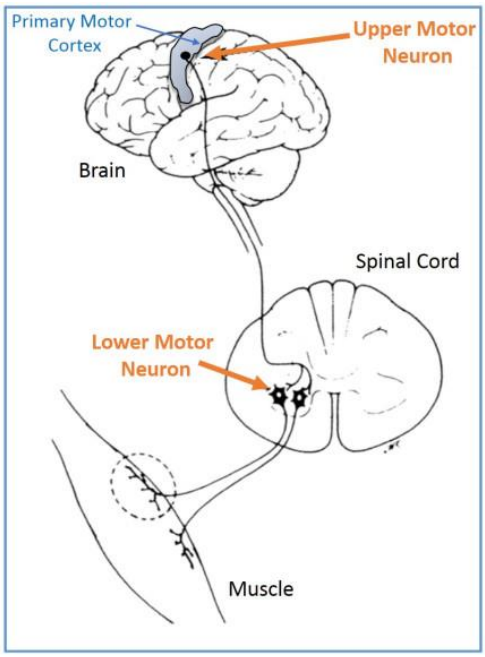
Precise ALS Worm Model Gives Insight into How Motor Neurons Die

Why motor neurons die in ALS largely remains a mystery. In a study funded by The ALS Association, Dr. Anne Hart, professor of neuroscience at the Carney Institute for Brain Science at Brown University, and her colleagues gained insight into why some types of motor neurons die, while other don't. A paper about the study was recently published in *PLOS Genetics*.

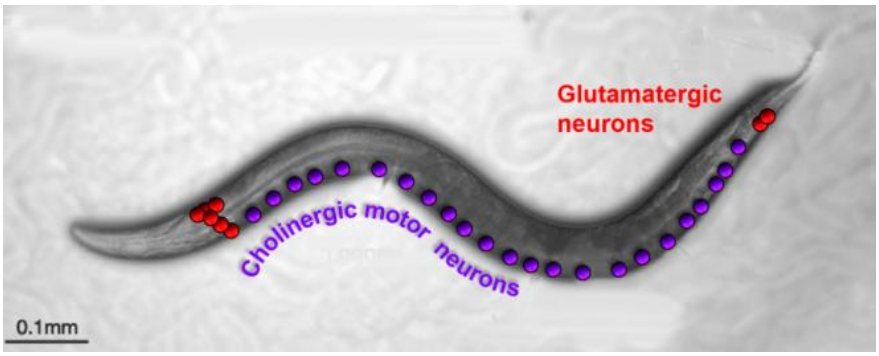
Interestingly, Dr. Hart and her team used microscopic worms, called *C. elegans*, which maintain conserved ALS genes seen in humans to create the first precise worm models for SOD1 ALS, the second most common genetic cause of inherited ALS, using gene editing.

Motor neurons are the cells that die in ALS. Basically, a person has two types of motor neurons. Upper motor neurons (UMNs) connect the primary motor cortex in the brain (area of the brain that controls voluntary movement) to the spinal cord. UMNs use glutamate, a type of neurotransmitter, to send signals and communicate with each other.

Lower motor neurons (LMNs) connect the spinal cord to muscle and use acetylcholine as a neurotransmitter. (See diagram below.) It is not clear why, in some people with ALS, one or both types of motor neurons die.



