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High Prevalence of Mutations in the Microtubule-Associated Protein Tau in a Population Study of Frontotemporal Dementia in the Netherlands

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Summary

Mutations in microtubule-associated protein tau recently have been identified in familial cases of frontotemporal dementia (FTD). We report the frequency of *tau* mutations in a large population-based study of FTD carried out in the Netherlands from January 1994 to June 1998. Thirty-seven patients had ⩾1 first-degree relative with dementia. A mutation in the *tau* gene was found in 17.8% of the group of patients with FTD and in 43% of patients with FTD who also had a positive family history of FTD. Three distinct missense mutations (G272V, P301L, R406W) accounted for 15.6% of the mutations. These three missense mutations, and a single amino acid deletion (ΔK280) that was detected in one patient, strongly reduce the ability of tau to promote microtubule assembly. We also found an intronic mutation at position +33 after exon 9, which is likely to affect the alternative splicing of *tau*. *Tau* mutations are responsible for a large proportion of familial FTD cases; however, there are also families with FTD in which no mutations in *tau* have been found, which indicates locus and/or allelic heterogeneity. The different *tau* mutations may result in disturbances in the interactions of the protein tau with microtubules, resulting in hyperphosphorylation of tau protein, assembly into filaments, and subsequent cell death.

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Introduction

Frontotemporal dementia (FTD) is a form of presenile dementia characterized by behavioral changes, cognitive decline, personality changes, speech deterioration, and, later in the disease, decline of memory. Sometimes, parkinsonian symptoms are prominent (Brun 1987; Knopman et al. 1990). Atrophy of the frontal and/or temporal cortex, as well as of the basal ganglia and substantia nigra, are the characteristic neuropathological features. Neuronal loss, gray-matter and white-matter gliosis, and superficial cortical spongiform changes generally are found in the cortex and some subcortical areas (Brun 1987; Lund and Manchester Groups 1994).

Prevalence of FTD in the Netherlands is estimated to vary between $1.2/10^6$ in the age group of 30–40 years and $28.0/10^6$ in the age group of 60–70 years (Stevens et al. 1998). FTD can occur in a sporadic form, but 30%–50% of persons with FTD have been found to have a positive family history of dementia (Gustafson 1987; Neary et al. 1988; Knopman et al. 1990; Stevens et al. 1998).

A number of families with an autosomal dominant mode of inheritance and almost complete penetrance have been described, and ⩾13 have been linked genetically to chromosome 17q21-22; these are now referred to as "frontotemporal dementia and parkinsonism linked to chromosome 17" (FTDP-17 [MIM 601630]; Wilhelmsen et al. 1994; Petersen et al. 1995; Wijker et al. 1996; Yamaoka et al. 1996; Baker et al. 1997; Poorkaj et al. 1998; Foster et al. 1997; Froelich et al. 1997; Heutink et al. 1997; Murrell et al. 1997; Lendon et al. 1998).

Most, if not all, families with FTDP-17 show microtubule-associated protein tau deposits in neurons or in both neurons and glial cells. In some FTDP-17 families, the tau deposits are identical to those found in Alzheimer disease (AD; Spillantini et al. 1996): they are present in neurons and consist of paired helical and straight filaments, which contain all six brain tau isoforms. Other families show tau deposits, in neurons and in glial cells,

Table 1

PCR Primers for Genomic Amplification of Tau Exons (5′→3′)

Exon	Forward	Reverse	Exon Size (bp)	PCR Product (bp)
1	CAACACTCCTCAGAACTTATC	CAGTGATCTGGGCCTGCTGTG	150	228
2	CACAGGGAGCGATTTTCAGC	CCACGCTGTCCTGCAAAGC	87	339
3	GGGCTGCTTTCTGGCATATG	CCTCACTTCTGTCACAGGTC	87	297
4	GGATGTGAACTTTCCTGAATG	GAGCTCAGGTCCAAATGATC	66	271
5	CAGTGAAAATGGAGTGTGAC	CAGCTGCAGAGCTCCGTGGC	56	136
7	CTAGGAGGCCAAGGGTCAC	GAGAGCTTCAGCTTCCTCTAAG	127	300
9	CGAGTCCTGGCTTCACTCC	CTTCCAGGCACAGCCATACC	266	379
10	GGTGGCGTGTCACTCATCC	GGTGGCGTGTCACTCATCC	93	200
11	CTTCTCATTGAGTTACACCC	CTCACCAGGACTCCTCCAC	82	174
12	AGATGCTCTTGTGTGTGTTGTG	CAGCATCCAACCCACCCTAC	113	173
13	CTTTCTCTGGCACTTCATCTC	CCTCTCCACAATTATTGACCG	208	299

which consist of wide, twisted ribbons and contain only tau isoforms with four microtubule-binding repeats (Spillantini et al. 1997).

