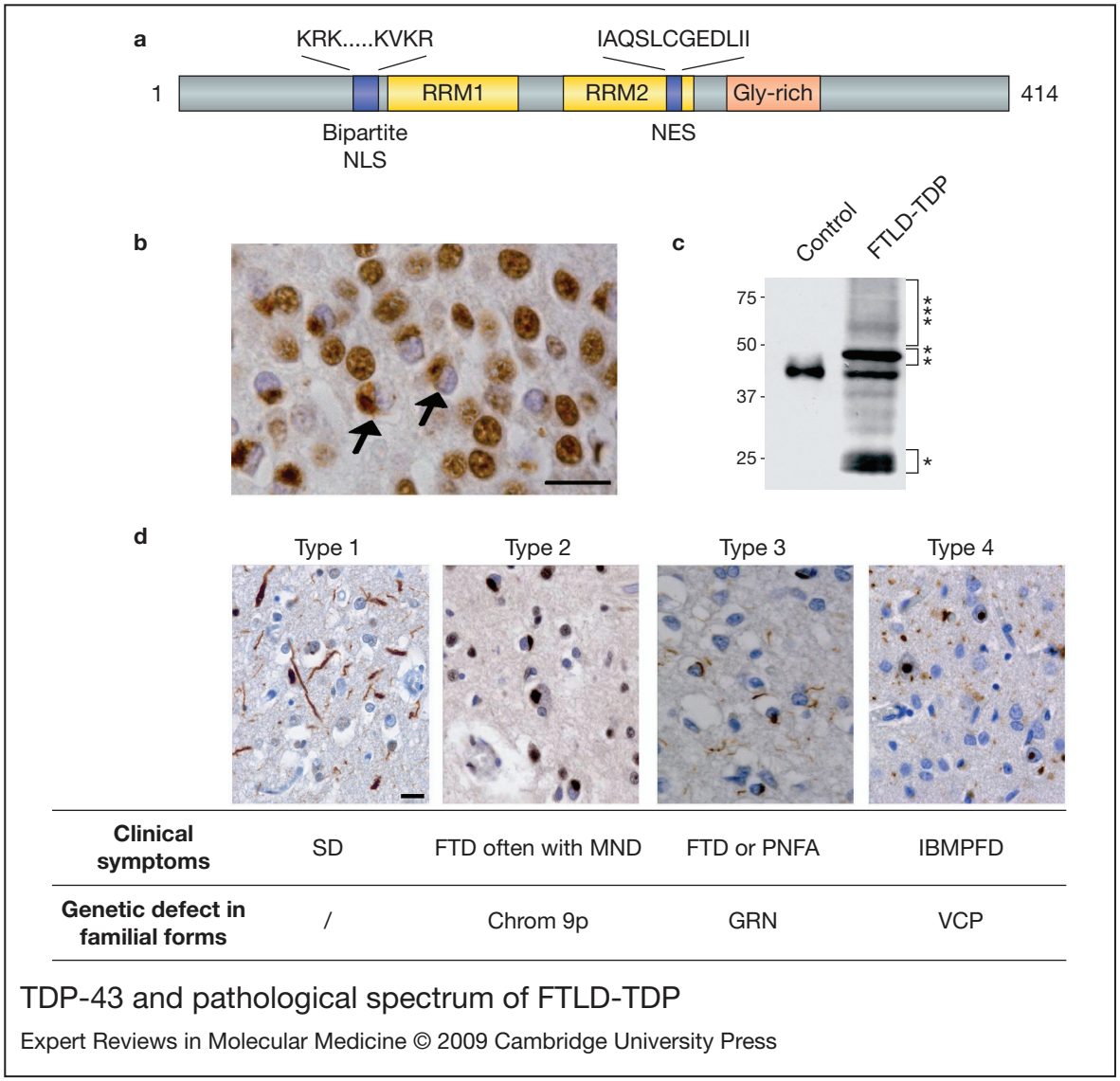


Figure 3. TDP-43 and pathological spectrum of FTLD-TDP. (a) Schematic diagram of TDP-43 with its characteristic functional domains. (b) TDP-43-positive cytoplasmic inclusions in the dentate granule cells. Note the absence of normal nuclear staining in cells with cytoplasmic inclusions (arrows). (c) Immunoblot analysis of urea fractions isolated from FTLD-TDP brain shows the highly characteristic biochemical signature with pathological bands at 25 kDa (*), 45 kDa (**) and a high molecular mass smear (***), in addition to the normal TDP-43 band. (d) Based on morphological parameters, four FTLD-TDP subtypes can be delineated, each of which correlates with specific clinical phenotype and genetic abnormalities. Scale bars: 20 μm (b, d). Abbreviations: RRM, RNA recognition motif; NLS, nuclear localisation sequence; NES, nuclear export sequence.

transcription and splicing, more recent studies suggest that TDP-43 is involved in other cellular processes such as micro RNA biogenesis, apoptosis, cell division, mRNA stabilisation and regulation of neuronal plasticity by acting as neuronal activity response factor (Refs 95, 96). The exon skipping and splicing inhibitory activity requires the C-terminal region of TDP-43, which interacts with other members of the heterogeneous nuclear ribonucleoprotein (hnRNP) family (Ref. 97). Finally, TDP-43 can also act as scaffold for nuclear bodies through interaction with survival motor neuron protein (Ref. 98).

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TDP-43 is the major pathological protein in FTLD-TDP

As demonstrated in the initial reports and rapidly confirmed by numerous subsequent studies, antibodies against TDP-43 have proven to be the most sensitive and specific tool to detect all of the different types of the ub-ir pathology found in most cases of FTLD-U, including the NCIs, DNs and neuronal intranuclear inclusions (NIIs) (Fig. 3b, d) (Refs 88, 89, 99, 100). Moreover, the pathological forms of TDP-43 demonstrate evidence of abnormal processing, being hyperphosphorylated, ubiquitinated and N-terminally truncated (Ref. 88) (Fig. 3c). Of potential functional importance, the formation of TDP-43-positive inclusion bodies (either NCIs or NIIs) is consistently associated with a dramatic reduction of the normally diffuse nuclear staining (Ref. 88) (Fig. 3b), raising the possibility that essential nuclear functions of TDP-43 might be lost in FTLD-TDP.

