

# From Protein Tangles to Genetic Variants: The Central Role of Tau in Neurodegenerative Disease

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## 1. Introduction

Since the first description in 1907 of intracellular tangles in degenerating neurons in the brain of a woman who had suffered from progressive dementia by Alois Alzheimer, research in the microtubule-associated protein tau (MAPT or tau), the major component of these intracellular deposits, and its involvement in neurodegenerative processes, has undergone a shift in paradigm. Originally regarded by many scientists as a second string player in Alzheimer's disease, it is now becoming increasingly clear that tau plays a crucial role in many neurodegenerative diseases. The discovery of neurofibrillary tangles in other progressive nervous system disorders – now commonly referred to as tauopathies – as well as the more recent association of *MAPT* genetic variants with Parkinson's disease have contributed to this heightened interest. In this chapter, we will review the developments of tau research from the beginnings to recent advances. We will focus on the increasing evidence implicating tau as a major player in neurodegeneration as well as on efforts to establish and optimize animal models of tauopathy to understand the molecular basis of this group of neurodegenerative diseases. In the final chapter section we will look forward and summarize the potential strategies for therapeutic strategies targeting tau for the treatment of tauopathic neurodegenerative diseases.

## 2. Tau protein

### 2.1 Tau structure and function

Tau proteins are low molecular weight polypeptides that are encoded by the gene *MAPT* (microtubule-associated protein tau) on chromosome 17q21. The *MAPT* gene spans ~135kb of genomic DNA and comprises 16 exons (Fig. 1). Alternative splicing of exons 2, 3 and 10 gives rise to six tau isoforms in the adult human central nervous system. Exons 6 and 8 are never found in mRNA transcripts in humans. Exon 4a is expressed in the form of high molecular weight tau in the peripheral nervous system, but never in the brain. Exon 0 is part of the promoter and while transcribed, is not translated (Buee et al., 2000). *MAPT* is primarily expressed in the central nervous system, and predominantly found in the axonal part of neurons. However, tau is expressed in glial cells as well. Trace amounts of *MAPT*

transcripts have been found and described in peripheral organs including testes, kidneys and heart (Buee et al., 2000).

The six tau isoforms found in the adult human CNS range from 352 to 441 amino acids in length and 45 - 65 kDa in molecular weight. The different isoforms have been found to be differentially expressed during development. While in the foetal human central nervous system only the shortest tau isoform is expressed, all six alternatively spliced isoforms are found in the adult human brain (Goedert et al., 1989). Furthermore, it is conceivable that the different tau splicing variants are expressed in distinct spatial patterns throughout the adult CNS, with different isoforms being predominant in different neuronal subpopulations.

Structurally, tau proteins are characterised by a C-terminal microtubule-binding domain, which is composed of repeats of highly conserved tubulin-binding motifs (Fig 1). The isoforms differ in their number of tubulin-binding repeats; inclusion of exon 10 (10<sup>+</sup>) gives rise to isoforms with 4 repeats (4R), exclusion leads to isoforms with 3 repeats (3R). The N-terminal projection domain is characterised by the absence (2-3-) or presence of either one (2+3- or 2-3+) or two (2+3+) 29 amino-acid-long inserts generated by alternative splicing of exons 2 and 3, as well as by a proline-rich region (Andreadis et al., 1992).

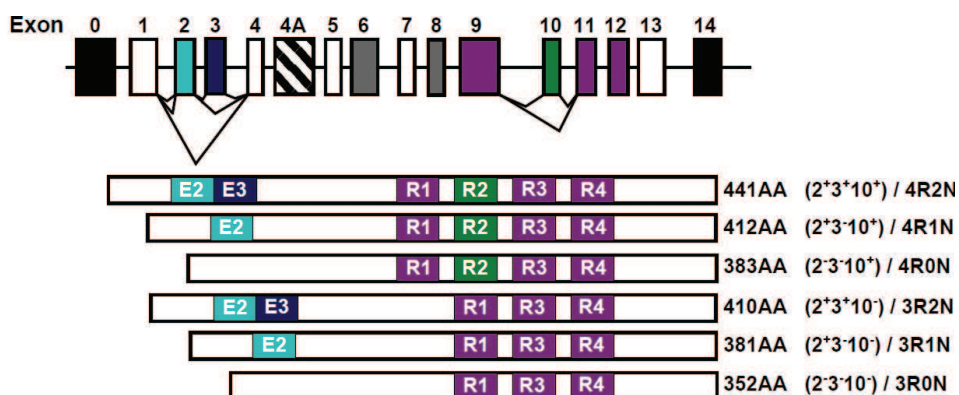


Fig. 1. Human *MAPT* gene and the six human adult isoforms in the CNS derived through alternative splicing. The *MAPT* gene encodes 16 exons, of which three (4A, 6 and 8) are not present in any of the six mature isoforms found in the human CNS. Exon 0 is part of the promoter region. Alternative splicing of exons 2, 3 and 10 gives rise to six tau isoforms. The isoforms differ by the number of tubulin-binding motifs in the MT-binding domain (R1-R4) as well as the absence or presence of either one or two 29-amino acid long motifs in the N-terminal domain (E2, E3)

## 2.2 Tau structure and function

The primary function of tau is the stabilisation of microtubules and the promotion of microtubule polymerisation, by binding to microtubules via the C-terminal MT-binding domain (Cleveland et al., 1977; Weingarten et al., 1975). It has been shown that 4R tau isoforms are more efficient promoters of tubulin polymerisation than 3R isoforms, hinting at different functions of the different isoforms (Goedert & Jakes, 1990). Through their polymerisation and stabilisation of microtubules, tau proteins thus have a pivotal role in maintaining the

appropriate neuron morphology. Since the microtubule network provides the railroad of the cellular transport machinery, tau is also implicated in axonal transport and thus in function and viability of neurons.

Aside from the stabilisation and polymerisation of microtubules, several studies have suggested tau to have a number of other functions in the cell: Tau proteins bind to spectrin and actin filaments, thereby possibly interconnecting different cytoskeletal elements (Carrier et al., 1984; Griffith & Pollard, 1982). Furthermore, it has been proposed that tau interacts with the neural plasma membrane, thus contributing to the development of cell polarity, and with mitochondria, enabling the interaction of the organelles with microtubules (Brandt et al., 1995; Jancsik et al., 1989). Tau proteins are also believed to have a direct role in regulating the function of motor proteins, as it has been shown that tau inhibits activity of both kinesin and dynamin (Dixit et al., 2008). While tau is predominantly found in axons in the cytosol, nuclear localisation of the protein has also been described. Recently, it has been shown that nuclear tau interacts with neuronal DNA and protects DNA integrity against mild heat-stress induced damage (Sultan et al., 2011). Furthermore, tau interacts with non-receptor tyrosine kinases such as fyn via its N-terminal projection domain (Lee et al., 1998). Through this interaction tau has been shown to sequester and relocate fyn, a kinase known to modulate NMDA receptor function (Ittner et al., 2010). Thus, tau is also involved in tyrosine kinase-mediated signal transduction processes.

### 2.3 Tau phosphorylation

Promoting microtubule polymerisation and maintaining microtubule stability are the main functions of tau proteins. These functions are regulated by post-translational modifications. The most common posttranslational modification of tau is the phosphorylation of serine, threonine and tyrosine residues. The longest tau isoform harbours 85 putative phosphorylation sites, most of which are serine residues (Martin et al., 2011). Phosphorylation of tau decreases the binding affinity to microtubules, thus reducing microtubule assembly and stability (Biernat et al., 1993; Bramblett et al., 1993). Non-physiologically phosphorylated or hyperphosphorylated tau species have been found in all known tauopathies and it has been shown that the accumulation of abnormally phosphorylated tau precedes the formation of tau tangles (Banerjee et al., 1989), indicating that dysregulation of the phosphorylation status of tau might be an early event in tau misfolding and subsequent formation of tangles. The phosphorylation status of tau proteins is dynamically regulated through a balance between kinase and phosphatase function. Disruption of this balance is believed to be at least partly responsible for the onset of tauopathies such as Alzheimer's disease. Three classes of kinases have been shown to be involved in the phosphorylation of tau proteins: proline-directed protein kinases (PDPKs, including GSK3 $\beta$  and Cdk5), non-PDPKs (such as PKA and CamKII) and tyrosine-specific protein kinases (Martin et al., 2011). Besides overactivation of kinases inhibition of protein phosphatases is thought to contribute to abnormal phosphorylation of tau. It has been shown that protein phosphatase 2A (PP2A), a ubiquitously expressed serine/threonine phosphatase, is involved in the regulation of the phosphorylation status of tau (Drewes et al., 1993; Gong et al., 2000). Investigation of brains of Alzheimer's disease patients has revealed a 50% decrease in PP2A activity compared to control brains (Gong et al., 1993).

