Researchers reveal how a common mutation causes neurodegenerative disease

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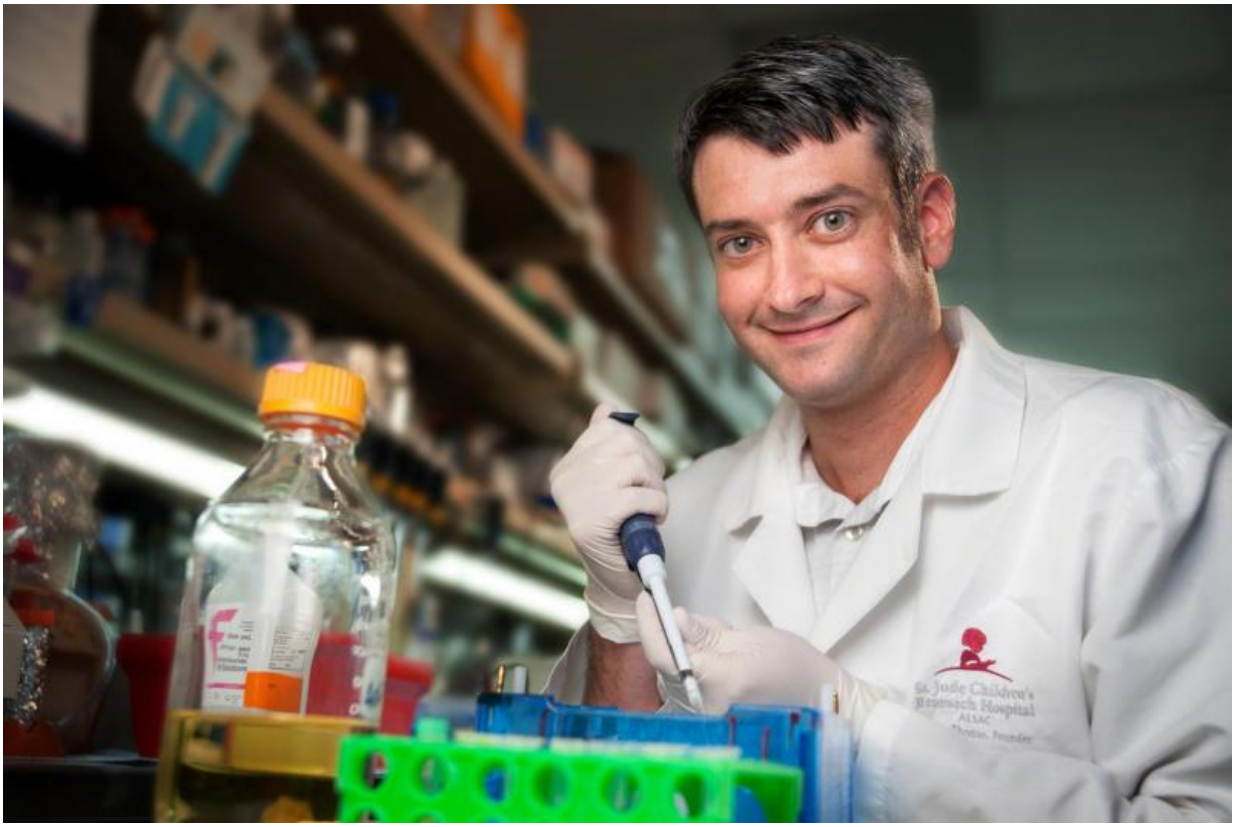

Brian Freibaum, Ph.D., is a postdoctoral fellow in the Cell & Molecular Biology Department at St. Jude Children's Research Hospital. Credit: St. Jude Children's Research Hospital / Seth Dixon

Researchers have determined how the most common gene mutation in

amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) disrupts normal cell function, providing insight likely to advance efforts to develop targeted therapies for these brain diseases. Scientists from St. Jude Children's Research Hospital and the University of Massachusetts Medical School (UMMS) led the research, which appears today in the science journal *Nature*.

