



(Tokyo, 7 June 2017) 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 help 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 state's 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.

Reference

H. Meng, C. Yamashita, K. Shiba-Fukushima, T. Inoshita, M. Funayama, S. Sato, T. Hatta, T. Natsume, M. Umitsu, J. Takagi, Y. Imai, & N. Hattori. Loss of Parkinson's disease-associated protein CHCHD2 affects cristae structure and destabilizes cytochrome c. *Nature Communications*

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About Juntendo University

Mission Statement

The mission of Juntendo University is to strive for advances in society through education,

research, and healthcare, guided by the motto “Jin – I exist as you exist” and the principle of “Fudan Zenshin - Continuously Moving Forward”. The spirit of “Jin”, which is the ideal of all those who gather at Juntendo University, entails being kind and considerate of others. The principle of “Fudan Zenshin” conveys the belief of the founders that education and research activities will only flourish in an environment of free competition. Our academic environment enables us to educate outstanding students to become healthcare professionals patients can believe in, scientists capable of innovative discoveries and inventions, and global citizens ready to serve society.

About Juntendo

Juntendo was originally founded in 1838 as a Dutch School of Medicine at a time when Western medical education was not yet embedded as a normal part of Japanese society. With the creation of Juntendo, the founders hoped to create a place where people could come together with the shared goal of helping society through the powers of medical education and practices. Their aspirations led to the establishment of Juntendo Hospital, the first private hospital in Japan. Through the years the institution's experience and perspective as an institution of higher education and a place of clinical practice has enabled Juntendo University to play an integral role in the shaping of Japanese medical education and practices. Along the way the focus of the institution has also expanded, now consisting of four undergraduate programs and three graduate programs, the university specializes in the fields of health and sports science and nursing health care and sciences, as well as medicine. Today, Juntendo University continues to pursue innovative approaches to international level education and research with the goal of applying the results to society.