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# Classification of Diseases with Accumulation of Tau Protein

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## INTRODUCTION

Abnormal filaments of known composition in neurons and glia define many sporadic and hereditary human neurodegenerative diseases. The pathogenic significance of filamentous inclusions became evident when cases of dominantly inherited disease were shown to be associated with mutations in the genes encoding the proteins that make up filaments, be they Tau [1–3], Aβ [4, 5], α-synuclein [6], prion protein [7], TDP-43 [8–10] or FUS [11, 12]. By extrapolation, it follows that a gain of toxic function resulting from the ordered assembly into filaments may also underlie sporadic forms of disease. Assemblies of the microtubule-associated protein Tau into filaments characterize many neurodegenerative diseases. In humans, *MAPT*, the gene encoding Tau protein, generates six isoforms (352–441 amino acids) by alternative mRNA splicing [13]. They differ by the presence or absence of three inserts encoded by exons 2, 3 and 10. Inclusion of exon 10 results in the production of three isoforms with 4 C-terminal repeats (each repeat is 31 or 32 amino acids long) (4R) and its exclusion in another three isoforms with 3 repeats (3R). Diseases characterised by the intracellular accumulation of Tau filaments can be divided into three groups, based on the isoform composition of filaments (3R, 4R, 3R+4R) [14]. In these diseases, be they sporadic or inherited, Tau is extensively modified post-translationally [15–17].

*Tauopathy* was coined to describe a dominantly inherited neurodegenerative disease with a +3 mutation in intron 10 of *MAPT* and abundant filamentous inclusions made of 4R Tau [3,

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Author contributions

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Conflicts of interest

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18]. However, this term is also used in neuropathology and neuroscience to refer to the mere presence of Tau in tissues.

The terms *primary and secondary tauopathies* are also being used [19–25], even though mutations in *MAPT* are the only known aetiology for Tauopathies. *Primary tauopathy* refers to conditions where the presence of Tau filaments is the main or sole known abnormality or where tau pathology is considered the major contributing factor to neurodegeneration interpreted as main 'driving force of pathogenesis', as opposed to other proteins such as Aβ [23, 25–28]. *Primary tauopathies* are also included in the group of frontotemporal lobar degeneration (FTLD). The latter is characterized by the predominant atrophy of frontal and temporal lobes of the cerebral cortex and occurs in association with several different proteinopathies [29]. *Secondary tauopathy* is used when additional 'driving pathogenic forces' are believed to be involved [19]. In our view, cases with mutations in *MAPT* are the only known example of a *primary tauopathy*, whereas familial Alzheimer's disease may be *secondary tauopathy*. These terms should not be used when referring to diseases of unknown aetiology.

Diseases with pathologic Tau can be classified on the basis Tau isoforms, 3R, 4R or both 3R and 4R being demonstrable with isoform-specific antibodies or Western blot patterns of sarkosyl-insoluble Tau. The anatomical distribution, along with the histological and cytological characterization of neuronal and glial tau immunoreactivities, is also needed for clinicopathological classification [19, 20, 30].

Formation of abnormal Tau filaments is a central event in several neurodegenerative diseases. Like the filaments of other pathologic amyloids, Tau filaments have a cross-β conformation [31]. Recently, the Tau folds of Alzheimer's disease [32, 33], Pick's disease [34], chronic traumatic encephalopathy (CTE) [35], corticobasal degeneration (CBD) [36, 37], argyrophilic grain disease (AGD), progressive supranuclear palsy (PSP), and globular glial tauopathy (GGT) [38] were shown to be different. The Tau filament fold of primary age-related tauopathy (PART) was identical to the Alzheimer fold, indicating that it can form in the absence of Aβ deposits [39]. The same filament structures have been found for different individuals with a given disease. It is also noteworthy that Tau folds identical to those of Alzheimer's disease co-existed with cerebral parenchymal Aβ amyloid, PrP amyloid, Abri and ADan amyloid [38, 40]. Tau filament structures from the brains of intron 10 *MAPT* mutation carriers were identical to those of AGD. Structural analysis of tau filament folds has also led to the discovery of potentially new disease entities [38].