The use of TDP-43 immunohistochemistry has clarified the spectrum of pathology in this FTLD subtype, by demonstrating previously unrecognised ubiquitin-negative pathology, including glial cytoplasmic inclusions (GCIs) in cells of presumed oligodendroglial lineage (Ref. 101), more diffuse neuronal cytoplasmic 'preinclusions' (Refs 102, 103) and delicate neurites in the CA1 region in a subset of FTLD-TDP (Ref. 104). Antibodies raised against phosphorylated epitopes of TDP-43 (serine residues 379, 403, 404, 409 and 410) have further facilitated the neuropathological assessment, because they label only abnormal TDP-43 in inclusions, not the physiological nuclear TDP-43 (Refs 105, 106, 107).

Pathological subtypes of FTLD-TDP

FTLD-TDP pathology is heterogeneous with respect to the morphology and laminar distribution of pathological inclusions, leading to the description of four distinct pathological subtypes (Fig. 3d) (Refs 86, 87, 100). Using the classification scheme originally described by Sampathu and colleagues, FTLD-TDP Type 1 is characterised by an abundance of long neuritic profiles, predominantly in superficial cortical laminae, with few or no NCIs, NIIs or GCIs. Type 2 shows a predominance of NCIs in both superficial and deep cortical layers and frequent 'preinclusions' and GCIs. Neurites may be present but NIIs are rare or absent. NCIs, which are typical of MND, are often present in lower motor neurons. Type 3 cases have abundant small neuritic profiles and NCIs, predominantly in the superficial cortical layers. Moderate numbers of lentiform NIIs can be found in affected cortical regions, especially in cases with a positive family history. The characteristic neuropathological feature of FTLD-TDP Type 4 pathology is an abundance of NIIs and DNs with only rare NCIs in cortical regions, and the absence of inclusions in the hippocampal dentate granule cells (Refs 108, 109). The relevance of this heterogeneity is supported by relatively specific correlations between the various patterns of pathology, the clinical phenotypes and the known genetic causes (Table 1, Fig. 3d, see below) (Refs 86, 99).

