

# Novel Tau Polymorphisms, Tau Haplotypes, and Splicing in Familial and Sporadic Frontotemporal Dementia

Maria-Jesús Sobrido, MD, PhD; Bruce L. Miller, MD; Necat Havlioglu, MD; Victoria Zhukareva, PhD; Zhihong Jiang, PhD; Ziad S. Nasreddine, MD; Virginia M.-Y. Lee, PhD; Tiffany W. Chow, MD; Kirk C. Wilhelmsen, MD, PhD; Jeffrey L. Cummings, MD; Jane Y. Wu, PhD; Daniel H. Geschwind, MD, PhD

**Background:** A subset of familial cases (FTDP-17) of frontotemporal dementia (FTD) are caused by mutations in the *tau* gene. The role of *tau* gene mutations and haplotypes in sporadic FTD and the functional consequences of *tau* polymorphisms are unknown.

**Objectives:** To investigate (1) the frequency of known FTDP-17 mutations in familial and sporadic FTD and compare these results with previous studies; (2) whether the tau H1 haplotype is associated with FTD; and (3) the functional effect of intronic *tau* sequence variations.

**Patients and Methods:** Patients with familial and sporadic FTD were screened for mutations in the microtubule-binding region of tau. The frequencies of tau haplotypes and genotypes were compared between patients with FTD and control subjects. We analyzed the splicing effect of novel intronic polymorphisms associated with FTD.

**Results:** The P301L mutation was detected in 11% of familial FTD cases. The H1 haplotype was not overrepresented in patients with FTD, but the P301L mutation appeared on the background of the H2 tau haplotype. We identified 4 novel single nucleotide polymorphisms in intron 9 and a 9-base pair deletion in intron 4A. A C-to-T transition 177 base pairs upstream from exon 10 was significantly increased in patients with FTD compared with controls. Direct analysis of brain tissue from a patient with this variant showed an increase in exon 10-containing tau transcripts.

**Conclusions:** Sequence variations in intronic or regulatory regions of *tau* may have previously unrecognized consequences leading to tau dysfunction and neurodegeneration.

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**T**HE TERM *frontotemporal dementia* (FTD) refers to a group of primary degenerative dementias producing focal atrophy of the frontal and/or temporal lobes, which is frequently associated with parkinsonism and amyotrophic lateral sclerosis.<sup>1,2</sup> Frontotemporal dementia is familial in up to 40% to 50% of the cases, and inheritance is most often consistent with an autosomal dominant pattern of inheritance.<sup>3</sup> Two classes of mutations in the microtubule-associated protein tau have been found in 10% to 40% of subjects with familial FTD—those directly affecting the microtubule binding sites of tau, and those that alter tau splicing.<sup>4-6</sup> The majority of the currently known *tau* mutations are located in exons 9 to 13, the region coding for the microtubule-binding domains of the protein. *Tau* mutations have not been identified in sporadic FTD cases in previous studies.<sup>7,8</sup>

Tau is also implicated in other related neurodegenerative conditions, eg, progressive supranuclear palsy and cortico-

basal degeneration (CBD).<sup>9,10</sup> Several polymorphisms throughout the *tau* gene are in complete linkage disequilibrium and inherited as 2 distinct haplotypes, H1 and H2. The H1 haplotype is overrepresented in progressive supranuclear palsy and other tauopathies, although the biological basis for this association is currently unknown. The absence of detectable exonic mutations in many familial and in virtually all sporadic cases of FTD, together with the identification of tau polymorphisms of unknown significance, raises the question of whether these polymorphisms or other sequence variations may have functional consequences that are not yet understood.

The present study was undertaken to evaluate the prevalence of the major currently recognized *tau* mutations in patients with familial FTD and patients with sporadic FTD from a well-characterized clinical sample,<sup>3,11,12</sup> to determine whether common *tau* polymorphisms confer an increased genetic risk of developing FTD, and to investigate the potential functional effects of rare sequence variations on tau splicing.

Author affiliations are listed at the end of this article.

