Sequence analysis of \textit{tau} in familial and sporadic progressive supranuclear palsy


Progressive supranuclear palsy (PSP) is a tau deposition neurodegenerative disorder which usually occurs in sporadic form and is associated with a common variant of the \textit{tau} gene. Rare familial forms of PSP have been described. Recently familial frontotemporal dementia linked to chromosome 17 (FTDP-17) has been shown to be due to mutations in \textit{tau} and there may be a clinical and pathological overlap between PSP and FTDP-17. In this study we have analysed the \textit{tau} sequence in two small families with PSP, and a number of clinically typical and atypical sporadic cases with pathological confirmation of the diagnosis. The \textit{tau} mutations described in FTDP-17 were not found in the most clinically diagnosed patients with PSP. This suggests that usually FTDP-17 and PSP, including the rare familial form of PSP, are likely to be separate conditions and that usually PSP and typical PSP-like syndromes are not due to mutations in \textit{tau}.

\textbf{RESULTS}

Analysis of \textit{tau} exons 9–13 showed no coding or splice site mutations in patients with familial PSP, patients with sporadic typical or atypical PSP, or in patients with a family history of other neurodegenerative diseases. One additional sporadic patient has recently been identified with clinically diagnosed PSP without \textit{tau} mutations which alter the alternative splicing of \textit{tau} exon 10. The association between PSP and \textit{tau}, and the similarity between FTDP-17 and PSP both suggest that \textit{tau} is a primary candidate gene for familial PSP and it is possible that PSP may simply be one phenotypic variant of FTDP-17.

We have addressed the role of \textit{tau} in sporadic and familial PSP and the possibility of a genetic explanation for the co-occurrence of PSP with disorders such as dementia and tremor by sequencing \textit{tau} in patients with pathologically confirmed PSP. The use of pathologically diagnosed rather than clinically diagnosed patients allowed us to address the possibility of clinical heterogeneity in pathologically diagnosed patients with PSP. The groups studied include (1) pathologically diagnosed clinically typical and atypical sporadic patients, (2) pathologically diagnosed patients with a family history of non-PSP neurodegenerative disease, and (3) two families with multiple affected members with PSP.

\textbf{METHODS}

Patients with PSP were identified as part of a national recruitment of patients with PSP, and from the Parkinson's Disease Society Brain Research Centre. Seven patients with no family history of neurodegenerative disease were studied, including three patients with clinically typical disease and four with atypical clinical features (table 1). Seven patients with a family history of other neurodegenerative disease, and patients from two previously reported non-consanguineous families with PSP with more than one clinically affected member were studied. \textsuperscript{14,15} Clinical diagnoses were made by retrospective note review and the NINDS and less stringent Tolosa criteria were applied to index cases of PSP. \textsuperscript{16} We included those with pathologically diagnosed PSP but atypical clinical features. \textsuperscript{17} In each of the families some affected patients met NINDS criteria for the diagnosis of probable PSP and pathological confirmation has been made in one patient from the family of case 16. \textsuperscript{18} For the sequencing of \textit{tau}, brain expressed exons 9–13 were amplified by polymerase chain reaction (PCR) using primers and conditions as previously described. \textsuperscript{19} The PCR products were purified using a Qiagen kit (Qiagen Inc, Valencia, CA, USA) and the sequencing was performed using a \textit{dRhodamine} sequencing kit (Perkin-Elmer-Applied Biosystems – PE-ABI, Foster City, CA, USA). Sequence products were analysed using an ABI 377 automated DNA sequencer (PE-ABI) and the sequence was analysed with Sequence Analysis and AutoAssembler software (PE-ABI).

\textbf{Abbreviations:} PSP, progressive supranuclear palsy; FTDP-17, frontotemporal dementia linked to chromosome 17
Table 1  Analysis of tau in PSP

