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The cytoskeleton in neurodegenerative diseases

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Abstract

Abundant abnormal aggregates of cytoskeletal proteins are neuropathological signatures of many neurodegenerative diseases that are broadly classified by filamentous aggregates of neuronal intermediate filament (IF) proteins, or by inclusions containing the microtubule-associated protein (MAP) tau. The discovery of mutations in neuronal *IF* and *tau* genes firmly establishes the importance of neuronal IF proteins and tau in the pathogenesis of neurodegenerative diseases. Multiple *IF* gene mutations are pathogenic for Charcot–Marie–Tooth (CMT) disease and amyotrophic lateral sclerosis (ALS) — in addition to those in the copper/zinc superoxide dismutase-1 (*SOD1*) gene. *Tau* gene mutations are pathogenic for frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), and tau polymorphisms are genetic risk factors for sporadic progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Thus, IF and tau abnormalities are linked directly to the aetiology and pathogenesis of neurodegenerative diseases. *In vitro* and transgenic animal models are being used to demonstrate that different mutations impair protein function, promote tau fibrilization, or perturb *tau* gene splicing, leading to aberrant and distinct tau aggregates. For recognition of these disorders at neuropathological examination, immunohistochemistry is needed, and this may be combined with biochemistry and molecular genetics to properly determine the nosology of a particular case. As reviewed here, the identification of molecular genetic defects and biochemical alterations in cytoskeletal proteins of human neurodegenerative diseases has facilitated experimental studies and will promote the development of assays of molecules which inhibit abnormal neuronal IF and tau protein inclusions.

Keywords

neuronal intermediate filament; tau; cytoskeleton; mutation; neurodegenerative disease; peripheral neuropathy

Introduction

Many chronic progressive neurodegenerative disorders are characterized by the presence of abnormal protein aggregates in neurons and glia of the central nervous system (CNS) [1–6]. The identification of disease-specific abnormal protein inclusions has illuminated mechanisms of pathogenesis as well as facilitating the molecular classification of the neurodegenerative diseases. Several sporadic and familial neurodegenerative diseases are characterized by the formation of filamentous deposits of abnormal brain proteins. Thus, a heterogeneous group of movement disorders and dementias is linked by the presence of

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pathological intra-cellular inclusions of neuronal intermediate filament (IF) proteins or the microtubule-associated protein (MAP) tau; each appears to share common mechanisms of disease [6]. These disorders are called, respectively, neuronal intermediate filamentopathies and tauopathies (Table 1). Despite the diverse phenotypic expression, brain dysfunction and neurodegeneration in both classes of disease are linked to the progressive accumulation of abnormal filamentous protein; and this, together with the absence of other disease-specific neuropathological abnormalities, provides evidence implicating neuronal IF and tau in disease onset and progression. The discovery of multiple mutations in neuronal *IF* genes in the hereditary neuropathy Charcot–Marie–Tooth disease (CMT) and amyotrophic lateral sclerosis (ALS) (Table 2) [7–17] and in the *tau* gene in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (Table 3) [18–47] has led to the unequivocal evidence that neuronal IF and tau abnormalities alone are sufficient to cause neurodegenerative disease. These discoveries have opened up new avenues of research into the roles of neuronal IF proteins and tau in mechanisms of brain dysfunction and neurodegeneration.

This review is designed to integrate and interpret the remarkable recent advances that have led to new insights into the nosology and mechanisms of action of neuronal IF proteins and tau in neurodegenerative diseases. It starts with brief summaries of the human neuronal IF and tau genes; the functions of neuronal IFs and the six alternatively spliced tau isoforms are reviewed; the role of neuronal IF proteins and tau abnormalities in neurodegenerative diseases is discussed; and data from transgenic (TG) models of neuronal intermediate filamentopathies and tauopathies are considered.

Structure, function, and molecular genetics of neuronal intermediate filaments

There are six types of IF proteins classified by gene structure and sequence homology. The name ‘intermediate’ derives from their diameter (10–12 nm), being intermediate between microtubules (25 nm) and microfilaments (7–10 nm). Five major neuronal IF proteins are expressed in the adult human CNS: three neurofilament (NF) proteins: light (NF-L), medium (NF-M), and heavy (NF-H) subunits of approximately 68, 145, and 200 kD, respectively; peripherin of 57 kD; and α-internexin of 66 kD (Figure 1). NFs and α-internexin genes have homologous intron–exon organization and are type IV, while peripherin encodes a type III IF protein resembling vimentin [6,48]. The IF proteins have a tripartite structure: a central rod domain of about 300 amino acids formed from a highly conserved α-helix, and amino- and carboxy-terminal regions called head and tail domains, respectively, which are less conserved [6].