**Table 1. Primers and Restriction Enzymes Used**

Exon/Intron	Mutations/Polymorphisms	Enzyme	Primer Pair
Exon 4A	735C→T	<i>MspI</i>	4AF: 5'-AGCCGCCAGAGAAGCCACCAG-3' 4AR: 5'-GGAACGTCAGAAGCAGCAGGAGTC-3'
Exon 9	G272V	<i>HinfI</i>	9F: 5'-GCCCAGGGCCTTTTCTGACC-3' 9R: 5'-CACTCTCACTTCCCGCCTC-3'
Intron 9	-177C→T*	<i>HinfI</i>	10F: 5'-AGCCCTCTATCCCTTCAG-3' 10RM: 5'-GCATGGGACGTGTGAAGGTAC-3'
	-58G→A*	<i>TaqI</i>	ModF: 5'-TCATCGAAAGTGGAGGCGTCCTTTC-3' ModR: 5'-GGCTACATTCACCCAGAGGTCGC-3'
Intron 10			10F: 5'-AGCCCTCTATCCCTTCAG-3' 10R: 5'-GGCTACATTCACCCAGAGGT-3'
Intron 12			12F: 5'-GCACAGAACCACAGAAGATGATGGCA-3' 12R: 5'-AGCATCCAACCCACCCTACCC-3'
Intron 13	G389R	<i>NciI</i>	13F: 5'-GTCCTCCCTTCTCTTCTTG-3'
	R406W	<i>NcoI</i>	13R: 5'-GAGTGACAAAAGCAGGTAAAGTGAT-3'

\*New sequence variations described in the present study (see "Results" and Table 3).

## METHODS

### SUBJECTS

The patients included in this study were recruited under a protocol approved by the University of California, Los Angeles, (UCLA) Institutional Review Board. The diagnosis of FTD was based on the extended Lund-Manchester criteria, including neuroimaging and neuropsychological testing.<sup>12</sup> Autopsy results confirmed the diagnosis of FTD in 12 cases. De-identified, anonymous control samples of different ethnic origins were obtained from the Molecular Pathology core at UCLA for testing single nucleotide variants identified.

### SCREENING FOR TAU MUTATIONS AND POLYMORPHISMS

Exons 9, 10, 12, and 13 and flanking intronic regions were amplified by polymerase chain reaction using the primer pairs shown in **Table 1**. Mutations in exons 9 (G272V) and 13 (R406W, G389R), and the -177C→T variant were screened by polymerase chain reaction amplification followed by restriction digestion. Direct sequence analysis was performed for exons 10 and 12 in all samples. In addition, exons 9 and 13 were sequenced in 3 cases in which either tau immunoblot or splicing analysis showed a pattern of imbalance in the ratio of tau isoforms (cases 9, 30, and 31). A mismatched primer pair (ModF + ModR) (Table 1) introducing a restriction site for *TaqI* was designed to screen for a G-to-A single nucleotide polymorphism (SNP) at position -58 upstream from exon 10. The -176G→A and the -47C→A polymorphisms were screened by direct sequencing or single-strand conformation polymorphism analysis of control samples.

### CONSTRUCTION OF TAU HAPLOTYPES

Two intragenic polymorphic markers in exon 4A and intron 9 were used to infer tau haplotypes.<sup>8,13</sup> The frequency of the tau H1 and H2 haplotypes in patients with FTD was compared with that in 36 nondemented white volunteers with normal results on neuropsychological evaluation.

### WESTERN BLOTTING

Frontal cortex (area 9) from 3 familial and 2 sporadic cases of FTD was used for biochemical analyses. Gray and white matter was dissected and processed separately. Soluble and sarcosyl-

insoluble (PHF) tau was extracted from 1 g of tissue, and tau dephosphorylation and Western blotting were performed.<sup>14</sup>

### TAU SPLICING ASSAY

A tau minigene construct<sup>15</sup> including the wild-type *tau* genomic DNA fragments containing a segment of the genomic region between exons 9 and 11 and the corresponding fragments containing the -177T allele was used to evaluate the potential effect of sequence variations on the alternative splicing of exon 10. Total RNA was obtained from frozen brain tissue (A9) of the same cases used for the Western blot analysis, as well as from formalin-fixed, paraffin-embedded frontal cortex from one of the patients with the -177C→T variation. The RNA was prepared from the cell lines and FTD tissues by means of a reagent (Trizol; Life Technologies, Rockville, Md), and reverse transcriptase polymerase chain reaction was performed in the presence of  $\gamma$ -phosphorus 32-labeled ( $\gamma$ -<sup>32</sup>P) deoxycytidine-trinucleotide phosphate (Amersham Biosciences Corp, Piscataway, NJ). Blots were quantitated with a phosphor screen (PhosphorImager; Molecular Dynamics, Sunnyvale, Calif).