Familial FTLD-TDP

FTD due to GRN mutations

Although many of the original FTDP-17 kindreds were found to have *MAPT* mutations (see section on FTLD-tau), there remained several families with FTD linked to the same region of chromosome 17 in which no *MAPT* mutation could be identified and some of these were known to have FTLD-U rather than tau pathology. This enigma was resolved in 2006, with the discovery of mutations in *GRN*, which is located just 1.7 Mb centromeric to *MAPT* (Refs 14, 15). Progranulin (PGRN) is a multifunctional secreted protein that probably serves as a neurotrophic growth or survival factor, with functions in wound healing and inflammation (Refs 110, 111, 112). To date, 66 different pathogenic mutations have been described in 199 families (AD&FTD Mutation database: http://www.molgen.ua.ac.be/FTDmutations), including all the remaining original FTDP-17 families. Mutations in *GRN* are at least as common a cause of familial FTD as *MAPT* (Refs 14, 15, 113, 114). Most pathogenic mutations are frameshift, splice site or nonsense mutations that produce premature stop codons, resulting in mutant mRNA transcripts that undergo nonsense-mediated decay (Refs 14, 15). The result of these null mutations is that the mutant protein is not produced, and there is a reduction of functional PGRN (haploinsufficiency). Consistent with this mechanism is the absence of PGRN in the ub-ir inclusions (Ref. 15). Instead, the pathology in all

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cases of FTD with *GRN* mutations is FTLD-TDP Type 3 with NIIs (Refs 88, 100, 115). A polymorphic variant in *GRN* located in the 3′-untranslated region in a binding site for miR-659, has recently been shown to be a major risk factor for sporadic FTD, by suppressing the translation of *GRN* mRNA (Ref. 116).

Chromosome-9p-linked FTD-MND

Several groups have reported genetic linkage to chromosome 9p in families with a combination of FTD and MND (Refs 18, 19, 20). The identity of the abnormal gene is currently unknown. A sequence variation in the intraflagellar transport 74 gene (*IFT74*) was found to segregate with disease in one family, but no *IFT74* mutations have been detected in other families with linkage to chromosome 9 (Ref. 117). Although only a small number of cases have been reported, the pathology is consistent with FTLD-TDP Type 2 combined with the characteristic features of MND (Ref. 100).

FTD due to VCP mutations

Mutations in *VCP* are the cause of a rare familial syndrome in which inclusion body myopathy, Paget disease of the bone and FTD (IMBPFD) show variable penetrance (Refs 16, 118). To date, 12 different missense mutations in *VCP* have been described in 29 families (AD&FTD mutation database: http://www.molgen.ua.ac.be/FTDmutations). The first detailed study of the neuropathology in cases of IMBPFD with FTD demonstrated a unique and highly specific subtype of FTLD-U pathology, characterised by numerous NIIs and DNs, with very few NCIs (Refs 109, 119). This was subsequently shown to be a subtype of FTLD-TDP (Ref. 108) and was designated as Type 4 (Ref. 21).

VCP is a member of the AAA-ATPase gene superfamily, and functions as a molecular chaperone in a plethora of distinct cellular activities, including ubiquitin-dependent, endoplasmic-reticulum-associated protein degradation (ERAD), stress responses, programmed cell death, membrane fusion, nuclear envelope reconstruction and post-mitotic Golgi reassembly. Many of these activities are directly or indirectly regulated by the UPS (Refs 118, 120). The mechanisms whereby *VCP* mutations cause neurodegeneration and TDP-43 accumulation are unclear, although it is tempting to speculate that alterations of ubiquitin-dependent protein degradation might have a role.