It is now timely to update the existing terminology and re-examine the grouping of disorders associated with intracellular tau accumulation, since: (1) There is an increased interest in the role of Tau assembly in neurodegeneration. (2) Inconsistent terminology has been used; and (3) High-resolution tau filament structures have been determined. Here we put forward definitions of terms to describe Tau in various conditions, as well as a simple and flexible stratification system that will also allow inclusion of novel pathological entities.

## CONCEPTS AND HYPOTHESES

Identification of high-resolution Tau filament structures from brain has provided a compelling argument for reconsidering nomenclature and group organization of conditions in which tau assembly is believed to play a role. Since the term ‘Tauopathy’ has not been rigorously defined, there is a need to establish its precise meaning, so as to avoid inconsistent use.

A new approach may take into consideration the following:

1. Soluble Tau assembles into insoluble filaments. At some point, as misfolding happens, the gain-of-toxic function that causes neurodegeneration occurs along with a partial loss of physiological function of tau [41].
2. The Tau isoform composition of filaments can vary between diseases. However, even within a given brain, tau isoforms in filaments may differ, for example when Alzheimer neurofibrillary lesions (3R+4R) co-exist with argyrophilic grains (4R) and ARTAG (4R).
3. The ordered assembly of Tau occurs through stages, with the so-called ‘pre-aggregates’ evolving into insoluble ubiquitinated inclusions [42]. While silver staining detects insoluble inclusions in histology, some anti-tau antibodies can also identify earlier stages of pathological assembly.
4. A three-level hierarchical classification of diseases with Tau pathology has been suggested on the basis of the cryo-EM structures of Tau filaments. All known tau folds comprise R3 and R4, as well as 10–13 amino acids after R4. **The first** level of classification takes into account the structure and composition of tau filament cores (3R, 4R or 3R+4R). **At the second level**, for diseases with filaments made of 3R+4R Tau isoforms, one can distinguish between Alzheimer and CTE folds, while for diseases with filaments made of 4R Tau, one can distinguish between three-layered (PSP, GGT) and four-layered (CBD, AGD) folds. **The third level** of classification for 4R tauopathies is based on the differences at the residue level between three- and four-layered folds [38].
5. Spreading of assembled tau may occur in different and currently undetermined ways in the presence of *MAPT* mutations, compared to other conditions for which spread may be secondary to local protein aggregation and other factors, be they genetic and/or environmental.
6. In some cases, Tau assembly may be the only proteinopathy. However, co-pathologies frequently occur; they may be characterised by either additional tau filament folds or the presence of other misfolded proteins.

## DEFINITIONS AND NOMENCLATURE

### Tau immunoreactivity:

This term refers to the staining for Tau by antibodies and does not provide information directly relevant to the assembly state of the protein. Tau immunoreactivity alone does not

necessarily indicate dysfunction of Tau protein or its relevance for a clinicopathological phenotype. Since antibodies to different tau epitopes may give rise to different labelling patterns, knowledge of these epitopes is essential for the interpretation of immunoreactivity.

### Tau pathology:

This term implies the presence of assembled Tau, through the interpretation of results obtained using at least one of the following: silver staining, immunohistochemistry, immunofluorescence, electron microscopy, immunoblotting and seeding. Tau pathology describes lesions, not clinicopathological entities.

### Tauopathy/Tau proteinopathy:

These terms, which are often used interchangeably, describe conditions that fulfil the following criteria:

1. Abundant filamentous Tau inclusions made of either 3R, 4R or 3R+4R tau, *and*
2. Consistent and typical patterns of cellular Tau pathologies in multiple cases that correlate with clinical signs and neurodegeneration.

This definition acknowledges that each condition is characterized by a spectrum of regional load of filamentous tau deposits (i.e., stages of sequential involvement of brain regions), thus implying that early disease stages may be recognizable in a given disorder. Therefore, early stages of a Tauopathy may be described as Tau pathology. In summary: 1) Cellular immunoreactivities are described as ‘Tau immunoreactivity’ in neurons, astrocytes, oligodendrocytes, etc’; 2) ‘Tau pathology’, but not ‘Tauopathy’, should be used for the definition of lesions revealed by routine diagnostic immunohistochemistry; 3) A condition should not be considered a ‘Tauopathy’ until a consistent staining pattern can be demonstrated in additional cases of disease.

