



A novel mutation (K317M) in the *MAPT* gene causes FTDP and motor neuron disease

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Abstract—Background: Frontotemporal dementia with parkinsonism is often linked to chromosome 17 and is related to mutations in the *MAPT* gene. In some families the genetic basis is still unknown. The authors report two pedigrees with FTDP-17 harboring a novel mutation (K317M) in exon 11 in the *MAPT* gene. **Methods:** The authors identified two apparently unrelated pedigrees with an autosomal dominant neurodegenerative condition. Thirteen patients were examined and eight autopsies were performed. **Results:** Mean age at onset was 48 years. Mean disease duration was 6 years. Dysarthria often heralded the disease. All cases had parkinsonism and pyramidalism and half of them had amyotrophy. Behavioral or personality changes were not a prominent feature. Cognitive decline appeared late in the evolution. Neuropathologically, a massive degeneration of the substantia nigra without Lewy bodies was a constant finding. A variable degree of frontotemporal atrophy was found. Corticospinal tract degeneration and anterior horn neuron loss were present in six of seven autopsies in which the spinal cord was examined. An extensive deposition of abnormal tau protein in a mixed pattern (neuronal, glial) was observed. Pick's bodies were not seen. Biochemical analysis of tau revealed two bands of 64 and 68 kDa. **Conclusion:** Genetic analysis revealed the same novel mutation (K317M) in exon 11 of the *MAPT* gene in both pedigrees. A common haplotype between members of the two pedigrees suggests that they belong to the same family.

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At least three broad pathologic categories can be delineated within familial frontotemporal dementia (FTD).¹ The main group is defined by the presence of neuronal and glial inclusions made of abnormally phosphorylated tau protein. Patients from this group have been discussed using different clinicopathologic terms.^{2,3} An extensive deposition of abnormal tau in the brain at autopsy and linkage to chromosome 17 were later found in several families.^{4–7} Consequently, the term FTD with parkinsonism linked to chromosome 17 (FTDP-17) was proposed to include all of them.⁸ Thereafter, the first pathogenic mutations in the *MAPT* gene in chromosome 17 were discovered.^{9,10} Since then, 34 different mutations have been reported,^{11–14} 2 of them in exon 11.^{15,16} However, no

mutations in the *MAPT* gene are found in many cases of FTD,^{17–20} suggesting that other genes are involved in this disorder. The frequency of *MAPT* gene mutations when a tauopathy is demonstrated at autopsy varies widely in the reported series between 33%²⁰ and 100%.¹

In this article, we report a novel point mutation in exon 11 of the *MAPT* gene (K317M) causing parkinsonism with motor neuron disease and frontotemporal degeneration in two apparently unrelated pedigrees. When the genetic results disclosed that they probably belonged to the same family, a genealogic search found a probable common ancestor born in 1782.

Methods. Pedigrees. Pedigree 2 (figure 1) was presented in a preliminary report as a Nigro-Pyramido-Spinal degeneration (XII-Ith Congress, World Federation of Neurology, Hamburg, 1985). Pedigree 1 is available online (figure E-1 on the *Neurology* Web site at www.neurology.org).

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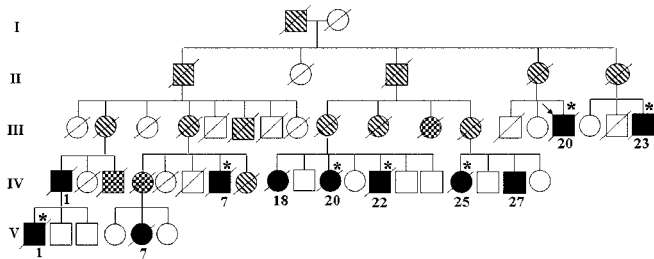


Figure 1. Pedigree 2. Square = male; round = female; slashed = deceased; filled = personally examined patient; hatched = affected by history; checkered = affected, examined in other institutions; arrow = proband; asterisk = autopsied.

