

Brain diseases with molecular diversity

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Parkinson's and multisystem atrophy (MSA), both neurodegenerative diseases, are associated with the accumulation of alpha-synuclein proteins in the brain. Researchers at the German Center for Neurodegenerative Diseases (DZNE) and the Max Planck Institute for Biophysical Chemistry (MPI-BPC) have investigated the molecular

makeup of these protein deposits finding structural diversity. Experts from South Korea, Australia and Argentina were also involved in the study. The results, published in the scientific journal *Nature Communications*, suggest that Parkinson's might be related to diverse types of protein aggregates.

Alpha-synuclein is a [protein](#) that occurs naturally in the body. It is assumed to be involved in signal transmission between neurons. The protein appears both at the cell membrane and in solution within the cell's interior. In addition to these "normal" variants, there are others that manifest in brain diseases. This applies, e.g., to Parkinson's [disease](#) and MSA. Both can be associated with neurological impairments, including movement disorders. In Parkinson's and MSA, [alpha-synuclein](#) molecules stick together. As a result, elongated aggregates arise that are deposited inside neurons and other brain cells.

"These deposits successively appear in various areas of the brain. They are a disease hallmark," explains Prof. Markus Zweckstetter, who heads a research group at the DZNE and the MPI-BPC. "There is evidence that these aggregates are harmful to neurons and promote disease progression."

A matter of folding

These deposits represent a potential starting point for medicines. The idea is that drugs might prevent alpha-synuclein molecules from sticking together or dissolve existing aggregates. To identify potential docking sites for agents, data on the aggregates' fine structure is required. Thus, the question is: What kind of shape (also known as "folding") do the molecules adopt within the aggregates?

So far, information on this topic had been limited to data from laboratory experiments. "Previous studies investigated the molecular

structure of aggregates that were synthesized in a test tube. We asked ourselves how well such artificially produced specimens reflect the patient's situation. That is why we studied aggregates generated from [tissue samples](#) from patients," said Zweckstetter. "We collaborated closely with international partners on this project. In fact, the tissue samples originated in Australia, and the aggregates were synthesized in South Korea. We then did the structural studies in Göttingen."

Aggregates from brain samples taken from five deceased Parkinson's patients and five deceased MSA patients were examined. For comparison, the researchers artificially produced variants of alpha-synuclein aggregates using standard procedures. To compare the structures of the aggregates, they used nuclear magnetic resonance spectroscopy and other methods.

Structural differences

"We found that aggregated proteins that came from the lab were structurally different to all aggregates generated from patient material," Dr. Timo Strohäker, first author of the study, commented on the findings. "In addition, proteins of MSA patients differed from those of Parkinson's patients. If one looks at the data more closely, you notice that the proteins of the MSA patients all had a largely similar shape. The proteins of the patients with Parkinson's were more heterogeneous. When comparing the proteins of individual Parkinson's patients, there is a certain structural diversity."

The alpha-synuclein proteins of all aggregates contain beta sheets, which is in line with previous investigations. Accordingly, the molecular backbone is twisted in a way that the proteins are largely two-dimensional. Within the aggregates, the proteins stick together in layers. However, folding does not encompass the whole protein. Each protein also contains areas that are unstructured. Orientation of the beta sheets is

important: "It is a question of how much of a protein is folded and also how it is folded," Zweckstetter said.

Various types of aggregates in Parkinson's

In the structure of the alpha-synuclein associated with Parkinson's, there were some significant differences between patients. This might be due to the fact that the course of Parkinson's can vary quite considerably between individuals.

"The variability of Parkinson's disease could be related to differences in the folding of aggregated alpha-synuclein. This would be in contrast to the 'one disease, one strain' hypothesis, that is to say that Parkinson's disease is associated with one clearly defined aggregate form. However, in view of our relatively small sample of five patients, this is just a guess," said Zweckstetter. "Yet, our results certainly prove that studies with tissue samples from patients are necessary to complement lab experiments in a sensible way."

More information: Timo Strohäker et al, Structural heterogeneity of α -synuclein fibrils amplified from patient brain extracts, *Nature Communications* (2019). [DOI: 10.1038/s41467-019-13564-w](https://doi.org/10.1038/s41467-019-13564-w)

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