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Review

Tau mutations in frontotemporal dementia FTDP-17 and their relevance for Alzheimer's disease

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Abstract

Alzheimer's disease is characterised by the degeneration of selected populations of nerve cells that develop filamentous inclusions prior to degeneration. The neuronal inclusions of Alzheimer's disease are made of the microtubule-associated protein tau, in a hyperphosphorylated state. Abundant filamentous tau inclusions are not limited to Alzheimer's disease. They are the defining neuropathological characteristic of frontotemporal dementias, such as Pick's disease, and of progressive supranuclear palsy and corticobasal degeneration. The discovery of mutations in the tau gene in familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) has provided a direct link between tau dysfunction and dementing disease. Known mutations produce either a reduced ability of tau to interact with microtubules, or an overproduction of tau isoforms with four microtubule-binding repeats. This leads in turn to the assembly of tau into filaments similar or identical to those found in Alzheimer's disease brain. Several missense mutations also have a stimulatory effect on heparin-induced tau filament formation. Assembly of tau into filaments may be the gain of toxic function that is believed to underlie the demise of affected brain cells.

Keywords: Tau protein; Frontotemporal dementia and parkinsonism linked to chromosome 17; Pick's disease; Progressive supranuclear palsy; Corticobasal degeneration; Alzheimer's disease

1. Introduction

Frontotemporal dementias are neurodegenerative diseases that constitute a common cause of dementia. They are characterised by a striking degeneration of the frontal and temporal lobes of the cerebral cortex, which is sometimes unilateral [1]. In many cases, additional degenerative changes are observed in subcortical brain regions, such as the substantia nigra. Onset of frontotemporal dementia is usually before 65 years of age and the most common clinical manifestation is a profound change in personality and social behaviour, with a relative preservation of memory until later stages of the disease [1,2]. Most cases of frontotemporal dementia are sporadic, with a proportion being inherited. In a population study from the Netherlands, 38% of cases of frontotemporal dementia were found to be familial [3].

In 1994, linkage of a familial disease called disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) to chromosome 17q21–22 was described [4]. It was followed by reports showing linkage of a number of inherited dementing diseases with preceding personality changes to the same re-

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gion of chromosome 17 [5–13]. In 1996, a consensus conference grouped these diseases under the heading of 'frontotemporal dementia and parkinsonism linked to chromosome 17' (FTDP-17) [14].

Neuropathologically, some of these familial frontotemporal dementias had been shown to be characterised by an abundant filamentous pathology made of hyperphosphorylated tau protein, similar to that observed in Alzheimer's disease [15–17]. Together with the fact that the tau gene maps to the region of the critical interval on chromosome 17, this made tau a strong candidate gene for the FTDP-17 locus. The discovery of over a dozen different exonic and intronic mutations in the tau gene in more than 40 families with frontotemporal dementia has now shown that the tau gene is indeed the FTDP-17 locus [18–29]. It follows that tau dysfunction causes neurodegeneration. This has implications for other diseases with a filamentous tau pathology, such as Alzheimer's disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration.

2. Tau protein in normal brain

Multiple tau isoforms are produced from a single gene by alternative mRNA splicing. The six tau isoforms expressed in adult human brain range from 352 to 441 amino acids in length and differ from each other by the presence or absence of three exons (Fig. 1a) [30–32]. Eleven exons (numbered 1–13) make up the longest human brain tau isoform, with exons 2, 3 and 10 being subject to alternative mRNA splicing [30–33]. The most striking feature of the tau sequences is the presence of three or four tandem repeats of 31 or 32 amino acids located in the carboxy-terminal half, each containing a characteristic Pro-Gly-Gly-Gly motif. The extra repeat of 31 amino acids (encoded by exon 10) in the isoforms with four repeats is inserted within the first repeat of the isoforms with three repeats in a way that preserves the periodic pattern [31]. Besides being distinguished by the presence of three or four tandem repeats, some tau isoforms contain 29 (encoded by exon 2) or 58 (encoded by exons 2 and 3) amino acid inserts located near the amino-terminus [32,33]. In immature human brain, only the shortest tau isoform with three repeats is expressed [31]. The developmental shift of human tau bands from a simple foetal to a more complex adult pattern thus involves the transition from the expression of the isoform with three repeats containing no amino-terminal inserts, to the expression of all six isoforms. Tau isoforms with a large additional insert in the amino-terminal half (encoded by exon 4A) have been described in the peripheral nervous system [34,35]).