Besides phosphorylation, several other forms of posttranslational modifications of tau have been described; among these are truncation, o-glycosylation, nitration, ubiquitination and glycation. Truncated and non-physiologically o-glycosylated forms of tau have been found

in Alzheimer's disease brains, but not in control brains (Martin et al., 2011), indicating that tau function is tightly regulated by posttranslational modifications and that aberrant modifications might at least be partly responsible for the formation of neurofibrillary tangles and the onset of neurodegeneration.

## 2.4 Tau aggregation

Neurofibrillary tangles (NFTs) are intracellular aggregates composed of hyperphosphorylated tau. These intracellular deposits are the defining hallmark of all tauopathies, such as Alzheimer's disease, FTDP-17 and Pick's disease. Ultrastructurally, tangles are composed of paired helical filaments (PHFs) and less prevalent straight filaments. PHFs are composed of two strands of hyperphosphorylated tau filament twisted around each other with a periodicity of 80 nm whereas straight filaments do not show this periodicity (Crowther, 1991).

Many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or Creutzfeldt-Jacob's disease share a common denominator: The initial misfolding and subsequent aggregation of specific proteins into highly organised and mostly thread-like structures termed amyloid. While many proteins with a propensity to self-aggregation are natively unfolded, they do not share an obvious sequence identity, suggesting that the ability to form amyloid structures is an inherent property of polypeptide chains (Chiti & Dobson, 2006). A recent physicochemical definition classifies amyloid as polymerised proteins forming a cross- $\beta$  structure (Fandrich, 2007). According to this definition, NFTs classify as amyloid structures, as there is strong evidence that tau fibrils display cross- $\beta$  structure both *in vitro* and *in vivo* (Berriman et al., 2003). *In vitro* aggregation of tau into filament structures has been shown to be dependent on a hexapeptide motif in the third repeat of the MT-binding domain (von Bergen et al., 2000).

Kinetic studies have shown that the aggregation of amyloid fibrils from polypeptides such as A $\beta$  peptide and  $\alpha$ -synuclein occurs through nucleation-dependent polymerisation, a chemical reaction characterised by an initial lag phase, an exponential growth phase and a steady-state phase (Harper & Lansbury, 1997). The same reaction scheme has been shown to apply to aggregation of tau *in vitro* (Friedhoff et al., 1998), indicating that similar mechanistic principles underlie the formation of PHFs as well as the formation of A $\beta$  plaques and  $\alpha$ -synuclein deposits. However, in contrast to aggregating polypeptides such as A $\beta$  and  $\alpha$ -synuclein, tau proteins do not exhibit stretches of hydrophobicity and a propensity to form cross- $\beta$  structures. Instead, tau is a hydrophilic protein with high solubility and a random coil conformation, structural characteristics that are unfavourable for aggregation. It is not fully understood how the initial transition of tau protein from random coil structure to aggregation-prone state with increased  $\beta$ -sheet content occurs in tauopathies. As discussed in section 2.3, tau hyperphosphorylation is believed to play a crucial role in the early events of NFT formation. Furthermore, point mutations of tau found in patients suffering from FTDP-17, a rare genetic tauopathy, lead to increased aggregation propensity. Truncation of the protein, most notably by caspase cleavage, is also indicated as an early event in tau aggregation (Gamblin et al., 2003).

## 2.5 Mechanisms of tau-mediated neurodegeneration

The precise mechanism by which aggregation of tau into neurofibrillary tangles induces neurodegeneration remains unclear. Neuronal cell death could result either from a loss of

tau protein function or from a toxic gain of function - or most probably, from a combination of both mechanisms. Modulation of cytoskeleton stability and dynamics is of crucial importance in maintaining proper cell morphology, intracellular transport and viability. In the loss-of-function model, hyperphosphorylated tau is detached from the microtubules and instead aggregates into fibrillary structures, thereby leading to a destabilisation of microtubules and thus compromised cell integrity. Furthermore, loss of tau function could compromise axonal transport. Transport of vesicles, mRNA and organelles is driven by motor proteins that use the microtubules as a railroad across the axons and requires a finely regulated balance between stability and plasticity of microtubules. However, the validity of the tau loss-of-function model has been somewhat questioned by the fact that tau knockout mice appear phenotypically normal, probably due to compensatory mechanisms by other microtubule-associated proteins (Dawson et al., 2001; Harada et al., 1994).

Amyloid aggregates such as A $\beta$  and  $\alpha$ -synuclein oligomers and fibrils have been widely shown to be toxic *in vitro* and *in vivo*. Together with the fact that the number of NFTs in Alzheimer's disease correlates with the degree of cognitive impairment (Arriagada et al., 1992) this suggests that tau aggregates are likely to be directly neurotoxic. The toxicity of tau aggregates has been shown in several cell culture models (Bandyopadhyay et al., 2007; Khlistunova et al., 2006). Intracellular NFTs could be toxic due to their large size, thereby disrupting cell function and axonal transport. Furthermore, tangles might sequester more tau proteins, thereby exacerbating the loss-of-function effects, or other proteins important for cell viability (Ballatore et al., 2007). However, as with A $\beta$  and  $\alpha$ -synuclein aggregates, recent studies suggest that the most toxic species might not be the end stage NFTs, but early oligomeric aggregation intermediates (Kay & Jackson, 2009; Maeda et al., 2007). A mouse model of tauopathy was discovered to exhibit synapse loss and microgliosis that preceded the formation of NFTs (Yoshiyama et al., 2007). A more recent study showed that caspase activation precedes NFT formation in another mouse tauopathy model (de Calignon et al., 2010). Furthermore, subcortical stereotactic injection of tau oligomers into wild-type mice leads to memory impairment and synaptic dysfunction (Lasagna-Reeves et al., 2011).

The loss-of function and gain-of-function models of tau-mediated neurodegeneration are not exclusive, and it is likely that neuronal impairment and cell death are the result of both mechanisms. However, while much progress has been made into elucidating these mechanisms, the link between tau misfolding and aggregation on the one hand and neurodegeneration on the other hand remains largely elusive.

### 3. From tangles to gene

#### 3.1 Alzheimer's disease and the beginnings of tau research

In 1907, Alois Alzheimer, a German psychiatrist and neuropathologist, published his historic case report "*Über eine eigenartige Erkrankung der Hirnrinde*" (about a peculiar disease of the cerebral cortex). In this report, Alzheimer described the case of a 51-old woman suffering from progressive memory loss, personality changes and impaired language ability. Less than five years after the onset of disease, the woman died and Alzheimer performed post-mortem analysis of her brain. Using the silver staining method by Bielschowsky, the psychiatrist was able to detect two pathological features in the patient's brain: a "peculiar matter in the cortex" as well as "tangled bundles" of fibrils on the insides of neuronal cells (Strassnig & Ganguli, 2005). However, almost 80 years elapsed before the molecular compositions of these two deposits were discovered: While

the extracellular plaques found in the cortex are composed of A $\beta$  peptide, the intracellular tangled bundles, now known as neurofibrillary tangles (NFTs), primarily consist of tau protein (Grundke-Iqbal et al., 1986; Masters et al., 1985). This progressive disorder of the central nervous system would eventually be given the name Alzheimer's disease (AD). To date, Alzheimer's disease is the most common neurodegenerative disorder worldwide, with almost 27 million people affected in 2006, and case numbers expected to quadruple by 2050 (Brookmeyer et al., 2007).

