Comparative Biochemistry of Tau in Progressive Supranuclear Palsy, Corticobasal Degeneration, FTDP-17 and Pick’s Disease

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Neurodegenerative disorders referred to as tauopathies have cellular hyperphosphorylated tau protein aggregates in the absence of amyloid deposits. Comparative biochemistry of tau aggregates shows that they differ in both phosphorylation and content of tau isoforms. The six tau isoforms found in human brain contain either three (3R) or four microtubule-binding domains (4R). In Alzheimer’s disease, all six tau isoforms are abnormally phosphorylated and aggregate into paired helical filaments. They are detected by immunoblotting as a major tau triplet (tau55, 64 and 69). In corticobasal degeneration and progressive supranuclear palsy, only 4R-tau isoforms aggregate into twisted and straight filaments respectively. They appear as a major tau doublet (tau64 and 69). Finally, in Pick’s disease, only 3R-tau isoforms aggregate into random coiled filaments. These differences in tau isoforms may be related to either the degeneration of particular cell populations in a given disorder or aberrant cell trafficking of particular tau isoforms. Finally, recent findings provide a direct link between a genetic defect in tau and its abnormal aggregation into filaments in fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) and Pick’s disease (PiD) (2, 31, 46).

Tau proteins

Tau belongs to the family of microtubule-associated proteins (131) and is involved in microtubule assembly and stabilization. In humans, tau is found in neurons, although non-neuronal cells also have trace amounts (52). In the adult human brain, six tau isoforms are produced from a single gene, located on chromosome 17q21, by alternative mRNA splicing. Exons 2, 3 and 10 are alternatively spliced and allow for six combinations (2-3-10–; 2+3-10–; 2+3+10–; 2-3-10+; 2+3-10+; 2+3+10+) (42, 43, 75).

At the protein level, tau proteins constitute a family of six isoforms ranging from 352 to 441 amino acids with molecular weights from 45 to 65 kDa, when run on SDS-PAGE (Figure 1). The tau variants differ from each other by the presence or absence of 29- or 58-amino acids inserts located in the amino-terminal part and a 31-amino acids repeat located in the carboxy-terminal part. In absence of the latter, which is encoded by exon 10, the spliced products give rise to three tau isoforms with three repeats (3R). The three other tau isoforms contain this 31 amino acids repeat and thus have four repeats (4R). These repeats and their adjacent domains constitute the microtubule-binding domains of tau (42,
In normal cerebral cortex, 3R-tau isoforms are slightly more predominant than 4R-tau isoforms (43). Furthermore, the two tau isoforms with the 58-amino acids insert are weakly expressed (64, 85) (Figure 1). Finally, tau isoforms may be differentially distributed in neuronal subpopulations. For instance, 4R-tau isoforms are not detected by in situ hybridization in granular cell of the dentate gyrus (43). These variations indicate that the different domains of tau are likely to be involved in various physiological functions.

There are 80 Ser or Thr residues in the longest human brain tau isoform (441 amino acids) and tau proteins can be phosphorylated at a number of these sites, some of which regulate their microtubule-binding properties. Using phosphorylation-dependent anti-tau antibodies, mass spectrometry and sequencing, at least thirty phosphorylation sites have been described (Table 1) (13, 54, 55, 68, 83, 91, 109, 125). All of these sites are localized outside the microtubule-binding domains with the exception of Ser 262 (R1), Ser 235 (between R1 and R2), Ser 305 (between R2 and R3), Ser 324 (R3), Ser 352 (R4) and Ser 356 (R4) (42, 43, 109, 117). Most of these phosphorylation sites are on Ser-Pro and Thr-Pro motives. A number of sites on non Ser/Thr-Pro sites have also been identified.