Experiments with synthetic peptides and with tau proteins produced by expression in *Escherichia coli* have shown that the carboxy-terminal repeats and some adjoining sequences constitute microtubule-binding domains [36–40] Microtubules assembled in the presence of tau show arms projecting from the surface [41]. Tau thus consists of a carboxy-terminal microtubule-binding domain and an amino-terminal projection domain, with the latter determining the spacing between adjacent microtubules [42]. Recombinant tau isoforms with four repeats promote faster microtubule assembly than those with three repeats, as might be expected if one tau molecule links a number of tubulin subunits [43].

When individual tau isoforms that have been expressed in *E. coli* are mixed together, they give a characteristic set of six bands, ranging from 48 to 67 kDa in apparent molecular mass [43]. Comparison of the pattern of recombinant tau isoforms with that of native tau shows that the four major tau isoforms in adult human brain correspond to isoforms with three and four repeats without amino-terminal inserts and to isoforms with three and four repeats containing the first amino-terminal insert of 29 amino acids. Isoforms with three and four repeats with the 58 amino acid amino-terminal insert are also found, albeit at lower levels. These findings establish that the six isoforms identified by cDNA cloning account for the tau isoforms in adult human brain, where similar levels of three-repeat and four-repeat isoforms are the norm. There exist true species differences in the expression of tau isoforms. Immature rodent brain expresses the shortest three-repeat tau isoform, like the immature human brain. However, unlike adult human brain, adult rodent brain only expresses three tau isoforms, each with four microtubule-binding repeats [44,45].

Tau is an abundant protein in both central and peripheral nervous systems. In brain, it is found predominantly in nerve cells, with lower levels in some

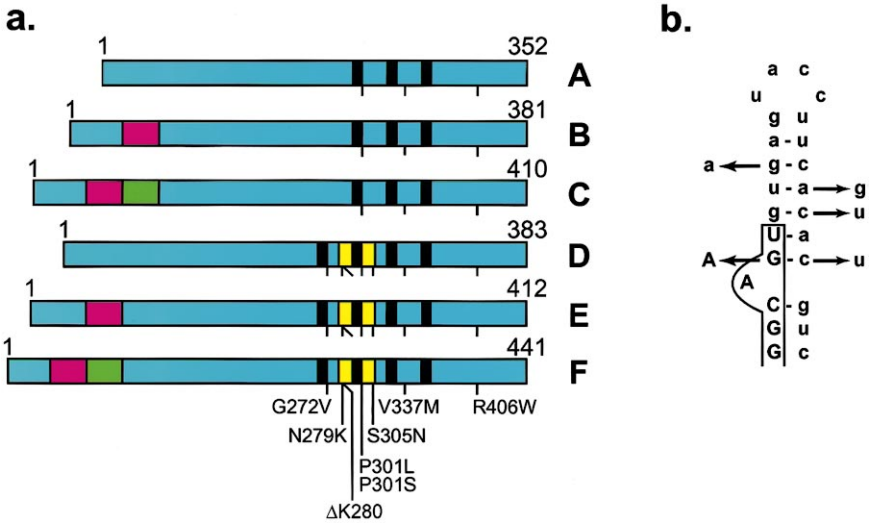

Fig. 1. Mutations in the tau gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). (a) Schematic diagram of the six tau isoforms (A–F) that are expressed in adult human brain. Alternatively spliced exons are shown in red (exon 2), green (exon 3) and yellow (exon 10). Black bars indicate the microtubule-binding repeats. Seven missense mutations and one deletion mutation in the coding region are shown. They affect all six tau isoforms, with the exception of N279K, ΔK280, P301L, P301S and S305N which affect only tau isoforms with four microtubule-binding repeats. Amino acid numbering corresponds to the 441-residue isoform of human brain tau. (b) Stem-loop structure in the pre-mRNA at the boundary between exon 10 and the intron following exon 10. Nucleotides −5 to +19 are shown, with the first nucleotide of the splice-donor site taken as +1. The S305N mutation at position −1 and the intronic mutations (at positions +3, +13, +14 and +16) are indicated. Exon sequences are shown in capital and intron sequences in lower-case letters.

glial cells. Within nerve cells, it is found mainly in axons [46]. The major known physiological function of tau derives from its ability to promote microtubule assembly and to bind to microtubules, which are thus stabilised. Inactivation of the tau gene by homologous recombination leads to no overt phenotype, indicating that tau is not an essential protein [47].

