17q-Linked Frontotemporal Dementia–Amyotrophic Lateral Sclerosis Without Tau Mutations With Tau and α-Synuclein Inclusions

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Background: Frontotemporal dementia (FTD) is a clinically heterogeneous condition that can be associated with clinical manifestations of an extrapyramidal disorder or motor neuron disease. A range of histologic patterns has been described in patients with FTD. The most common familial form of this condition is caused by mutations in the microtubule-associated protein tau gene (MAPτ) and is associated with neuronal or glial tau inclusions.

Objectives: To determine the clinical, anatomic, and pathological features of San Francisco family A and to map the mutation responsible for disease in this family.

Design: A systematic clinical, neuropsychologic, neuroimaging, and chromosome segregation analysis of San Francisco family A was performed. A pathological and biochemical assessment of a family member was made.

Setting: Family study.

Patients: San Francisco family A, with FTD, variable extrapyramidal symptoms, and prominent motor neuron disease. Afflicted family members do not have a MAPτ coding or splice regulatory sequence mutation, and the MAPτ is genetically excluded.

Main Outcome Measures: Comparison of clinical, neuropsychologic, neuroimaging, and linkage findings of San Francisco family A with other familial forms of FTD and amyotrophic lateral sclerosis (ALS).

Results: The most probable location for the mutation responsible for this condition is on chromosome arm 17q, distal to the MAPτ. All previously identified susceptibility loci for FTD and ALS are excluded. Autopsy findings from an afflicted family member show distinctive tau and α-synuclein inclusions. Another unique feature is that the insoluble tau protein consists predominantly of the 4R/0N isoform.

Conclusion: The condition affecting members of San Francisco family A is clinically, pathologically, and genetically distinct from previous familial forms of FTD and ALS.

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Background: Frontotemporal dementia (FTD) is a relatively common degenerative dementia with a strong genetic component. In 1994, linkage to chromosome band 17q21-22 was established in a family with autosomal dominantly inherited FTD. Soon afterward, a series of families with FTD was shown to have a similar genetic association. These families had in common multiple affected family members who manifested early-onset frontal or anterior temporal dysfunction, generally before age 50 years, and in one family, the first clinical manifestation was an atypical parkinsonian syndrome. Most of the chromosome 17-linked families were found to have disease-causing mutations in the microtubule binding domain coding or splicing regulatory sequences of the microtubule-associated protein tau gene (MAPτ) on chromosome 17. In most cases, pathology showed prominent tau-positive inclusions in neurons and glia without other disease-specific inclusions, such as β-amyloid deposits or Lewy bodies, directly linking mutations in tau to the pathology of FTD. After this exciting flurry of discoveries, it was determined that MAPτ mutations were present in only a few familial cases and almost never in sporadic forms of FTD, suggesting that other genetic or environmental mechanisms contribute to the etiology of FTD. Furthermore, in several families linked to
the 17q21-22 region, no tau mutations have been found, suggesting that a second gene close to tau or noncoding regions within the tau gene may play a role in the pathogenesis of this condition.\textsuperscript{13-15}

Despite the relative rarity of tau mutations, their discovery has helped elucidate important links between FTD and other disorders, including corticobasal ganglionic degeneration (CBD), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS). The term disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) was used to describe the first family linked to chromosome 17, pointing to the co-occurrence of cortical, basal ganglia, and motor neuron dysfunction with this disease.\textsuperscript{16} Similarly, many patients with familial or sporadic forms of the illness begin with behavioral or language disturbances and later develop movement abnormalities with features of PSP, CBD, or ALS.\textsuperscript{17-20} Still others start with a movement disorder and subsequently develop frontal lobe abnormalities.\textsuperscript{21} Even in families with known mutations in tau, there is remarkable clinical variability, with FTD described in one family member and CBD in another.\textsuperscript{21-23} Likewise, neuropathologic features vary in the genetic and sporadic forms of FTD. However, virtually all cases with MAP\textsubscript{T} mutations demonstrate intracellular accumulations of filamentous material composed of the MAP\textsubscript{T} in either neurons or neurons and glia, similar to what has been observed in many sporadic cases of FTD.