As indicated above, the carboxy-terminal part of tau proteins is characterized by the presence of 3 or 4 microtubule-binding domains. These repetitive domains are the repeats encoded by exons 9-12 (Figure 2). The 3R or 4R are made of a highly conserved 18-amino acids repeat separated from each other by less conserved 13- or 14-amino acids inter-repeat domains. It has been demonstrated that adult 4R tau isoforms are more efficient at promoting microtubule assembly than 3R tau isoforms. The R1-R2 inter-repeat is likely to enhance this binding (48). A heptapeptide (K224 KV A VVR 230) located in the proline-rich region has also a high microtubule binding activity in combination with the repeat regions (Figure 2) (48). However, microtubule assembly also depends partially upon the phosphorylation state of tau proteins: phosphorylated tau proteins are less effective than non-phosphorylated tau on microtubule polymerization (5, 8, 20, 21, 32, 80). Phosphorylation of Ser 262 alone dramatically reduces the affinity of tau for microtubules in vitro (5). Nevertheless, this site alone is

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<th>Phosphorylated tau sites</th>
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<tr>
<td>T181</td>
<td>AT270</td>
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<td>S202/T205</td>
<td>AT8</td>
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<td>T212/S214</td>
<td>AT100</td>
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<td>T231/S235</td>
<td>PHF-27/TG3</td>
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<tr>
<td>S262</td>
<td>12E8</td>
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<tr>
<td>S396/S404</td>
<td>AD2/PHF1</td>
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<td>S422</td>
<td>988/AP422</td>
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Numbering is given according to the 441 amino-acid tau isoform. Antibodies that recognize abnormal tau phosphorylation are in italic. They are likely to recognize conformational epitopes.

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insufficient to eliminate tau binding to microtubules (117). Thus, phosphorylation outside the microtubule-binding domains can also influence tubulin assembly by modifying tau-microtubule affinity (48, 87).

**Alzheimer’s disease**

Phosphorylation modifies tau biochemical properties, in that they become longer and stiffer (53). In neurodegenerative disorders, hyperphosphorylated tau proteins aggregate into intracellular filamentous inclusions. In AD, these filaments are named paired helical filaments (PHF). The major antigenic components of PHF are tau proteins (9), and several groups have reported phosphorylation as the major modification in these proteins (38, 49, 51, 66). Their biochemical characterization by SDS-PAGE and immunoblotting reveals the presence of a triplet of proteins at 55, 64 and 69 kDa (tau55, 64 and 69), and also referred to as A68, or PHF-tau (25, 44, 49, 79). A 72-74 kDa component is also present in only very low amounts (114). Using PHF-tau preparations and recombinant tau proteins, Goedert and colleagues showed that dephosphorylated PHF-tau proteins have a similar electrophoretic mobility than the six tau isoforms expressed in human brain (44). The following scheme is now well established (Figure 3): tau 55 results from the phosphorylation of the shortest isoform (2-, 3-, 10-); tau 64 from the phosphorylation of tau variants with one cassette exon (2+, 3-, 10- and/or 2-, 3-, 10+); tau 69 from the phosphorylation of tau variants with two cassette exons (2+, 3+, 10- and/or 2+, 3-, 10+). Phosphorylation of the longest tau isoform (2+, 3+, 10+) induces the formation of the additional hyperphosphorylated tau74 variant (85, 93, 113, 114).

Despite the fact that many phosphorylation sites are common to aggregated tau proteins, referred to as PHF-tau in AD, and native tau in control biopsy-derived materials, there are biochemical differences that differentiate them and support the concept of abnormal phosphorylation in AD (88, 113). First, insoluble polymers of phosphorylated tau are present exclusively in AD brain extracts and are visualized by immunoblotting as smears using anti-tau antibodies. Second, two-dimensional immunoblot analysis reveals that PHF-tau are more acidic than native tau derived from biopsy samples (113). Third, hyperphosphorylation generates differences that can be visualized by a few phosphorylation-dependent antibodies such as AT100 (86, 88, 133), AP422 (56), 988 (17), PHF-27 (63) and the TG/MC antibodies (i.e. TG3) (130). (Figure 4) With the exception of ser422, these sites in PHF-tau are conformation-dependent epitopes. Recently, it was also shown that TG3 epitope was selectively expressed in mitotic cells, but not in quiescent cells (130). These data suggest that cell cycle mechanisms may be affected in AD and lead to neurodegeneration (74, 84, 130).