The microtubule-associated protein tau is believed to function in the assembly and stabilization of microtubules. The tau protein isoforms found in human brain samples are encoded by 11 exons (Andreadis et al. 1992). A total of six different major tau mRNA transcripts are generated, resulting from alternative splicing, which encode proteins of 352–44l amino acids (Goedert et al. 1989*a*). The alternative splicing of exon 10 generates tau proteins with three or four microtubule-binding motifs that are imperfect repeats of 31 or 32 residues each (Goedert et al. 1989*b*).

Recently, we and others sequenced the *tau* gene in FTDP-17 families (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998*b*) and identified missense mutations in coding exons 9, 10, 12, and 13, which are predicted to affect the microtubule-binding properties of the tau protein (MIM 157140). Mutations also were found in a predicted stem-loop structure at the 5′ side of the intron, between exons 10 and 11, causing a shift in the normal splicing ratio of transcripts containing exon 10, and resulting in a higher proportion of four-repeat tau isoforms. In the present study, we report the contribution of *tau* mutations as a cause of FTD in a large group of patients ascertained in a genetic epidemiological study of FTD in the Netherlands.

Patients and Methods

Patients

Ninety patients with FTD were identified in a genetic-epidemiological study in the Netherlands (population ~15 million), between January 1994 and June 1998. Part of this study has been described elsewhere (Stevens et al. 1998). Neurologists, psychiatrists, and physicians at nursing homes were asked to report all patients with FTD with age at onset <65 years, irrespective of family history. We excluded secondary cases of FTD mentioned in family history, to avoid referral bias resulting from familial clustering. The diagnostic criteria were the clinical and neuroimaging findings defined by the Manchester and Lund groups (1994). Progressive behavioral changes and speech disturbances were characteristic early symptoms in all patients, whereas memory problems were initially absent. The diagnosis of FTD was supported by neuropsychological test results at ascertainment or by review of previous neuropsychological reports, when available. All patients showed frontotemporal atrophy, on computed tomography or magnetic resonance scan, or showed anterior hypoperfusion on single-photon-emission–computed tomography. Two independent neurologists, blinded for family history and neuroimaging, checked the clinical diagnosis, and a neuroradiologist with no knowledge of the patients' family history of FTD evaluated the presence of neuroimaging changes. Data on dementia and other neurodegenerative disorders in first-degree relatives were collected by use of a family questionnaire.

The study was approved by the Medical Ethics Committee of The University Hospital Dijkzigt. Informed consent for venipuncture for DNA studies was obtained from the spouse or from a first-degree relative of each patient.

DNA studies

Blood samples were collected from 90 patients with FTD. DNA was prepared according to standard procedures (Miller et al. 1988). Exons of the *tau* gene were amplified by use of specific primers derived from the 5′ and 3′ intronic sequences (table 1). The annealing temperature for all primer pairs was 58°C. Amplification conditions were as follows: reaction volume was 50 μl, with a final concentration of 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, and 200 μM dNTPs; *Taq* polymerase at 1.5 units/50 μl; primers at 25 pmol/μl; and 50 ng template genomic DNA. The PCR reactions

were analyzed on a 2% agarose gel to verify the size and quantity of the PCR product.

For SSCP, 3 μl PCR product was applied to the Pharmacia GenePhor Electrophoresis system. Gels were run for 70 min at 18°C and for 90 min at 5°C. Running conditions for both gels were 600V, 400 mA, and 30W, respectively. Bands then were visualized by use of a DNA silver staining kit (Pharmacia) in a Hoefer automated gel stainer. All 11 coding exons of the *tau* gene, including flanking intronic sequences, were amplified from genomic DNA of each FTD patient by use of PCR primers specified in table 1. SSCP analysis was performed on exons 1, 2, 3, 4, 5, 7, 9, 11, and 13, and the exons presenting band shifts were subsequently analyzed by direct sequence analysis of the PCR products, on an automated DNA sequencer (ABI 377), by use of the BigDye terminator cycle sequencing kit. Exons 10 and 12 of all 90 cases of FTD were sequenced directly on both strands.

