

# Tau pathology: a marker of neurodegenerative disorders

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Tau is not only a basic component of neurofibrillary degeneration, but is also an aetiological factor, as demonstrated by mutations on the *tau* gene responsible for frontotemporal dementias with parkinsonism linked to chromosome 17. Polymorphisms on the *tau* gene and the hierarchical invasion of neocortical areas by tau pathology in numerous sporadic neurodegenerative diseases also suggest that tau pathology is a primary pathogenic event in non-familial dementing diseases and a lead for solid diagnostic and therapeutic approaches. *Curr Opin Neurol* 13:371–376. © 2000 Lippincott Williams & Wilkins.

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## Abbreviations

<b>AD</b>	Alzheimer's disease
<b>CBD</b>	corticobasal degeneration
<b>CSF</b>	cerebrospinal fluid
<b>FTDP-17</b>	frontotemporal dementia with parkinsonism linked to chromosome 17
<b>PSP</b>	progressive supranuclear palsy
<b>3R</b>	three microtubule-binding domains
<b>4R</b>	four microtubule-binding domains

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## Introduction

The characterization and classification of numerous neurodegenerative diseases have been dramatically improved after the discovery of molecular markers such as  $A\beta$ , PrP, tau, alpha-synuclein. These markers are the basic components of specific brain lesions: amyloid plaques, prion plaques, tangles and Lewy bodies, respectively [1]. Tau pathology, or tauopathy, which are the molecular words for neurofibrillary degeneration, is a process affecting cortical and subcortical brain areas and is found in more than 20 different dementing disorders (Table 1). Numerous familial tauopathies have recently been characterized. They have in common genetic defects on the *tau* gene, but clinical and neuropathological phenotypes are extremely heterogeneous. Understanding the basic mechanisms of tau pathology will certainly bring new opportunities for the diagnosis and treatment of most dementing disorders.

## Tau pathology as a marker of neurofibrillary degeneration

Tau pathology corresponds to the intraneuronal aggregation of microtubule-associated tau proteins into abnormal

**Table 1. Presentation of the different neurodegenerative disorders with a tau pathology, and their different biochemical tau signatures, from class I to class IV**

Disease	Classes of tau pathology
Ageing (hippocampal region, patients over 75 years)	I
Alzheimer's disease, familial and sporadic	I
Amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam	I
Argyrophilic grain dementia	I
British type amyloid angiopathy	I
Corticobasal degeneration	II
Dementia pugilistica/autism with self-injury behaviour	I
Down's syndrome	I
FTDP-17	II, I and III
Gerstmann–Straussler–Scheinker disease (Indiana kindred)	I
Hallervorden–Spatz disease	I
Inclusion body myositis	I
Multiple system atrophy	I
Myotonic dystrophy	IV
Niemann–Pick disease type C	I
Pick's disease	III
Presenile dementia with tangles and calcifications	I
Prion protein cerebral amyloid angiopathy	I
Progressive supranuclear palsy	II
Post-encephalitic parkinsonism	I
Subacute sclerosing panencephalitis	I
Tangle only dementia	I

FTDP-17, Frontotemporal dementias with parkinsonism linked to chromosome 17.

filaments [2]. The normal role of tau is to stabilize microtubules, which are the tracks of the intraneuronal transport. There are six tau isoforms in the human brain that exhibit either three (3R) or four microtubule-binding domains (4R) (Fig. 1). The three tau isoforms with 4R are more efficient than 3R tau isoforms in stabilizing microtubules. Conversely, phosphorylation of tau destabilizes microtubules, and it is suggested that abnormal phosphorylation, as observed in Alzheimer's disease (AD), provokes a collapse of the microtubule network. At the electron microscopic level, the filamentous material of neurofibrillary degeneration is either helical, twisted or straight, according to the neurodegenerative disorder (Table 2) [3]. At the optical level, it accumulates in bundles to constitute the so-called neurofibrillary tangles, neuropile threads, dystrophic

neurites of neuritic plaques and Pick bodies. Tau inclusions have different biochemical signatures that are disease specific. They vary from a major triplet (60 000, 64 000, 69 000 M<sub>r</sub>) observed in AD, as revealed by Western blots using phospho-dependent anti-tau antibodies (class I), to an upper doublet in progressive supranuclear palsy (PSP) (tau 64, 69) and corticobasal degeneration (CBD) (class II), a lower doublet tau 60, 64 in Pick's disease (class III) and a major tau 60 band in myotonic dystrophy (class IV) (Table 2) [4]. More than 20 different disorders are affected by tau pathology (Table 2). All of them with a neocortical involvement are characterized by cognitive impairment and generally dementia, as recently documented in PSP [5] and in AD [6,7,8]. Conversely, there is no correlation between clinical symptoms and the biochemical signature. For

