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Frontotemporal Dementia: Implications for Understanding Alzheimer Disease

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Frontotemporal dementia (FTD) comprises a group of behavioral, language, and movement disorders. On the basis of the nature of the characteristic protein inclusions, frontotemporal lobar degeneration (FTLD) can be subdivided into the common FTLD-tau and FTLD-TDP as well as the less common FTLD-FUS and FTLD-UPS. Approximately 10% of cases of FTD are inherited in an autosomal-dominant manner. Mutations in seven genes cause FTD, with those in tau *(MAPT)*, chromosome 9 open reading frame 72 (*C9ORF72*), and progranulin (*GRN*) being the most common. Mutations in *MAPT* give rise to FTLD-tau and mutations in *C9ORF72* and *GRN* to FTLD-TDP. The other four genes are transactive response–DNA binding protein-43 (*TARDBP*), fused in sarcoma (*FUS*), valosin-containing protein (*VCP*), and charged multivesicular body protein 2B (*CHMP2B*). Mutations in *TARDBP* and *VCP* give rise to FTLD-TDP, mutations in *FUS* to FTLD-FUS, and mutations in *CHMP2B* to FTLD-UPS. The discovery that mutations in *MAPT* cause neurodegeneration and dementia has important implications for understanding Alzheimer disease.

THE CONCEPT OF FRONTOTEMPORAL DEMENTIA: HISTORICAL OVERVIEW

Frontotemporal dementia (FTD) results from degeneration of the cortex of the frontal and temporal lobes, often in conjunction with the degeneration of subcortical brain regions. This gives rise to a spectrum of behavioral, language, and movement disorders. A link exists between FTD and forms of motor neuron disease (MND). Work on FTD stretches back to the end of the 19th century.

Arnold Pick was Professor of Neuropsychiatry at the German University in Prague from 1886 to 1921. In 1892, he described a 71-year-old man with behavioral disturbances, aphasia, and dementia (Pick 1892). At autopsy, marked atrophy of the left temporal lobe rather than the diffuse atrophy characteristic of senile dementia was present. Although Pick was doubtful of the primacy of these observations, his paper is considered to be the first description of lobar cortical atrophy. At the time, there was much interest in language abnormalities,

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following the description of motor and sensory aphasias (Broca 1861; Wernicke 1874; see also Freud 1891). A few years later, Déjerine and Sérieux (1897) described a case of sensory aphasia with bilateral temporal atrophy. Pick went on to report four additional cases with temporal lobe atrophy and language disturbances (Pick 1901, 1904). In 1906, he described a patient with disinhibition and mixed apraxia who had severe bilateral frontal and left-sided parietal atrophy, with a more moderate atrophy of the left temporal lobe (Pick 1906). Pick was mainly interested in comparing the clinical picture with the macroscopic appearance of the brain. He made no systematic attempt at identifying histopathological abnormalities. Alzheimer discovered the association of argyrophilic intracytoplasmic inclusions and ballooned neurons with lobar cortical atrophy, in the absence of the plaques and tangles he had described four years earlier (Alzheimer 1907, 1911). This revealed the existence of a second type of intraneuronal inclusion and established that different inclusions can characterize distinct clinical entities.

Richter proposed that lobar cortical atrophies are hereditary diseases (Richter 1918) and Gans, a pupil of Pick, linked his mentor's name to cases of lobar cortical atrophy (Gans 1923). Additional examples of frontal and/or temporal cortical atrophy with or without argyrophilic inclusions were subsequently reported and the clinical condition was called "Pick's disease" (Onari and Spatz 1926; Stertz 1926). Unlike Pick, who believed to have described atypical forms of senile dementia, Onari and Spatz considered Pick's disease to be a distinct entity. One of their patients (Therese Mühlich) had already been described by Alzheimer. Carl Schneider proposed a three-stage model for the clinical course of Pick's disease (Schneider 1927, 1929). In most individuals, the first stage is characterized by disinhibition and impaired judgement, although Schneider recognized that amnestic aphasia is the presenting symptom of temporal lobe atrophy. The second stage is dominated by progressive dementia and focal symptoms, such as apathy in frontal lobe atrophy and sensory aphasia in temporal lobe atrophy. Stereotyped perseverations of speech, movement, and facial expression also appear. The third stage is characterized by dementia and severe language problems, resulting in a vegetative state with flexion contractures. Schneider concluded that the argyrophilic inclusions and ballooned cells described by Alzheimer were diagnostic of Pick's disease. Similar cases were described in the 1930s, when it became clear that lobar cortical atrophy has a high degree of heritability, irrespective of the presence of argyrophilic inclusions (Grünthal 1930; Verhaart 1930; Von Braunmühl and Leonhard 1934). The link between frontal lobe dementia and MND was also recognized (Meyer 1929; Von Braunmühl 1932). The early work was summarized and discussed by Van Mansvelt (1954) and Lüers and Spatz (1957).

Interest in the focal dementias waned after World War II, before it was rekindled in the 1970s and 1980s. Cases of Pick's disease with argyrophilic inclusions and ballooned neurons (type A) were now distinguished from those with ballooned neurons lacking argyrophilic inclusions (type B) and those lacking both ballooned neurons and argyrophilic inclusions (type C) (Constantinidis 1974). Work by Brun, Gustafson, and Neary showed that some individuals with frontal lobe atrophy lacked a distinctive histopathology (Brun 1987; Gustafson 1987; Neary et al. 1988). Clinically, these patients suffered from a severe personality disorder, which is now known as behavioral-variant FTD (bvFTD). Mesulam described primary progressive aphasia (PPA), with an isolated language deficit as the most prominent presenting feature, in the absence of strokes or tumors (Mesulam 1982, 1987, 2001). PPA has been divided into three syndromes (Gorno-Tempini et al. 2011): (1) Semantic dementia (SD), also known as semantic variant PPA, a fluent aphasia with loss of word meaning (Snowden et al. 1989); (2) progressive nonfluent aphasia (PNFA), also known as nonfluent/agrammatic variant PPA, a disorder characterized by effortful, nonfluent speech (Grossman et al. 1996); and (3) logopenic progressive aphasia (LPA), also known as logopenic variant PPA, a nonfluent aphasia with deficits in word

retrieval and sentence repetition (Gorno-Tempini et al. 2004b).

Symptoms correlate better with specific patterns of brain atrophy than with the underlying neuropathology. Prediction of the neuropathology based on clinical picture remains challenging. FTD is the third most common cause of early-onset dementia (disease onset <65 years), after Alzheimer disease and vascular dementia (Rossor et al. 2010). Approximately 40% of patients with FTD have a family history, but only 10% of cases are inherited in a dominant manner. Links exist with the corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), parkinsonism, and MND.