Oligonucleotides with a length of 15 bases for allele-specific oligo (ASO) hybridization were designed for the mutated and normal sequence. ASO hybridizations were performed at 42°C for 1 h. Filters were washed, until a final stringency of 0.3XSSC/0.1SDS was obtained, for 15 min at 42°C.

Microtubule Assembly Assays

Site-directed mutagenesis was used in the four-repeat 412–amino acid isoform of tau (expressed from cDNA clone htau46; Goedert et al. 1989*a*), to change the proline residue at position 301 to a leucine (P301L) and to delete the lysine at position 280 (ΔK280), in the numbering of the 441–amino acid isoform of human tau. Wild-type and mutated tau proteins were expressed in *Escherichia coli* BL21 (DE3), as described elsewhere (Goedert and Jakes 1990). Bacterial pellets were resuspended in 50 mM PIPES, 1 mM EGTA, 1 mM DTT, 0.5 mM PMSF, and 0.5 μg/ml leupeptin (pH 6.8), followed by a 2 × 1 min sonication on ice, by use of a Kontes Micro Ultrasonic Cell Disrupter. The homogenates were centrifuged at 27,000 × *g* for 15 min, and the supernatants were filtered through a 0.45 μm Acrodisc. The filtrate was loaded onto a phosphocellulose column (bed volume 2 ml) that was equilibrated in extraction buffer. The column was washed in extraction buffer and then in extraction buffer + 0.1 M NaCl. Protein was eluted batchwise with 6 ml extraction buffer containing 0.3 M NaCl. This was followed by overnight dialysis against a saturated ammonium sulphate solution and then precipitation by a 10-min centrifugation at 50,000 rpm (Beckman TL100). The pellet was resuspended in extraction buffer and reprecipitated by addition of an equal volume of saturated ammonium sulphate solution. After centrifugation, the pellet was resuspended in 1 ml extraction buffer containing 0.5 M NaCl and 1% 2-mercaptoethanol and was then boiled for 3 min. After a 10-min centrifugation at 50,000 rpm, the supernatant was loaded onto a NAP10 column equilibrated in 80 mM PIPES, 1 mM EGTA, 0.2 mM $MgCl_2$, 1 mM DTT (microtubule assembly buffer minus GTP), and eluted with 1.5 ml of the same buffer. GTP was added until a final concentration of 1 mM. Tau protein concentrations were determined by densitometry (Molecular Dynamics), with bovine serum albumin used as the standard. In all experiments, wild-type and mutant proteins were expressed and purified in parallel.

Purified recombinant wild-type and mutated htau46 (0.1 mg/ml, 2.3 μM) proteins were incubated with bovine brain tubulin (1 mg/ml, 20 μM, Cytoskeleton, Inc.) in assembly buffer at 37°C, as described elsewhere (Hasegawa et al. 1997). The assembly of tubulin into microtubules was monitored over time by a change in turbidity at 350 nm.

Results

The group of patients with FTD consisted of 59 women and 31 men. The mean age at onset of FTD was 54.6 years ± 8.4 years, with a mean duration of illness of 5.4 years ± 2.7 years. Family history of dementia was positive in 37 patients (41.1%). The clinical diagnosis of FTD was confirmed by pathological examination in 13 cases. Pick disease was diagnosed in three cases. Nine patients died without pathological verification.

We systematically performed SSCP and sequence analysis in our collection of patients with FTD, to detect mutations in the *tau* gene. Thirteen sites were detected in patients who were heterozygous for the sequence alterations; no homozygous sequence alterations were detected. To determine whether these alterations were potential disease-related mutations or nonpathogenic polymorphisms, we looked for the presence of each sequence alteration in healthy family members or in 192 (96 males and 96 females) unaffected individuals from the Dutch population, using ASO hybridization.

Eight of the 13 sequence alterations also were found in healthy control individuals and were identified as non–disease-related polymorphisms (table 2). These eight base changes are all silent mutations that do not affect the amino acid sequence of tau protein. Five sequence alterations were not detected in healthy family members or in the 192 control individuals and therefore could be disease-related mutations (table 3).

Three different missense mutations were detected in a total of 14 patients, resulting in the following amino acid substitutions: G272V, P301L, and R406W, numbered according to the longest isoform of human brain tau (Goedert et al. 1989*a*; table 3). In addition, we found

a single amino acid deletion (ΔK280) in one patient and a base change (G→A) at position +33 in the intron after exon 9 in another patient.

