Investigating the most common genetic contributor to Parkinson's disease

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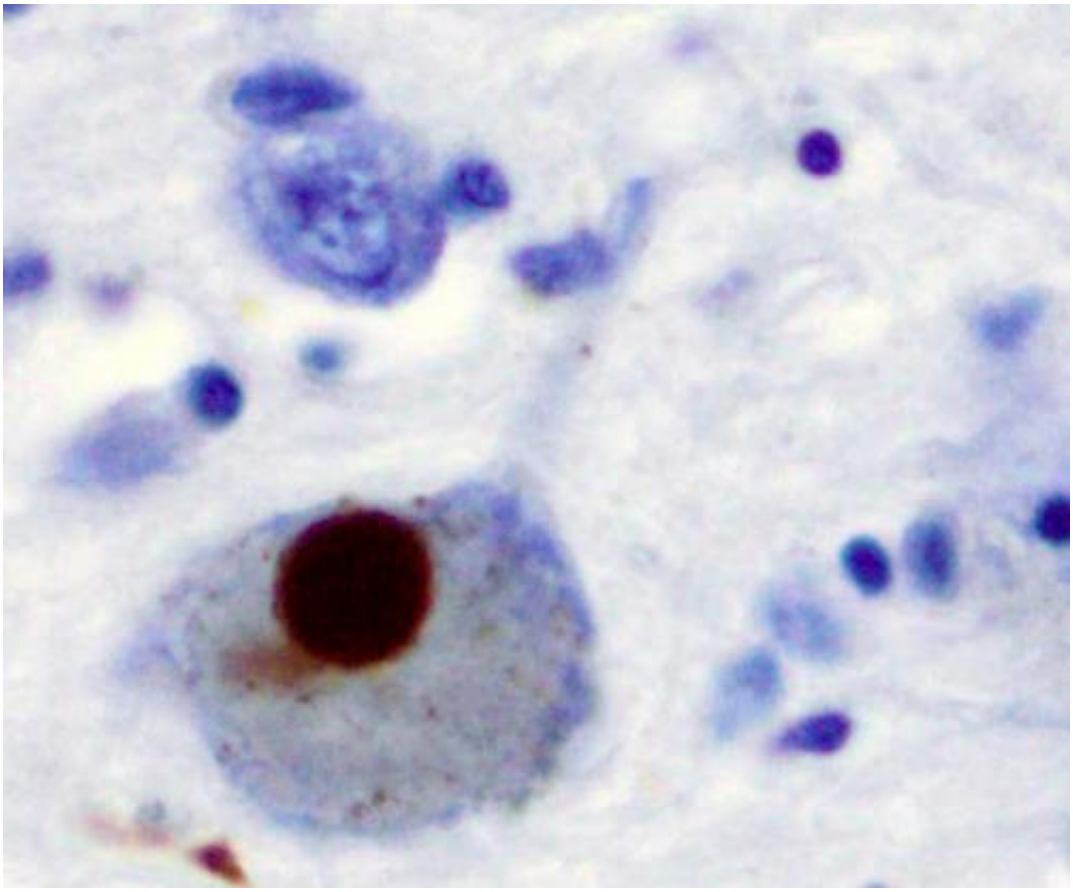

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

LRRK2 gene mutations are the most common genetic cause of

Parkinson's disease (PD), but the normal physiological role of this gene in the brain remains unclear. In a paper published in *Neuron*, Brigham and Women's Hospital principal investigator, Jie Shen, PhD, of the Department of Neurology, and her team describe an essential role of LRRK in the brain during aging that may help to shed light on the causes of PD in human patients. Their results appear this week in *Neuron*.

The team generated LRRK-deficient mice where both the LRRK2 gene and the LRRK1 gene were inactivated using a genetic technique called gene knock out. These mice showed signs of age-dependent dopaminergic (DA) neuron degeneration. Surprisingly, this double knock out, where two genes are simultaneously rendered inoperative, caused mice to exhibit earlier mortality and body-weight loss but largely normal brain-weight. Mice with only one gene knocked out did not develop the age-dependent DA neuron degeneration that the double knock out mice experienced.

Previous investigations by Shen's team connected the LRRK2 gene to the autophagy-lysosomal pathway. This pathway is an important mechanism for the cell to remove excess and abnormal proteins, and impairment of this pathway is increasingly recognized as a factor in neurodegenerative disorders like PD. The PD-like phenotypes of LRRK2 knockout mice, however, are only present in the aged kidney but not in the brain.

"A logical explanation for the lack of phenotypes in LRRK2 knockout mice was that the LRRK1 gene is still there to carry out normal LRRK function and compensate for the loss of LRRK2," said Shen. "So we generated the double knock out used in this study. With both LRRK genes removed, the double knockout mice lost the LRRK1 protection of the brain and developed age dependent degeneration."

In the study published in *Neuron*, the research team reports age-

dependent, significant DA neuron degeneration in double knock out mice accompanied by several other complications including impaired autophagy-lysosomal pathways. Further analysis revealed increased programmed cell death, or apoptosis, and higher levels of alpha-synuclein, a hallmark of PD.

"These findings revealed an essential role of LRRK in the survival of DA neurons and in the regulation of the autophagy-lysosomal pathway in the aging brain," said Shen.

More information: Giaime E et al. "Age-dependent dopaminergic neurodegeneration and impairment of the autophagy-lysosomal pathway in LRRK-deficient mice." *Neuron* DOI: 10.1016/j.neuron.2017.09.036

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