According to the widely accepted amyloid cascade hypothesis, overproduction and aggregation of amyloid- $\beta$  (A $\beta$ ) is the central trigger in the pathogenesis of AD. A $\beta$  peptides are 40 or 42 amino acid-long cleavage products of the transmembrane protein APP, whose function remains unknown to this day. In the amyloid cascade hypothesis, aggregation of tau proteins into NFTs is considered a secondary downstream event, triggered by A $\beta$  aggregation. This view is supported by genetic evidence, which shows linkage of mutations in APP with FAD, whereas no genetic link between *MAPT* and Alzheimer's disease has been described so far. Furthermore, it has been shown that overproduction of A $\beta$  induces increased tau phosphorylation and that cerebral injection of A $\beta$  fibrils exacerbates the formation of tangles in a tau transgenic mouse model (Gotz et al., 2001b; Wang et al., 2006).

The evidence supporting the amyloid cascade hypothesis was so great that some scientists were sceptical whether tau pathology in AD played a role in pathogenesis or whether the observed neurofibrillary tangles represented a mere epiphenomenon of the disease. Several studies, however, have implicated an important role of tau in Alzheimer's disease pathogenesis. It has been shown that the number of NFTs, but not of plaques, can be correlated with severity of the disease (Arriagada et al., 1992). Furthermore, experiments have suggested that tau is required for A $\beta$ -induced toxicity, as cultured hippocampal cells from a tau knockout mouse are not susceptible to A $\beta$ -induced neurodegeneration, and for A $\beta$ -induced impairment of hippocampal long-term potentiation (Rapoport et al., 2002; Shipton et al., 2011). These results corroborate the amyloid hypothesis, placing tau as a downstream player of amyloid- $\beta$  in AD, while at the same time underlining the central role of the microtubule-binding proteins.

The last 25 years since the identification of tau as the major component of PHFs have not only led to a new understanding of the importance of tau in Alzheimer's disease. In fact, it is becoming increasingly clear that tau is a major player in many neurodegenerative diseases. Three discoveries have paved the way for this shift of paradigm: 1) A group of sporadic neurodegenerative diseases exist displaying tau tangle pathology in the absence of A $\beta$  plaques, such as corticobasal degeneration and progressive supranuclear palsy. All diseases exhibiting tau pathology including AD are now collectively referred to as *tauopathies* (Table 1). 2) Mutations in the *MAPT* gene are associated with a familial neurodegenerative tauopathy termed frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). 3) Association studies have pulled out *MAPT* as an important risk factor in Parkinson's disease, the second most prevalent neurodegenerative disease worldwide. In the following sections, we will discuss these findings in more detail.

### 3.2 Sporadic tauopathies

While Alzheimer's disease is characterised by the presence of both tau deposits and amyloid plaques, several other tauopathies have been described with tau pathology in the absence of other forms of fibrillary deposits (Table 1). Three such neurodegenerative disorders are corticobasal degeneration, progressive supranuclear palsy and Pick's disease. Due to their

neuropathological and phenotypical overlaps, these diseases are now grouped as frontotemporal dementias.

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder with a prevalence of ca. 6 per 100,000. Clinically, cases of PSP typically present with levodopa-unresponsive parkinsonism with prominent postural instability, supranuclear gaze palsy, speech difficulties, depression and mild dementia. The affected brain regions are typically neurons and glial cells in the basal ganglia (most notably globus pallidus and substantia nigra), diencephalon, brain stem and spinal cord. The fibrillary inclusions found in PSP brains predominantly consist of 4R isoforms in the form of straight filaments (Dickson et al., 2007). This is in stark contrast to AD, where NFTs are composed of equimolar ratios of 3R and 4R isoforms in the form of paired helical filaments.

Tauopathies
Alzheimer' disease ( <i>a</i> )
Amyotrophic lateral sclerosis/parkinsonism-dementia complex ( <i>b</i> )
Argyrophilic grain dementia ( <i>b</i> )
Creutzfeld-Jacob disease ( <i>a</i> )
Dementia pugilistica ( <i>a</i> )
Diffuse neurofibrillary tangles with calcification ( <i>b</i> )
Down's syndrome ( <i>a</i> )
Frontotemporal dementia with parkinsonism linked to chromosome 17 ( <i>b</i> )
Gerstmann-Sträussler-Scheinker disease ( <i>a</i> )
Hallervorden-Spatz disease ( <i>c</i> )
Multiple system atrophy ( <i>c</i> )
Niemann-Pick disease, type C
Pick's disease ( <i>b</i> )
Postencephalitic parkinsonism
Prion protein cerebral amyloid angiopathy ( <i>a</i> )
Progressive subcortical gliosis ( <i>b</i> )
Progressive supranuclear palsy ( <i>b</i> )
Subacute sclerosing panencephalitis
Tangle-only/tangle-predominant dementia ( <i>b</i> )

Table 1. Neurodegenerative tauopathies. (*a*) Tauopathies with amyloid deposits, (*b*) neurofibrillary lesions most predominant, (*c*) tauopathies with predominant synuclein-positive lesions

Another sporadic tauopathy that predominantly shows 4R pathology is corticobasal degeneration (CBD), but in contrast to PSP, NFTs are primarily composed of twisted filaments. The cardinal symptoms are similar to those of PSP, but typically include cortical features such as myoclonus and lack vertical gaze palsy. Whereas in PSP the affected brain regions are predominantly hindbrain structures, forebrain regions including the cerebral cortex show atrophy in CBD (Kouri et al., 2011; Mahapatra et al., 2004). Due to their overlapping pathology and symptoms, there is a widespread opinion that PSP and CBD

might in fact represent two different ends of a disease spectrum that is caused by the accumulation of 4R tau isoforms.

In contrast to both CBD and PSP, Pick's disease is classified as a 3R tauopathy. The disease stems from frontotemporal lobar and limbic atrophy and histologically is characterised by the appearance of deposits called Pick bodies. The symptoms correspond to a cognitive phenotype, with progressive dementia and personality changes such as obsessive-compulsive disorder, apathy and frontal disinhibition. A motor phenotype is usually absent (Buee et al., 2000; Mahapatra et al., 2004).

### 3.3 Frontotemporal dementia with parkinsonism linked to chromosome 17

Frontotemporal dementias (FTD) are a heterogeneous group of neurodegenerative diseases characterised by progressive dementia due to atrophy of the frontal and temporal lobes. FTD is one of the most common forms of dementia besides Alzheimer's disease. While the majority of cases are thought to occur sporadically, familial cases of the disease were described as far back as 1939 (Gasparini et al., 2007). In 1994, a familial case of dementia with parkinsonism was described. The disease was termed disinhibition-dementia-parkinsonism-amyotrophy complex and was linked to a locus on chromosome 17q21-22 (Wilhelmsen et al., 1994). Subsequently, other families with hereditary frontotemporal dementia-parkinsonism syndromes were also assigned this locus (Baker et al., 1997; Froelich et al., 1997). In 1996, the term frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) was coined to describe the two major symptoms associated with the rare familial disease (Foster et al., 1997). As it was already known at that time that the *MAPT* gene was located on chromosome 17q21 and that the product of this gene, tau protein, was associated with AD, another neurodegenerative dementia, it was speculated that aberrations in the *MAPT* gene could be associated with FTDP-17. In 1998, the first mutations in the *MAPT* gene were identified in association with FTDP-17 (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998), providing the ultimate demonstration of a causative role of tau in the onset of neurodegeneration. To date, 41 *MAPT* mutations in over 100 families have been described.

