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# Pathogenesis of the Tauopathies

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**Abstract** Microtubule-associated protein tau is the most commonly misfolded protein in human neurodegenerative diseases, where it becomes hyperphosphorylated and filamentous. Mutations in *MAPT*, the *tau* gene, cause approximately 5% of cases of frontotemporal dementia. They are frequently accompanied by parkinsonism. The existence of *MAPT* mutations has established that dysfunction of tau protein is sufficient to cause neurodegeneration and dementia. However, most tauopathies are not inherited in a dominant manner. The hyperphosphorylated sites are similar between diseases, but filament morphologies and tau isoform compositions vary. This is consistent with the existence of multiple tau conformers and recent findings have provided experimental support for this concept.

**Keywords** Tau protein · Tauopathies · Alzheimer's disease · Pick's disease · Progressive supranuclear palsy · Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T)

## Historical Overview

Alois Alzheimer reported the case of Auguste Deter in 1907 (Alzheimer 1907). His was the first description of the combined presence of extracellular plaques and intracellular neurofibrillary tangles. Kraepelin subsequently named the disease after his pupil. In the same year as Alzheimer, Oskar Fischer described 12 cases of senile dementia with neuritic plaques (Fischer 1907; Goedert 2009). Four years later, Alzheimer discovered the association of argyrophilic intracytoplasmic inclusions and ballooned neurons with frontotemporal degeneration (FTD), in what is now known as Pick's disease (PiD) (Alzheimer 1911). This revealed the existence of a second type of intraneuronal inclusion and established that different inclusions can characterize distinct clinical entities (Fig. 1).

By electron microscopy, plaques and tangles are made of abnormal filaments. Although Michael Kidd described the paired helical filament (PHF) as the major structural component of the neurofibrillary tangle and the abnormal neurites surrounding plaques in the 1960s (Kidd 1963), its molecular nature was only uncovered in the 1980s (Brion et al. 1985; Goedert et al. 1988; Wischik et al. 1988). By the early 1990s, it was clear that the PHF is made of all six brain tau isoforms, each full length and hyperphosphorylated (Grundke-Iqbal et al. 1986; Lee et al. 1991; Goedert et al. 1992a). By this time, tau had also been found in the pathological deposits of PiD, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and argyrophilic grain disease (AGD) (Goedert et al. 2006). In contrast to Alzheimer's disease (AD), the abnormal deposits of PiD, PSP, CBD and AGD are found in both nerve cells and glial cells (Komori 1999). Based on its involvement in many maladies, it is now clear that tau is the most commonly misfolded protein in human neurodegenerative diseases (Table 1).

## Tau Isoforms

Tau is a microtubule-associated protein (MAP) that is believed to stabilise microtubules and to promote micro-

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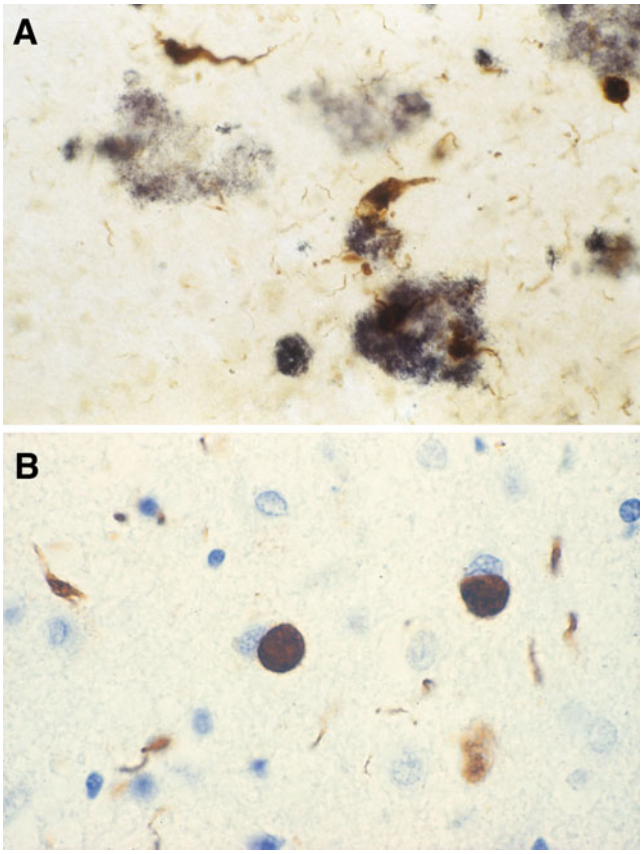


