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Mutations in the *Tau* gene cause frontotemporal dementia

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BACKGROUND

Deposits of intracellular filamentous material composed of microtubule associated protein tau are present in numerous sporadic and hereditary neurodegenerative diseases characterized by dementia. Intraneuronal tau filaments are found in association with extracellular deposition of amyloid-β and prion protein amyloid as in Alzheimer disease and in Gerstmann-Sträussler-Scheinker disease Indiana kindred variant, respectively, while intracellular tau deposits may occur in neurons and glia in the absence of any other abnormal protein deposition as in progressive supranuclear palsy, corticobasal degeneration, and Pick disease. Knowledge of the molecular pathology of Alzheimer disease in its sporadic and hereditary forms has been extensively developed over the past two decades; however, only recently has the focus been placed on hereditary frontotemporal dementias. In 1994, our group identified a form of familial frontotemporal dementia in which the presenting signs were disequilibrium and paralysis of the vertical eye movements [2]. A major neuropathologic characteristic was the filamentous pathology made of hyperphosphorylated tau protein. The presence of abnormal tau deposits in multiple regions of the brain, in both neurons and glial cells, led us to call the disease in this family Multiple System Tauopathy with Presenile Dementia (MSTD) [7]. Since 1994, several autosomal-dominant forms of similar disorders were linked to chromosome 17q21.2, the region that contains the *Tau* gene [1,9]. Genetic linkage in MSTD revealed that the gene responsible for the disease maps to chromosome 17q21.2 [5]. Thus, neuropathological findings and genetic linkage studies showed the *Tau* gene a strong candidate for MSTD. In 1996, following the clinical and genetic linkage assessment of several hereditary forms of frontotemporal dementia at a consensus conference, the name of frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) was chosen to characterize a select group of familial dementias, including MSTD [1]. It was following this conference that the search for *Tau* gene mutations became a priority.

HIGHLIGHT

In adult human brain, six tau isoforms are produced from a single gene by alternative splicing. They differ from each other by the presence or absence of 29- or 58-amino acid inserts located in the amino-terminal half and a 31-amino acid repeat located in the carboxy-terminal half. The latter, which is encoded by exon 10 of the *Tau* gene, gives rise to the three four-repeat tau isoforms. The repeats constitute the microtubule binding domains of tau.

We found that in MSTD, the tau deposits are characterized by wide, twisted, ribbon-like filaments, which consist exclusively of four-repeat tau isoforms, while the soluble tau contains a clear preponderance of tau isoforms with four repeats over isoforms with three repeats [7,8]. This observation led to the hypothesis that a mutation might be present in the structure regulating the alternative splicing of tau exon 10. In June 1998, three papers [4,6,8], including ours on MSTD, reported mutations in the *Tau* gene. MSTD is caused by a G to A transition in the nucleotide adjacent to the GT splice-donor site in the intron following exon 10, where it destabilizes a predicted RNA stem loop.

Thus far, more than fifteen different mutations associated with FTDP-17 have been found in the *Tau* gene. They are located in exons 9, 10, 12, and 13 and in the intronic regions outside exons 9 and 10. Some of these mutations affect the ability of tau to bind microtubules and others affect the splicing of exon 10 so that more four-repeat tau is produced.

SIGNIFICANCE

The discovery of tau mutations is of fundamental importance since it clearly shows that a primary lesion in tau causes nerve cell degeneration. These findings will clarify the mechanisms leading to filamentous tau pathology including that of Alzheimer disease. In fact, at this time, the mutations in tau can be subdivided into three groups according to the prevalence of tau isoforms present in the inclusions and the morphology of the filaments. In the exon 10 mutations, the tau filaments contain mainly four-repeat isoforms with only a small amount of three-repeat isoforms, in the intronic mutations following exon 10, the tau filaments are composed of four-repeat isoforms exclusively, and in the exon 12 and 13 mutations, it is composed of all six isoforms.

The mechanism leading from a *Tau* gene mutation to nerve cell degeneration is being elucidated; in fact, experimental studies *in vitro* indicate that mutations cause a partial loss of tau function resulting in microtubule destabilization and conceivably an alteration of the axoplasmic transport [3]. It is also possible that the

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overproduction of four-repeat tau alters the ratio of tau isoforms needed for normal neuronal function.

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