# On the trail of Parkinson's disease

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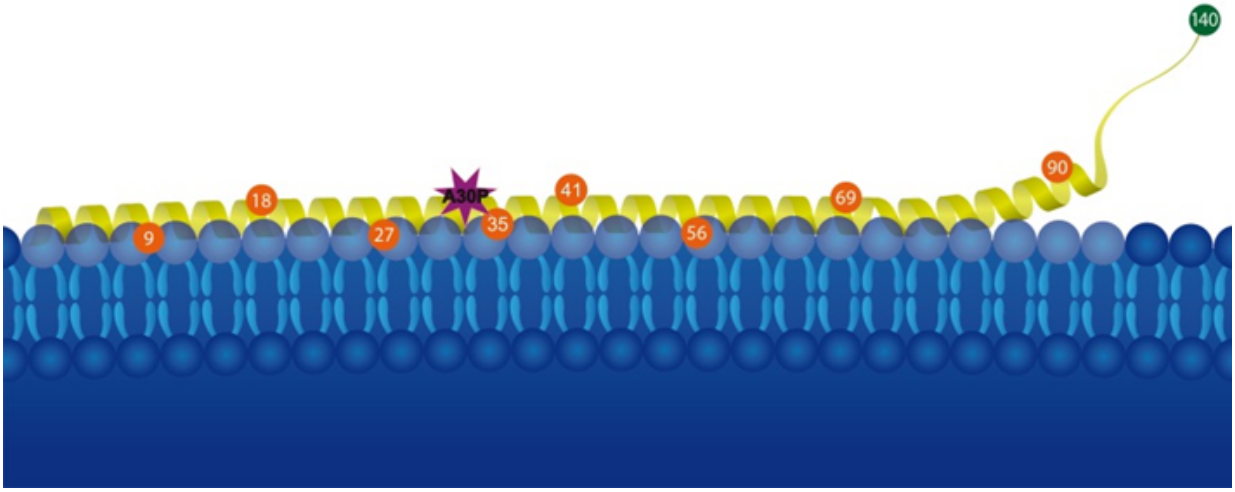


Caption: Binding of the alpha-synuclein protein (yellow) to lipid-membranes (blue). To examine the effect of a selective mutation of the 30th Amino acid (A30P) of alpha-synuclein, Malte Drescher's research group applied magnetic probes (see numbered circles) to the protein. Credit: University of Konstanz

The molecular causes of diseases such as Parkinson's need to be understood as a first step towards combating them. University of Konstanz chemists working alongside Professor Malte Drescher recently succeeded in analysing what happens when selective mutations of the alpha-synuclein protein occur—a protein that is closely linked to Parkinson's disease.

In a complex series of experiments they examined what the effects were

of changing a single amino acid in the protein. The physicochemists were able to prove how this tiny change disturbs the binding of alpha-synuclein to membranes. "We hope that the finding of this selectively defective membrane binding will help us to understand how Parkinson's develops on a molecular level. Ultimately, this will facilitate the devising of therapeutic strategies," outlines Julia Cattani, a doctoral student, who played a major role in the success of the research. The research results were revealed in the prestigious specialist *Journal of the American Chemical Society* publication in its 16 March 2017 online edition; a print version is to follow.

The human brain contains large quantities of the small alpha-synuclein protein. Its exact biological function is still unknown, yet it is closely linked to Parkinson's disease; the protein "clumps together" in the nerve cells of Parkinson patients. Alpha-synuclein consists of a chain of 140 amino acids. In rare cases Parkinson's disease is hereditary; where this occurs one of these 140 components has been replaced. Malte Drescher and his working group in the Department of Chemistry at the University of Konstanz have now found out the influence these selective changes in the protein sequence can have on the behaviour of alpha-synuclein. "We can show that the selective mutations disturb the membrane binding of alpha-synuclein on a local level," explains Malte Drescher.

To find out more about the influence of selective mutations, the Konstanz-based chemists Dr Marta Robotta and Julia Cattani applied tiny magnetic probe molecules to various places on the alpha-synuclein protein. With the help of electron paramagnetic resonance spectroscopy - a procedure similar in method to magnetic resonance imaging (MRI) used in the medical field - the researchers were able to measure the rotation of these nanomagnets. At every residue at which alpha-synuclein binds to a membrane, the rotation slows down. In this way they were able to find out precisely when and where a binding to the membranes takes place - and when it does not. In the case of the exchanged amino acids

the physicochemists from Konstanz discovered a disturbance of the membrane binding of alpha-synuclein - an important clue for the molecular context of Parkinson's disease.

"We went to great lengths, performing over 200 spectroscopic experiments, the results of which we compared with our models by means of a specially developed simulation algorithm. The outcome certainly compensated our efforts," says Julia Cattani. Project leader Malte Drescher believes that alongside the huge commitment of his staff, an important prerequisite for the success of the research was, above all, the environment of the Collaborative Research Centre (SFB) 969, "Chemical and biological principles of cellular proteostasis" which formed the basis for sponsoring the project: "By networking on an interdisciplinary level and discussing with colleagues we managed to solve the many problems we faced," emphasises Malte Drescher.

**More information:** Marta Robotta et al, Alpha-Synuclein Disease Mutations Are Structurally Defective and Locally Affect Membrane Binding, *Journal of the American Chemical Society* (2017). DOI: 10.1021/jacs.6b05335

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