**Table 2. Presentation of the different characteristics of diseases with tauopathies**

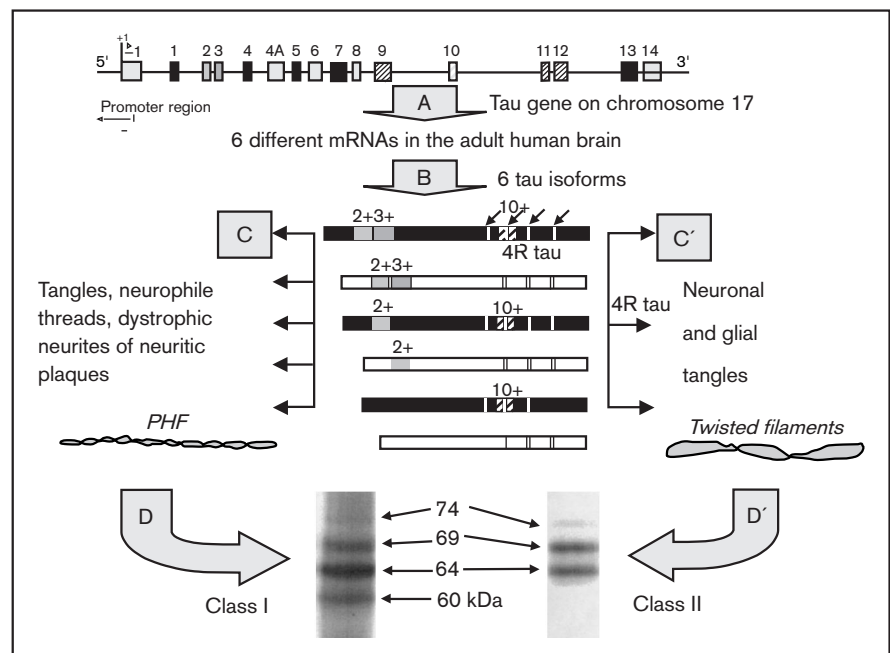
Tau isoforms	Tau binding	Type	EM	Inclusion	Cells	Brain areas	Pathology	First symptoms
3R+4R	Normal	Class I	PHF	NFT, NP	II, V, N	Cortical, subcortical	Sporadic AD	Memory
3R+4R	Normal	Class I	PHF	NFT, NP	II, V, N	Cortical, subcortical	Familial AD	Memory
4R	Normal	Class II	SF or TF	NFT	II, N, G	Subcortical, cortical	PSP, CBD	Extrapyramidal
3R	Normal	Class III	RCF	Pick bodies	II, III, N	Cortical, subcortical	PiD	Frontal disturbances
Short 3R +++	Normal	Class IV	N/A	NFT	N	Cortical	MyoD	Mild cognitive impairment

The content in tau isoforms found in the different types of tau lesions is indicated. The different profiles of pathological tau observed in Alzheimer's disease (AD) (class I), in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (class II), in Pick's disease (PiD) (class III) and in myotrophic dystrophy (MyoD) (class IV) are represented.

EM, Electron microscopic level; NFT, neurofibrillary tangles; NP, neuritic plaques; PHF, paired helical fragments; RCF, random coiled filaments; SF, straight filaments; TF, twisted filaments; N/A, data not available.