FTDP-17 is a very rare neurodegenerative disease transmitted in an autosomal-dominant inheritance pattern and showing high penetrance (>95%). The age of onset of the disease is usually between 25 - 65 years of age and the duration from the onset of the first symptoms to death varies between 3 - 10 years (Boeve & Hutton, 2008). The mutation R406W is an exception, as it is associated with a slower disease progression (van Swieten et al., 1999). The symptoms associated with FTDP-17 are various. Patients usually present either a dementia predominant or a parkinsonism predominant phenotype. The range of symptoms associated can be grouped into three categories: personality changes, motor function impairment and cognitive decline. The list of changes in personality of affected individuals is long and includes disinhibition, apathy, aggressive behaviour, obsessive-compulsive behaviour, hyper-religiosity, bluntness and hyperorality. Paranoia and hallucinations can lead to an initial misdiagnosis as a psychiatric disorder. Cognitive dysfunctions are manifested as memory impairment, loss of orientation and judgement and language difficulties progressing to mutism. The cardinal symptoms associated with parkinsonism are rigidity, bradykinesia, postural instability and resting tremor, though the latter symptom is frequently absent. In contrast to Parkinson's disease, motor symptoms do not or only slightly improve with levodopa treatment (Basun et al., 1997; Wilhelmsen et al., 1994; Wszolek et al., 2006). Histologically, FTDP-17 is characterised by atrophy of the frontal and



temporal lobes, and sometimes subcortical nuclei, amygdala and brainstem, with gliosis and spongiosis. Tau deposits can appear in neurons or in neurons and glial cells. The morphology of these deposits can vary considerably depending on patient and mutation and can appear either as neurofibrillary tangles, Pick bodies or diffuse (Tsuboi, 2006).

### 3.4 *MAPT* mutations in FTDP-17

Mutations in the *MAPT* gene encompass intronic mutations and missense, deletion and silent mutations in the coding regions (Table 2). The majority of mutations known to cause FTDP-17 are found in the latter category. The effects of mutations can be grouped into two categories: mutations that alter the alternative splicing of primary tau mRNA transcripts or/and have an effect on tau protein. The majority of mutations affect either the mRNA or the protein level, but a few mutations exert their effects on both splicing and protein function. The type of effect seen depends both on the location and the type of mutation. The most common mutations are the missense mutation P301L, which has been observed in 25 families, and the intronic mutation +16, described in 22 families (Rademakers et al., 2004).

All coding region mutations exert their effects on the physicochemical properties of tau protein. The majority of mutations cluster in exons 9 - 12, the microtubule-binding domain, especially in the alternatively spliced exon 10. The only known mutations outside the microtubule-binding domain have been found in exons 1 (R5H and R5L) and 13 (G389R, R406W and T427M). While most mutations in these exons as well as exons 9, 11 and 12 affect all tau isoforms, only 4R tau is affected by mutations in exon 10 (Gasparini et al., 2007). The primary mechanism by which missense and deletion mutations in the coding regions alter the properties of tau protein is by decreasing affinity for microtubules. This can be shown by an *in vitro* assay monitoring microtubule assembly (Hong et al., 1998). Exceptions are the S305N mutation in exon 10 and Q336R in exon 12, which have been shown to increase microtubule assembly (Hasegawa et al., 1999; Pickering-Brown et al., 2004). Reduced affinity of tau for microtubule-binding sites could lead to a destabilisation of microtubules and, as a result, impaired neuron morphology, axonal transport and neurotransmitter release. Furthermore, a low binding affinity could result in a net increase of free soluble tau, thereby reaching the critical concentration required to trigger a nucleation-dependent polymerisation reaction. Besides their effect on microtubule binding, some mutations in the coding regions result in an increased propensity to heparin or arachidonic acid-induced self-aggregation *in vitro*. Some mutations have an effect on specific tau isoforms only. Mutations in exon 10 such as  $\Delta$ K280, N296H, P301S and P301L, can only increase aggregation of 4R tau. The missense mutation I260V in exon 9 has the same effect, while K257T only increases tau fibril formation in 3R isoforms (Grover et al., 2003; Rizzini et al., 2000).

All intronic mutations described so far lie in the introns 9 and 10, surrounding the alternatively spliced exon 10. These intronic mutations as well as several coding region mutations, most of them found in exon 10, have an effect on alternative splicing of exon 10, thereby shifting the ratio of 3R to 4R tau. In the healthy adult human CNS, the ratio of 3R to 4R tau is approximately equimolar (Hong et al., 1998). Most intronic mutations as well many of the coding region mutations in exon 10 lead to an increase of exon 10 inclusion, thereby shifting the ratio of tau isoforms towards 4R (Table 2). The deletion  $\Delta$ K280 as well as the intronic +19 mutation are exceptions, as they have been shown to decrease exon 10 splicing *in vitro* (D'Souza et al., 1999; Stanford et al., 2003). The fact that an imbalance in the ratio between 3R and 4R isoforms is sufficient to cause neurodegeneration suggests that maintaining this ratio is important for maintaining normal CNS function. The reason why a

Region	Mutation	Exon 10 inclusion	Microtubule assembly	Tau filament formation
Exon 1	R5H	no effect	↓	↑
Exon 1	R5L	no effect	↓	↑
Exon 9	K257T	no effect	↓	3R ↑
Exon 9	I260V	no effect	4R ↓	4R ↑
Exon 9	L266V	↑	↓	4R ↑
Exon 9	G272V	ND	↓	↑
Exon 10	N279K	↑	no effect	ND
Exon 10	ΔK280	↓	4R ↓	4R ↑
Exon 10	L284L	↑	no effect	no effect
Exon 10	ΔN296	↑	4R ↓	4R ↑
Exon 10	N296H	↑	4R ↓	4R ↑
Exon 10	N296N	↑	no effect	no effect
Exon 10	P301L	no effect	4R ↓	4R ↑
Exon 10	P301S	no effect	4R ↓	4R ↑
Exon 10	G303V	↑	ND	ND
Exon 10	S305N	↑	4R ↑	ND
Exon 10	S305S	↑	no effect	no effect
Exon 11	L315R	ND	↓	no effect
Exon 11	K317M	ND	ND	ND
Exon 11	S320F	ND	↓	ND
Exon 12	G335V	ND	↓	↑
Exon 12	Q336R	ND	↑	↑
Exon 12	V337M	ND	↓	↑
Exon 12	E342V	↑	ND	ND
Exon 12	S352L	ND	↓	↑
Exon 12	S356T	ND	ND	ND
Exon 12	K369I	ND	↓	altered
Exon 13	G389R	ND	↓	ND
Exon 13	R406W	ND	↓	conflicting
Exon 13	T427M	ND	ND	ND
Intron 9	IVS9-10	↑	no effect	no effect
Intron 10	ISV10+3	↑	no effect	no effect
Intron 10	ISV10+11	↑	no effect	no effect
Intron 10	ISV10+12	↑	no effect	no effect
Intron 10	ISV10+13	↑	no effect	no effect
Intron 10	ISV10+14	↑	no effect	no effect
Intron 10	ISV10+16	↑	no effect	no effect
Intron 10	ISV10+19	↓	no effect	no effect

Table 2. *MAPT* mutations found in FTDP-17 and their effects on exon 10 inclusion, microtubule assembly and tau filament formation. ↑ = increased, ↓ = decreased, ND = not determined

shift of isoform ratio has such detrimental effects remains unclear. Tau containing four repeats has been shown to have a greater affinity towards microtubules and promote a faster assembly of microtubules than 3R isoforms (Goedert & Jakes, 1990). Furthermore, *in vitro* studies have indicated that 4R tau is more effective at microtubule stabilisation than 3R tau, by decreasing both the rate and the overall length of shortening of microtubules (Panda et al., 2003). These results suggest that an equimolar ratio of three- and four-repeat tau might be needed to maintain a balance between microtubule stability and plasticity and thereby ensure proper neuron function and morphology. Furthermore, it is conceivable that an overproduction of 4R tau leads to an increased concentration of unbound 4R tau in the cytosol, thereby facilitating the formation of four-repeat containing tau aggregates. However, this proposed model possibly requires the existence of two different binding sites on microtubules for 3R and 4R isoforms (Goode et al., 2000). Tau aggregation assays *in vitro* have furthermore shown that 3R tau isoforms directly inhibit the assembly of 4R tau into filaments, suggesting that restoring an equimolar tau isoform ratio might have therapeutic implications in tauopathies (Adams et al., 2010).

