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Hereditary Frontotemporal Dementia Caused by *Tau* Gene Mutations

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Tau protein is involved in microtubule assembly and stabilization. Filamentous deposits made of tau constitute a defining characteristic of several neurodegenerative diseases. The relevance of tau dysfunction for neurodegeneration has been clarified through the identification of mutations in the *Tau* gene in cases with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Although the mechanisms by which these mutations lead to nerve cell death are only incompletely understood, it is clear that they cause the formation of tau filaments with distinct morphologies and isoform compositions. The range of tau pathology identified in FTDP-17 recapitulates that in sporadic tauopathies, indicating a major role for tau dysfunction in these diseases.

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FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) has a prevalence of 5–15 cases per 100 000 in the age group of 45–65 years (7, 91, 100). Clinically, it is characterized by severe behavioral changes and language difficulties, with cognitive dysfunction appearing later (75). Most cases of FTD are sporadic, with 20%–30% being familial (87, 100). The major pathological hallmark of FTD is an atrophy of the frontotemporal cortex, with neuronal loss, gliosis and spongiosis of the superficial layers. Cases of FTD are pathologically heterogeneous and can be divided into three subtypes based on the presence of protein inclusions in the brain: those with tau-positive inclusions, those with ubiquitin-positive, tau-negative inclusions and those lacking distinctive histopathology (66). The term Pick's disease is now reserved for cases of FTD with intraneuronal argyrophilic inclusions, so-called Pick bodies, which consist of abnormal tau protein. Pick bodies are present in 10%–30% of sporadic FTD cases (42, 67, 100).

Around 30% of cases of familial FTD are caused by *Tau* mutations and characterized by tau pathology (72, 87, 100). A substantial proportion (20%–40%) of hereditary FTD does not have *Tau* mutations (54, 89, 98). Some of these families are characterized by ubiquitin-positive, tau-negative inclusions and show linkage to chromosome 17q21-22. Recently, it has been shown that they have mutations in the *Progranulin* gene (4, 13). Ubiquitin inclusions are also present in hereditary FTD linked to loci on chromosome 9 (45, 121). Mutations in the *Valosin-containing protein* gene on chromosome 9p21-p12 have been identified and shown to lead to hereditary FTD with inclusion body myopathy and Paget's disease of the bone (124). Furthermore, FTD in a Danish family has been linked to chromosome 3 (3). The disease in this family and some cases with FTD and amyotrophic lateral sclerosis is caused by mutations in the *CHMP2B* (charged multivesicular body protein 2B) gene (80, 103). *CHMP2B* mutations are associated with ubiquitin inclusions (49, 80) and occasional tau pathology (36, 127). Ubiquitin inclusions in familial cases of FTD have been shown to contain TDP-43 (TAR DNA-binding protein-43) (1, 49, 78).

TAU PROTEIN AND NEURODEGENERATION

Filamentous tau inclusions are the pathological hallmark of a number of neurodegenerative disorders, of which Alzheimer's disease (AD) is the most common. It is characterized by the presence of intraneuronal neurofibrillary tangles (NFTs) and extracellular amyloid-β plaques. NFTs consist predominantly of paired helical filaments (PHFs) that contain tau protein in a hyperphosphorylated state (12, 22, 30, 31, 62). Tauopathies, such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease and argyrophilic grain disease (AGD) show tau pathology in the absence of amyloid-β plaques and are distinguished by different types and distributions of tau-positive inclusions (62).

Tau is involved in microtubule (MT) assembly and stabilization. In adult human brain there are six tau isoforms that are produced from a single gene by alternative mRNA splicing of exons 2, 3 and 10 (Figure 1) (28). They differ by the presence of three or four repeats, which constitute the MT-binding domains of tau (53, 61). Three isoforms contain three repeats each, encoded by exons 9, 11 and 12, whereas alternatively spliced exon 10 encodes the additional repeat that distinguishes three- from four-repeat forms (29). In adult human brain, the ratio between three- and four-repeat tau isoforms is close to 1 (27). Tau is a phosphoprotein and in the human diseases it becomes hyperphosphorylated and assembles into filaments (62). The etiological role of tau protein in neurodegeneration has been convincingly demonstrated through the identification of mutations in *Tau* in familial disorders with dementia and/or parkinsonism (48, 86, 109).

MUTATIONS IN *TAU*

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is an autosomal-dominantly inherited