**Figure 1. The tau gene is a long 100 kb gene located on chromosome 17**

A. Six different messenger RNAs are produced in the adult human brain, by alternative splicing. B. Consequently, six tau isoforms are expressed. Three of them have an additional repeat binding site to microtubules, corresponding to the sequence encoded by exon 10. C (left part). Alzheimer brain lesions (tangles, neuropile threads and dystrophic neurites of neuritic plaques) are composed of the six isoforms. They assemble into paired helical filaments (PHF) with a width of 8–20 nm and a periodicity of 80 nm. D. The biochemical signature of PHF is a class I profile, with a major triplet of electrophoretic band (tau 60, 64, 69). C' (right part). In frontotemporal dementia with parkinsonism linked to chromosome 17, many pathogenic mutations on the tau gene provoke the aggregation of three tau isoforms with four repeats. The three 4R tau isoforms aggregate into 15 nm wide twisted filaments with a crossover spacing of 130 nm. These filaments are found in neurons and astrocytes. D'. A class II biochemical signature (a major tau 64, 69 doublet) is observed.



instance, on one hand, British type cerebral angiopathy is caused by a point mutation at the stop codon of the *BRI* gene [9]. This disease is characterized by a class I tau pathology [10]. On the other hand, numerous familial frontotemporal dementias including pallido-nigro-luysian degeneration, disinhibition–dementia–parkinsonism–amyotrophy complex, familial multiple system tauopathy, and progressive subcortical gliosis result from pathogenic mutations on tau, whose gene is on chromosome 17. These diseases are now gathered in the group of frontotemporal dementias with parkinsonism linked to chromosome 17 (FTDP-17) and display class I, II or III tau pathologies, according to the location of the genetic defect on the *tau* gene (see next section).

The natural history of AD has also been investigated at the molecular level. Several groups have detailed the pathway of tau pathology spreading in the different brain areas, showing that it is sequential, progressive, invariable, hierarchical, predictable [7,8,11]. Generally, cognitive impairment is observed when association brain areas are affected by tau pathology. Surprisingly, in some non-demented cases, huge amounts of lesions can be found [7,8,12]. These findings demonstrate that the degenerating process can be balanced for a while (several years?) by a powerful compensating effect. They suggest that cofactors of AD, such as vascular factors [13–15], could weigh either on the pathology itself, or on the neuronal reservoir. Together, these observations could mean that neuroprotection can greatly influence the fate of AD, either by slowing down the pathology or also by sustaining neuronal plasticity.

Because lesion antigens are overabundant at the infra-clinical stage of AD, their detection in the cerebrospinal fluid (CSF) could help to set up an early biological diagnosis. The simultaneous significant increase of tau and decrease of  $A\beta$  1–42 levels in the CSF in AD is likely to be useful for clinical diagnosis in the near future [16].

### Tau pathology as an aetiological agent

The presence of brain lesions in neurodegenerative disorders usually arouses the same question: is this a cause or a consequence? Some answers are already available for tau pathology.

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

The discovery that Tau mutations are directly involved in numerous FTDP-17 has been dramatically documented. More than 20 different mutations have been spotted. Familial diseases such as familial progressive subcortical gliosis also belong to the FTDP-17 group [17]. Most of the pathogenic mutations are responsible for an increase of 4R tau isoforms, giving a class II tau pathology (see Table 3). 4R tau isoforms, with the

additional peptidic sequence of exon 10, have a much stronger affinity towards microtubules than 3R isoforms, and an excess could modify microtubules, which will be stiffer and less dynamic. The other mutations are missense mutations that also affect microtubule polymerization and stability by decreasing tau–microtubule binding and lead to one of the class I, II, III tau pathologies (see Table 3). The striking feature of these familial tauopathies is the heterogeneity of the phenotype, which results from the different effects on tau (overexpression, loss of function). Early parkinsonism and stronger involvement of the substantia nigra are confined to mutations affecting the 3R:4R tau isoform ratio [2–4,17,18]. Surprisingly, for the same mutation in the same family, different onsets and different phenotypes can be observed (Table 3), showing that numerous additional factors can bring more heterogeneity to the phenotype.

We also noted that the neuropathological profile in FTDP-17 is quite different from AD, with a special involvement of astrocytes and cortical white matter, but also with an important heterogeneity for each mutation. Interestingly, but surprisingly, different groups have reported that numerous amyloid deposits were found in the brains of some young FTDP-17 patients [19,25]. This is really puzzling and deserves further investigation.

However, not all diseases with a tau pathology have mutations on the tau gene. This has been verified for CBD, PSP [46,47], amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam [48], and AD [49].

