Pathophysiology

Tauopathies
- Alzheimer's disease (AD)
- Frontotemporal dementia (FTDP-17)
- Pick's disease
- Corticobasal degeneration (CBD)
- Progressive supranuclear palsy (PSP)

α-Synucleinopathies
- Parkinson's disease
- Multiple system atrophy (MSA)
- Dementia with Lewy bodies (DLB)

β-amyloid

TRENDS in Molecular Medicine
Model for tau binding
Lower motor neuron disease with respiratory failure caused by a novel MAPT mutation.


Abstract

OBJECTIVE: To investigate the molecular defect underlying a large Italian kindred with progressive adult-onset respiratory failure, proximal weakness of the upper limbs, and evidence of lower motor neuron degeneration.

METHODS: We describe the clinical features of 5 patients presenting with prominent respiratory insufficiency, proximal weakness of the upper limbs, and no signs of frontotemporal lobar degeneration or semantic dementia. Molecular analysis was performed combining linkage and exome sequencing analyses. Further investigations included transcript analysis and immunocytochemical and protein studies on established cell models.

RESULTS: Genome-wide linkage analysis showed an association with chromosome 17q21. Exome analysis disclosed a missense change in MAPT segregating dominantly with the disease and resulting in D348G-mutated tau protein. Motor neuron cell lines overexpressing mutated D348G tau isoforms displayed a consistent reduction in neurite length and arborization. The mutation does not seem to modify tau interactions with microtubules. Neuropathologic studies were performed in one affected subject, which exhibited α-motoneuron loss and atrophy of the spinal anterior horns with accumulation of phosphorylated tau within the surviving motor neurons. Staining for 3R- and 4R-tau revealed pathology similar to that observed in familial cases harboring MAPT mutations.

CONCLUSION: Our study broadens the phenotype of tauopathies to include lower motor neuron disease and implicate tau degradation pathway defects in motor neuron degeneration.

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