Altogether, these results show that the main feature of PHF-tau is their aggregation into polymers that constitute neurofibrillary lesions. The aggregation process may be enhanced by a number of co-factors as suggest-
ed in amyloidosis. Among them, glycosaminoglycans and other polyanions might be of particular interest (41, 45, 69, 98, 120). In addition, and possibly in association with the aggregation process, specific phosphorylation sites are also present on PHF-tau. Tau aggregation is not specific to AD, and is also described in many other neurodegenerative disorders. Interestingly, the tau electrophoretic profile is often disease-specific.

**Progressive supranuclear palsy**

Progressive supranuclear palsy (PSP) is a cause of late-onset atypical Parkinsonism described by Steele, Richardson, and Olszewski in 1964 (121). Dementia is also a common feature at the end-stage of the disease (81, 82). Neuropathologically, PSP is characterized by neuronal loss, gliosis and NFT formation. Neurofibrillary tangles were first described in basal ganglia, brain stem, and cerebellum (121). Subsequently, neuronal degeneration was described in the perihinal, inferior temporal and prefrontal cortex, with the same features as subcortical NFT (4, 59, 61). Furthermore, glial fibrillary tangles have also been described (4, 18, 59, 72, 73). Ultrastructural analyses further support differences between AD and PSP, since PHF are found in AD (71), while straight filaments are observed in PSP (123, 124).

The electrophoretic profile of aggregated tau proteins in PSP is substantially different from that in AD, as a characteristic doublet is found (Tau 64 and Tau 69) instead of the triplet of AD (40, 127). A minor 74 kDa band is also detected. In fact, only hyperphosphorylated tau isoforms with sequence encoded by exon10 (4R-tau isoforms) aggregate into filaments in PSP whereas tau isoforms without exon 10 (3R-tau isoforms) are not detected (85, 116) (Figure 5). Nevertheless, most of the phosphorylation sites in PHF-tau are also encountered in aggregated tau proteins from PSP patients (111). Biochemical mapping performed on several cortical and subcortical areas from PSP brain has revealed that the doublet of tau 64 and 69 is first detected in the subcortical regions where NFT are found, neocortical areas being affected later (127, 129). These results are in good agreement with previous neuropathological results that show cortical involvement in these areas in advanced disease (59, 61).

Although most cases of PSP are considered to be sporadic, familial cases such as those reported by De Yebenes and coworkers have a pattern of inheritance consistent with an autosomal dominant disorder (24). More recently, a study of clinical genetics of familial PSP suggests that hereditary PSP is more frequent than previously thought and that the scarcity of familial cases may be related to the lack of recognition of the variable phenotypic expression of the disease (110). Conrad et al. first identified a polymorphic dinucleotide repeat sequence in the intron 9 (between exon 9 and exon 10) of the tau gene, in a Caucasian population with PSP (22). They described a significant over representation of the most common allele (A0), characterized by the presence of 11 TG repeat, and of the homozygous genotype A0/A0 in the PSP cohort (95.5%), compared to normal controls (57.4%) or patients with AD (49.7%). Recently, these data were subsequently confirmed by several studies considering Caucasian series (3, 60, 92, 96). Conversely, it was not observed in Japanese populations (23). Moreover, Baker et al. (1999) described two extended haplotypes that cover the gene (2). In unrelated Caucasians, there was complete disequilibrium between polymorphisms that span the gene. These authors showed that the most common haplotype, designated H1, is significantly over represented in patients with PSP, extending earlier reports of the association between the intronic dinucleotide polymorphism and the disorder (2). While not likely to be directly involved in splicing given the distance from the splice site, it is interesting to speculate that the dinucleotide polymorphism influences in some way exon 10 splicing and, thus, the proportion of 4R-tau isoforms. Even if polymorphisms in the tau gene are important to the pathogenesis of PSP, it remains to be determined at what level it is involved. It is noteworthy that in some familial forms of PSP, no linkage to chromosome 17 is observed (110).