We describe the clinical and pathological features of a neurodegenerative disease in a family, referred to as San Francisco family A, whose disease is heterogeneous and linked to chromosome arm 17q but in whom a MAP\textsubscript{T} mutation was excluded by direct sequencing and chromosome segregation analysis. In contrast to the other kindreds whose disease is linked to this chromosomal region, in San Francisco family A motor neuron disease was a prominent clinical feature and was responsible for many deaths. The pathological characteristics in this family are distinctive, with both tau and \textalpha;-synuclein (\textalpha;-syn) inclusions in the anterior temporal lobes, limbic system, basal ganglia, and brainstem. Also unique is the finding of insoluble tau consisting predominantly of the 4R/ON isoform (i.e., the tau isoform with 4 microtubule repeats and no amino terminal inserts), localized almost exclusively to the affected regions of the brain. In addition to extending the spectrum of clinical FTD syndromes associated with a locus on chromosome 17 to include motor neuron disease, this study provides the first description of \textalpha;-syn and 4R/ON tau pathology in a family with FTD linked to chromosome 17.

METHODS

CLINICAL EVALUATION AND DESIGNATION OF AFFECTED AND UNAFFECTED FAMILY MEMBERS

Extensive clinical evaluation was pursued for every member of San Francisco family A from whom blood samples could be obtained for genetic testing. All clinical evaluations were conducted at the Memory and Aging Center at the University of California at San Francisco (UCSF) in San Francisco or at the UCSF-Fresno Alzheimer’s Disease Center. Neurologists (B.L.M., K.C.W., and L.I.A.) obtained a history and performed a neuropsychologic examination. Neuropsychologists (K.P.R. and J.H.K.) tested family members by using a 2-hour test battery designed to assess a broad range of cognitive functions, including memory, language, visuospatial, and executive function.

Selected family members also underwent magnetic resonance imaging (MRI) and electromyographic and nerve conduction velocity testing to look for evidence of motor neuron disease. Magnetic resonance imaging consisted of a double spin-echo sequence (repetition time/echo time/echo time\textsubscript{1}/echo time\textsubscript{2} = 5000/20/80 milliseconds) to obtain proton-density and T2-weighted images and a volumetric magnetization–prepared rapid gradient-echo MRI (repetition time/echo time/inversion time = 10/4/300 milliseconds) to obtain T1-weighted images of the entire brain; MRI was performed on all family members willing to undergo this test.

Because there was a clear history of dementia and motor neuron disease in several members of San Francisco family A (Figure 1), patients underwent a complete neuromuscular examination. In 7 patients with neuromuscular symptoms, electromyographic studies were performed. At the time of the first evaluation, 2 living members of San Francisco family A were diagnosed as having ALS, and several others were also known by family members to manifest unusual personality traits suggestive of a frontal disorder, but no individuals were as yet diagnosed as having dementia.

To classify family members, we used findings from a recent study\textsuperscript{20} of another family with a known P301L mutation in exon 10 in which it was discovered that carriers of the MAP\textsubscript{T} mutation demonstrated frontal executive deficits by the third decade of life, although dementia did not typically manifest until the sixth decade of life. Based on this finding, we hypothesized that neuropsychologic testing would be sensitive to the effects of a genetic mutation, even in patients without clinical evidence of overt dementia. Thus, the designation of affected vs unaffected individuals depended on the following criteria: (1) clinical features satisfying the research criteria for FTD outlined by Neary and colleagues,\textsuperscript{20} (2) clinical evidence of motor neuron disease (documented by clinical examination and electromyographic testing), (3) clear evidence of major behavioral disorder with profound apathy or sociopathy, (4) clear and persistent deficits in executive function on neuropsychologic testing, or (5) any combination of these features. Because some of these criteria involve a degree of subjective judgment, an additional variable was scored, indicating the degree of confidence with which the designation was being made, at 3 levels: class 1, definitely affected with either FTD or motor neuron disease or definitely unaffected and older than 65 years; class 2, probably affected on the basis of deficits in executive function greater than 1.5 SD from normal or probably normal and aged 30 to 65 years; and class 3, possibly affected but unclear owing to the presence of mild executive dysfunction or behavioral disturbances, or possibly unaffected and younger than 30 years. These classifications were used to weigh each individual’s contribution to the linkage analysis, as described in the following subsection.

