

SHORT REPORT

Sequence analysis of *tau* in familial and sporadic progressive supranuclear palsy

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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 *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 *tau* and there may be a clinical and pathological overlap between PSP and FTDP-17. In this study we have analysed the *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 *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 *tau*.

Progressive supranuclear palsy (PSP) is a parkinsonian syndrome due to neurofibrillary degeneration. The formation of tau protein containing neurofibrillary tangles is associated with widespread neuronal loss in the brain stem and basal ganglia.^{1,2} The clinical features of PSP include early postural instability, a supranuclear gaze palsy, dysarthria, and dysphagia.³ The aetiology of PSP is unknown. However, it has been shown that sporadic PSP is associated with one allele (A0) of a dinucleotide polymorphism in *tau*.⁴ The association of sporadic PSP with this polymorphism has been confirmed in several studies.^{5–9} This association extends to other polymorphisms in *tau*, which are in linkage disequilibrium leading to a 100 Kb haplotype, called H1, which may contain pathogenic mutations or other genetic variations which increase the susceptibility to PSP.¹⁰ The H1 haplotype may be associated with a small increased risk of PSP in the general population, or alternatively a rare pathogenic *tau* mutation with high penetrance may have occurred on the H1 haplotype background.

Progressive supranuclear palsy has occasionally been described as occurring in familial form,^{11–17} and to date no genetic linkage or gene mutations have been described which account for familial PSP.^{10,18} It has been suggested that the familial occurrence of PSP may have been underestimated as within families, PSP may have a wider clinical phenotype than is usually recognised.¹⁷ Possibly, dystonia, tremor, or tics may occur as a variable phenotypic expression of familial PSP.¹⁷ The disease has clinical and pathological similarities to familial frontotemporal dementia linked to chromosome 17 (FTDP-17),¹⁹ which is due to pathogenic mutations in *tau*.^{20–22} These mutations may either be protein coding or they may be splice mutations which alter the alternative splicing of *tau* exon 10.²² The association between PSP and *tau*, and the similarity between FTDP-17 and PSP both suggest that *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 *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 *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.

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.^{14,17} Clinical diagnoses were made by retrospective note review and the NINDS and less stringent Tolosa criteria were applied to index cases of PSP.²³ We included those with pathologically diagnosed PSP but atypical clinical features.²⁴ 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 16.¹⁴ For the sequencing of *tau*, brain expressed exons 9–13 were amplified by polymerase chain reaction (PCR) using primers and conditions as previously described.²⁵ The PCR products were purified using a Qiagen kit (Qiagen Inc, Valencia, CA, USA) and the sequencing was performed using a 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).

RESULTS

Analysis of *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

Abbreviations: PSP, progressive supranuclear palsy; FTDP-17, frontotemporal dementia linked to chromosome 17

Table 1 Analysis of tau in PSP

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

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.^{10, 26, 27} FTDP-17 kindreds in which the pathogenic mutation is a *tau* exon 10 coding or splice mutation are particularly similar to PSP.^{28, 29} 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.³⁰ 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.²² Progressive supranuclear palsy may also involve a change in the alternative splicing of *tau*,³¹ but this has not been demonstrated in all brain areas, or in all cases.^{18, 31} In addition, FTDP-17 involves degeneration of frontal and temporal cortex and often involves marked personality change, obsessional symptoms, and progressive dysphasia.²⁸

Although personality change and withdrawal may be early features of PSP, the most characteristic features are of early imbalance and a supranuclear gaze 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.^{21, 28, 32, 33} 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.³⁴⁻³⁶ Progressive supranuclear palsy distribution pathology has been described in some FTDP-17 families.^{22, 35, 37} 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.³⁸ In addition, FTDP-17 exon 10 mutation cases may involve extensive oligodendroglial 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.³⁹

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,¹⁸ our data suggest that a separate gene may determine neurofibrillary degeneration in familial PSP.

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