In 17.8% of all patients with FTD, a mutation was detected (table 3). All patients with a mutation had a positive family history of dementia, except the patient with the ΔK280 mutation, who had a positive family history of Parkinson disease.

In genetic diseases, pathogenic mutations must be absent in healthy control individuals and must segregate with the disease phenotype. The G272V mutation, resulting from the nucleotide change 1051G→T in exon 9, was found in two patients (2.2%). Both patients were members of the HFTD II family, for which segregation of the mutation with the disease has been reported (Hutton et al. 1998).

The P301L mutation, resulting from the nucleotide change C→T in exon 10, was present in 11 cases (12.2%). Cosegregation of the P301L mutation for five affected family members has been described elsewhere, for the HFTD I family (Hutton et al. 1998). Six additional cases were found in the present study. Nine of the 11 total cases with a P301L mutation share a common ancestor, on the basis of a genealogical study and construction of haplotypes for polymorphic markers in and around the *tau* gene.

The R406W mutation, resulting from the nucleotide change C→T in exon 13, initially was observed in a single patient (1.1%). From the relatively small R406W family (HFTD IV), three affected individuals were tested, and the mutation segregated with the disease phenotype.

The ΔK280 mutation, resulting from a deletion of the nucleotides AAG in exon 10, was detected in a single case (1.1%). The base change G→A at position +33 in the intron after exon 9 was also observed, in one patient (1.1%) from a small family with no additional affected family members available for study. Thus, additional evidence that this mutation is pathogenic and not merely a rare polymorphism can be obtained only by in vitro studies.

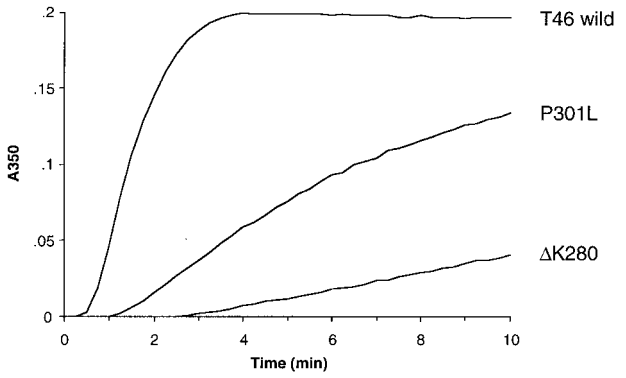

Figure 1 Effects of the ΔK280 mutation in tau on the ability of four-repeat htau46 (412–amino acid isoform of human tau) to promote microtubule assembly. Comparison with the P301L missense mutation in tau. Polymerization of tubulin induced by wild-type htau46, htau46 ΔK280, and htau46 P301L, as monitored over time by turbidimetry. A typical experiment is shown; similar results were obtained in three separate experiments.

Table 2

Polymorphic Sites Identified in the Tau Gene

Position in Tau Gene	Nucleotide Change	Frequency in FTD Cases (%)
Exon 1 position −13 from ATG	A→G	18
3′ Exon 2 + 18	C→T	18
3′ Exon 3 + 9	A→G	33
Exon 7 codon 176	G→A	18
Exon 9 codon 227	A→G	30
Exon 9 codon 255	T→C	30
Exon 9 codon 270	G→A	6
3′ Exon 11 + 34	G→A	28

NOTE.—Sequence alterations were also detected in healthy family members of patients or in a series of Dutch healthy controls.

The present study includes 30 independent families, each with at least two affected family members, that could not be linked to a common ancestor by genealogical studies or haplotype data. In seven (23.3%) of these families, a mutation in the *tau* gene was detected.

Tau protein promotes microtubule assembly, stabilizes microtubules, and affects their dynamic behavior. The G272V, P301L, and R406W mutations strongly reduce the ability of tau protein to promote microtubule assembly (Hasagawa et al. 1999). To strengthen the evidence that the ΔK280 reported here is indeed pathogenic, we performed microtubule assembly assays using recombinant wild-type four-repeat tau and tau with the Δ280K mutation. We compared their ability to promote microtubule assembly with that of the same four-repeat tau isoform with the P301L mutation. The effect of the Δ280K mutation on microtubule assembly was dramatic and larger than the effect of the P301L mutation (fig. 1). Recombinant tau protein with the Δ280K mutation showed a greatly reduced ability (≤1% of activity of wild-type tau, after 2 min) to promote microtubule assembly (fig. 1). The effect was much larger than for the other known missense mutations in *tau*.

