

ANALYSIS OF THE MODULATORY EFFECT OF MUTANT LRRK2 ON TAU- AND TAU-AGGREGATION

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Objectives: Mutations in MAPT, the gene encoding Tau, have been identified to be causally linked to frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Mutations in LRRK2 and alpha-synuclein are linked to familial Parkinson's disease. While genome-wide association studies indicate that naturally occurring sequence variants in alpha-synuclein and LRRK2, confer an increased risk for late onset, sporadic PD. Previous reports have demonstrated a link between alpha-synuclein and Tau-aggregation. Here we analyse a potential link between LRRK2 and Tau.

Methods: To analyse the modulatory effect of LRRK2 (mutations) on Tau and Tau-aggregation we are using a Tau-*in vitro* aggregation assay in HEK293 cells in combination with crosses of LRRK2 and Tau transgenic mice and an *in vivo* Tau-aggregation assay.

Results: To analyse the modulatory role of LRRK2, mutant and wild type LRRK2 are co-transfected with Tau in HEK293 cells and effects on Tau-aggregation and Tau-phosphorylation are analysed. Furthermore, we have generated double transgenic LRRK2 (R1441C) and TauP301S transgenic mice, further denoted L+/T+ mice. Immunohistochemical and biochemical analysis of Tau and Tau-aggregation is performed in L+/T+ double transgenic mice and their respective single transgenic littermates (L-/T+), and correlated with the behavioral phenotype, to assess the modulatory effect of mutant LRRK2 on Tau and Tau-aggregation.

Conclusions: We here present novel *in vivo* and *in vitro* models to analyse the modulatory role of LRRK2 on Tau and Tau-aggregation and its phenotypic consequences.