Frequency of Tau Gene Mutations in Familial and Sporadic Cases of Non-Alzheimer Dementia

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Background: Mutations in the tau gene have been reported in families with frontotemporal dementia (FTD) linked to chromosome 17. It remains uncertain how commonly such mutations are found in patients with FTD or non-Alzheimer dementia with or without a positive family history.

Objective: To determine the frequency of tau mutations in patients with non-Alzheimer dementia.

Patients and Methods: One hundred one patients with non-Alzheimer, nonvascular dementia, most thought to have FTD. Of these, 57 had a positive family history of dementia. Neuropathologic findings were available in 32. The tau gene was sequenced for all exons including flanking intronic DNA, portions of the 3' and 5' untranslated regions, and at least 146 base pairs in the intron following exon 10.

Results: Overall, the frequency of the tau mutations was low, being 5.9% (6/101) in the entire group. No mutations were found in the 44 sporadic cases. However, 6 (10.5%) of the 57 familial cases and 4 (33%) of the 12 familial cases with tau pathologic findings had mutations in the tau gene. The most common mutation was P301L.

Conclusions: We conclude that tau mutations are uncommon in a neurology referral population with non-Alzheimer dementia, even in those with a clinical diagnosis of FTD. However, a positive family history and/or tau pathologic findings increase the likelihood of a tau mutation. There must be other genetic and nongenetic causes of FTD and non-Alzheimer dementia, similar to the etiologic heterogeneity present in Alzheimer disease.

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FRONTOTEMPORAL dementia (FTD) has been increasingly recognized as a common form of non-Alzheimer disease (AD) dementia that is clinically characterized by behavioral problems predominating over memory loss and frontal and temporal lobar cortical atrophy.1 A familial subtype of FTD, often with parkinsonian features, has been linked to chromosome 17, and several mutations in the tau gene have been discovered to segregate with the disease in most of these families.2-6 Because FTD and other non-AD dementias are relatively common, especially in the presenile age group (younger than 65 years), it is important to determine the frequency of tau mutations in this population. Thus far, only 2 studies have addressed this issue. Rizzu et al,7 in an FTD population from the Netherlands, found that 17.8% of cases had a tau mutation and 43% of cases with a positive family history had a tau mutation. Houlden et al8 studied non-AD dementia cases from Minnesota and the United Kingdom. They found no tau mutations in 71 non-AD cases, whereas 9.4% to 13.6% of those with pathologic findings of FTD had tau mutations. We report herein the largest series to date from North America of FTD and non-AD cases of dementia evaluated for mutations in the tau gene.

For editorial comment see page 351

The results are summarized in Table 2 and Table 3. Fifty-seven cases were familial and 44 were sporadic. There were no differences in the mean ages at onset for the familial and sporadic cases. Eighteen of the familial cases and 14 of the sporadic cases had autopsies, 22 of which showed some form of tau pathologic changes. Twenty cases had neurofibrillary tangles and 9 had Pick bodies. Six tau mutations were discovered in the total

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PATIENTS AND METHODS

We ascertained 101 unrelated index patients with non-AD, nonvascular dementia who were thought most likely to have FTD or some variant of FTD. The majority of these were ascertained from the Neurology and Alzheimer's Disease Research Center clinics at the University of Washington, Seattle, and the University of Pennsylvania, Philadelphia. Additional individual cases were referred by several neurologists (see acknowledgments). Criteria for inclusion were initial behavioral problems exceeding memory loss, often with neuroimaging or neuropathologic evidence of lobar atrophy.1 Exclusion criteria were a diagnosis of typical AD, progressive supranuclear palsy, Parkinson disease, alcoholism, vascular dementia, and Lewy body dementia. Most of the patients had a clinical diagnosis of FTD conforming to the guidelines of Neary et al.1 Family histories were available for 86 cases, and those having a first-degree relative with dementia were considered familial. Subjects with a negative family history or no available family history were considered sporadic. These cases do not represent a random or community-based sample but have a bias of ascertainment toward unusual dementia referred to special academic research units. Subjects participated through informed consent protocols approved by the relevant institutional review boards.

