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Study identifies new gene associated with ALS

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A collaborative research effort spanning nearly a decade between researchers at Massachusetts General Hospital (MGH) and King's College London (KCL) has identified a novel gene for inherited amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). This is the fourth gene associated with familial forms of the devastating neurological disorder. Two papers, published in the February 27 edition of *Science*, report mutations in FUS/TLS, a gene known to play a role in DNA repair and the regulation of gene expression. The mutations affect the behavior of the FUS/TLS protein within cells and lead to deposits of abnormal protein within motor neurons.

"We found a series of mutations in a gene that interacts with biological pathways already implicated in ALS and other neurological diseases, resulting in familial ALS of differing inheritance patterns and varying severity," says Thomas Kwiatkowski, MD, PhD, of the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND), lead author of the MGH report. "This puts us closer to identifying the link between inherited and sporadic ALS as well as to new targets for drug design."

ALS is a progressive neurodegenerative disease affecting motor neurons in the brain and spinal cord. Death of these nerve cells stops the transmission of neural impulses to muscle fibers, leading to weakness, paralysis and usually death from respiratory failure. Most cases of ALS are sporadic, with no evidence of inheritance, but 10 percent of cases appear to be inherited. The first gene associated with familial ALS, SOD1, was discovered in 1993 by a multi-institutional team led by

Robert Brown, MD, PhD, senior author of the MGH paper. Formerly director of the Day Neuromuscular Research Laboratory at MGH-MIND, Brown is now professor and chair of Neurology at the University of Massachusetts Medical School.

Mutations in SOD1 are believed to cause up to 25 percent of familial ALS, and finding additional genetic causes has been challenging. Several rare mutations that cause atypical forms of the disorder have been identified, and the second gene associated with the classic form, VAPB, has been observed in a few families in Brazil. In 2008, mutations in a gene called TARDBP, leading to abnormal neuronal deposits of the associated protein, were found by the KCL team in another group of familial ALS patients.

The current findings began with the MGH team's analysis of a family from the Cape Verde islands in which four individuals developed a form of ALS primarily affecting their arms and legs but not their respiratory system. The patients' maternal grandparents were first cousins, and the fact that many Cape Verde residents in small communities are closely related to each other increased the possibility that the disorder was caused by a recessive mutation inherited from both parents. The researchers screened affected and unaffected members of the family for instances in which both copies of a chromosomal region were identical. Affected family members were found to have such an area in a segment of chromosome 16, which previous studies by both groups had suggested might harbor an ALS gene.

Detailed sequencing of several candidate genes in that region identified an ALS-associated mutation in FUS/TLS, two copies of which were present in all four affected family members. Some apparently unaffected family members who also had two mutated copies had not reached the age where ALS symptoms typically appear. Several unaffected family members had a single copy of the variant, which was also seen in one

unrelated Cape Verdean but not in a control group of 1,446 North American individuals.

The MGH researchers then fully sequenced the protein-coding regions of FUS/TLS in two families that previous research had implicated as having an ALS-associated gene on chromosome 16 and found distinct FUS/TLS mutations in affected members of both families. Analysis of the gene in 81 unrelated familial ALS cases and almost 300 sporadic cases led to finding a total of 13 different FUS/TLS mutations in 17 familial ALS families, but no mutations were found in the sporadic cases or the control group.

The MGH researchers sought to validate their early data implicating FUS/TLS mutations by asking the team at King's College London, led by Christopher Shaw, MBChB, MD, to screen the families they had been studying. As described in their Science paper, the KCL team reported three mutations in eight apparently unrelated families and went on to characterize the effect of the mutations in cultured cells. They also identified deposits of FUS/TLS protein in motor neurons of three patients with FUS/TLS mutations, deposits absent from patients with SOD1 mutations or sporadic ALS.

The MGH team then analyzed brain tissue from one of its patient and also found abnormal deposits of the FUS/TLS protein in the nucleus of both neuronal and non-neuronal cells, along with degenerative changes typical of ALS. "Finding genes for rare and rapidly fatal diseases is extremely challenging - I can't stress enough how important it has been to have this international collaboration involving so many dedicated scientists and physicians on both sides of the Atlantic," says Kwiatkowski.

"We've just begun to look at how these apparent FUS/TLS aggregates relate to the disease process - whether they contribute to neuronal

damage or protect against it," he continues. "We're also developing a genetic test for mutations in this gene, which could help screen at-risk individuals and aid clinicians in diagnosis. It's been wonderful working together to try to solve ALS, and I hope our continued cooperation will make even greater strides." Kwiatkowski is an instructor in Neurology at Harvard Medical School.

Brown adds, "This discovery identifies new pathways implicated in ALS and will almost certainly lead to new animal- and cell-based models for this disease, which should accelerate efforts to find a therapy for ALS."

Source: Massachusetts General Hospital