The assembly and transport of neuronal IF proteins are probably regulated by post-translational modification of the head region by phosphorylation and *O*-glycosylation [5]. All subunits are constitutively phosphorylated and most of the phosphorylation sites containing lysine–serine–proline (KSP) motifs are located in the tail domains of NF-M and NF-H [5,6,49]. Most of the serines in these motifs may be phosphorylated, which makes NF-M and NF-H highly phosphorylated proteins. The phosphorylation state of these proteins relates to their function, ie phosphorylation of the tail domain modifies the axonal diameter, which is important for controlling axonal conductivity, an important function of motor neurons. After synthesis in the perikaryon, neuronal IFs are rapidly assembled into filaments and actively transported along microtubules (MTs) in axons by motors like kinesin and dynein, where they move at a net slow velocity of 0.2–1 mm/day [6].

Assemblies of IFs form 10 nm filaments. NFs copolymerize requiring NF-L with either NF-M or NF-H for proper filament formation [5,6]. Peripherin and α-internexin, in contrast, can

self-assemble and co-assemble with NFs [6,50]. α-Internexin is widely expressed during development and throughout the adult CNS, but at lower levels than NFs. Peripherin is found predominantly in the peripheral nervous system (PNS), although it is also expressed in specific populations of neurons including spinal motor neurons, cranial nerve nuclei of sensory origin, and small interneurons.

Neuronal IFs and disease

The use of phosphorylation-dependent and -independent antibodies to NF epitopes has enabled the immunohistochemical dissection of these proteins and has revealed that NFs within the perikaryon and proximal segments of axons and dendrites are normally hypophosphorylated, while NFs in axons are heavily phosphorylated [51,52]. In neurodegenerative diseases including Alzheimer's disease (AD), neuronal IF proteins are present either as innocent bystanders or as chaperone-like proteins together with tau in neurofibrillary tangles (NFTs), dystrophic neurites of neuritic plaques (NPs), and neuropil threads. In Parkinson's disease (PD) and dementia with Lewy bodies (DLB), α-internexin and NF triplet proteins are found in a subset of α-synuclein-positive Lewy bodies, although their role in lesion formation or neurodegeneration is uncertain [53,54]. In ALS, abnormal accumulations of phosphorylated NF proteins are present in the perikaryon of affected neurons, swollen axons, and spheroids, although the significance of the phosphorylation of NF proteins within the cytoplasm is unclear [49,55,56]. However, abnormal phosphorylation may impede axonal transport and contribute to neuronal dysfunction, while constitutive phosphorylation of NFs may protect them against proteolysis [57].

α-Internexin is expressed by most, if not all, neurons as they commence differentiation and precedes the expression of the NF triplet proteins. In the adult brain, α-internexin is expressed at relatively low levels in comparison to the NF proteins and there is selective anatomical expression with greater immunoreactivity being seen in the cerebellar granule cells, the source of thin-calibre parallel fibres, and in the neuron cell bodies and processes of cortical layer II neurons [58]. α-Internexin has recently been identified as a major component of the pathological inclusions of the frontotemporal dementia, neuronal intermediate filament inclusion disease (NIFID) (Figure 2). The signature lesion of this disease is the neuronal cytoplasmic inclusion, which is tau- and α-synuclein negative, variably ubiquitinated, and contains epitopes of all type IV IF proteins [59–61]. In addition to NFs in swollen axons and spheroids in ALS, peripherin has also been demonstrated by immunohistochemistry (IHC) in the ubiquitinated inclusions of ALS [62]. However, protein chemistry has not revealed any change in mobility on western blots of NFs, α-internexin or peripherin in ALS, PD, DLB, or NIFID when compared with normal controls [59,63]. Thus, other factors may play a role in the formation of abnormal neuronal IF aggregates including dysregulation of protein synthesis, failure of axonal transport, abnormal phosphorylation, and proteolysis.