<table>
<thead>
<tr>
<th>Case</th>
<th>Tau seq</th>
<th>FH</th>
<th>Clinical features</th>
<th>Age at onset</th>
<th>Pathological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>--</td>
<td>Atypical: IPD-like</td>
<td>53</td>
<td>Typical</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>--</td>
<td>Typical: Tolosa</td>
<td>72</td>
<td>Typical</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>--</td>
<td>Atypical: IPD-like</td>
<td>76</td>
<td>Vascular disease</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>--</td>
<td>Typical: NINDS</td>
<td>62</td>
<td>Typical</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>--</td>
<td>Typica: Tolosa</td>
<td>66</td>
<td>Typical</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>--</td>
<td>Atypical: gait disorder without documented eye movement disorder</td>
<td>77</td>
<td>Typical+cortical involvement</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>--</td>
<td>Atypical: chorea</td>
<td>60</td>
<td>Typical</td>
</tr>
<tr>
<td>8</td>
<td>N</td>
<td>+ve: 1 brother and father tremor</td>
<td>Typical: Tolosa</td>
<td>63</td>
<td>Typical+BD features</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>+ve: 1 brother parkinsonism</td>
<td>Atypical: IPD-like</td>
<td>79</td>
<td>Typical</td>
</tr>
<tr>
<td>10</td>
<td>N</td>
<td>+ve: father and nephew parkinsonism</td>
<td>Typical: NINDS</td>
<td>66</td>
<td>Typical</td>
</tr>
<tr>
<td>11</td>
<td>N</td>
<td>+ve: sister AD</td>
<td>Typical: NINDS</td>
<td>69</td>
<td>Typical</td>
</tr>
<tr>
<td>12</td>
<td>N</td>
<td>+ve: uncle PD</td>
<td>Typical: NINDS</td>
<td>66</td>
<td>Typical</td>
</tr>
<tr>
<td>13</td>
<td>N</td>
<td>+ve: brother parkinsonism</td>
<td>Typical: NINDS</td>
<td>73</td>
<td>Typical</td>
</tr>
<tr>
<td>14</td>
<td>N</td>
<td>+ve: mother and father tremor</td>
<td>Atypical: non-Levodopa responsive parkinsonism</td>
<td>70</td>
<td>Typical</td>
</tr>
<tr>
<td>15</td>
<td>N</td>
<td>+ve: brother PSP, brother AD</td>
<td>Typical: NINDS</td>
<td>67</td>
<td>Not available</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
<td>+ve: cousin PSP</td>
<td>Typical: NINDS</td>
<td>64</td>
<td>Typical</td>
</tr>
</tbody>
</table>

PSP, Progressive supranuclear palsy; AD, Alzheimer’s disease; PD, Parkinson’s disease; CBD, corticobasal degeneration; NINDS, National Institute for Neurological Disorders and Stroke; PSP, criteria positive for clinically probable or possible PSP; Tolosa, Tolosa criteria for PSP positive.

likely PSP, although not meeting NINDS criteria for clinically probable PSP with a young age at onset and a tau exon 10+16 mutation. Full details of this case will be published separately.

DISCUSSION

Mutations in tau have not been identified in most patients with PSP in this study, in common with other groups who have investigated PSP in clinically based series.

FTDP-17 kindreds in which the pathogenic mutation is a tau exon 10 coding or splice mutation are particularly similar to PSP.

These conditions both involve degeneration of the basal ganglia and brain stem, with deposition of neurofibrillary tangles consisting of two major hyperphosphorylated tau bands at 64 kDa and 68 kDa on western blotting. These bands consist predominantly of four repeat isoforms of tau, and in exon 10 splice mutations this occurs because of a change in the alternative splicing of tau RNA. Progressive supranuclear palsy may also involve a change in the alternative splicing of tau, but this has not been demonstrated in all brain areas, or in all cases. In addition, FTDP-17 involves degeneration of frontal and temporal cortex and often involves marked personality change, obsessional symptoms, and progressive dysphasia.

Although personality change and withdrawal may be early features of PSP, the most characteristic features are of early imbalance and a supranuclear gait palsy and this probably reflects predominant damage to the brain stem. These features may be seen in FTDP-17, and some families and members affected seem to be indistinguishable from sporadic PSP.

However, many of the FTDP-17 kindreds described with supranuclear or oculomotor gaze abnormalities have features atypical for PSP such as prominent asymmetry, prominent cortical sensory signs, psychosis, levodopa induced dyskinesias, prominent neuropsychiatric symptoms, late gait disturbance, or young age at onset. Progressive supranuclear palsy distribution pathology has been described in some FTDP-17 families. Exon 10 FTDP-17 involves extensive neuronal and glial tau deposition and this may include the tufted astrocyte type tau inclusion which has been considered to be relatively specific for PSP.

In addition, FTDP-17 exon 10 mutation cases may involve extensive oligodendrogial tau deposition and the formation of astrocytic plaques, considered to be more characteristic of CBD. At the electron microscopic level a distinction can be made between exon 10 FTDP-17 tau filaments and PSP tau filaments, as FTDP-17 involves the deposition of a novel type of filament form, the twisted ribbon filament, which contrasts with the straight filaments typically seen in PSP.

Although PSP has many similarities to FTDP-17 and there may be overlapping features, there are clinical and molecular differences between these conditions, and the absence of tau mutations in the families and most sporadic cases described in this paper reinforces that distinction. Usually PSP or typical PSP-like syndromes are not due to mutations in tau. Furthermore, taken together with the work of Hoenicka et al in excluding tau in the largest PSP family described to date, our data suggest that a separate gene may determine neurofibrillary degeneration in familial PSP.

ACKNOWLEDGEMENTS

HRM was an MRC Clinical Training Fellow and this work is supported by the PSP (Europe) Association and the Reta Lila Weston Trust.

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Received 27 April 2001

In revised form 12 October 2001

Accepted 25 October 2001

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J Neurol Neurosurg Psychiatry 2002 72: 388-390
doi: 10.1136/jnnp.72.3.388

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