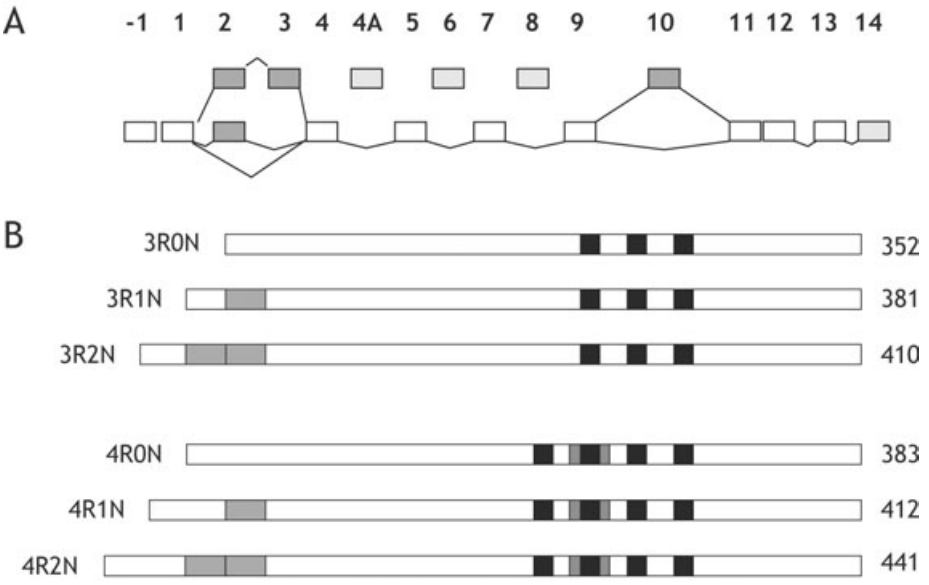

Figure 1. *Schematic representation of the Tau gene and the six tau isoforms expressed in adult human brain.* **A.** The human *Tau* gene contains 16 exons, of which exons 2, 3 and 10 (dark gray boxes) are alternatively spliced. Exons 4A, 6 and 8 (light gray boxes) are not transcribed in human brain. **B.** Six tau isoforms are generated by alternative mRNA splicing of exons 2, 3 and 10 (dark gray boxes). They range from 352 to 441 amino acids in length. The black boxes represent the microtubule-binding repeats of tau.

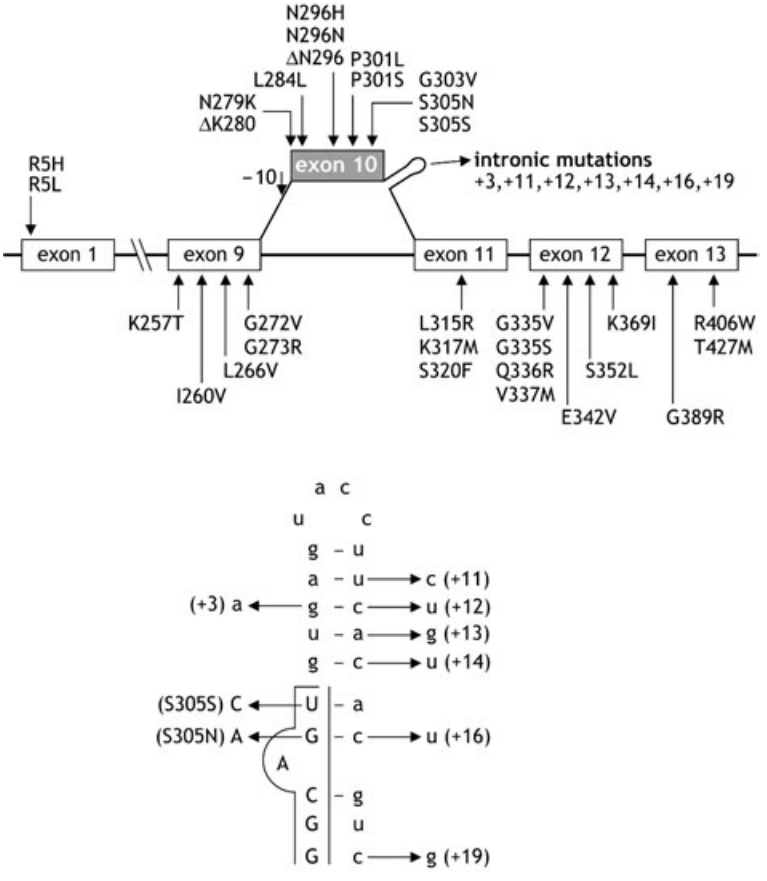

Figure 2. Overview of Tau mutations identified in frontotemporal dementia and parkinsonism linked to chromosome 17. All known coding region mutations are located in exons 1, 9, 10, 11, 12 and 13. The alternatively spliced exon 10 is depicted in gray. Mutations are numbered according to the longest tau isoform (441 amino acids).

disease that consistently shows severe frontotemporal atrophy with neuronal loss, gliosis and spongiform changes in layer 2. Involvement of medial temporal lobe structures, for example, entorhinal cortex, hippocampus and amygdala, is more variable. Degeneration of substantia nigra and basal ganglia is common (23, 107). Despite substantial neuropathological heterogeneity, the formation of abundant tau inclusions in nerve cells or in both nerve cells and glia is an invariant feature of FTDP-17. In 1998, exonic and intronic mutations in *Tau* were identified in cases of FTDP-17, demonstrating that genetic defects in *Tau* can cause neurodegeneration (48, 86, 109).

Molecular mechanisms. Thirty-nine mutations in *Tau* have been identified to date (Figure 2). They can be grouped according to their positions in the gene, which in turn defines their effects on tau mRNA and protein, as well as the type of resultant pathology. The majority of mutations occurs in the coding region of *Tau* and includes missense, deletion and silent mutations. Intronic mutations located close to the splice-donor site of the intron following exon 10 are also common. Most coding region mutations are located in the MT-binding region (exons 9–12) or close to it (exon 13). Two mutations in exon 1 of *Tau* have also been reported (39, 88). Mutations in exons 1, 9, 12, and 13 affect all six tau isoforms. In contrast, mutations in exon 10 affect only four-repeat tau isoforms or their expression (25, 40, 35, 44, 77, 82, 119). The primary effect of the intronic mutations and some mutations that affect splicing regulatory elements is exerted at the level of mRNA splicing and leads to an altered expression of tau isoforms (11, 48, 109, 117). *Tau* mutations can be classified as those that affect tau-microtubule interactions and/or fibril formation, and those that affect exon 10 splicing. This distinction is not absolute, as some mutations have multiple effects.