### STATISTICAL ANALYSIS

The  $\chi^2$  or Fisher exact tests were used to compare allele and haplotype frequencies between white patients and controls and to test for an association between novel sequence variants and tau haplotype. The statistical analysis was performed with the program SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill), and significance level was set at  $P = .05$ .

## RESULTS

### TAU MUTATION SCREENING

Forty-eight patients with FTD (23 women, 25 men) were screened for the common known FTDP-17 mutations. Demographic and clinical characteristics of the patients included in the present study, including ethnicity, as well as all haplotype and mutation data are summarized in a supplemental data table (available at: <http://geschwindlab.medsch.ucla.edu>). The mean age at onset was 54.2 years (range, 25-75 years). Eleven patients (23%) developed motor neuron signs in addition to dementia. The P301L C→T mutation was observed in 2 families of French Canadian origin. None of the previously reported *tau* mutations were

**Table 2. Tau Haplotypes and Genotypes Among Patients With FTD and Control Subjects**

	No. (%)			
	Controls	FTD Global	FTD Sporadic	FTD Familial
<b>Haplotypes</b>				
No. of subjects	<b>72</b>	<b>90</b>	<b>54</b>	<b>36</b>
H1	54 (75)	67 (74)	43 (80)	23 (64)
H2	18 (25)	23 (26)	11 (20)	13 (36)
<b>Genotypes</b>				
No. of subjects	<b>36</b>	<b>45</b>	<b>27</b>	<b>18</b>
H1/H1	23 (64)	26 (58)	17 (63)	8 (44)
H1/H2	8 (22)	15 (33)	9 (33)	7 (39)
H2/H2	5 (14)	4 (9)	1 (4)	3 (17)

Abbreviation: FTD, frontotemporal dementia.

**Table 3. Novel Sequence Variations in Tau\***

Position	Cases, No. (%)	Controls, No. (%)	P
-47 (C→A)	3/90 (3.3)	1/120 (0.8)	.42†
-58 (G→A)	1/90 (1.1)	0/112	NA
-176 (G→A)	33/90 (36.7)	78/152 (51.3)	.04†
-177 (C→T)	3/90 (3.3)	1/624 (0.2)	.003†
Intron 4A deletion	1/90 (1.1)	6/170 (3.5)	.45†

Abbreviation: NA, not applicable.

\*Frequencies refer to number of chromosomes.

† $\chi^2$  with Yates correction.

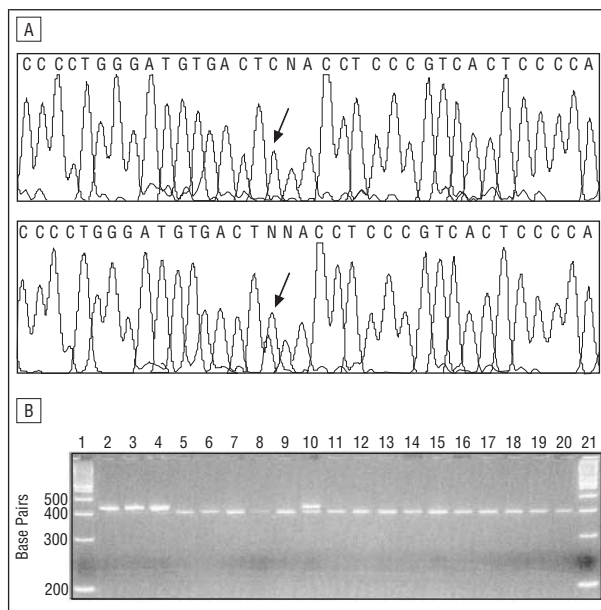
detected in sporadic cases. One of the families has been described in detail in a previous report.<sup>16</sup> It should be emphasized that the abnormality in this family shared significant features with CBD and Pick disease, a finding that highlights the overlap between FTD, Pick disease, and CBD. The second patient with the P301L mutation (case 16) presented at age 45 years with a progressive syndrome of aggressive behavior, paranoid delusions, apathy, and dementia. Several other family members had a similar condition. Three patients had 4R tau imbalance on biochemistry, but had no *tau* mutations in exons 9 to 13.

