Clinical Features and Disease Haplotypes of Individuals With the N279K tau Gene Mutation

A Comparison of the Pallidopontonigral Degeneration Kindred and a French Family

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Background: An N279K missense mutation in exon 10 of the tau gene reported in an American family with pallidopontonigral degeneration (PPND family) was recently found in members of a French kindred with dementia and supranuclear palsy.

Objectives: To compare clinical phenotypes of both families and to perform genealogical and molecular genetic studies to determine whether they are derived from a common founder.

Design and Methods: We performed clinical examinations of affected members of both families and compared clinical phenotypes, existing genealogical family records, and chromosome 17 microsatellite repeat markers in the vicinity of the tau gene.

Results: The inheritance pattern is autosomal dominant in the PPND family and appears so in the French family. Average age at onset of clinical symptoms was 43 years in the PPND family and 41 years in the French family. Mean disease duration was 8 years in the PPND family and 6 years in the French family. Parkinsonism, personality changes, and dementia of the frontotemporal type were seen in both kindreds. All affected patients exhibited rapidly progressive parkinsonism characterized by bradykinesia, tremor, postural instability, and rigidity. Some had a transient response to levodopa therapy during the initial stages. Pyramidal signs and eye movement abnormalities, including supranuclear gaze palsy, were common. Results of linkage studies of the tau region in chromosome 17 did not reveal a haplotype common to both kindreds.

Conclusions: Affected members from both families had more clinical similarities than differences. Results of genealogical and molecular genetic studies determined that the families were not related. The N279K mutations found in both families have independent origins.

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PALLIDOPONTONIGRAL degeneration (PPND) is a hereditary neurodegenerative syndrome that belongs to the group of disorders called frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).1-3 Pallidopontonigral degeneration was found in an American family (the PPND family) that can be traced back for more than 200 years. This kindred is the largest and most thoroughly investigated of all families with FTDP-17. Pallidopontonigral degeneration is an autosomal dominant disorder with early onset of rapidly progressive symptoms. Results of molecular genetic studies in affected individuals have demonstrated the presence of an N279K missense mutation in exon 10 of the tau gene in chromosome 17.4 This mutation causes increased splicing-in of exon 10 and a corresponding increase in the proportion of tau with 4 microtubule-binding repeats (4R tau), which is sufficient to cause neurodegeneration.4

Recently, the same missense mutation was found in members of 1 French6,7 and 2 Japanese families.8,9 The objectives of the present study were to compare the clinical phenotypes of the original PPND family with those of the French family and to determine whether these 2 kindreds are genealogically and genetically related.

RESULTS

FINDINGS IN BOTH FAMILIES

The pedigrees of both families are presented in Figure 1, and the clinical fea-
The pedigree of the PPND family has 311 members and spans 8 generations. Of 39 affected individuals, 19 were examined by one of us (Z.K.W.). The pedigree of the French family has 28 members. Of 3 affected individuals, 2 were examined by one of us (O.R.). We based clinical comparisons of affected members from the 2 families on the review of published reports and results of personal examinations of individuals (from both kindreds) by one of us (Z.K.W.). We used the Mini-Mental State Examination (MMSE) for evaluation of cognitive status.

Informed consent was obtained from all participants after the nature of the procedures was fully explained.

We extracted DNA from blood samples drawn from 3 affected individuals of the PPND family, from their 3 respective spouses, and from 8 unaffected or at-risk family members; the samples had been systematically collected by one of us (Z.K.W.) since 1987. The DNA was also extracted from brain tissue of 1 affected individual from the French family.

We analyzed 10 microsatellite repeat markers spanning 16 centimorgans of chromosome 17 that included the tau gene region in individuals from both families. The genotypes of these markers were generated by means of analysis of fluorescently tagged polymerase chain reaction (PCR) products using an automated sequencer with Genescan/Genotyper software (ABI 377; Perkin Elmer, Norwalk, Conn).