**Fig. 1** The abnormal deposits that Alzheimer described. **a** Neuritic plaques made of β-amyloid (*blue*) and neurofibrillary tangles made of tau (*brown*) in Alzheimer's disease. **b** Pick bodies and neurites made of tau (*brown*) in Pick's disease

**Table 1** Diseases in which tau inclusions have been described

| |
|---|
| Alzheimer's disease |
| Amyotrophic lateral sclerosis/parkinsonism-dementia complex |
| Argyrophilic grain disease |
| Chronic traumatic encephalopathy |
| Corticobasal degeneration |
| Diffuse neurofibrillary tangles with calcification |
| Down's syndrome |
| Familial British dementia |
| Familial Danish dementia |
| Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations |
| Gerstmann–Sträussler–Scheinker disease |
| Guadeloupean parkinsonism |
| Mytotonic dystrophy |
| Niemann–Pick disease, type C |
| Non-Guamanian motor neuron disease with neurofibrillary tangles |
| Pantothenate kinase-associated neurodegeneration |
| Pick's disease |
| Postencephalitic parkinsonism |
| Prion protein cerebral amyloid angiopathy |
| Progressive subcortical gliosis |
| Progressive supranuclear palsy |
| SLC9A6-related mental retardation |
| Subacute sclerosing panencephalitis |
| Tangle-only dementia |
| White matter tauopathy with globular glial inclusions |

tubule assembly. Of the neuronal MAPs, it is one of the most abundant. Six tau isoforms are expressed in the adult human brain by alternative mRNA splicing from a single *MAPT* (Goedert et al. 1989a, b; Andreadis et al. 1992). They differ from each other by the presence or absence of 29- or 58-amino acid inserts located in the amino-terminal half and an additional 31-amino acid repeat in the carboxy-terminal half (Fig. 2a). Inclusion of the latter produces the three isoforms with four repeats each; the other three isoforms have three repeats each. The repeats and some adjoining sequences constitute the microtubule-binding domains of tau (Ennulat et al. 1989; Lee et al. 1989). Similar levels of three- and four-repeat tau isoforms are expressed in adult human cerebral cortex (Goedert and Jakes 1990).

## Assembly of Tau

Tau assembles into filaments through its tandem repeat region, with the amino-terminal half and the carboxy terminus forming the "fuzzy coat" of the filament (Wischik et al. 1988). Following assembly, a proportion of tau becomes truncated at the amino terminus, which appears to be necessary for its ubiquitination (Morishima-Kawashima et al. 1993). Following the death of tangle-bearing cells, the pathological material remains in the extracellular space in the form of the so-called "ghost tangles" which consist largely of the ubiquitinated repeat region of tau. It follows that in AD, the ubiquitination of tau filaments is a late, secondary event.

Methods have been developed for forming PHF-like filaments from purified full-length tau (Goedert et al. 1996; Pérez et al. 1996; Kampers et al. 1996). They are based on the interaction of non-phosphorylated tau protein with negatively charged substances, such as sulphated glycosaminoglycans and RNA. The characteristics of these filaments closely resemble those of tau filaments from AD brain. However, the mechanisms causing soluble tau protein to assemble into insoluble filaments in brain cells remain to be discovered.