Tau is a phosphoprotein and phosphorylation is also developmentally regulated [48,49]. Thus, tau from developing brain is phosphorylated more than tau from adult brain, implying selective dephosphorylation of the shortest tau isoform during brain maturation. Tau from developing brain is phosphorylated at 15 known sites in the shortest isoform, whereas tau from adult brain is phosphorylated at at least nine sites in the six isoforms [49]. With the exception of S262, which is located at the beginning of the first repeat, all the known phosphorylation sites in tau are located outside the microtubule-binding repeat region. Many of these sites are serine or threonine residues that are followed by a proline. Accordingly, mitogen-activated protein kinase, glycogen synthase kinase-3, neuronal cdc2-like kinase and stress-activated protein kinases phosphorylate tau at many of these sites in vitro [50–53]. Studies using lithium chloride as a specific inhibitor have strongly suggested that glycogen synthase kinase-3 is a tau kinase in brain [54,55]. Tau phosphorylation by a number of protein kinases is markedly stimulated by sulfated

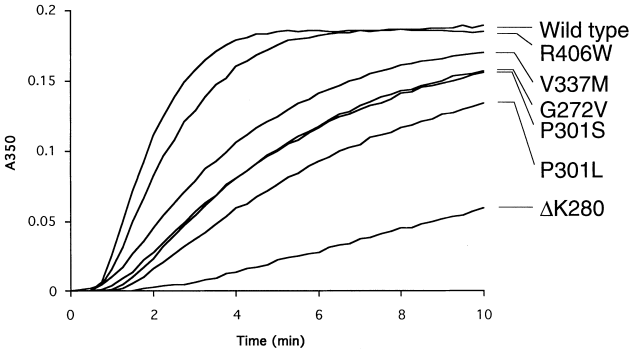

Fig. 2. Effects of coding region mutations in tau on the ability of four-repeat htau46 (412 amino acid isoform of human tau) to promote microtubule assembly. Polymerisation of tubulin induced by wild-type htau46 and six mutant proteins (G272V, ΔK280, P301L, P301S, V337M, R406W), as measured over time by turbidimetry.