CLINICAL PRESENTATIONS OF FRONTOTEMPORAL DEMENTIA

Behavioral-Variant Frontotemporal Dementia (bvFTD)

bvFTD comprises more than half of the cases of FTD and is the most heritable form. Presenting features are insidious and include progressive changes in the patient's personality, interpersonal conduct, and emotional modulation (Gustafson 1987; Neary et al. 1988; Piguet et al. 2011a). A variable degree of language impairment is also present. Apathy manifesting as passivity, inertia, reduced motivation, and social withdrawal, associated with a lack of insight, is common. Disinhibition often coexists alongside apathy and manifests itself by impulsivity. Emotional blunting characterized by a lack of empathy is common. Abnormal eating behavior can be extensive, resulting in marked weight gain. Stereotypic and ritualistic behavior is common, as expressed by motor stereotyping, including humming, lip smacking, hand ruffling, and foot tapping. Neglect of self-care and impairment of other activities of daily living are common. Most patients are unable to manage their financial affairs. Memory is relatively spared in the early stages of bvFTD. By neuroimaging, four subtypes have been identified based on relative grey matter loss: frontal-dominant, frontotemporal, temporofrontoparietal, and temporal-dominant (Whitwell et al. 2009a). Combined frontotemporal and basal ganglion atrophy can also be present, as can atrophy of a number of other subcortical regions. bvFTD and Alzheimer disease lead to divergent network activity patterns, with atrophy in an anterior salience network in bvFTD and a posterior default mode network in Alzheimer disease (Zhou et al. 2010).

Semantic Dementia (SD)

SD is a progressive fluent aphasia, which is characterized by the loss of word meaning (Snowden et al. 1989; Hodges and Patterson 2007). Patients have difficulty in finding words, with anomia being a defining feature. They also complain of memory loss, but this does not in general reflect true amnesia. Although language deficits predominate, behavioral alterations also occur. SD is the least heritable FTD syndrome. A deficit in naming and word comprehension predominates, with the patient's vocabulary being depleted of all but the most common words. However, speech is fluent and the syntax correct. This is often coupled with deficits in person recognition, especially when the right temporal lobe is affected. Although patients are insightful and can be distressed by their condition, lack of empathy and mental inflexibility are common. Restriction of food preferences is present without the overeating characteristic of bvFTD. Compulsive behavior is prominent and centers on visual objects (left temporal lobe predominance) or on letters, words, and symbols (right temporal lobe predominance). By neuroimaging of grey matter, bilateral, often asymmetric, anterior temporal lobe atrophy is most prominent. The hippocampus can also be affected (Mummery et al. 1999). White matter changes are found in the ventral language pathways and the temporal components of the dorsal language pathways (Galantucci et al. 2011).

Progressive Nonfluent Aphasia (PNFA)

PNFA is a disorder of expressive language. Patients lose the ability to speak fluently, with relative preservation of word comprehension and nonlinguistic cognition (Grossman et al.

1996). Several speech changes characterize PNFA. At an early stage, patients speak less than normal and in shorter sentences. They show speech apraxia, with effortful speech and phonological errors. Word finding difficulty is commonly observed, often resulting in muteness. Behavioral features similar to those of bvFTD may occur, but they are usually mild, with apathy being most common. As the disease progresses, extrapyramidal features become widespread and can lead to a change in diagnosis (Gorno-Tempini et al. 2004a). Heritability of PNFA is intermediate between that of bvFTD and SD. Neuroimaging shows a widening of the Sylvian fissure, with atrophy of left posterior frontal and insular regions (Neary et al. 2003; Nestor et al. 2003). In white matter, the most prominent changes are found in the dorsal language pathways (Galantucci et al. 2011).

Logopenic Progressive Aphasia (LPA)

LPA is a progressive nonfluent aphasia, which is characterized by a slow speech rate and word retrieval difficulties (Gorno-Tempini et al. 2004b, 2008). Repetition of phrases is also markedly impaired, in part as a result of limited auditory-verbal short-term memory. Single-word comprehension and semantic association are largely preserved. It differs from the fast output typical of patients with SD and the agrammatism and articulation deficits characteristic of PNFA. However, a language variant of Alzheimer disease overlaps with LPA (Galton et al. 2000; Alladi et al. 2007). It has been suggested that LPA and posterior cortical atrophy are clinical presentations of sporadic, early-onset Alzheimer disease (Migliaccio et al. 2009). This nonmemory phenotype characterizes about one quarter of patients (Van der Flier et al. 2011). Inheritance of the *APOE* ε4 allele appears not to be a risk factor for LPA and posterior cortical atrophy, distinguishing them from the more common amnestic forms of Alzheimer disease (Strittmatter and Roses 1995). Neuroimaging of LPA shows atrophy or hypoperfusion of the left posterior superior and middle temporal regions, and of the inferior parietal region (Gorno-Tempini et al. 2004b). Brain atrophy is located more posteriorly than in SD and PNFA. White matter changes are most marked in the temporoparietal component of the dorsal language pathway (Galantucci et al. 2011).

Frontotemporal Dementia and Corticobasal Syndrome (CBS)

CBS and PSP are atypical parkinsonian disorders. CBS is characterized by extrapyramidal symptoms consisting of progressive asymmetric rigidity and dystonia, and by signs of cortical dysfunction in the form of PNFA, apraxia, cortical sensory loss, alien limb syndrome, myoclonus, and hemineglect. For many years, the emphasis was on the extrapyramidal component, even though similarities with Pick's disease were noticed early on (Rebeiz et al. 1968). More recent work has shown that patients with CBS can have aphasia or a behavioral disorder characteristic of bvFTD (Lippa et al. 1991; Kertesz et al. 1994). Pathologically, CBS is heterogenous, but its most common form is corticobasal degeneration (CBD). Some cases of CBS are dominantly inherited. Neuroimaging shows variable frontoparietal and basal ganglion atrophy (Whitwell et al. 2010).

Frontotemporal Dementia and Progressive Supranuclear Palsy (PSP)

The clinical presentation of PSP includes vertical supranuclear ophtalmoplegia with difficulty looking up, bradykinesia, axial dystonia and rigidity, pseudobulbar palsy and postural instability with backward falls (Steele et al. 1964; Litvan et al. 1996). More than half of the patients develop cognitive impairment. Apathy and emotional blunting, accompanied by mental slowness and reduced verbal fluency, are common. A small percentage of cases of PSP is inherited. By neuroimaging, atrophy in premotor and supplemental motor areas is observed, with sparing of the inferior frontal lobe (Whitwell et al. 2010). Some patients show PNFA with early apraxia of speech (Josephs et al. 2006). Three subtypes of PSP have been described: Richardson's syndrome,

PSP-parkinsonism, and PSP-pure akinesia with gait freezing (Williams and Lees 2009). Cognitive impairment and cortical atrophy are most prominent in Richardson's syndrome, which corresponds to classical PSP.

