Researchers discover rare sequence variants that associate with a high risk of Parkinson's disease

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Scientists at deCODE genetics, a subsidiary of AMGEN, have discovered rare sequence variants, predicted to cause a loss of function of ITSN1, that are associated with a high risk of Parkinson's disease. The findings also support less studied pathways involved in the pathogenesis

of the disease.

The study, published in *npj Parkinson's Disease*, used whole-genome sequence data from Iceland (deCODE genetics), the UK (UK Biobank), and the US (Accelerating Medicines Partnership Parkinson's disease).

The role of ITSN1, Intersectin-1, is to activate CDC42, a small Rho GTPase involved in the growth and maintenance of dopaminergic neurons and the regulation of vesicle exocytosis of α-synuclein, whose accumulation is a pathological hallmark of Parkinson's disease.

The researchers propose that loss of ITSN1 function may contribute to Parkinson's disease pathogenesis through inactive CDC42 and its downstream pathways, degeneration of dopaminergic neurons and dysregulated vesicle exocytosis of α-synuclein, and/or through disrupted synaptic vesicle transport via clathrin-mediated endo- and exocytosis.

This suggests that targeting CDC42 or its upstream regulator, ITSN1, might offer a therapeutic approach for Parkinson's disease.

More information: Loss-of-function variants in ITSN1 confer high risk of Parkinson's Disease., *npj Parkinson's Disease* (2024). DOI: 10.1038/s41531-024-00752-9.

Provided by deCODE genetics

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