Research shows genetic evidence that new therapies targeting Parkinson's disease may cause harm

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(Medical Xpress)—NorthShore University HealthSystem (NorthShore) and Mayo Clinic researchers have partnered on a study that shows genetic and clinical evidence that therapies targeting the expression of alpha-synuclein—a gene whose function is involved in the development and progression of Parkinson's disease—may accelerate disease progression and increase the risk of physical incapacitation and dementia. If replicated, the findings will have profound implications for therapies under development for Parkinson's disease.

"Our research suggests therapies that seek to suppress alpha-synuclein in Parkinson's disease may actually accelerate the disease process and increase the risk for developing severe physical disability and dementia," says lead author Demetrius Maraganore, M.D., Ruth Cain Ruggles Chairman, Department of Neurology at NorthShore. "We believe it is our responsibility to release these data because this type of treatment may have long-term harmful effects."

Alpha-synuclein is a major component of Lewy bodies—a characteristic brain cell abnormality that occurs in all cases of Parkinson's disease. Since its discovery as a cause of familial Parkinson's disease nearly 20 years ago, alpha-synuclein has been the focus of intensive efforts by researchers working to definitively characterize the protein's role in idiopathic Parkinson's disease and its potential as a target for neuroprotective therapies. It has also been the focus of multiple efforts

to develop a molecule that suppresses the protein function. A vaccine that targets alpha-synuclein (reducing alpha-synuclein levels) is currently in Phase I clinical trials, and a number of molecules that target the protein for reduction are in advanced stages of preclinical development.

"For the first time we observed that while over-expression of alpha-synuclein increases the risk for developing Parkinson's disease, conversely, under-expression is associated with worse motor and cognitive outcomes after the disease starts," says first author Katerina Markopoulou, M.D., Ph.D., a neurologist at NorthShore. "This raises concerns about the efficacy and safety of therapies designed to reduce alpha-synuclein expression in Parkinson's disease."

The researchers followed 1,098 Mayo Clinic patients for nearly 15 years (median: eight years), and sequenced the patients' DNA to determine the presence of gene variants that regulate how much alpha-synuclein protein is made. They studied the association of these gene variants with patients' survival that was free of severe motor and cognitive disabilities. Patient outcomes were measured by telephone interviews.

The scientists found that patients who had the reduced expression genotype had a 23 percent greater risk of becoming wheelchair-dependent or developing dementia.

"This is the first large genetic association study of alpha-synuclein and longitudinal outcomes in Parkinson's disease," says Eric Ahlskog, M.D., Ph.D., a Mayo Clinic neurologist and author on the study. "If replicated, this research may change the treatment paradigm focused on alpha-synuclein reduction for Parkinson's disease."

The study will be discussed at 5 p.m. EST, March 20 at the 2013 American Academy of Neurology (AAN) Annual Meeting in San Diego. This research is one example of the collaborative efforts between

NorthShore and Mayo Clinic under the Mayo Clinic Care Network, a unique partnership that provides NorthShore patients with access to medical resources and experts from both systems working together on their behalf.

Provided by Mayo Clinic