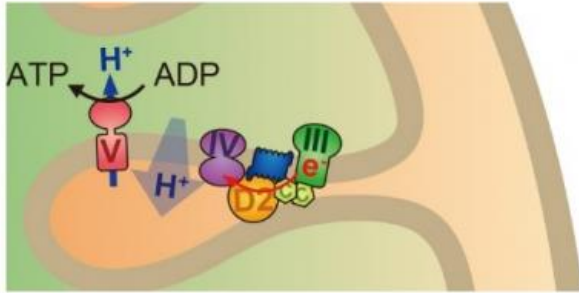
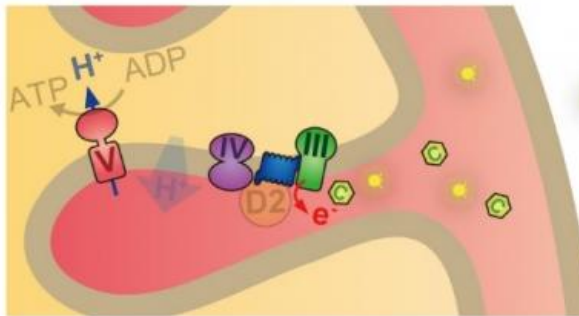


Potential therapeutic target for Parkinson's disease

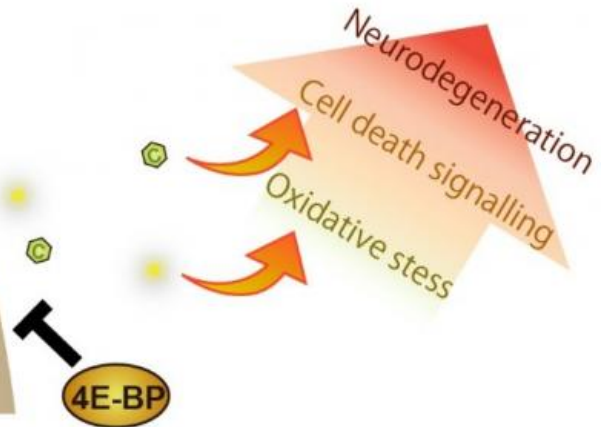
June 7 2017



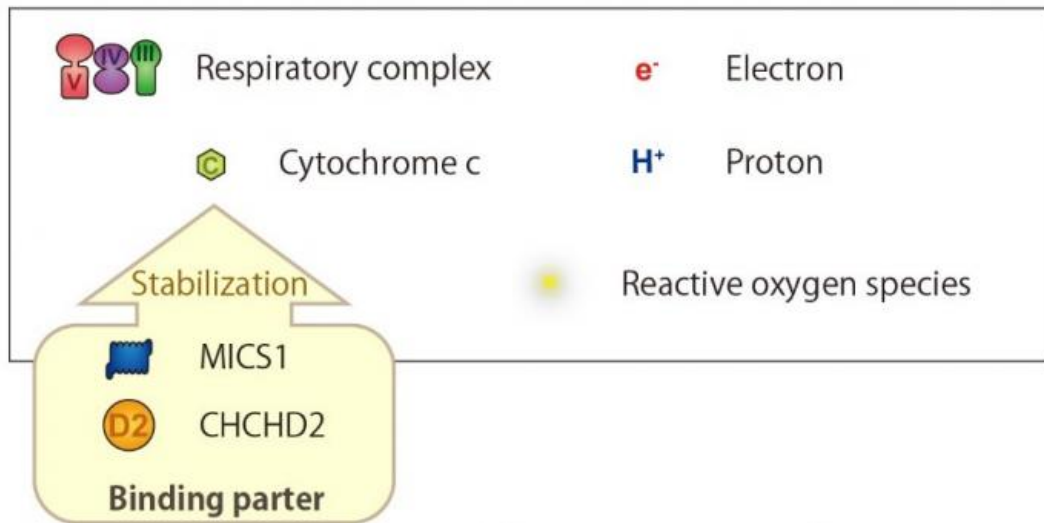
Healthy mitochondria



Degenerative mitochondria due to the loss of CHCHD2



Regulation of respiratory rate and increased resistance to oxidative stress



Credit: Juntendo University

Investigations by scientists in Japan illustrate how the loss of a key mitochondrial protein facilitates the progression of Parkinson's disease. The findings are published in *Nature Communications* (June 2017).

There is much evidence to suggest that dysfunction within cellular components contributes to the development and progression of the neurodegenerative disorder Parkinson's disease. However, exactly how individual genes and proteins contribute to the degradation of this integral cellular structure is unclear.

Mitochondria are sub-units within cells that control biochemical processes such as energy production. They have a double-membrane structure, the inner membrane of which forms multiple layers or 'cristae.' Each crista structure must remain intact in order for the mitochondria to perform their tasks effectively.

Now, Hongrui Meng and Chikara Yamashita at Juntendo University Graduate School of Medicine in Tokyo, and co-workers across Japan, have shown how a [mitochondrial protein](#) called CHCHD2 plays a key role in maintaining cristae structure and mitochondria integrity.

Meng and Yamashita's team generated CHCHD2 mutant fruit flies (*Drosophila*), and examined what happened when CHCHD2 protein expression was lost. They found that this loss resulted in abnormal matrix structures and impairments to oxygen respiration in mitochondria. This in turn led to neuron loss through oxidative stress, and also to motor dysfunction – such as loss of climbing ability—as the flies aged.

When the researchers introduced a wild-type form of human CHCHD2 and a metabolic regulator 4E-BP to the flies, the dysfunctions were reversed. Further investigations showed that CHCHD2 binds to a mitochondrial protein cytochrome c along with a cell death regulator

MICS-1. This binding helps cells to function properly and ensure correct cell death signaling in both mammalian cells and *Drosophila*.

As the team states in their paper published in *Nature Communications*, their results shed light on the role of CHCHD2 mutations in Parkinson's disease and offer "potential therapeutic targets in Parkinson's caused by mitochondrial dysfunction."

Background

The recent discovery of a gene related to Parkinson's disease, CHCHD2, is allowing scientists to directly investigate the molecular details behind the disorder in more depth. The gene encodes a protein, CHCHD2, the role of which Hongrui Meng and his team in Japan aimed to investigate using fruit fly and mouse models.

The mutant fruit flies lacked the CHCHD2 protein, resulting in flies with shorter life spans and problems with motor function as they aged. The loss of the protein resulted in the integral structure of the flies' mitochondria was disrupted. The researchers also discovered that by affecting the oxygen respiration processes within mitochondria, the loss of CHCHD2 generates excess reactive oxygen species in the body. This in turn exacerbates [oxidative stress](#) and directly affects the function and survival of neurons in the body. Importantly, these phenotypes were not rescued by the reintroduction of CHCHD2 missense mutants associated with Parkinson's disease, strongly suggesting that this disease develops by the loss of CHCHD2 function.

Implications of the current study

These findings suggest that CHCHD2 is a key protein that regulates the mitochondrial respiratory function through stabilizing cytochrome c.

Without it, through mutations in the CHCHD2 gene, mitochondria cannot function correctly, leading to the progression of Parkinson's disease. The researchers believe their insights into the gene, its associated protein, and how the [protein](#) works to facilitate healthy functioning of [mitochondria](#) could inform future therapies for Parkinson's disease and help scientists better understand the condition.

More information: Loss of Parkinson's disease-associated protein CHCHD2 affects crista structure and destabilizes cytochrome c. *Nature Communications* [DOI: 10.1038/ncomms15500](https://doi.org/10.1038/ncomms15500)

Provided by Juntendo University

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