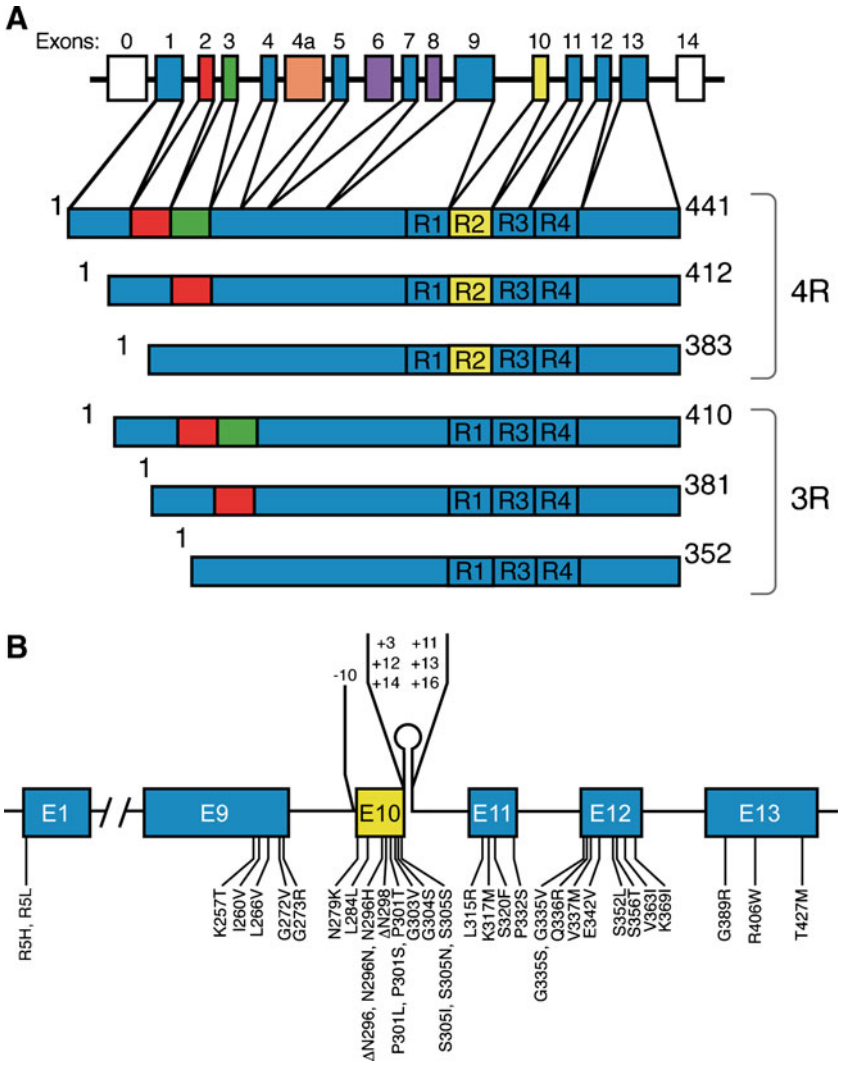


**Fig. 2** **a** *MAPT* and the six tau isoforms expressed in adult human brain. *MAPT* consists of 16 exons (*E*). Alternative mRNA splicing of E2 (*red*), E3 (*green*) and E10 (*yellow*) gives rise to the six tau isoforms (352–441 amino acids). The constitutively spliced exons (*E1*, *E4*, *E5*, *E7*, *E9*, *E11*, *E12* and *E13*) are indicated in *blue*. E0, which is part of the promoter, and E14 are non-coding (*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. The exons and introns are not drawn to scale. **b** Mutations in *MAPT* in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T). Thirty-seven coding region mutations in E1, E9, E10, E11, E12 and E13 of *MAPT* and seven intronic mutations flanking E10 are shown

## Hyperphosphorylation of Tau

The abnormal hyperphosphorylation that characterizes PHF-tau appears to precede filament assembly and renders PHF-tau unable to interact with microtubules (Bramblett et al. 1993; Yoshida and Ihara 1993). It is common to all diseases with tau filaments. Much effort has gone into the mapping of phosphorylation sites in normal and abnormal tau and the identification of candidate protein kinases and phosphatases. In particular, proline-directed kinases, protein kinases that phosphorylate the KxGS motifs in the microtubule-binding repeat region and protein phosphatase 2A have been implicated in the phosphorylation and dephosphorylation of tau protein (Drewes et al. 1992, 1997; Hanger et al. 1992; Goedert et al. 1992b; Kobayashi et al. 1993). It remains to be seen if the abnormal hyperphosphorylation of tau is either necessary or sufficient for filament assembly.