In Patient 1/III-21, only the brain was available for neuropathologic study. A sample of the frontal cortex was immediately frozen on dry ice and stored at -80°C until its use for biochemical and genetic studies. The brains and spinal cords of Cases 2/III-20 and 2/III-23 were fixed and representative samples were embedded in celloidin and paraffin, and stained with hematoxylin-eosin, Nissl, Wolcke, Holzer, Bodian, and Masson trichrome methods. The remaining brains and spinal cords were fixed in formalin and embedded in paraffin. De-waxed sections, $7\ \mu\text{m}$ thick, were stained with hematoxylin and eosin, luxol fast blue-Klüver Barrera, and silver methods (Glees, methenamine).

Immunohistochemistry for phosphorylated neurofilaments of 170 kD or 200 kD (clones BF10 and RT97, Roche), glial fibrillary acidic protein (GFAP, Dako, Dakopats), βA4 -amyloid (Roche), ubiquitin (Dako), pan-tau (Sigma), and phospho-specific tau rabbit polyclonal antibodies (Thr181, Ser199, Ser202, Ser214, Ser231, Ser262, Ser396 and Ser422, all of them from Calbiochem), was performed in the samples from Cases 1/III-21, 2/IV-7, 2/IV-22, 2/IV-27, and 2/V-1 following the methods described elsewhere.²¹

For gel electrophoresis and Western blotting, frozen samples of the frontal cortex (5 g) of Case 1/III-21 were processed in parallel with similar samples of the frontal cortex of one case with Alzheimer disease, one case of progressive supranuclear palsy, and one patient with Pick's disease for comparison of the band patterning.²¹

In pedigree 1 the DNA was obtained from the fresh-frozen postmortem brain tissue of Patient 1/III-21. A tissue sample weighing 25 mg was cut into small pieces and DNA was extracted using the QIAamp Tissue Kit (Qiagen) according to the manufacturer's recommendations. The yield was $20\ \mu\text{g}$ of DNA and it was stored at -20°C before use.

In pedigree 2 the DNA was obtained from blood samples following standard procedures. Four patients and several asymptomatic members of the family who volunteered for anonymous screening were studied.

Mutation screening was done by direct sequencing of exons 9 to 13 of the *MAPT* gene, where most of the mutations found are shown to cluster (primer sequences and PCR conditions available upon request to J.P.-T.).

The observed variation in exon 11 created a *Nla*III restriction site that was used for screening a control population. This RFLP assay was resolved on a 3% agarose gel where a wild-type allele yields a 200 bp band and a mutated allele shows two fragments of 70 bp and 130 bp.

To test whether the two pedigrees were related to each other, three microsatellite markers were studied (D17S1804, D17S958, D17S1795) in the proband from Family 1 and all available individuals from Family 2. After PCR amplification (primers and conditions available upon request from J.P.-T.) the PCR products were pooled and subjected to fragment analysis on an ABI Prism 3100 Genetic Analyzer and analyzed with the accompanying software (GeneScan, Applied Biosystems). Genotypes from the proband from pedigree 1 were compared with the haplotypes constructed for pedigree 2 with the help of SimWalk 2.8.

Results. Both pedigrees are native to the Basque country in Spain, a small community of approximately 2,100,000 inhabitants.

A summary of the main clinical features of all the cases is shown in table 1. Mean age at onset was 48 years (range 37 to 57 years, SD 6.57). Mean duration of the disease was 6 years ($n = 11$, range 3 to 11 years, SD 2.49). Dysarthria, akinesia, or tremor were the main presenting symptoms. In an intermediate stage of the disease an asymmetric parkinsonism resistant to levodopa was observed in several patients. The full clinical picture, with some interindividual differences, comprises a combination of generalized parkinsonism, pyramidalism and amyotrophy, bulbar palsy with anarthria and severe dysphagia, supranuclear gaze palsy, frontal signs (loss of verbal fluency, mutism, working memory impairment, dysexecutive syndrome, apathy, emotional lability, or pathologic anxiety), dystonia, and focal reflex myoclonus in a few patients. In the majority of the patients a detailed neuropsychological examination was possible only early in the evolution. Thereafter it was rendered impossible by the severity of speech loss and motor impairment (figure E-2). Treatment with levodopa and dopaminergic agonist was useless except in Patient 2/IV-25. In this woman, levodopa in monotherapy produced no benefit, yet a dramatic response was observed when lisuride was added to levodopa. However, lisuride produced severe psychotic symptoms and had to be interrupted. Eventually all the patients became fully dependent, wheelchair or bedbound, tetraplegic, mute, and unable to feed orally.