## CATEGORIES

We propose the following approach for categorizing conditions associated with intracellular Tau accumulation or Tau immunoreactivity of unknown relevance into six groups. It requires knowledge of the following: aetiology, if known, presence of Tau-only pathology versus co-existence with a parenchymal amyloid made of a protein other than Tau, and role of assembled Tau in disease pathogenesis. Each group can then be subdivided according to the Tau isoforms involved, as demonstrated by immunostaining and/or immunoblotting using well-characterized 3R and 4R Tau-specific antibodies. In the absence of such knowledge, we say ‘awaiting isoform classification’. It follows that Tauopathy conditions can be defined on the basis of the spectrum of specific morphological changes, their clinicopathological phenotypes, as well as historically assigned disease names. Finally, based on the cryo-EM structures of Tau folds, Tauopathies can be classified further [38]. Our knowledge of filament folds is still evolving and cryo-EM may lead to the identification of novel Tau folds in previously unrecognised conditions.

Rather than divide disorders into primary and secondary Tauopathies, we propose to classify **Tauopathies** into five different groups (Table 1). Group 1 includes cases with

mutations in *MAPT*. Some clinicopathological phenotypes and filament structures may be similar to those in sporadic forms of disease [38, 43]. Group 2 includes disorders with filamentous Tau deposits that are pivotal for neuropathological diagnosis and correlate with clinical symptoms and neurodegeneration, but in the absence of mutations in *MAPT*. Nomenclature of these conditions is based on either clinical presentation (i.e., PSP), anatomical distribution of neurodegeneration (i.e., CBD), morphology of Tau pathologies (i.e., GGT and AGD), or disease eponyms (i.e., Pick's disease). Groups 1 and 2 are summarized as 'Main Tauopathies' (Figure 1). Group 3 includes filamentous Tau deposits in dominantly inherited diseases with mutations in genes encoding the proteins that make up extracellular filamentous deposits (Aβ, prion protein, Bri). Group 4 includes filamentous Tau deposits in idiopathic forms of Alzheimer's disease. Groups 3 and 4 are summarized as 'Extracellular filamentous deposit-related Tauopathies' (Figure 1). Group 5 comprises other Tauopathies that may show overlapping features with those of Group 3. However, they are reported less frequently than those of Group 3. Group 6 includes various conditions with Tau immunoreactivity or Tau pathology. In some cases, Tau immunoreactivity has been described, but filamentous Tau inclusions have not been demonstrated. Tau immunoreactivities or tau pathologies can also be observed in individuals who are clinically normal, where they may represent a preclinical stage and/or an early cytopathological phase of fibril formation [27]. We recommend that 'Tau pathology' rather than 'Tauopathy' be used for conditions in which filamentous Tau may be detected, but where the following may constitute an obstacle for a more precise characterization: 1) Tau cytopathology is inconsistently detected between cases belonging to the same group of conditions; 2) there are only single case reports; 3) the clinical or pathogenic relevance of Tau cytopathology related to the condition is unclear. Moreover, we also include conditions with neurofibrillary tangles in anatomically circumscribed areas and often unrelated to the leading brain lesions, or constellations of Tau pathologies reported in case reports and not compatible with Tauopathies of groups 1–5. The proposed grouping is summarized in Figure 1. Finally, coexistence of main Tauopathy-like conditions has been described in various disorders with diverse aetiologies (Table 2). However, these conditions can also present without Tauopathy and the direct relation of the primary disorder to a Tauopathy has not been demonstrated.

## CONCLUSION

As a consequence of developments in our understanding of neurodegenerative diseases and their relation to Tau protein, several terms have been generated, which are widely and inconsistently used. We propose a nomenclature of the various groups of diseases involving Tau that are based on the knowledge of aetiology, relation to non-Tau proteinopathies, presence of Tau isoforms, genetics of *MAPT* and accumulated experience of clinicopathological correlations, further complemented by high-resolution tau filament structures. We propose a simple system that can easily accommodate future discoveries (i.e., disorders can be moved between groups). This will hopefully allow those working on the understanding of the role of Tau in various conditions to communicate their findings in more concise and unambiguous ways and will inform therapeutic developments.