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 (FTDP-17)

In the 1980s and 1990s, dominantly inherited forms of FTD were identified (Ghetti et al. 2011). Extrapyramidal signs resembling CBS and PSP also featured prominently. Amyotrophy was present in some cases. These forms of inherited FTD were given different names according to their predominant clinical and pathological features, including familial Pick's disease, disinhibition-dementia-parkinsonism-amyotrophy complex, familial progressive subcortical gliosis, familial presenile dementia with tangles, autosomal-dominant parkinsonism, dementia with pallido-ponto-nigral degeneration, and multiple system tauopathy with presenile dementia. Despite this heterogeneity, disease was linked to the long arm of chromosome 17 (Wilhelmsen et al. 1994). The syndrome received its name at a consensus conference during which 13 families were presented (Foster et al. 1997). FTDP-17 is divided into a dementia-dominant and a parkinsonism-dominant type. Neuroimaging shows variable frontotemporoparietal and basal ganglion atrophy (Whitwell et al. 2009b).

Frontotemporal Dementia with Motor Neuron Disease (MND)

MND can be associated with cognitive dysfunction (Morita et al. 1987). Mild frontal lobe involvement is found in 30% of cases and in ~3% of cases FTD is present (Shaw 2010). A psychotic phase consisting of vivid delusions is an early sign. Behavioral and cognitive changes tend to predate MND. Bulbar signs are common and electromyography is as in MND. Inherited cases of FTD-MND have been linked to chromosome 9p21 (Vance et al. 2006). Neuroimaging shows posterior frontal lobe atrophy (Whitwell et al. 2006). Based on the presence of isolated upper MND in some cases, further subclassification of FTD-MND has been proposed (Josephs and Dickson 2007).

HISTOPATHOLOGY OF FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

FTLD-Tau

In 1986, the argyrophilic inclusions of Pick's disease were shown to be immunoreactive for hyperphosphorylated tau (Pollock et al. 1986), a normally soluble microtubule-associated protein that stabilizes microtubules and promotes microtubule assembly. It followed the finding that the intracellular inclusions of Alzheimer disease stain for hyperphosphorylated tau (Brion et al. 1985; Grundke-Iqbal et al. 1986). In adult human brain, six tau isoforms are expressed from a single *MAPT* gene through alternative mRNA splicing (Fig. 1A) (Goedert et al. 1989a,b). Three isoforms have three repeats each and three isoforms have four repeats each. By 1992, the paired helical filament of Alzheimer disease had been shown to be made of the six tau isoforms, each full-length and hyperphosphorylated (Goedert et al. 1988, 1992; Wischik et al. 1988; Lee et al. 1991). Filamentous tau inclusions were subsequently shown to be characteristic of many cases of FTDP-17 (Spillantini et al. 1996, 1998a).

Around 40% of patients with FTD show tau inclusions (Fig. 2). They include most cases of PNFA, ~45% of cases of bvFTD and some cases of SD (Piguet et al. 2011a). Most cases of LPA are characterized by focal Alzheimer disease pathology (Aβ plaques and tau tangles), as are some cases of SD and PNFA (Mesulam et al. 2008; Rabinovici et al. 2008). Focal Alzheimer disease pathology accounts for ~25% of autopsy cases of PPA. A frontal variant of Alzheimer disease has also been described (Johnson et al. 1999). Tau inclusions are characteristic of Pick's disease, PSP, and CBD, which belongs to the CBS spectrum (Goedert and Spillantini 2006). They are not typical of FTD-MND, even though MND can occur in conjunction with FTD and tauopathy (Fu et al. 2010).

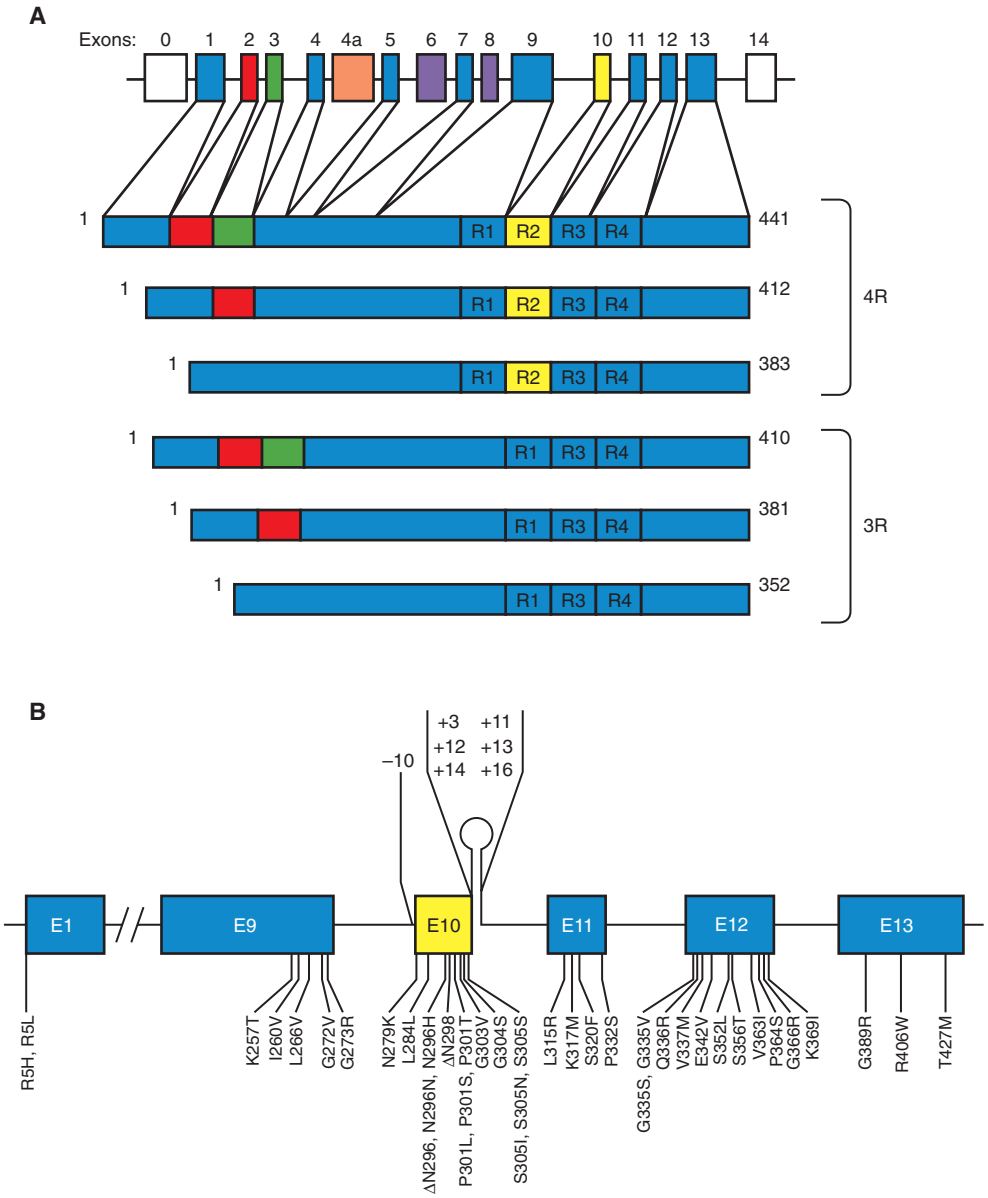

Figure 1. *MAPT* and the six tau isoforms expressed in adult human brain and mutations in *MAPT* in frontotemporal dementia and parkinsonism linked to chromosome 17. (*A*) *MAPT* consists of 16 exons (E). Alternative mRNA splicing of E2 (red), E3 (green), and E10 (yellow) gives rise to six tau isoforms (352-441 amino acids). The constitutively spliced exons (E1, E4, E5, E7, E9, E11, E12, E13) are indicated in blue. E0, which is part of the promoter, and E14 are noncoding (white). E6 and E8 (violet) are not transcribed in human brain. E4a (orange) is only expressed in the peripheral nervous system. The repeats of tau (R1–R4) are shown, with three isoforms having four repeats each (4R) and three isoforms having three repeats each (3R). Each repeat is 31 or 32 amino acids in length. (*B*) Shown are 39 coding region mutations in E1, E9, E10, E11, E12, and E13 as well as seven intronic mutations flanking E10.

