AI brings hope for patients with lysosomal storage disease

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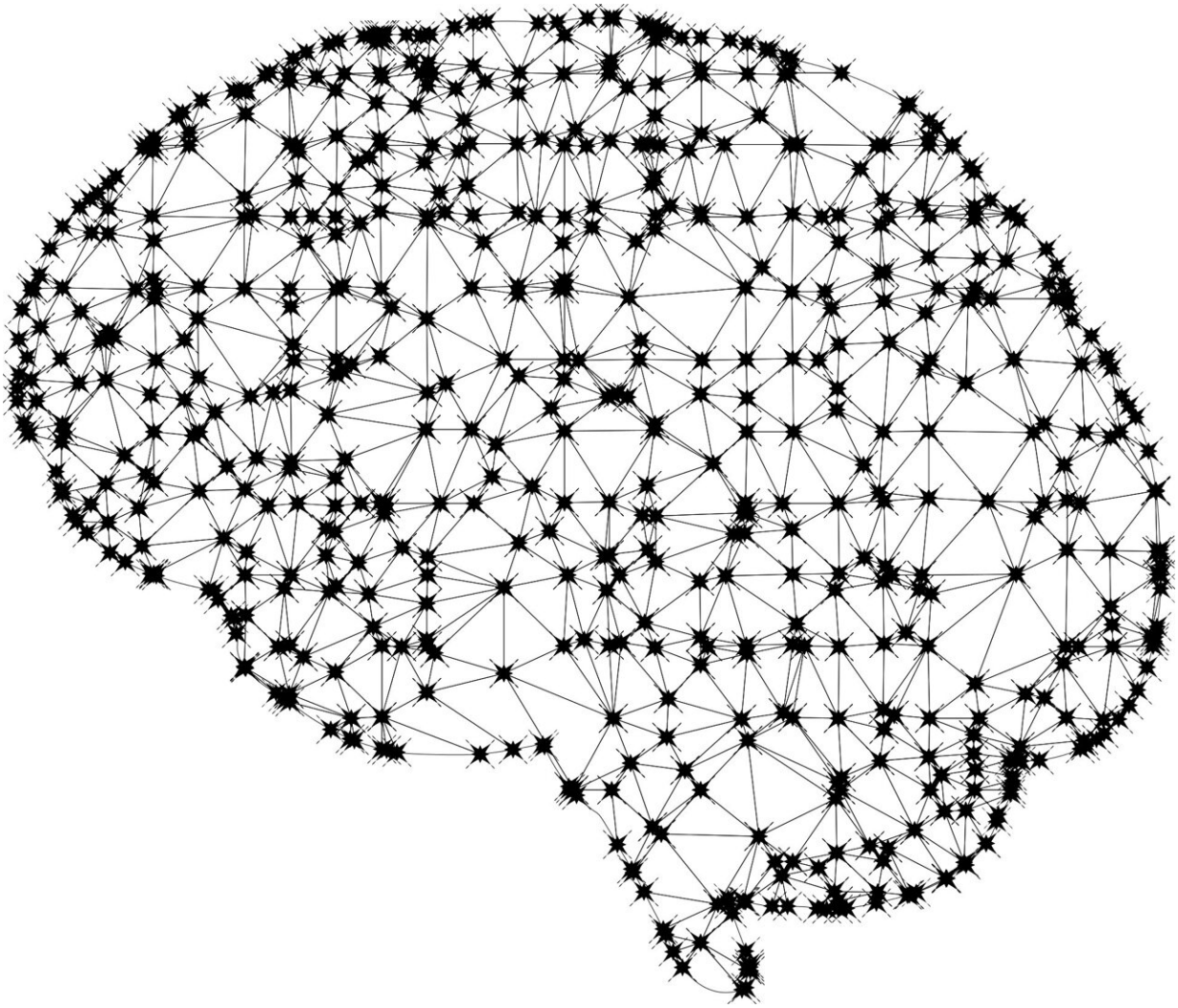

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Artificial intelligence is becoming increasingly important in drug discovery. Advances in the use of Big Data, learning algorithms and powerful computers have now enabled researchers at the University of Zurich (UZH) to better understand a serious metabolic disease.

Cystinosis is a rare lysosomal storage disorder affecting around 1 in 100,000 to 200,000 newborns worldwide. Nephropathic (non-inflammatory) cystinosis, the most common and severe form of the disease, manifests with kidney disease symptoms during the first months of life, often leading to kidney failure before the age of 10.

"Children with cystinosis suffer from a devastating, multisystemic disease, and there are currently no available curative treatments," says Olivier Devuyst, head of the Mechanisms of Inherited Kidney Disorders (MIKADO) group and co-director of the ITINERARE University Research Priority Program at UZH.

The UZH researchers worked with Insilico Medicine, a company that uses AI for drug discovery, to uncover the underlying cellular mechanism behind kidney disease in cystinosis. Leveraging model systems and Insilico's PandaOmics platform, they identified the disease-causing pathways and prioritized therapeutic targets within cystinosis cells.

Their findings revealed a causal association between the regulation of a protein called mTORC1 and the disease. Alessandro Luciani, one of the research group leaders, explains, "Our research showed that cystine storage stimulates the activation of the mTORC1 protein, leading to the impairment of kidney tubular cell differentiation and function."

Promising drug identified for treatment

As patients with cystinosis often require a kidney transplant to restore

kidney function, there is an urgent need for more effective treatments. Utilizing the PandaOmics platform, the UZH research team therefore embarked on a search for existing drugs that could be repurposed for cystinosis. This involved an analysis of the drugs' structure, target enzymes, potential side effects and efficacy in the affected tissues. The already-licensed drug rapamycin was identified as a promising candidate for treating cystinosis.

Studies in cell systems and model organisms confirmed that treatment with rapamycin restored the activity of lysosomes and rescued the cellular functions.

Olivier Devuyst and Alessandro Luciani are optimistic about future developments: "Although the therapeutic benefits of this approach will require further clinical investigations, we believe that these results, obtained through unique interdisciplinary collaboration, bring us closer to a feasible therapy for cystinosis patients."

The research is published in *Nature Communications*.

More information: Olivier Devuyst et al, Lysosomal cystine export regulates mTORC1 signaling to guide kidney epithelial cell fate specialization, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39261-3

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