The Genetic and Pathological Classification of Familial Frontotemporal Dementia

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Background: Frontotemporal dementia (FTD) is an important cause of neurodegenerative dementia, particularly in younger patients. TAU has been identified as the gene responsible for FTD linked to chromosome 17, but it is likely that there is pathological and genetic heterogeneity among families with FTD.

Objective: To explore the genetic and pathological basis of familial FTD.

Design: Clinical case series with genetic analysis of each family, and pathological confirmation of diagnosis where possible.

Setting: Specialist dementia research group, particularly recruiting patients with young-onset dementia.

Patients: Twenty-two families with an index member with FTD, meeting Lund-Manchester criteria, and a family history of other affected members with dementia were ascertained.

Results: Half of the families had mutations in the TAU gene (TAU exon 10 +14, +16, and P301S), and pathological diagnoses were available in 17 of 22 families. Three main pathological diagnoses were made: FTD with neuronal and glial tau deposition, FTD with ubiquitin inclusions, and FTD with neuronal loss and spongiosis but without intracellular inclusions. No cases of familial Pick disease were identified. With the use of the pathological diagnoses, each family with FTD with neuronal and glial tau deposition had a TAU mutation, whereas TAU mutations were not identified in families in the other 2 diagnostic groups.

Conclusions: This study illustrates the value of TAU sequencing in FTD and suggests that around one half of individuals with familial FTD have TAU mutations and dementia with tau pathological findings. Furthermore, these data suggest that there are at least 2 additional genes to be identified among families with autosomal dominant FTD.

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FRONTOTEMPORAL dementia (FTD) is a clinical diagnosis based on progressive personality change and language impairment related to frontotemporal lobar atrophy. It is a frequent cause of dementia, particularly in the younger age group, accounting for between 12% and 20% of all dementia cases.1 Pick disease is the archetypal pathological form of FTD. It is characterized pathologically by the presence of swollen α-B-crystallin-positive neurons (Pick cells), and argyrophilic, tau-positive round inclusions (Pick bodies) that are particularly numerous in the granule cells of the hippocampal dentate fascia and the superficial layers of the frontotemporal neocortex. Pick disease is sometimes also used as a clinical term for patients presenting with a progressive frontal syndrome or language disorder, and as a diagnosis for neurological conditions with radiologic frontotemporal lobar atrophy; strictly, however, Pick disease should be reserved for pathologically diagnosed disease.

Although Pick disease is one pathological form of clinically diagnosed FTD, FTD may be caused by a number of other pathological substrates.1 These include (1) dementia with ubiquitinpositive inclusions, first associated with motor neuron disease; (2) dementia lacking distinctive histopathologic features; (3) corticobasal degeneration; (4) Alzheimer disease; and (5) familial frontotemporal dementia linked to chromosome 17 (FTDP-17).1-4 Immunocytochemistry has greatly facilitated the diagnosis of these conditions, in particular with the identification of ubiquitin and/or tau-positive inclusions.

Analysis of the genetic basis of familial diseases has proved to be a powerful and successful approach to the study of neurodegeneration. The identification of pathogenic gene mutations in familial Alzheimer disease has helped our understanding of the pathogenesis of the more common sporadic forms of this disease.2 This approach is likely to be more difficult in FTD because of the underlying pathological heterogeneity. Although analysis of a patho-
PATIENTS AND METHODS

Twenty-two families with autosomal dominant FTD were studied as part of an ongoing London, England–based study of early-onset dementia. Blood for DNA analysis and agreement for autopsy examination were obtained after patients gave informed consent. Exons 9 to 13 of TAU were sequenced after standard polymerase chain reaction and sequencing reactions were performed (Big-Dye terminator sequencing kits; ABI, Foster City, Calif), as previously described. Mutations in TAU were confirmed by both sequence analysis and restriction enzyme digestion. Sequence products were analyzed on a sequencer (ABI 377) and the results were visualized with software (Sequence Analysis and Auto Assembler; ABI). Autopsy examination was available in 17 of 22 families. From each brain, a comprehensive and standardized set of tissue blocks was taken, processed, sectioned, and stained with a variety of histologic and immunohistochemical stains, including antibodies to tau (AT8, monoclonal mouse; 1:200; Innogenetics N.V., Gent, Belgium) and ubiquitin (ubiquitin, polyclonal rabbit, 1:500; Dako Ltd, Ely, England).