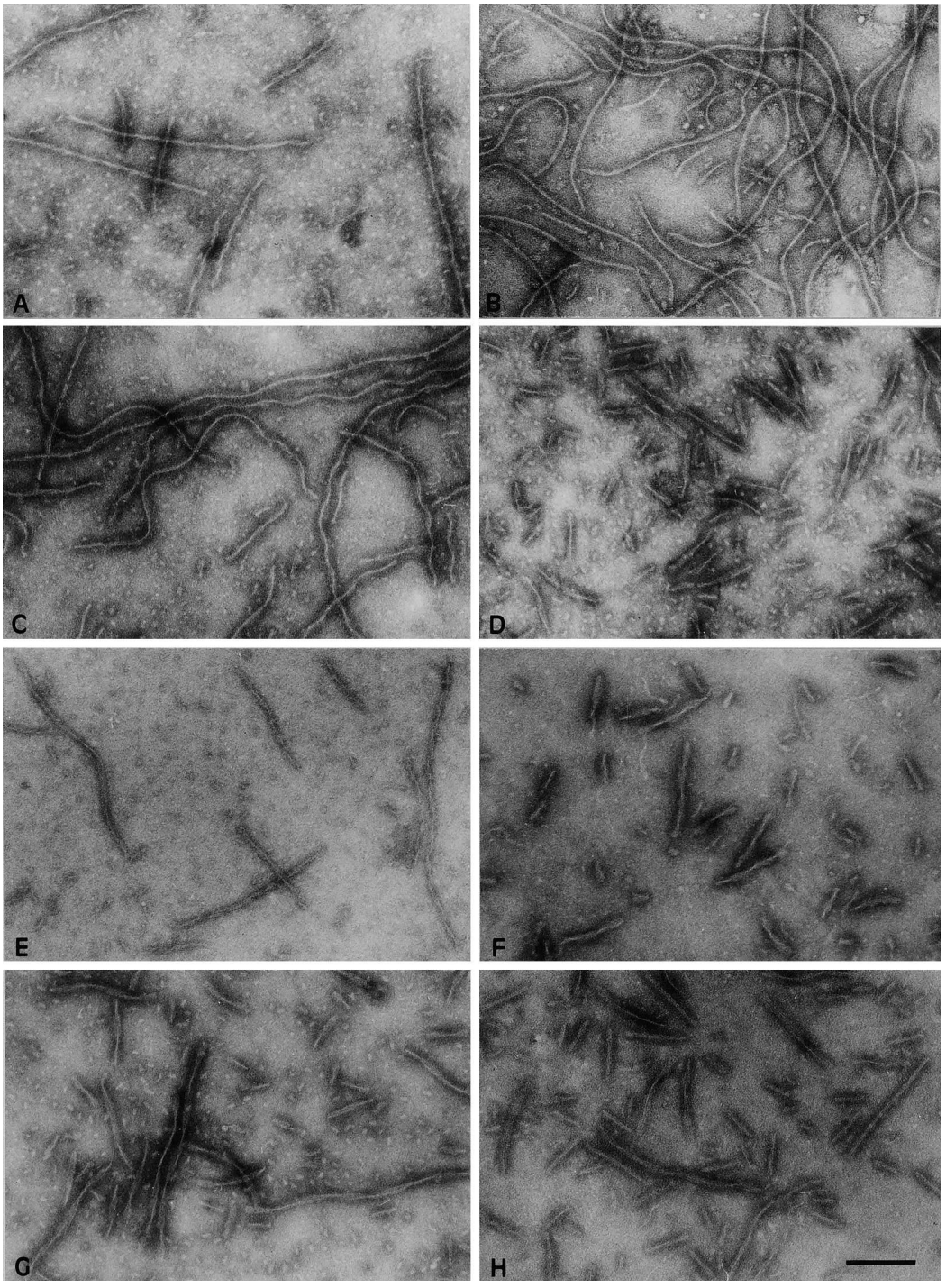

Fig. 3. Effects of coding region mutations in tau on heparin-induced assembly of tau filaments. Representative fields of filaments assembled from various wild-type and mutant tau proteins. A–E, Four-repeat tau (htau46). F–H, Three-repeat tau (htau37). (A) Wild-type; (B) P301S; (C) P301L; (D) G272V; (E) R406W; (F) Wild-type; (G) G272V; (H) V337M. Scale bar: 200 nm.

glycosaminoglycans, such as heparin and heparan sulfate [56–60].

Of the major phosphatase activities in brain, tau is dephosphorylated predominantly by the trimeric form of phosphatase 2A [61,62]. The use of SV40 small t as a specific inhibitor has shown that PP2A controls the phosphorylation state of tau in vivo [63]. Phosphorylation negatively regulates the function of tau [64,65]. Thus, the more phosphorylated tau is, the less able it is to bind to microtubules and to promote microtubule assembly. Hyperphosphorylation is an invariant feature of the filamentous tau deposits that characterise a number of neurodegenerative diseases [66].

3. Tau mutations in FTDP-17

Tau mutations in FTDP-17 are either missense or deletion mutations in the coding region, or intronic mutations located close to the splice-donor site of the intron following the alternatively spliced exon 10 [18–20] (Fig. 1). Missense mutations are located in the microtubule-binding repeat region or close to it. Mutations in exon 9 (G272V), exon 12 (V337M) and exon 13 (R406W) affect all six tau isoforms (Fig. 1a) [18,19]. By contrast, mutations in exon 10 (N279K, ΔK280, P301L, P301S and S305N) only affect tau isoforms with four microtubule-binding repeats or their expression (Fig. 1a) [18,19,21–24,27–29]. Most missense mutations reduce the ability of tau to interact with microtubules, as reflected by a marked reduction in the ability of mutant tau to promote microtubule assembly (Fig. 2) [23,29,67–69]. Mutations in exon 10 (ΔK280, P301L and P301S) produce the largest effects, with intermediate reductions for mutations in exons 9 (G272V) and 12 (V337M), and a smaller reduction for the R406W mutation in exon 13 [23,29,67]. Moreover, a number of missense mutations have a direct stimulatory effect on heparin-induced assembly of tau into filaments (Fig. 3) [70,71]. This effect is particularly marked for the P301L and P301S mutations, with smaller effects for the G272V and V337M mutations. A study using synthetic peptides derived from each of the four microtubule-binding repeats of tau has shown increased heparin-induced filament formation for the P301L mutation in the second repeat [72].

