Study identifies new genetic risk factor for Lou Gehrig's disease

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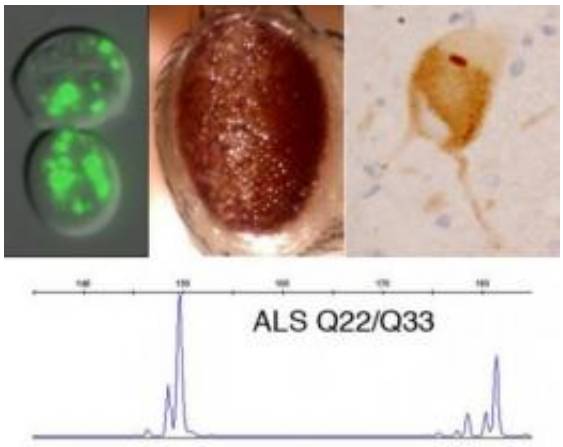

A role for the polyQ protein ataxin 2 in ALS was identified using yeast (top left), fruit fly models (top middle), human ALS motor neurons (top right) and genetic analysis in ALS patients (above). Credit: University of Pennsylvania

An international study led by biologists and neuroscientists from the University of Pennsylvania has identified a new genetic risk factor for amyotrophic lateral sclerosis, commonly known as ALS or Lou Gehrig's disease.

Using yeast and fruit flies as simple, yet rapid and powerful models, then following up with human DNA screening, the team found evidence that mutations in the ataxin 2 gene were a genetic contributor to the disease. More specifically, the study shows that expansions of a run of the amino acid glutamine in ataxin 2 are associated with an increased risk for ALS, with a frequency of 4.7 percent of ALS cases examined. The findings were published this week in *Nature*.

There is no cure for ALS and the current treatment only slows disease progression. The identification of pathological interactions between ataxin 2 and TDP-43, another ALS-associated disease protein, together with the strong genetic association of ataxin 2 intermediate-length polyQ expansions and ALS, should aid in the development of biomarkers and empower the development of new therapies for this disease.

The research began in the laboratory of co-senior author Aaron Gitler, assistant professor of cell and developmental biology at Penn's School of Medicine, by identifying genes that could suppress or enhance TDP-43 toxicity in yeast. The team transferred 5,500 yeast genes into a strain of yeast they had engineered to express human TDP-43. Among the genes that modified toxicity was the yeast counterpart of ataxin 2.

The Gitler lab then teamed up with Nancy Bonini, Penn's Lucille B. Williams Professor of Biology, an investigator with the Howard Hughes Medical Institute and co-senior author of the study, and transferred the genes to the fruit fly to assess effects of the genes and their interactions in the nervous system.

Results of the study were confirmed in fruit fly models, in biochemical analyses and in human cells, revealing that ataxin 2 is a potent modifier of TDP-43. The study showed that ataxin 2 and TDP-43 interact in animal and cellular models to promote pathogenesis.

The results indicated a link between the proteins and the disease. For example, when the researchers directed expression of TDP-43 to the eye of the fruit fly, a progressive, age-dependent degeneration began. When directed to the motor neurons, flies experienced a progressive loss of motility. The higher the levels of ataxin 2, the greater was the toxicity of TDP-43, resulting in more severe degeneration. The less the amount of ataxin 2, the less was the toxicity.

"Because reducing ataxin 2 levels in yeast and flies was able to prevent some of the toxic effects of TDP-43, we think that this might be a novel

therapeutic target for ALS," Gitler said.

The researchers extended these findings to ask if ataxin 2 showed alterations indicative of an association with ALS. Teaming up with Penn Medicine's John Trojanowski and Virginia Lee, they found that ataxin 2 appeared altered in spinal cord neurons from ALS patients. Following this up with analysis of the type of mutation that is found in ataxin 2 in its other disease, spinocerebellar ataxia 2, or SCA2, a polyQ expansion, they showed a link between expanded ataxin 2 repeats and risk for ALS. The expansions associated with risk for ALS were shorter than those associated with SCA2 but longer than in controls.

The ataxin 2 gene had previously been implicated in another neurodegenerative disease called spinocerebellar ataxia 2, or SCA2. Ataxin 2 contains a repeated stretch of the amino acid glutamine, abbreviated Q. This tract, called polyQ, is usually short, only about 22 or 23 Qs; however, if the polyQ tract expands to greater than 34 Qs, patients develop SCA2.

The new results show that intermediate-length polyQ repeats, between 27 and 33 Qs, longer than normal but shorter than what causes SCA2, increase the risk for developing ALS.

"There have been previous hints of similarities between ALS and SCA2," said Michael Hart, a Penn graduate student in Gitler's laboratory and co-first author of the study. "Our findings suggest a molecular explanation for these similarities and raise the possibility that treatments for one disease might be effective for the other."

"Our findings do not mean that if you have 27Qs or more in your ataxin 2 gene that you will definitely get ALS, only that it increases risk for it," Gitler said.

In prior Penn research, Gitler and his team previously showed that TDP-43 is toxic in yeast in a manner that reflects the toxicity in ALS and that ALS-causing mutations in TDP-43 make the protein clump more rapidly, resulting in increased toxicity. Bonini and her team had previously worked with ataxin 2 in studies showing that it could cause neurodegeneration in flies.

"The identification of a novel and potentially common ALS disease gene from a simple yeast screen, leveraged by the more complex model created in fruit flies, underscores the extraordinary power of yeast and fly as model systems for gaining insight into human disease pathogenesis," Bonini said.

Provided by University of Pennsylvania