One member of this family (case II:5) died less than 6 months after initial assessment. This patient’s pathological characteristics proved highly informative and is described in the “Results” section. In addition, we describe the clinical history and neuropsychologic assessment in the 5 patients from this family seen by members of our team (B.L.M., K.C.W., L.I.A., K.P.R., and J.H.K.) who were rated as class 1 (definitely affected).

LINKAGE ANALYSIS AND MAP\textsubscript{T} SEQUENCING

DNA was isolated from blood samples of 24 family members using a DNA purification kit (Puregene; Gentra Systems Inc, Minneapolis, Minn). DNA was genotyped for 811 microsatel-
and Research Center. All the pooled amplimers from a single individual were subjected to capillary electrophoresis after standards were added to each pool in a single run of an automated DNA sequencing machine (model ABI3700; Applied Biosystems). The sizes of the 811 amplimers relative to internal standards were determined using a software program (Genotyper; Applied Biosystems), masked to pedigree structure and phenotype. Alleles were binned with a collection from 660 white patients from another study using an automated protocol developed at the Ernest Gallo Clinic and Research Center that assumes a sine-squared distribution of alleles. Population marker allele frequencies were estimated from the population of 660 white patients from 200 families. Nine markers were excluded from further analysis because of a high frequency of genotypes inconsistent with other family members.

Family structure and sample identity were tested by confirming sex based on X-linked markers and the degree of allele sharing between all pairs of relatives using a software program (PREST). PedCheck was used to identify genotypes that were inconsistent with the genotypes of other relatives. All problematic genotypes were reviewed masked to phenotype but not to family structure. Genotype problems that could not be resolved by inspection were removed from final analysis (<0.2% of all genotypes). To further reduce genotype errors, genotypes that were determined to have a probability of error greater than 0.25 when analyzed as part of haplotypes, using SimWalk2, were removed from the analysis (<0.1% of genotypes).

Multipoint logarithm of odds (LOD) scores were calculated using SimWalk2 assuming a disease allele frequency of 0.00001 and a variable penetrance rate dependent on the confidence in the clinical diagnosis. The penetrance rates assumed for each diagnosis class for individuals with 0, 1, or 2 disease alleles were assumed to be 0.0001, 0.9999, and 0.9999 for class 1; 0.1, 0.6, and 0.6 for class 2; and 0.2, 0.4, and 0.4 for class 3. The most probable haplotypes were determined independent of phenotype using routines implemented in SimWalk2.

Each of the MAPt coding sequence exons were amplified by means of polymerase chain reaction and sequenced as previously described elsewhere.

NEUROPATHOLOGIC ASSESSMENT

The brain tissue of the previously referenced affected member of San Francisco family A was fixed in 10% formalin, paraffin embedded, and cut into 6-μm-thick sections. For thioflavine S staining to visualize taut tangles or other types of amyloid deposits, rehydrated sections were immersed in 0.05% potassium permanganate in phosphate-buffered saline solution for 20 minutes and then differentiated in 0.2% potassium metabisulfite and 0.2% oxalic acid in phosphate-buffered saline solution. Subsequently, the slides were immersed in 1% thioflavine S in the dark for 3 minutes and further differentiated in 50% ethanol in phosphate-buffered saline solution, rinsed, and mounted. Immunohistochemical analysis was carried out using anti–α-syn monoclonal antibodies Syn 303 and Syn 203, and anti–tau monoclonal antibodies PHF1 and AT8 with or without pretreatment with 88% formic acid, as described elsewhere. Immunostaining was visualized using an avidin-biotin complex detection system (Vectastain ABC Kit; Vector Laboratories, Burlingame, Calif) and 3,3′-diaminobenzidine as chromogen followed by counterstaining with hematoxylin-eosin.