Structural neuroimaging (CT or MRI) is not available from Cases 2/III-20 and 2/III-23. In the remaining patients variable signs of frontal or temporal atrophy or both were observed. A SPECT-HMPAO was obtained in the most recently examined patients and showed a frontotemporal hypoperfusion that usually correlated with the CT or MRI findings.

Neuropathologic study. The macroscopic aspect of the brain was unremarkable in four cases. In Case 1/III-21 a severe atrophy mainly involving the frontal lobes and the inferior and internal part of the temporal lobes was observed. In Case 2/IV-25 a severe atrophy of the precentral motor gyri and a moderate diffuse atrophy of the frontal lobes were noted. In Case 2/IV-22 the frontal lobes were normal but a moderate atrophy of the temporal poles and basal temporal gyri was evident. A striking bifrontal lobar atrophy was obvious in Case 2/V-1. The anterior roots of the spinal cord were macroscopically atrophic in some cases.

A summary of the histologic findings is presented in table 2. A severe degeneration of the substantia nigra marked by a massive neuronal loss and a dense gliosis was a constant feature in all the cases (figure 2). Lewy bodies were not found. The severity of the histologic damage in the frontotemporal neocortex varied from case to case. In the less involved areas a laminar microspangiosis of layers I and II was observed, whereas in the more degenerated areas the whole cortex exhibited a marked neuronal loss and gliosis. The primary motor cortex in the precentral gyrus was constantly affected usually with a superior to inferior gradient. The neurons of Betz often showed signs of degeneration or chromatolysis. The putamen, pallidum, thalamus, and other subcortical nuclei were in general well preserved with some patchy neuronal loss and gliosis,

Table 1 Summary of the main clinical findings

Pedigree/case	Sex/age at onset, y	First symptoms	Parkinsonism	Pyramidal syndrome	Amyotrophy	Early cognitive and behavioral disorders	Other symptoms and signs	Duration of illness, y
1/III-18	M/48	Dysarthria	+++	+++	No	Irritability	Unmotivated laughter	5
1/III-21	F/57	Dysarthria, bradykinesia	+++	+	No	No	Slowing of ocular saccades, ideomotor apraxia, mutism, echolalia, mirror movements	11
2/III-20	M/46	Hypokinesia (right hand)	+++	+++	++ (hands)	No	Slow saccades, dysphagia, mutism	4
2/III-23	M/52	Dysarthria	+++	+++	No	No	No	3
2/IV-1	M/45	Tremor (right hand)	+++	+++	No	No	Supranuclear gaze palsy	?
2/IV-7	M/53	Tremor (both hands)	+++	+++	+++ (hands, legs)	No	Unsteady gait, falls, unmotivated laughing and crying, supranuclear gaze palsy, eyelids apraxia, hands dystonia	5
2/IV-18	F/37	Dysarthria	+++	+++	No	No	Dysphagia, mutism, supranuclear gaze palsy	7
2/IV-20	F/54	Dysarthria	+++	+++	+	Disinhibition, euphoria, working memory loss	Reduced verbal fluency, anomia, agrammatism	9
2/IV-22	M/52	Tremor (right hand)	+++	+++	+(hands)	Anxiety, emotional lability, loss of working memory, dysexecutive syndrome	Reduced verbal fluency, dysarthria, supranuclear gaze palsy, focal reflex myoclonus	4
2/IV-25	F/44	Dysarthria	+++	+++	+++ (hands, legs)	Emotional lability	Reduced verbal output Spastic dysphonia, Unmotivated laughing and crying Left hand dystonia Slow saccades	4
2/IV-27	M/55	Depression, anxiety, insomnia	++	++	++ (legs)	Apathy, loss of verbal fluency, reduced verbal memory	Broken speech, slow saccades, irregular ocular pursuit	Still alive
2/V-1	M/39	Dysarthria	+++	+++	+(hands)	No	Supranuclear gaze palsy, dysphagia, anomia, reduced verbal fluency and working memory, irritability, apathy, compulsive feeding	6
2/V-7	F/40	Loss of verbal fluency, dysarthria	+++	+++	No	No	Progressive mutism and anarthria, focal reflex myoclonus, apraxia right hand, supranuclear gaze palsy	8

Grading of severity of clinical features: (–) absent, + mild, ++ moderate, +++ severe.

