Study uncovers genetic variation that predicted type and rate of physical decline in patients with Parkinson's disease

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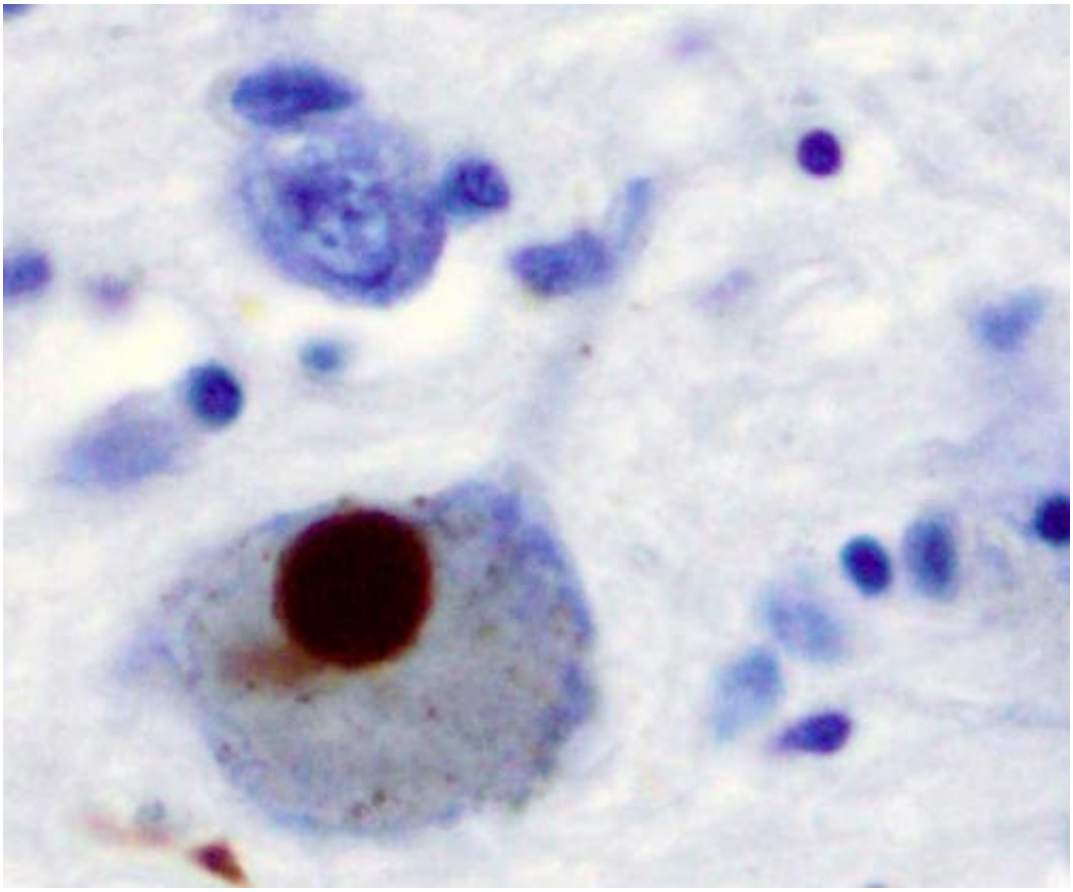

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Researchers at the Perelman School of Medicine at the University of Pennsylvania and other institutions have uncovered a site of genetic variation that identified which patients with Parkinson's disease are more likely to have tremors versus difficulty with balance and walking. The Penn team also found that patients with this genetic variation had a slower rate of Parkinson's disease progression, and lower amounts of alpha-synuclein in the brain. Alpha-synuclein is a protein that experts know plays a role in the development of Parkinson's disease.

Clinicians have long noted that the presence of tremors, rather than balance and walking problems, as the initial or dominant symptom of Parkinson's may suggest slower progression of the disease. The Penn-led study is one of the first to link this difference to a specific genetic variation. Tremor-dominant patients are also less likely to develop dementia, although this symptom was not assessed in the study.

The finding will be presented at the 68th Annual Meeting of American Academy of Neurology taking place April 15-21 in Vancouver. "We have never understood the reason why some people present with more tremor vs. walking/balance difficulties in Parkinson's disease," said the study's lead author, Christine A. Cooper, MD, a fellow in movement disorders at Penn Medicine. "This finding gives us information, for the first time, that has implications for diagnosis, prognosis, treatment, and prevention efforts."

In the study, the investigators ranked 251 Parkinson's disease patients at the University of Pennsylvania Health System on tremor and balance/walking scores. They then looked at the patients' genotypes to see if there were correlations between ten genetic variations previously associated with Parkinson's disease and the primary symptoms that the patients displayed.

The researchers found that 39 of the 251 patients who had a genetic

variation known as the GG genotype at the rs356182 SNP 3' to the SNCA gene were more likely to have: 1) tremors rather than walking/balance problems; 2) slower physical progression of the disease; and 3) lower levels of alpha-synuclein in the brain. Patients were followed up to seven years in some cases. The investigators carried out the same type of analysis with an additional group of 559 patients at three other clinical sites in the United States and found similar results for the association between the genotype and the type of PD symptoms.

"This is how we can start thinking about precision medicine in action," said the study's senior author, Alice S. Chen-Plotkin, MD, an assistant professor of neurology at Penn. "We found that a relatively common genetic variation can both serve as a biomarker for and influence the disease course of Parkinson's patients. This opens up the possibility of achieving a hallmark of precision medicine: targeted therapies for different 'versions' of what was once thought to be a single disease."

Single nucleotide polymorphisms of the kind the Penn-led team investigated, frequently called SNPs (pronounced "snips"), are the most widespread kind of genetic variation among people. There are about 10 million of them in the human genome (often found in the DNA between genes), and most have no effect on health or development. But when SNPs occur within a gene or in a regulatory region near a gene, they may play a more active role in disease by affecting the gene's function. The investigators found that this indeed may be the case in Parkinson's patients with the GG genotype, a relatively common SNP near the alpha-synuclein (SNCA) gene. The human alpha-synuclein protein is made of 140 amino acids and is encoded by the SNCA gene. Alpha-synuclein is the primary structural component of Lewy bodies, which are clumps of protein that develop inside nerve cells in Parkinson's disease and some other disorders.