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**Key points:**

- We put forward definitions of terms to describe Tau in various conditions
- We propose a flexible stratification system and six groups
- Tauopathies are classified into five different groups
- A further group includes conditions with Tau immunoreactivity or Tau pathology

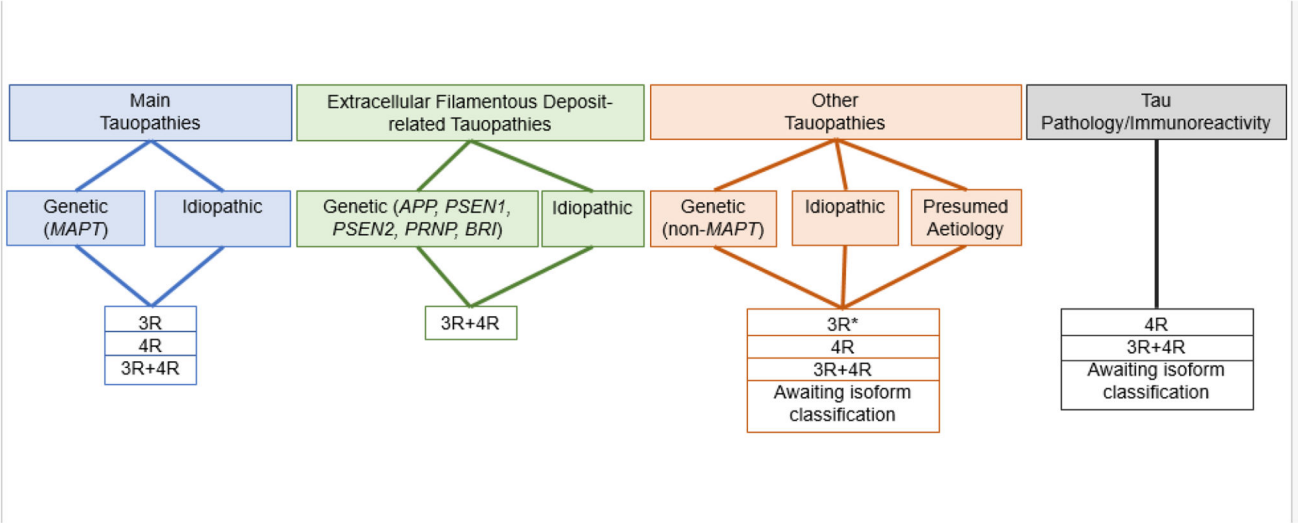


**Figure 1.**

Classification of diseases with accumulation of Tau protein.

*: Myotonic dystrophy, characterized by the preferential aggregation of 0N3R Tau. There have also been reports of the presence of 4R Tau.

**Table 1.**

Stratification of conditions with pathological Tau deposition.

**1) Tauopathy, autosomal-dominant, associated with *MAPT* mutation: *MAPT*-Tauopathies**

**3R**

**4R**

**3R+4R**

**2) Clinically and pathologically defined idiopathic Tauopathies**

**3R**

- Pick's disease

**4R**

- Corticobasal degeneration (CBD)
- Argyrophilic grain disease (AGD)
- Progressive supranuclear palsy (PSP)
- Globular glial tauopathy (GGT)

**3R+4R**

- Primary age-related Tauopathy (PART)/Tangle-only associated cognitive impairment

**3) Tauopathy, obligatory association with extracellular filamentous deposits caused by genetically determined other proteinopathy**

**3R+4R**

- Dominantly inherited Alzheimer's disease (mutations in *APP, PSEN1* and *PSEN2;* Protein: Aβ)
- Chromosome 21 trisomy-related Alzheimer's disease (Down's syndrome; Protein: Aβ)
- Dominantly inherited prion protein cerebral amyloidoses (PrP cerebral amyloid angiopathy and certain mutations in *PRNP* i.e., Gerstmann-Straussler-Scheinker disease; Protein: Prion protein)
- Dominantly inherited British dementia (mutations in *ITM2B*; Protein: ABri)
- Dominantly inherited Danish dementia (mutations in *ITM2B*; Protein ADan)

