EFFECTS OF WILD-TYPE AND G2019S MUTANT LRRK2 ON THE PROGRESSION OF TAU PATHOLOGY

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Overlapping pathology is common in many neurodegenerative disorders and suggests that there are modifiers that lie upstream of particular pathological cascades. Patients with mutations in the Leucine-rich repeat kinase 2 (LRRK2) gene, the most common genetic cause of autosomal dominant Parkinsonism, are clinically indistinguishable from idiopathic late-onset Parkinson's disease (PD) cases. Interestingly, pathology of LRRK2 carriers can be pleomorphic ranging from typical Lewy Bodies to non-specific neuronal loss, and even to the accumulation of intracellular neurofibrillary tangles, which contain species of abnormally phosphorylated tau. Mutations in the gene encoding tau, MAPT, cause Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) and the H1 haplotype within the MAPT locus has shown linkage with sporadic PD. To study the interaction between Lrrk2 and tau we have generated four novel transgenic mouse lines. Using the Tet-Off system, we have created inducible transgenic mice over-expressing either human wild-type (WT) or mutant G2019S LRRK2, allowing us to study the effects of human LRRK2 on endogenous mouse tau. We have also crossed two bacterial artificial chromosome (BAC) transgenic mouse strains overexpressing human WT or mutant G2019S LRRK2 with a conditional mouse model of tauopathy (rTg4510). The rTg4510 model expresses human P301L mutant tau associated with FTDP-17 and has well-characterized NFT formation and pathological progression. We will show the neuropathology and biochemical analyses of our mouse lines and present the effects of wild-type and mutant LRRK2 on the onset of tau pathology in vivo.