### TAU HAPLOTYPES

The results of haplotype and genotype analysis are summarized in **Table 2**. A trend toward a more frequent presentation of the H2 haplotype was observed among patients with FTD with a positive family history, compared with both sporadic FTD cases and controls ( $P < .08$ ) (Table 2). In both families, the P301L mutation was associated with the H2 haplotype (not shown).

### NOVEL TAU INTRONIC VARIATIONS

Four novel SNPs were detected in the intron upstream from exon 10 (see supplemental table and **Table 3**). A C-to-A change at position -47 in intron 9 was present in 3 patients with FTD and was also seen in 1 control chromosome, associated with the H1/H1 genotype. A common G→A SNP was identified -176 base pairs (bp) upstream from exon 10. The A allele in this position was in linkage



**Figure 1.** A, C-to-T substitution at position -177 of intron 9; case 30 (lower panel); control sample (upper panel). Both samples are also heterozygous for the -176G→A polymorphism. B, Exon 10 polymerase chain reaction products were digested with *HinI* and run on an agarose gel. Lanes 2 to 4 contain undigested polymerase chain reaction products. Case 30 is shown in lane 10.

disequilibrium with the H1 haplotype (Fisher exact test,  $P = .01$ ). Another novel SNP was detected at position -177 (C→T) 5' of exon 10 (**Figure 1**) in 3 sporadic cases. Since this variant was not detected in any of 229 white (American) control samples, 83 additional French Canadian controls were analyzed and the -177T allele was detected in 1 (0.6%) of 166. This change was not seen in any of 100 Native American, 100 Hispanic, 100 African American, and 100 Asian control chromosomes. The T allele at this position was transmitted with the H2 haplotype (Fisher exact test,  $P = .03$ ).

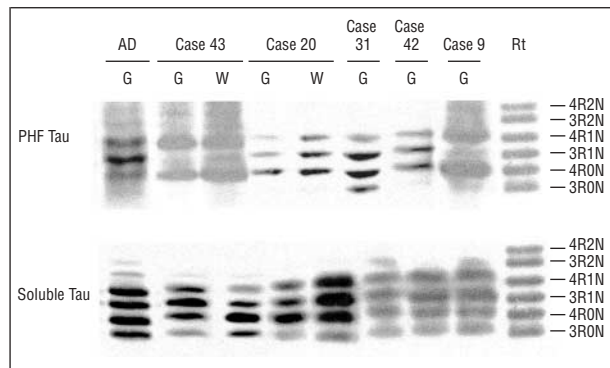
A novel 9-bp deletion polymorphism 46 bp 3' of exon 4A was also detected. This deletion was present in 1 patient with sporadic FTD and in 6 of 170 controls (Table 3).

### TAU PROTEIN ISOFORMS

Frozen postmortem samples from 4 familial (cases 20, 31, 42, and 43) and 1 sporadic (case 9) cases of FTD were analyzed (**Figure 2**). The PHF tau isolated from the cortex of a patient with the P301L mutation (C43) showed an overexpression of 4R tau.<sup>14</sup> Another case (case 9) without a known *tau* mutation showed a similar pattern of increased 4R tau in PHF preparations. Neuropathologically, this case was characterized by the presence of Pick bodies and ballooned neurons typical of Pick disease or CBD, similar to those observed in the P301L-positive case.<sup>16</sup> This observation supports recent findings that tau isoform composition in Pick disease is not restricted to the 3R isoform only.<sup>17</sup>

### TAU SPLICING

To assess the functional consequences of the intron 10-177 C-to-T polymorphism that was significantly increased in patients with FTD relative to controls, an *in vitro* splicing assay was performed with the use of a tau minigene