**Corticobasal degeneration**

Corticobasal degeneration (CBD) was first described
in 1967 by Rebiez and coworkers as corticodentatoroni-
gral degeneration with neuronal achromasia (103, 104).
CBD is a rare, sporadic and slowly progressive late-
onset neurodegenerative disorder that is clinically char-
acterized by cognitive disturbances and extrapyramidal
motor dysfunction (104). Moderate dementia emerges
sometimes late in the course of the disease (107). There
is a clinical and pathological overlap between PSP and
corticobasal degeneration (37, 81, 82, 112).
Neuropathological examination reveals glial and neu-
ronal abnormalities. The glial pathology includes astro-
cytic plaques and numerous tau-immunoreactive inclu-
sions in the white matter. Achromatic ballooned neurons
are detected in cortex, brainstem and subcortical struc-
tures, as are neuritic changes and NFT. These lesions
can be readily visualized with phosphorylation-depend-
ent anti-tau antibodies (14, 36, 37, 73, 76, 97).
Ultrastructural studies indicate that tau aggregates in
CBD form twisted filaments that differ from PHF of
AD. In CBD, filaments are shorter in length (less than
400 nm), 10 to 20% wider and the periodic twist (169 to
202 nm) is twice as long as that in AD (76).

The electrophoretic profile of tau pathological pro-
teins in CBD is similar from that of PSP (14, 36, 76),
and is described as a major tau 64, 69 doublet (Figure 5).
The components may be different since this doublet is
not detected in CBD using antibodies raised against the
region encoded by exon 3 (76). These data have been
confirmed by immunohistochemistry (36). Conversely,
in recent studies, tau isoforms with sequence encoded
by exon10 (4R tau isoforms) were found solely in CBD,
whereas tau isoforms without exon 10 were not detect-
ed. These data suggest that only 4R-tau isoforms aggre-
gate into filaments in CBD as observed in PSP (85,
116). In this respect, the only isoform with sequence encoded by both exons 3 and 10 is the longest tau iso-
form (Figure 5). Since the longest tau isoform is found
in very low amounts in human brain, it may explain why
previous works did not find any immunoreactivity of
sequence encoded by exon 3 in their experiments (36,
76). These data confirm our observations that both size
and phosphorylation of tau isoforms are responsible for
the observed differences in tau electrophoretic mobility.
It should be noted that to date no tau polymorphism has
been reported in CBD.

Pick’s disease

Pick’s disease is a rare neurodegenerative disorder
characterized by a progressive dementia and personality
deterioration. Early in the clinical course, patients often
show signs of frontal disinhibition (11, 100).
numerous in granular cell neurons of the dentate gyrus, in CA1, subiculum and entorhinal cortex, whereas in the neocortex, they are mainly found in layers II and VI of the temporal and frontal lobes. Ultrastructurally, Pick bodies consist of random coiled and straight filaments.

Biochemical analysis, using a quantitative western blot approach with phosphorylation-dependent anti-tau antibodies has revealed that in all cases of Pick’s disease studied, a major 55 and 64 kDa tau doublet is observed in the isocortex, in the limbic areas and in subcortical nuclei (Figure 5) (26). In addition, a very faint band is observed at 69 kDa (14). In the neocortex, all Brodmann areas of the frontal and temporal lobes are affected. The parietal cortex is frequently involved while the occipital cortex is generally spared. In subcortical structures, the tau doublet is found in the striatum, substantia nigra, locus coeruleus, and brainstem (26). The presence of the tau doublet correlated well with brain areas with Pick bodies (26). The 55 and 64 kDa doublet characteristic of Pick’s disease is different from the tau-triplet in AD and tau-doublet in PSP and CBD (14, 85). Interestingly, Pick bodies and the tau doublet tau 55 and 64 are not labeled with immunological probes directed against the sequence encoded by exon 10 (85,115) indicating only 3R-tau isoforms aggregate into Pick bodies (Figure 5). Moreover, aggregated tau proteins in Pick’s disease can not be detected by the monoclonal antibody 12E8 raised against the phosphorylated residue ser262. In contrast, this phosphorylation site is readily detected in other neurodegenerative disorders (28,102) (Figure 6). Since