#### Polymorphisms in progressive supranuclear palsy

Conrad and colleagues [50] identified a polymorphic dinucleotide repeat sequence in a Caucasian population with PSP. This polymorphism, named A0, corresponding to an 11 TG dinucleotide repeat in intron 9 of the *tau* gene, is found in 95% of the PSP cohort (95.5%) and only in 57% of normal controls and 50% of patients with AD. Recently, these data were confirmed by several studies and extended to a haplotype including a number of polymorphisms in linkage disequilibrium with A0 and named H1. This haplotype corresponds to A0 polymorphism, numerous single nucleotide polymorphisms along the entire *tau* gene and one intronic 238 bp deletion flanking exon 10 [46,51,52,53,54–58]. These polymorphisms may influence exon 10 splicing and thus the proportion of 4R:3R tau isoforms, leading to a class II tau pathology [59]. It should be noted that these A0 polymorphisms or H1 haplotypes were recently described in other pathologies including CBD and Parkinson's disease [60,61]. Some other polymorphisms in the *tau* gene were also described as being associated with a risk of AD [62,63], but these data are still controversial [64].

Table 3. Tau mutations in FTDP-17

Tau mRNA silent mutations	Missense mutations on Tau protein	Tau isoforms	Tau binding	Type	EM	Inclusion	Cells	Family	Onset	Duration	First symptoms	Authors
Exon 9	R1: K257T	3R+4R	↓	3R>4R	N/A	Pick bodies	N	Cambridge, UK	46-52	8	Disinhibition	Spillantini, pers. comm. [18, 19]
	I260V	3R+4R	↓	3R>4R	N/A	NFT, Pick-like body	N	HFTD2	41	8	Memory and attention disturbance	[20-23]
Exon 10	R1: G272V	3R+4R	↓	Class I	TF	NFT	N, G	PPND	53	4	Restlessness	[18, 24, 25]
	N279K	4R++	Normal	Class II	TF	NFT	N, G	French	47-61	4-10	Memory	[25]
	ΔK280	3R++	↓	N/A	N/A	N/A	N/A	Family history of Parkinson disease	40-60	5-8	Disinhibition, initiative loss	[19, 25-31]
L284L	P301L/S	3R+4R	↓	Class II	TF?	NFT, Aβ	N, G	LKL	35-38	11	Disequilibrium, deficits	[36]
S305S	S305N	4R	Normal	Class II	TF?	NFT	N, G	HFTD1	49±10		short-term memory	[37]
+3 Intron 10		4R	Normal	Class II	TF	NFT	N, G	French	65	13	Personality change	[38]
+12		4R	Normal	Class II	TF	NFT	N, G	Man19UK	45	11-17	Memory, personality change	[39]
+13		4R	Normal	Class II	TF	NFT	N, G	DDPAC	41-58		FTD	[24]
+14		4R	Normal	Class II	TF	NFT	N, G	PSG-1, Australian, Man6, 23UK	<65	?	Prominent antisocial behaviour (paranoid schizophrenia)	[42-44]
+16		4R	Normal	Class II	TF	NFT	N, G	Small Dutch family	42-61	13±7	Memory	[45]
+33	V337M	3R+4R	↓	Class I?	N/A	N/A	N/A	FPDT	38	5	Memory	[18, 24]
Exon 12		3R+4R	↓	Class I	PHF+SF	NFT	N	Dutch, USA	59±5	13±1.5	Memory	[18, 24]
Exon 13	G389R	3R+4R	↓	3R+++4R+	SF+TF	Pick-like bodies	N	Family F (Italy)				
	R406W	3R+4R	Slightly ↓	Class I	PHF+SF	NFT, Pick-like bodies	N	Dutch, USA				

The shape of pathological filaments at the electron microscopic level (EM) are paired helical filaments (PHF), twisted filaments (TF), straight filaments (SF) or random coiled filaments (RCF).

Inclusions at the optical level are neurofibrillary tangles (NFT), neuritic plaques (NP) or Pick bodies.

Cells affected are neurones (N) or glial cells (G) sometimes more specifically found in neocortical layers II, III, V.