Insoluble tau was extracted from fresh or frozen brain tissue, as described elsewhere. Briefly, the insoluble pellets were homogenized in 1M sucrose in Tris-buffered saline solution (50mM Tris, pH 7.6, 750mM sodium chloride, 10mM ethyl-
Table. Clinical Features of Class 1 (Definitely Affected Family Members)

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>II:5</td>
<td>Dementia, parkinsonism</td>
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<tr>
<td>II:6</td>
<td>Motor neuron disease, FTD</td>
</tr>
<tr>
<td>III:1</td>
<td>Executive dysfunction, “schizophrenia”</td>
</tr>
<tr>
<td>III:4</td>
<td>Motor neuron disease, FTD</td>
</tr>
<tr>
<td>III:6</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>III:7</td>
<td>Progressive (over 1 y) executive dysfunction</td>
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Abbreviation: FTD, frontotemporal dementia.

Case III:4

A right-handed woman was first seen at UCSF at age 58 years. She completed an associate in arts degree, married, and worked successfully as a businesswoman until her mid-40s when she retired. At age 55 years, she exhibited a combination of irritability, disinhibition, and apathy, insulting family and strangers. Compulsive collecting started, and she became fiscally irresponsible. At age 56 years she noticed slurred speech and, soon afterwards, developed difficulty with swallowing. She was completely aphonic and unable to swallow by age 57 years, and a gastrostomy tube was placed. Walking difficulty and arm weakness began at age 57 years, and she began to use a wheelchair to get around a few months before our assessment. Six months before assessment, she complained of memory difficulty and required help with activities of daily living. Her neurologist made a diagnosis of ALS after performing electromyography. On examination, she was a slightly euphoric woman who communicated via a talking computer. She insulted physicians and other family members. Her Mini-Mental State Examination score was 28 of 30. She showed significant deficits on the Wisconsin Card Sorting Test, California Card Sorting Test, Trail-Making Test, and Tower Test. She was concrete on proverbs interpretation. Cranial nerves were normal except for symmetrical facial weakness, an absent gag reflex, and no tongue movement. Motor examination revealed atrophic hand muscles, fasciculation in the triceps muscles, and increased tone in both legs. She exhibited symmetrical 4/5 (4 on a scale of 5) weakness throughout except for foot extensors that were 2/5. Arm reflexes were normal, knee and ankle reflexes were 3+/4, and she had a Babinski sign. She refused to undergo MRI but had previously undergone computed tomography, which showed marked bifrontal atrophy. A diagnosis of FTD with ALS was made. She died within a few months of our assessment, and her family denied an autopsy.

Case III:6

The brother of Case III:4 was a 54-year-old right-handed man with a 3-year history of progressive weakness in his arms and legs who was diagnosed 2 years earlier as having ALS. One year before examination he required a wheelchair for ambulation and was having difficulty with hand strength. He continued to work as a mechanic and to build cabinets at his home at the time of our assessment. There was no history of disinhibition.
or behavioral disturbance, but his thinking had slowed and he was becoming socially withdrawn. On examination, he was pleasant and cooperative. Neurologic examination revealed normal cranial nerves. Up gaze was slightly diminished, but cranial nerves were otherwise normal. Arms and legs were 4−/5 in strength. Reflexes were pathologically brisk, and he had a Babinski sign. His Mini-Mental State Examination score was 18 of 30. Neuropsychologic examination revealed mild verbal and visuomotor memory deficits and profound deficits on word generation, using the Wisconsin Card Sorting Test, the Stroop color test, and letter fluency. Electromyography showed acute and chronic denervation, with reinnervation in muscles innervated by more than 1 nerve or root in multiple limbs. A diagnosis of FTD with ALS was made. Brain MRIs showed extensive frontal atrophy compared with those of his older but unaffected brother (Figure 2).