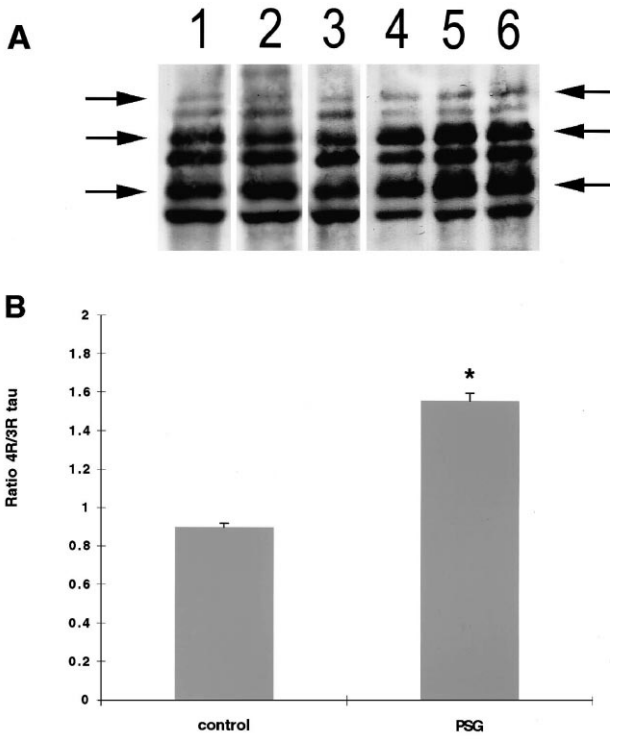

Fig. 4. Soluble tau from familial subcortical gliosis (PSG) brain (with the +16 intronic mutation in the tau gene). Comparison with soluble tau from control brain. (A) Immunoblots of dephosphorylated soluble tau protein extracted from the frontal cortex of three control subjects (lanes 1–3) and three affected individuals from the PSG-1 kindred (lanes 4–6). Arrows (lanes 1 and 6) indicate the positions of the three tau isoforms with four repeats; the other isoforms have three repeats each. (B) Quantitation of the ratio of four-repeat to three-repeat (4R/3R) tau isoforms in frontal cortex from control and familial PSG brains. Results are expressed as means ± S.D. ($n = 3$). *$P < 0.0001$.

Intronic mutations are located at positions +3, +13, +14 and +16 of the intron following exon 10, with the first nucleotide of the splice-donor site taken as +1 (Fig. 1b) [18,20,25,26]. Secondary structure predictions have suggested the presence of an RNA stem-loop structure at the exon 10-intron boundary that is disrupted by the intronic mutations [18,20]. In addition, the +3 mutation is predicted to lead to increased binding of U1snRNA to the 5′ splice site [20]. Exon trapping experiments have shown that intronic mutations lead to increased splicing in of exon 10 [19,73]. Increased production of transcripts encoding exon 10 has also been demonstrated in brain tissue from patients with tau intronic mutations [19,73]. This is in turn reflected by a change in the

ratio of three-repeat to four-repeat tau isoforms, resulting in a net overproduction of four-repeat isoforms (Fig. 4) [20,26,68,73].

The proposed existence of a stem-loop structure at the boundary between exon 10 and the intron following exon 10 [19,20] has received strong support from the determination of the three-dimensional structure of a 25-nucleotide-long RNA (extending from positions −5 to +19) by NMR spectroscopy (Fig. 1b) [73]. The stem of this exon 10 regulatory element RNA consists of a single stable G-C base pair which is separated from a double helix of six base pairs by an unpaired adenine. The apical loop consists of six nucleotides that adopt multiple conformations in rapid exchange. The structure differs in several respects from the two proposed representations of the stem-loop [19,20]. Known intronic mutations are located in the upper part of the stem of the tau exon 10 regulatory element. All four mutations reduce the thermodynamic stability of the stem-loop structure, but to various extents [73]. The largest drop in melting temperature was observed for the +3 mutation. The +14 mutation also produced a large reduction in melting temperature, whereas the effects of the +13 and +16 mutations were smaller. The differential reductions in stem-loop stability resulting from the intronic FTDP-17 mutations were reflected in exon trapping experiments [73]. The +3 mutation produced the largest increase in the splicing in of exon 10, followed by the +14 mutation, with smaller increases for the +13 and +16 mutations.

The emerging picture is one of missense mutations that lead to a reduced ability of tau to interact with microtubules and to a stimulatory effect on tau filament assembly, and of intronic mutations whose primary effects are at the RNA level, resulting in an overproduction of tau isoforms with four microtubule-binding repeats [74]. However, two missense mutations in exon 10 deviate from this rule in that they do not lead to a reduction in the ability of tau to promote microtubule assembly [68,75]. Instead, they increase splicing in of exon 10, as is the case of the intronic mutations. The N279K mutation (AAT to AAG) in tau creates a purine-rich splice enhancer sequence that explains its effects on exon trapping and soluble four-repeat tau in brain [22,68,75]. The S305N mutation (AGT to AAT) in tau changes the last amino acid in exon 10 [24]. This sequence forms part of the predicted stem-loop structure, where the mutation produces a G to A transition at position −1. It is therefore not surprising that the S305N mutation leads to a reduction in the thermodynamic stability of the stem-loop structure and to a marked increase in the splicing in of exon 10 [73,75]. Like the +3 mutation, the −1 mutation is also expected to lead to increased binding of U1snRNA to the 5′ splice site. Besides mutations in the intron following exon 10, additional pathogenic mutations may exist in other introns of the tau gene. Thus, a G to A transition at position +33 of the intron following exon 9 has been described in a patient with familial frontotemporal dementia [23]. It disrupts one of several (A/T)GGG repeats that may play a role in the regulation of the alternative splicing of exon 10.

