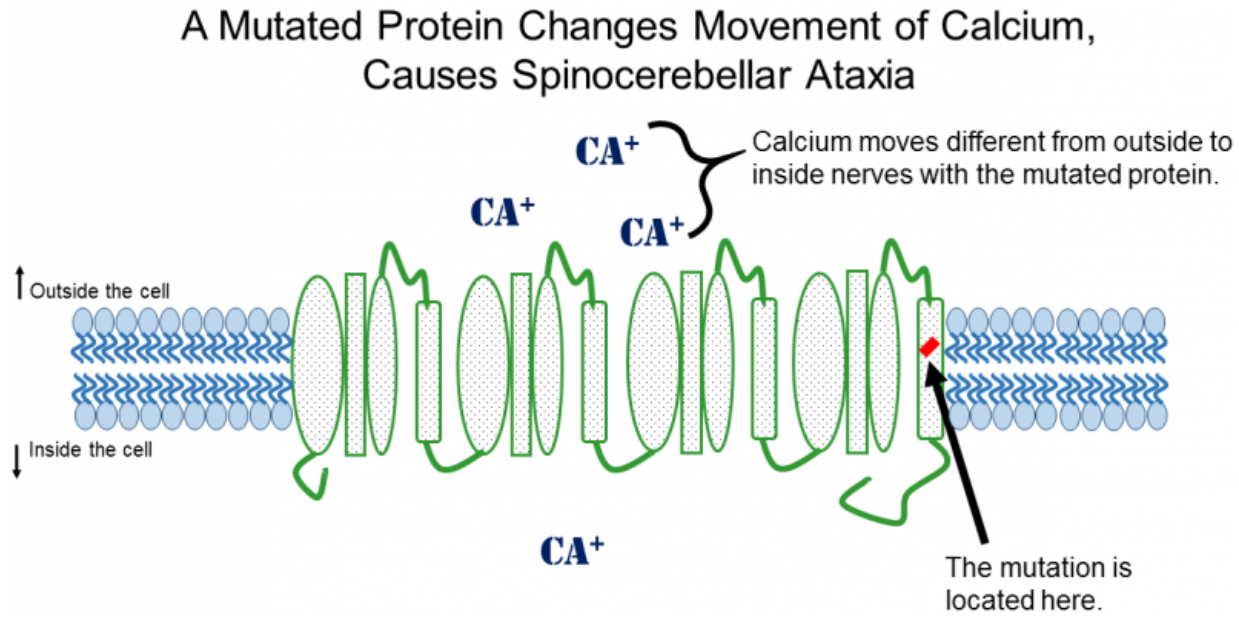
Genetic cause of neurological disease identified

March 14 2016



The mutation (red rectangle) changes the way the protein (green) opens and closes a pathway through neurons' cell membrane (blue). This change alters the way Calcium (Ca+) moves between the outside and inside of cells and is responsible for patients' disease symptoms. Credit: Hiroshima University

Using the genetic information of two different families with three generations of disease, researchers have identified a new mutation responsible for a degenerative and ultimately fatal movement disorder. Through induced pluripotent stem cell techniques, researchers also grew

neurons from one patient in the laboratory to be used in future experiments.

Spinocerebellar ataxia (SCA) is a genetic disease that causes wasting away of the cerebellum, the portion of the brain responsible for controlling voluntary muscle movement, like walking, speaking, and even the direction of our eyes.

Currently, SCA has no cure or treatment. The mutations responsible for about 30 percent of cases are still unidentified.

Two different families with SCA sought treatment at two different hospitals in Japan. After preliminary testing on the symptomatic individuals, doctors identified none of the known genetic mutations. Researchers at Hiroshima University then received the patient's genetic samples and began the process of searching for the new mutation.

After genetic sequencing of four family members with SCA, a research team led by Professor Hideshi Kawakami, MD, PhD, from the Department of Epidemiology at Hiroshima University used statistical analysis to compare the families' DNA to that of unrelated people without SCA. This statistical analysis allowed researchers to identify which genetic variation the family members with SCA shared that healthy people did not.

The gene responsible for causing both families' SCA is located on Chromosome 17. The gene, called CACNA1G, encodes the Cav3.1 protein. Cav3.1 serves as a type of ion channel, or gateway, between the inside of nerve cells and the rest of the body. Scientists in different fields of research already know Cav3.1 controls how many Calcium ions are allowed into nerves when they send an electrical impulse through the brain. Cav3.1 had never been linked to SCA before.

Changing a single letter in the DNA sequence of CACNA1G switches a single amino acid in the chain of 2377 amino acids that cells connect to build the Cav3.1 protein.

Researchers performed the experiments to examine the way the mutated Cav3.1 channel behaves in cells growing in a dish. This mutation makes the Cav3.1 channels open at a lower threshold, meaning they let Calcium into the cell differently from healthy cells.

"In the future, a drug modifying this channel may cure the patients," said Prof. Kawakami.

Skin cells from one patient were used in induced pluripotent stem cell experiments to grow this patient's neurons in the laboratory. These new neurons showed no obvious physical deformities, which might fit with normal SCA progression. Depending on which SCA mutation they have, some patients may not experience symptoms until middle-age.

"We might need some age-related factors to reproduce life-like cell behavior," said Prof. Kawakami.

Researchers plan to use the neurons in future experiments to study the disease-causing Cav3.1 under more life-like conditions and in greater detail.

More information: Hiroyuki Morino et al. A mutation in the low voltage-gated calcium channel CACNA1G alters the physiological properties of the channel, causing spinocerebellar ataxia, *Molecular Brain* (2015). DOI: 10.1186/s13041-015-0180-4

Provided by Hiroshima University