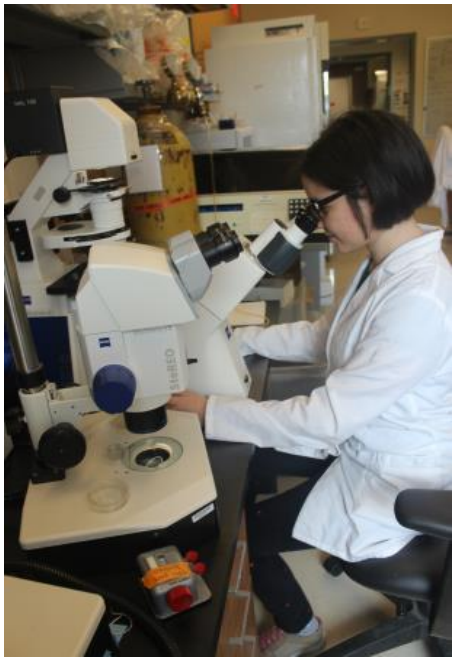
In this study, Dr. Hart and her colleagues used genetic tools to precisely model ALS in *C. elegans*, which are microscopic worms (adults are 1 mm in length – the size of a pinhead) that are inexpensive to maintain (eat bacteria) and have short lifespans (~three weeks).
Importantly, its genome is completely sequenced and found to have conserved human ALS genes like SOD1. Also, the connections of all its 302 neurons have been completely mapped and *C. elegans* have motor neurons that are very similar to human motor neurons.

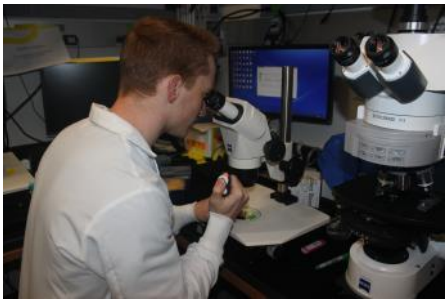


To precisely model disease in *C. elegans*, the research team directly edited the worm's genome, changing "one letter" or amino acid in the worm's SOD1 gene to recreate a single gene mutation found in some patients. This precise editing is important, as earlier worm models were made by adding extra copies of a patient disease gene to worms, called gene overexpression, which forces expression of the patient version of SOD1 at high levels.
Gene overexpression can have toxic effects on motor neurons, making it difficult to fully understand the impact of the ALS mutation.

The team discovered that, in response to single-copy SOD1 mutations introduced into *C. elegans*, the mechanism of how UMNs and LMNs die is different. Glutaminergic UMNs die

primarily from loss of the SOD1 gene's normal function, compared to cholinergic LMNs, which die primarily due to the toxic accumulation of SOD1 proteins.
These findings reveal a new disease paradigm that contrasts to a previous understanding in the ALS field that they die the same way.





"We can now use these new ALS models to find other proteins and genes that we can use to stop neurodegeneration in worms," explained Dr. Hart.

She next plans to use the models to carry out screens to uncover therapeutic targets that prevent motor neurons from dying. Colleagues at Brown University and elsewhere who collaborate on ALS projects will also test the discovered therapeutic targets in flies, mice, and in human cells to understand if their findings are reproducible in other animals.

Ultimately, the hope is to increase their understanding of why motor neurons die and to bring their discovered therapeutic targets into clinical trials someday.

“This work simply wouldn’t have been possible without help from The ALS Association. When we had early and encouraging preliminary results, their support allowed us to look at more patient mutations and to figure out that something unexpected was going on,” stated Dr. Hart.

“This study reveals a new understanding of how motor neurons die in ALS; thus, taking a step forward in unlocking the mysteries of the disease,” said Dr. Jill Yersak, director of mission strategy at The ALS Association and a co-author on this study. “Precisely modeling ALS in such a small organism like *C. elegans* is ideal, because it’s inexpensive to carry out experiments in the lab but it has potential to render big results, as seen in this study.” The ALS Association is proud to support Dr. Hart’s work that contributed to this important paper.

This article is open access.
Single copy/knock-in models of ALS SOD1 in *C. elegans* suggest loss and gain of function have different contributions to cholinergic and glutamatergic neurodegeneration
Saba N. Baskoylu, Jill Yersak, Patrick O’Hern, Sarah Grosser, Jonah Simon, Sarah Kim, Kelsey Schuch, Maria Dimitriadi, Katherine S. Yanagi, Jeremy Lins, Anne C. Hart. *PLOS Genetics.*
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For more information, read here.