MedicalXpress

Scientists identify new gene that influences survival in amyotrophic lateral sclerosis

August 26 2012

A team of scientists, including faculty at the University of Massachusetts Medical School (UMMS), have discovered a gene that influences survival time in amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). The study, published today in *Nature Medicine*, describes how the loss of activity of a receptor called EphA4 substantially extends the lifespan of people with the disease. When coupled with a UMMS study published last month in Nature identifying a new ALS gene (profilin-1) that also works in conjunction with EphA4, these findings point to a new molecular pathway in neurons that is directly related to ALS susceptibility and severity.

"Taken together, these findings are particularly exciting because they suggest that suppression of EphA4 may be a new way to treat ALS," said Robert Brown, MD, DPhil, a co-author on the study and chair of neurology at UMass Medical School.

ALS is a progressive, neurodegenerative disorder affecting the motor neurons in the central nervous system. As motor neurons die, the brain's ability to send signals to the body's muscles is compromised. This leads to loss of voluntary muscle movement, paralysis and eventually respiratory failure. The cause of most cases of ALS is not known. Approximately 10 percent of cases are inherited. Though investigators at UMMS and elsewhere have identified several genes shown to cause inherited or familial ALS, almost 50 percent of these cases have an unknown genetic cause. There are no significant treatments for the disease.

Wim Robberecht, MD, PhD, lead investigator of the Nature Medicine study and a researcher at the University of Leuven in Belgium and the Vesalius Research Center, screened for genes in zebrafish that blunt the adverse effect of the ALS mutant gene SOD1. Through this process, his team identified EphA4 as an ALS modifier. Dr. Robberecht's team went on to show that when this gene is inactivated in mice with ALS, the mice live longer.

Dr. Robberecht then turned to UMass Medical School to confirm that turning off EphA4 in human ALS cells would slow the progression of the disease. Dr. Brown and his team identified two human ALS cases with mutations in the EphA4 gene which, like the zebrafish and the mice, had unusually long survival times. This suggests that blocking EphA4 in patients with ALS may be a potential therapeutic target in the future.

In an exciting, related development, a new ALS gene (profilin-1) identified last month by UMMS scientists works in conjunction with EphA4 in neurons to control outgrowth of motor nerve terminals. In effect, gene variants at both the top and the bottom of the same signaling pathway are shown to effect ALS progression. Together these discoveries highlight a new molecular pathway in neurons that is directly related to ALS susceptibility and severity and suggests that other components of the pathway may be implicated in ALS.

"It is exciting that these two studies identify the same pathway in ALS," said John Landers, PhD, associate professor of neurology and lead author of the PFN1 study. "Hopefully this discovery will accelerate efforts to finding a treatment for ALS."

More information: DOI: 10.1038/nm.2901