The alternative splicing of exon 10 is regulated by mRNA splice sites as well as by both exonic and intronic regulatory sequences. Alterations of the splice site and regulatory sequences are responsible for dysregulated inclusion of exon 10 in the intronic and several coding region mutations. Like most alternatively spliced exons, exon 10 contains a weak 5' splice site, leading to a weak interaction with the U1 snRNP. This site is strengthened by the coding region mutations S305N/S and the intronic mutation +3, which results in increased exon 10 splicing (Hutton et al., 1998; Spillantini et al., 1998; Stanford et al., 2000). Notably, a large part of exon 10 is directly involved in splicing regulation, as it harbours several exonic splicing enhancers and a silencer. Exon splicing enhancers are elements that increase the inclusion of an alternatively spliced exon, while an exon splicing silencer decreases inclusion. Likewise, intronic sequences that increase or decrease splicing are termed intron splicing enhancers or silencers (D'Souza & Schellenberg, 2005). Three exon splice enhancer (a SC35-like enhancer, a polypurine enhancer PPE and a AC-rich element ACE) are located at the 5' end of exon 10, followed by an exon splicing silencer element and another ESE at the 3' end of the exon (D'Souza & Schellenberg, 2005). While the mutation N279K strengthens the PPE, thereby increasing exon 10 inclusion, the opposite result is achieved through the lysine deletion at position 280. The silent mutation L284L has been shown to lie close to and affect the ACE enhancer (D'Souza et al., 1999; D'Souza & Schellenberg, 2005). The mutations N296H and N296N are thought to enhance exon 10 inclusion by converting a silencer to an enhancer sequence (D'Souza & Schellenberg, 2000).

The regulation of exon 10 splicing through intronic sequences is explained by two alternative models: The stem-loop theory proposes that a secondary stem loop structure blocks binding of U1 snRNP to the 5' splice site. The intronic mutations +10, +11, +12, +13, +14 and +16 disrupt the stem loop in this model, thereby increasing exon 10 splicing (Gasparini et al., 2007; Hutton et al., 1998; Spillantini et al., 1998). The alternative linear sequence theory suggests that three sequences in the intron following exon 10 modulate splicing: an intron splicing silencer and an intron splicing modulator, which are located downstream of the 5' splicing site. In this model, protein regulators bind to these sites; silencing of splicing via the splicing silencer element is counterbalanced by a splicing modulator. Mutations in the intron are thought to disrupt the interactions of the splicing silencer element with its bound factors. The +19 mutation is an exception, as it lies within

the intron splicing modulator sequence and disrupts its repression of the splicing silencer (D'Souza et al., 1999; D'Souza & Schellenberg, 2000).

Several coding region mutations (L266V,  $\Delta$ K280,  $\Delta$ N296, N296H and S305N) exert their effects both on the mRNA splicing and on the protein level. The deletion mutations as well as the missense mutations L266V and N296H decrease microtubule assembly *in vitro*, while S305N leads to an enhanced assembly (D'Souza et al., 1999; Hasegawa et al., 1999; Hogg et al., 2003; Yoshida et al., 2002). All these mutations enhance inclusion of exon 10, except  $\Delta$ K280. While this mutation might result in an increased production of 3R tau, it also strongly decreases the affinity for microtubules and enhances tau polymerisation *in vitro* (D'Souza et al., 1999).

In conclusion, mutations in the tau gene lead to a pathological aggregation of tau protein through several mechanisms: 1) by decreasing the affinity of tau for microtubules, 2) by enhancing self-aggregation of tau into fibrils and 3) by altering the ratio of 3R and 4R isoforms on the mRNA level. Most mutations exert their effects through more than one of these mechanisms and a few mutations have been shown to affect tau on all three levels.

Establishing phenotype-genotype relationships for *MAPT* mutations has proven to be difficult. Patients harbouring the same mutation, even within the same family, can present with very different clinical symptoms. Assessment of nine patients harbouring the P301S mutation showed a frontotemporal dementia predominant phenotype in three, and a parkinsonism predominant phenotype in six individuals (Baba et al., 2007). The missense mutation N279K on the other hand results in similar parkinsonism-predominant clinical symptoms with dementia even between affected individuals with different ethnic backgrounds (Arima et al., 2000; Delisle et al., 1999; Soliveri et al., 2003). The variability in clinical phenotypes of patients harbouring the same mutation might be the result of environmental factors, interaction with other genes or the interaction between tau mutation and tau haplotype. In contrast to the clinical phenotype, mutations and their locations can be correlated to the type of tau tangle pathology, isoform distribution and affected cell types. Missense and deletion mutations in exon 10 and intronic mutations in the downstream intron result in tau pathology with a twisted ribbon morphology that affect both neuronal and glial cells. The deposits are predominantly - or in the case of exon 10 coding region mutations solely - composed of 4R isoforms. Mutations in coding regions outside of exon 10 present neuronal tau pathology with glial cells unaffected. The tau inclusions are formed by filaments that are composed of both 3R and 4R isoforms and that resemble the PHFs and SFs found in Alzheimer's disease or show twisted ribbon morphology (Gasparini et al., 2007; Goedert, 2005). However, the mutation K257T in exon 9 leads to the deposition of tangles predominantly composed of 3R tau species (Rizzini et al., 2000).

### 3.5 Tau as a genetic risk factor for neurodegenerative diseases

Even before the description of the first *MAPT* mutations in familial cases of frontotemporal dementia, an association between progressive supranuclear palsy and the *MAPT* gene was identified: A dinucleotide TG repeat allele termed A0 in intron 9 was shown to be overrepresented in patients with PSP compared to healthy controls (Conrad et al., 1997). Subsequently, genetic analysis revealed eight single nucleotide polymorphisms in exons 1, 2, 3 and 9 that were in complete linkage disequilibrium with each other and the A0 allele (Baker et al., 1999). This region of disequilibrium spans the entire *MAPT* locus and the resulting two haplotypes are termed H1 and H2. In addition to the eight SNPs, a 238 bp

deletion in intron 9 was found to be inherited as part of the H2 haplotype. This deletion is now frequently used for haplotype assessment in *MAPT* association studies. The most common allele H1 and genotype H1/H1 were shown to be significantly overrepresented in PSP compared to healthy controls (Baker et al., 1999). In Caucasians, the frequency of the H1 haplotype is about 78% in healthy controls compared to ca 94% in PSP. The genotype H2/H2 seems to be protective against PSP, as no cases with that genotype were described. Interestingly, the H2 haplotype is only found in Caucasians and is absent in Asian and Native American populations (Evans et al., 2004).

Subsequently, the H1 haplotype was further expanded to include the promoter region of *MAPT* and now spans a region of ~1.8Mb in complete linkage disequilibrium (de Silva et al., 2001; Pittman et al., 2004). This extended haplotype contains several genes in addition to *MAPT*, including *CRHR1* (corticotrophin-releasing hormone receptor 1), *NSF* (N-ethylmaleimide sensitive factor), *IMP5* (intramembrane protease 5), *WNT3* and *STH* (saitohin), a gene nested in the intron 9 of *MAPT* (Conrad et al., 2002; Pittman et al., 2004). A ~900kb segment of the H2 haplotype including *MAPT* has been found to be inverted in respect to H1. Subsequently, the H1 haplotype was further divided into sub-haplotypes with SNPs that show variation only in the H1 haplotype and the association of these sub-haplotypes with PSP and CBD was investigated. One subhaplotype, termed H1c, was shown to be highly associated with PSP and CBD in case-control cohorts (Pittman et al., 2005).

Shortly after the association between the H1 haplotype and PSP was discovered, association studies showed that H1 was also overrepresented in the sporadic tauopathy CBD (Di Maria et al., 2000; Houlden et al., 2001). Many other association studies have been performed to investigate a possible association between *MAPT* haplotypes and other sporadic tauopathies, most notably Alzheimer's disease. However, genetic analyses showed no association between AD and *MAPT* (Abraham et al., 2009; Baker et al., 2000; Mukherjee et al., 2007). Conversely, studies showed a significant association of the *MAPT* locus with amyotrophic lateral sclerosis and parkinsonism dementia complex of Guam (ALS-G-PDC-G) (Poorkaj et al., 2001; Sundar et al., 2007).

The mechanisms underlying the association of the H1 haplotype with sporadic tauopathies is not completely clear. It has been shown that while total mRNA transcript levels are comparable between H1 and H2 haplotype carriers, the H1 haplotype expresses significantly higher levels of exon 10-containing mRNA compared to H2 in the globus pallidus and frontal cortex, two brain regions affected by neurodegeneration in tauopathy (Caffrey et al., 2006), suggesting that a subtle increase of 10<sup>+</sup> transcripts confers an increased susceptibility to neurodegeneration. Furthermore, post-mortem analysis of H1/H2 heterozygous brain tissue revealed that the neuroprotective haplotype H2 expresses significantly higher levels of transcripts containing exons 2 and 3 (2<sup>+</sup>3<sup>+</sup>) in comparison to H1 (Caffrey et al., 2008).