Mutations altering tau-MT interactions and fibril formation. In accordance with their location in the MT-binding region of tau, most missense mutations reduce the affinity of tau for MTs, as indicated by a reduction in the ability of mutant tau to promote MT assembly (14, 37, 44). This

mechanism applies to coding region mutations in exons 9, 11, 12 and 13. The P301L and P301S mutations in exon 10 also share this mechanism, whereas the Q336R mutation in exon 12 slightly increases the ability of tau to promote MT assembly (84). A reduction in MT binding has also been reported for mutations located outside the repeat region, that is, exon 1 mutations (39, 57). This effect may be mediated through a conformational change in the amino-terminal projection domain, leading to alterations in tau trafficking and/or compartmentalization, affecting tau interactions with MTs and possibly altering the regulation of MT dynamics. Additional functional changes could be caused through the introduction or removal of potential phosphorylation sites by some mutations, such as K257T, P301S and S320F (37, 94, 99)

Several mutations affecting tau-MT interactions also have pro-fibrillogenic effects (32). They have a direct stimulatory effect on heparin-induced tau filament assembly *in vitro*, with some mutations leading to the aggregation of specific tau isoforms. For example, the K257T mutation stimulates heparin-induced assembly of three-repeat tau into filaments *in vitro*, but has no effect on the fibrillogenesis of four-repeat tau (94). This may mirror the pathogenic events occurring *in vivo*, since filaments extracted from brains of patients with this mutation are predominantly made of three-repeat tau (94).

Mutations altering tau mRNA splicing. All intronic mutations and some coding region mutations affect the splicing of exon 10 and alter the ratio of tau isoforms. The vast majority of intronic mutations are located in the intron following exon 10 (I10; Figure 2). Exon trapping has shown that most intronic mutations increase the splicing-in of exon 10. This leads to the increased expression of four-repeat tau isoforms, which assemble into filaments in the brains of mutation carriers (62). The +19 and +29 mutations have been reported to reduce exon 10 splicing, leading to an increase in three-repeat tau (113). The +29 change was reported as a rare polymorphism (18), before being considered a mutation (113). The family has now been found to have a *Progranulin* mutation (85), establishing that it is a benign polymorphism. A few exonic mutations also alter the ratio of tau isoforms by increasing the splicing-in of exon 10. In particular, missense mutations N279K, G303V and S305N, and silent mutations L284L, N296N and S305S increase exon 10 splicing (11, 18, 38, 97, 110, 113), though through different mechanisms, as detailed below. Furthermore, the magnitude of the increase in splicing of exon 10 differs between mutations, depending on their position (32, 38, 71, 109).

Tau mutations alter splicing by disrupting the secondary structure of the mRNA splice site and by modifying regulatory sequences. Secondary structure analysis has predicted the presence of a stable, folded RNA stem-loop at the boundary of exon 10 and the downstream intron (Figure 2) (48, 109, 122). All intronic mutations analyzed to date affect the thermodynamic stability of this stem-loop and disrupt its structure (122). The S305N mutation changes the last amino acid of exon 10, thus reducing the thermodynamic stability of the stem-loop (50, 122) and, similar to the +3 intronic mutation, increases the binding of U1 snRNP to the 5′ splice site. This leads to increased splicing of exon 10 (109, 122). Instead, the silent S305S mutation disrupts the stem-loop structure without altering U1 snRNP binding (112).

An alternative mechanism is based on the disruption of splicing regulatory sequences. Several *Tau* mutations in the coding region (N279K, L284L, N296N, S305N) disrupt splicing regulatory sequences, leading to splicing-in of exon 10 and excessive production of 4R tau (17). An array of local splicing-enhancer and splicing-inhibitor elements that modulate the 5′ and 3′ splice sites of exon 10 has also been identified. Mutations N279K and L284L strengthen an exon splicing-enhancer element located in the 5′ region of exon 10, resulting in increased levels of exon 10-containing mRNA and soluble 4R tau (17, 18). The same mechanism has recently been found for a mutation located at position –10 of the intron that precedes exon 10 (68). The silent mutation N296N leads to increased levels of exon 10-containing transcripts by disrupting an exon splicing-silencer (17, 110) or by creating an exon splicing-enhancer sequence (34). Conversely, it has been reported that the +19 mutation increases the splicing-out of exon 10 by altering a splicing silencer sequence (17, 113).

Intronic mutations and some coding region mutations thus affect tau mRNA splicing and lead to an altered ratio of three- to four-repeat isoforms. In particular, most mutations increase the expression of four-repeat tau and result in the formation of tau deposits consisting mainly or exclusively of four-repeat tau, indicating the importance of a normal balance between three- and four-repeat tau for neuronal function (26).

Mutations altering tau-MT interactions, fibril formation and tau mRNA splicing. Several missense mutations located in exon 10 potentially exert their effects at both protein and RNA levels. Mutations ΔK280, ΔN296 and N296H greatly reduce the ability of tau to promote MT assembly *in vitro* (34, 51, 95, 130). Instead, mutations S305N and Q336R slightly stimulate the ability of tau to promote MT assembly (38, 84). Divergent findings have been reported for the effects of these mutations on heparin-induced tau filament assembly, ranging from a stimulatory (5, 34) to no (32, 130) effect.

