Medical Xpress

Researchers discover new piece of the puzzle for Parkinson's disease

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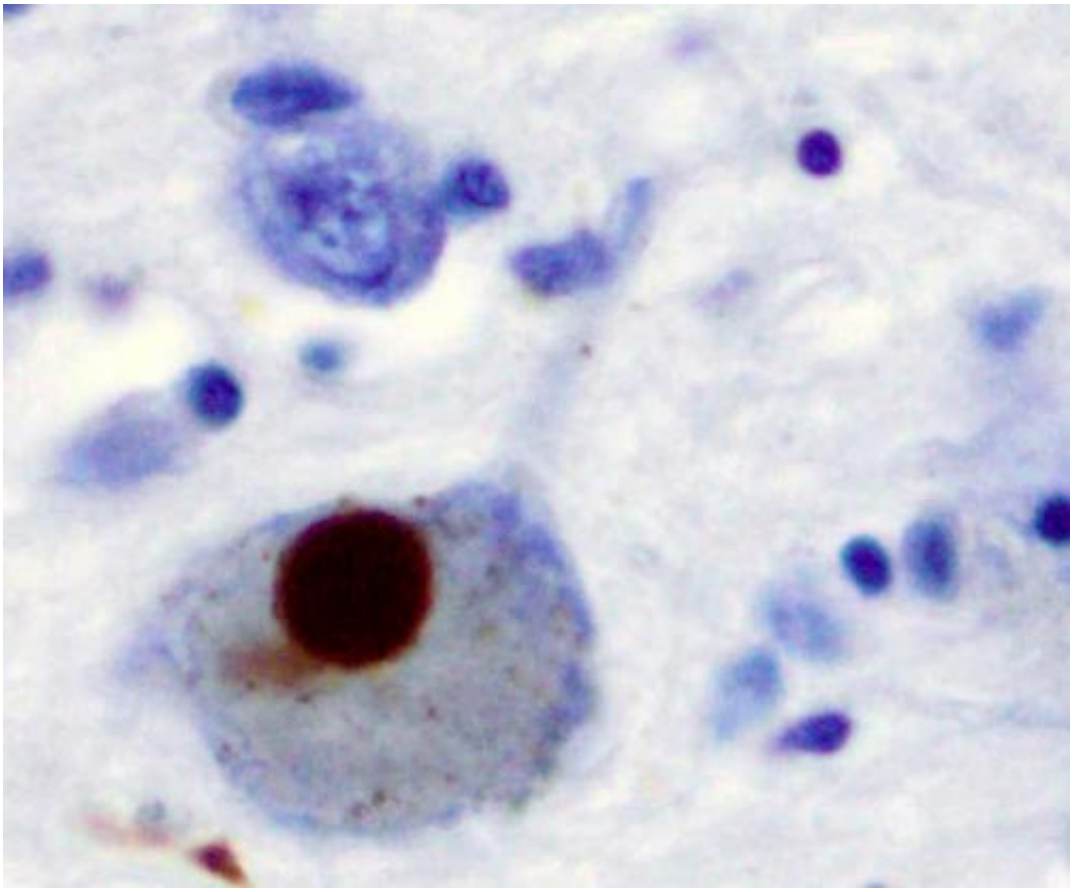

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Biomedical scientists at KU Leuven have discovered that a defect in the

ATP13A2 gene causes cell death by disrupting the cellular transport of polyamines. When this happens in the part of the brain that controls body movement, it can lead to Parkinson's disease.

Parkinson's disease is one of the most common neurodegenerative disorders, afflicting more than 6 million patients around the world. Around 20 genetic defects have already been linked to the disease, but researchers don't understand function of many of these genes. The researchers at KU Leuven have now discovered how a defect of the ATP13A2 gene can cause Parkinson's disease.

"We found that ATP13A2 transports polyamines and is crucial for their uptake into the cell," explains senior author Peter Vangheluwe from the Laboratory of Cellular Transport Systems at KU Leuven. "Polyamines are essential molecules that support many cell functions and protect cells in stress conditions. But how polyamines are taken up and transported in human cells was still a mystery. Our study reveals that ATP13A2 plays a vital role in that process."

"Our experiments showed that polyamines enter the cell via lysosomes and that ATP13A2 transfers polyamines from the lysosome to the cell interior. This transport process is essential for lysosomes to function properly as the 'waste disposal system' of the cell, where obsolete cell material is broken down and recycled."

"However, mutations in the ATP13A2 gene disrupt this transport process, so that polyamines build up in lysosomes. As a result, the lysosomes swell and eventually burst, causing the cells to die. When this happens in the part of the brain that controls body movement, this process may trigger the motion problems and tremors related to Parkinson's disease."

Unravelling the role of ATP13A2 is an important step forward in

Parkinson's research and sheds new light on what causes the disease, but a lot of work remains to be done. Professor Peter Vangheluwe: "We now have to investigate how deficient polyamine transport is linked to other defects in Parkinson's disease such as the accumulation of plaques in the brain and malfunctioning of the mitochondria, the 'energy factories' of the cell. We need to examine how these mechanisms influence each other."

"The discovery of the polyamine transport system in animals has implications beyond Parkinson's disease as well, because polyamine transporters also play a role in other age-related conditions, including cancer, cardiovascular diseases, and several neurological disorders."

"Now that we have unravelled the role of ATP13A2, we can start searching for molecules that influence its function. Our lab is already collaborating with the Centre for Drug Design and Discovery—a tech transfer platform established by KU Leuven and the European Investment Fund—and receives support from the Michael J. Fox Foundation."

More information: Sarah van Veen et al, ATP13A2 deficiency disrupts lysosomal polyamine export, *Nature* (2020). DOI: 10.1038/s41586-020-1968-7

Provided by KU Leuven