

Study Reveals Connection between Genetic and Environmental Causes of Parkinson's Disease

Scientists at the Whitehead Institute for Biomedical Research have found that a single gene, known as PARK9, protects cells from manganese toxicity and rescues neurons from over-expression of the protein alpha-synuclein. Misfolded alpha-synuclein is the hallmark of Parkinson's disease.

"This is one of the first connections between Parkinson's disease genetics and the environment," says Aaron Gitler, one of the co-authors of a paper published online in the February 1 edition of *Nature Genetics*.

Parkinson's disease is a neurodegenerative disorder characterized by tremors, muscle rigidity, and slowed movements. In the neural cells of Parkinson's patients' brains, researchers have noted Lewy bodies, abnormal spheres composed of the protein alpha-synuclein. There is currently no cure for the disease, and current Parkinson's therapies only address disease symptoms.

"Using yeast to study Parkinson's means that we will be able to start understanding the underlying pathobiology of the disease and eventually design rational therapeutic strategies based on what's causing the disease rather than what's the outcome," says Whitehead Member Susan Lindquist. "In other words, treating the root cause rather than the symptoms."

The specific causes of the disease remain unknown. Growing evidence in the research and medical communities implicates baffling and disconnected genetic and environmental factors. One genetic factor seems to be alpha-synuclein overexpression, which can be caused by too many copies of its gene. Another is mutations in a gene of previously unknown function PARK9. And overexposure to the metal manganese can lead to parkinsonism, a Parkinson's disease-like syndrome. Now researchers in the laboratory of Whitehead Member Susan Lindquist have associated these three factors.

"One of the reasons PARK9 is so interesting is when it's mutated, it leads to early onset parkinsonism," says Melissa Geddie, a Lindquist postdoctoral researcher and co-author of the paper.

First, Gitler (then in the Lindquist lab) found that wild-type (no mutations) PARK9 suppresses alpha-synuclein toxicity in a yeast model of Parkinson's disease. Gitler, Geddie and University of Pennsylvania postdoctoral fellow Alessandra Chesi then examined the function of the yeast version of the gene, called yeast PARK9 (YPK9). When yeast cells possessing a normal YPK9 gene exposed to various metals were more resistant to manganese than cells lacking the YPK9 gene. Mutations engineered to mimic those associated with early onset PD in humans failed to provide protection.

"These results suggest that one of the gene's functions is to protect cells from manganese," says Gitler.

The relationship between PARK9 and alpha synuclein in yeast were later confirmed in additional Parkinson's models, including those in *C. elegans* and rat neurons, in collaboration with investigators at the University of Alabama and Purdue University. Lindquist says that the yeast model exploits the biological similarities between yeast cells and human cells, making it particularly well-suited to enhancing our knowledge of what actually happens in cells affected by Parkinson's.

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