# Scientists identify ATP10B as novel risk gene for Parkinson's disease

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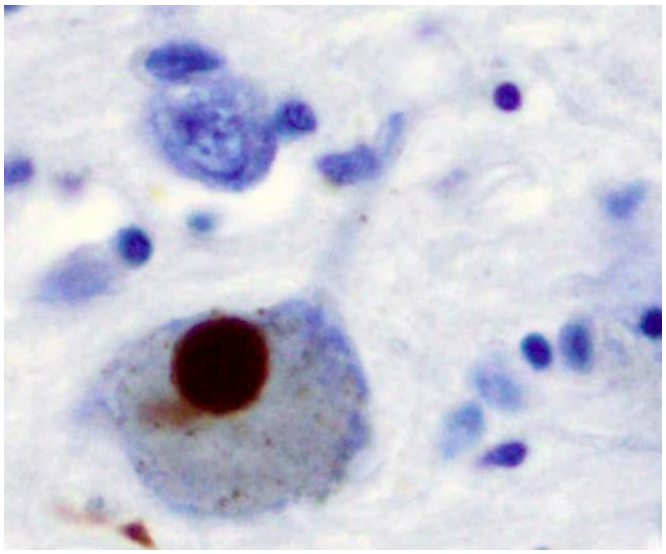

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Screening DNA of Parkinson's patients in the Christine Van Broeckhoven laboratory (VIB-UAntwerpen Center for Molecular Neurology) identified a new risk gene for Parkinson's disease. Mutations in ATP10B resulted in loss of ATP10B protein. The function of the ATP10B gene was revealed by the Peter Vangheluwe lab (KU Leuven, Laboratory of Cellular Transport Systems). They identified ATP10B as a transporter for glucosylceramide, a lipid that plays a central role in Parkinson's disease. Disease mutations disturb this function. Also, a reduced expression of ATP10B leads to neuronal loss and sensitizes neurons to environmental risk factors of Parkinson's disease. Therefore, ATP10B is emerging as an interesting therapeutic target for Parkinson's disease.

Parkinson's disease affects over 10 million people worldwide and more than 2 million people in Europe. Clinically, patients display a variety of motor and non-motor symptoms, impeding their ability to perform basic everyday activities. With currently no effective therapy, the chronic and progressive nature of Parkinson's disease has a profound impact on the quality of life of patients and caregivers.

The identification of Parkinson's disease genes and mutations contributed substantially to our understanding of the underlying disease mechanisms. In 5 to 15% of Parkinson's patients, genetic studies identified mutations in different genes that explained the segregation of disease in Parkinson's families between generations. Familial mutations are considered high penetrant, meaning that the carrier of the mutation is highly likely to get Parkinson's disease during their lifespan. In the larger part of non-familial Parkinson's patients, so-called sporadic patients, much less is known of the genetic contribution to Parkinson's disease, but several genes have been associated with increased genetic disease risk. In sporadic patients, different risk genes and mutations, in combination with environmental factors, might contribute to the overall genetic etiology of sporadic Parkinson's disease.

**Identification of the ATP10B gene**

Mutations in ATP10B were identified by Stefanie Smolders in the VIB-UAntwerpen laboratory in children with Parkinson's disease at an early age while the parents were healthy. These children carried two mutations in ATP10B, one on each chromosome inherited from the parents, mimicking recessive inheritance. In a group of 617 unrelated Parkinson's patients she identified another six carriers of two ATP10B mutations. Among the carriers we observed a high variability in the onset age at disease. This can indicate that the combination of multiple mutations might have different effects on ATP10B expression leading to

variable losses of ATP10B protein and function.

**From risk gene to disease mechanism**

Shaun Martin in the KU Leuven team studied the gene function of ATP10B and found that ATP10B works as a transporter that removes lipids out of the lysosome, the compartment in the cell that degrades and recycles obsolete cell material. In particular, ATP10B transports glucosylceramide, a lipid that plays an important role in Parkinson's disease. This process is disturbed by the disease mutations. ATP10B is important to preserve the health of the lysosomes and protects neuronal cells against environmental risk factors of Parkinson's disease.

**A new potential target for therapeutic intervention**

A better understanding of key targets and pathways in Parkinson's disease pathogenesis is necessary to overcome the major hurdle in the development of effective therapies for the disease. Glucosylceramide homeostasis seems to play a major role in the pathogenesis of Parkinson's disease. With the identification and characterization of ATP10B, we provide a new potential target involved in glucosylceramide homeostasis to tackle Parkinson's disease. Without any doubt, strategies to modulate ATP10B activity will be further explored for Parkinson's disease therapy, which is already under investigation by our teams and has raised interest of pharmaceutical companies.

**More information:** Martin S, Smolders S. et al. Mutated ATP10B increases Parkinson's disease risk by compromising lysosomal glucosylceramide expo. *Acta Neuropathologica* 2020.

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