Molecular mechanisms underlying FTLD-TDP

The mechanistic aspects of abnormal TDP-43 processing and accumulation, the functional consequences of these abnormalities (loss-of-function versus toxic gain-of-function) as well as the links with *GRN* and *VCP* mutations are currently not well understood. The dramatic change in subcellular distribution of TDP-43 from the nucleus to the cytoplasm in inclusion-bearing cells suggests that loss of pivotal nuclear TDP-43 functions in transcription and mRNA processing might have a pathogenic role. Consistent with this hypothesis, knockdown of TDP-43 in cell lines has been shown to have important consequences on essential metabolic processes, such as regulation of nuclear shape, cell cycle and apoptosis (Ref. 121). Moreover, TDP-43-knockout mice are embryonic lethal (M. Neumann, unpublished). Alternatively, the generation and sequestration of abnormal TDP-43 species might have a toxic effect. Cortical inclusions in FTLD-TDP are selectively enriched for hyperphosphorylated C-terminal fragments (CTFs), compared with spinal cord inclusions, which contain more full-length TDP-43 (Refs 107, 122). This suggests that TDP-43 is differentially processed in different neuroanatomical regions and that TDP-43 CTFs might act as seeds for inclusion formation and aggregation, particularly in cortical neurons. Recently, one specific cleavage site (Arg208) was identified in the pathological TDP-43 CTFs purified from FTLD-TDP brains (Ref. 123). Overexpression of this CTF in cultured cells recapitulated some key features of FTLD-TDP, such as the formation of ubiquitinated and phosphorylated cytoplasmic aggregates; however, no clear effect on cell viability was observed (Ref. 123). An interesting link between TDP-43 and PGRN was recently reported by Zhang and co-workers who demonstrated caspase-dependent cleavage of TDP-43 upon PGRN knockdown in cultured cells (Ref. 124). Although it is widely accepted that TDP-43 can be cleaved by caspases, the influence of PGRN levels on this process was not replicated by another group (Ref. 125). Finally, an in vitro study showed that restricting TDP-43 from

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entering the nucleus by changing the NLS motif leads to the formation of cytoplasmic TDP-43 aggregates, with subsequent sequestration of endogenous TDP-43, resulting in a depletion of nuclear TDP-43 (Ref. 93). Thus, perturbation of the normal shuttling of TDP-43 between the nucleus and cytoplasm might predispose to both the formation of cytoplasmic inclusions and a loss of nuclear TDP-43.

Although initial studies failed to identify mutations in the *TARDBP* gene in FTLD-TDP (Refs 126, 127, 128), mutations were identified in familial and sporadic ALS, in early 2008 (Refs 129, 130). At least 30 different *TARDBP* mutations have now been identified, mostly in familial and sporadic ALS (Refs 131, 132, 133, 134, 135, 136, 137, 138, 139, 140). However, very recently, a *TARDBP* mutation (G295S) was reported in two unrelated patients with FTD and MND (Ref. 141). Except for the Y374X truncation mutation, all others are missense mutations, mostly in exon 6, which effect highly conserved amino residues in the C-terminal region of TDP-43. Elucidating the functional consequences of ALS-causing *TARDBP* mutations is likely to also provide important insights into the mechanism of neurodegeneration in FTLD-TDP. One current hypothesis is that *TARDBP* mutations might interfere with protein–protein interaction, thereby affecting intracellular transport or crucial transcriptional and splicing activities. Alternatively, the mutations might increase the generation of CTFs, promote the aggregation of TDP-43 and/or result in abnormal phosphorylation (Refs 129, 131, 135).

