

# Two new genes linked to amyotrophic lateral sclerosis and related disorders

18 March 2013

(Medical Xpress)—A study led by St. Jude Children's Research Hospital has discovered mutations in two genes that lead to the death of nerve cells in amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, and related degenerative diseases.

The same mutation occurred in both genes and led to the abnormal build-up of the proteins inside cells. These proteins play an essential role in normal RNA functioning and have also been linked to cancer, including the Ewing sarcoma, the second most common type of [bone cancer](#) in children and adolescents. The finding is the latest in a series of discoveries suggesting [degenerative diseases](#) and cancer may have common origins. RNA is the molecule that directs [protein assembly](#) based on instructions carried in DNA.

The study also adds to evidence that seemingly unrelated [neurodegenerative diseases](#) may involve similar defects in [RNA metabolism](#). Researchers linked the problems to a specific region of the mutated proteins whose normal function was unclear. The study was published today in the advanced online edition of the scientific journal *Nature*.

"I hope this study helps to build the foundation for desperately needed treatments for ALS and perhaps a broad range of diseases caused by abnormal RNA metabolism," said J. Paul Taylor, M.D., Ph.D., an associate member of the St. Jude Department of [Developmental Neurobiology](#) and senior author of the study. Taylor and James Shorter, Ph.D., an assistant professor in the biochemistry and biophysics department at the University of Pennsylvania's Perelman School of Medicine, are the study's corresponding authors.

Each year approximately 5,600 people in the U.S. are found to have ALS. The disease is nearly always fatal, often within five years. Patients suffer muscle wasting and paralysis that affects their

limbs and trunk as well as their ability to talk, swallow and breathe. There is no cure.

For this project, St. Jude sequenced just the portion of the genome called the exome, which carries instructions for making proteins. Researchers sequenced the exomes of two families affected by rare inherited degenerative disorders that target cells in the muscle, bone and brain. Neither family carried mutations previously tied to ALS or related diseases. The project built on the infrastructure developed by the St. Jude Children's Research Hospital—Washington University Pediatric Cancer Genome Project, which played an important role in finding the mutations.

Researchers found the families carried a single, previously unknown mutation in a pair of RNA-binding proteins named hnRNPA2B1 and hnRNPA1. The proteins both bind RNA and help regulate its function. When researchers checked for the same mutations in 517 ALS patients they found hnRNPA1 protein mutated in two patients. One patient had the inherited form of ALS. The other ALS patient had no family history of the disease.

The new mutations occurred in a region of the proteins Taylor refers to as a prion-like domain because it has similarities with yeast proteins called prions. Prions are proteins that can alternate between shapes as needed for different functions. "Until recently we did not know these domains existed in humans and now we realize that hundreds of human proteins have them," Taylor said. "We're only beginning to understand their function in human cells."

Researchers showed the prion-like domains are responsible for the shape change that occurs when these proteins convert into slender threads called fibrils. The mutations accelerate fibril formation and recruit normal proteins to form fibrils. This phenomenon called propagation may explain how ALS and related diseases spread throughout the

nervous system.

Taylor speculated that the normal function of prion-like domains is to assemble RNAs into temporary structures called granules, which are part of the cell's normal [protein](#) production machinery.

Granules are normally short lived, and the RNA-binding proteins involved in their formation are recycled. But in cells with hnRNPA2B1 or hnRNPA1 mutation, RNA granules accumulated in the cytoplasm instead of being disassembled.

"That's bad news for RNA regulation, which is bad news for those cells," Taylor said.

The study has several important implications, Taylor said. Recognition that the mutations adversely impact regulation of RNA could lead to targeted therapy to correct the problem. The mutation's location in the prion-like domain might also prove significant. Although the mutations in hnRNPA2B1 or hnRNPA1 appear to be rare, hundreds of other RNA-binding proteins have prion-like domains. Taylor said patients with unexplained neurodegenerative diseases may have mutations in these proteins.

Provided by St. Jude Children's Research Hospital

APA citation: Two new genes linked to amyotrophic lateral sclerosis and related disorders (2013, March 18) retrieved 31 October 2022 from <https://medicalxpress.com/news/2013-03-genes-linked-amyotrophic-lateral-sclerosis.html>

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