Strong evidence for the role of neuronal IFs in pathogenesis has come from the discovery of mutations in *IF* genes in ALS and CMT in particular (Table 2). For example, both the Q333P mutation in the rod domain and to a lesser degree the P8R mutation in the head domain of NF-L disrupt the self-assembly of NF-L and the formation of NF-L/NF-M heteropolymers in a transient transfection system [64]. Codon deletions and insertions in the phosphorylation domain (KSP) of the tail region of NF-H have been reported in sporadic cases of ALS, and mutations in the NF-L gene located on chromosome 8 have been reported in several cases of CMT with neuroaxonal degeneration [7–17]. Thus, mutations in neuronal *IF* genes can directly cause selective motor neuron degeneration, axonal disorganization, and death.

Experimental animal models of neuronal intermediate filamentopathies

Although no gross developmental abnormalities have been reported in mouse knock-out experiments, the differential expression of neuronal IF proteins during development indicates a role for these proteins in axon formation and maintenance [4–6]. The absence of IFs in these TG models is, however, associated with measurable functional deficits in axogenesis. Models over-expressing single or multiple neuronal *IF* genes have replicated some of the features of human diseases. For example, overexpression of NF-M and NF-H has been shown to produce perykaryal inclusions of IFs resembling those seen in human disease [65], and a TG mouse model with overexpression of rat *α*-internexin has been shown to cause abnormal neurofilamentous accumulations and motor co-ordination deficits [66]. A model of CMT, type 2 (CMT-2) has been associated with NF assembly disruption and transport, mechanisms probably underlying neurodegeneration in this disease [5]. In a mouse model with a leucine to proline mutation at residue 394, selective motor neuron degeneration developed probably as a result of NF assembly disruption [67]. Ribonucleic acid (RNA) processing has also been implicated in the pathogenesis of neurodegenerative diseases: the expression of an NF-L transgene with a mutant messenger RNA (mRNA) stability determinant disrupts enteric and motor neurons in a TG mouse, indicating that motor neuron degeneration may be attributable to expression of mutant mRNA rather than mutant protein by the NF-L transgene [68]. The expression of neurotoxic splice variants of peripherin may also contribute to the neurodegenerative mechanism in ALS [69]. In a TG model, mice overexpressing peripherin developed a late-onset, and progressive, motor neuron disease with neuronal IF inclusions comparable to the spheroids seen in ALS [70]. However, these mice also developed motor neuron death during ageing. The mechanism leading to peripherin-induced neurodegeneration is unclear. Although familial PD has been linked to mutations in *α-synuclein* and *parkin* genes, a point mutation has been reported in the *NF-M* gene causing a substitution of serine for glycine at residue 336 in an affected woman at age 16 years [14]. Thus, mutations in *NF* genes can generate heterogeneous clinical and neuropathological phenotypes and although TG models recapitulate features of these human diseases, additional models are required to elucidate the mechanisms of action of each genetic defect.

Structure, function, and molecular genetics of tau

Several sporadic and familial neurodegenerative disorders that are characterized clinically by dementia and/or motor dysfunction are characterized pathologically by abnormal intracellular accumulations of the MAP tau, collectively called tauopathies (Table 1). The progressive accumulation of filamentous tau inclusions in the absence of other disease-specific neuropathological abnormalities provides evidence implicating tau dysfunction in disease onset and progression. However, the discovery of pathogenic *tau* gene mutations in the heterogeneous group of disorders known as FTDP-17 provided confirmation of the central role of tau abnormalities in the aetiology of neurodegenerative disorders [24,43,71,72]. These findings have opened novel areas of investigation into the mechanisms of tau dysfunction and the relationship of tau abnormalities to brain degeneration.

Tau proteins are low-molecular-weight MAPs that are abundant in the CNS, where they are expressed predominantly in axons [73,74], and at low levels in astrocytes and oligodendrocytes [75,76]. They are also expressed in axons of PNS neurons [77]. Human tau proteins are encoded by a single copy gene on chromosome 17q21 of 16 exons, with CNS isoforms generated by alternative mRNA splicing of 11 of these exons (Figure 3) [78–80]. In adult human brain, alternative splicing of exons 2, 3, and 10 generates six tau isoforms ranging from 352 to 441 amino acids in length which differ by the presence of either three or four MT binding repeats (3R tau or 4R tau, respectively) consisting of carboxy-terminal

tandem repeat sequences of 31 or 32 amino acids each that are encoded by exons 9–12 [81,82]. Additionally, alternative splicing of exons 2 and 3 leads to the absence (0N) or presence of inserted sequences of 29 (1N) or 58 (2N) amino acids in the amino-terminal third of the molecule. In the adult human brain, the ratio of 3R : 4R tau isoforms is approximately 1 : 1, while the 0N, 1N, and 2N tau isoforms comprise about 37%, 54%, and 9%, respectively, of total tau [83,84].