In recent years, gene and genome-wide association studies have been performed to investigate an association between *MAPT* and Parkinson's disease (PD). Several studies have shown an overrepresentation of the H1 haplotype in PD compared to controls (Healy et al., 2004; Simon-Sanchez et al., 2009). The association of tau with sporadic PD is puzzling insofar as it is a neurodegenerative disease that is not classified as a tauopathy due to the absence of NFTs in the majority of patients. The role of tau in the disease pathogenesis of PD is unknown. However, FTDP-17, CBD and PSP are parkinsonism-plus-syndromes, showing a motor phenotype that overlaps with PD. In rare instances, localisation of tau in Lewy bodies, the

defining pathological hallmark of PD, has been described (Arima et al., 1999). Furthermore, it has been shown that tau binds  $\alpha$ -synuclein and that  $\alpha$ -synuclein stimulates protein kinase A to phosphorylate tau protein (Jensen et al., 1999). *In vitro* aggregation assays have shown that co-incubation of tau and  $\alpha$ -synuclein promotes the aggregation of both protein species (Giasson et al., 2003). A recent association study confirmed the genetic link between *MAPT* and PD and showed a significantly higher expression of 4R tau in PD brains compared to controls (Tobin et al., 2008). While the mechanism by which tau influences PD pathogenesis remains unclear, tau protein has emerged as the central player in many neurodegenerative diseases. The assumption that tau protein or at least some of its isoforms might be involved in modulating the detrimental effects of  $\alpha$ -synuclein is thus not far-fetched.

#### 4. Animal models of tauopathy

The discovery that mutations in tau are sufficient to cause neurodegeneration prompted an increased desire to understand the functional relationship between tau, tangles and cell death in the CNS. For this purpose, transgenic animals have been created to model the histopathological and clinical phenotypes observed in tauopathies.

##### 4.1 Mouse models expressing one wild-type tau isoform

The first transgenic mouse models of human tauopathy were generated before *MAPT* mutations were shown to cause the rare familial neurodegenerative disorder FTDP-17. Thus, early models were created by introducing cDNA under the regulation of different promoters into the mouse genome to overexpress human wild-type tau (Gotz et al., 1995; Ishihara et al., 1999). In the first published model, the longest human tau isoform was expressed under the control of the Thy-1 promoter (Gotz et al., 1995). The resulting mouse showed localisation of human tau in neuron soma, axons and dendrites. While NFTs were not present, tau was found to be phosphorylated at sites that were previously shown to be hyperphosphorylated in AD. Other models expressing single tau isoforms under the control of different promoters soon followed. Characterisation of a mouse expressing the shortest human tau isoform driven by the mouse prion protein promoter (MoPrP) revealed insoluble hyperphosphorylated tau and argyrophilic intraneuronal inclusions at a young age, which matured into PHFs in old mice. These mice also showed signs of axonal degeneration (Ishihara et al., 1999; Ishihara et al., 2001). This mouse model was remarkable insofar as it was the first transgenic rodent to display an age-dependent accumulation of hyperphosphorylated tau and assembly into *bona fide* fibrillary tau deposits as well as axonal degeneration. However, while being a valuable effort to elucidate the mechanisms of neurofibrillary tangle formation and tau-mediated neurodegeneration, wild-type transgenic mouse models of tauopathy generated by placing tau cDNA under the control of high-expression promoters presented several shortcomings: 1.) Formation of neurofibrillary tangles was rarely observed and only at an advanced age. Furthermore, NFT localisation and axon degeneration was not necessarily reflecting human tauopathies, as the tangles were detected in abundance in spinal cord neurons (Ishihara et al., 2001). 2.) The phenotype of the mouse models was heavily dependent on the promoter chosen to drive expression. 3.) The models allowed only expression of one tau isoform, whereas six isoforms are found in the adult human CNS. 4.) Confounding effects caused by the co-existence of both human and murine tau could not be excluded. Subsequent mouse models of tauopathy were thus designed to address all of these concerns.

## 4.2 Mouse models expressing one mutant tau isoform

After the discovery of *MAPT* mutations and their causative role in familial neurodegenerative disease and findings that mere overexpression of tau did not yield a phenotype that accurately resembled the neuropathological and behavioural changes found in human tauopathies, efforts were focused on generating mouse models expressing mutant human tau. As with the wild-type tau models, animals were created by inserting cDNA constructs under the control of a suitable promoter into the mouse genome, resulting in the expression of one mutant tau isoform harbouring mutations found in FTDP-17. Since most *MAPT* mutations are found in the exons encoding the microtubule-binding domain, most notably exon 10, research has also been focused on transgenic mouse models harbouring mutations in this domain. In 2000, the first mutant tau mouse model (termed JNPL3) was reported. The animals expressed the 4R tau isoform lacking the two N-terminal domains (2-3-10<sup>+</sup>) with the missense mutation P301L, the most common observed coding region mutation in FTDP-17, under the mouse prion promoter (Lewis et al., 2000). Neurofibrillary tangles were observed in the diencephalon, brain stem, cerebellar nuclei and spinal cord and an even wider distribution of pre-tangle tau species was observed. Areas with high NFT load displayed gliosis. The spinal cord motor neurons showed axonal degeneration, leading to a progressive motor deficit. The widespread pathology was especially remarkable as the expression level of the transcript was low in comparison to previously described wild-type models, indicating that tau mutations confer great pathogenicity to the protein (Lewis et al., 2000).

In another study, mice harbouring the P301L mutation in the longest tau isoform under the regulation of the promoter Thy1.2 were compared to mice expressing the wild-type longest human isoform at comparable expression levels (Terwel et al., 2005). While the wild-type tau mice lived a normal lifespan, they displayed axonopathy in the brain and spinal cord and a severe motor phenotype in beam walk and accelerated rotarod tests starting at a young age (6-8 weeks). No tau aggregates were observed in these mice. The P301L mutant transgenic mice on the other hand developed NFTs from about 6 months onwards, but showed no axonopathy and only minor motor function impairment; however, all mice died before the age of 13 months (Terwel et al., 2005). These two mouse lines thus gave an early indication that NFTs might not be the toxic, disease-causing tau species but that formation of late-stage tangles and axonal degeneration and cell death might be distinct, albeit overlapping, events.

Comparison of the two described P301L tau mouse models again highlights that choice of promoter and expressed tau isoform has a significant influence on the phenotype of the resulting transgenic animal. As the missense mutation P301L is the most common mutation, many other cDNA-based mutant mouse models have been created (Gotz et al., 2001a; Higuchi et al., 2005; Murakami et al., 2006). Apart from the P301L mutation, two other FTDP-17 mutations in exon 10 have been used to create classic cDNA models, the missense mutations N279K and P301S (Allen et al., 2002; Taniguchi et al., 2005). The N279K mutation was shown to cause hyperactivity and cognitive deficits in the absence of discernible NFTs, suggesting, as other studies before, that formation of NFTs might be a late event and that pre-NFT tau species might cause the behavioural phenotype (Taniguchi et al., 2005). The 4R P301S model (driven by the Thy1 promoter) on the other hand displayed abundant tau filaments, most notably in the brain stem and spinal cord, but also the hippocampus and cortex. At 5 - 6 months the animals developed paraparesis and widespread brain and spinal cord degeneration (Allen et al., 2002).

Outside of exon 10, research has focused on coding region mutations in exon 9 (G272V), exon 11 (V337M), exon 12 (K369I) and exon 13 (R406W). The G272V model presented filament formation in oligodendrocytes, a rare instance of glial tau pathology, although the animals did not develop any overt neurological deficits (Gotz et al., 2001c). The mutation V337M in a 4R tau isoform, under the regulation of the PDGF- $\beta$  promoter, led to the formation of filamentous tau aggregates and neurodegeneration in the hippocampus. The behavioural phenotype was characterised by an inability to experience a state of fear in response to environmental stimuli (Tanemura et al., 2002). Another mouse model was based on the K369I mutation in exon 12, controlled by the murine Thy1.2 promoter. The mice exhibited a progressive histopathology with an age-dependent increase in tau inclusions as well as an early-onset motor phenotype characterised by the classical parkinsonism signs tremor, bradykinesia, postural instability and gait abnormalities, possibly due to the transgene being expressed in the substantia nigra (Ittner et al., 2008).