4**) Tauopathy, obligatory association with extracellular filamentous deposits in idiopathic diseases**

**3R+4R**

- Tau and AP proteinopathy
  - Young-onset Alzheimer's disease
  - Late-onset Alzheimer's disease

**5) Other Tauopathies**

**3R**

- Myotonic dystrophy types 1 and 2-related Tauopathy [45, 46] *§

**4R**

- Worldwide documented/Aetiology unknown
  - Neuro-astroglial Tauopathy variants in the elderly [47–49]

- Tauopathy with hippocampal 4-repeat Tau immunoreactive spherical inclusions [50–52] or limbic-predominant neuronal inclusion body 4R Tauopathy (LNT) [38]

**3R+4R**

- Aetiology unknown
  - Diffuse NFTs with calcification (Kosaka-Shibayama disease) [53]
- Aetiology unknown / Geographical cluster
  - Western Pacific ALS/PDC (Guam, Kii Peninsula) [54–57]
  - Nodding syndrome-related Tauopathy [58] *
- Presumed association with aetiology
  - Chronic traumatic encephalopathy (CTE)
  - IgLON5 antibody-related Tauopathy [59] *
  - Post-encephalitic parkinsonism [60] *
- Associated to hereditary conditions
  - Familial behavioural variant frontotemporal dementia associated with astrocyte-predominant Tauopathy [61, 62]
  - Vacuolar Tauopathy in autosomal-dominant *VCP* hypomorph mutation (D395G) [63]
  - Niemann-Pick disease type C-related tauopathy [64–67] *

**Awaiting isoform classification**

- Aetiology unknown
  - Progressive ataxia and palatal tremor-related Tauopathy **(**one study 3R+4R, another study 4R, based on immunostaining, no biochemistry) [68, 69]
- Presumed association with aetiology
  - Subacute sclerosing panencephalitis-related Tauopathy [70–74] *

**6) Tau pathology or Tau immunoreactivity or biochemical alterations of Tau protein**

**4R**

- Aging-related Tau astrogliopathy (ARTAG) [75]
- Tau pathology associated with familial parkinsonism and progressive respiratory failure [76]
- Tau pathology associated with *SLC9A6* gene-related mental retardation [77]
- Tau pathology associated with *SPG7* gene mutation [78]
- Striatal 4R Tau pathology associated to X-linked parkinsonism with spasticity (ATP6AP2)[79, 80]
- *SYNJ1* (PARK20) early-onset recessive form of parkinsonism with seizures and dystonia associated nigral Tau pathology [81]
- Limbic predominant neuronal-glial Tau pathology in *TARDBP* gene mutations (I383; P112H)[82, 83]
- Neuronal 4R Tau pathology in fatal familial insomnia *(PRNP* D178N mutation) [84]
- Astrocytic predominant 4R Tau pathology in genetic Creutzfeldt-Jakob disease *(PRNP* V203I)[85]
- 4R Tau-immunoreactive intranuclear rods in Huntington's disease [86]
- Peri-infarct 4R Tau immunoreactive neurons [87]

**3R+4R**

- Tau pathology associated with ADCY5-dyskinesia [88]
- Tau pathology in chronic temporal lobe epilepsy [89, 90]
- Tau pathology in NBIA *PANK2* [91] and *WDR45* [92] gene mutations
- Neuritic Tau immunoreactivity in various forms of Creutzfeldt-Jakob disease
- Neuronal 4R > 3R subcortical Tau pathology in genetic Creutzfeldt-Jakob disease (*PRNP* E200K mutation) [93]

- Neuropil threads, pretangles, and NFTs in HIV negative opiate abusers [94, 95]
- Fukuyama congenital muscular dystrophy (postfetal) related NFTs [96]