Neuropathologic examination was performed on 32 brains and included staining of microscopic sections from neocortex, hippocampus, basal ganglia, cerebellum, and brainstem with hematoxylin-eosin, Bielschowsky silver, tau-2, paired helical filament, and Aβ-amyloid. Pathologic changes related to tau were defined as any taurpositive cytoplasmic inclusion, which included neurofibrillary tangles and Pick bodies.2 Eight cases subjected to autopsy met criteria for dementia lacking distinctive histopathologic features.9

The initial family (BK or Seattle A) with a tau mutation discovered at the University of Washington was excluded from this study.1

DNA samples from affected persons in the families with dementia were prepared from peripheral leukocytes as previously described.10,11 Primer pairs for each exon from tau were used to amplify 200 ng of patient genomic DNA in 50-μL reactions (35 cycles) containing 1X polymerase chain reaction buffer, 200 ng of each primer, 2.5 U of Taq DNA polymerase (Promega Corp, Madison, Wis), and 400-μmol/L deoxynucleoside triphosphates (Perkin-Elmer, Norwalk, Conn) (Table 1). Polymerase chain reaction products were subjected to electrophoresis with the use of 2.5% agarose/0.1X TAE (Tris-acetate-ethylenediaminetetraacetate) gels and the appropriate fragments purified with a DNA purification kit (Bio 101 Inc, La Jolla, Calif). The purified fragments were sequenced automatically with dye terminator cycle sequencing (TaqFS DNA polymerase or Big Dye Terminator RR Mix; Perkin-Elmer), and an ABI 373 or 377 DNA Sequencer (Applied Biosystems, Foster City, Calif).

Primer pairs for amplification and sequencing tau have been described previously.4 New primers were designed for 9 of the 11 exons to sequence deeper into the introns (Table 1) and were used for sequencing in approximately 50 of the 100 patients. Both strands of the tau gene were sequenced for all exons, including at least 7 base pairs (bp) of flanking intronic DNA, 50 bp of the 5'-untranslated region, and 70 bp of the 3' untranslated region. For all cases, more than 146 bp of flanking sequence for intron 10 were analyzed. DNA samples were available from a panel of 96 unrelated normal control subjects to determine whether any changes occurred in the general population.

These results demonstrate that mutations in the tau gene are a relatively uncommon cause of FTD and non-AD, nonvascular dementia in a neurology referral population. The frequency of mutations in this population is approximately 6%, and all were found in subjects with a positive family history. Frontotemporal dementia can be familial (45% in the study by Chow et al19). A positive family history of dementia and/or evidence of tau-related neuropathologic features greatly increases the probability of a tau mutation (10% to 30%). However, even familial cases and cases with tau pathologic features may not have demonstrable mutations.

One caveat concerning these results is that no group, including our own, has performed a complete exhaustive screen of the entire tau gene including all regulatory, noncoding, and intronic regions. It is conceivable that rare disease-related mutations lie in these regions, but the number of such mutations is likely to be small. One possible example of this phenomenon is the hereditary dysphasic dementia 2 (HDD2) family linked to chromosome 17 but having no demonstrable tau mutation.19 The tau gene has a large number of polymorphisms (Table 4) that occur fairly frequently in the general population.

