Ataxia research news, directly from researchers to the SCA community.

The importance of balancing Sacsin protein levels in ARSACS

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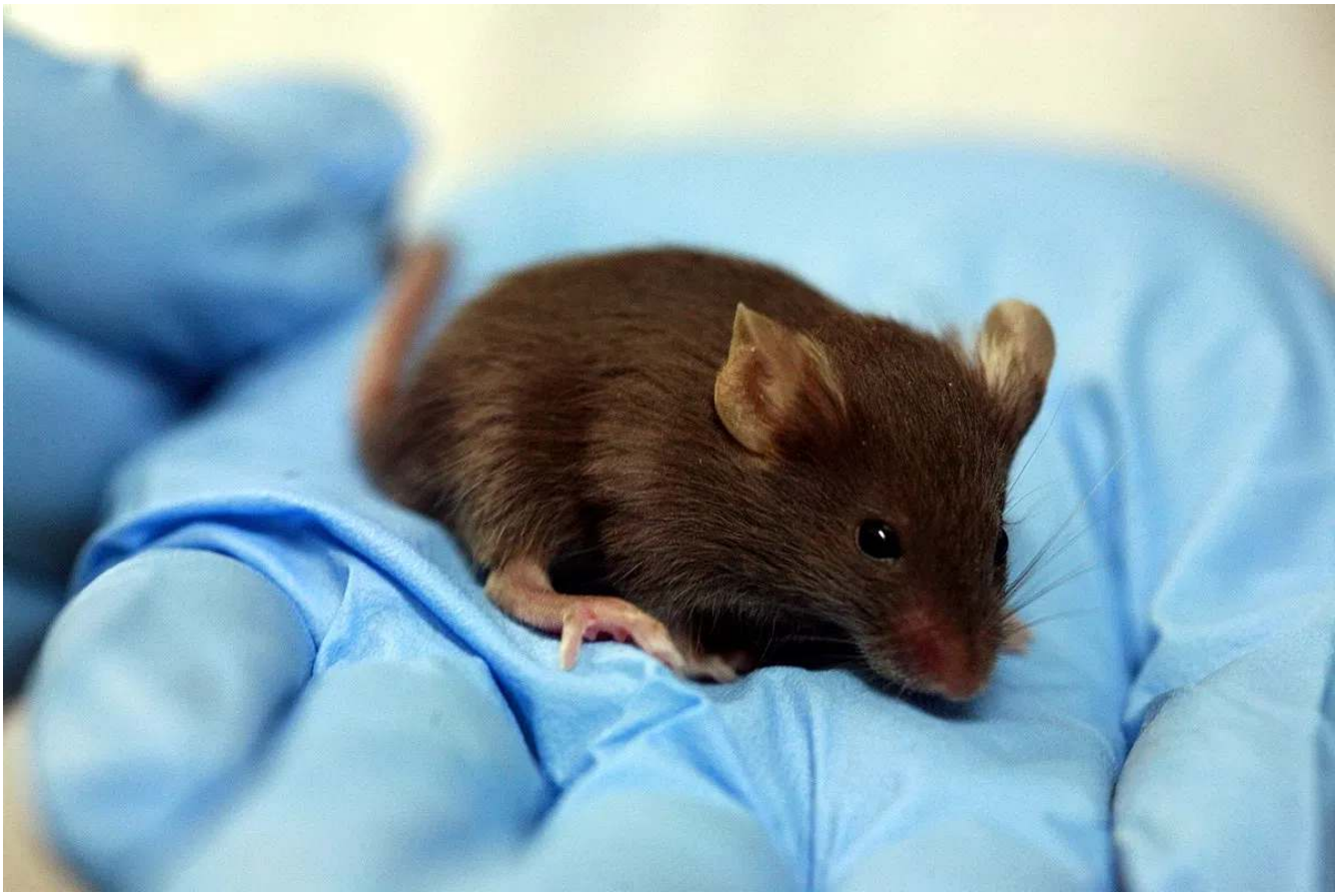
> *Tipping the balance of the protein Sacsin alters outcomes in a mouse model of ARSACS*

There are many different types of ataxia, each with a unique cause. For several ataxias, the mutated gene that causes the disorder has been identified. This is a great achievement that we owe to recent advancements in genome sequencing. Knowing the gene that is altered in a disorder provides researchers with a solid foundation to understand the mechanisms underlying the disease. In the neurodegenerative disorder Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), this alteration occurs in the SACS gene. Currently, over 170 different SACS gene mutations have been identified in human patients. Because each gene is equipped with a specific set of instructions to make a protein, each mutation can cause a change in these instructions. This usually results in the production of very little sacsin protein – or no protein at all. In several disorders, it has been shown that maintaining optimal levels of a variety of proteins is crucial to the proper functioning of the nervous system.