**Awaiting isoform classification**

- Accelerated hippocampal neuronal Tau (AT8) immunoreactivity in HIV-infected individuals (both before and after the advent of effective anti-retroviral therapy) [97]
- Tau (AT8) immunoreactive neurites in neuroferritinopathy [98]
- NFTs in neuronal ceroid lipofuscinosis [99], sialic acid storage disease [100], and Cockayne syndrome† [101]
- Tau pathology in NBIA *PLA2G6* mutation [102, 103]
- Tau pathology in NBIA associated with autosomal dominant mitochondrial membrane protein-associated neurodegeneration (MPAN)[104, 105]
- Phosphorylated pS422 Tau immunoreactive structures in fetuses with Fukuyama congenital muscular dystrophy [96]
- Tau pathology associated with with *SPAST* gene-related hereditary spastic paraplegia [106, 107]
- Nigral NFTs, following West-Nile encephalomyelitis [108]
- Neuronal NFT predominant subcortical Tau pathology in *TTBK2* gene-related spinocerebellar ataxia 11 [109]
- Tau (AT8) immunoreactive neurons in survivors of herpes simplex encephalitis [110]
- Developmental and neoplastic conditions with NFTs
  - Ganglioglioma [111]
  - Meningioangiomatosis [112–114]
- Infantile disorders with phospho-Tau immunoreactivity
  - Hemimegalencephaly [115]
  - Tuberous sclerosis complex [116]
  - Focal cortical dysplasia [116]
- Altered Tau expression (protein or mRNA) in diverse conditions
  - Multiple sclerosis: abnormal Tau phosphorylation in soluble/insoluble fractions [117, 118]
  - Huntington's disease: reduction of soluble Tau protein, increase in Tau phosphorylation at some epitopes, reduction of Tau monomers; increase in Tau exon 10 inclusion and upregulation in 4R-Tau protein levels; increase in the 4R:3R ratio and complex pattern of weaker bands of sarkosyl-insoluble Tau [86, 119, 120]

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NFT: Neurofibrillary Tangle;

* conditional, the spectrum to be defined in future studies;

§: Myotonic Dystrophy: characterized by the preferential aggregation of the smaller 0N3R isoform. However, there are reports where 4R was also detected;

† Another study failed to confirm the presence of NFTs in Cockayne syndrome [44].

**Table 2.**

Coexistence of well-characterized or other Tauopathy-like conditions with various disorders.

- Sporadic neurodegenerative diseases (for review see: [121])
  - PART/AD, AGD or PSP-like pathology associated with multiple system atrophy or Lewy body disorders
  - Pick's disease pathology associated with Lewy body disorders
  - AGD, PSP, CBD, GGT and Pick's disease type pathology associated with AD
  - PART/AD, AGD or PSP-like pathology associated with frontotemporal lobar degeneration/motor neuron disease with TDP-43 proteinopathy
  - PART/AD, ARTAG, PSP, or AGD-like pathology in Creutzfeldt-Jakob disease and variably protease-sensitive prionopathy [85, 122]
  - ARTAG in various conditions [123]
- Various hereditary disorders
  - AGD-like pathology in cerebrotendinous xanthomatosis [124]
  - AGD-like pathology in DOORS (deafness, onychodystrophy, osteodystrophy, intellectual disability, and seizures) syndrome [125]
  - PSP-like pathology in myotonic dystrophy type 1 [126]
  - PSP-like pathology in an asymptomatic myotonic dystrophy type I gene mutation carrier and in an individual with mental retardation [127]
  - PSP, AGD and AD-like pathology in *LRRK2* [128, 129]
  - PSP-like pathology in *PRKN* gene variants [130]
  - PART/AD in genetic Creutzfeldt-Jakob disease [85, 93]
  - AD/PART-like pathology in variants of *C9ORF72, GRN, SNCA* genes [131–137]
  - AD, ARTAG, CTE, PART-like pathology in Huntington's disease [138–140]
  - PSP-like pathology in benign hereditary chorea mapped to chromosome 8q 21.3-q23.3 [141]
  - Pick body pathology in *PSEN1* mutation [142, 143]
  - Pick body pathology in *C9ORF72* and *MAPT* A239T variant [144]
  - AD- and AGD-like pathology in spinocerebellar ataxia 31 [145]