Effects at the mRNA level have also been demonstrated for these mutations. The N296H and S305N mutations increase the splicing-in of exon 10 (34, 38). Accordingly, accumulation of sarkosyl-insoluble four-repeat tau has been observed in the brain of an individual with the N296H mutation (51). It has been reported that the ΔN296 mutation leads either to increased (130) or unaltered (34) exon 10 splicing. The ΔK280 mutation represents an exception, since it reduces the splicing-in of exon 10, possibly leading to an overproduction of 3R tau (18). This effect has recently been confirmed by quantitative analysis of 3R and 4R mRNA levels in brain tissue from a patient with this mutation (117). Experimentally, the ΔK280 mutation also reduces the ability of tau to promote microtubule assembly (37). The significantly greater amount of 3R tau in the sarkosyl-insoluble fraction from the brain of the proband with the ΔK280 mutation has established that the primary effect of this mutation is at the RNA level (117).

A mutation in exon 12 (E342V) also affects tau at both RNA and protein levels. It reduces the ability of tau to promote MT

assembly *in vitro* and appears to affect the splicing-in of exon 10. Indeed, it has been reported that exon 10-containing tau mRNA is increased in a patient with the E342V mutation (63). This was accompanied by an increase in four-repeat tau without N-terminal inserts and a decrease in four-repeat tau with N-terminal inserts (63). These findings suggest that the E342V mutation may cause FTDP-17 through unprecedented mechanisms that alter splicing of exons 2, 3, and 10, to preferentially increase four-repeat tau without N-terminal inserts, and to promote tau filament assembly.

In summary, mutations in *Tau* exert their pathogenic effects through three primary mechanisms: (i) alteration of MT assembly; (i) promotion of tau filament formation; (iii) alteration of tau mRNA splicing and isoform expression. A few mutations only act through one of these mechanisms, but most share several modes of action. The primary mechanism appears to determine the type of pathology that will develop in the brain, at least with regard to the isoform composition of tau deposits.

GENETIC EPIDEMIOLOGY

An etiological role for *Tau* was first suspected, when a family with the so-called dementia-disinhibition-parkinsonism-amyotrophy complex showed significant linkage to chromosome 17q21-22. (65, 125). Subsequently, this linkage was also found in several familial disorders described as different nosological entities in the older literature, including hereditary Pick's disease, familial subcortical gliosis and autosomal-dominant dementia with widespread NFTs (23, 41, 59, 105, 106, 115). The descriptive term FTDP-17 now denotes these entities (23). Pathological tau changes are present in neuronal and glial cells of the brain in most of these disorders. In 1998, three research groups identified mutations in *Tau* in eight families with FTDP-17 (48, 86, 109) and a total of 39 different *Tau* mutations has been identified to date in families from Europe, the USA, Japan and Australia (Figure 2). Interestingly, Pick's disease-like pathology has been described in a patient with a novel *Presenilin-1* mutation who lacked amyloid-β deposits in brain (16).

FTDP-17 usually shows an autosomal-dominant mode of inheritance, but recessive forms have also been described (79, 89). The mode of inheritance is less obvious in some families, due to a lack of information of family history and the possibility of non-paternity (73). Incomplete penetrance was convincingly demonstrated for the L315R mutation (40). Some families with mutations N279K and P301L are large, with more than 20 affected members over several generations (116, 126). Other families consist of only a few affected members, and sometimes a mutation has only been identified in the proband (43). This may reflect the fact that affected relatives from earlier generations had clinical diagnoses other than FTD during life, including multiple sclerosis and Parkinson's disease (43, 116).

A few *Tau* mutations have been identified worldwide, (2, 7, 15, 48, 57, 95, 118, 128), whereas others have only been described in single families (40, 43, 63, 94, 99, 131). Intronic mutations have been found almost exclusively outside Continental Europe (48, 83, 129). P301L appears to be the most prevalent mutation, with more than affected 20 families in the USA, France, the Netherlands, Japan, Italy and Poland (19, 48, 57, 58, 70, 87, 95, 132). It is not clear whether this high frequency can be explained by a common ancestor. Haplotype analysis has shown that the N279K and R406W mutations have occurred as independent events in several families (90, 92, 118). In contrast, all families with the +16 intronic mutation share a common haplotype, probably derived from a common ancestor in Wales, although recombinational events have resulted in a reduced size of shared alleles in some cases (82).

The frequency of *Tau* mutations in FTD varies between different studies (6, 20, 46, 87, 95, 100, 132). The high prevalence of individuals with a clinical diagnosis of FTD in the Netherlands (14%) and North West Britain (10%) contrasts with the much lower prevalence in the USA (6%) and elsewhere (0%) (20, 114, 132). The frequency is obviously higher in familial cases of FTD, but even here it varies considerably between the USA (8%) and Europe (20%–30%). It is unclear whether this geographical variation reflects true differences in prevalence between specific populations or is the result of different methods of case ascertainment. A selection bias towards familial cases is unlikely, since the percentage of familial cases was similar in these studies (87, 100). The frequency of *Tau* mutations is higher in cases of familial FTD with tau pathology (72, 87). All studies agree that the absence of tau pathology in familial FTD cases excludes the presence of *Tau* mutations (72, 87).