FTLD-UPS

Although initial data suggested that all FTLD-U cases are characterised by TDP-43 pathology, recent follow-up studies have demonstrated that there are some cases in which the pathological inclusions are only detectable with markers of the ubiquitin proteasome system (FTLD-UPS), in which the pathological ubiquitinated protein(s) is still unknown (Refs 100, 104, 142, 143). The most common subtype of FTLD-UPS, representing 10–20% of all FTLD-U cases, was recently described in detail (Refs 144, 145). The highly unusual and consistent clinical and pathological features of these cases suggest that they represent a newly recognised, discrete entity and the term atypical FTLD-U (aFTLD-U) was introduced. The clinical phenotype is sporadic, early-onset FTD with severe progressive behavioural and personality changes in the absence of aphasia or significant motor features. In addition to frontotemporal atrophy, severe degeneration of the anterior striatum and hippocampal sclerosis are common findings in aFTLD-U. TDP-43-negative, ubiquitin-positive and p62-positive NCIs are most abundant in the frontal and temporal neocortex and hippocampus (Fig. 4a). However, the most intriguing pathological feature is the presence of NIIs in the dentate granule cells and cortical pyramidal neurons with a unique morphology, where they appear as elongated straight or curved bars or thick twisted filaments (Fig. 4b, c). The immunohistochemical profile of these NIIs is also unusual and different from the NCIs, because they are reactive for ubiquitin but not for p62 (Fig. 4d).

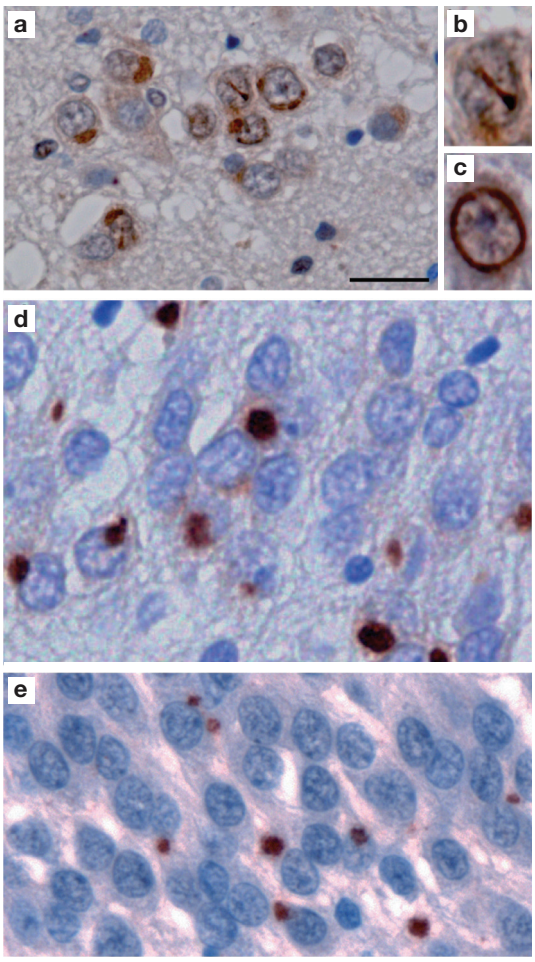
Familial FTD linked to chromosome 3 (FTD-3), due to mutations in *CHMP2B* (Ref. 17) has also recently been shown to have FTLD-UPS pathology (Ref. 146). So far, four families have been identified with different *CHMP2B* mutations (AD&FTD Mutation database: http://www.molgen.ua.ac.be/FTDmutations). CHMP2B belongs to the chromatin-modifying protein/charged multivesicular body protein family and is a component of ESCRT-III (endosomal sorting complex required for transport III), a complex involved in the degradation of surface receptor proteins and the formation of endocytotic multivesicular bodies. Although previous reports failed to detect abnormal protein deposits in brains of patients with FTD-3, a recent study demonstrated the presence of granular NCIs that were immunoreactive for ubiquitin and p62, but negative for TDP-43 and tau, predominantly in the dentate granule cells of the hippocampus (Fig. 4e) (Ref. 146).