In 2015, a group of researchers wanted to understand why the loss of the protein sacsin produced certain symptoms in ARSACS patients. To study this, they removed

the entire SACS gene from a mouse (known as the $Sacs^{-/-}$ line), which meant that these mice made no sacsin protein. Mice with only one copy of this mutation ($Sacs^{+/-}$) could produce up to 50% of the protein. In this same study, the researchers also wanted to make a more disease-relevant mouse model, so they made a mouse with a mutation known as "R272C." R272C was a SACS gene mutation that was initially identified in a patient with ARSACS. Mice with two copies of the mutated gene ($Sacs^{R262C/R262C}$) had sacsin levels reduced to 21%, whereas mice with one copy ($Sacs^{R262C/+}$) had 65% of sacsin levels. Together, these mouse models provided the researchers with a group of mice that had a range of sacsin protein levels. These mice could then be used to understand how changes in the levels of sacsin affect behavior, especially in the ways that we might observe in ARSACS.



Stock image of a laboratory research mouse, similar to the R272C ARSACS mouse. Image courtesy of Rama on Wikimedia Commons.

ARSACS patients have a childhood onset of ataxia that worsens over time. This is due to the loss of Purkinje cells in the cerebellum, the area of the brain that controls motor coordination. Without Purkinje cells, the cerebellum cannot properly function, resulting in the uncoordinated gait that we call "ataxia." The researchers

found that mice with less than 50% sacsin protein also displayed progressive motor abnormalities (measured using three well-established mouse coordination tests). These mice also showed degeneration of Purkinje cells, which became more apparent with increasing age. Moreover, as protein levels decreased, motor performance and Purkinje cell loss became more pronounced.

Another feature of ARSACS is the accumulation of neuronal intermediate filaments (NF) in the patients' brains. NF provides structural support to neurons (the primary cells of the nervous system, which transmit messages to all areas of the brain and body) and also help transport cargo across these cells. NF accumulations are found in several disorders of the brain that involve neuronal loss, such as Alzheimer's disease, Parkinson's disease, and SCA1. While the exact connection between NF accumulation and the loss of neurons is still unknown, one hypothesis is that NF accumulation interrupts transport across neurons. Without the proper transport system, there can be problems in the localization and functioning of organelles, which power the cell and keep it alive. In this study, the researchers found that the $Sacs^{-/-}$ and $Sacs^{R262C/R262C}$ mice, which have the lowest levels of sacsin (0% and 21% respectively), had neurofilament accumulation in several neuron populations throughout the brain. This means that sacsin may indeed regulate the transport of NF, and that altered levels of sacsin would likely impair this process in ARSACS.

Peripheral neuropathy, which can contribute to limb weakness and ataxia, is another common symptom in ARSACS patients. It occurs when neurons that communicate between the brain/spinal cord and the rest of the body (such as muscles and skin) are damaged. Here, researchers found that only the $Sacs^{-/-}$ mice (which had a complete loss of sacsin protein), showed a decrease in the number of spinal motor neurons – a hallmark of peripheral neuropathy.

In most cases, the animal models that are used to study human disorders do not replicate every feature of the disease. In the case of ARSACS, muscle stiffness or spasticity can occur later in the course of the disease in patients. This symptom, which is due to the slow loss of upper motor neurons, was not observed in any of the mouse models tested (even those with a complete loss of sacsin). Because mice have a relatively short lifespan (2 years), modelling aspects of human disease that begin later in life can be challenging. Besides late upper motor neuron loss, the reduced

life expectancy that patients experience was also not observed in any of these mouse models.

In summary, the authors of the study very elegantly used a range of mouse models to show that maintaining a certain level of the protein sacsin is important in preventing the onset of ARSACS symptoms: in this case, a mouse model with *more* than 50% of sacsin protein showed *no* motor abnormalities or brain pathology, while mouse models with *less* than 50% of sacsin showed the *majority of ARSACS disease features*. Though the authors did not discuss the specific benefits of this finding, it is quite feasible to adjust specific protein levels in order to treat neurological diseases. Future studies in these mice that are aimed at increasing sacsin levels will determine whether this is a suitable option for therapeutics.

Key Terms

Neurofilament: An important component of nerve cells/fibres that provide structural support

Gene: The basic unit of heredity; contains DNA, the instructions to make proteins

Phenotype: The observable characteristics of an individual or organism

Organelle: Specialized structures with specific functions found within a living cell

Neurons: Specialized cells that transmit messages, in the form of electrical signals, throughout the brain and the entire body.

Conflict of Interest Statement

The author and editor declare no conflict of interest.

Two authors on the original paper (B. Toscano Márquez and A.J. Watt) are contributors to SCAsource. None of these authors had any contribution to the

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Citation of Articles Reviewed

Larivière, R. et al., *Sacs R272C missense homozygous mice develop an ataxia phenotype.* Molecular Brain, 2019. **12**(1):19. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6416858/)

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