Discussion

We describe here the results of a systematic screen for mutations in the microtubule-associated protein tau in 90 patients with FTD, obtained through a genetic epidemiological study performed in the Netherlands since January 1994. Our analysis revealed a mutation in the *tau* gene in 17.8% of patients with FTD and in 40.5% of patients with a positive family history for dementia. Although we excluded secondary cases to avoid referral

Table 3

Mutations Identified in the Tau Gene

Exon	Nucleotide Change	Amino Acid Change	No. of Cases	No. with Positive Family History
9	G→T	G272V	2	2
3′ exon 9	+33 G→A	…	1	1
10	C→T	P301L	11	11
10	ΔAAG	ΔK280	1	0

NOTE—Positions are numbered according to the longest human brain tau isoform (441 amino acids).

bias resulting from familial clustering, the 37 nuclear families have been reduced to 30 independent families by use of extensive genealogical studies and haplotype analysis. In seven (23.3%) of these families, a mutation in *tau* was detected.

Three distinct missense mutations, one 3-bp deletion, and one mutation in the intron after exon 9 were found. No nonsense mutations were found and none of the previously described intronic mutations in the predicted stem loop after exon 10 were found (Hutton et al. 1998; Spillantini et al. 1998*b*). No large insertions or deletions were detected.

In samples of adult human brain, six tau isoforms were expressed from a total of 11 exons (Goedert et al. 1989*a*; Andreadis et al. 1992). In this study, we analyzed all 11 coding exons. We used SSCP analysis for mutation detection and, although we used different experimental conditions, this method might detect effectively only 80%–90% of mutations present. Furthermore, additional sequences, such as coding exons that are expressed in the peripheral nervous system, or regulatory elements, such as the promoter region of *tau*, were not tested in this study. That we did not find mutations in ~60% of the familial cases, and that we did not find a mutation in patients from family HFTD III, which is linked to chromosome 17 (Heutink et al. 1997), clearly indicate that the present findings may constitute an underestimate of the percentage of mutations in the *tau* gene in cases of FTD.

We therefore currently are extending our mutational analysis to the noncoding region of the *tau* gene. For many familial cases, we could not determine whether they were linked to chromosome 17, because additional family members were not available. We therefore cannot exclude locus heterogeneity for FTD.

Additional evidence that the G272V, P301L, and R406W mutations are pathogenic comes from the observation that all three mutations segregated with the clinical phenotype in families HFTD II, HFTD I (Hutton et al. 1998), and HFTD IV, respectively. Furthermore, the P301 substitution occurs in a highly conserved region of the tau protein sequence. A proline residue is present at the equivalent position in all species from which tau has been sequenced. The G272V mutation in exon 9 also affects a highly conserved residue within the microtubule-binding domain. Within the imperfect repeat sequences that make up the four microtubule-binding domains, the G272V and P301L mutations affect positions that are separated by only one residue. Thus, for P301L, the invariant PGGG motif in the binding repeat becomes LGGG, and for G272V, it becomes PGVG. In contrast to the P301L mutation (exon 10), the G272V mutation (exon 9) affects all tau isoforms. Analysis of tau filaments extracted from HFTD 1 brain samples has revealed that the filaments are narrow, twisted ribbons that consist mainly of four-repeat tau isoforms, which is consistent with the P301L mutation only affecting four-repeat tau isoforms (Spillantini 1998*a*). The R406W missense mutation in exon 13 alters a highly conserved residue near the C-terminus, outside the microtubule-binding repeats, in close proximity to residues S396 and S404, that are phosphorylated in hyperphosphorylated filaments (Goedert 1993).

Experimental confirmation that the mutations are pathogenic has been obtained by means of functional studies of microtubule assembly. All three missense mutations reduce the ability of tau to promote microtubule assembly in vitro, with the P301L mutation having the strongest effect (Hasegawa et al. 1999). In the present study, we compared the effects of the P301L mutation and of the ΔK280 deletion mutation on microtubule assembly. Tau protein with the ΔK280 mutation showed a strongly reduced ability to promote microtubule assembly. This effect was much larger than for the P301L mutation. The ΔK280 mutation is located in the exon 10 "linker region," between two microtubule-binding repeats that contain the following amino acids, starting at amino acid 274, using the numbering for the longest tau isoform: KVQIINKKLD. The deletion removes either the second or the last lysine residue at position 280 or 281. Two other studies have used site-directed mutagenesis to mutate the K280 and/or K281 residues (Goode and Feinstein 1994; Trinczek et al. 1995). By use of microtubule binding and assembly assays, it was shown that the mutated proteins had a 3.6 times lower affinity for microtubules than the wild-type tau. In addition, the dynamic instability of microtubules was increased strongly, demonstrating that these lysine residues are critical for tau function.