Tau binds to and stabilizes MTs and promotes MT polymerization [73,85]. The MT binding domains of tau are localized within the four MT binding motifs (Figures 3 and 4). These motifs are composed of highly conserved binding elements [85–87]. The function of tau as an MT binding protein is regulated by phosphorylation [87–92]. Phosphorylation at approximately 30 of these sites has been reported in normal tau proteins [93–95]. Several Ser/Thr protein kinases and Ser/Thr protein phosphatases have been implicated in regulating the phosphorylation state and thus the function of tau. The phosphorylation sites are clustered in regions flanking the MT binding repeats, and increasing tau phosphorylation at multiple sites negatively regulates MT binding [89–92]. However, in both sporadic and familial tauopathies including AD and FTDP-17, tau is hyperphosphorylated and it is this ‘abnormal’ tau that is the principal component of the filamentous aggregates in neurons and glia that are the pathological hallmarks of these disorders [96–98].

Although there is clinical and neuropathological overlap between the neurodegenerative tauopathies, each can be distinguished with variable probability by the distribution, severity, and morphology of tau-positive inclusions. In cases with a *tau* gene mutation, in addition to extensive neuronal loss and astrocytosis, tau-positive neuronal and glial inclusions may resemble those seen in AD, PSP, CBD, and Pick’s disease. This neuropathological heterogeneity is a striking feature of FTDP-17 and it is complemented by biochemical heterogeneity where there is variation in the proportions of tau isoforms, not only with different mutations, but also within the same brain. Nevertheless, cases with *tau* gene mutations may be broadly grouped according to the pattern of tau immunostaining and tau isoform ratios as demonstrated by western blotting (Figure 5).

Tau gene mutations cause tau dysfunction by several distinct mechanisms. Intronic and some exonic mutations affect the alternative splicing of exon 10 and consequently alter the relative proportions of 3R and 4R tau. Other exonic mutations impair the ability of tau to bind MTs and to promote MT assembly. Some mutations also promote the assembly of tau into pathological amyloid filaments. Moreover, additional mechanisms may play a role in the case of some coding region mutations [1]. The intronic mutations clustered around the 5′ splice site of exon 10, as well as several mutations within exon 10 (Figure 4), increase the ratio of 4R : 3R tau by altering exon splicing [24,27,99–105]. As a result of these mutations, there is a relative increase in mRNA containing exon 10. Biochemical analysis of insoluble tau extracted from FTDP-17 brain tissue reveals predominantly 4R tau isoforms (Figure 5) [72,106–108]. Furthermore, 4R tau protein levels are increased in both affected and unaffected regions of FTDP-17 brains [72,84,107].

Mutations in the *tau* gene may alter exon 10 splicing by affecting several of the regulatory elements described above. For example, the intronic mutations as well as the exonic mutations at codon 305 (S305N and S305S) may destabilize the inhibitory stem-loop structure and alter the ratio of 3R : 4R tau [24,27,102]. The mechanisms by which changes in the ratio of 3R : 4R tau lead to neuronal and glial dysfunction and cell death remain unclear. However, 3R and 4R tau may bind to distinct sites on MTs [109] and it is possible that a specific ratio of tau isoforms is necessary for normal MT function [110]. Thus, the altered ratio of 3R : 4R tau may directly affect MT function. In addition, overproduction of

4R tau isoforms may lead to an excess of free tau in the cytoplasm that is prone to aggregate and polymerize into filaments over time.

Another subset of the *tau* mutations has no effect on *tau* splicing, but instead alters the ability of tau to interact with MTs: missense mutations K257T, G272V, ΔK280, ΔN296, P301L, P301S, V337M, G389R, and R406W reduce the binding of tau to MTs and decrease its ability to promote MT stability and assembly *in vitro* [20,25,31,83,111,112]. In contrast to mutations that affect the splicing of *tau*, these mutations do not alter the expression pattern of 3R and 4R tau [84]. The P301L mutation causes a moderate (25%) decrease in soluble 4R tau due to the selective aggregation of mutant 4R tau isoforms [84,113,114]. Biochemical analysis of insoluble tau extracted from brain tissue of patients with these mutations reveals a variety of patterns.