AGE AT ONSET

The clinical presentation correlates to some extent with the type or location of mutations within *Tau*. However, the inter- and intrafamilial variation in age at onset may be considerable for some mutations. For others, the average age at onset in families from different continents is remarkably similar, despite different genetic backgrounds and environments (2, 7, 15, 57).

The age at onset for P301L and several other mutations is usually between 45 and 65 years. Dementia may occasionally present between 65 and 70 years of age, but never after the age of 70 years (7, 116). Intronic mutations show the same distribution of age at onset, although a few cases have an earlier onset (around the age of 40) (83, 106). Clinical symptoms may develop even earlier, between 20 and 30 years, in patients with mutations P301S, L315R, G335S and G335V (10, 40, 79, 104, 111), or between 30 and 44 years in patients with mutations L266V and N279K (43, 56, 126). Late-onset dementia after the age of 70 years may also occur, as observed for cases with the R5H and I260V mutations (35, 39). The healthy status of an 82-year-old carrier with the L315R mutation suggests that genetic or environmental factors can play a role in determining the age of onset (40). The duration of illness is on the average between 8 and 10 years for patients with FTDP-17. An exception is mutation R406W, which is characterized by a slow rate of disease progression lasting up to 25 years (92, 116). Patients with an early age at onset often show a more aggressive disease progression, leading to death within 5 years (10, 40, 102, 104).

CLINICAL PRESENTATION

Two major clinical subtypes can be distinguished among FTDP-17 patients: dementia-predominant and parkinsonism-predominant (128). Both subtypes can occur in patients with the same mutation

and even within the same family. The dementia phenotype is usually associated with mutations G272V and P301L (7, 74, 116). Personality changes are characteristic, with disinhibition, jocularity and asocial behavior as salient features. Apathy and loss of initiative are also prominent in the initial presentation. Obsessive-compulsive behavior in some patients or the occurrence of paranoid delusions and hallucinations in others, may initially suggest a psychiatric disorder (102, 111, 114, 116). Memory problems may dominate the clinical presentation to such an extent that a clinical diagnosis of AD is considered during life (92, 99). Patients may have trouble with planning, suffer from a loss of concentration and develop judgment impairment and loss of insight sufficient to disrupt their social and professional lives. Emotional bluntness is often embarrassing for family members. Other common clinical features are hyperorality and roaming behavior.

Patients develop early language difficulties consisting of word finding problems and stereotyped words and phrases are frequently used (10, 15, 43, 64, 116, 126). Semantic paraphasias and impaired language comprehension are sometimes observed (83), but a true semantic dementia has not been reported. Paucity of speech results in mutism within 5 years in all patients, except for a long preservation of language abilities in some patients with the R406W mutation (116). Partial or generalized epileptic seizures are a specific feature of some cases with the P301S mutation, whereas mental retardation has been reported in a patient with the +11 intronic mutation (71, 104).

While parkinsonism is the dominant clinical presentation in some, but not all, patients with mutation N279K or the intronic mutations (51, 71, 83, 126, 128), it may also occur in other cases (123). Characteristic features include gait impairment, rigidity, bradykinesia, postural instability and resting tremor, with no or only a transient effect of levodopa treatment. Corticospinal tract signs are occasionally present in the parkinsonism-predominant type (2). Vertical gaze palsy, saccadic eye movements and axial rigidity are early symptoms in patients with a few mutations (ΔN296 and S305N) and are consistent with a clinical diagnosis of PSP (81, 112). Patients with parkinsonism may develop these symptoms later in the disease (106, 126). Unilateral rigidity, dystonia and contractures, in combination with impaired eye movements, occur in cases with some mutations and suggest a clinical diagnosis of CBD (10, 15, 112). These observations indicate that there is a clinical overlap between FTDP-17, PSP and CBD (10). At present, the question whether to consider these conditions as clinical phenotypes of a single disease or as distinct clinical entities is irrelevant. The main issue is to determine whether FTDP-17, as well as sporadic and familial PSP and CBD, all have the same underlying pathophysiology.

NEUROPSYCHOLOGY

Patients with FTDP-17 differ in cognitive function from those with AD. They have a relatively intact episodic memory and do not lose their way. Orientation and visuoconstructive functions are usually intact. Intelligence scores are normally low. Verbal fluency, abstract thinking and executive functions, including planning and mental set-shifting (Wisconsin Card Sorting Test), are impaired, reflecting frontal dysfunction. Attention and concentration are decreased, often contributing to low test results (7, 116). Poor performance on formal memory tests may be present, but immediate and delayed recall in verbal and nonverbal memory tests is often relatively preserved (104). Language dysfunction may consist of inefficient word retrieval, anomia and sometimes mildly impaired comprehension, although it is never consistent with the cognitive profile of semantic dementia. The pattern of cognitive dysfunction is similar for all individuals with *Tau* mutations. Cognitive function may be impaired decades before the presentation of dementia, since asymptomatic mutation carriers have already reduced verbal fluency, attention and motor speed and set shifting in their twenties and early thirties (7, 21, 24).

