The discovery of close to 20 different mutations in the gene encoding the microtubule-associated protein tau in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) has shown that dysfunction of tau protein causes neurodegeneration and dementia (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998; reviewed in Spillantini et al., 2000). It has implications for an understanding of Alzheimer’s disease (AD), Pick’s disease (PD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). All these diseases are characterized neuropathologically by an abundant filamentous tau pathology in nerve cells and, for some, in glial cells. The paper by Stanford and colleagues published in this issue of Brain is the latest in a series of studies reporting novel mutations in the tau gene in FTDP-17 (Stanford et al., 2000). It adds to our understanding of how tau mutations lead to neurodegeneration and throws light on the pathogenesis of PSP.

Six tau isoforms are expressed in adult human brain by alternative mRNA splicing from a single gene (Fig. 1). They differ from each other by the presence or absence of three inserts encoded by exons 2, 3 and 10. Inclusion of exon 10 gives rise to the three tau isoforms with four repeats each. The other three isoforms have three repeats each. Normal adult human brain expresses similar levels of three- and four-repeat tau isoforms. In contrast, mutations in exon 10 (N279K, (V337M) and exon 13 (G389R and R406W) affect all six tau isoforms. In contrast, mutations in exon 10 (N279K, (V337M) and exon 13 (G389R and R406W) affect all six tau isoforms. In contrast, mutations in exon 10 (N279K and S305N) deviate from this in that they do not lead to a reduced ability of tau to interact with microtubules. Instead, they increase splicing-in of exon 10, like the intronic mutations (D’Souza et al., 1999; Hasegawa et al., 1999). The N279K mutation creates a splice-enhancer sequence, which explains its effects (Clark et al., 1998). Similarly, the L284L mutation disrupts a splice-silencer sequence, resulting in increased splicing-in of exon 10 (D’Souza et al., 1999). This work has uncovered the existence of sequence elements regulating the alternative splicing of exon 10 within exon 10 itself. The S305N mutation (AGT to AAT) changes the last amino acid in exon 10 (Iijima et al., 1999). This sequence forms part of the stem-loop structure, where the mutation produces a destabilizing G to A transition at position –1 (Fig. 1b). Like the +3 mutation, the –1 mutation is also expected to lead to increased binding of U1 snRNA.

Stanford and colleagues describe a novel mutation in codon 305 (AGT to AGC) that is silent at the amino acid level (S305S) (Stanford et al., 2000). However, the T to C transition at position 0 disrupts the stem-loop structure, without a predicted effect on U1 snRNA binding (Fig. 1b). By exon trapping, it produced increased splicing-in of exon 10, as has previously been shown for the other six mutations that disrupt the stem–loop structure. Fixed brain tissue from an individual with the S305S mutation was used for neuropathological analysis. It showed an abundant tau pathology in nerve cells and glial cells, with the presence of straight and twisted
filaments by electron microscopy. A neuronal and glial tau pathology has previously been found in all cases with mutations in exon 10 or in the intron following exon 10 (Spillantini et al., 2000). The lack of unfixed brain tissue from the patient with the S305S mutation precluded further analysis. It therefore remains to be seen whether isolated filaments are wide twisted ribbons made of four-repeat tau, as in cases with the +3, +12 and +16 mutations. It also remains to be determined whether soluble four-repeat tau is overexpressed, as has been shown for the +3, +12, +14 and +16 mutations.

Unlike most tau mutations, the S305S mutation produced only mild frontotemporal atrophy. Instead, basal ganglia, subthalamic nucleus and several midbrain regions were found to be severely affected. The distribution of tau pathology, as well as its cellular distribution, were reminiscent of PSP. The same was true of the clinical picture, with early postural instability and supranuclear vertical gaze palsy. The tau gene has recently been implicated in the aetiology of PSP, by virtue of the association of an intronic polymorphic dinucleotide marker and an extended haplotype with the disease (Conrad et al., 1997; Baker et al., 1999).

Although the S305S mutation led to a clinical and neuropathological picture resembling PSP in one individual, it produced a clinical picture of pre-senile dementia in two other individuals from the same family. This underscores the previously noted variability in clinical expression resulting from a given mutation in tau (Bugiani et al., 1999). So far, tau mutations have been shown to give rise to the clinical picture of frontotemporal dementia, AD, PD, PSP, CBD or progressive subcortical gliosis. The factors determining these different clinical phenotypes remain to be discovered. Meanwhile, the new work has firmly established the pivotal role that tau protein plays in a large number of neurodegenerative diseases.

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References


fig. 1 Mutations in the tau gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). (a) Schematic diagram of the six tau isoforms (A–F) that are expressed in adult human brain. Alternatively spliced exons are shown in red (exon 2), green (exon 3) and yellow (exon 10); black bars indicate the microtubule-binding repeats. Eight missense mutations, one deletion mutation and two silent mutations in the coding region are shown. Amino acid numbering corresponds to the 441 amino acid isoform of human brain tau. (b) Stem–loop structure in the pre-mRNA at the boundary between exon 10 and the intron following exon 10. Seven mutations that reduce the stability of this tau exon 10 splicing regulatory element RNA are shown. Exon sequences are shown in capital and intron sequences in lower-case letters.