**Figure 2.** Biochemical profile of tau in brains of patients with familial frontotemporal dementia. Soluble and insoluble (PHF) tau were isolated from gray (G) and white (W) matter. An equal amount of total protein was loaded in each lane. Case 43 is a P301L-positive case. A mixture of 6 recombinant tau isoforms (Rt) was used as a standard. AD indicates Alzheimer disease.

containing either the C or T variant. A 2- to 3-fold increase of tau transcripts lacking exon 10 was observed in the presence of the T variant compared with wild-type tau in all 3 cell lines analyzed (**Figure 3A**). To extend this observation in vivo, the pattern of tau exon 10 splicing in frozen and fixed brain specimens of patients with familial and sporadic FTD was assessed. Rather than a decrease, a relative increase of exon 10-containing tau was detected in 1 patient (case 30) with the  $-177C \rightarrow T$  polymorphism and in 1 additional patient (case 31), both of whom had familial FTD (Figure 3B). In addition, case 31, without mutations in or around exon 10, was homozygous for several tau SNPs inherited as part of the H2 haplotype.

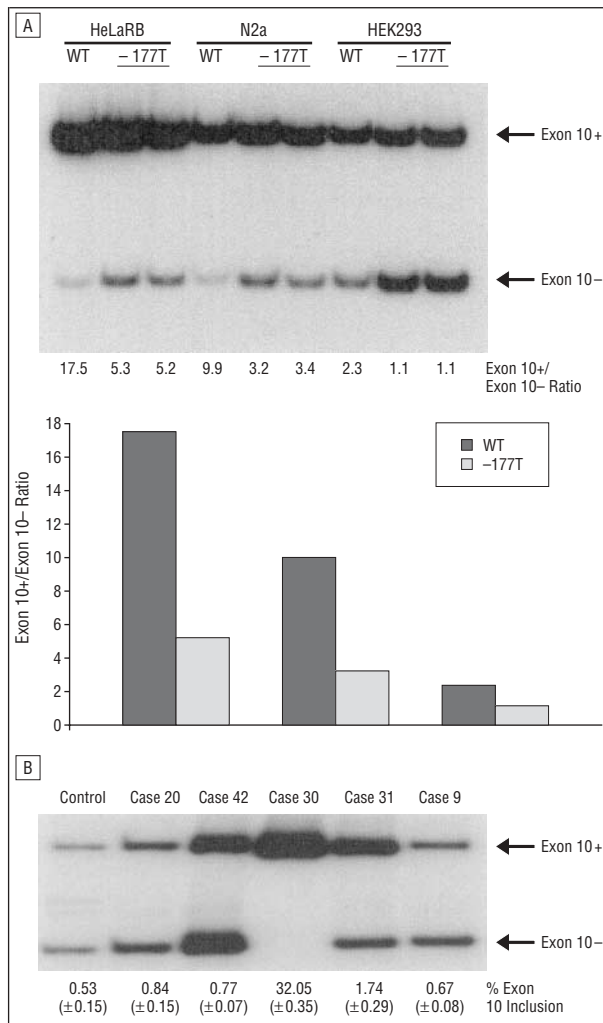
## COMMENT

### TAU MUTATIONS UNDERLIE FEW CASES OF FAMILIAL FTD

In the current study, we report the analysis of known FTDP-17 causal *tau* mutations in a series of familial and sporadic FTD. The frequency of *tau* mutations among familial cases in our series was 11%, similar to the figures obtained by others.<sup>7,8</sup> The absence of *tau* mutations in patients with sporadic FTD in our series is in agreement with previous reports.<sup>7,8</sup> Therefore, mechanisms other than the currently recognized *tau* mutations must explain most familial cases, as well as sporadic FTD.