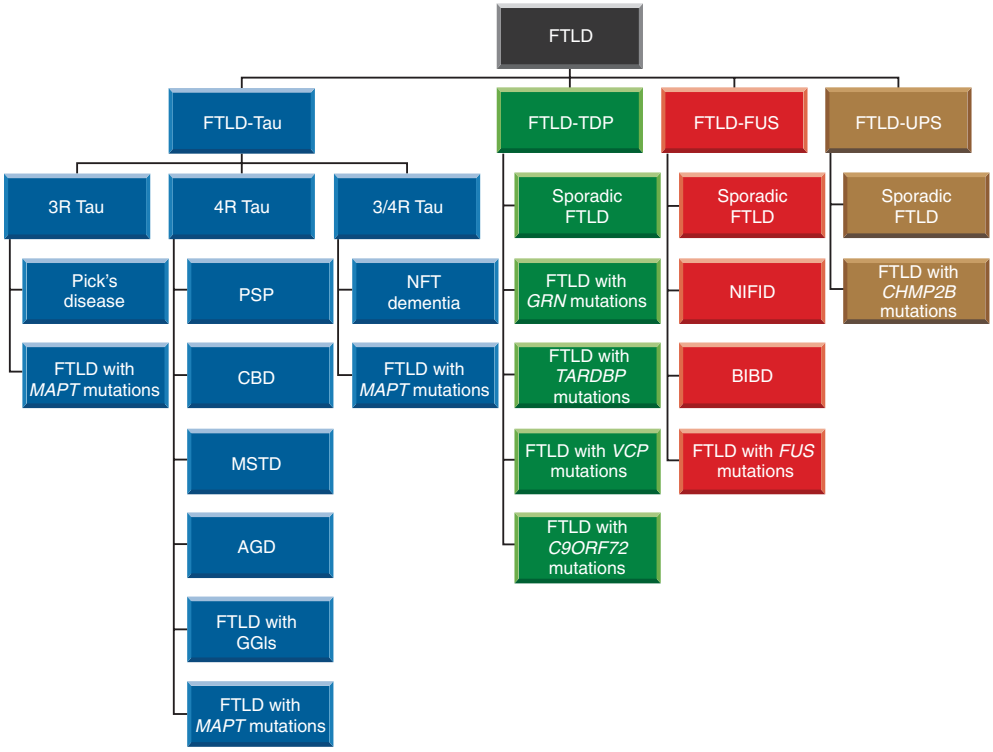

Figure 2. Frontotemporal lobar degeneration (FTLD) molecular classification. Four subtypes (FTLD-Tau, FTLD-TDP, FTLD-FUS, and FTLD-UPS) can be distinguished, based on what is known about the major components that make up the pathological deposits (Tau protein, TDP-43, FUS and unknown protein). FTLD-Tau and FTLD-TDP are more common than FTLD-FUS and FTLD-UPS. Tau deposits are made of either three-repeat (3R), four-repeat (4R) or all six (3/4R) brain isoforms of tau. Together, FTLD-TDP, FTLD-FUS, and FTLD-UPS make up FTLD-U, which is characterized by the presence of tau-negative, ubiquitin-positive inclusions. In some cases of FTLD-U, the ubiquitinated protein is unknown; they are classified as FTLD-UPS, to indicate that the inclusions can currently only be identified by markers of the ubiquitin-proteasome system. Abbreviations: PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSTD, multiple system tauopathy with presenile dementia; AGD, argyrophilic grain disease; GGI, globular glial inclusion; NIFID, neuronal intermediate filament inclusion disease; BIBD, basophilic inclusion body disease; UPS, ubiquitin-proteasome system.

The anatomical distribution of pathology rather than its molecular identity determines the nature of the clinical syndromes. In most cases of Alzheimer disease, the locus coeruleus, entorhinal cortex, and hippocampus are the initial targets of neurofibrillary pathology, with the neocortex becoming affected later (Braak and Del Tredici 2011). In Pick's disease, tau inclusions predominate in the cerebral cortex, resulting in FTD (Piguet et al. 2011b). In PSP, patients with Richardson's syndrome have a higher tau burden and a different distribution of inclusions than patients with PSP-parkinsonism (Williams et al. 2007). The subthalamic nucleus, substantia nigra, and globus pallidus are the most affected brain regions. In CBD, apraxia, rigidity, dystonia, and frontal lobe signs reflect the presence of neuronal and glial tau deposits in brainstem, basal ganglia, and cerebral cortex (Feany and Dickson 1995).

The repeats of tau form the core of the filaments whose isoform composition varies between diseases. The assembly of four-repeat tau into filaments is characteristic of PSP,