The patient with the ΔK280 mutation has a negative family history of dementia, but his father was diagnosed with Parkinson disease. Clark et al. (1998) recently have reported a mutation that introduces an additional lysine residue (N279K), directly adjacent to K280, in a family with pallido-ponto-nigral degeneration. Characteristic of the clinical phenotype in this family is the rapidly progressive parkinsonism. Unfortunately, the limited clinical and genetic data available for the patient with

the ΔK280 mutation and other family members do not permit us to determine the significance of these similarities.

We could not determine whether the intronic mutation after exon 9 at position +33 segregates with the clinical phenotype, since no other family members were available. The mutation may affect the alternative splicing pattern of tau, although the mechanism is not yet clear. Exon 9 itself is not spliced alternatively, and no potential stem-loop structure was observed after exon 9. No sample of brain material was available from the patient, which precluded experiments to determine whether the mutation causes a change in tau mRNA transcripts.

A possible explanation for the effect of the mutation could come from two recent reports implicating multiple copies of short intronic (A/U)GGG repeats in splicing efficiency (Sirand-Pugnet et al. 1995; Cogan et al. 1997). The disruption of these short motifs reduces splicing efficiency. In the ±200 bp of intronic sequence currently available, eight (A/U)GGG motifs were found. The +33 G→A base change disrupts the first of these motifs. The expected effect would be inhibition of splicing. We are currently in the process of obtaining additional intronic sequences, and we hope this will enable us to design an assay for testing the significance of this mutation in vitro.

How can the mutations that have been found so far provide an explanation of the clinical phenotype and neurodegeneration found in patients? At first sight, the missense and deletion mutations, on one hand, and the intronic mutations, on the other hand, appear to produce opposite effects on tau function, whereas the clinical phenotype of patients with these different types of mutations is highly similar (Foster et al. 1997). Both the missense and deletion mutations reduce the ability of tau to promote microtubule assembly, which is the product of microtubule nucleation and/or growth. The intronic mutations lead to increased levels of four-repeat tau isoforms (Hutton et al. 1998; Spillantini et al. 1998*b*), which could lead to an increase in microtubule assembly. It is well established that four-repeat tau isoforms are better at promoting microtubule assembly than are isoforms with three repeats (Goedert and Jakes 1990).

There is some evidence to suggest that tau may nucleate microtubules in nerve cells (Bré and Karsenti 1990; Hirokawa 1994). A possible explanation of why mutations with opposite effects do not seem to influence clinical phenotype might be that a reduced ability to promote microtubule assembly, resulting from the missense and deletion mutations, could lead to an excess in free, unbound cytoplasmic tau. An increase in four-repeat tau isoforms, resulting from the intronic mutations, similarly leads to an excess of four-repeat tau over available binding sites on microtubules, because three- and four-repeat tau isoforms may bind to different sites on microtubules, as has been suggested by Goode and Feinstein (1994). A reduced ability of tau molecules to interact with microtubules thus could be the primary defect resulting from the different mutations in tau. This may in turn lead to the hyperphosphorylation of tau, which could reinforce the primary effect of the mutations. It is well known that hyperphosphorylated tau from samples of brains affected by Alzheimer disease is unable to bind microtubules or to promote microtubule assembly (Bramblett et al. 1993; Yoshida and Ihara 1993). Over time, perhaps in conjunction with other factors (Goedert et al. 1996), hyperphosphorylated tau will then assemble into filaments. In addition to effects on microtubule assembly and microtubule binding, mutations in tau may also have additional, direct effects on phosphorylation of tau and may favor its assembly into filaments.

In this view, the formation of tau filaments is the gain of the toxic function that is believed to underlie autosomal dominantly inherited, late-onset neurodegenerative diseases (Goedert et al. 1998). Future studies will show whether this view is correct or whether tau filament formation is only a by-product of the underlying pathogenic process. It will be important to understand how mutations in *tau* lead to neurodegeneration, because it is already clear that the *tau* gene is a major locus of inherited dementing disease. The discovery of mutations in the *tau* gene will advance the study of dementia in general, since Alzheimer disease, the most common dementing illness, is characterized by an abundant *tau* pathology whose presence correlates with the degree of cognitive impairment.

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for FTDP-17 [MIM 601630] and microtubule binding–associated protein tau [MIM 157140])

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