COMMENT

Table 4 lists the 22 normal polymorphisms found in the tau gene in the control samples. Nine of these polymorphisms have been previously published and 13 are new. This list will be of value to other investigators searching for mutations in tau.

group (6/101; 5.9%), the most common of which was P301L (proline-to-leucine substitution at nucleotide 301) (3/6). Other mutations were L284L (leucine-to-leucine silent substitution at nucleotide 284), S305N (serine-to-asparagine substitution at nucleotide 305), and E10+16 (nucleotide substitution at position +16 in intron 10). The detailed descriptions of these families have been reported elsewhere.4,12-15 Fifty-seven patients had a positive family history of dementia in at least 1 first-degree relative, and all 6 tau mutations came from this group (10.5%). No tau mutations were found in the 44 sporadic cases. There were 4 tau mutations in the familial cases with neuropathologic features (22%), and all 4 came from the familial group with tau pathologic features (4/12; 33%). Of all 22 cases in the total familial and sporadic groups with tau pathologic features at autopsy, 4 (18%) were found to have tau mutations. None of the 9 sporadic cases with Pick bodies and none of the 8 cases of dementia lacking distinctive histopathologic features had tau mutations.

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and are not likely to be disease related, but may be difficult to interpret in small focused studies. One exception appears to be the A0 polymorphism, which shows a consistent and significant association with progressive supranuclear palsy.20

Even though no tau mutations have yet been found in a sporadic case of FTD, an occasional case is likely to be discovered. The most common explanations for such a phenomenon would be nonpaternity, a new mutation, decreased penetrance in other family members, or early presymptomatic death of a mutation-carrying parent.21

Our results are similar to those of Houlden et al,8 who evaluated cases from Minnesota and the United Kingdom. They, too, found no mutations in sporadic non-AD cases and a 9.4% to 13.6% frequency of mutations in cases with tau pathologic features. Rizzu et al7 found a higher frequency of tau mutations in an FTD population in the Netherlands (17.8% overall and 43% in the familial cases). These latter results may reflect the presence of a few large families with FTD linked to chromosome 17 in the relatively small population of the Netherlands. Nevertheless, all investigators have documented many FTD cases without tau mutations.

These results have important practical implications. Neurologists and/or clinical laboratories screening patients with dementia for tau mutations will have a low yield of positive results, unless there is a strong family history of dementia and tau-related neuropathologic findings. However, discovering a patient with a tau mutation has utmost importance to the family in providing genetic counseling.

Mutations in the tau gene appear to cause neuronal dysfunction and death by at least 2 mechanisms.22,23 One is by altering the ability of tau to bind microtubules. The
and R, reverse. Because AD, by definition, has tau pathologic features, but there have been a few exceptions, including 1 of the cases in this series (family LKL, reported previously).14,24,25 Because AD, by definition, has tau pathologic findings (neurofibrillary tangles), the interaction between tau and amyloid require much more attention and elucidation.

We conclude that, although mutations in the tau gene represent a powerful insight into the pathogenesis of neurodegenerative diseases, the frequency of such mutations in the general population of non-AD dementia is small. Such mutations are more common in cases with an FTD phenotype with a positive family history and neuropathologic evidence of abnormal tau inclusions. There must be additional causes of the FTD syndrome, including other genes involved in the familial cases. This evidence of heterogeneity in FTD is remarkably similar to that found in AD, where 3 genes (amyloid precursor protein and presenilins 1 and 2) cause some instances of early-onset familial cases and there is a genetic risk factor (apolipoprotein E), but the largest numbers of both familial and sporadic cases still have no known cause.