Several mouse lines have been created harbouring 4R human tau with the R406W mutation in exon 13 (Ikeda et al., 2005; Tatebayashi et al., 2002; Zhang et al., 2004). All models developed age-dependent neuronal accumulation of hyperphosphorylated tau and NFTs composed of straight, not paired helical, filaments. Mutant tau expressed under the control of the hamster prion promoter led to formation of tau inclusions in the hippocampus, amygdala, neocortex, cerebellum and spinal cord and the transgenic animals developed motor impairment and progressive memory loss (Ikeda et al., 2005). Expression of R406W tau under the mouse prion promoter showed a similar pattern of NFT-like pathology excepting the amygdala; however, no behavioural analysis was reported (Zhang et al., 2004). Interestingly, in mouse models expression of tau under regulation of the forebrain-specific CaMKII promoter, tau was barely detected in the spinal cord, resembling human expression, where tau gene expression is weak in the spinal cord. The transgenic mice showed memory impairment, but no motor deficit, mirroring the human condition, in which R406W is associated with an AD-like phenotype. This result is probably due to the low expression of tau in spinal cord neurons, which excludes a confounding effect of the behavioural phenotype due to neurogenic muscle atrophy (Tatebayashi et al., 2002).

The use of cDNA-based transgenes harbouring tau mutations found in FTDP-17 marked an important step in creating a model that resembles human condition. The mutant models overwhelmingly showed accumulation of hyperphosphorylated tau and formation of NFT-like inclusions. Furthermore, several lines were behaviourally characterised and displayed motor or cognitive deficits or both. The use of these mouse models gave an early indication that NFTs as the final stage of tau aggregate formation might not be the tau species responsible for neurodegeneration and associated memory deficits. However, the models still had several drawbacks, most notably the variability of the resulting phenotype depending on the promoter chosen and the fact that only a single isoform was expressed.

### 4.3 Other cDNA-based mouse models

Following the generation of mouse models expressing tau with mutations found in FTDP-17, several transgenic lines were created expressing human tau harbouring two tau mutations (G272V+P301S; K257T+P301S) or three mutations (G272V+P301L+R406W) (Lim et al., 2001; Rosenmann et al., 2008; Schindowski et al., 2006). Especially noteworthy is the K257T+P301S mutant model by Rosenmann et al., as transgene expression in this mouse line is driven by a rat genomic tau promoter, which shares 75% sequence similarity with the mouse tau promoter (Rosenmann et al., 2008). The resulting mice displayed formation of



neurofibrillary tangles in hippocampus, cortex and brain stem. The animals showed spatial memory deficits, signs of anxiety (assessed as excessive defecation) and impaired *in vivo* LTP but no overt motor phenotype.

Other models were created using transgenes driven by inducible promoters. The advantage of these animals over models with constitutive promoters is that the expression of the transgene can be switched on and off. Ramsden et al. created a mouse expressing 4R tau with the mutation P301L under the control of the forebrain-specific CaMKII promoter (Ramsden et al., 2005). This promoter was controlled by the tet-operon response element, which suppresses expression in response to doxocycline. The resulting animal developed age-dependent progression of tau pathology with NFT formation in the neocortex and later in hippocampus and limbic structures. Forebrain atrophy and prominent loss of neurons in the neocortex and hippocampus was accompanied by impairment of spatial memory (Ramsden et al., 2005). Suppression of transgene expression by doxocycline at a young age (2.5 months) halted the progression of tangle pathology in comparison to untreated animals, though tangle numbers were not reduced. However, the progression of tau pathology became independent of transgene expression at 4 months of age (Santacruz et al., 2005). Long-term suppression of tau expression (4 - 4.5 months) was shown to protect against neuronal loss and brain atrophy. Administration of doxocycline even after 4 months of age, when NFT-progression became independent of tau transgene expression, significantly improved spatial memory (Santacruz et al., 2005). These highly significant results proved earlier speculations that the mechanisms that lead to NFT formation and those that lead to cell death and memory loss are at least partly uncoupled.

While mutations in tau are associated with FTDP-17, there has never been any link between tau mutations and Alzheimer's disease. However, models of AD with mutations found in patients with early-onset AD were overwhelmingly unsuccessful in triggering tau pathology. Thus, transgenic models which combine *APP* and *MAPT* mutations have been created to achieve the reproduction of both neuropathological hallmarks and to better understand the relationship between tau and A $\beta$  in AD. Perhaps the most well-known model of AD was created by Oddo et al., a triple transgenic model (3xTg-AD) harbouring the *MAPT* mutation P301L but also two mutations associated with AD, M146V in *PS1* and the Swedish mutation in *APP* (a double mutation KM670/671NL). The resulting mouse developed both plaque and tangle pathology as well as deficits in LTP (Oddo et al., 2003b). Furthermore, plaque development preceded tangle pathology in these mice, a finding that is consistent with and supporting of the amyloid hypothesis (Oddo et al., 2003a).

#### 4.4 Genomic DNA mouse models

While the introduction of *MAPT* mutations associated with FTDP-17 led to a significant improvement in the capacity of the mouse models to produce NFT pathology and degeneration more closely reflecting the situation in human disease, some of the basic drawbacks remained, such as the dependency of the phenotype displayed by the animals on the promoter chosen, and the restriction to expression of one tau isoform. However, in 2000 Duff et al. introduced a genomic *MAPT* mouse model (Duff et al., 2000). In this model, the whole genomic human *MAPT* locus including its endogenous promoter were introduced into the mouse genome using the PAC transgene technology. The resulting mouse expressed all six human tau isoforms. However, no tangle pathology was observed and mice did not show hindlimb-clasping or spinal cord abnormalities, as often shown by

cDNA-based models of tauopathy (Duff et al., 2000). However, as the results might have been confounded by the presence of endogenous mouse tau protein, another genomic *MAPT* mouse model was created by Andorfer et al., in which the original mouse created by Duff et al. was backcrossed onto an endogenous mouse *MAPT* knockout background (Andorfer et al., 2003). The animals displayed hyperphosphorylated tau and NFT formation as well as changes in neuronal morphology and a decrease in cortical thickness due to extensive cell death (Andorfer et al., 2005; Andorfer et al., 2003).

#### 4.5 Other models of tauopathy

While rodent models are often the species of choice to reproduce the molecular and cellular pathology of neurodegenerative diseases, the use of models from other branches of the phylogenetic tree can be advantageous. *Caenorhabditis elegans*, *Drosophila melanogaster* and the zebrafish *Danio rerio* are easily genetically manipulated, have a short generation time, low maintenance costs and can be used for high-throughput screening experiments. Tauopathy models of all of these species have been created displaying key features of tauopathic neurodegenerative disease.

Neuronal expression of wild-type or mutant (P301L and V337M) 4R human tau in a model of *C.elegans* results in a decreased life-span, uncoordinated movement, accumulation of insoluble and phosphorylated tau species with a phosphorylation pattern similar to the pattern of hyperphosphorylation observed in AD and FTDP-17 in humans, progressive axonal degeneration and neuronal loss as well as defective presynaptic cholinergic transmission. While both the wild-type and the mutant transgene resulted in a phenotype, expression of mutant tau led to a more pronounced deterioration (Kraemer et al., 2003).

A study using *Drosophila* models of tauopathy expressing wild-type or mutant (R406W) human tau showed a shortened life-span, vacuolisation, degeneration of cortical cells and phosphorylation of tau at sites found abnormally phosphorylated in tauopathies, but no formation of NFTs (Wittmann et al., 2001). The phenotype was more pronounced in flies expressing mutant tau. Expression of mutant tau in photoreceptor cells triggered an abnormal rough eye phenotype (Wittmann et al., 2001). Co-expression of wild-type human tau and *shaggy*, the *Drosophila* homolog of GSK-3 $\beta$ , however, led to the formation of NFTs in another study, and exacerbated the neurodegenerative phenotype (Jackson et al., 2002).