## Isoform Composition of Tau Filaments

The existence of filamentous deposits made of hyperphosphorylated tau raises the question why there are multiple tauopathies rather than a single disease. The answer to this question may reside in the fact that different brain regions and, to some extent, distinct cell types, are affected in the human tauopathies. These differences correlate to some extent with the presence of specific tau isoforms in the abnormal filaments. Thus, all six brain isoforms are present in the tau filaments of AD (Goedert et al. 1992a). In the process leading to AD, neuronal tau inclusions appear first in the locus coeruleus from where they appear to spread to the transentorhinal cortex, the hippocampal formation and the neocortex (Braak and Braak 1991; Braak and Del Tredici 2011). In contrast to AD, four-repeat isoforms are characteristic of the tau filaments of PSP and CBD (Flament et al. 1991;

Ksiezak-Reding et al. 1994; Spillantini et al. 1997), and three-repeat isoforms characterize the tau filaments of PiD (Delacourte et al. 1996). These differences in isoform composition are also reflected by the presence of distinct tau filament morphologies (Crowther and Goedert 2000). This is reminiscent of mammalian and yeast prions, for which different strains have been described, based on the existence of separate conformers of assembled proteins (Colby and Prusiner 2011).

Tauopathy can be transmitted experimentally (Clavaguera et al. 2009). Injection of brain extract from human mutant P301S tau-expressing mice (with silver-positive inclusions) into the brain of human wild-type four-repeat tau-expressing mice (without silver-positive inclusions) induced the assembly of wild-type tau into silver-positive inclusions and the spreading of pathology from the site of injection to neighbouring brain regions. The induction of tau pathology was dependent on the presence of insoluble human P301S tau. In parallel, the intercellular transfer of tau inclusions has been demonstrated in cell culture (Frost et al. 2009). This ongoing work has revealed the existence of mechanisms resembling those by which prions spread through the nervous system (Goedert et al. 2010). The pattern of spreading pathology raises the possibility that the disease process may initiate in a single nerve cell, with implications for sporadic disease. If disease initiates at one site and spreads by propagation, it may be due to stochastic rather than predictable events, making it impossible to predict with certainty who will be affected by sporadic tauopathy.

## Genetics

Molecular studies gave a complete description of the PHF and provided important clues regarding the mechanisms underlying its formation. However, they did not say anything about the relevance of tau dysfunction for the neurodegenerative process. As a result, tau-positive inclusions were frequently considered to be nothing more than epiphenomena of little or no consequence. What was required was genetic evidence linking dysfunction of tau protein to neurodegeneration and dementia. In 1994, a dominantly inherited form of FTD with parkinsonism was linked to chromosome 17q21–22, a region that contains *MAPT* (Wilhelmsen et al. 1994). This was followed by the identification of additional forms of FTD linked to this region, resulting in the denomination "frontotemporal dementia and parkinsonism linked to chromosome 17" (FTDP-17) for this class of disease. Some cases of FTDP-17 were found to exhibit tau-positive inclusions in either nerve cells or in both nerve cells and glial cells (Spillantini et al. 1998a). In 1998, the first mutations in *MAPT* were reported in what is now known as FTDP-17T (Poorkaj et al. 1998; Hutton et al. 1998; Spillantini et al. 1998b). By June 2011, 44 pathogenic *MAPT* mutations had been identified (Fig. 2b). Not all cases of FTDP-17 are accounted for by *MAPT* mutations. Since 2006, it has been known that FTDP-17 can be caused by mutations in either *MAPT* or the progranulin gene (Baker et al. 2006; Cruts et al. 2006).