Case II:5

The patient was a 76-year-old right-handed man who was institutionalized at the time of our initial assessment. He was described as an unusual child who had difficulty getting along with others. At age 12 years he would put a string across his driveway and knock children off their bicycles. He enlisted in the US Army but was hospitalized because of a depressive episode. He worked for a decade as a roofer, but he stopped working because of a pre-}

reductive posttraumatic stress disorder at approximately 40 years of age. A diagnosis of schizophrenia was made when he was in his 50s, and he was institutionalized in his late 50s, requiring help with activities of daily living. He began to develop problems with movement and swallowing in his eighth decade of life. He became mute in the year before our assessment. On examination, case II:5 was a quiet, thin, elderly gentleman with a flat and blunted affect. He had a sparse and dysarthric output that was not comprehensible. He did not follow simple commands. On examination, he had marked bradyphrenia and bradykinesia, with moderate axial rigidity and mild limb rigidity. He had diminished up gaze and right lateral gaze. Down gaze was normal. Gag reflex was decreased, and he drooled profusely. Muscles were diffusely weak, and he had a parkinsonian tremor in both hands (right worse than left). His reflexes were normal, and a Babinski sign was absent. A diagnosis of FTD with PSP-like features was made. Case II:5 died within a year of our assessment. The autopsy findings are described in detail in the “Neuropathologic Assessment” subsection.

MAPτ SEQUENCING

Resequencing of the MAPτ exons and splice donor and acceptor sequences in 3 affected individuals did not identify any known or novel sequence changes. It is formally possible that noncoding sequence changes in the MAPτ sequence that were not resequenced could lead to disease.

GENETIC ANALYSIS

Multipoint chromosome segregation analysis based on the final clinical diagnoses indicates that the most probable location for the mutation in this family is on chromosome 17 between markers D17S1862 and D17S928. The multipoint LOD score for this region (based on the individuals who were either definitely affected or definitely unaffected) is 2.05. No other location in the genome gave a multipoint LOD score greater than 1, including the regions implicated in FTD and ALS on chromosomes 3, 9, and 22. Including the phenotype of individuals with a diagnosis designation of class 2 or 3 increased the multipoint LOD score to 2.95. No other chromosome location gave a multipoint LOD score greater than 1.0. This region is approximately 30 cM, which is 11 million base pairs of DNA length.

The MAPτ is centromeric to the linkage support region identified by this analysis. Inspection of the haplotypes indicates that at least 1 individual has an incorrect diagnosis if MAPτ mutations are responsible for disease in this family (Figure 1). It is possible that recombination events that were not detected could obscure the location of the mutation responsible for disease in this family.

NEUROPATHOLOGIC ASSESSMENT

Case II:5 from this family came to autopsy at age 77 years. Results of postmortem examination revealed an 1180-g brain with marked atrophy of the anterior aspects of the superior temporal gyrus and mild atrophy of the frontal lobe. On coronal sectioning, there was marked atrophy of the anterior aspects of the superior and middle temporal gyri, with gray discoloration of the underlying white matter. The lateral ventricles were moderately dilated. The hippocampus and amygdala were severely atrophic. In addition, there was depigmentation of the substantia nigra and the locus ceruleus. The remainder of the brainstem and the subcortical nuclei were normal.

Microscopic examination revealed superficial microvacuolation, neuron loss, and gliosis in the anterior aspects of the superior and middle temporal gyri and entorhinal cortex with occasional balloononed neurons (Figure 3A). There was also prominent neuron loss and gliosis in the amygdala and hippocampus and in the substantia nigra and locus ceruleus (Figure 3B). Scattered residual pigmented neurons in the substantia nigra and locus ceruleus contained eosinophilic inclusions that dis-
placed the neuromelanin (Figure 3J). Most of these inclusions lacked the morphologic features of classic Lewy bodies. Thioflavine S staining revealed rare globose tangles in the brainstem but was otherwise negative for neurofibrillary tangles, senile plaques, and amyloid angiopathy (Braak stage 0).