INVESTIGATIONS

A clinical diagnosis of FTDP-17 can be supported by neuroimaging. Frontotemporal atrophy is the most common neuroradiological feature (7, 116, 129). Patients with some mutations show a predominantly temporal pattern of atrophy (Figure 3), often asymmetric (10, 39, 112), and occasionally also have hippocampal atrophy. Diffuse cerebral atrophy is a common finding in other patients, especially those with intronic mutations (15, 33, 71, 81, 92, 106). Single-Photon Emission Computed Tomography (SPECT) shows hypoperfusion of the anterior part of the brain early in the disease, even in patients with normal brain morphology (74). Glucose metabolism is reduced in frontal and temporal lobes of the brain on Positron Emission Tomography (73). In patients with parkinsonism, FluoroDopa metabolism in the globus pallidus is significantly impaired (126). SPECT with the radiologand ^{123}I-N-

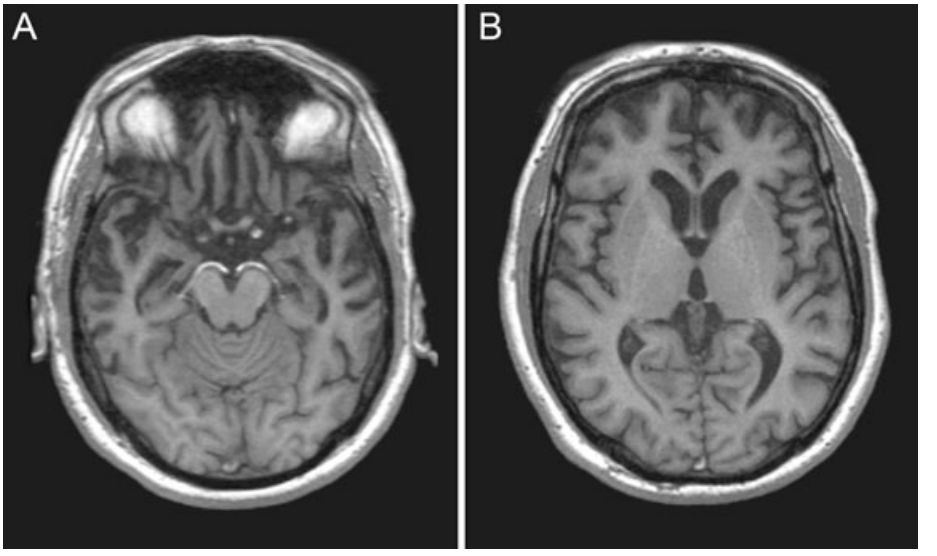

Figure 3. Magnetic resonance imaging. Moderate atrophy of the anterior temporal lobes in a patient with the P301L mutation in exon 10 of *Tau*.

omega-fluoropropyl-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropane (FP-CIT) shows a severe symmetrical decrease of presynaptic dopamine transporter binding in the striatum in individuals with the P301S mutation (104). Electroencephalography tends to be normal (7), except for the interictal epileptic discharges described in some patients with the P301S mutation (104). Denervation potentials and fasciculations on electromyography reflecting anterior horn cell disease have been found in one series (74), but understanding their significance awaits further investigation. Normal levels of total and hyperphosphorylated tau are found in cerebrospinal fluid in FTD with tau pathology (101). This finding has yet to be explained in the context of increased levels of cerebrospinal fluid (CSF) tau in AD and PSP (52, 120).

PATHOLOGY

Macroscopic features. FTDP-17 is characterized by nerve cell loss and gliosis in cerebral cortex, subcortical nuclei, white matter and brainstem. For the most common mutations (N279K, P301L, intronic), the pathological variation is known, whereas for others, observations have been confined to single patients. The brain weight at autopsy is often reduced, being frequently less than 1000 g. The lateral ventricles can be grossly enlarged (83). The brain shows frontal and temporal atrophy in patients with most mutations, often in a knife-edge pattern. Temporal atrophy is most prominent in the anterior part, with relative preservation of the posterior part of the superior temporal gyrus (7, 93). The atrophy occasionally extends into the parietal lobe (43, 104). Frontotemporal atrophy may be mild in patients with some mutations (47, 88, 93, 106). Atrophy of the hippocampus and amygdala often accompanies temporal lobe atrophy (7, 43, 83), although these structures can also be normal (70, 115). Subcortical nuclei range from normal (84, 88, 92) to severely atrophic (43, 60, 70, 71, 93). Substantia nigra and locus coeruleus show depigmentation in some patients (52, 60, 74, 92, 93), but may be normal in others (94, 99, 115). The brainstem is sometimes atrophic, whereas the dentate nucleus of the cerebellum usually has a normal appearance (8, 73, 74).

Microscopy. Severe neuronal cell loss and gliosis are present in the frontal and/or temporal cortex in patients with most, but not all, *Tau* mutations (47, 88, 93). Ballooned cells can often be found in deep cortical layers (52, 93). The hippocampus usually shows loss of pyramidal cells in *cornu ammonis* and subiculum, although there is no or only focal neuronal loss in some cases (60, 93, 110, 115). The amygdala is affected in most cases. Subcortical nuclei show neuronal loss (94, 129) or are normal (33, 47, 50, 51, 56, 60, 76, 84, 102, 109, 110). Gliosis and/or loss of myelin of the subcortical white matter may be present (73, 104), with occasional degeneration of the corticospinal tract (51). Substantia nigra and locus coeruleus often exhibit severe neuronal loss (83, 111), but may be normal in patients with mutations in exons 12 and 13 (64, 115, 116). Neuronal loss may also be present in other brainstem nuclei, the dentate nucleus of the cerebellum and the spinal cord (71, 88, 93, 106, 111). Diffuse and neuritic amyloid-β plaques have been described in cortical regions in several cases (18, 39, 60, 70, 116). It appears likely that their presence is a secondary and coincident pathological feature in older patients (69). Silver staining (Bodian, Bielschowsky, methenamine silver and Gallyas) has been used to visualize neuronal and glial inclusions. These techniques have given positive staining of NFTs, neuropil threads, dystrophic neurites, coiled bodies and astrocytic processes (10, 35, 39, 43, 56, 64, 73, 88, 93, 109, 116). Pick or Pick-like bodies have also been identified in this manner (51).