*MAPT* mutations account for about 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. Mutations fall into two largely non-overlapping 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, reducing the ability of tau to interact with microtubules (Hasegawa et al. 1998; Hong et al. 1998). This partial loss of function of tau may be necessary for causing its abnormal aggregation. Some mutations also promote the assembly of tau into filaments (Nacharaju et al. 1999; Goedert et al. 1999). Mutations with a primary effect at the RNA level are intronic or exonic and increase the alternative mRNA splicing of exon 10 of *MAPT*. This changes the ratio of three- to four-repeat isoforms, resulting in the relative overproduction of four-repeat tau and the formation of filamentous inclusions made of four-repeat tau (Hutton et al. 1998; Spillantini et al. 1998b).

Cases with *MAPT* mutations exhibit abundant filamentous inclusions made of hyperphosphorylated tau in either nerve cells or in both nerve cells and glial cells. Known mutations do not give rise to additional phosphorylation sites, implying that hyperphosphorylation of tau is not the primary event in FTDP-17T. Clinical and neuropathological phenotypes similar or identical to those of PiD, PSP, CBD and AGD have been described (Ghetti et al. 2011). A given mutation can lead to different clinical syndromes in an individual family. Thus, mutation P301S in exon 10 of *MAPT* caused behavioural-variant FTD in a father and CBD in his son (Bugiani et al. 1999), supporting the view that FTD and CBD 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/non-inversion (H1/H2) polymorphism (Stefansson et al. 2005). Because of the suppression of H1/H2 recombination and normal inter-H1 recombination, there are multiple H1 subhaplotypes but only one common H2 haplotype. The latter protects against PSP. Inheritance of the H1 haplotype is a risk factor for PSP and CBD (Williams and Lees 2009). Of the most common H1 subhaplotypes, H1c is associated with disease risk, which localises to a regulatory region in intron 0 of *MAPT* and which can be explained by one single-nucleotide polymorphism (rs242557)

(Pittman et al. 2005; Rademakers et al. 2005). This has been confirmed in a genome-wide association study of PSP, which also implicated proteins involved in vesicle trafficking, white matter function and the unfolded protein response (Höglinger et al. 2011). The association of H1 with PSP had a stronger odds ratio than that for the *ApoE* ε3/ε4 genotype as a risk locus for AD.

Heterozygous microdeletions in the chromosomal region which defines the H1 and H2 haplotypes give rise to 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 other genes (corticotrophin-releasing hormone receptor 1, intramembrane protease 5, *NP 689679.1*, *NP 787078.1* and *KIAA1267*). Deletions occur on the H2 haplotype through low-copy repeat-mediated non-allelic homologous recombination.

An association has also been described between the H1 haplotype and idiopathic Parkinson's disease (PD) (Pastor et al. 2000; Simón-Sánchez et al. 2009), a disease without tau inclusions. Unlike PSP, the association with PD is limited to the H1/H2 inversion polymorphism, without involvement of the H1 subhaplotypes (Vandrovcova et al. 2009). The elevated disease risk conferred by the H1c allele appears to promote *MAPT* transcription and incorporation of exon 10, resulting in increased levels of four-repeat tau (Myers et al. 2007).

## Future Directions

Much has been learned about the tau inclusions that characterize human neurodegenerative diseases. In FTDP-17T, a toxic property of tau causes disease. The same may be true of other diseases with tau inclusions. Despite these advances, major questions remain. It is, thus, important to know if the inclusions contribute to pathogenesis or if they are innocent or even beneficial bystanders. A related question concerns the molecular events that lead from conformational changes in tau to the spreading of pathology, neuronal dysfunction and cell death. Answers to these questions may well lead to the development of mechanism-based therapeutic strategies for the tauopathies (Gozes 2010; Morris et al. 2011).

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