4. Neuropathology of FTDP-17

All cases of FTDP-17 examined to date have shown the presence of an abundant filamentous pathology made of hyperphosphorylated tau protein [17,66,74]. Strikingly, the morphologies of tau filaments and their isoform compositions appear to be

Table 1
Tau mutations, isoforms and filaments in FTDP-17

Tau mutation	Soluble tau	Filamentous tau	Tau filaments
P301L (exon 10)	Normal ratio of 3- to 4-repeat isoforms (4-repeat isoforms mutated)	4-Repeat isoforms. Small amount of 3-repeat isoform	Narrow twisted ribbons in neurones and glia. Rope-like filaments
Intron following exon 10. N279K (exon 10)	Abnormal preponderance of 4- over 3-repeat isoforms	4-Repeat isoforms	Wide twisted ribbons in neurones and glia
V337M (exon 12). R406W (exon 13)	Normal ratio of 3- to 4-repeat isoforms (all isoforms mutated)	All 6 isoforms	Paired helical filaments and straight filaments in neurones

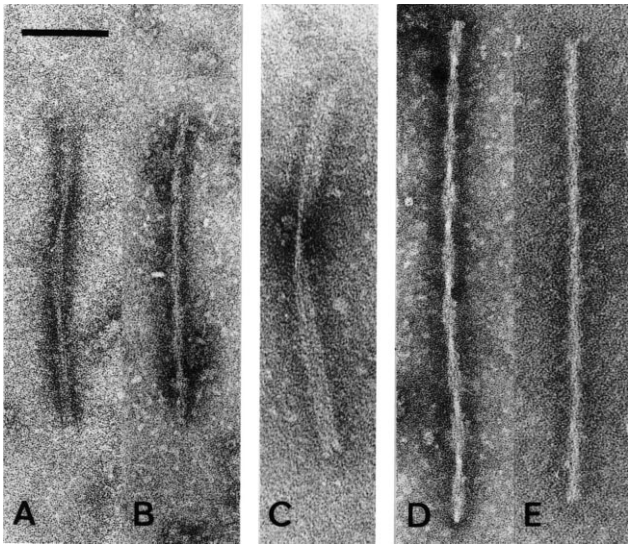

Fig. 5. Tau filaments in FTDP-17. Dutch family 1 (with the P301L mutation in exon 10) is characterised by the presence of narrow twisted ribbons (A) and occasional rope-like filaments (B). The tau pathology is both neuronal and glial. Familial multiple system tauopathy with presenile dementia (with the +3 intronic mutation) and familial progressive subcortical gliosis (with the +16 intronic mutation) are characterised by wide twisted ribbons (C), which might be formed by two copies of the narrow twisted ribbons joined across the central axis. The tau pathology is both neuronal and glial. Seattle family A (with the V337M mutation in exon 12) and a family with the R406W mutation in exon 13 are characterised by the presence of paired helical (D) and straight (E) filaments, like those found in Alzheimer's disease brain. The tau pathology is largely neuronal. Scale bar: 100 nm.

determined by whether tau mutations affect mRNA splicing of exon 10, or whether they are missense mutations located inside or outside exon 10 (Table 1, Fig. 5).

Mutations in tau that affect splicing of exon 10 lead to the formation of wide twisted ribbon-like filaments which contain only four-repeat tau isoforms [16,26]. This has been shown in familial multiple system tauopathy with presenile dementia (MSTD) with the +3 intronic mutation and in familial progressive subcortical gliosis with the +16 mutation (Fig. 5). Similar results have been obtained in pallido-ponto-nigral degeneration with the N279K mutation in exon 10 whose primary effect is at the RNA level [22,68,75]. The same may be true of the family with the S305N mutation in exon 10 whose primary effect is also at the RNA level [24,75]. In all these FTDP-17 families, the tau pathology is widespread and present in both nerve cells and glial cells, with an abundant glial component.