FTLD-IF

Neuronal intermediate filament inclusion disease (NIFID) is an uncommon neurological disorder (Ref. 147) with pathology characterised by neuronal inclusions that are immunoreactive for all of the Class IV intermediate filaments (IFs) [light, medium and heavy neurofilament (NF) subunits and α-internexin] (Refs 148, 149). The typical clinical presentation is early-onset sporadic FTD, associated with a pyramidal and/or extrapyramidal movement disorder

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Pathological spectrum of FTLD-UPS

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Figure 4. Pathological spectrum of FTLD-UPS. An aFTLD-U case with ubiquitin-immunoreactive cytoplasmic (a) and intranuclear inclusions (b, c) in dentate granule cells. (d) The cytoplasmic inclusions are also immunoreactive for p62 but the intranuclear inclusions are not. (e) Familial FTD caused by CHMP2B mutations (FTD-3) also have ubiquitin-positive cytoplasmic inclusions in the dentate granule cells. a–c, e, ubiquitin immunohistochemistry; d, p62 immunohistochemistry. Scale bar: 20 μm (a, d, e); 10 μm (b, c).

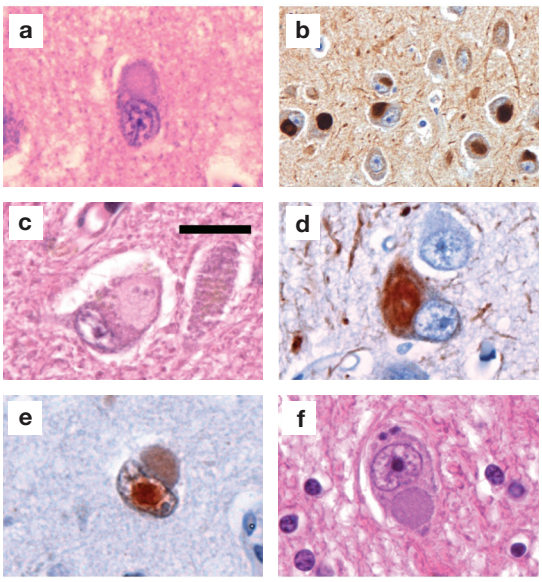
(Refs 148, 150, 151, 152, 153, 154, 155, 156, 157). Additional clinical manifestations that have been reported include falls, dystonia, myoclonus, ophthalmoplegia, memory deficits, seizures, eating disorders and psychiatric symptoms. There have been two cases published with possible childhood onset (Refs 151, 153) and two with a questionable family history (Refs 152, 153).

The neuropathological findings in NIFID are heterogeneous, but have a number of consistent features (Refs 148, 150, 151, 152, 153, 154, 155, 156, 157). Chronic degenerative changes may affect a variety of cortical and subcortical regions, with the frontal and temporal lobes and caudate nucleus most consistently and severely involved. Several types of neuronal inclusions are found. The most common are small round Pick-body-like inclusions that are well-defined, slightly eosinophilic or basophilic and rarely argyrophilic (Fig. 5a). These are variably immunoreactive for ubiquitin, NF and α-internexin but negative for tau, α-synuclein and TDP-43 (Fig. 5b) (Ref. 149). The ultrastructure is a combination of electron-dense granular material and dispersed short filaments (Refs 156, 158, 159). These are numerous in affected regions of cerebral neocortex, hippocampus and in select subcortical regions. Hyaline conglomerate inclusions are less frequent, and appear as irregular, multilobulated masses that often compress the nucleus (Fig. 5c). They are weakly eosinophilic, with a glassy, filamentous appearance and sometimes have a dense, brightly eosinophilic core. These stain intensely with the Bielschowsky silver method and are more consistently and intensely immunoreactive for IFs (Fig. 5d). The ultrastructure is compact, interlacing bundles of filaments (Ref. 158). NCI with other morphologies may also be present, and there are often IF-immunoreactive swollen axons. A less consistent feature is the presence of eosinophilic NIIs that are intensely immunoreactive for ubiquitin but generally not reactive for IFs (Fig. 5e) (Refs 149, 153, 154, 158).

