Phosphorylation of Rab proteins predicts disease severity in neurodegeneration:

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Mutations in the *LRRK2* gene, encoding the Rab-like GTPase and serine/threonine kinase known as LRRK2, represent a common cause of familial Parkinson's disease. LRRK2 phosphorylates nearby its own GTPase domain in *cis*, but also phosphorylates other Rab small GTPases in *trans*. Among the few known LRRK2 Rab substrate pairs, Rab10 presents highly expressed in biofluids and different types of cells. While inhibitors of the LRRK2 enzyme are sought to block idiopathic neurodegenerative diseases including Alzheimer's disease and Parkinson's disease, a paucity is yet known in how LRRK2 activity, manifested through phosphorylated Rab proteins, might predict disease progression or change in different disease states. Our recent efforts have led to the development of robust sensitive and specific high-throughput assays for the assessment of LRRK2 expression and Rab substrate phosphorylation in deeply-phenotyped longitudinal cohorts. These ongoing assessments may shed light into disease pathways linked to alter Rab function and how these changes modify important disease phenotypes. With better descriptions of Rab changes in disease, it is anticipated that additional precision may emerge to help guide successful therapeutic leveraging of aberrant Rab function in different neurodegenerative disease outcomes.