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PARKINSON DISEASE

Unravelling the genetic contributors and their functional roles in sporadic PD

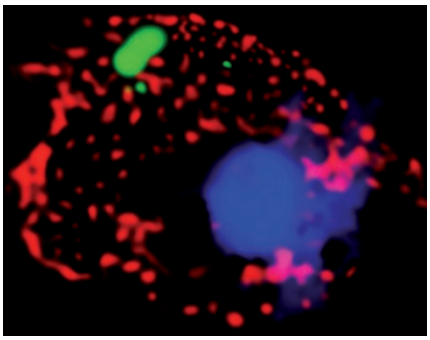
In a new study, published in *Neuron*, researchers have found that variants of leucine-rich repeat kinase 2 (*LRRK2*) and *RAB7L1* interact genetically and functionally to enhance the risk of sporadic Parkinson disease (PD). The findings highlight the protein-sorting pathway as a therapeutic target in PD.

Studies of familial PD have provided evidence of genetic and functional associations between risk genes, but whether such interactions occur in the more-common sporadic form was unclear. "We used a brain transcriptomic approach as a starting point, and focused initially on unaffected carriers of PD risk variants," explains Asa Abeliovich, lead researcher of the study. "The working hypothesis was that although carriers of the risk alleles generally don't develop PD, these variants could still affect aspects of brain pathology."

Variants at two PD-associated risk loci, LRRK2 and PARK16, had similar and overlapping effects on the brain. "We showed that the effect of these variants on PD risk are not independent, suggesting a common mechanistic pathway," explains Abeliovich. Notably, the PARK16 locus encompasses five possible PD risk genes, but only overexpression of one, *RAB7L1*, could suppress *LRRK2* mutation-induced shortening of neurites *in vitro*.

The PD-linked PARK16 haplotype is associated with alternative splicing of *RAB7L1* that leads to exclusion of a key activation domain of the gene. *In vitro* studies revealed that truncated *RAB7L1* could not rescue the mutant-*LRRK2* phenotype of neurites. Furthermore, a significant reduction in full-length *RAB7L1* was found in the brains of patients with PD.

Knockdown of *LRRK2* or *RAB7L1* in rat neurons caused lysosomal swelling, indicating that these genes are linked to the retromer pathway, which is involved in intraneuronal trafficking of proteins. Overexpression of wild-type, but not mutant, VPS35—a retromer component in which rare mutations have recently been linked to familial PD—suppressed the mutant *LRRK2* or *RAB7L1* phenotype in rodent neurons *in vitro* and *Drosophila* dopaminergic neurons *in vivo*.



Knockdown of *RAB7L1* in rat neurons reduces localization of lysosomes (red) with the Golgi apparatus (blue). Image courtesy of A. Abeliovich.

"These data suggest that improving retromer pathway function in PD would be therapeutic, so we are pursuing this direction," says Abeliovich.

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Original article MacLeod, D. A. *et al.* RAB7L1 interacts with LRRK2 to modify intraneuronal protein sorting and Parkinson's disease risk. *Neuron* doi:10.1016/j.neuron.2012.11.033