Immunohistochemical analysis using antibodies to α-syn revealed a moderate-to-dense burden of cortical Lewy bodies and Lewy neurites in the temporal cortex and limbic structures, including the hippocampus, amygdala, entorhinal cortex, and cingulate gyrus (Figure 3G and H). There was also abundant α-syn–positive pathology throughout the brainstem consisting of Lewy bodies and Lewy body–like cellular inclusions and dystrophic neurites (Figure 3I and M). In the brainstem, the α-syn–positive pathology was most abundant in the pars compacta of the substantia nigra (Figure 3I), oculomotor nucleus, locus ceruleus, tegmentum of pons, and dor-

Figure 3. Tau and α-synuclein (α-syn) pathology. A, Superficial microvacuolation, neuron loss, and gliosis in the entorhinal cortex (hematoxylin-eosin). B, Marked neuron loss in the pars compacta of the substantia nigra (hematoxylin-eosin). C-E, A high density of tau pathology consisting of grains and threads in the gray (C) and white (D) matter of the superior temporal gyrus and in the entorhinal cortex (E). Insets show high-power magnification of grains in gray and white matter and in coiled body–like inclusions in white matter (D) (anti–tau monoclonal antibody PHF1). F, Tau pathology in locus ceruleus is composed of dystrophic neurites and globose tangle–like inclusions. Inset shows high-power magnification of neuronal inclusions (anti–tau monoclonal antibody AT8). G through I, α-syn pathology in the superior temporal gyrus (G), amygdala (H), and pars compacta of the substantia nigra (I). Numerous α-syn–positive Lewy bodies (arrowheads) and Lewy neurites are noted throughout (anti–α-syn monocular antibody Syn 303). (The same magnification was used in A through I.) J, Pale eosinophilic inclusion displacing nucleus and neuromelanin in pigmented neuron of the substantia nigra (hematoxylin-eosin). K and L, Tau pathology in the temporal cortex shows the morphologic features of tufted astrocytes (K) and balloononed neurons (L) (PHF1). M, High-power magnification of α-syn–positive Lewy bodies (arrow) and dystrophic neurites (arrowheads) in the substantia nigra (Syn 303). (The same magnification was used in J through M.)
matter was composed of 2 major protein bands of approximate 64 and 68 kDa. The insoluble tau in gray and white forms were similar to that observed in normal brain tissue white matter, and the relative proportions of the 6 tau isoforms are indicated to the right of the panel. Molecular weight standards are as indicated to the left of the panel. The row marked with deP indicates whether a sample in the lane is native or dephosphorylated.

To further analyze the tau pathology, we performed Western blot analysis of soluble and insoluble fractions (indicated by deP) extracted from gray (G) and white (W) matter of the temporal lobe were resolved by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and immunoblotted with T14. For gray and white matter, 20 μL of insoluble extract was loaded in each lane that represents approximately 20 mg of tissue. The insoluble tau protein is composed predominantly of 2 major proteins of 64 and 68 kDa. The insoluble tau fractions from gray and white matter comigrate predominantly with the 4R/0N tau isoform. Prolonged exposure of the immunoblot revealed a minor protein that comigrated with the 4R/1N tau isoform. Recombinant tau (rTau) isoforms are indicated to the right of the panel. Molecular weight standards are as indicated to the left of the panel. The row marked with deP indicates whether a sample in the lane is native or dephosphorylated.

San Francisco family A has distinctive clinical, genetic, and neuropathologic features, all of which broaden the spectrum of phenotypes and genotypes associated with FTD. More than twice as many markers were genotyped for San Francisco family A compared with typical genome scans. This high-density genotyping allowed us to systematically search the entire genome for linkage. The likely chromosomal location of the mutation that causes the disease that occurs in San Francisco family A is 17q, distal to MAPT. The evidence that there is a locus on 17q that produces this disease is below the customary threshold for significance used for linkage analysis for autosomal dominant traits. All other locations in the genome were 10-fold less likely. It is possible that misdiagnosis of several family members due to either the presence of phenocopies or incomplete penetrance could obscure the chromosomal location of the mutation responsible for disease in this family. Other families with inherited FTD linked to chromosome 17 have been identified that do not have MAPT mutations, such as hereditary dysphasic disinhibition dementia and familial FTD with ubiquitin-positive inclusions, as noted earlier. It is possible that the gene mutated in San Francisco family A is also mutated in these disorders. This linkage result should be used as a candidate locus for other families with FTD and ALS.