Neuronal IFs include the triplet of light (68 kDa), medium (145 kDa) and heavy (200 kDa) NF subunits, α-internexin and peripherin (Ref. 160). Based on sequence homology, the NF proteins and α-internexin have been grouped together as Class IV IFs (Ref. 161). The expression of α-internexin precedes that of NFs during development and, in the adult brain, α-internexin is expressed at lower levels and in more restricted neuronal populations (Ref. 162). The Class IV IFs can coassemble (Ref. 163), and

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Neuropathology of rare FTLD subtypes

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Figure 5. Neuropathology of rare FTLD subtypes. (a–d) Neuronal intermediate filament inclusion disease. The most common type of inclusion is Pick-body-like inclusions that are visible with haematoxylin and eosin stain (a) and immunoreactive for α-internexin (b). Hyaline conglomerate inclusions are also present (c) and are immunoreactive for phosphorylated neurofilament (d). (e) Neuronal intranuclear inclusions that are present in some cases of FTLD-IF are strongly immunoreactive for ubiquitin but do not stain for intermediate filaments. Note the presence of a Pick-body-like inclusion in the cytoplasm of the same neuron. (f) Typical inclusion of basophilic inclusion body disease. Scale bar: 20 μm (a, c–f); 40 μm (b).

are part of the normal neuronal cytoskeleton, that is involved in maintaining cell structure and intracellular transport (Ref. 164). The degree and pattern of phosphorylation of NFs is essential for normal intracellular localisation and function (Ref. 160). The inclusions in NIFID are variably reactive with antibodies against phosphorylated and phosphorylation-independent epitopes of all three NF subunits; however, α-internexin immunohistochemistry is the most sensitive (Refs 148, 149). Although NF can be a minor component of the characteristic inclusion bodies of many different neurodegenerative conditions (including AD, PD, DLB and MND) (Ref. 160), α-internexin immunoreactivity is relatively specific for NIFID (Ref. 165). Because the abnormal protein aggregates found in NIFID are immunoreactive for IFs but not for any other proteins currently known to be associated with neurodegenerative disease, the designation of NIFID or FTLD-IF is appropriate. However, the fact that IF proteins show no abnormal molecular modification in NIFID (Refs 149, 158, 165) and no pathogenic variants of the corresponding genes have been identified (Ref. 166), leaves open the possibility that some other protein might have a more central role in the pathogenesis of this condition (Refs 150, 153).

BIBD

BIBD is a term that has been used for a small number of clinically and pathologically heterogeneous cases, in which the common finding is neuronal cytoplasmic inclusions that are basophilic with haematoxylin and eosin stain (Fig. 5f). The clinical phenotypes include sporadic ALS (Ref. 167), familial ALS (Ref. 168), ALS with dementia (Refs 150, 169, 170) and pure FTD (Refs 150, 171). Although cases of BIBD with clinical FTD show chronic degeneration of the frontotemporal neocortex, the inclusions tend to be most numerous in subcortical regions, such as the basal ganglia and brainstem tegmentum (Refs 150, 171). The inclusions are round, oval or crescentic, weakly argyrophilic and can be detected with histochemical stains for RNA (such as cresyl violet, methyl green pyronine and acridine orange). Immunohistochemical studies have found them to be negative for tau, α-synuclein, NF, α-internexin, tubulin, actin and TDP-43 (Refs 100, 150, 169, 171). Reports of ubiquitin immunoreactivity are inconsistent but some are positive for p62 (Ref. 150). The biochemical composition of the signature inclusions in BIBD is not presently known.

FTLD-ni

Until recently, most cases of tau-negative FTLD were thought to have no cellular inclusions and were classified as DLDH (Ref. 78). However, with the use of sensitive immunohistochemical techniques, most of these cases are found to have ubiquitin-immunoreactive pathology (previously designated FTLD-U) (Ref. 85) that is usually also reactive for TDP-43 (Ref. 99).

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Cases of true DLDH are now considered to be uncommon, and the existence of DLDH as a distinct entity has been questioned. The terminology that is now recommended for rare cases of FTLD in which no inclusions can be demonstrated with special histochemical stains or immunohistochemistry is FTLD-ni (no inclusions) (Ref. 22).

