Two genes that cause familial ALS shown to work together

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Although several genes have been linked to amyotrophic lateral sclerosis (ALS), it is still unknown how they cause this progressive neurodegenerative disease. In a new study, Columbia University Medical Center (CUMC) researchers have demonstrated that two ALS-associated genes work in tandem to support the long-term survival of motor neurons. The findings were published in the September 1 online edition of the *Journal of Clinical Investigation*.

"Any therapy based on this discovery is probably a long way off. Nonetheless, it's an important step toward piecing together the various factors that contribute to ALS," says lead author Brian McCabe, PhD, assistant professor of pathology & cell biology in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain and a member of the Center for Motor Neuron Biology and Disease at Columbia University Medical Center (CUMC).

ALS, also known as "Lou Gehrig's disease," is a progressive disease that affects motor neurons — specialized nerve cells in the spinal cord and brainstem essential for controlling muscle strength and movement. ALS typically begins after age 50, eventually affecting one's ability to move, speak, and breathe. Some 30,000 Americans suffer from ALS at any given time. About 90 percent have a sporadic, or noninherited, form of the disease. The cause of sporadic ALS is unknown but likely involves a combination of genetic and environmental factors. The remaining 10 percent have a familial form of ALS, which is caused by an inherited genetic mutation. There is no cure for ALS. Symptoms are managed

with medication, physical and speech therapy, assistive devices, and nutritional support. Many people with ALS die of respiratory complications within two to three years of diagnosis.

In the current experiment, the researchers examined the roles of two recently discovered ALS genes, FUS/TLS and TDP-43. Both genes are involved in the processing of messenger RNAs, which carry the genetic codes to make particular proteins. "The two genes make proteins with similar form and function, which suggested to us that they could work together, and that disruptions of either gene would affect neuronal survival," says Dr. McCabe. A competing view was that mutations to these genes cause abnormalities in their respective proteins that are toxic to motor neurons independent of their normal functions.

To determine which model is correct, the researchers turned to the fruit fly (*Drosophila melanogaster*), which has genes similar to FUS/TLS and TDP-43 and reproduces quickly, making it a good model for genetic studies of ALS. For the study, Dr. McCabe's team created a line of flies with mutant FUS/TLS; flies with mutant TDP-43 had already been developed by an Italian research group.

In the first part of the study, the researchers found that flies with mutant FUS/TLS have decreased adulthood viability, diminished locomotor speed, and reduced longevity, compared with normal flies. The mutant flies were rescued (returned to normal) by inserting normal human FUS/TLS into their genome. The mutant flies were not rescued with ALS mutant human FUS/TLS. "This means that the gene works similarly in flies and in humans," says Dr. McCabe.

Flies with mutant TDP-43 showed similar deficits in survival, locomotion, and longevity. This line of flies was rescued with insertion of normal human TDP-43.

To determine whether the two genes interact, the team attempted to cross-rescue FUS/TLS or TDP-43 mutants by forcing overexpression of the other gene. Overexpression of FUS/TLS rescued flies with TDP-43 mutations, while overexpression of TDP-43 did not rescue flies with FUS/TLS mutations. "This finding demonstrates that FUS/TLS acts together with, and downstream of, TDP-43 in a common genetic pathway in neurons."

Whether these findings can be translated into therapy remains to be seen. "But one could imagine that if you could develop a drug or gene therapy that could make FUS/TLS more active, it might help in patients who have TDP-43 mutations," says Dr. McCabe.

"Our results show that these two genes work together in a familial ALS model," Dr. McCabe adds. "How ALS genes cause disease, and whether other genes work together, are big questions. The hope is that if we can eventually understand how all ALS genes interact, we can figure out how to intervene."

Dr. McCabe's paper is titled, "The ALS-associated proteins FUS and TDP-43 function together to affect Drosophila locomotion and life span." The paper's first authors are Ji-Wu Wang and Jonathan R. Brent at CUMC. Their coauthors include Andrew Tomlinson and Neil A. Shneider, also at CUMC.

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