Logical classification of FTD has been previously described, it is worthwhile focusing on the classification of the familial forms of this disease, since each of these families is likely to have an identifiable pathogenic gene mutation. The description of kindreds with FTDP-17 and the identification of pathogenic mutations in TAU has wider implications for neurodegenerative disease, but it is also the first step toward the genetic classification of the different FTD subtypes. In this study, we reviewed the pathological and genetic findings in a series of autosomal dominant families with FTD, in an attempt to define the pathological subtypes and to predict the minimum number of genes that remain to be identified in this condition.

RESULTS

Half (11/22) of the families identified had TAU mutations (Table). Nine families had the TAU exon 10 +16 mutation, 1 family had the TAU exon 10 +14 mutation, and 1 family with the exon 10 codon 301 proline-toserine mutation (P301S) was identified. Two of these cases have been previously reported. The average age at onset for the family with the P301S mutation was 34 years, as compared with an average age at onset for the families with the +16 mutation (family 21), and this family did not have typical neuronal ubiquitin inclusions, although some granular neuronal ubiquitin immunoreactivity was identified.

This study indicates the genetic and pathological heterogeneity of familial FTD; in this series, 11 (50%) of 22 familial FTD cases had TAU mutations. Three other groups have studied the prevalence of TAU mutations in familial FTD. Rizzu and colleagues report that 47% of patients with FTD and a positive family history had mutations in TAU, whereas Houlden and colleagues suggested that only 11% (6/54) of FTD families had identifiable TAU mutations. However, neither of these studies provided a pathological analysis of the families studied. More recently, Poorkaj and colleagues studied a large series of familial FTD cases and identified TAU mutations in 10.5% of the familial cases and only 33% of the familial cases with tau pathological findings.

In contrast, our study suggests that the presence of tau pathological findings in a familial FTD case strongly predicts the presence of a TAU mutation, whereas the presence of FTD-NLS or FTD-UB pathological findings effectively excludes a mutation in TAU. Possible reasons for the discrepancies between these studies include the age at onset of families studied and the strength of evidence of a concordant family history. Our results correlate well with analysis of pathological findings in the families with unequivocally chromosome 17q21–linked FTD, in which practically all affected members had significant tau deposition and concomitant mutations in TAU. Although neurodegeneration in familial tau deposition without TAU mutations can occur in families with clinically diagnosed progressive supranuclear palsy, this has not been commonly described in families with pathologically diagnosed tau-deposition FTD with multiple affected members. One exception may be the family with hereditary dysphasic disinhibition.

COMMENT

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Clinical Features of Families With FTD Studied*

<table>
<thead>
<tr>
<th>Family No.</th>
<th>AAO, y</th>
<th>Clinical Features</th>
<th>Pathological Diagnosis</th>
<th>Genetic Diagnosis/TAU Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Frontal syndrome</td>
<td>FTD-NLS</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>Frontal syndrome, amnesia, nonfluent dysphasia</td>
<td>FTD-NLS</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>Frontal syndrome, amnesia, gait apraxia</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>Frontal syndrome, nonfluent dysphasia, parkinsonism</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>Nominal dysphasia, amnesia</td>
<td>P1D/AD</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>Frontal syndrome, amnesia, nonfluent dysphasia</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>Frontal syndrome, amnesia, nonfluent dysphasia, antipsychotic-induced parkinsonism</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>Frontal syndrome, dressing apraxia, parkinsonism (asymmetric bradykinesia and rigidity), alien limb syndrome</td>
<td>FTD-NLS</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>Personality change with semantic dysphasia, parkinsonism, dressing apraxia</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>Frontal syndrome, dressing apraxia, antipsychotic-induced parkinsonism</td>
<td>FTD-Ub</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>Frontal syndrome, amnesia, nonfluent dysphasia</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>Amnesia, frontal syndrome, parkinsonism</td>
<td>NA</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>66</td>
<td>Social disinhibition, dysphasia</td>
<td>NA</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>53</td>
<td>Frontal syndrome, cognitive slowing</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>44</td>
<td>Frontal syndrome, antipsychotic-induced parkinsonism, nominal dysphasia</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>53</td>
<td>Frontal syndrome</td>
<td>NA</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>60</td>
<td>Frontal syndrome, amnesia, nominal dysphasia</td>
<td>FTD-Ub</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>43</td>
<td>Frontal syndrome, nominal dysphasia, parkinsonism</td>
<td>FTD-tau Exon 10+16</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>51</td>
<td>Frontal syndrome with disinhibition</td>
<td>FTD-Ub</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>34</td>
<td>Frontal syndrome, dysphasia, poor balance</td>
<td>NA</td>
<td>Exon 10 P301S</td>
</tr>
<tr>
<td>21</td>
<td>52</td>
<td>Frontal syndrome, left-sided pyramidal weakness, fasciculations, dysphasia</td>
<td>FTD-NLS</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>45</td>
<td>Frontal syndrome with dyspraxia</td>
<td>NA</td>
<td>Exon 10+14</td>
</tr>
</tbody>
</table>