Table 3. Six Families With Tau Mutations*

<table>
<thead>
<tr>
<th>Family</th>
<th>Mutation†</th>
<th>Mean Age (Range), y</th>
<th>Clinical Diagnosis</th>
<th>Neuropathologic Findings</th>
<th>Mutation Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAA</td>
<td>P301L</td>
<td>49.5 (41-57)</td>
<td>FTD, atypical dementia, atypical PD</td>
<td>NFT, tau + inclusions</td>
<td>Abnormal MTB</td>
<td>4, 12</td>
</tr>
<tr>
<td>LBL</td>
<td>P301L</td>
<td>61.0 (56-67)</td>
<td>FTD, atypical dementia</td>
<td>Ballooned neurons, NFT</td>
<td>Abnormal MTB</td>
<td>4, 12</td>
</tr>
<tr>
<td>OREL</td>
<td>P301L</td>
<td>64.3 (57-75)</td>
<td>FTD, atypical dementia</td>
<td>NA</td>
<td>Abnormal MTB</td>
<td>4, 12</td>
</tr>
<tr>
<td>EKR</td>
<td>E10+16</td>
<td>48 (48-55)</td>
<td>FTD, atypical dementia</td>
<td>NA</td>
<td>Abnormal splice E10</td>
<td>Present study, 15</td>
</tr>
<tr>
<td>LKL</td>
<td>L284L</td>
<td>51.8 (47-52)</td>
<td>FTD, AD</td>
<td>NFT, neuritic amyloid plaques</td>
<td>Abnormal splice E10</td>
<td>14</td>
</tr>
<tr>
<td>TAB</td>
<td>S305N</td>
<td>36.7 (29-38)</td>
<td>FTD, atypical dementia</td>
<td>NFT</td>
<td>Unknown</td>
<td>13</td>
</tr>
</tbody>
</table>

*FTD indicates frontotemporal dementia; PD, Parkinson disease; AD, Alzheimer disease; NFT, neurofibrillary tangles; NA, no pathologic findings available; MTB, microtubule binding; and splice E10, splicing of exon 10.
†See the “Results” section for an explanation of the mutations.

Table 4. Polymorphisms in the Tau Gene*

<table>
<thead>
<tr>
<th>Location</th>
<th>Polymorphic Nucleotide</th>
<th>Primer Pair Relative to Exon of Primer Pair</th>
<th>Codon†</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>S’UTR</td>
<td>A/G</td>
<td>1EF/1ER −13 from ATG</td>
<td>4, 7, 16</td>
<td></td>
</tr>
<tr>
<td>I1</td>
<td>C/T</td>
<td>2EF/2ER +18</td>
<td>7, 16</td>
<td></td>
</tr>
<tr>
<td>I2</td>
<td>C/G</td>
<td>3EF/3ER −163</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I2</td>
<td>T/G</td>
<td>3EF/3ER −162</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I3</td>
<td>A/G</td>
<td>3EF/3ER +9</td>
<td>7, 17</td>
<td></td>
</tr>
<tr>
<td>I3</td>
<td>T/A</td>
<td>4EF/4ER +103</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I4</td>
<td>A insertion</td>
<td>1EF/1ER −26</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I5</td>
<td>T/C</td>
<td>5EF/5ER −72</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>E7</td>
<td>G/A</td>
<td>6EF/6ER −176</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>I8</td>
<td>G/A</td>
<td>9EF/9ER −26</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>E9</td>
<td>A/G</td>
<td>9EF/9ER +227</td>
<td>7, 16</td>
<td></td>
</tr>
<tr>
<td>E9</td>
<td>T/C</td>
<td>9EF/9ER +255</td>
<td>4, 7, 16</td>
<td></td>
</tr>
<tr>
<td>E9</td>
<td>G/A</td>
<td>9EF/9ER −70</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>I9</td>
<td>G/A</td>
<td>9EF/9ER +103</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I10</td>
<td>G/A</td>
<td>10EF/10ER +129</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>I11</td>
<td>G/A</td>
<td>11EF/11ER +34</td>
<td>7, 16, 17</td>
<td></td>
</tr>
<tr>
<td>3’UTR</td>
<td>T/C</td>
<td>13F/13R −76</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>3’UTR</td>
<td>T insertion</td>
<td>13F/13R +250</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>3’UTR</td>
<td>C insertion</td>
<td>13F/13R +321</td>
<td>Present study</td>
<td></td>
</tr>
</tbody>
</table>

*UTR indicates untranslated region; I, intron; E, exon; F, forward; and R, reverse.
†Numbering based on the full-length tau sequence with exons 2, 3, and 10.

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386

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