New study reveals reversibility of genetic nervous system disease

20 December 2017

In children and adults with Friedrich's ataxia, an inherited disease that causes damage to the nervous system, a loss of coordination typically progresses to muscle weakness and can involve vision, diabetes, and other problems over the course of several years. Until now, mimicking those symptoms and progression in mice for research studies has been difficult.

UCLA researchers, after developing a mouse model of Friedrich's ataxia that shows symptoms similar to patients, have found that many early symptoms of the disease are completely reversible when the genetic defect linked to the ataxia is reversed. The new findings, which still need to be replicated in humans, appear in the journal *eLife*.

"Remarkably, most of the dysfunction we were seeing in the mice was reversible even after the mice showed substantial neurologic dysfunction," said Dr. Daniel Geschwind, the Gordon and Virginia MacDonald Distinguished Chair in Human Genetics, a UCLA professor of Neurology and Psychiatry, and senior author of the new work. "We were very surprised by the extent to which the mice improved since we had assumed that this degree of behavioral dysfunction would be due to cell loss."

Friedrich's ataxia can begin causing symptoms in childhood or early adulthood. It causes a loss of coordination, or "ataxia," that makes patients stumble and stagger, among other early symptoms. The disease is known to be caused by a genetic mutation in the gene FXN. The mutation leads to reduced levels of the protein encoded by FXN, called frataxin. While doctors can manage some specific symptoms, there are no current treatments.

"The lack of treatments for Friedrich's Ataxia has been frustrating for many and has been, in part, due to the lack of good animal models of the disease," said Geschwind. "There was really a need for a mouse model to help researchers determine the consequences of whole body reduction of frataxin."

In the new work, Geschwind and colleagues developed a mouse in which the FXN gene can be blocked by a strand of RNA that's controlled by an antibiotic. Higher levels of the antibiotic lead to more blockage of the gene, and therefore lower levels of frataxin protein. This system allowed the researchers to have tight control over frataxin levels throughout a mouse's life, letting the mice develop normally for three months before administering antibiotic to turn down frataxin levels.

After 12 weeks with low frataxin levels, the study found, mice have symptoms similar to those seen in humans with the disease, including weight loss, ataxia, impaired walking, hunched backs, and reduced muscular strength. When the researchers stopped giving antibiotics to the diseased mice, letting frataxin levels return to normal, most of the symptoms disappeared.

The study findings suggest that "quite a bit of dysfunction that's being seen in patients, in the first few years of disease, represents reversible neuronal dysfunction rather than cell death and loss of neurons," said Geschwind.

The researchers also used the mouse model to study which other genes and proteins are immediately affected by reductions in frataxin, helping point the way toward new drug targets. They hope to continue this line of work, studying the biochemical changes that occur in conjunction with Friedrich's ataxia. They're also making this model available for academic and commercial laboratories that are already pursuing drugs that aim to increase frataxin levels in human patients. In these cases, the new mouse model can be used to test the effectiveness of the drugs.

"Going forward, this model provides an important

new potential avenue for therapeutic development," said Geschwind.

More information: Vijayendran Chandran et al, Inducible and reversible phenotypes in a novel mouse model of Friedreich's Ataxia, *eLife* (2017). DOI: 10.7554/eLife.30054

Provided by University of California, Los Angeles