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A mutation in a protein-sorting gene is linked with Parkinson's disease

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Parkinson disease (PD) is a devastating incurable disease in which degeneration of dopamine neurons in the brainstem leads to tremors and problems with movement and coordination. An increasing proportion of patients appear to be genetically predisposed to disease. Now, two independent research groups have identified a mutation associated with an inherited form of PD. The papers, published by Cell Press in the July 9 issue of *The American Journal of Human Genetics,* provide new insight into the pathogenesis of late-onset PD and present compelling evidence that implicates a novel protein-recycling pathway in neurodegeneration.

"Previous studies of familial parkinsonism have identified pathogenic mutations in several genes, providing mechanistic insight and novel targets for therapeutic intervention," say the lead authors of one of the studies, Dr. Carles Vilariño-Güell and Dr. Matthew J. Farrer from the University of British Columbia. "In our study, we identified a pathogenic mutation associated with PD in a Swiss family where multiple individuals presented with disease. Confirmation of the discovery was an international effort embraced by neurologists in Canada, Israel, Norway, Switzerland, Taiwan, Tunisia, and the United States."

A second independent study, led by Dr. Tim M. Strom from the Institute of Human Genetics in Neuherberg, Germany and Dr. Alexander Zimprich from the Medical University of Vienna, used the same sophisticated sequencing techniques to look for causal mutations in a family from Austria with multiple incidences of late-onset PD.

Both groups discovered the same mutation in the vacuolar protein-sorting-associated protein 35 (VPS35) gene in affected family members. The VPS35 protein is part of a complex called the "retromer" that mediates the intracellular transport and sorting of membrane-associated cell-surface proteins that are going to be recycled or destroyed. "A single variant in the VPS35 gene was found in all affected family members investigated, was absent in general population samples, and was detected in two additional PD families," say Dr. Strom and Dr. Zimprich.

Taken together, the findings suggest that the VPS35 mutation is the genetic determinant of the late-onset PD examined in the studies and that perturbation of retromer-mediated protein sorting is linked with neurodegeneration. Interestingly, recent studies have suggested that retromer sorting defects are also associated with Alzheimer disease.

"Screening of VPS35 and its interacting partners, not only in PD patients but in other movement and cognitive disorders, is warranted to fully understand the role of the retromer in disease development. However, it is unclear how mutant VPS35 impairs retromer function or the transport of specific cargos or why dopaminergic neurons are selectively vulnerable," concludes Dr. Farrer's team. "Model systems based on VPS35 mutations can now focus on these issues and will facilitate the development of novel therapeutics."

Provided by Cell Press