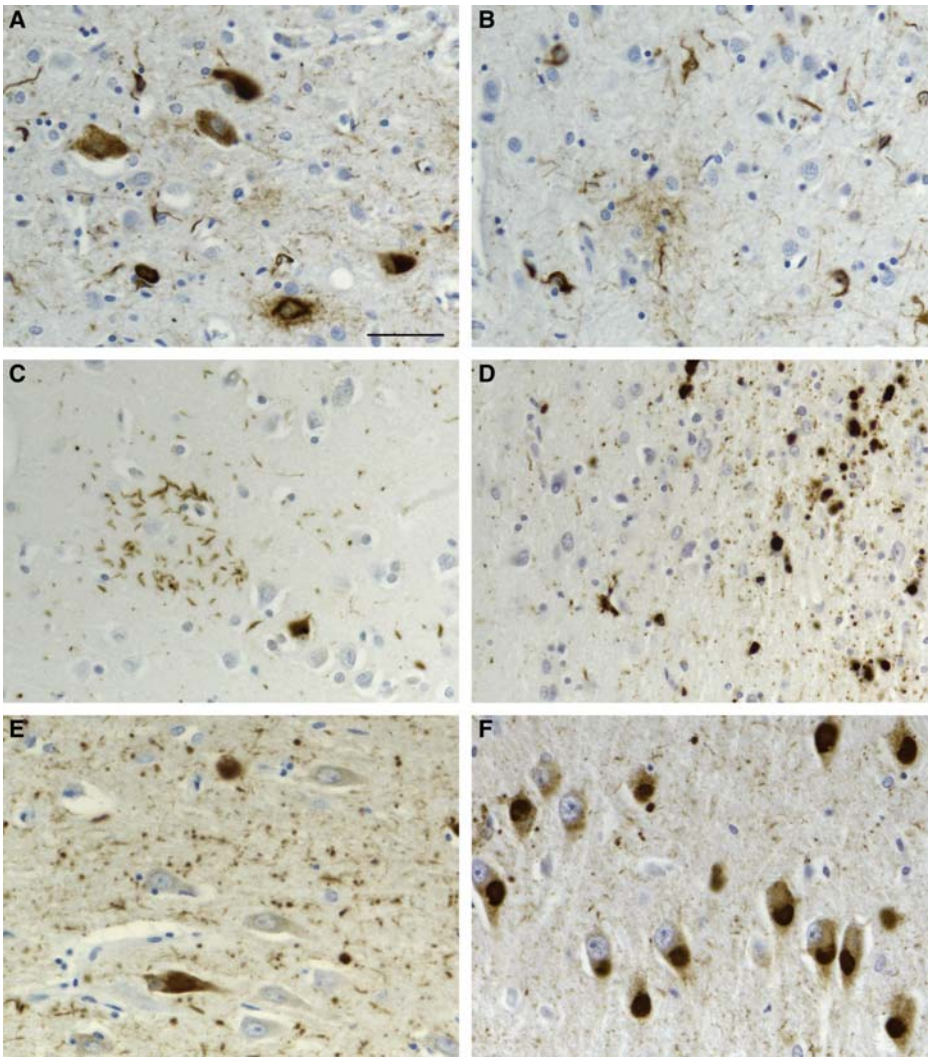

Figure 3. FTLD-Tau. Inclusions in progressive supranuclear palsy (*A*,*B*), corticobasal degeneration (*C*), white matter tauopathy with globular glial inclusions (*D*), argyrophilic grain disease (*E*), and Pick's disease (*F*). Progressive supranuclear palsy, corticobasal degeneration, white matter tauopathy with globular glial inclusions and argyrophilic grain disease are four-repeat tauopathies with abundant neuronal and glial tau filaments. Pick's disease is a three-repeat tauopathy with abundant neuronal tau filaments. Scale bar, 50 μm.

CBD, and many cases of FTDP-17 (Fig. 3). It is also typical of argyrophilic grain disease and white matter tauopathy with globular glial inclusions, which belong to the FTD spectrum. A combination of neuronal and glial tau pathology is in evidence, with the glial pathology predominating in white matter tauopathy with globular glial inclusions (Kovacs et al. 2008). In contrast, in Pick's disease and some cases of FTDP-17, three-repeat tau predominates in the neuronal inclusions (Fig. 3), whereas in Alzheimer disease, other diseases with extracellular deposits, Guam Parkinsonism-dementia complex, tangle-only dementia, and some cases of FTDP-17, both three- and four-repeat tau isoforms make up the neurofibrillary lesions.

Distinct sets of tau isoforms in different neurodegenerative diseases and the presence of morphologically distinct filaments have led to the suggestion that self-propagating conformers of tau may exist (Goedert et al. 2010), akin to the prion strains accounting for the conformational variability of PrP^{Sc} (Colby and Prusiner 2011). In support, experimental evidence for the intercellular transfer of tau aggregates has been adduced (Clavaguera et al. 2009; Frost et al. 2009).

FTLD-TDP

By 2006, most cases of FTLD were known to exhibit either tau-positive or tau-negative inclusions (FTLD-U) (Fig. 2). The latter were first described in patients with MND (Okamoto et al. 1991). Four histological subtypes (A–D) of FTLD-U can be distinguished (Fig. 4) (Mackenzie et al. 2006, 2011; Sampathu et al. 2006). Type A is associated with bvFTD and PFNA, type B with bvFTD and FTD-MND, type C with SD, and type D with familial inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia (IBMPFD).

In 2006, transactive response-DNA binding protein-43 (TDP-43) was identified as the major component of the inclusions in most cases of FTLD-U (Figs. 2 and 4), MND, and FTLD-MND (Arai et al. 2006; Neumann et al. 2006). Around 50% of patients with FTD have TDP-43 inclusions. They include most cases of SD, ~45% of cases of bvFTD, as well as some cases of PNFA, LPA, FTDP-17, CBS, and PSP (Piguet et al. 2011a). Most cases of FTD-MND belong to the TDP-43 proteinopathy group. In Alzheimer disease, TDP-43 deposits

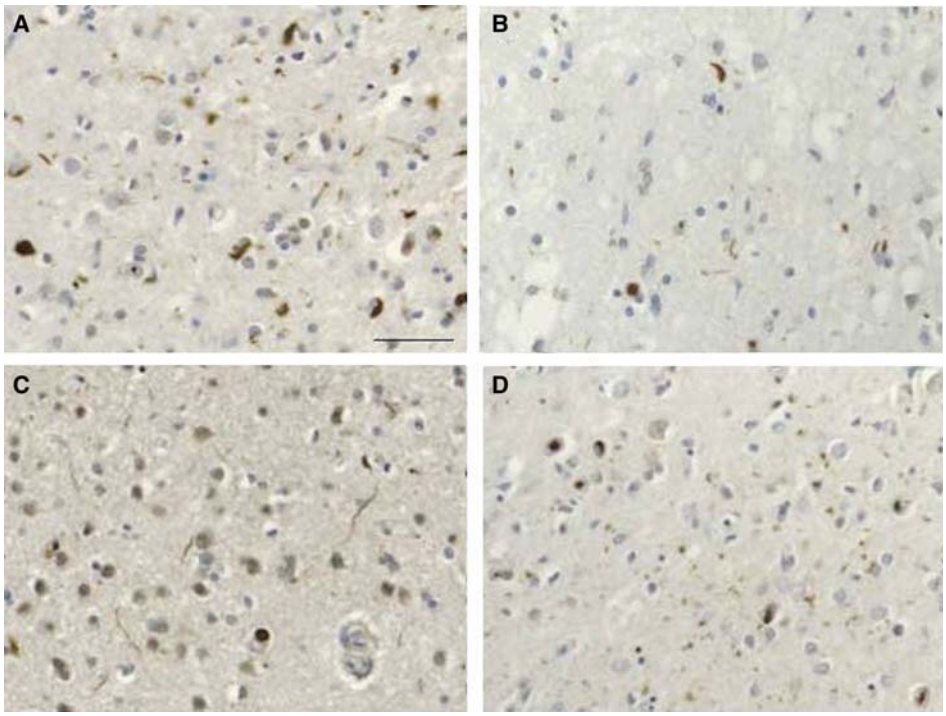

Figure 4. FTLD-TDP: Histological subtypes (A–D). Type A is characterized by abundant TDP-43-immunoreactive compact neuronal cytoplasmic inclusions and short dystrophic neurites, often with neuronal intranuclear inclusions (*A*); type B by abundant compact and granular cytoplasmic inclusions (*B*); type C by abundant long dystrophic neurites (*C*); and type D by abundant lentiform neuronal intranuclear inclusions and many short dystrophic neurites (*D*). Scale bar, 50 μm.

are found in a minority of cases in conjunction with the characteristic plaques and tangles (Amador-Ortiz et al. 2007).