The PCR analysis included 25 ng of DNA in a 15-µL reaction mixture containing 6 pmol of each primer, 0.2mM deoxyribonucleotide triphosphates, 1 U of Taq polymerase (Qiagen, Valencia, Calif), 1X PCR buffer, and 10% PCR enhancer (Q-solution; Qiagen). The oil-free amplifications were performed in Touchdown thermal cyclers (ThermoHybaid, Franklin, Mass), for 35 cycles of 94°C for 30 seconds, 58°C to 48°C touchdown annealing for 30 seconds, and 72°C for 45 seconds, with a final extension of 72°C for 10 minutes. Forward primers for each marker were labeled at the 5′ end with 6-carboxy-fluorescein (FAM)–, tetrachloro-6-carboxy-fluorescein (TET)–, or hexachloro-6-carboxy-fluorescein (HEX)–fluorescent dye; reverse markers were unlabeled.

Alleles were scored for fragment length (base pairs) using the Genotyper software for the following markers: D17S798, D17S1294, D17S1293, D17S800, D17S1860, D17S791, D17S806, D17S1299, D17S1868, and ATC6A06. Centre d’Etude du Polymorphisme Humain (CEPH) samples 1331-01 and 1331-02 were run as standards (available at: http://www.cephb.fr/cephdb). Once the genotypes were obtained for each marker, the PPND haplotype was compared with marker information from the French family to investigate the possibility of a common founder for the N279K mutation.

Parkinsonism, personality changes, and dementia of the frontotemporal type were seen in both kindreds during the course of illness. Initial symptoms almost always included parkinsonian features in both families. The parkinsonism was characterized by the presence of bradykinesia, rigidity, and postural instability. Resting tremor was sometimes encountered, usually at the initial stages of the clinical manifestation and always as a transient feature. Response to levodopa and dopamine agonist therapy was limited to the initial stages of clinical presentation in both kindreds.

The personality changes often occurred at the onset of symptoms, sometimes concomitantly with parkinsonism and sometimes a few weeks or months later. These changes are characterized by relatively minor behavior aberrations, such as irritability, excessive religiosity, or other minor changes in most cases. However, violent behavior was present in 2 affected members of the PPND family. Dementia of the frontotemporal type was seen in all affected individuals of both families and was characterized by impairments in cognitive processing and verbal and visual memory and by diminished cognitive flexibility. Dementia almost always occurred in the later stages of the disease. However, because of the profound motor impairment and mutism, full exploration of cognitive functions in the later stages of the disease was not possible.

Other clinical features included pyramidal signs; dystonia (unrelated to medications); eye movement abnormalities such as supranuclear gaze palsy, eyelid opening and closing apraxia; perseverative vocalization; and urinary incontinence (Table 1 and Figure 1). The clinical course of the disease is relentlessly progressive and can be delineated into 4 stages (Table 2). The mean disease duration for affected individuals was 8 years (range, 5-19 years) for the PPND family and 6 years (range, 5-7 years) for the French family.

Genealogically, the PPND family is an American kinred traced back to the Crown Colony of Virginia in the 18th century. We were not able to trace the origin of this family to France, and most settlers of this colony were English. The French family has long resided in southern France. Available family records and historical notes do not indicate that any family members emigrated to the New World. Thus, we found no genealogical connections between these 2 families.

Polymorphic marker analyses covering the tau gene region in chromosome 17 did not reveal shared disease haplotypes between the 2 families (Table 3). However, a common mutation-bearing haplotype for the markers D17S1294, D17S1293, D17S800, D17S1860, D17S791, D17S806, and D17S1299 was shared in the 3 affected patients from the PPND family.

ILLUSTRATIVE CASE REPORTS

Case 1

Stooped posture became apparent in a 57-year-old right-handed man (V:26 of the PPND family) (Figure 1). The symptoms was 43 years (range, 32-58 years) in the PPND family and 41 years (range, 38-45 years) in the French family.

The inheritance pattern was autosomal dominant in the PPND family and most likely in the French family. The average age at onset of clinical symptoms was 43 years (range, 32-58 years) in the PPND family and 41 years (range, 38-45 years) in the French family.

