Researchers identify protein associated with sporadic ALS

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Researchers at the University of Massachusetts Medical School have uncovered new evidence suggesting that the SOD1 gene, which is implicated in 20 percent of inherited cases of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), also plays a part in sporadic forms of the disease. Discovery of this common pathology is described in the October 17 online edition of *Nature Neuroscience*.

While the SOD1 gene has long been understood to play a role in familial ALS, scientists suspected a connection to the more common form of ALS, for which there is no known cause, and sought to establish a shared pathological pathway. "This common ALS pathology between sporadic and familial ALS means that current gene silencing and immunotherapeutic treatments being developed in academic and commercial labs that target the mutant SOD1 gene may be extended to target non-mutant SOD1 protein found in sporadic ALS cases," said Daryl Bosco, PhD, assistant professor of neurology and lead author of the study.

ALS is a progressive, neurodegenerative disorder affecting the motor neurons in the central nervous system. It is estimated that 5,000 people in the U.S. are newly diagnosed with the disease each year. As motor neurons die, the brain's ability to send signals to the body's muscles is compromised, leading to the loss of voluntary muscle movement, paralysis and eventually death from respiratory failure. The average survival rate for patients with ALS is three to five years. In 1993, a team of researchers led by Robert H. Brown Jr., MD, DPhil, chair of

neurology at the University of Massachusetts Medical School, discovered the first gene linked to familial ALS, a protein anti-oxidant known as superoxide dismutase, or SOD1. Only 10 percent of ALS cases are familial, while roughly 90 percent are sporadic in nature—meaning there is no identifiable familial risk or family history.

When Dr. Brown began researching the genetic causes of familial ALS, he hoped that one day research would provide insight into the more common sporadic form of the disease. "It's been hypothesized that there are common pathogenic pathways between familial and sporadic ALS," said Brown. "Our new findings strongly suggest that is the case."

To determine whether the SOD1 protein found in sporadic ALS cases had become toxic via non-inherited modifications, Bosco and colleagues showed that an antibody known to bind specifically to mutant SOD1 also binds to SOD1 modified by oxidation indicating that the oxidized SOD1 protein shared characteristics with the mutant SOD1 protein. Additional experiments showed further that in four out of nine samples from individuals with sporadic ALS, the same antibody recognized the SOD1 protein in spinal motor neurons, evidence that the protein had been modified in a similar way as the mutant SOD1 in familial ALS and in samples oxidized in the lab. Moreover, the SOD1 protein extracted from three of these cases proved toxic to the function of motor neurons in an experimental model.

"This research shows that under certain conditions and absent a mutation in the gene, a normal SOD1 protein can have the same toxic characteristics that are found in familial ALS where SOD1 gene is mutated," said Brown. "What's more, we found the presence of these aberrant proteins in select cases of sporadic ALS."

"Until now, factors linking both forms of ALS have been lacking," said Bosco. "These results demonstrate that this protein plays a role in both

forms of the disease."

Bosco cautions that while a modified form of the SOD1 protein may play a part in sporadic cases of ALS, it's still unclear what is causing the modification, how many cases may be as a result of the modification or whether it is the primary cause of the disease. "Despite the presence of the normal gene, we show that modifications to the protein made by the gene makes it behave like the toxic, mutated forms of protein," said Bosco. "Further research is needed to understand properties of this toxic protein and how it's being modified."

Provided by University of Massachusetts Medical School

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