TDP-43 is a ubiquitously expressed 414 amino acid RNA-binding protein of the heterogenous nuclear ribonucleoprotein (hnRNP) family with two RNA recognition motifs, nuclear localization and export signals, and a carboxy-terminal glycine-rich region. The glycine-rich region is predicted to show a prion domain, based on an algorithm that identifies yeast prion domains (Cushman et al. 2010). TDP-43 binds to noncoding RNAs, introns, and the 3′-untranslated regions of mRNAs, indicating a role in the integration of gene regulation. It functions as a transcriptional repressor and splicing modulator. UV-cross-linking and immunoprecipitation analysis has shown that TDP-43 has thousands of potential targets, with a preference for long clusters of UG-rich intronic sequences (Polymenidou et al. 2011; Tollerey et al. 2011). It binds to ~30% of the mouse transcriptome. TDP-43 negatively regulates its own mRNA and protein through binding to a long UG-rich region in its 3′-untranslated region (Ayala et al. 2011). It is predominantly nuclear, even though it normally shuttles between nucleus and cytoplasm. In FTD, TDP-43 it is found mainly in the cytoplasm in a hyperphosphorylated, ubiquitinated, and truncated form (Hasegawa et al. 2008).

FTLD-FUS

Most cases of FTLD-U show TDP-43 inclusions. In 2009, inclusions made of fused in sarcoma (FUS) were shown to account for the bulk of TDP-43-negative FTLD-U (Fig. 2) (Neumann et al. 2009a), following the discovery that mutations in *FUS* cause familial forms of ALS (Kwiatkowski et al. 2009; Vance et al. 2009). Less than 10% of cases of FTLD have FUS inclusions. They include atypical cases of FTLD-U, basophilic inclusion body disease, and neuronal intermediate filament inclusion body disease (Munoz et al. 2009; Neumann et al. 2009a,b). Neuroimaging of FTLD-FUS shows atrophy of frontoinsular and cingulate cortex, and of the head of the caudate nucleus (Josephs et al. 2010; Seelaar et al. 2010). FTD-FUS should be suspected when disease onset is before 40 years of age, in the absence of a family history of FTD, and the presence of caudate atrophy. This is reminiscent of a case from the early literature (Bonfiglio 1938). The existence of cases of PPA with FUS inclusions remains to be demonstrated.

FUS is a widely expressed 526 amino acid protein with an amino-terminal region rich in QGSY residues, a glycine-rich region, an RNA recognition motif, two RGG domains, and a zinc finger motif. Like TDP-43, it is a DNA/RNA-binding protein that is involved in transcriptional and translational regulation, as well as in mRNA splicing and transport. The predicted prion domain of FUS resides in the amino-terminal region (Cushman et al. 2010). In normal brain, FUS is concentrated in the nucleus, with smaller amounts in the cytoplasm. In FTD, the ability of FUS to shuttle to the nucleus is impaired, resulting in its cytoplasmic accumulation. FUS inclusions contain the full-length protein (Neumann et al. 2009a). Staining for TDP-43 and FUS appears to be mutually exclusive, suggestive of distinct subtypes of FTLD-U.

FTLD-UPS

FTLD-TDP and FTLD-FUS account for the majority of cases of FTLD-U. Additional forms remain to be discovered, because inclusions that are negative for TDP-43 and FUS, but positive for components of the ubiquitin-proteasome system (UPS), have been described (Fig. 2) (Holm et al. 2009).

GENETICS OF FRONTOTEMPORAL DEMENTIA

Dominantly inherited FTD is caused by mutations in seven genes. Mutations in *MAPT* (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998b), chromosome 9 open reading frame 72 (*C9ORF72*) (DeJesus-Hernandez et al. 2011; Renton et al. 2011), and progranulin (*GRN*) (Baker et al. 2006; Cruts et al. 2006) are the most common. The other four genes are *TARDBP* (Benajiba et al. 2009; Kovacs et al. 2009), *FUS*

(Ticozzi et al. 2009), valosin-containing protein (*VCP*) (Watts et al. 2004), and charged multivesicular body protein 2B (*CHMP2B*) (Skibinski et al. 2005).

Mutations in *MAPT*

Mutations in *MAPT* account for ~5% of cases of FTD and are believed to cause disease through a gain of toxic function mechanism. Most mutations are located in exons 9–12 (which encode the repeats) and the adjacent introns (Fig. 1B). It remains to be determined whether the amino acid changes in codon 5 of exon 1 are pathogenic. Mutations fall into two largely nonoverlapping groups: those with a primary effect at the protein level and those influencing the alternative splicing of tau pre-mRNA. Mutations acting at the protein level change or delete single amino acids in tau. This reduces the ability of tau to interact with microtubules, suggesting that this interaction is crucial for preventing the self-assembly of tau (Hasegawa et al. 1998). Some mutations also promote the assembly of tau into filaments (Goedert et al. 1999; Nacharaju et al. 1999). Mutations having their primary effect at the RNA level are intronic or exonic and increase the alternative mRNA splicing of exon 10. This changes the ratio of 3- to 4-repeat isoforms, resulting in the relative overproduction of 4-repeat tau and the formation of filamentous inclusions made of 4-repeat tau.

Cases with *MAPT* mutations show abundant filamentous inclusions made of hyperphosphorylated tau in either nerve cells or in both nerve cells and glial cells. Clinical and neuropathological phenotypes similar or identical to those of Pick's disease, PSP, CBD, and argyrophilic grain disease have been described. A given mutation can lead to different clinical syndromes in an individual family. Thus, mutation P301S in exon 10 of *MAPT* caused bvFTD in a father and CBD in his son (Bugiani et al. 1999), supporting the view that FTD and CBS are part of the same disease spectrum (Kertesz et al. 2000).

Haplotypes H1 and H2 characterize *MAPT* in populations of European descent. They result from a 900 kb inversion/noninversion (H1/H2) polymorphism (Stefansson et al. 2005). Inheritance of the H1 haplotype is a risk factor for PSP and CBD (Williams and Lees 2009). This was confirmed in a genome-wide association study of PSP, which also implicated proteins involved in vesicle traffic, the unfolded protein response and the innate immune system (Höglinger et al. 2011). Heterozygous microdeletions in the chromosomal region, which defines the H1 and H2 haplotypes, give rise to a clinical phenotype consisting of mental retardation, hypotonia, and a characteristic face (Koolen et al. 2006; Sharp et al. 2006; Shaw-Smith et al. 2006). Besides *MAPT*, the deleted region comprises five additional genes [corticotrophin-releasing hormone receptor 1 (*CRHR1*), intramembrane protease 5 (*IMP5*), *NP 689679.1*, *NP 787078.1*, and *KIAA1267*]. Deletions occur on the H2 haplotype through low-copy repeat-mediated nonallelic homologous recombination. An association has also been described between the H1 haplotype and idiopathic Parkinson's disease (Pastor et al. 2000), a disease without tau inclusions. The elevated risk of PSP and CBD conferred by the H1 haplotype appears to promote *MAPT* transcription and incorporation of exon 10, resulting in increased levels of four-repeat tau (Caffrey et al. 2006).