Mutations in exon 10 of tau lead to the formation of narrow twisted ribbons that contain four-repeat tau isoforms, with a small amount of the most abundant three-repeat isoform (Fig. 5). This has been shown in Dutch family 1 and in an American family, both with the P301L mutation [27,76]. Based on electron microscopy of tissue sections, the same also appears to be true of the family with the P301S mutation [29]. At present, no neuropathological information is available for the family with the ΔK280 mutation in exon 10 [23]. The P301L, P301S and ΔK280 mutations all lead to a markedly reduced ability of tau to promote microtubule assembly [23,29,67]. This is not the case of the N279K and S305N mutations that increase splicing in of exon 10, and whose tau pathologies are therefore like those in families with intronic mutations [22,24]. In brain tissue from individuals with the P301L and P301S mutations, tau pathology is widespread and present in both nerve cells and glial cells [27,29,76]. When compared with mutations that affect the splicing in of exon 10, the glial component is less pronounced.

Coding region mutations located outside exon 10 of tau lead to the formation of PHFs and SFs that contain all six tau isoforms (Fig. 5) [15,77]. This has been shown for Seattle family A with the V337M mutation in exon 12 and for a family with the R406W mutation in exon 13. In Seattle family A, the morphologies of tau filaments have been found to be indistinguishable from those of Alzheimer's disease [15]. In these families, tau pathology is found in nerve cells, without a significant glial component.

5. Pathogenesis of FTDP-17

The pathway leading from a mutation in the tau gene to neurodegeneration is unknown. The likely primary effect of most missense mutations is a reduced ability of mutant tau to interact with microtubules [67,68]. It may be equivalent to a partial loss of function, with resultant microtubule destabilisation and deleterious effects on cellular processes, such as rapid axonal transport. However, in the case of the intronic mutations and the N279K and S305N missense mutations in exon 10, this appears

unlikely. The net effect of these mutations is increased splicing in of exon 10, leading to a change in the ratio of three-repeat to four-repeat tau isoforms, and resulting in the overproduction of four-repeat isoforms [19,20,22,78]. Moreover, missense mutations in exon 10 will only affect 20–25% of tau molecules, with 75–80% of tau being normal.

It is possible, however, that a correct ratio of wild-type three-repeat to four-repeat tau is essential for the normal function of tau in human brain. An alternative hypothesis is that a partial loss of function of tau is necessary for setting in motion the mechanisms that ultimately lead to filament assembly. Earlier work had suggested that three-repeat and four-repeat tau isoforms may bind to different sites on microtubules [79]. Overproduction of tau isoforms with four repeats may result in an excess of tau over available binding sites on microtubules, thus creating a gain of toxic function similar to that of most missense mutations, with unbound excess tau available for assembly into filaments.

Where studied, pathological tau from FTDP-17 brain is hyperphosphorylated [66,74]. As known mutations in tau do not create additional phosphorylation sites (with the possible exception of the P301S mutation), hyperphosphorylation of tau must be an event downstream of the primary effects of the mutations and may be a consequence of the partial loss of function. It probably reinforces the effects of the mutations, since it is well established that hyperphosphorylated tau is unable to bind to microtubules [64,65]. At present, there is no experimental evidence linking hyperphosphorylation of tau to filament assembly, and it is unclear whether hyperphosphorylation is either necessary or sufficient for assembly. Thus, assembly of full-length hyperphosphorylated tau into filaments has not been observed. In fact, experimental studies in vitro have shown that interactions between tau and negatively charged sugar polymers, such as sulfated glycosaminoglycans and RNA, lead to rapid assembly into twisted and straight filaments in a phosphorylation-independent manner [59,80–83]. These studies have provided a first robust method for the assembly of synthetic filaments from full-length tau protein. They have also permitted studies investigating the effects of missense mutations in tau on filament assembly, resulting in the demonstration of marked stimulatory effects of some mutations, such as G272V, P301L and P301S [70,71].

The mechanisms that lead to assembly of tau into filaments in brain remain to be discovered. It is possible that a reduced ability to interact with microtubules, which could have several different causes, is a necessary step for filament assembly. Assembly is an energetically unfavourable, nucleation-dependent process that requires a critical concentration of tau [80,83]. Many cells may have levels of tau below the critical concentration. Other cells may have effective mechanisms for preventing the formation of tau nuclei, or may be able to degrade them once they have formed. Insufficient protective mechanisms and high tau concentrations may underlie the selective degeneration of nerve cells and glial cells, which is especially striking in FTDP-17, with the characteristic, sometimes unilateral, razor-sharp demarcations between affected and unaffected areas in cerebral cortex.

