

## **Genetic and Transcriptional Analysis of Susceptibility for Parkinson's Disease Neuropathology**

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### **Abstract:**

Parkinson's disease (PD) is a common, disabling, and incurable neurodegenerative disorder with evidence for substantial heritability. Genome-wide association studies (GWAS) have begun to show success; however, the clinical outcome of PD diagnosis is limited by heterogeneity in the patient sample and the presence of substantial but sub-clinical PD pathology in control subjects. In order to enhance power for gene discovery, I am therefore performing GWAS based on direct assessment of midbrain substantia nigra Lewy bodies (LBs), the defining neuropathology of PD, in two large autopsy cohorts, the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). Here, I propose to replicate the discovered loci in independent autopsy cohorts, and in order to establish their clinical relevance, I will also test for direct associations with PD susceptibility. In addition, I will investigate the impact of discovered variants on gene expression in both postmortem brain and cell lines from patients with PD. These studies will define a causal pathway from genetic variants to impact on gene expression and the ultimate development of both nigral pathology and clinical disease, providing novel insights into mechanisms of PD pathogenesis.