Mutations in *C9ORF72*

The cause of chromosome 9p21-linked FTD-MND has been identified as a hexanucleotide (GGGGCC) expansion in the noncoding region of *C9ORF72*, a gene that encodes a protein of unknown function (DeJesus-Hernandez et al. 2011; Renton et al. 2011). The hexanucleotide expansion leads to the loss of an alternatively spliced transcript and the formation of nuclear RNA foci. The latter may be toxic. The repeat expansion in *C9ORF72* is also a common cause of isolated FTD and MND.

Mutations in *GRN*

Mutations in *GRN* account for ~5% of cases of FTD and cause disease by a loss of function mechanism. Progranulin is a 593 amino acid

glycoprotein consisting of 7.5 tandem repeats of a 12-cysteine granulin motif. Although its function is only incompletely understood, progranulin may be a physiological antagonist of tumor necrosis α signaling (Tang et al. 2011). It has been reported to act on nerve cells by binding to sortilin following release from activated microglial cells (Hu et al. 2010). Mutations in *GRN* include gene deletions, as well as nonsense, frameshift, and splice-site mutations that cause premature termination, creating null alleles with the mutant RNAs being degraded by nonsense-mediated decay (Van Swieten and Heutink 2008). Known mutations result in haploinsufficiency, implying that progranulin is critical for the survival of neurons in adult brain. Reduced levels of plasma progranulin have been used to identify mutation carriers (Ghidoni et al. 2008). Mutations in *GRN* cause diseases belonging to the whole spectrum of FTD, with a predominance of bvFTD and PNFA (Yu et al. 2010). Parietal deficits and CBS have been observed (Spina et al. 2007). This is reflected in frontotemporoparietal cortical atrophy. Cases with *GRN* mutations show type A TDP-43 inclusions (Mackenzie et al. 2006), showing that a reduction in progranulin levels causes the accumulation of TDP-43. Unlike *TARDBP* mutations, mutations in *GRN* do not appear to cause MND. In a genome-wide study of FTLD-TDP, significant association was detected with three single nucleotide polymorphisms in the transmembrane protein 106B locus (*TMEM106B*) (Van Deerlin et al. 2010). It was most significant in patients with *GRN* mutations.

Mutations in *TARDBP*

Mutations in *TARDBP* are mostly associated with inherited forms of MND, consistent with the presence of TDP-43 inclusions in upper and lower motor neurons in patients with the disease (Gitcho et al. 2008; Sreedharan et al. 2008; Yokoseki et al. 2008). *TARDBP* mutations have also been described in two patients with bvFTD and SD who went on to develop MND (Benajiba et al. 2009). Histopathological changes were not documented. One patient with a K263E change in *TARDBP* developed FTD, supranuclear palsy, and chorea, in the absence of MND. Abundant neuronal and glial TDP-43 deposits were in evidence, especially in brainstem and subcortical nuclei (Kovacs et al. 2009). The mechanisms by which mutations in *TARDBP* cause neurodegeneration are unclear. Pathological assembly is associated with a marked reduction in nuclear TDP-43 staining (Neumann et al. 2006) and the cytoplasmic accumulation of TDP-43 is believed to be an early event (Giordana et al. 2010). A combination of loss of function and gain of toxic function mechanisms may be at play. Wild-type TDP-43 is prone to aggregation and disease-causing mutations increase its aggregation and toxicity (Johnson et al. 2009). Many disease-causing mutations are located in the carboxy-terminal domain of TDP-43.

Mutations in *FUS*

Mutations in *FUS* cause inherited forms of MND (Kwiatkowski et al. 2009; Vance et al. 2009). Patients have FUS inclusions in spinal cord and cerebral cortex. Cases of FTD and/or FTD-MND may also be caused by mutations in *FUS* (Ticozzi et al. 2009), but larger clinicopathological series must be awaited. Like mutant TDP-43, mutant FUS accumulates in the cytoplasm, where it is found in stress granules (Dormann et al. 2010; Nishimoto et al. 2010). Wild-type FUS is prone to aggregation, but disease-causing mutations do not increase its aggregation or toxicity (Sun et al. 2011). The mutations appear to cause cytoplasmic mislocalization instead. Although several disease-causing mutations are present in its amino-terminal region, most mutations are located in the carboxy-terminus of FUS.

Mutations in *VCP*

Mutations in *VCP* cause IBMPFD through what appears to be a gain of function (Watts et al. 2004), possibly as the result of a dominant negative effect. IBMPFD affects skeletal muscle, bone, and nervous system, with dementia developing in ~30% of patients. It is characterized

by the presence of type D TDP-43 inclusions (Neumann et al. 2007). Some missense mutations in *VCP* cause inherited MND (Johnson et al. 2010) and motor neuron abnormalities are present in many patients with IBMPFD. Furthermore, a missense mutation in *vacuolar protein sorting 54* (*Vps54*), the homolog of *VCP*, causes motor neuron degeneration in the wobbler mouse, a model of MND (Schmitt-John et al. 2005). VCP belongs to the type II AAA^+ (ATPases associated with a variety of activities) family and takes part in multiple cellular processes, including protein quality control, nuclear functions, and the regulation of membrane dynamics. It extracts ubiquitinated proteins from complexes, so that they can be degraded by the proteasome. VCP promotes autophagic protein degradation, with disease-causing mutations giving rise to defective autophagosome maturation (Ju and Weihl 2010). Transgenic mice expressing mutant VCP show many characteristics of IBMPFD, including involvement of skeletal muscle, bone and brain, and show increased activation of NF-κB signaling (Custer et al. 2010). In the brain of these mice, TDP-43 is redistributed from the nucleus to the cytoplasm, in the absence of nuclear inclusions. In a *Drosophila* model of IBMPFD, a genetic screen has identified TBPH, the fly ortholog of TDP-43, as one of three RNA-binding proteins that dominantly suppress degeneration (Ritson et al. 2010). In this model, VCP mutations lead to the redistribution of TDP-43 to the cytoplasm.