A subset of missense *tau* gene mutations may cause FTDP-17, at least in part, by promoting tau aggregation. *In vitro* studies demonstrated that mutations, including K257T, G272V, ΔK280, ΔN296, P301L, P301S, V337M, and R406W, promote heparin- or arachidonic acid-induced tau filament formation relative to wild type tau [114–118]. The missense *tau* gene mutations may also affect tau function by altering its phosphorylation state, and several mutations decrease the binding affinity of tau for protein phosphatase 2A, a major phosphatase implicated in the regulation of the MT-binding activity of tau [119].

Experimental animal models of tauopathies

Several TG models of tau pathology have been generated by overexpressing human tau proteins in mice [120,121]. However, these mice either were asymptomatic or developed pathology that was localized to the spinal cord and/or lacked many of the key features of tau-based disorders. In contrast, the introduction of the P301L mutation led to the development of TG mice that develop age- and gene dose-dependent accumulation of tau tangles in the brain and spinal cord with associated nerve cell loss and gliosis, as well as behavioural abnormalities [120,122]. Similar to human disease, the tau aggregates were composed of only mutant human tau, further implicating the P301L change in promoting the selective aggregation of mutant tau. Other systems were also developed to model various aspects of human tauopathies including a transgenic mouse overexpressing the shortest human tau isoform which acquired age-dependent tau pathology similar to that seen in FTDP-17 and ALS/PDC [123]. Overexpression of either wild-type or mutant tau (R406W and V337M) in *Drosophila melanogaster* demonstrated features of tauopathy including adult-onset progressive neurodegeneration with accumulation of abnormal tau [124]. However, the neurodegeneration occurred in the absence of NFT formation. More recent studies demonstrated NFT-like pathology when tau was co-expressed with *shaggy*, a homologue of glycogen synthase 3-kinase, an enzyme implicated in tau phosphorylation [125]. Neurodegeneration and defective neurotransmission have also been demonstrated in a *tau* TG *Caenorhabditis elegans*. In this model, pan-neuronal expression of normal and mutant tau resulted in altered behaviour, accumulation of insoluble phosphorylated tau, age-dependent loss of axons and neurons, and structural damage to axonal tracts [126]. Clearly, these models recapitulate various features of the tauopathies that will facilitate understanding of the molecular mechanisms underlying tau neurodegeneration.

Conclusions

The accumulation of filamentous neuronal IF and tau proteins are common features of a wide variety of sporadic and familial neurodegenerative disorders. These diseases are distinguished by the distinct topographic and cell type-specific distribution of inclusions. The biochemical and ultrastructural characteristics of the inclusions also reveal a significant

phenotypic overlap. The discovery that multiple mutations in neuronal *IF* and *tau* genes lead to the abnormal protein aggregation demonstrates that neuronal IF and tau dysfunction are sufficient to produce neurodegenerative disease. Experimental evidence indicates that mutations lead to specific alterations in expression, function, and biochemistry of neuronal IF and tau proteins. The identification of additional gene mutations or polymorphisms at distinct genetic loci that either cause or are risk factors for disease will provide additional insights into disease pathogenesis. Taken together, these new insights will lead to the development of novel strategies for treatment and prevention.

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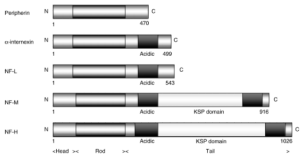

Figure 1.

Structure of neuronal IF proteins. All proteins share a conserved structure of a head, rod with coils forming an α-helix, and tail domains containing glutamic acid-rich sequences and repeat phosphorylation motifs of lysine–serine–proline (KSP). Figures refer to the initial and terminal amino acids of each protein