Immunohistochemistry. Tau staining is more widespread than silver staining. A large number of phosphorylation-dependent anti-tau antibodies have been used, with antibodies AT8 and PHF1 giving the strongest staining. Different types of neuronal tau inclusions are associated with distinct *Tau* mutations; they include diffuse or punctate staining, Pick bodies, NFTs and pretangles (Figure 4). Pick bodies usually do not stain with antibody 12E8 (9), which is specific for tau phosphorylated at S262 and/or S356. Cases with the G389R mutation are an exception (73). Tau-positive inclusions are most often found in frontotemporal cortex and subcortical nuclei, but can also occur in midbrain, brainstem, cerebellum and spinal cord. Tau-positive inclusions often mirror the severity of neuronal loss, but can also be prominent in regions with less severe nerve cell loss (40, 93). Depending on the type of mutation, tau pathology may be confined to nerve cells (94) or may be most

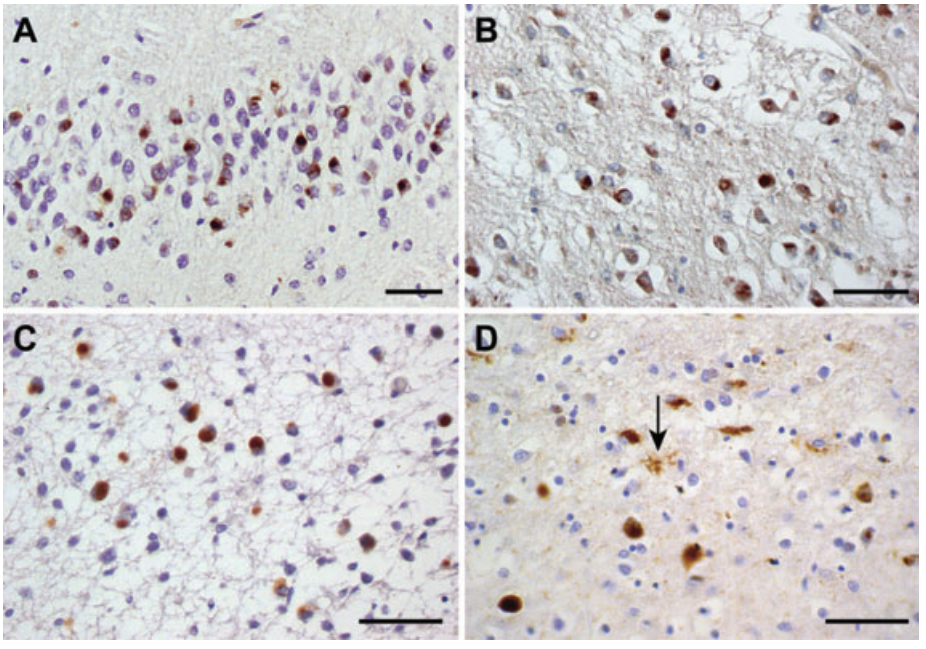

Figure 4. *Tau pathology in cases with the G272V and ΔK280 Tau mutations*. Tau-immunoreactive Pick bodies in the dentate gyrus of the hippocampus (**A,C**), the caudate nucleus (**B**) and the frontal cortex (**D**). Note the tau-positive astrocyte (arrowed) in (**D**). (**A,B**), case with mutation G272V in exon 9 of *Tau*. (**C,D**), case with mutation ΔK280 in exon 10 of *Tau*.

severe in astrocytes and oligodendroglia (10, 35, 56, 93). NFTs are often most numerous in frontotemporal cortex, but may be more widespread in subcortical nuclei and brainstem (51, 93, 110, 111). Flame-shaped or globose NFTs are associated with intronic mutations and some mutations in exons 12 and 13 (60, 93, 105, 111, 115). Extracellular tangles are only occasionally present (84). Granule cells of the dentate gyrus of the hippocampus frequently contain Pick-like bodies and pyramidal cells of the *cornu ammonis* sector and subiculum often show NFTs (60, 108); however, occasionally, the hippocampus is free of tau pathology (115).

Substantia nigra and locus coeruleus often show NFTs, neuropil threads and glial inclusions (60, 93, 111), but lack tau pathology altogether in some patients with mutations in exons 12 and 13 (64, 92, 99, 115). Cerebellar nuclei, brainstem and spinal cord may show a few NFTs, neuropil threads and glial inclusions. Neuropil threads are often present in variable severity and distribution, whereas thick axonal swellings are occasionally seen (73).

Pre-tangles are characteristic of cases with the P301L mutation (108, 116), but also occur in patients with other mutations. The P301L mutation gives rise to characteristic ring-like tau staining around the nucleus (70, 108, 116). Several mutations are associated with Pick bodies, which vary in number in cortex, hippocampus, amygdala and subcortical nuclei (40, 43, 76, 94, 108, 117). They usually stain with three-repeat specific anti-tau antibodies and are negative with four-repeat specific antibodies.

