

# Mechanism that leads to sporadic Parkinson's disease identified

25 September 2012

Researchers in the Taub Institute at Columbia University Medical Center (CUMC) have identified a mechanism that appears to underlie the common sporadic (non-familial) form of Parkinson's disease, the progressive movement disorder. The discovery highlights potential new therapeutic targets for Parkinson's and could lead to a blood test for the disease. The study, based mainly on analysis of human brain tissue, was published today in the online edition of *Nature Communications*.

Studies of rare, familial (heritable) forms of Parkinson's show that a protein called alpha-synuclein plays a role in the development of the disease. People who have [extra copies](#) of the alpha-synuclein gene produce excess alpha-synuclein protein, which can damage neurons. The effect is most pronounced in dopamine neurons, a population of [brain cells](#) in the [substantia nigra](#) that plays a key role in controlling normal movement and is lost in Parkinson's. Another key feature of Parkinson's is the presence of excess alpha-synuclein aggregates in the brain.

As the vast majority of patients with Parkinson's do not carry rare familial mutations, a key question has been why these individuals with common sporadic Parkinson's nonetheless acquire excess alpha-synuclein protein and lose critical [dopamine neurons](#), leading to the disease.

Using a variety of techniques, including [gene-expression analysis](#) and gene-network mapping, the CUMC researchers discovered how common forms of alpha-synuclein contribute to sporadic Parkinson's. "It turns out multiple different alpha-synuclein transcript forms are generated during the initial step in making the disease protein; our study implicates the longer transcript forms as the major culprits," said study leader Asa Abeliovich, MD, PhD, associate professor of pathology and neurology at CUMC. "Some very common genetic variants in the alpha-synuclein gene, present in many people, are known to impact the likelihood

that an individual will suffer from sporadic Parkinson's. In our study, we show that people with 'bad' variants of the gene make more of the elongated alpha-synuclein transcript forms. This ultimately means that more of the disease protein is made and may accumulate in the brain."

"An unusual aspect of our study is that it is based largely on detailed analysis of actual patient tissue, rather than solely on animal models," said Dr. Abeliovich. "In fact, the longer forms of alpha-synuclein are human-specific, as are the disease-associated genetic variants. Animal models don't really get Parkinson's, which underscores the importance of including the analysis of human brain tissue."

"Furthermore, we found that exposure to toxins associated with Parkinson's can increase the abundance of this longer transcript form of alpha-synuclein. Thus, this mechanism may represent a common pathway by which environmental and genetic factors impact the disease," said Dr. Abeliovich.

The findings suggest that drugs that reduce the accumulation of elongated alpha-synuclein transcripts in the brain might have therapeutic value in the treatment of Parkinson's. The CUMC team is currently searching for drug candidates and has identified several possibilities.

The study also found elevated levels of the alpha-synuclein elongated transcripts in the blood of a group of patients with sporadic Parkinson's, compared with unaffected controls. This would suggest that a test for [alpha-synuclein](#) may serve as a biomarker for the disease. "There is a tremendous need for a biomarker for Parkinson's, which now can be diagnosed only on the basis of clinical symptoms. The finding is particularly intriguing, but needs to be validated in additional patient groups," said Dr. Abeliovich. A biomarker could also speed clinical trials by giving

researchers a more timely measure of a drug's effectiveness.

**More information:** "Alternative alpha-synuclein transcript usage as a convergent mechanism in Parkinson's disease pathology," *Nature Communications*, 2012.

Provided by Columbia University Medical Center

APA citation: Mechanism that leads to sporadic Parkinson's disease identified (2012, September 25) retrieved 2 May 2021 from <https://medicalxpress.com/news/2012-09-mechanism-sporadic-parkinson-disease.html>

*This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.*