Table 2 Semiquantitative estimation of the severity of neuropathologic lesions

Structure	Severity of lesions	Number of cases (n = 8)
Locus niger	+++	8
Frontotemporal cortex	+++	5
	++	2
	+	1
Primary motor cortex	+++	4
	++	4
Motor nuclei in the medulla	++	5
	+	2
	0	1
Motorneurons in anterior horns*	+++	4
	++	2
	+	1
Corticospinal tracts*	+++	6
	+	1

* Seven spinal cords were removed at autopsy.

+++ = severe; ++ = moderate; + = mild; 0 = absent.

which varied from case to case. A severe neuron loss in the motor bulbar nuclei and in the anterior horn of the spinal cord was recognized in the majority of cases. The remaining neurons in the anterior horn showed either signs of atrophy and nuclear picnosis or prominent chromatolysis. The corticospinal tracts appeared clearly degenerated up to the spinal level in the myelin staining (figure 3) in six cases, and only slightly pale in one.

Immunocytochemical staining revealed a widespread deposition of abnormal tau protein in the four cases in which these methods were performed. Sections stained



Figure 3. Cervical spinal cord. Case 2/III-20. Celloidin. Wolcke myelin staining. Marked demyelination of anterolateral columns. Posterior columns and dorsal spinocerebellar tracts are preserved.

with phospho-specific anti-tau antibodies disclosed a massive phospho-tau accumulation in neurons and astrocytes in the upper and inner layers of the cerebral neocortex (figure 4, A and B), entorhinal cortex and hippocampus, thalamus (figure 4C), striatum (figure 4D), subthalamus, amygdala, hypothalamus, including the mammillary bodies (figure 4E), and some nuclei of the brainstem. Several neurons in the CA1 hippocampal sector contained pretangles. Tau-immunoreactive neurons were also common in the dentate gyrus. No tau-positive grains were observed in the hippocampus. No tau-immunoreactive inclusions were seen in the cerebellar cortex. Massive tau inclusions were seen in astrocytes and oligodendrocytes in the white matter throughout the brain (figure 4F), including the cerebellar white matter. Many phospho-tau inclusions in astrocytes in the gray matter resembled astrocytic plaques (figure 4G), but more compact tau-positive inclusions were also seen in other astrocytes (figure 4H). Tau-immunoreactive inclusions in oligodendrocytes (figure 4I) were reminiscent of the coiled bodies found in other tauopathies.

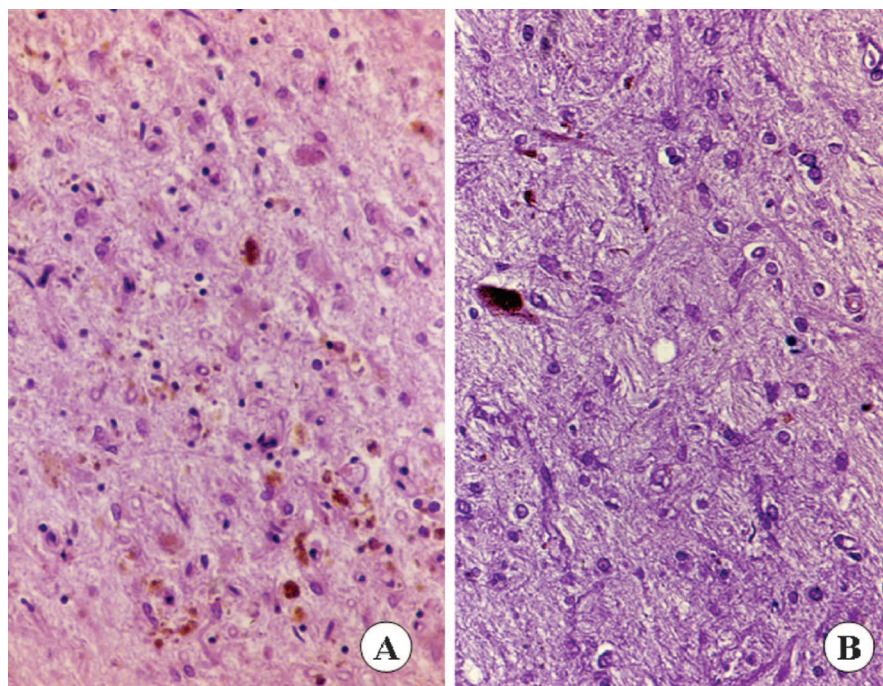


Figure 2. Locus niger. Case 2/III-20. (A) Massive neuronal loss in hematoxylin-eosin staining. (B) Dense fibrillary gliosis. Holzer.