DDPAC, Disinhibition-dementia-parkinsonism-amyotrophy complex; FPDT, familial form of presenile dementia; HFTD, hereditary frontotemporal dementia; MSTD, multiple system tauopathy with presenile dementia; PPND, pallido-ponto-nigral degeneration; PSG-1, progressive subcortical gliosis; N/A, data not available.

### 'Sporadic' Alzheimer's disease

Non-autosomal dominant AD represents 99.7% of all AD cases [65\*\*]. The first risk factor for 'sporadic' AD is age. Genetic risk factors are also important, such as epsilon 4 alleles of apolipoprotein E [65\*\*]. It is interesting to note that there is an important and systematic vulnerability of the hippocampal region to tau pathology in ageing. Indeed, aggregated tau proteins are always detected in the hippocampal region at the age of 75 years [7\*,8\*], sometimes independently of amyloid deposits [8\*]. This hippocampal vulnerability is probably a springboard for Alzheimer pathology, namely amyloid precursor protein dysfunction, which will exacerbate and extend tau pathology in other brain areas [11,66]. Together, neuropathological and biochemical data concur to indicate that tau pathology is instrumental in AD. In that respect, it should be pointed out that recent criteria for the neuropathological diagnosis have rehabilitated tau pathology [67], in good agreement with Alois Alzheimer observations and the natural history of AD.

The spread of tau pathology is also an important feature of other diseases, such as PSP and CBD, but the pathway is different, from subcortical to neocortical, mainly frontal and hippocampal areas [5,68]. For all tauopathies, either sporadic or familial, the spread of neurofibrillary degeneration along specific neuronal populations probably relies on factors such as neuronal vulnerability and trophic factors. The characteristics of neuronal populations, and their vulnerability, could be driven partly by the specific sets of tau isoforms that they express. Analysing the factors that fuel the dynamic of tauopathy spreading in cortical areas will certainly give clues for neuroprotection [66].

### Conclusion

Tau pathology is an event occurring in all human brains, at least in the hippocampal region, and systematically after 75 years of age. Tau pathology is also observed in many dementing disorders. Some of them, such as AD, have a high prevalence. *Tau* gene defects are responsible for FTDP-17, and the *tau* gene also displays numerous polymorphisms that may contribute to the development of neurofibrillary degeneration. Therefore, the interest in tau pathology has increased dramatically in the past few years. At present, we need relevant experimental models to understand this many-sided degenerating process. Tau transgenic mice are already on the bench. Surprisingly, transgenic mice with a mutated *APP* gene, generating a load of A $\beta$  20 times that found in the human brain, are reluctant to develop an extensive tau pathology. The explanation could be that the regulation of tau is more complex in the human brain [69\*], and that age is an important factor (the main risk factor in AD), which cannot be used optimally with short-lived animals.