*FTD indicates familial frontotemporal dementia; AAO, average age at onset; NLS, without neuronal inclusions; P1D, Pick disease; AD, Alzheimer disease; tau, with tau-positive inclusions; Ub, with ubiquitin-positive, tau-negative inclusions; NA, not available; N, normal; and P301S, codon 301 proline-to-serine mutation.
†No immunohistochemical analysis available.
‡No ubiquitin-positive inclusions were seen, although some sparse granular ubiquitin immunoreactivity was noted.

(HDD2), linked to the TAU region with a maximum lod score of 3.68. Tau immunocytochemical analysis has identified variable tau deposition in this family, although a recent report described depletion of tau on Western blot analysis. A mutation in TAU has not been reported in the family with HDD2.

Our series suggests that there are no clinical features that can reliably distinguish these 3 familial FTD subtypes, and clinical features of motor neuron disease with FTD were uncommon. We identified FTD-Ub pathographical features in 3 (18%) of 17 families with pathologically diagnosed FTD. These are similar to the family with ubiquitin inclusion described by Kertesz and colleagues, the sporadic cases with semantic dementia identified by Rosser and colleagues, and the sporadic and familial cases identified by Jackson and colleagues and described as motor neuron disease inclusion dementia. These pathological reports confirm that superficial neocortical cell loss with vacuolation and ubiquitin inclusions in the dentate gyrus are core features of this disease.

We have also identified 4 (24%) of 17 families with FTD-NLS. The relationship between the FTD-NLS reported herein and other reported FTD subtypes is harder to establish given the overall pathological similarities between all of these diseases and the absence of tau and/or ubiquitin immunohistochemical analysis in some reports. The diseases described as “dementia lacking distinctive histopathology,” “dementia lacking distinctive histological features,” “familial dementia of adult onset with pathological features of a nonspecific nature,” and “dementia with microvascular pathology and laminar spongiosis” may all correspond to either FTD-Ub or FTD-NLS, depending on the results of ubiquitin immunohistochemical analysis. Genetic linkage to chromosome 3 has been reported in a Danish kindred originating in Jutland, apparently without distinctive pathological features (OMIM No. 600795). A recent study using ubiquitin immunohistochemical analysis did not show intraneuronal ubiquitinized inclusions in the chromosome 3–linked kindred, and, conversely, analysis of a large family with ubiquitin inclusion dementia excluded linkage to chromosome 3. This suggests that chromosome 3–linked dementia may correspond to FTD-NLS described in this series. Assuming continuing pathological-genetic correlation across FTD, this series suggests that there are at least 2 additional genes to be identified that may be responsible for familial FTD.

In conclusion, we have demonstrated 3 pathological subtypes of familial FTD and a close correlation between the presence of a TAU mutation and the presence of tau pathological findings. Despite earlier reports suggesting that Pick disease was a common familial dementia, this was not supported by this study. There is genetic and pathological heterogeneity in familial FTD and, undoubtedly, additional genes will be identified that are responsible for these disorders.

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From the Neurogenetics Section (Drs Morris and Wood), Dementia Research Group (Drs Janssen and Rosser), and Department of Neuropathology (Dr Revesz), Institute of Neurology, and Reta Lila Weston Institute of Neurological Studies (Drs Morris and Lees and Mr Ozansoy), ©2001 American Medical Association. All rights reserved.
High-power view of dentate gyrus showing lack of ubiquitin immunoreactivity in frontotemporal dementia with neuronal loss and spongiosis but without intracellular inclusions (A), dense ubiquitin inclusions in frontotemporal dementia with ubiquitin inclusions (B), and dense and granular tau immunoreactivity in frontotemporal dementia with neuronal and glial tau deposition (C). Bar indicates 50 µm.

University College London, London, England; MRC Brain Bank, Department of Neuropathology, Institute of Psychiatry, London (Mr Khan and Dr Lantos); Department of Neurology, Addenbrooke's Hospital, Cambridge, England (Dr Brown); Unitat de Genetica Molecular, Institut de Biomedicina de Valencia-CSIC, Valencia, Spain (Dr Perez-Tur); and Neurogenetics Laboratory, Mayo Clinic Jacksonville, Jacksonville, Fla (Mr Baker and Drs Hardy and Hutton).

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REFERENCES