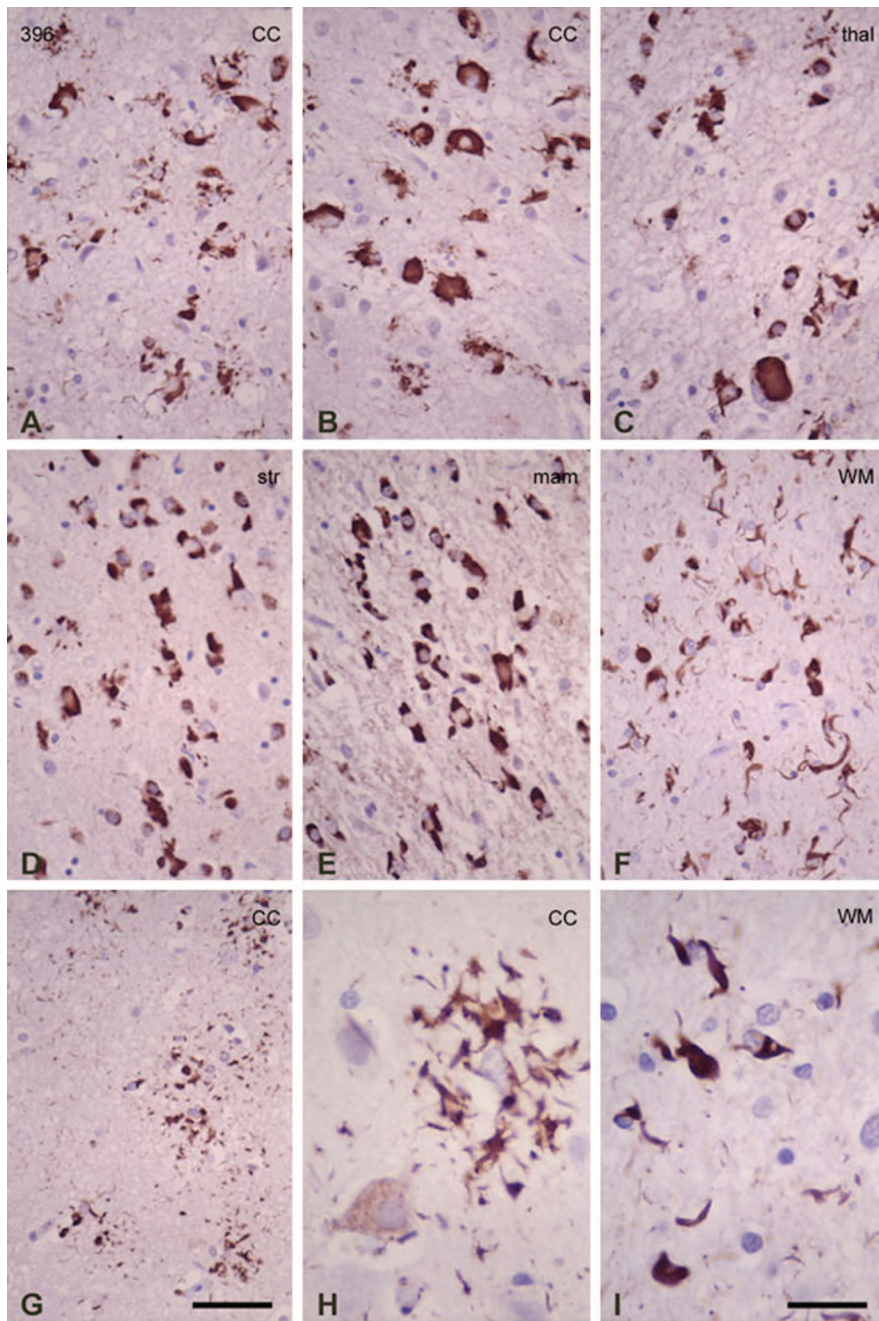


Figure 4. Immunohistochemistry with anti-phospho-tauSer396 antibody. (A, B, G, H) Cerebral neocortex. (C) Thalamus. (D) Striatum. (E) Mammillary bodies. (F, I) White matter. Neuronal tangles are observed in cerebral neocortex, thalamus, and striatum. Variegate astrocytic inclusions resembling tufted astrocytes (A, B), astrocytic plaques (G, H), and other compact tau-positive inclusions are seen. Tau-immunoreactive inclusions in oligodendrocytes in the white matter are reminiscent of the coiled bodies (F, I).

Similar findings were obtained with the various antibodies used in the present study. Neurons, astrocytes, and oligodendrocytes were stained equally with anti-phospho-tauSer396 antibodies and with anti-phospho-tauSer422, tauThr181, tauSer199, tauSer202, tauSer231, and tauSer214. However, inclusions were not stained with anti-phospho-tauSer262.

Most tau-positive inclusions in astrocytes and oligodendrocytes were decorated with anti-ubiquitin antibodies. Some tau deposits in neurons were ubiquitinated, but pre-tangle neurons and tau-immunoreactive inclusions in neurons of the dentate gyrus were not stained with ubiquitin antibodies. No ballooned neurons were observed in the cerebral cortex, although α B-crystallin antibodies stained the cytoplasm of astrocytes in the cerebral cortex and oligodendrocytes in the white matter. No α -synuclein inclu-

sions and no β A4-amyloid deposits were found. Pick's bodies were not observed.

Biochemical studies. Biochemical studies of total homogenates and sarkosyl-insoluble fractions from the brain of Case 1/III-21 disclosed a pattern of two bands of phospho-tau of 68 kDa and 64 kDa. Interestingly, the same results were obtained with the different antibodies used in the present study, including anti-phospho-tau Ser262. Frozen samples for dephosphorylation studies were not available.

Genetic analysis. Direct sequencing of those exons where mutations causing familial FTD often cluster revealed a missense mutation on codon 317 (K317M) caused by an A \rightarrow T transversion. The mutation was present in all the patients examined but it was not found in 160 chromosomes of Basque origin. Haplotype analysis using micro-