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change in posture was noted by his neighbors, who brought it to the attention of his wife. Six months later, his supervisor at work sent him to the factory physician. His movements had become slow, and the supervisor was
concerned that he would injure himself while operating electrical tools. The patient’s balance also deteriorated, and this led to occasional falls. He was examined at his home by one of us (Z.K.W.) about a year after the onset of his symptoms. At that time, features of parkinsonism, including rigidity, bradykinesia, and postural instability, were documented. Resting tremor was absent, but postural tremor was present in both upper extremities. He was excessively emotional, crying easily and becoming withdrawn. His MMSE score was 25 of 30 points; he missed 4 points on the calculations and 1 point on the recall scales. Shortly after this evaluation, he was treated with levodopa, without any significant change in his parkinsonian features.

The patient was reexamined 18 months later, at 59 years of age. His parkinsonism was noticeably worse. His posture was stooped and his head was bent forward (Figure 2). His face was masklike and his voice was hypophonic. Muscle rigidity was expressed more in axial than in appendicular muscles. His speed in performing repetitive movements was impaired. Resting tremor was again absent, but postural tremor was still present. His family reported several episodes of violent behavior, but at the time of examination, his behavior and mood were

Table 1. Characteristics, Symptoms, and Signs in the Family With Pallidopontonigral Degeneration (PPND) and the French Family With the N279K Mutation of the tau Gene

<table>
<thead>
<tr>
<th>Feature</th>
<th>PPND Family</th>
<th>French Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Crown Colony of Virginia</td>
<td>Southern France</td>
</tr>
<tr>
<td>No. of generations</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>No. of family members</td>
<td>311</td>
<td>28</td>
</tr>
<tr>
<td>No. of affected members</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>M:F ratio of affected</td>
<td>17:22</td>
<td>2:1</td>
</tr>
<tr>
<td>Inheritance pattern</td>
<td>Autosomal dominant</td>
<td>Most likely autosomal dominant</td>
</tr>
<tr>
<td>Penetrance</td>
<td>High</td>
<td>Most likely high</td>
</tr>
<tr>
<td>Average age at disease onset, y</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Average disease duration, y</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>First symptom</td>
<td>Parkinsonism, personality changes, or both</td>
<td>Parkinsonism, personality changes, or both</td>
</tr>
<tr>
<td>Features of parkinsonism</td>
<td>Bradykinesia, rigidity, postural instability, mixed tremor with postural and resting components in some patients in the initial stages of disease, partial and only transient response to levodopa and dopamine agonist treatment in the initial stages of the disease</td>
<td>Bradykinesia, rigidity, postural instability, atypical mild resting and postural tremor in only 1 patient, partial and transient response to levodopa and ropinirole hydrochloride</td>
</tr>
<tr>
<td>Personality changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Violence</td>
<td>Present in only 2 patients in the initial stages of disease and characterized by physical abuse of spouse</td>
<td>Episode of anger in 1 patient, no verbal or physical spouse abuse</td>
</tr>
<tr>
<td>Depression</td>
<td>Present in only 1 patient</td>
<td>Not present</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>Present in 1 patient</td>
<td>Present in 1 patient</td>
</tr>
<tr>
<td>Substance abuse or alcoholism</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>Occasionally present</td>
<td>Not present</td>
</tr>
<tr>
<td>Compulsive behavior</td>
<td>Present</td>
<td>Present in 1 patient</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Dementia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Eye movement abnormalities</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Eyelid opening and closing apraxia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Perseverative vocalizations</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Joint contractures</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Anosmia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Sensory impairment</td>
<td>Present in only a few patients</td>
<td>Not present</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Seizures</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Sensitivity to neuroleptics</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Dysarthria and mutism</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Weight loss and cachexia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Drooling</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>After disease onset, prolonged healing of simple scratches or skin cuts</td>
<td>Not reported</td>
<td>Present in 1 patient (skin biopsy site needed 1 y to heal)</td>
</tr>
<tr>
<td>Edema</td>
<td>Not reported</td>
<td>Hands and feet; night rest produced no benefit, but local massage and exercise led to some improvement</td>
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</tbody>
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stable. He denied having depression. On the MMSE test, he scored 22 of 30 points, missing points on the orientation, calculations, and recall scales. He had frontal lobe release signs, including glabellar and palmmontal reflexes. His tendon reflexes were brisk but symmetrical. He had equivocal Babinski sign bilaterally.  