### References and recommended reading

- Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
  - of outstanding interest
- 1 Pasquier F, Delacourte A. Non-Alzheimer degenerative dementias. *Curr Opin Neurol* 1998; 11:417–427.
  - 2 Goedert M. Filamentous nerve cell inclusions in neurodegenerative diseases: tauopathies and alpha-synucleinopathies. *Phil Trans R Soc Lond B Biol Sci* 1999; 354:1101–1118.
  - 3 Buée L, Bussièrè T, Buée-Scherrer V, et al. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Rev* 2000; 33: (in press, published on line: <http://www.elsevier.nl/gej-ng/29/19/37/23/52/article.html>).
- A complete review of tau biology and tau pathology.
- 4 Buée L, Delacourte A. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick's disease. *Brain Pathol* 1999; 9:681–693.
  - 5 Bigio EH, Brown DF, White CL III. Progressive supranuclear palsy with dementia: cortical pathology. *J Neuropathol Exp Neurol* 1999; 58:359–364.
  - 6 Arendt T, Holzer M, Gertz HJ, Bruckner MK. Cortical load of PHF-tau in Alzheimer's disease is correlated to cholinergic dysfunction. *J Neural Transm* 1999; 106:513–523.
  - 7 Braak E, Griffing K, Arai K, et al. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Eur Arch Psychiatry Clin Neurosci* 1999; 249:14–22.
- A recap of Braak stages, showing that neurofibrillary degeneration cannot be ignored in AD.
- 8 Delacourte A, David JP, Sergeant N, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology* 1999; 52:1158–1165.
- The understanding of AD physiopathology must be spatiotemporal.
- 9 Vidal R, Frangione B, Rostagno A, et al. A stop-codon mutation in the *BRI* gene associated with familial British dementia. *Nature* 1999; 399:776–781.
  - 10 Revesz T, Holton JL, Doshi B, et al. Cytoskeletal pathology in familial cerebral amyloid angiopathy (British type) with non-neuritic amyloid plaque formation. *Acta Neuropathol (Berl)* 1999; 97:170–176.
  - 11 Duyckaerts C, Colle MA, Dessi F, et al. The progression of the lesions in Alzheimer disease: insights from a prospective clinicopathological study. *J Neural Transm Suppl* 1998; 53:119–126.
  - 12 Price JL, Morris JC. Tangles and plaques in nondemented aging and 'preclinical' Alzheimer's disease. *Ann Neurol* 1999; 45:358–368.
- An interesting paper showing the high number of tangles and plaques at the infraclinical stages of AD.
- 13 Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; 352:1347–1351.
  - 14 Tzourio C, Dufouil C, Ducimetiere P, Alperovitch A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. *Epidemiology of Vascular Aging. Neurology* 1999; 53:1948–1952.
  - 15 Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord* 1999; 13 (Suppl. 3):S115–123.
  - 16 Andreasen N, Minthon L, Clarberg A, et al. Sensitivity, specificity, and stability of CSF-tau in AD in a community-based patient sample. *Neurology* 1999; 53:1488–1494.
  - 17 Goedert M, Spillantini MG, Crowther RA, et al. Tau gene mutation in familial progressive subcortical gliosis. *Nat Med* 1999; 5:454–457.
- One of the papers showing how heterogeneous are the clinical and neuropathological phenotypes of FTDP-17.
- 18 van Swieten JC, Stevens M, Rosso SM, et al. Phenotypic variation in hereditary frontotemporal dementia with tau mutations. *Ann Neurol* 1999; 46:617–626.
- An excellent analysis of the relationships between genotypes and phenotypes.
- 19 Spillantini MG, Crowther RA, Kamphorst W, et al. Tau pathology in two Dutch families with mutations in the microtubule-binding region of tau. *Am J Pathol* 1998; 153:1359–1363.
  - 20 Reed LA, Schmidt ML, Wszolek ZK, et al. The neuropathology of a chromosome 17-linked autosomal dominant parkinsonism and dementia ('pallido-ponto-nigral degeneration'). *J Neuropathol Exp Neurol* 1998; 57:588–601.
  - 21 Yasuda M, Kawamata T, Komure O, et al. A mutation in the microtubule-associated protein tau in pallido-nigro-lusian degeneration. *Neurology* 1999; 53:864–868.