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**Figure 7.** A. Partial sequence of the 441 amino-acid tau isoform (Pro223-Asn410) showing FTDP-17 mutations. Consensus sequences among the four microtubule-binding domains are gray-boxed. The heptapeptide with microtubule-binding properties in exon 9 is blue boxed. The sequence encoded by exon 10 is in red. Beginning of the sequences encoded by exons 10, 11, 12 and 13 are indicated by an arrow. Ser396 and 404 are also indicated (light green circle). All FTDP-17 mutated amino acids are in green in an explosion scheme. B. Nucleotidic sequence of the exon 10 and its 5’ and 3’ intronic regions. All FTDP-17 mutated nucleotides are in green. The exon 10 sequence is in red caps letters. The intronic sequence is in light brown. Mutations are only shown in the stem loop structure.
it was shown that 3R-tau isoforms can be phosphorylating at Ser262, the lack of 12E8-immunoreactivity is likely to be related to either inhibition of a kinase in neurons that degenerate in Pick's disease or absence of these kinases within degenerating neurons (85). The present evidence suggests that only 3R-tau isoforms that are not phosphorylated at ser262 aggregate in Pick bodies (28, 85).

Frontal lobe degeneration non-Alzheimer non-Pick

Frontal lobe degeneration is a neurological disorder that has been not widely recognized until recently, despite the fact that it is the second most common presenile dementing disorder in Europe after AD. As in Pick’s disease, it is associated with “frontal” pathology. Pick’s disease is neuropathologically distinguished by the presence of Pick bodies, whereas frontal lobe degeneration has no specific neuropathologic hallmarks. Morphological changes include neuronal cell loss, spongiosis and gliosis mainly in the superficial cortical layers of the frontal and temporal cortex. No tau pathology is observed in this disorder (11, 27, 118).

FTDP-17

Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) has been related to mutations on the tau gene (65, 101, 118, 119). Tau mutations segregate with the pathology and are not found in the control subjects, suggesting their pathogenic role. Although clinical heterogeneity has been described between and within families with FTDP-17, the usual symptoms include behavioral changes, loss of frontal executive functions, language deficit and hyperorality. Parkinsonism and amyotrophy are described in some families. Neuropathologically, brains of FTDP-17 patients exhibit severe neuronal cell loss in frontal and temporal lobes and gliosis in both white and gray matter. One of the main histopathologic features is filamentous pathology affecting neuronal cells, or both neuronal and glial cells.

At present 20 mutations in the tau gene have been described among the different families with FTDP-17, including missense mutations in coding regions (K257T, I260V, G272V, N279K, L284L, P301L, P301S, S305N, V337M, G389R, R406W), amino acid deletions (ΔK280) and intronic mutations in the intronic region following exon 10 at position +3, +13, +14 and +16 (6, 16, 19, 30, 33, 34, 47, 50, 58, 64, 65, 67, 90, 94, 95, 101, 106, 108, 119, 126) (Table 2; Figure 7).

Mutations may be divided in two groups: 1) those affecting alternative splicing of exon 10 leading to changes in the ratio of tau mRNAs containing or lacking exon 10 and thus the proportion of 4R-and 3R-tau isoforms and 2) those modifying microtubule interactions. All intronic mutations disturb a putative stem-loop structure at the splicing site that stabilizes this region of the pre-mRNA and may decrease access of U1snRNP to this RNA region (50, 65, 119, 126). Without this stem loop, access of U1snRNP may be facilitated, which increases the formation of tau mRNAs containing exon 10 (33, 50, 126) (Figure 7). Furthermore, sequence analysis of this splicing region in different animals indicates that the lack of the stem-loop structure is associated with an increase in tau mRNAs containing exon 10 (50). All intronic mutations lead to an increase in tau mRNAs containing exon 10, and thus in 4R-tau isoforms. Interestingly, in those families, only abnormally phosphorylated 4R-tau isoforms aggregate into filaments and display a tau electrophoretic profile similar to that found in PSP and CBD (a major tau doublet at 64 and 69 kDa) (14, 40, 76, 118, 119, 129). Some missense mutations (N279K, ΔK280, L284L and S305N) also modify the splicing of exon 10 (33). For instance, the change in nucleotide for N279K and S305N mutations also creates an exon-splicing enhancer sequence (33).