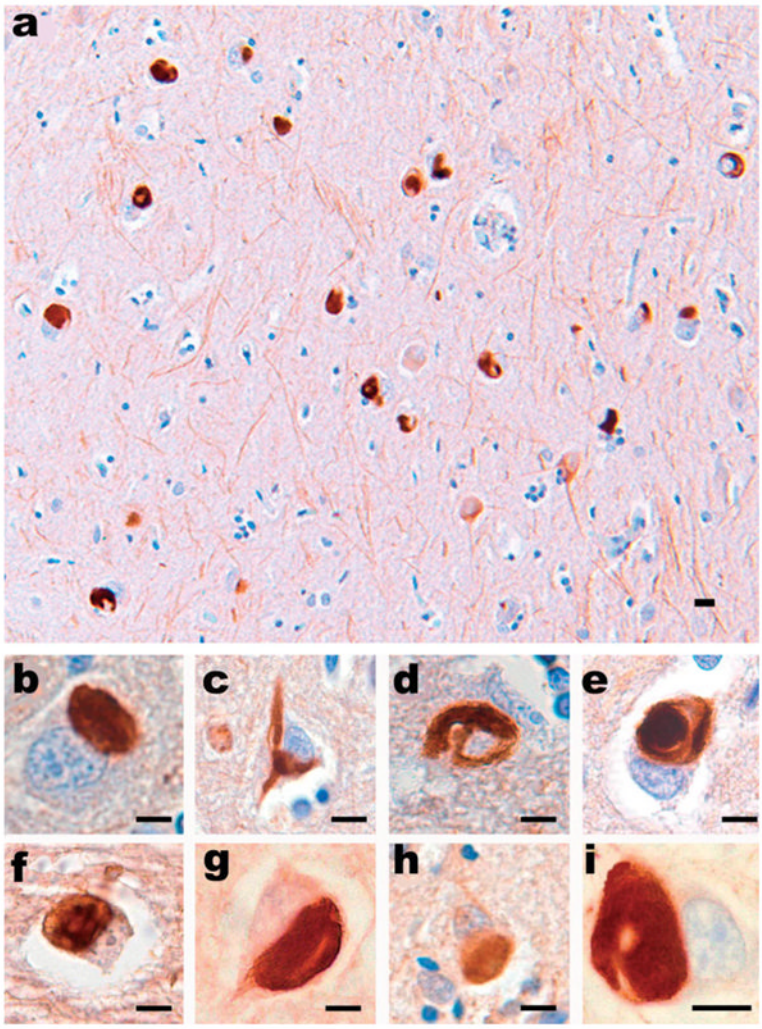

Figure 2.

All type IV neuronal IF proteins are present in the pathological inclusions of NIFID. (a) Neuronal inclusions in the subiculum of a case of NIFID contain *α*-internexin. *α*-Internexin immunohistochemistry. Neuronal inclusions in NIFID are pleomorphic. (b) Pick body-like inclusions are the most common morphological type. (c) A flame-shaped, NFT-like inclusion. (d) A filamentous serpiginous inclusion. (e) A globose NFT-like inclusion. *α*-Internexin immunohistochemistry. Epitopes of NF triplet proteins are present in inclusions of NIFID and are recognized by (f) phosphorylation-dependent NF-H; (g) non-phosphorylation-dependent NF-H; (h) phosphorylation-independent NF-M; and (i) phosphorylation-independent NF-L antibodies. NF immunohistochemistry. Scale bars = 10 μm

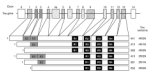

Figure 3.

Schematic representation of the human *tau* gene and six human CNS tau isoforms generated by alternative splicing. The human *tau* gene contains 16 exons, including exon 0 that is part of the promoter. Exons 1, 4, 5, 7, 9, and 11–13 are constitutively expressed. Alternative splicing of exons 2 (E2), 3 (E3), and 10 produces the six alternative tau isoforms. Exons 6 and 8 are not transcribed in the human CNS. Exon 4a, which is also not transcribed in the human CNS, is expressed in the PNS leading to the larger tau isoforms, termed ‘big tau’. The black bars depict the 18 amino acid MT binding repeats and are designated R1 to R4. The relative sizes of the exons and introns are not drawn to scale

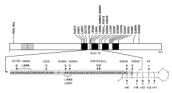

Figure 4.

Schematic representation of mutations in the *tau* gene in FTDP-17. The structure of the largest tau isoform is shown, with known coding region mutations indicated above. The grey boxes near the amino terminus represent the alternatively spliced inserts encoded for by exons 2 and 3, while the black boxes represent each of the four MT binding repeats (not drawn to scale). The second MT binding repeat is encoded by exon 10. Part of the mRNA sequence encoding exon 10 and the intron following exon 10 is enlarged to visualize the 5′ splice site as well as the mutations both in exon 10 and within the 5′ splice site. Nucleotides that are part of intron 10 are shown in lower case