satellite markers in this region showed that a common ancestral haplotype could be inferred for both pedigrees (see table E-1).

Discussion. We present the clinical, pathologic, biochemical, and genetic data of two pedigrees, with an autosomal dominant tauopathy due to a novel missense mutation (K317M) in the *MAPT* gene, the third known in exon 11.^{15,16} There are striking differences in many clinical, pathologic, and biochemical features among the effects of the three mutations in exon 11. From the clinical point of view, the presenting symptoms in the L315R mutation are anomia, memory loss, personality changes, and behavioral disorders, and in the S320F mutation the first symptom is a memory decline. In both mutations the full clinical picture is dominated by a global or frontal type dementia. In contrast, in the K317M mutation, dysarthria and tremor are the more frequent presenting symptoms, and motor features such as parkinsonism, pyramidalism, and amyotrophy are in the forefront of the developed clinical picture. The behavioral abnormalities observed in some of our patients (disinhibition, apathy, irritability, anxiety, emotional lability) were mild or moderate and never disturbed the patient's familial or social relationships. Severe disorders such as aggressiveness, sociopathic behavior, paranoia, sexual, or feeding misconduct were never observed.

From the pathologic side, Pick's bodies were found in both the L315R and S320F mutations,^{15,16} while in the K317M mutation pre-tangles and tangles were the characteristic intraneuronal phospho-tau inclusions and Pick's bodies were never seen. In the S320F mutation¹⁵ only rare coiled bodies were found in oligodendroglial cells, whereas astrocytic tau inclusions were present in the L315R mutations.¹⁶ In contrast, all types of oligodendroglial and astrocytic inclusions were particularly abundant in the K317M mutation. Finally, the tau biochemical profile of both the L315R and S320F mutations was a double band of 60 and 64 kDa, while a 64 and 68 kDa banding was found in the K317M mutation.