The precise significance of the different filament morphologies observed in FTDP-17 is not clear. It is known that the repeat region of tau forms the densely packed core of PHFs and SFs, with the amino- and carboxy-terminal parts of the molecule forming a proteolytically sensitive coat [84–86]. Also, for filaments assembled in vitro in the presence of sulfated glycosaminoglycans, the morphology of the filaments depends on the number of repeats in the tau isoform used [80]. Thus, mutations in the repeat region or a change in the relative amounts of three- and four-repeat isoforms could well influence filament morphology. Treatment of PHFs with acid leads to untwisted, ribbon-like filaments like those seen in familial MSTD [87], suggesting a close similarity in packing of tau molecules in the various structures. The most important aspect may be the extended filamentous nature of the assemblies and the deleterious effects that this has on intracellular processes, rather than the detailed morphology of the different filaments.

6. Implications for Alzheimer's disease and other tauopathies

A major implication deriving from the work on FTDP-17 is that a normal ratio of functional tau

isoforms to microtubules appears to be essential for preventing neurodegeneration. This finely tuned balance may be very sensitive to disruption, in line with the fact that a large percentage of the general population develops limited filamentous tau pathology with ageing [88]. The new work has firmly established that the events leading to a filamentous tau pathology or the mere presence of tau filaments are sufficient for the degeneration of affected nerve cells and glial cells and the onset of dementia. This had long been suspected to be the case, largely because of the good correlation between neurofibrillary lesions and nerve cell degeneration in Alzheimer's disease [89].

The findings in FTDP-17 may shed light on the mechanisms that lead to the filamentous tau pathology of Alzheimer's disease. Seattle family A has shown that the V337M mutation in the third microtubule-binding domain of tau is sufficient to lead to a tau pathology that is indistinguishable from that of Alzheimer's disease in its ultrastructural and biochemical characteristics [15]. As in Alzheimer's disease, the tau filaments are PHFs and SFs that consist of all six tau isoforms. The proportion of PHFs (90–95%) to SFs (5–10%) in Seattle family A is also identical to that found in Alzheimer's disease. It suggests that in Alzheimer's disease a reduced ability of tau to interact with microtubules may also be upstream of hyperphosphorylation and filament assembly.

The presence of mutations in the amyloid precursor protein (APP) gene in about 30 families with early-onset Alzheimer's disease has revealed a genetic lesion that leads to a filamentous tau pathology, as has the larger number of families with mutations in the presenilin genes [90,91]. In these families, tau pathology must be downstream of APP and presenilin dysfunction, but it may be the tau pathology that eventually causes neurodegeneration. The various FTDP-17 families now show that primary lesions in tau itself lead to neurodegeneration. It remains to be seen whether one can generalise from these familial cases to the 20–25 million cases of sporadic Alzheimer's disease.

Filamentous tau deposits are also the defining neuropathological characteristic of neurodegenerative diseases that have been subsumed under the heading of a 'Pick complex' [66,92]. They include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease and several other diseases. The tau pathology of PSP and CBD bears a striking resemblance to that of cases of FTDP-17 with mutations that destabilise the exon 10 splicing regulatory element RNA. Thus, filamentous tau deposits are present in both nerve cells and glial cells [93]. Moreover, tau filaments are either straight or have the appearance of twisted ribbons, and consist of only four-repeat isoforms [94,95]. The similarities with FTDP-17 suggest that PSP and CBD may be exon 10 splicing diseases that are caused by an overproduction of four-repeat tau isoforms.

Although PSP is usually sporadic, several case-control studies have shown a genetic association between PSP and a GT dinucleotide polymorphism located in the intron between exons 9 and 10 of the tau gene [96–101]. In healthy Caucasians, approximately 50% of subjects are homozygous for the a0 allele (with 11 GT repeats). This figure is approximately 95% for patients with PSP. The known alleles are thought to be in linkage disequilibrium with the disease locus that is believed to be the tau gene. Mutations within additional, as yet unknown tau exon 10 splicing regulatory elements may thus well predispose to PSP. Two extended haplotypes covering the tau gene have been described in Caucasians [100]. The more common haplotype H1 is over-represented in patients with PSP, reflecting the association of the a0 allele with that haplotype. With respect to the isoform composition of tau filaments, Pick's disease is the opposite of PSP and CBD. It is characterised by filaments that are made of tau isoforms with three microtubule-binding repeats [102,103]. Although most cases of Pick's disease are thought to be sporadic, mutations that lead to reduced splicing in of exon 10 could predispose to Pick's disease.

The emerging picture is one where FTDP-17, PSP, CBD and Pick's disease are all primary tauopathies. On clinical grounds, the P301S mutation in tau leads to either frontotemporal dementia or CBD in different members of the same family, indicating that genetic background can influence clinical presentation [29].

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