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Tiny changes in Parkinson's protein can have 'dramatic' impact on processes behind onset

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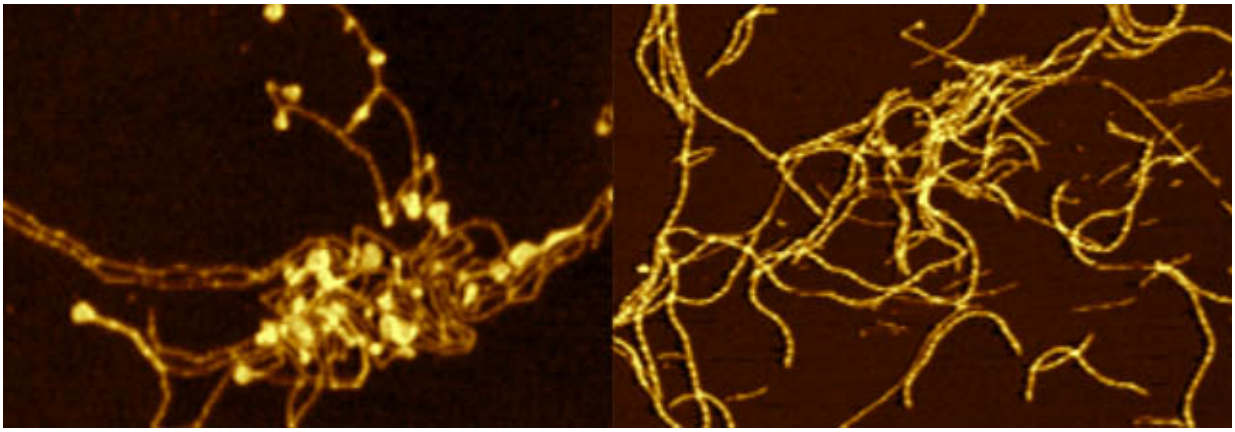

Images of "amyloid fibrils"; thread-like structures which form after the protein alpha-synuclein aggregates. Plaques (protein deposits) consisting of this protein have been found in the brains of Parkinson 's Disease patients and linked to disease. Credit: Patrick Flagmeier

Specific mutations in the protein associated with Parkinson's Disease, in which just one of its 140 building blocks is altered, can make a dramatic difference to processes which may lead to the condition's onset, researchers have found.

In a new study, a team of academics at the Centre for Misfolding Diseases, in the Department of Chemistry at the University of Cambridge, show that tiny changes in the sequence of the protein alpha-

synuclein can have a dramatic effect on microscopic processes that may occur in the brain, potentially eventually resulting in someone being diagnosed with Parkinson's.

Alpha-synuclein is a protein made up of 140 amino acids, and under normal circumstances plays an important part in helping with the smooth flow of chemical signals in the brain.

Parkinson's Disease is thought to arise because, for reasons researchers still do not fully understand, the same protein sometimes malfunctions. Instead of folding into the specific shape needed to do its job, it misfolds and begins to cluster, creating toxic, thread-like structures known as amyloid fibrils. In the case of Parkinson's Disease, these protein deposits are referred to as Lewy-bodies.

The new study examined mutated forms of alpha-synuclein which have been found in people from families with a history of Parkinson's Disease. In some cases, these mutations involved just one change to the protein's amino acid sequence.

Although the differences are small, the researchers found that they can have a profound effect on how quickly or slowly fibrils start to form. They also found that the mutations strongly influence a process called "secondary nucleation", in which parts break off to form more fibrils elsewhere and thus enable the disease to spread.

The study stresses that these findings do not explain why humans get the disease. Parkinson's does not always emerge as a result of the mutations and has multiple, complex causes, which are not fully understood.

Patrick Flagmeier, a PhD student at St John's College, University of Cambridge, and the study's lead author, said: "As a finding, it helps us to understand fundamental things about the system by which this disease

emerges. In the end, if we can understand all of this better, that can help us to develop therapeutic strategies to confront it. Our hope is that this study will contribute to the global effort towards comprehending why people with these mutations get the disease more frequently, or at a younger age."

Although people who do not have mutated forms of alpha-synuclein can still develop Parkinson's Disease, the five mutations studied by the research team were already known as "familial" variants - meaning that they recur in families where the disease has emerged, and seem to increase the likelihood of its onset.

What was not clear, until now, is why they have this effect. "We wanted to know how these specific changes in the protein's sequence influence its behaviour as it aggregates into fibrils," Flagmeier said.

To understand this, the researchers conducted lab tests in which they added each of the five mutated forms of alpha-synuclein, as well as a standard version of the protein, to samples simulating the fibril growth process at three different stages of development.

The first round of tests examined the initial aggregation, using artificial samples recreating conditions in which misfolded alpha-synuclein attaches itself to small structures that are present inside brain cells called lipid vesicles, and then begins to cluster.

The researchers then studied the elongation stage, testing how the different versions of the protein influence the ability of pre-formed fibrils to extend and grow. Finally, they tested the impact of mutated proteins on secondary nucleation, in which, under specific conditions, parts of the fibrils break off and start to spread.

Overall, the tests revealed that while the mutated forms of alpha-

synuclein do not notably influence the second stage (fibril growth), they do have a dramatic effect both on the initial formation of the fibrils, and their secondary nucleation. Some of the mutated forms of the protein made these first and third-stage processes considerably faster, while others made it almost "undetectably slow", according to the researchers' report.

Why the mutations have this impact remains unclear, but the study opens the door to understanding this in detail by identifying, for the first time, that they have such a dramatic impact on very particular stages of the process.

"The changes we observed were by several orders of magnitude and it was unexpected to observe such notable effects from single-point mutations," Flagmeier said. "It seems that these very specific, tiny differences in the sequence of a protein play an important role in influencing particular microscopic steps in the aggregation process that may lead to Parkinson's Disease."

The full study is published in the journal, *Proceedings of the National Academy of Sciences*.

More information: Mutations associated with familial Parkinson's disease alter the initiation and amplification steps of α-synuclein aggregation, www.pnas.org/cgi/doi/10.1073/pnas.1604645113

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