Glial tau pathology can be more severe than neuronal pathology. Glial tangles and coiled bodies are more abundant in white matter than in cortex in cases with inclusions consisting predominantly of four-repeat tau isoforms (10, 51, 60, 71, 110). Tufted astrocytes characteristic of PSP are found in the cortex and subcortical nuclei in patients with several exonic and intronic mutations (43, 55, 60, 88, 129). Their presence in brains from patients with mutations affecting all six tau isoforms (R5H, L266V, S305N, L315R) contrasts with the observation of abundant glial tau pathology associated with mutations that only affect four-repeat tau or increase the relative amount of four-repeat tau. Another interesting observation is that tufted astrocytes associated with these mutations appear to be more abundant in cortical areas with severe neuronal loss than in areas that are less severely involved (40, 55). This suggests that astrocytic inclusions may develop later than neuronal deposits or may be longer-lived. Phagocytosis of neuronal deposits by astrocytes provides a possible explanation, but the connection between a given *Tau* mutation and astrocytic tau pathology awaits clarification.

Biochemistry. Immunoblotting of sarkosyl-insoluble tau shows distinct profiles according to the location of *Tau* mutations. For mutations in exon 10 and at the splice-donor site of the intron following exon 10, four-repeat tau isoforms predominate. Two different mechanisms underlie the deposition of four-repeat tau. First, the intronic mutations and some mutations in exon 10 (at positions 279, 296 and 305) produce a twofold to tenfold increase in exon 10+ transcripts over exon 10– transcripts (38, 44, 109). The resulting overexpression of soluble four-repeat tau leads to its deposition. Second, mutations in exons 9–13 result in reduced binding to microtubules (37, 40, 99). For the P301L mutation in exon 10, this change affects only four-repeat tau and results in its aggregation (96). Neuronal and glial tau pathology is usually associated with the deposition of four-repeat tau isoforms, while neuronal tau pathology is associated with all six isoforms. In cases with mutations V337M and R406W, NFTs consist of all six tau isoforms, as expected (105, 111, 116). Pick bodies contain exclusively or predominantly three-repeat tau in cases with mutations K257T, L266V and G272V in exon 9 and mutation ΔK280 in exon 10 (9, 43, 55, 94, 117), whereas for other mutations, Pick bodies contain both three- and four-repeat tau isoforms, as judged by western blotting (40, 63, 73, 76, 99). Although associated glial tau pathology may be responsible for the presence of four-repeat tau in these cases, staining with specific anti-tau antibodies has also shown a mixture of three- and four-repeat tau in Pick bodies in a case with the Q336R mutation (84).

The association between mutation location and insoluble tau isoform profiles is less clear for other mutations (40, 64, 99). Unlike the observation of a predominance of three-repeat tau in some exon 9 mutations, only four-repeat tau was found in the case of mutation I260V in exon 9 (35). The neuronal and glial tau pathology in the R5L mutation in exon 1 consists mainly of four-repeat tau, despite the fact all six isoforms carry this mutation (88).

Electron microscopy. The inclusions of FTDP-17 consist of abnormal filaments made of hyperphosphorylated tau protein (62, 106). These filaments can be studied in sarkosyl-insoluble brain extracts or in fixed brain tissue. Tau filaments show specific morphologies, which vary with the different mutations. PHFs with a diameter of 8–20 nm and a periodicity of 80 nm are found in AD, but also in FTDP-17 with mutations in exons 12 and 13 (64, 102, 105, 108, 111). Slender twisted filaments or ribbons with an irregular periodicity of 90–130 nm are characteristic of intronic and some exonic mutations with a predominance of four-repeat tau (2, 47, 93, 106). Narrow, irregularly twisted filaments or ribbons of 15 nm and a periodicity of 130 nm or greater are found in some other cases, including those with mutation P301L (70, 94, 108). Several mutations produce predominantly straight filaments (10, 43, 84). Phosphorylation-dependent and phosphorylation-independent anti-tau antibodies decorate these filaments.

CONCLUSION

The recognition of the etiological role of *Tau* in some disorders with dementia and parkinsonism has implications for clinical practice, that is, genetic counseling. It has shown that dysfunction or dysregulation of tau protein can cause neurodegenerative changes accompanied by the presence of hyperphosphorylated tau protein deposits in neurons and glial cells. In addition, observations from clinical and pathological studies in other tauopathies, such as PSP, CBD, Pick's disease and AGD, support the hypothesis that tau plays an important role in the pathogenesis of these disorders (26). Some functional consequences of *Tau* mutations have been clarified, such as their effects on microtubule assembly and the change in the ratio of three- vs. four-repeat tau. However, it is unknown how this change in isoform composition leads to neuronal and glial tau pathology. The cor-

relation between the location of mutations in *Tau* and tau pathology or tau isoform profiles is weaker than believed earlier. It is not known how missense mutations outside exons 9–12 lead to a reduction in microtubule binding. Furthermore, the significance of glial tau pathology in both FTDP-17 and related disorders awaits further explanation. The factors contributing to the variation in clinical phenotype, including incomplete penetrance, remain to be determined. Elucidation of the genetic factors that are necessary to cause PSP, CBD, Pick's disease and AGD will be a major step forward in the understanding of the mechanisms modulating the tauopathy phenotypes.

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