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Parkinson's disease and cognitive decline—a genetic connection revealed

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Although the hallmark symptoms of Parkinson's disease (PD) – such as involuntary shaking, slowness of movement and muscle rigidity – are related to movement, recent evidence has suggested that memory impairment plays an outsized role in diminished quality of life and the burden placed on caregivers. A new study led by investigators in the Ann Romney Center for Neurological Diseases at Brigham and Women's Hospital finds that mutations in the gene for glucocerebrosidase (GBA), known to be a risk factor for PD, also have a powerful influence on the development of cognitive decline. The study is available online and published in the November edition of *Annals of Neurology*, the journal of the American Neurological Association.

"I believe this is the dawn of personalized medicine for Parkinson's disease," said corresponding author Clemens Scherzer, MD, associate professor of Neurology, who leads the Neurogenomics Lab and Parkinson Personalized Medicine Initiative of Brigham and Women's Hospital and Harvard Medical School. "This is one of the largest longitudinal assessments of patients with Parkinson's disease, and we believe that its insights will help to fix what is currently broken with clinical trials for patients. We see more precise clinical trials that will help match the right therapist with the right patient as the next logical step."

Two defective copies of the GBA gene are known to cause Gaucher's disease, a childhood disorder that causes death by age two or severe neurologic complications. One defective copy of the gene was once

thought to be of little consequence, but has recently emerged as a common risk factor for Parkinson's disease.

The new report examined 2,304 patients from the US, Canada and Europe, finding that 10 percent carried one (or more) defects in copies of the GBA gene. Patients carrying one defective GBA gene copy had an increased risk of memory troubles. This effect was most troublesome for patients carrying a GBA copy with the most severe type of defect—known as a neuropathic GBA mutation—whose risk of developing cognitive decline over time was increased by 217 percent. Approximately half of the carriers of a neuropathic GBA mutation developed global cognitive impairment within ten years of being diagnosed with Parkinson's. Among the PD patients without a mutation, only about 20 percent developed this decline in cognitive function.

Therapies for Gaucher disease have been available since 1994. Scherzer and colleagues hope that their findings will open the door for a completely new type of clinical trials in Parkinson's—GBA-directed trials designed to proactively prevent memory troubles in patients with movement-related symptoms. They estimate that such innovative, nimble trials would need 25-fold fewer patients then conventional trials, with reduced costs and a better chance of success.

More than 15 previous clinical trials for medications designed to slow or halt Parkinson's have been inconclusive or failed, perhaps in part, Scherzer notes, due to cumbersome and inefficient trial designs. Scherzer and his colleagues hope that their findings will breathe new life into better trial design and interest from pharmaceutical companies to tackle Parkinson's.

"We have now launched a Consortium with The Michael J. Fox Foundation and industry to put together a tool kit for GBA-directed, molecularly targeted trials in PD," said Scherzer. "This tool kit will be an

open resource for all scientists and pharma, and will comprise gene tests, biomarkers, and clinical parameters needed for successful proof-of-concept trials in PD. Smaller, more efficient trials remove a big entry barrier for pharma companies. This is good news for drug development and patients."

More information: Ganqiang Liu et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's, *Annals of Neurology* (2016). DOI: 10.1002/ana.24781

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