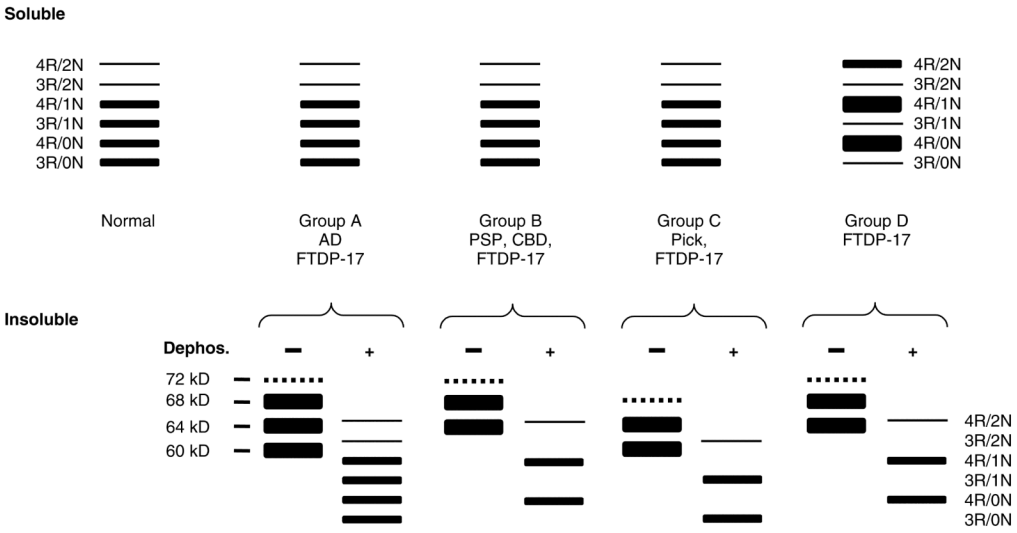

Figure 5.

Schematic representation of western blot banding patterns of soluble and insoluble tau from different tauopathies. The drawing depicts the typical banding pattern of soluble tau (top panels) and insoluble/filamentous tau (bottom panels) from the brains of patients with FTDP-17 as well as sporadic tauopathies following resolution with SDS-PAGE and immunoblotting with anti-tau antibodies. The FTDP-17 mutations show several different western blot banding patterns of soluble and insoluble tau protein that are depicted as groups A to D. The soluble fraction from the brains of unaffected (normal) individuals, sporadic tauopathies, and FTDP-17 with mutations that do not affect tau splicing (groups A, B, and C) shows expression of all six tau isoforms. Insoluble tau from the brains of patients with FTDP-17, group A (S320F, V337M, K369I, G389R, and R406W), resolves as three major proteins of 68, 64 and 60 kD; and a minor band of 72 kD similar to that observed in AD. When dephosphorylated, they resolve into six proteins that correspond to all six tau isoforms similar to the soluble fraction. In FTDP-17 group B (R5H, P301L, and G342V), two prominent 68- and 64-kD protein bands are detected (the 72 kD minor band is variably detected) that align with 4R tau following dephosphorylation similar to that observed in PSP and CBD, indicating the selective aggregation of 4R tau. In FTDP-17 group C (K257T) and Pick's disease, the 64 and 60 kD insoluble tau protein isoforms predominate and align with 3R tau isoforms following dephosphorylation, indicating selective aggregation of 3R tau. In contrast, in FTDP-17 mutations that affect mRNA splicing (group D: N279K, L284L, N296N, N296H, S305S, S305N, and intron 10 mutations), there is expression of predominantly 4R tau throughout the entire brain, which is reflected in the insoluble tau aggregates

Table 1

Neurodegenerative diseases with neuronal intermediate filament- and tau-positive filamentous inclusions

Neuronal intermediate filaments	Tau
Alzheimer's disease* Amyotrophic lateral sclerosis	Alzheimer's disease
Charcot–Marie–Tooth disease	Amyotrophic lateral sclerosis/parkinsonism–dementia complex of Guam (ALS/PDC)†
Diabetic neuropathy	Argyrophilic grain disease†
Dementia with Lewy bodies*	Corticobasal degeneration†
Giant axonal neuropathy	Dementia pugilistica†
Neuronal intermediate filament Inclusion disease	Diffuse neurofibrillary tangles with calcification†
Parkinson's disease*	Down's syndrome
	Frontotemporal dementia with parkinsonism linked to chromosome 17†
	Gerstmann–Sträussler–Scheinker disease
	Myotonic dystrophy
	Niemann–Pick disease, type C
	Non-Guamanian motor neuron disease with neurofibrillary tangles
	Pick's disease†
	Post-encephalitic parkinsonism
	Prion disease with neurofibrillary tangles
	Progressive supranuclear palsy†
	Subacute sclerosing panencephalitis
	Tangle only dementia†

*Neuronal intermediate filaments are chaperone proteins and a minor component of inclusions.