- 22 Clark LN, Poorkaj P, Wszolek Z, *et al.* Pathogenic implications of mutations in the *tau* gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. *Proc Natl Acad Sci U S A* 1998; 95:13103–13107.
- 23 Delisle MB, Murrell JR, Richardson R, *et al.* A mutation at codon 279 (N279K) in exon 10 of the *Tau* gene causes a tauopathy with dementia and supranuclear palsy. *Acta Neuropathol (Berl)* 1999; 98:62–77.
- 24 Rizzu P, Van Swieten JC, Joosse M, *et al.* High prevalence of mutations in the microtubule-associated protein tau in a population study of frontotemporal dementia in the Netherlands. *Am J Hum Genet* 1999; 64:414–421.
- 25 D'Souza I, Poorkaj P, Hong M, *et al.* Missense and silent *tau* gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci U S A* 1999; 96:5598–5603.
- 26 Heutink P, Stevens M, Rizzu P, *et al.* Hereditary frontotemporal dementia is linked to chromosome 17q21-q22: a genetic and clinicopathological study of three Dutch families. *Ann Neurol* 1997; 41:150–159.
- 27 Dumanchin C, Camuzat A, Campion D, *et al.* Segregation of a missense mutation in the microtubule-associated protein tau gene with familial frontotemporal dementia and parkinsonism. *Hum Mol Genet* 1998; 7:1825–1829.
- 28 Bird TD, Nochlin D, Poorkaj P, *et al.* A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). *Brain* 1999; 122:741–756.
- 29 Nasreddine ZS, Loginov M, Clark LN, *et al.* From genotype to phenotype: a clinical pathological, and biochemical investigation of frontotemporal dementia and parkinsonism (FTDP-17) caused by the P301L tau mutation. *Ann Neurol* 1999; 45:704–715.
- 30 Bugiani O, Murrell JR, Giaccone G, *et al.* Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. *J Neuropathol Exp Neurol* 1999; 58:667–677.
- 31 Sperfeld AD, Collatz MB, Baier H, *et al.* FTDP-17: an early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. *Ann Neurol* 1999; 46:708–715.
- 32 Stanford PM, Halliday GM, Brooks WS, *et al.* Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: expansion of the disease phenotype caused by tau gene mutations. *Brain* 2000; 123:880–893.
- 33 Grover A, Houlden H, Baker M, *et al.* 5' Splice site mutations in tau associated with the inherited dementia FTDP-17 affect a stem-loop structure that regulates alternative splicing of exon 10. *J Biol Chem* 1999; 274:15134–15143.
- 34 Hasegawa M, Smith MJ, Iijima M, *et al.* FTDP-17 mutations N279K and S305N in tau produce increased splicing of exon 10. *FEBS Lett* 1999; 443:93–96.
- 35 Iijima M, Tabira T, Poorkaj P, *et al.* A distinct familial presenile dementia with a novel missense mutation in the tau gene. *Neuroreport* 1999; 10:497–501.
- 36 Spillantini MG, Murrell JR, Goedert M, *et al.* Mutation in the *tau* gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci U S A* 1998; 95:7737–7741.
- 37 Yasuda M, Takamatsu J, D'Souza I, *et al.* A novel mutation at position +12 in the intron following exon 10 of the *tau* gene in familial frontotemporal dementia (FTD-Kumamoto). *Ann Neurol* 2000; 47:422–429.
- 38 Hutton M, Lendon CL, Rizzu P, *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998; 393:702–705.
- 39 Lynch T, Sano M, Marder KS, *et al.* Clinical characteristics of a family with chromosome 17-linked disinhibition-dementia-parkinsonism-amyotrophy complex. *Neurology* 1994; 44:1878–1884.
- 40 Petersen RB, Tabaton M, Chen SG, *et al.* Familial progressive subcortical gliosis: presence of prions and linkage to chromosome 17 [published erratum appears in *Neurology* 1995; 45:1430]. *Neurology* 1995; 45:1062–1067.
- 41 Baker M, Kwok JB, Kucera S, *et al.* Localization of frontotemporal dementia with parkinsonism in an Australian kindred to chromosome 17q21-22. *Ann Neurol* 1997; 42:794–798.
- 42 DeTure M, Ko L, Yen S, *et al.* Missense tau mutations identified in FTDP-17 have a small effect on tau-microtubule interactions. *Brain Res* 2000; 853:5–14.
- 43 Poorkaj P, Bird TD, Wijsman E, *et al.* *Tau* is a candidate gene for chromosome 17 frontotemporal dementia [published erratum appears in *Ann Neurol* 1998; 44:428]. *Ann Neurol* 1998; 43:815–825.
- 44 Sumi SM, Bird TD, Nochlin D, Raskind MA. Familial presenile dementia with psychosis associated with cortical neurofibrillary tangles and degeneration of the amygdala. *Neurology* 1992; 42:120–127.