The second group of tau mutations found in FTDP-17 includes mutations that alter the microtubule-binding properties of tau. Goedert and co-workers reported the effects of mutations G272V, P301L, V337M and R406W in an in vitro system of microtubule assembly. Mutated tau isoforms did not bind microtubules and induce microtubule disassembly as readily a normal tau (57). These data have been confirmed by additional laboratories (33, 64) and are discussed by Yen and co-workers in this symposium. When missense mutations are located in tau regions common to all isoforms, tau isoforms do not bind to microtubules as well as normal and they gradually aggregate into filaments. Their biochemical characterization shows a tau electrophoretic profile similar to that encountered in AD and is composed of a tau triplet (tau55, 64 and 69). Conversely, when missense mutations are located in exon 10 (P301L, P301S), only 4R-tau isoforms show poor binding to microtubules and subsequently aggregate into filaments. Their biochemical characterization shows a tau electrophoretic profile similar to that encountered in PSP and CBD.
and is composed of a tau doublet (tau64 and 69) (Figures 5 and 7).

The ΔK280 mutation, which is located in exon 10, is a particularly interesting one. Despite being in a coding region, it may act similar to the splice site mutations by decreasing the formation of tau mRNAs containing exon 10 and thus, enhancing the formation of 3R tau isoforms. Interestingly, this tau missense mutation also affects tau binding. Thus, it should only affect 4R-tau isoforms. No data are currently available on the biochemistry of tau aggregates or the pathology in this family (108).

In summary, these findings suggest that reduced ability of tau to interact to microtubules may be upstream of hyperphosphorylation and aggregation. The tau mutations may also lead to an increase in free cytoplasmic tau (especially 4R-tau isoforms) that ultimately facilitates their aggregation into filaments (132). In this respect, it is interesting to note that over expression of tau was reported to block dynein-mediated axonal transport (35).

**Conclusions**

Despite the fact that many neurodegenerative disorders display specific electrophoretic tau profiles, it should be noted that there are overlapping patterns for some of them. The AD tau electrophoretic profile characterized by a major tau triplet tau 55, 64 and 69 and a minor variant at 74 kDa is also found in some forms of FTDP-17 (see above), amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (12, 89), Down syndrome (39), Niemann-Pick type C disease (1), postencephalitic parkinsonism (15) and in the hippocampal formation in aging (29). The tau electrophoretic profile is identical for CBD and PSP even if their clinical features are different (116). Conversely, some disorders have unique electrophoretic tau profiles. For instance, PiD tau doublet has not been observed in any other disorder. Similarly, in myotonic dystrophy, tau pathology is mostly present in temporal areas and is characterized by an unique electrophoretic tau profile made of a major tau 55 variant (128). Whatever the electrophoretic tau profile, tau aggregation in association areas is always correlated to dementia (14, 15, 28, 29, 127, 129).

In conclusion, tau isoforms with 3R and 4R may be differentially expressed and their aggregation may lead to different biochemical signatures characterized by tau doublets and the tau triplet. Different processes may explain these observations. First, Goedert and co-workers (43) previously showed that neurons do not express 3R and 4R tau isoforms equally (for instance granule cells of the dentate gyrus express 3R-tau isoforms) and Delacourte and coworkers (28) clearly demonstrated that only 3R tau isoforms aggregate in Pick bodies in granule cells. Second, tau proteins are principally found in axons in normal neurons, but accumulate in somatodendritic neuronal compartments in neurodegenerative disorders. Since tau trafficking is phosphorylation-dependent (7, 10, 70, 105, 122), it suggests that abnormal phosphorylation of tau proteins may lead to aberrant cell trafficking and tau aggregation. Third, in some tauopathies, tau isoforms may be expressed in other cell types than neurons. For instance, tau aggregates are also found in glial cells (73). Finally, in hereditary disorders, differences in tau isoform expression are related to either mutations in tau (as in FTDP-17 or in tau polymorphisms (as in PSP). Most of tauopathies, however, including CBD, PiD, amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam are not associated with tau mutations or polymorphisms (99, 101).

Altogether, these observations indicate that in many tauopathies, different processes including tau mutations or polymorphisms, aberrant cell trafficking and selective cell vulnerability act to determine specific patterns of neurodegeneration and corresponding tau biochemical profiles.

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**References**


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