A wide range of interindividual variability in the clinical phenotype was observed in the course of the evolution in our patients. In some of them, a levodopa-resistant parkinsonism associated with supranuclear gaze palsy, brisk reflexes, and pseudobulbar palsy mimicked the clinical picture of progressive supranuclear palsy (PSP) as it has been observed in other tau mutations (R51, N279K, delN296, S305S).²²⁻²⁵ However, Cases 1/III-21 and 2/V-7 exhibited prominent signs of parietal involvement and their clinical picture was for some time reminiscent of corticobasal ganglionic degeneration (CBD) like in other *MAPT* mutations (N296N, P301S).^{26,27} CBD and PSP share many clinical, pathologic, biochemical, and genetic traits. At the pathologic level it has been postulated that astrocytic plaques are typical of CBD while tufted astrocytes are a histologic hallmark of PSP. Some

authors²⁸ stated that astrocytic plaques and tufted astrocytes never coexist in the same brains. However, other researchers have found atypical tauopathies with a mixed glial pathology as in our cases.^{29,30}

While a CBD or a PSP phenotype are common presentations of the tau mutations, overt motor neuron features resembling a classic ALS are unusual findings.^{1,31,32} However, pyramidalism was present in all of our patients and amyotrophy was observed in seven of them. Indeed, a typical ALS neuropathologic pattern was observed in six of seven spinal cords examined. Motor neuron loss in the spinal cord has been reported only in some cases bearing a *MAPT* mutation, and corticospinal tract degeneration is rarely mentioned.³³ Few spinal cord studies have been reported in the *MAPT* mutations. In the original family with the +14 intronic mutation associated with the disinhibition-dementia-parkinsonism-amyotrophy complex,² 3 of 13 patients had a moderate or mild pyramidal syndrome and only one had fasciculations, amyotrophy, and denervation in the EMG study, fulfilling the clinical criteria of ALS. Two spinal cords were examined and motor neuron loss in anterior horns with reactive gliosis was found in an irregular distribution, but no mention is made of a corticospinal tract degeneration. In one case with the +3 intronic mutation, some neurofibrillary tangles in the anterior horn in the upper cervical spinal cord were found but no pyramidalism or amyotrophy were observed.³⁴ Pyramidal signs are often described in patients with *MAPT* mutations but without neuropathologic correlation.^{35,36} Only in single cases with the N296N^{27,37} and the N279K mutations³⁸ has a degeneration of the corticospinal tract been neuropathologically confirmed. In the latter mutation an involvement of the anterior horn motor neurons has been found in one family.³⁹ However, amyotrophy is not described in a comparative study of the clinical features between the large original family with the pallido-ponto-nigral degeneration linked to the N279K mutation and a French family with the same mutation.^{40,41} Thus, the K317M mutation is the first familial tauopathy in which motor neuron disease is a consistent component of the clinicopathologic picture.

In the K317M mutation brains, the neuronal inclusions were stained with several phosphorylation-dependent anti-tau antibodies with the exception of phospho-tau Ser262, although this antibody recognized specific bands on Western blots. Discrepancies between immunohistochemical and Western blot results have been previously observed in other tauopathies, including Pick's disease and argyrophilic grain disease, with the phospho-specific anti-tau Ser262 antibody. Ser262 immunoreactivity in tissue sections is lost with prolonged postmortem delay and, probably, with the method of fixation, yet the epitope is visualized following treatment of the tissue samples in homogenates.⁴² This is not unimportant because

tau phosphorylation at Ser262 impairs tau-microtubule interactions and aggregation of abnormal tau-containing filaments.⁴³

The biochemical study in our Case 1/III-21 has shown two bands of phospho-tau of 68 kDa and 64 kDa in sarkosyl-insoluble fractions. This pattern is most commonly encountered in PSP, CBD, argyrophilic grain disease,^{12,21} and in missense and deletion mutations of the exon 10 in the tau gene,²⁹ yet the mutation in the present case occurs in exon 11. It is interesting to note that the biochemical study in the other two known mutations in exon 11 is characterized by two bands of 64 kDa and 60 kDa of phospho-tau reminiscent of those found in Pick's disease.^{15,16} Therefore, the neuropathology, covering distribution of cell vulnerability, neuronal inclusions, astroglial tau deposits, as well as the clinical profiles, differs between the S320F/L315R mutations and K317M mutation, although all of them affect exon 11. To date, most of the mutations found within exon 10 or its surrounding regions have been shown to increase the proportion of exon 10-containing isoforms whereas those mutations affecting other exons seem to act through a different mechanism.⁴³ To our knowledge, the mutation that we present here is the first one in an exon other than exon 10 that seems to increase the proportion of exon-10 containing tau in the intracellular deposits observed in the brain. This suggests that this particular mutation, or mutations affecting at least this part of the gene, can also produce an increase in exon 10 containing PHF either by interfering with the processing of the mRNA or by inducing specifically these isoforms to form tangles.