Case 2  
This right-handed man (VI:9 of the PPND family [Figure 1]) reported that he first noticed a tremor in his right leg at 40 years of age. When he was driving an automobile, his left leg would sometimes feel stiff and occasion-
ally shake. His wife noted that when he turned his body, his turning had become en bloc. At 41 years of age, he had a shuffling gait with reduced arm swing. His facial expression changed little, and he had prominent drooling. He had resting tremor in both legs (the left more than the right) and occasionally in his hands. His balance deteriorated steadily. He experienced many falls throughout the day and had difficulty standing up. His balance was better in the morning than in the evening. Treatment with a combination of carbidopa and levodopa did not benefit him.

At 44 years of age, the patient reported generalized stiffness in the muscles of his neck, tongue, and extremities. The stiffness was more pronounced in the afternoon and 3 hours after he had taken levodopa. The tremor in his legs (particularly the left one) was also worse several hours after levodopa administration. He reported frequent yawning and chewed gum constantly to avoid yawning and to reduce excessive drooling. He was still independent in almost all daily living activities, but his wife had to help him occasionally with cutting food. On examination, his MMSE score was 30 of 30 points, with difficulties on visuospatial and attention deficits, but he was still independent in all daily living activities. Bradykinesia, rigidity, and apathy were noted. He was treated with selegiline hydrochloride and a combination of carbidopa and levodopa. His symptoms improved during the initial 6 months of treatment but then worsened; his work performance also deteriorated. Eyelid-opening apraxia and frontal lobe release signs developed. At 43 years of age, his MMSE score was 25 of 30 points, with difficulties on the scales for orientation, calculations, and recall. His eyes were fixed in a neutral position, with absent vertical gaze and slow horizontal gaze. Oculocephalic maneuvers were normal. His posture was stooped and he had a masklike face. His speech was soft and slow. He was able to say only a few words. He was rigid, especially on the left side of the body. Frontal lobe release signs, including glabellar and palomental reflexes, were present. He also had hyperreflexia and bilateral Babinski sign. He walked with assistance from his wife. He shuffled, had gait ignition difficulties, and had postural instability.

The course of disease in the French family with the N279K mutation appeared similar to that of the PPND family, with a similar age at onset and duration of disease. However, if differences existed, they would not have been detected by means of statistical tests in this study because of the small number of patients and the wide range of values.

Table 3. Linkage Analysis of 2 Families With the N279K Mutation of the tau Gene

<table>
<thead>
<tr>
<th>Marker</th>
<th>cM</th>
<th>PPND Family†</th>
<th>French Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>D17S798</td>
<td>57</td>
<td>314, 316</td>
<td>310, 316</td>
</tr>
<tr>
<td>D17S1294</td>
<td>58</td>
<td>314, 316</td>
<td>310, 316</td>
</tr>
<tr>
<td>D17S1293</td>
<td>61</td>
<td>252, 260</td>
<td>252, 256</td>
</tr>
<tr>
<td>D17S800</td>
<td>63</td>
<td>262, 274</td>
<td>262, 266</td>
</tr>
<tr>
<td>D17S1860</td>
<td>64</td>
<td>176, 176</td>
<td>172, 172</td>
</tr>
<tr>
<td>D17S791</td>
<td>65</td>
<td>213, 207</td>
<td>205, 207</td>
</tr>
<tr>
<td>D17S806</td>
<td>67</td>
<td>181, 163</td>
<td>177, 173</td>
</tr>
<tr>
<td>D17S1299</td>
<td>69</td>
<td>165, 173</td>
<td>165, 181</td>
</tr>
<tr>
<td>D17S1868</td>
<td>72</td>
<td>258, 261</td>
<td>260, 264</td>
</tr>
<tr>
<td>ATC6A06</td>
<td>73</td>
<td>119, 122</td>
<td>119, 122</td>
</tr>
</tbody>
</table>

*PPND indicates pallidopontoniral degeneration; cM, centimorgan. Family pedigree is described in the legend to Figure 1.
†PPND disease haplotype is given in boldface type.

