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Commentary

The tangled biology of tau

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With the aging of the population comes a heightened sense of urgency to do something about Alzheimer's disease (AD), the most common dementia disorder. Treatment for AD is essentially nonexistent, but progress in understanding its molecular basis is encouraging. Recently, studies on the etiology of AD focused on the pathogenesis of two pathognomonic features, senile plaques and neurofibrillary tangles. First seen almost a century ago by Alois Alzheimer (1), these plaques and tangles are composed principally of the proteins Aβ (2) and tau (3), respectively. Identification of Aβ mutations in patients with AD argues that Aβ plays an important role in AD pathogenesis (4). But the role of tau in neurodegeneration was less certain until recent discoveries that mutations in the *tau* gene can cause non-Alzheimer's dementia (5–9).

In the latest of a series of articles describing *tau* mutations, D'Souza *et al.* (10) describe a new mutation and evidence that there is much to learn about the mechanisms by which *tau* mutations lead to neurodegeneration. The family described by D'Souza *et al.* further blurs the distinction between familial frontotemporal dementia (FTD) caused by *tau* mutation and AD.

Patients with *tau* mutations have a wide variety of clinical abnormalities but can usually be distinguished from patients with AD (11). Arnold Pick first described the most common syndrome associated with *tau* mutations (12). In a series of papers between 1892 and 1906 Pick reported several demented patients who exhibited language and behavioral disturbance associated with frontal lobe atrophy (13). Such patients with lesions in the frontal lobes characteristically have problems with their behavior (e.g., being crude) and affect (e.g., being depressed or overly gregarious) (14). In contrast, patients with AD have more widespread brain atrophy that begins in the temporal and parietal lobes (between the frontal and occipital lobes). Because of the brain region affected first, patients with AD characteristically have trouble with recent memory, a function of the temporal lobe, and with visuospatial function and performance of over-learned tasks (e.g., grooming or using eating utensils), functions of the parietal lobes. This simple clinical distinction based on regional brain involvement is very useful to physicians. Patients with temporal and parietal lobe pathology usually have AD, whereas those with frontal lobe pathology usually do not.

After Pick's seminal clinical descriptions of patients with frontal lobe atrophy, cases of frontal lobe atrophy were reported with round intraneuronal inclusions, presumably aggregated protein, that are now called Pick bodies (12). But, most patients with dementia with frontal lobe atrophy do not have Pick bodies. The association of Pick bodies with the clinical syndrome described by Pick led to a state of nosologic purgatory for most cases of patients with frontal lobe atrophy. These "lost" cases have been rediscovered several times in systematic attempts to identify the most common pathology in brains of demented patients. The most elaborated nomenclature uses the designation frontotemporal dementia (FTD) (15). FTD accounts for between 5% and 15% of autopsied patients with dementia (16) and probably a similar percentage of living patients seen in dementia clinics. The actual incidence and prevalence of FTD is difficult to estimate because (*i*) most affected patients are not seen by neurologists; (*ii*) many neurologists did not appreciate the distinction between FTD and AD; and (*iii*) there may be biases in referral patterns of patients with FTD.

Over the last decade many neurologists have accepted the FTD classification because criteria for the diagnosis of FTD are more well defined (17), and linkage of a family with this disorder to chromosome 17q21–22 has been reported (18). Soon after the report of the first family, other affected families with dementia linked to chromosome 17q21–22 were identified (11), and most of these have FTD. In addition, *tau* mutations have been found in most of the chromosome 17q21–22 families (5–9).

A common theme among FTD families is the finding of abnormal tau protein aggregates in neuronal or glial cells in the absence of Aβ aggregates (19). A few *tau* mutations cause neurofibrillary tangles that appear to be identical to those seen in AD, again, in the absence of *Aβ* aggregates (5, 20). In contrast, Aβ pathology is always accompanied by tau pathology in AD even with mutations in the Aβ precursor protein gene. This has lead to the simple model that Aβ is "upstream" of tau and that tau mediates the neurodegeneration seen in AD. This hypothesis is further supported by the observation that adding Aβ to cells in culture leads to changes in tau phosphorylation (21). Consistent with the idea that tau mediates neurodegeneration is the finding of the earliest pathological finding in AD, tau deposition in the entorhinal cortex (22).

