

# Lack of mitochondria causes severe disease in children

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Researchers at Karolinska Institutet in Sweden have discovered that excessive degradation of mitochondria, the power plants of cells, plays an important role in the onset of mitochondrial disease in children. These inherited metabolic disorders can have severe consequence such as brain dysfunction and neurological impairment. The study is published in *EMBO Molecular Medicine*.

"This is a completely new disease mechanism for [mitochondrial disease](#) which may provide a novel entry point for treating affected patients," says Nils-Göran Larsson, professor at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet, who led the study.

Mitochondrial diseases are inherited [metabolic disorders](#) that affect about one in 4,300 individuals and are caused by dysfunctional [mitochondria](#). Mitochondria are crucial for converting energy derived from food into the energy that drives the cell's biochemical functions. Not surprisingly, organs with a high energy demand are particularly affected, including the brain, heart, skeletal muscles, eyes and ears. In children, severe multisystem involvement and neurodegeneration are frequent manifestations.

FBXL4 is a gene that is implicated in controlling mitochondrial function, and mutations in this gene are the most common cause of mitochondrial diseases. FBXL4 mutations have been linked to encephalopathy, a form of brain dysfunction causing neurological impairment. The manifestations are impaired cognitive function, developmental regression, epileptic seizures and other types of neurological deficits. Despite the severe consequences of FBXL4 mutations in humans, the function of the protein that FBXL4 codes for has remained poorly understood.



Nils-Göran Larsson, professor at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Sweden. Credit: Gustav Mårtensson

In the current study, researchers generated mice that lack FBXL4 and showed that these mice recapitulate important characteristics present in patients with FBXL4 mutations. They were able to demonstrate that the reduced mitochondrial function is caused by increased degradation of mitochondria via a process called autophagy.

In the absence of FBXL4, mitochondria are more frequently delivered to the lysosome, the recycling station of the cell that contains enzymes that break down organic compounds. FBXL4 thus acts as a break on mitochondrial degradation. Patients who lack FBXL4 have too few mitochondria in their tissues which leads to [disease](#).

"Further studies are needed to explore the therapeutic potential of these findings, in particular whether inhibition of the degradation of mitochondria may provide a new treatment strategy," says Nils-Göran Larsson.

**More information:** "FBXL4 deficiency increases mitochondrial removal by autophagy". David Alsina, Oleksandr Lytovchenko, Aleksandra Schab, Ilian Atanassov, Florian Schober, Min Jiang, Camilla Koolmeister, Anna Wedell, Robert W. Taylor, Anna Wredenberg, Nils-Göran Larsson. *EMBO Molecular Medicine*, online 11 June 2020, [DOI: 10.15252/emmm.201911659](https://doi.org/10.15252/emmm.201911659)

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