Discovery and systematic functional validation of Parkinson's disease genes from exome sequencing

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OBJECTIVE: To discover novel susceptibility genes for Parkinson's disease (PD).

BACKGROUND: Recently, whole-exome sequencing (WES) has accelerated the identification of familial PD genes, but this approach has yet to be deployed successfully in large cohorts of unrelated subjects. Challenges to definitive confirmation of genes and variants include the potential heterogeneity and relative rarity of the implicated alleles. Advances in cellular and animal models enable an integrated approach, in which variant discovery is coupled with a functional screening pipeline, linking candidate genes to established PD mechanisms.

DESIGN/METHODS: WES was performed in the International PD Genetics Consortium discovery cohort, including 1,148 unrelated cases and 503 control subjects, recruited from across the United States and Europe. Candidate genes were subsequently validated for roles in mitochondrial dynamics or α-synuclein mediated neurodegeneration, based on parallel RNA-interference (RNAi) screens in human neuronal cell culture or *Drosophila* transgenic models, respectively. The most promising candidates were subsequently examined for replication in several independent genetic datasets.

RESULTS: Assuming autosomal recessive inheritance, we discovered 27 genes with either homozygous or compound heterozygous loss-of-function variants in PD cases. Following RNAi-mediated knockdown, 15 genes modulated neuronal mitochondrial dynamics and 4 candidates enhanced α-synuclein induced neurodegeneration in *Drosophila*. Based on complementary analyses in independent human datasets, 5 functionally-validated genes—*GPATCH2L, UHRF1BP1L, PTPRH, ARSB* and *VPS13C*—also showed evidence consistent with genetic replication.

CONCLUSIONS: Our integrative approach pinpoints several excellent PD susceptibility gene candidates for further investigation, and highlights a powerful experimental strategy with broad applicability for future studies of PD and other complex genetic disorders.

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