In a very elegant and sophisticated approach, Paquet et al. generated transgenic zebrafish larvae expressing fluorescently-labelled P301L mutant human tau, allowing *in vivo* imaging of neuronal cell death (Paquet et al., 2009). The model showed tau phosphorylation and tangle formation, neuronal cell death, abnormal motor neuron morphology as well as behavioural deficits. The phenotype occurred rapidly within the first few days of embryonic development, even though zebrafish have a life-span comparable to that of mice under laboratory conditions, marking a big advantage over classic rodent models, which only develop a phenotype after months or even years (Paquet et al., 2009).

## 5. Outlook

Almost 20 years ago the amyloid hypothesis of Alzheimer's disease was put forward; overwhelming evidence indicates A $\beta$ , the proteolytic cleavage product of APP, as the culprit protein in disease initiation. In the amyloid hypothesis, aggregation of tau into NFTs is a downstream event and for years it was doubted whether tau played any role in disease etiopathology. Since then, however, several lines of evidence have shown that

while tau misfolding and aggregation is in all probability not causative of AD, the protein is a fundamental factor in the disease cascade. The findings that tau deposits are found in other neurodegenerative diseases in the absence of amyloid plaques and that mutations in tau are sufficient to cause a familial neurodegenerative dementia and parkinsonism syndrome have added to the heightened interest in tau and its role in neurodegenerative processes.

The association of tau haplotype variants with an increased risk of idiopathic Parkinson's disease have put tau and its encoding gene *MAPT* in the centre of neurodegenerative pathways. Thus, tau is implicated in the two most common neurodegenerative diseases worldwide, Alzheimer's disease and Parkinson's disease, as well as several other rare disorders such as PSP, CBD, FTDP-17, Pick's disease and ALS-G/PDC-G. The association of NFTs with several neurodegenerative diseases, collectively referred to as tauopathies (PD not being classified as a tauopathy, as NFTs are usually, though not necessarily, absent), has highlighted the need for transgenic models of tau-mediated neurodegenerative disease.

The first mouse models of tauopathy were created before mutations in *MAPT* were found to cause FTDP-17 and were based on overexpression of either 3R or 4R human wild-type tau. While these models reproduced some key features of tauopathies such as hyperphosphorylation of tau as well as motor deficits, discernible NFT formation was usually not observed or at an advanced age only. However, this changed with the generation of mouse models expressing mutant human tau. Mice harbouring mutations in the tau transgene found to cause FTDP-17 in humans show age-dependent formation of NFTs in neuronal and in some instances glial cells. However, several studies indicate that the appearance of NFTs is independent of axonal degeneration, neuronal cell death and motor and cognitive deficits. This is especially surprising as the number of NFTs in the brains of Alzheimer's disease patients correlates well with severity of disease. It is now widely believed that NFTs represent late-stage pathology of tauopathies that might in fact be neuroprotective and that pre-tangle tau species are responsible for tau-mediated neurodegeneration. Further studies are required to shed light onto the role of NFTs in degeneration and cell death.

Early mouse models of tauopathy were limited in their capacity to accurately represent human condition. Most notably, the created animals were cDNA-based models. This approach allowed only expression of one tau isoform, which was heavily dependent on the promoter chosen. Furthermore, in most models tau was heavily expressed in spinal cord neurons, which does not reflect human disease; the associated degeneration and cell death is very likely to be responsible for the regularly observed motor phenotype, whereas the motor deficit in human tauopathies is not caused by degeneration of spinal cord neurons. Those shortcomings were addressed in genomic models of tauopathy, which express all tau isoforms under the regulation of the human endogenous tau promoter. However, only two genomic tau mouse lines have been created so far, expressing wild-type human tau isoforms. In a next step, genomic rodent models of tauopathy with mutant tau will hopefully lead to an improved understanding of the mechanisms underlying tau-mediated neurodegeneration, and accurately represent all key features of human tauopathy in terms of isoform ratios, affected brain areas and cell types and associated motor and cognitive deficits. Other models of tauopathy such as *Drosophila melanogaster* or *Danio rerio* can assist in the investigation of disease mechanisms, as they have been shown to reproduce several aspects of human tauopathic disease in a very short timespan, enabling for example high-throughput screening of potential intervention strategies. This will be especially important

as the central role of tau in neurodegenerative processes has led to a heightened interest in tau as a potential therapeutic target, most notably in AD.

Several therapeutic strategies are being investigated for the treatment of tauopathies. Paclitaxel, a microtubule-stabilising agent, has been shown to reverse axonal transport deficits and ameliorate a motor phenotype in a mouse model of tauopathy (Zhang et al., 2005), possibly by rescuing the loss of microtubule integrity caused by tau loss of function. Hyperphosphorylation of tau is considered to be an early event in disease pathogenesis, and inhibition of kinases responsible for tau phosphorylation, notably GSK-3 $\beta$ , which has also been implicated in the processing of APP, is under intense investigation, with several studies in advanced clinical stages. Lithium, which has been shown to inhibit GSK-3 $\beta$  activity and is used for the treatment of bipolar disorder, resulted in lower levels of tau phosphorylation and reduced load of aggregated tau and axonal degeneration in the JNPL3 mouse model (Noble et al., 2005). Furthermore, treatment of a mouse model of AD with a thiazolidinone compound reduced tau phosphorylation, decreased amyloid deposition (possibly through decreased processing of APP), protected against neuronal cell death and prevented memory deficits (Serenio et al., 2009).

Transgenic tau mouse models have implicated that NFTs are not the aggregate species responsible for axonal degeneration and cell death, but that earlier aggregation intermediates might be the neurotoxic species. Inhibition of the aggregation pathway or redirection of aggregated species into monomers or off-pathway, non-toxic aggregates could help decrease the load of neurotoxic tau species. Screening of small molecule aggregation inhibitors can be performed in high-throughput fashion *in vitro* by monitoring heparin-induced assembly of tau proteins into well-defined filaments. Several classes of small molecules have been shown to inhibit tau aggregation *in vitro* (Ballatore et al., 2010; Bulic et al., 2009). One of the first compounds found to inhibit tau fibril assembly was the phenothiazine methylene blue (Wischnik et al., 1996). A concluded phase II clinical study showed significant efficacy of methylene blue to arrest disease progression in mild and moderate AD (Wischnik et al., 2008). Originally believed to exert its effect by inhibition of tau aggregation, studies now suggest that the compound also improves mitochondrial function, which has been shown to be impaired in AD brains (Atamna et al., 2008). Furthermore, a decrease of tau levels might prove a therapeutic strategy in neurodegenerative tauopathies. Cytosolic proteins can be degraded either by the ubiquitin-proteasome system (UPS) or by lysosomal degradation. Hsp90 is a molecular chaperone, whose function is the assistance of protein folding and stabilisation against UPS-mediated degradation. Inhibition of Hsp90 has been shown to decrease levels of phosphorylated tau and to facilitate the elimination of aggregated tau through degradation via the UPS (Dickey et al., 2007; Luo et al., 2007).

These findings illustrate the manifold mechanisms through which tau-targeted therapeutic strategies can slow or possibly reverse disease progression in tauopathies. While most of therapeutic intervention strategies targeting tau are investigated for the treatment of Alzheimer's disease, it is very likely that they would also be effective in other tauopathies such as PSP, CBD and FTDP-17. In order to further investigate the molecular principles underlying these therapeutic strategies it will be vital to improve animal models of tauopathies that reproduce the key aspects of this class of neurodegenerative diseases. As the numbers of AD cases is expected to rise sharply in the next decades, tau as a central player in neurodegeneration is and will be at the forefront of research into neurodegenerative mechanisms and therapeutic intervention strategies.

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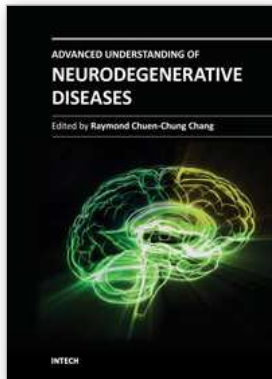
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## **Advanced Understanding of Neurodegenerative Diseases**

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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