### THE TAU H1 HAPLOTYPE IS NOT ASSOCIATED WITH FTD

Since an association between the tau H1 haplotype and other neurodegenerative disorders involving tau has been consistently reported,<sup>9,10,18,19</sup> we investigated whether either the H1 or the H2 haplotype was also overrepresented in FTD. Unlike progressive supranuclear palsy and other sporadic tauopathies, no significant association was detected between either the H1 haplotype or the *H1/H1* genotype and FTD in our series. A trend toward association of the H2 haplotype and *H2/H2* genotype was observed in patients with familial FTD compared with both sporadic FTD and controls. Such an association has been recently reported in Pick disease.<sup>20</sup> We also observed the



**Figure 3.** Effect of the  $-177T$  polymorphism on exon 10 splicing. A, Alternative splicing of exon 10 from 3 cell lines transfected with tau minigenes containing wild-type tau (WT) and the  $-177T$  intronic polymorphism. The intensity of tau transcript with (exon 10+) and without (exon 10-) exon 10 was measured, and the ratios are indicated below each lane. B, Autoradiograph of tau exon 10 reverse transcriptase polymerase chain reaction products from brain specimens with frontotemporal dementia. The percentage of exon 10 inclusion is expressed as mean ( $\pm$ SD) below each lane. Cases 20, 42, and 9 were not significantly different from normal tau.

P301L mutation coinherited with the H2 haplotype, as was seen in 4 of 5 other families.<sup>7</sup> Larger samples are needed to assess a potential founder effect in this mutation.

### TAU ISOFORMS AND SPLICING

The result of biochemical analysis of tau in pathological specimens was consistent with the genetic data. The PHF tau from the brain with the P301L mutation showed a biochemical profile typical of this mutation,<sup>14,16</sup> whereas no *tau* mutations were identified in 3 patients with a biochemical profile similar to that typically observed in Alzheimer disease. Both patients with FTD with 4R tau deposition had Pick bodies and ballooned neurons that are observed in Pick disease and CBD, emphasizing the clinical and pathological overlap of FTD with these conditions.

Previous data have highlighted the involvement of abnormal splicing in the pathogenesis of FTD.<sup>5,6,14,21</sup> Few stud-

ies have looked at regions more than 100 bp from the splice junctions. In the present series, we identified 4 novel SNPs within 200 bp in the intron upstream from exon 10, one of which (-177C→T) was significantly increased in patients with FTD relative to a large number of control chromosomes. In vitro experiments demonstrated that the -177C→T change causes an imbalance in the splicing of tau toward isoforms in which exon 10 has been omitted. There are no identifiable splicing regulatory elements in this region. However, the -177T variant alone cannot completely account for the final pathological alteration, since analysis of postmortem tissue from the same case demonstrated an increase in 4R to 3R tau transcript. Thus, other factors that may be in linkage disequilibrium with the -177T allele, or other splicing regulatory elements, must be involved. The common -176 G→A polymorphism was seen more frequently in controls and was in linkage disequilibrium with the H1 haplotype.

These results highlight the importance of confirming any in vitro splicing changes, especially those obtained with simple exon trapping vectors, in vivo. While the splicing alterations observed in vitro may reflect the effect of that specific sequence variant, the final balance of tau isoforms in vivo is likely to be the result of more complex interactions. Moreover, the mechanisms by which common tau polymorphisms confer increased risk for progressive supranuclear palsy,<sup>9,18</sup> CBD,<sup>10</sup> and primary progressive aphasia<sup>19</sup> are unknown. Whether these extended tau haplotypes affect disease risk by altering splicing or other aspects of tau regulation or, alternatively, whether they implicate additional genes nearby, remains to be determined.

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From the Department of Neurology, The David Geffen School of Medicine at UCLA (University of California, Los Angeles), Los Angeles (Drs Sobrido, Cummings, and Geschwind); Department of Neurology, University of California, San Francisco (UCSF) School of Medicine (Dr Miller), and the Gallo Clinic and Research Center (Dr Wilhelmsen), San Francisco; Department of Pediatrics and Department of Molecular Biology and Pharmacology, Washington University School of Medicine, St Louis, Mo (Drs Havlioglu, Jiang, and Wu); Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia (Drs Zhukareva and Lee); Service de Neurologie, Hôpital Charles LeMoine, Greenfield Park, Université de Sherbrooke, Sherbrooke, Québec (Dr Nasreddine); and Department of Neurology, University of Southern California/Rancho Los Amigos Medical Center, Downey (Dr Chow).

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Corresponding author: Daniel H. Geschwind, MD, PhD, UCLA Department of Neurology, 710 Westwood Plaza, Los Angeles, CA 90095 (e-mail: dhg@ucla.edu).

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