Other pathological causes of FTD

There are a number of rare neurodegenerative conditions, with unknown biochemical defects, that can present as FTD, such as hereditary diffuse leukoencephalopathy with spheroids (Ref. 172) and neuronal intranuclear inclusion disease (Ref. 173). In addition, most of the common neurodegenerative causes of dementia can occasionally fulfill clinical diagnostic criteria for FTD. Although the frequency of these 'frontal variants' and their overall contribution to FTD is difficult to determine, some studies have found more than 20% of clinical FTD to be associated with the pathology of AD, DLB, CJD or vascular disease (Refs 174, 175). The frontal variant of AD is best recognised and could account for 17% of all FTD (Refs 174, 175). Attempts to demonstrate a correlation between the regional severity of the AD pathology and the clinical phenotype have been inconsistent (Refs 56, 57, 176). One recent study has described additional glial tau pathology in cases of AD with clinical PPA, suggesting a pathological overlap with FTLD-tau (Ref. 177). Another recent finding of interest is the presence of TDP-43 pathology in a significant proportion of AD and DLB cases (Refs 178, 179, 180, 181, 182). Although this often has a restricted anatomical distribution, it is sometimes extensive and might closely resemble FTLD-TDP (Ref. 181). Whether or not this additional pathology alters the clinical phenotype is yet to be determined.

Outstanding research questions

Despite the enormous gains made over the past few years in our understanding of the molecular basis of FTD, many fundamental issues are still unresolved. The FTLD gene on chromosome 9 remains to be identified and there is probably at least one other genetic cause of familial FTLD-tau. The normal functions of PGRN and TDP-43 in the nervous system need to be clarified, as do the mechanisms by which mutations in *GRN*, *VCP* and *TARDBP* lead to TDP-43 pathology. The possible role of *GRN* and *TARDBP* genetic variants in other (non-FTLD) neurodegenerative disease requires further investigation. The development of new animal models, particularly of FTLD-TDP, should help to answer these questions and will be crucial in the development of targeted therapies. Efforts to develop in vivo biomarkers that distinguish different subgroups of FTLD and aid in diagnosis and monitoring of disease are still preliminary (Refs 183, 184, 185, 186). Despite the enormous amount of work that lies ahead, recent discoveries have greatly improved our ability to offer meaningful genetic counselling for FTLD families and bring us much closer to developing useful diagnostic tests and rational therapies.

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Further reading, resources and contacts

Publications

Ballatore, C., Lee, V.M. and Trojanowski, J.Q. (2007) Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nature Reviews Neuroscience 8, 663-672
A review of role of tau protein in neurodegeneration.

Buratti, E. and Baralle, F.E. (2008) Multiple roles of TDP-43 in gene expression, splicing regulation, and human disease. Frontiers in Bioscience 13, 867-878
This is an excellent review on the biology of TDP-43.

Ahmed, Z. et al. (2007) Progranulin in frontotemporal lobar degeneration and neuroinflammation. Journal of Neuroinflammation 4, 7
A review of progranulin function and role in FTD.

Websites

The website of the Association for Frontotemporal Dementias (AFTD), a US nationwide non-profit organisation whose mission is to promote and fund research into finding the cause and cure for FTD, provides information, education, and support to persons diagnosed with FTD and their families and caregivers; and educates physicians and allied health professionals about FTD:
http://www.ftd-picks.org/

The website from University of California, San Francisco provides information on clinical and research aspects of FTD and gives information on clinical trials:
http://memory.ucsf.edu/ftd/

The AD&FTD Mutation database provides a current list of known FTLD gene mutations, including the number of affected families:
http://www.molgen.ua.ac.be/FTDmutations

Features associated with this article

Figures

Figure 1. Tau isoforms and tau gene mutations.
Figure 2. Pathological features in FTLD-tau.
Figure 3. TDP-43 and pathological spectrum of FTLD-TDP.
Figure 4. Pathological spectrum of FTLD-UPS.
Figure 5. Neuropathology of rare FTLD subtypes.

Table

Table 1. Recommended nomenclature for frontotemporal lobar degenerations.

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