Investigators reported evidence the mutation interferes with the movement of RNAs and proteins into and out of the nucleus. Instructions for assembling new proteins are encoded in DNA in the cell nucleus. RNA carries this information out of the nucleus to the cytoplasm where proteins are made. The discovery reveals that the most common gene mutation in ALS and FTD blocks this transfer of information, setting the stage for the deterioration and death of neurons in the brain and spinal cord.

The findings come four years after mutations in the gene C9ORF72 were discovered and identified as the most common genetic cause of ALS, which is also known as Lou Gehrig disease. Mutations in the same gene also cause FTD, another neurodegenerative disorder that includes changes in behavior and personality as well as problems with motor function. Until now, however, how the mutation disturbed cell function was unknown.

"C9ORF72 mutations are by far the most common genetic defect associated with both ALS and FTD, so understanding how the mutation causes disease is tremendously important for efforts to develop therapies to stop or reverse the death of neurons in the brain and spinal cord of patients," said co-corresponding author J. Paul Taylor, M.D., Ph.D., Chair of the St. Jude Department of Cell and Molecular Biology and a Howard Hughes Medical Institute investigator. "Such therapies are desperately needed since there are no treatments proven to halt or reverse the disorders. Most patients die within five years of diagnosis."

Added co-corresponding author Fen-Biao Gao, Ph.D., professor of neurology at UMMS: "Combining a simple fruit fly model with experiments in cells donated by ALS and FTD patients was essential for discovering the disease mechanism underlying mutations in C9ORF72."

This year ALS will be diagnosed in about 5,600 U.S. residents. Ninety percent or more of patients report no family history of the disease. C9ORF72 mutations account for 4 to 6 percent of ALS in these patients and for 25 to 40 percent of ALS in those with family histories of the disease. FTD will be identified in a similar number of individuals.

The C9ORF72 gene normally includes a short sequence of DNA that is repeated 20 times or less. In the mutant gene, however, this sequence—GGGGCC—is expanded and abnormally repeated dozens or thousands of times. The resulting RNA reflects the repetitions and can lead to abnormally shaped RNA and proteins that damage cells.

To determine how the repetitions affect the cell, co-first author Brian Freibaum, Ph.D., a St. Jude staff scientist, developed a fruit fly model of the human neurodegenerative diseases FTD and ALS that includes C9ORF72 with expanded repetitions. Flies with 58 repetitions had more severe symptoms than flies with the normal number.

Researchers in Memphis and in Worcester, MA., then divided up the work and screened more than 80 percent of the mutant fly genome to track the consequences of the C9ORF72 repetitions.

By sequentially knocking out one copy of each gene, researchers identified 18 modifier genes whose loss led to an easing or worsening of symptoms. The 18 genes were all involved in the nuclear transportation system. Some genes encoded proteins that were part of the nuclear pore complex; others were part of the machinery that coordinates the export of RNA from the nucleus and the import of proteins needed for the

nucleus to function properly.

Checking neurons generated from patients with the C9ORF72 mutation revealed a buildup of RNA in the nucleus of cells. When researchers compared RNA concentration inside and outside the nucleus, they found RNA density was about 35 percent greater in neurons from patients with the mutation than in those without. The study included neurons generated from five patients with C9ORF72 mutations and three without. The mutation did not have a similar impact on RNA concentrations in skin fibroblast cells from the same patients. That suggests the damage caused by C9ORF72 mutation is limited to brain cells.

"While work continues to determine exactly why the newly identified defect is toxic to neurons, this study reveals the key defect we need to reverse in treatment, for example by knocking out or silencing the mutant gene," said Taylor, whose research focuses on reducing death and disability associated with neurological disease.

More information: GGGGCC repeat expansion in C9ORF72 compromises nucleocytoplasmic transport, *Nature*, DOI: 10.1038/nature14974

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