The family with a *tau* mutation described by D'Souza *et al.* (10) has an affected individual who died at age 61 and had both tau and Aβ pathology. This description suggests that the simple model that Aβ is upstream of tau should be reconsidered. However, the single case reported by D'Souza *et al.* cannot distinguish between *tau* mutations and Aβ pathology. This argument would be far more compelling if Aβ pathology were shown to be inherited with the *tau* mutation. At least two other families have been identified in which a single member with presenile dementia had both Aβ and tau pathology (23, 24). In these cases most affected family members did not have Aβ pathology. It is conceivable that the Aβ abnormalities in these patients occurred independently of the *tau* mutation. Another possibility is that ongoing damage to the nervous system can predispose some individuals to the development of AD pathology with Aβ aggregation. To further confuse the issue, the patient reported by D'Souza *et al.* had an *apoE4* allele, which predisposes to AD (25). The observations that injection of tau paired helical filaments into rat brains induces Aβ deposition (26) and tau pathology can occur before Aβ pathology (22) are additional evidence that the simple model described above is not adequate.

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The important report by D'Souza *et al.* (10) also addresses a major issue concerning FTD: How do mutations in *tau* produce disease? The *tau* gene is very large and undergoes alternative splicing. Exon 10, which is differentially spliced, is 93 nucleotides in length and codes for 31 amino acids that represent a complete permuted version of a domain that has a microtubule-binding motif. The differential splicing of exon 10 produces transcripts with three and four repeats of the microtubule-binding domains. All of the mutations reported in the literature are in or near the sequences implicated by microtubule binding, including a clustering of mutations in both coding and noncoding sequences in and near exon 10. Many of the coding sequence mutations affect microtubule-binding properties and the assembly of tau into filaments (19). Other mutations in both the coding sequences and noncoding sequences affect the differential splicing of exon 10. Furthermore, distortion in the splicing of exon 10 appears to be sufficient to produce disease. A cluster of mutations that disrupt a sequence that can form a potential hairpin loop structure has been found 3′ to exon 10 (6). It has been postulated that the formation of this hairpin loop structure in the primary transcripts limits their accessibility to splicing and their hybridization to some nuclear RNA transcript factors.

Using an *in vitro* model to assess the effect of mutations on splicing efficiency, D'Souza *et al.* (10) have called the hairpin loop model into question. They demonstrated that a mutation (E10 + 3) that causes disease is predicted to disrupt the sequence of this hairpin structure and cannot be repaired by mutating the base (E10 + 12) that should restore base pairing. This finding suggests that the sequences found at the 3′ end of exon 10 do not, in fact, rely on the hairpin loop structure physiologically. Instead the primary transcript sequence is used somehow to affect splicing, possibly by binding of the primary transcript with other macromolecules.

The new *tau* mutation described by D'Souza *et al.* (10) and the analysis of the additional mutations detected in exon 10 suggest that there are at least two additional domains of sequences within the exon that affect the efficiency of its inclusion in messenger RNA. One of these domains resembles an exon splicing enhancer element. The other domain appears to be similar to an HIV exon splicing silencing element. The domains are separated by mutations that produce disease but do not affect splicing efficiency.

These data suggest that the *tau* gene interacts with several factors that affect differential splicing of exon 10, which in turn affects other cellular systems. Each of these factors may be a target for therapeutic intervention or may be susceptible to mutations that can cause disease. This level of complexity in the regulation of the splicing event presents a challenge to define the elements that interact with these regulatory sequences and to determine how they affect splicing in both normal and diseased states. This insight into a complex system offers a new opportunity for understanding the molecular pathogenesis of dementias and new hope for treatment.

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