Mutations in *CHMP2B*

Mutations in *CHMP2B* appear to cause disease through a gain of toxic function mechanism (Skibinski et al. 2005). The early signs are those of bvFTD, with extrapyramidal symptoms developing later, resulting in a clinical picture of CBS (Gydesen et al. 2002). In a Danish family with a truncating *CHMP2B* mutation, the intracytoplasmic inclusions are ubiquitin-positive, but negative for TDP-43 and FUS (Holm et al. 2009). CHMP2B is a component of the endosomal-sorting complex required for transport-III (ESCRT-III), which is involved in the degradation of proteins in the endocytic and autophagic pathways. A disruption of these processes results in the accumulation of autophagosomes, possibly leading to FTD (Lee et al. 2007).

IMPLICATIONS FOR UNDERSTANDING ALZHEIMER DISEASE

For a long time, tau inclusions were believed by many to be epiphenomena of little relevance. Reasons underlying this negative stance were the absence of genetic evidence linking dysfunction of tau to neurodegeneration and the presence of tau pathology in diseases other than Alzheimer disease. Things changed with the identification of mutations in *MAPT* in cases of FTDP-17 with filamentous tau pathology, establishing that dysfunction of tau is sufficient to cause neurodegeneration and dementia (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998b). Thus, a pathway leading from soluble to insoluble, filamentous tau is central to the neurodegenerative process in the human tauopathies. It is therefore important to understand the mechanisms underlying tau aggregation and its downstream consequences for cell function. With the benefit of hindsight, it is clear that Alzheimer's description of silver-positive inclusions in cases with either presenile dementia or lobar cortical atrophy marked the beginning of the tauopathy field.

The crucial importance of FTDP-17T is that it proves that mutations in *MAPT* can lead to neurofibrillary assembly, neurodegeneration and dementia, in the absence of Aβ amyloid deposits. The morphologies of tau filaments observed in the various forms of FTDP-17T vary (Crowther and Goedert 2000). Some mutations, such as V337M and R406W, produce filaments that appear identical to the paired helical and straight filaments of Alzheimer disease (Spillantini et al. 1996; Reed et al. 1997; Hutton et al. 1998; Poorkaj et al. 1998). All six tau isoforms are affected by the mutations and are incorporated into the filaments, which give rise to a pattern of tau bands on SDS-PAGE identical to that seen in Alzheimer disease. Mutation G389R also affects all six tau isoforms

and the majority of filaments resemble the straight filaments of Alzheimer disease (Murrell et al. 1999), despite the presence of Pick-like bodies by light microscopy. In contrast, in the case of mutations that increase the splicing of exon 10, the filaments appear as irregularly twisted ribbons, which are made of tau isoforms with four repeats (Spillantini et al. 1997). In the case of mutation P301L in exon 10, which affects only four-repeat tau isoforms, the majority of filaments consists of narrow, irregularly twisted ribbons, with a smaller number of straight filaments (Spillantini et al. 1998c).

Unlike Alzheimer disease and several other neurodegenerative diseases with tau inclusions, most cases of FTD lack extracellular deposits. However, focal Alzheimer disease pathology is diagnostic of a significant proportion of cases of PPA. Crossing mice transgenic for human mutant amyloid precursor protein with mice transgenic for human mutant tau results in increased tau deposition in some brain regions (Lewis et al. 2001). Similarly, in mice transgenic for the Danish mutant form of human BRI2 and mutant tau, the extracellular deposition of Dan-amyloid promotes tau phosphorylation and aggregation (Coomaraswamy et al. 2010). Phosphorylation of tau by GSK3β and AMP-activated protein kinase is a potential mechanism. This is consistent with the coexistence of extracellular amyloid deposits and intraneuronal tau inclusions in Alzheimer disease, familial British and Danish dementias, and in some diseases caused by mutations in the prion protein gene (Ghetti et al. 1994; Vidal et al. 2004; Goedert and Spillantini 2006). It suggests that extracellular amyloid deposits with a certain conformation trigger the intraneuronal assembly of tau into filaments.

Tau is required for Aβ toxicity in experimental models (Roberson et al. 2007). The absence of Aβ toxicity in mice lacking *MAPT* may result from a reduction in excitotoxicity, because of the decreased dendritic localization of the tyrosine kinase Fyn, resulting in hypophosphorylation of the NMDA receptor and a reduced interaction with postsynaptic density protein-95 (Ittner at al. 2010). Haploinsufficiency of p73, a member of the p53 protein family, has been found to be associated with the formation of tau aggregates in nerve cells and to potentiate Aβ toxicity, possibly through the activation of stress-activated protein kinases (Wetzel et al. 2008).

The intraneuronal pathology of Alzheimer disease may originate in a single cell and become self-sustaining, irrespective of upstream factors. Thus, injection of sonicated brain extract from mice with abundant tau inclusions into the cerebral cortex and hippocampus of transgenic mice lacking inclusions induces the assembly of human wild-type tau into filaments and leads to the spreading of pathology from the injection sites to neighboring brain regions (Clavaguera et al. 2009). Injection of brain extract immunodepleted of tau or divided into soluble and insoluble fractions shows that insoluble tau induces aggregation, in the absence of obvious signs of neurodegeneration. Parallel work has shown the transfer of aggregated tau between transfected cells (Frost et al. 2009). It thus appears that the tau species responsible for transmission and toxicity are not identical. An uncoupling of prion infective titre and neurotoxicity has been described (Sandberg et al. 2011).

Although tau inclusions form in many neurodegenerative diseases, their relevance for neurotoxicity remains a subject for debate. Studies using transgenic mice overexpressing human mutant tau in a conditional manner have reported a dissociation between tangle formation and nerve cell death (Santacruz et al. 2005). It appears that soluble hyperphosphorylated tau can contribute to nerve cell dysfunction prior to assembly into filaments. This is reminiscent of *Drosophila* and *Caenorhabditis elegans* lines expressing human wild-type or mutant tau, in which nerve cell loss and a reduced lifespan are observed, in the apparent absence of tau filaments (Wittmann et al. 2001; Kraemer et al. 2003). In genetic modifier screens in *Drosophila*, an increase in kinase activity enhanced tau toxicity, whereas an increase in phosphatase activity was beneficial (Feany et al. 2010). Activation of oxidative defences was also beneficial. In *C. elegans*, loss of *Sut-2* (suppressor of tau pathology-2),

eliminated the toxic effects of human mutant tau, possibly via an increase in autophagic clearance (Guthrie et al. 2009).

The main goal behind work on tauopathies is to transform the treatment of common neurodegenerative diseases through an understanding of the underlying molecular pathways. There is an unmet need for mechanism-based therapies of Alzheimer disease. Tau binds to microtubules and boosting this interaction may be beneficial. This may be achieved through a reduction of the hyperphosphorylation of tau (Le Corre et al. 2006). In Alzheimer disease, tau assembles into paired helical and straight filaments. The assembly pathway is being defined and inhibitors of aggregation are being developed (Pickhardt et al. 2005; Taniguchi et al. 2005). Immunotherapy has been shown to clear tau aggregates from transgenic mouse brain and to reduce functional impairment (Asuni et al. 2007). Because aggregation is a concentration-dependent process, a reduction in production and/or increased clearance of tau are also potential targets (Morris et al. 2011).

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