Researchers identify new gene involved in Parkinson's disease

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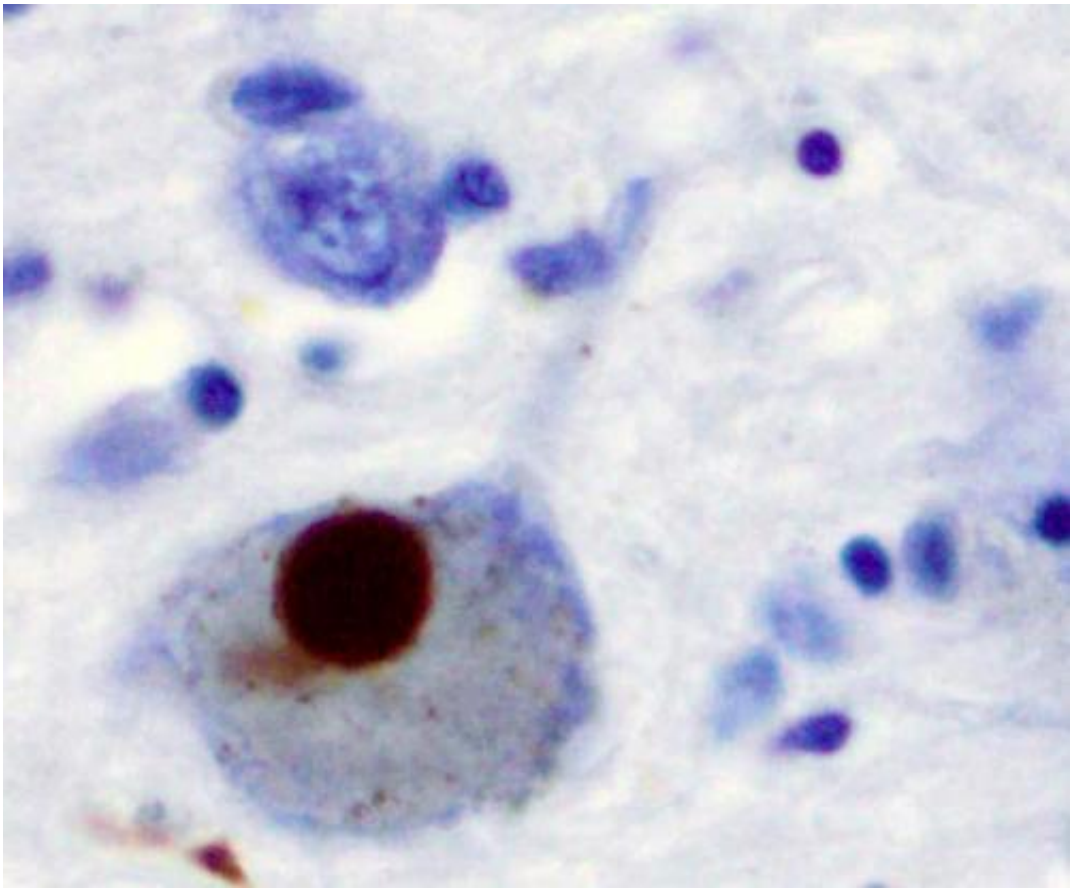

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A team of UCLA researchers has identified a new gene involved in

Parkinson's disease, a finding that may one day provide a target for a new drug to prevent and potentially even cure the debilitating neurological disorder.

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease, and there is no cure for the progressive and devastating illness. About 60,000 Americans are diagnosed with Parkinson's disease each year. It is estimated that as many as 1 million Americans live with Parkinson's disease, which is more than the number of people diagnosed with multiple sclerosis, muscular dystrophy and Lou Gehrig's disease combined.

In Parkinson's disease, multiple neurons in the brain gradually break down or die. This leads to the movement impairments, such as tremor, rigidity, slowness in movement and difficulty walking, as well as depression, anxiety, sleeping difficulties and dementia, said Dr. Ming Guo, the study team leader, associate professor of neurology and pharmacology and a practicing neurologist at UCLA.

A handful of genes have been identified in inherited cases of Parkinson's disease. Guo's team was one of two groups worldwide that first reported in 2006 in the journal *Nature* that two of these genes, PTEN-induced putative kinase 1 (PINK1) and PARKIN, act together to maintain the health of mitochondria – the power house of the cell that is important in maintaining brain health. Mutations in these genes lead to early-onset Parkinson's disease.

Guo's team has further shown that when PINK1 and PARKIN are operating correctly, they help maintain the regular shape of healthy mitochondria and promote elimination of damaged mitochondria. Accumulation of unhealthy or damaged mitochondria in neurons and muscles ultimately results in Parkinson's disease.

In this study, the team found that the new gene, called MUL1 (also known as MULAN and MAPL), plays an important role in mediating the pathology of the PINK1 and PARKIN. The study, performed in fruit flies and mice, showed that providing an extra amount of MUL1 ameliorates the mitochondrial damage due to mutated PINK/PARKIN, while inhibiting MUL1 in mutant PINK1/PARKIN exacerbates the damage to the mitochondria. In addition, Guo and her collaborators found that removing MUL1 from mouse neurons of the PARKIN disease model results in unhealthy mitochondria and degeneration of the neurons.

The five-year study appears June 4, 2014, in *eLife*, a new, open access scientific journal for groundbreaking biomedical and life research sponsored by the Howard Hughes Medical Institute (United States), the Wellcome Trust (United Kingdom) and Max Plank Institutes (Germany).

"We are very excited about this finding," Guo said. "There are several implications to this work, including that MUL1 appears to be a very promising drug target and that it may constitute a new pathway regulating the quality of mitochondria."

Guo characterized the work as "a major advancement in Parkinson's disease research."

"We show that MUL1 dosage is key and optimizing its function is crucial for brain health and to ward off Parkinson's disease," she said. "Our work proves that mitochondrial health is of central importance to keep us from suffering from neurodegeneration. Further, finding a drug that can enhance MUL1 function would be of great benefit to patients with Parkinson's disease."

Going forward, Guo and her team will test these results in more complex organisms, hoping to uncover additional functions and mechanisms of

MUL1. Additionally, the team will perform small molecule screens to help identify potential compounds that specifically target MUL1. Further, they will examine if mutations in MUL1 exist in some patients with inherited forms of Parkinson's.

Provided by University of California, Los Angeles

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