Discovery of genetic drivers linked to progression in Parkinson's disease

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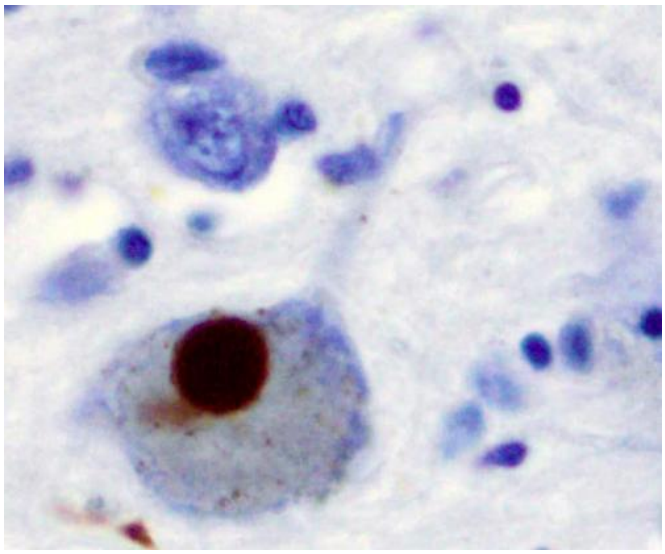

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A key driver of patients' well-being and clinical trials for Parkinson's disease (PD) is the course the disease takes over time. However, nearly all that is known about the genetics of PD is related to susceptibility—a person's risk for developing the disease in the future. A new study by investigators from Brigham and Women's Hospital published in *Nature Genetics* uncovers the genetic architecture of progression and prognosis, identifying five genetic locations (loci) associated with progression. The team also developed the first risk score for predicting progression of PD over time to dementia (PDD), a major determinant of quality of life.

"The patients who come to see me in the clinic are concerned about their future, rather than their past risk factors," said corresponding author Clemens Scherzer, MD, the director of the Center for Advanced Parkinson Research at the Brigham and director of the Brigham Precision Neurology Program. "They want to know how they will be doing in the future and need medications designed to stop the disease from rapidly progressing. This is the central question in our study: Which genes determine whether a patient will have an aggressive or benign course, and which variants influence who will develop dementia?"

As part of an international initiative, Scherzer and colleagues performed a genome-wide survival study (GWSS) of 11.2 million genetic variants in 3,821 PD patients over 31,578 longitudinal study visits conducted over the course of 12 years.

The team found five progression loci—points in the genome where genetic variants were associated with time from the onset of PD to progression to dementia. These included three novel loci: RIMS2, a gene involved in synaptic vesicle docking; TMEM108; and WWOX. The researchers also confirmed the importance of GBA and APOE4 as progression loci for PD. RIMS2 variants had a more than 2.5-times stronger effect on cognitive prognosis than GBA and APOE4.

The authors note that analyses of larger populations studied over time will be needed to detect other variants with small effect sizes and to further understand the overlap and differences in genetic contributors to susceptibility, progression and dementias. Surprisingly, the GWSS progression loci diverge from previously identified susceptibility loci, suggesting that the genetic triggers responsible for starting the disease and the genetic drivers progressively advancing the disease might be largely different.

"This is a different way to think about the disease and drug development," said Scherzer. "Disease-modifying drugs that target the genetic drivers of disease progression should be prime targets for turning fast progressors into slow progressors and

improve patients' lives."

More information: Genome-wide survival study identifies a novel synaptic locus and polygenic score for cognitive progression in Parkinson's disease, *Nature Genetics* (2021). DOI: 10.1038/s41588-021-00847-6

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