- 45 Murrell JR, Spillantini MG, Zolo P, *et al.* *Tau* gene mutation G389R causes a tauopathy with abundant pick body-like inclusions and axonal deposits. *J Neuropathol Exp Neurol* 1999; 58:1207–1226.
- 46 Bonifati V, Joosse M, Nicholl DJ, *et al.* The *tau* gene in progressive supranuclear palsy: exclusion of mutations in coding exons and exon 10 splice sites, and identification of a new intronic variant of the disease-associated H1 haplotype in Italian cases. *Neurosci Lett* 1999; 274:61–65.
- 47 Higgins JJ, Litvan I, Nee LE, Loveless JM. A lack of the R406W tau mutation in progressive supranuclear palsy and corticobasal degeneration. *Neurology* 1999; 52:404–406.
- 48 Perez-Tur J, Buee L, Morris HR, *et al.* Neurodegenerative diseases of Guam: analysis of TAU. *Neurology* 1999; 53:411–413.
- 49 Roks G, Dermaut B, Heutink P, *et al.* Mutation screening of the *tau* gene in patients with early-onset Alzheimer's disease. *Neurosci Lett* 1999; 277:137–139.
- 50 Conrad C, Andreadis A, Trojanowski JQ, *et al.* Genetic evidence for the involvement of tau in progressive supranuclear palsy. *Ann Neurol* 1997; 41:277–281.
- 51 Bennett P, Bonifati V, Bonuccelli U, *et al.* Direct genetic evidence for involvement of tau in progressive supranuclear palsy. European Study Group on Atypical Parkinsonism Consortium. *Neurology* 1998; 51:982–985.
- 52 Oliva R, Tolosa E, Ezquerro M, *et al.* Significant changes in the tau A0 and A3 alleles in progressive supranuclear palsy and improved genotyping by silver detection. *Arch Neurol* 1998; 55:1122–1124.
- 53 Baker M, Litvan I, Houlden H, *et al.* Association of an extended haplotype in the *tau* gene with progressive supranuclear palsy. *Hum Mol Genet* 1999; 8:711–715.
- An article outlining the association between tau polymorphisms and PSP.
- 54 Ezquerro M, Pastor P, Valldeoriola F, *et al.* Identification of a novel polymorphism in the promoter region of the *tau* gene highly associated to progressive supranuclear palsy in humans. *Neurosci Lett* 1999; 275:183–186.
- 55 Higgins JJ, Adler RL, Loveless JM. Mutational analysis of the *tau* gene in progressive supranuclear palsy. *Neurology* 1999; 53:1421–1424.
- 56 Hoenicke J, Perez M, Perez-Tur J, *et al.* The *tau* gene A0 allele and progressive supranuclear palsy. *Neurology* 1999; 53:1219–1225.
- 57 Morris HR, Janssen JC, Bandmann O, *et al.* The *tau* gene A0 polymorphism in progressive supranuclear palsy and related neurodegenerative diseases. *J Neurol Neurosurg Psychiatry* 1999; 66:665–667.
- 58 Morris HR, Lees AJ, Wood NW. Neurofibrillary tangle parkinsonian disorders – tau pathology and tau genetics. *Mov Disord* 1999; 14:731–736.
- 59 Hutton M. Molecular genetics of chromosome 17 tauopathies. *Ann NY Acad Sci* 2000; in press.
- 60 Di Maria E, Tabaton M, Vigo T, *et al.* Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann Neurol* 2000; 47: in press.
- 61 Pastor P, Ezquerro M, Munoz E, *et al.* Significant association between the *tau* gene A0/A0 genotype and Parkinson's disease. *Ann Neurol* 2000; 47:242–245.
- 62 Bullido MJ, Aldudo J, Frank A, *et al.* A polymorphism in the *tau* gene associated with risk for Alzheimer's disease. *Neurosci Lett* 2000; 278:49–52.
- 63 Lilius L, Froelich Fabre S, Basun H, *et al.* *Tau* gene polymorphisms and apolipoprotein E epsilon4 may interact to increase risk for Alzheimer's disease. *Neurosci Lett* 1999; 277:29–32.
- 64 Crawford F, Freeman M, Town T, *et al.* No genetic association between polymorphisms in the *Tau* gene and Alzheimer's disease in clinic or population based samples. *Neurosci Lett* 1999; 266:193–196.
- 65 Campion D, Dumanchin C, Hannequin D, *et al.* Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet* 1999; 65:664–670.
- An excellent study detailing the prevalence of familial Alzheimer's disease.
- 66 Delacourte A. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology* 2000; 54:538.
- 67 Working Group. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging* 1997; 18 (Suppl.4):S1–2.
- 68 Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 1999; 246 (Suppl.2):S6–15.
- 69 Gao QS, Memmott J, Lafyatis R, *et al.* Complex regulation of tau exon 10, whose missplicing causes frontotemporal dementia. *J Neurochem* 2000; 74:490–500.
- A basic paper that explains the mechanisms of tau splicing in vertebrates.