# Case 3

This 41-year-old right-handed man (III:6 of the French family [Figure 1]) began to experience generalized fatigue, forgetfulness, and slowness of movement. He was hospitalized shortly after the onset of his illness. At that time, he complained of slowness of movement and deterioration of motor skills. His family reported social withdrawal and attention deficits, but he was still independent in all daily living activities. Bradykinesia, rigidity, and apathy were noted. He was treated with selegiline hydrochloride and a combination of carbidopa and levodopa. His symptoms improved during the initial 6 months of treatment but then worsened; his work performance also deteriorated. Eyelid-opening apraxia and frontal lobe release signs developed. At 43 years of age, his MMSE score was 25 of 30 points, with difficulties on the scales for orientation, calculations, and recall. His eyes were fixed in a neutral position, with absent vertical gaze and slow horizontal gaze. Oculocephalic maneuvers were normal. His posture was stooped and he had a masklike face. His speech was soft and slow. He was able to say only a few words. He was rigid, especially on the left side of the body. Frontal lobe release signs, including glabellar and palomental reflexes, were present. He also had hyperreflexia and bilateral Babinski sign. He walked with assistance from his wife. He shuffled, had gait ignition difficulties, and had postural instability.

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Kindreds with FTDP-17 can be divided into the following 2 major clinical groups on the basis of phenotype: dementia predominant and parkinsonism predominant. Families in which dementia predominates are more common, but both types of presentation can occur with the same mutation and even within a single family. Age at onset of disease varies, ranging approximately from 30 to 60 years. However, in some families, symptomatic disease onset may occur at younger than 30 years or at older than 60 years. The course of disease can be very aggressive, terminating in death within 5 years, or it can be quite prolonged, lasting 20 years. The clinical picture is dominated by progressive dementia with personality...
changes, although parkinsonian features are sometimes seen. If parkinsonism does appear, it is usually in the form of rigidity during the final stages of the disease.

The phenotype of the 2 families described in this report was quite different from that of the dementia-predominant kindreds and shares more similarities with the parkinsonism-predominant group of kindreds. One family with a parkinsonism-predominant phenotype has been described as having disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC) and was the first kindred with the disease that was linked to chromosome 17. A detailed comparison of clinical, laboratory, and pathological features in the families with PPND and DDPAC has been published elsewhere. In brief, the DDPAC kindred shares the presence of parkinsonian features and dementia of the frontotemporal type with our PPND and French families. However, in the PPND and French families, the clinical course is more aggressive, without the prodromal stage seen in the DDPAC family. In addition, the amytrophy seen in the DDPAC family is not seen in our kindreds. The DDPAC kindred has a mutation in the intron at position +14 of the intron following exon 10 (E10 +14) of the tau gene. The N279K mutation in our kindreds and the E10 +14 mutation seen in the DDPAC family lead to similar biochemical abnormalities characterized by the excessive production of 4R tau that in turn results in the selective accumulation of these isoforms in insoluble form.

In another study, family A with familial progressive subcortical gliosis, which had a mutation at position +16 of the intron following exon 10 (E10 +16) of the tau gene, was characterized by profound dementia, but parkinsonism was seen in all cases relatively early in the disease course. The response to levodopa has not been reported. Patients from this family did not have supranuclear gaze palsy. However, in multiple-system atrophy with presenile dementia, affected members had a mutation at intron +3 after exon 10 and presented with parkinsonism and vertical gaze palsy accompanied by dementia and disinhibition.

Recently, a family with a novel mutation of S305S (E10 −2) was described. One of the affected members presented with progressive parkinsonism associated with vertical supranuclear gaze palsy and minimal dementia. This mutation again affects alternative splicing of exon 10.