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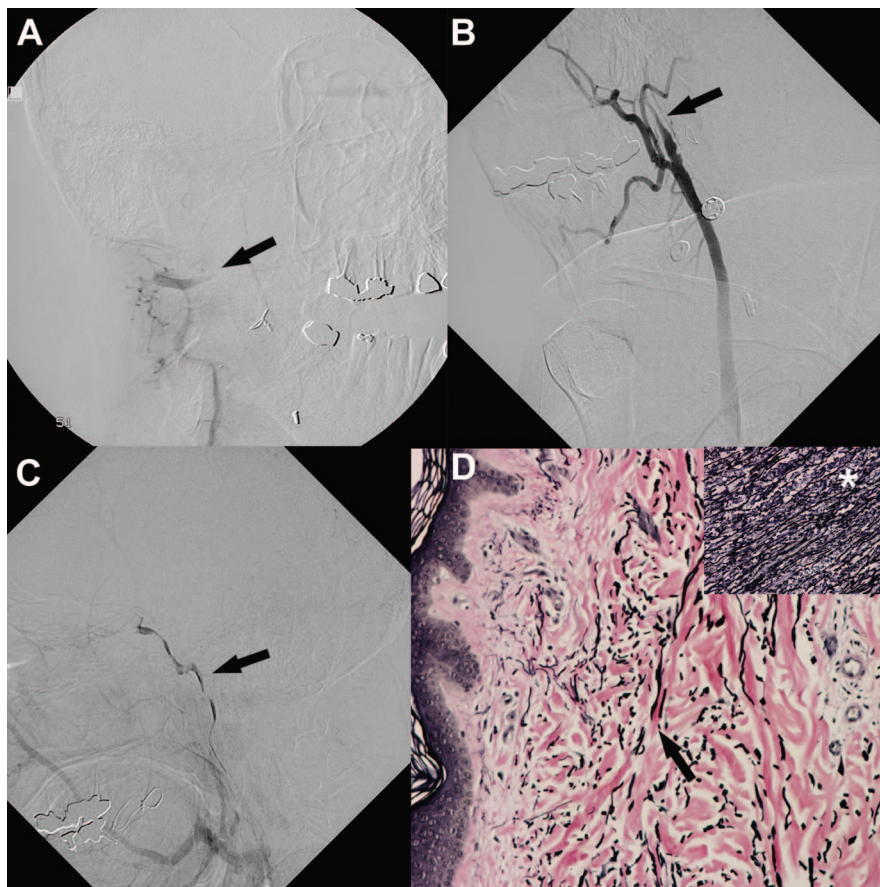
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*Figure. (A) Vertebral artery occlusion on right vertebral injection from angiogram in 1996. (B) Left extracranial internal carotid artery (ICA) dissection and occlusion noted on digital subtraction angiography, characterized by tapering of affected segment. (C) Extremely poor filling of the intracranial left ICA. (D) Skin biopsy with elastin staining (*normal elastin from aorta).*

Multiple cervical artery dissections

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A 49-year-old man with a history of bilateral vertebral artery dissections (figure, A) presented with a left internal carotid artery dissection. A new left internal carotid artery dissection was found on angiography (figure, B, C). There were no findings of connective tissue disease on examination. A skin biopsy with elastin staining

(figure, D) showed marked fragmentation. Patients with cervical artery dissections (CAD) have a risk of recurrent dissection of 1% per year.¹ Skin biopsies in patients with spontaneous CAD may show ultrastructural connective tissue abnormalities, even with no clinical disease,² but our patient demonstrated abnormalities on light microscopy.

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