Clinically, many members of this family exhibited early-life manifestations of frontal and anterior temporal lobe dysfunction, with decades of psychiatric and behavioral disturbances seen before the onset of FTD or ALS. Disinhibition, mood, affect, and thought disorders often were evident by middle childhood; loss of employment and disruption of social relationships occurred by the third, fourth, or fifth decades of life; and FTD or ALS was observed in the sixth decade. Often, gene carriers were diagnosed as having either bipolar illness or schizophrenia early in life. Amyotrophic lateral sclerosis typically began in the fifth or sixth decade of life, and 3 patients seen by UCSF and UCSF-Fresno investigators met El Escorial research criteria for ALS; all 3 died of this illness within a few years of initial diagnosis. In one family member, who lived into his eighth decade of life, clinical manifestations of ALS never emerged, but a PSP-like syndrome was present shortly before death.

There are remarkable clinical parallels between San Francisco family A and 2 other families in whom mutations have been found in an intron (DDPAC family) and...
exon (Montreal family) of MAPT10,11 As with the DDPAC and Montreal families, San Francisco family A gene carriers had behavioral and executive deficits evident early in life, before expression of a frank dementia. These early deficits were helpful in linking San Francisco family A to chromosome 17, and we based our genetic classification system on the finding by Geschwind and colleagues44 that MAPT mutation carriers exhibit frontal executive deficits decades before the age at risk for dementia. These previous studies in conjunction with the findings in our family members demonstrate that FTD can have a long clinical prodrome during which behavioral deficits secondary to frontal and anterior temporal dysfunction profoundly impact a patient’s day-to-day function without necessarily reaching the threshold for the diagnosis of dementia. However, in contrast to the DDPAC and Montreal families, San Francisco family A did not have a MAPT mutation, at least not in the regions of MAPT examined in this study.

It was the familial predilection for ALS, not dementia, that first brought this family to neurologic attention and triggered testing for a superoxide dismutase mutation. Testing proved negative for known mutations. The coassociation of FTD and ALS has been reported in sporadic and familial ALS, but most patients with FTD and ALS show ubiquitin-positive inclusions,59 not the tau-positive neuronal inclusions seen in San Francisco family A. The only previously reported family with MAPT mutations in whom motor neuron deficits were described was the DDPAC family,10 although only 4 of 13 patients had evidence of amyotrophy, and none exhibited the classic findings for ALS that were evident in San Francisco family A. Unlike other patients with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) in whom subtle motor deficits were evident, most patients in San Francisco family A visited physicians for ALS. Thus, this family broadens the spectrum of neuropathologic findings seen with FTD-ALS and suggests that there are other genetic mutations that predispose to this disorder.

Another feature of San Francisco family A is the PSP-like syndrome that developed in the patient who came to pathology. This individual seemed to pass the age of risk for ALS but manifested clinically the co-occurrence of FTD and PSP. The distribution of the pathology was consistent with the clinical syndrome, with neurodegeneration of the temporal lobe, limbic system, basal ganglia, and brainstem. However, this patient’s brain showed combined features of an α-synucleinopathy and tautopathy. The α-syn pathology most closely resembled diffuse Lewy body disease,38 and the tau pathology was not readily classifiable but was reminiscent of argyrophilic grain disease and CBD.36-37

The convergence of tau and α-syn pathology is becoming increasingly recognized.38,39 For example, tau pathology is detected at least focally in the brains of most patients with diffuse Lewy body disease.39 Moreover, the Contursi kindred with the A53T mutation in α-syn shows abundant tau pathology throughout the brain.38 Similarly, the brain from patient II:5 from San Francisco family A has abundant tau and α-syn pathology in an overlapping topographic distribution, but with linkage to a novel site on chromosome 17. In addition, the 4R/0N insoluble tau seen in this patient has not been reported be-

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