Other families with mutations in exons 9, 10, 12, and 13 of the tau gene have been studied. Families with a P301L mutation in exon 10 have been described most frequently. The largest and best investigated of these families was a Dutch family. In this kindred, the most prominent behavioral changes included disinhibition, loss of executive function, and language abnormalities. Parkinsonian features may be present, but only in the late stage of the illness. Rigidity and bradykinesia have been described. Results of biochemical studies in affected brain material have shown that, as with the N279K mutation, the P301L mutation results in selective accumulation of insoluble 4R tau. However, the P301L mutation does not alter exon 10 alternative splicing and is indeed associated with a deletion of soluble 4R tau in the brains of patients. Three kindreds with a P301S mutation have been described in Italy, Germany, and Japan. As a group, patients with this mutation have the youngest age at onset of symptomatic disease (28 years in the Italian, third decade of life in the German, and 37 years in the Japanese kindreds). Rapidly progressive courses of dementia and parkinsonism have been seen in these families. The affected individuals in the German kindred also have seizures, and some of them died of status epilepticus.

One family with a G272V mutation in exon 9 (Dutch family II) has been studied. Affected family members present with dementia of the frontotemporal type similar to that seen in Pick disease. Some affected family members also have parkinsonism present, but only in the late stage of the illness. A family with a V337M mutation in exon 12 (the Seattle A family) has presented with mood changes, social withdrawal, and behavioral abnormalities (schizophreniform symptoms). Parkinsonism has not been observed in this family, except in 1 patient who experienced resting tremor. Two families with an R406W mutation in exon 13 presented with memory loss like that seen in typical cases of Alzheimer disease and personality changes. Parkinsonism characterized by bradykinesia was present in 2 of 15 patients in the late stage of the disease. Patients with a G389R mutation in exon 13 presented with progressive aphasia and memory problems followed by dementia. Parkinsonism developed in the late stage.

Parkinsonism was also described recently in families harboring the E10 +12, delN296, and N296N mutations. Families with S305N (E10 −2), I260V, K257T, E342V, del280K, L284L, and E10 +13 mutations are also known. However, the phenotypic description of these families is somewhat limited and does not permit their clinical characterization.

The findings from multiple families with tau mutations, summarized above, suggest that exon 10 mutations that cause 4R tau overproduction or accumulation, or both, may be more commonly associated with a parkinsonism-predominant phenotypic presentation than other tau mutations in exons 9, 12, and 13. However, this correlation remains uncertain because considerable phenotypic variability exists in families with exon 10 mutations and because these families have not consistently been examined by specialists in dementia and movement disorder.

In addition to the families we studied, 2 families of Japanese origin have been shown to have the N279K mutation and presented with a parkinsonism-predominant phenotype. Disease onset and duration and clinical course are similar to those observed in our 2 families. Collaboration with Japanese researchers on genealogical, genetic, and clinical aspects of these kindreds is planned. The findings at present strongly suggest that the N279K mutation produces a consistent phenotype, even in markedly different genetic backgrounds. This is in contrast to other exon 10 mutations (P301L and E10 +16 splice site) that have been associated with markedly variable clinical presentations (dementia predominant and parkinsonism predominant), even in the same family.

Direct comparison of available pathological material from the PPND and the French families is in progress. Widespread neuronal loss and gliosis are known to be present in both kindreds. On the basis of published reports, the cortical abnormalities appear to be slightly more pronounced in the French family. The substantia
nigra, globus pallidus, and pontine and mesencephalic tegmenta appear to be equally affected in both kindreds. The distribution and severity of other abnormalities, including the presence of ballooned neurons and neuronal and glial tau inclusions, appear to be similar in both kindreds.

The PPND and French families share more similarities than differences in clinical features. The N279K mutation can develop independently in different parts of the world. Further understanding of the pathogenesis of the FTDP-17 disorders continues to hinge on study of their clinical and pathological presentation and the presence of common founder effects.

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