†Diseases in which neurofibrillary pathology is the most predominant neuropathological feature.

Table 2

Neuronal intermediate filament mutations in human diseases

IF	Mutation	Domain	Phenotype	Reference
Peripherin	ND	—	—	—
α-Internexin	ND	—	—	—
NF-L	E7L + P8R	Head	CMT-unspecified	7
NF-L	P8R	Head	CMT-2	8
NF-L	P8Q	Head	CMT-1	7
NF-L	P8A	Head	CMT-1	7
NF-L	P8L	Head	CMT-1	7
NF-L	P22T	Head	CMT-1	9
NF-L	P22S	Head	CMT-2	10,11
NF-L	E89K	Head	CMT-1	7
NF-L	N97S	Rod	CMT-1	9
NF-L	N148V	Rod	CMT-unspecified	9
NF-L	Q333P	Rod	CMT-2	12
NF-L	E393K	Rod	CMT-2	13
NF-L	ΔE528	Tail	CMT-unspecified	7
NF-M	G336S	Rod	PD	14
NF-H	Δ34 aa 528–561	KSP	ALS	15
NF-H	Δ8 aa 655–662	KSP	ALS	16
NF-H	Δ6 aa 663–668	KSP	ALS	16
NF-H	Δ14 aa 663–677	KSP	ALS	16
NF-H	28 aa insert 708	KSP	ALS	17
NF-H	Δ6 aa 743–748	KSP	ALS	16
NF-H	ΔK790	KSP	ALS	15

ND = none detected; PD = Parkinson's disease; CMT-1 = Charcot–Marie–Tooth disease, type 1; ALS = amyotrophic lateral sclerosis; Δaa = amino acid deletion.

Table 3

Tau mutations in FTDP-17

Mutation	Location	Exon 10 splicing	MT binding	Phenotype	Reference
R5H	Exon 1	No change	Reduced	FTDP-17	18
R5L	Exon 1	No change	Reduced	PSP-like	19
K257T	E9, R1	No change	Reduced	PiD-like	20,21
I260V	E9, R1	ND	ND	NA	22
L266V	E9, R1	Decreased*	Reduced	PiD-like	23
G272V	E9, R1	No change	Reduced	FTDP-17	24
E9 + 33	I9	ND	NA	NA	25
N279K	E10, IR1–2	Increased†	Variable	PSP-like	26
ΔK280	E10, IR1–2	Decreased	Reduced	FTDP-17	25
L284L	E10, IR1–2	Increased	NA	AD-like	27
N296N	E10, R2	Increased	NA	CBD-like	28
N296H	E10, R2	Increased	Decreased	FTDP-17	29
ΔN296	E10, R2	No change	Decreased	PSP-like	30
P301L	E10, R2	No change	Reduced	FTDP-17	24
P301S	E10, R2	No change	Reduced	CBD-like, FTDP-17	31,32
S305N	E10, IR2–3	Increased	No effect	CBD-like	33,34
S305S	E10, IR2–3	Increased	NA	PSP-like	35
E10 + 3	I10	Increased	NA	FTDP-17	36
E10 + 11	I10	Increased	NA	FTDP-17	37
E10 + 12	I10	Increased	NA	FTDP-17	38
E10 + 13	I10	Increased	NA	NA	24
E10 + 14	I10	Increased	NA	PSP-like, FTDP-17	24
E10 + 16	I10	Increased	NA	AD-, PiD-, PSP-, CBD-like, FTDP-17	24,39
L315R	E11	No change	Reduced	PiD-like	40

Mutation	Location	Exon 10 splicing	MT binding	Phenotype	Reference
S320F	E11	No change	Reduced	PiD-like	41
Q336R	E12	No change	Increased	PiD-like	42
V337M	E12, IR3–4	No change	Reduced	FTDP-17	43
E342V	E12, IR3–4	Increased	ND	FTDP-17	44
S352L	E12, IR3–4	ND	No effect	Atypical	45
K369I	E12, IR3–4	ND	Reduced	PiD-like	46
G389R	E13	No change	Reduced	PiD-like	47
R406W	E13	No change	Reduced	PSP-like	24

E = exon; I = intron; R = MT binding repeat; IR = inter-repeat regions; ND = not determined; NA = not applicable.

*Decreased indicates reduced exon 10 utilization.

†Increased indicates enhanced exon 10 utilization.