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Genetic errors linked to more ALS cases than scientists had thought

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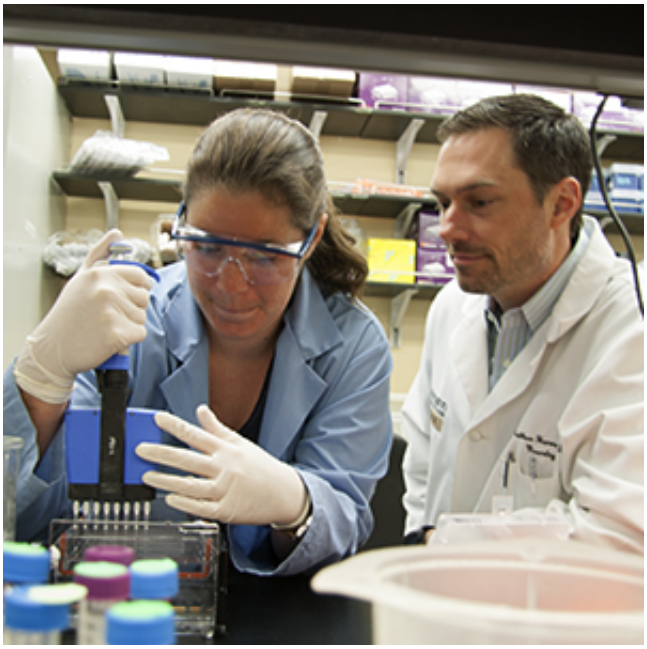

Washington University graduate student Janet Cady and assistant professor of neurology Matthew Harms, MD, found evidence that genetic mutations may contribute to more cases of amyotrophic lateral sclerosis (ALS) than scientists had realized. The illness destroys nerve cells that control muscles, eventually leading to paralysis and death. Credit: Michael C. Purdy

Genetic mutations may cause more cases of amyotrophic lateral sclerosis (ALS) than scientists previously had realized, according to researchers at Washington University School of Medicine in St. Louis and Cedars-Sinai Medical Center in Los Angeles. The scientists also showed that the

number of mutated genes influences the age when the fatal paralyzing disorder first appears.
ALS, also known as Lou Gehrig's disease, destroys the nerve cells that control muscles, leading to loss of mobility, difficulty breathing and swallowing, and eventually paralysis and death. Understanding the many ways genes contribute to ALS helps scientists seek new treatments.

The study appears online in *Annals of Neurology*.

Scientists have linked mutations in more than 30 genes to ALS. Alone or in combination, mutations in any of these genes can cause the disease in family members who inherit them.

Roughly 90 percent of patients with ALS have no family history of the disease, and their condition is referred to as sporadic ALS. Scientists had thought mutations contributed to barely more than one in every 10 cases of sporadic ALS.

But researchers recently started to suspect that patients with sporadic ALS carry mutations in the 30 genes linked to ALS more often than previously thought. The new study is among the first to prove this suspicion correct.

"To our surprise, we found that 26 percent of sporadic ALS patients had potential mutations in one of the known ALS genes we analyzed," said co-senior author Matthew Harms, MD, assistant professor of neurology at Washington University. "This suggests that mutations may be contributing to significantly more ALS cases."

The scientists used a sequencing technique devised at Washington University to look at 17 known ALS genes in the DNA of 391 patients with ALS. Like the overall ALS patient population, 90 percent of the patients had no family history of disease.

It's not yet clear why some patients with sporadic ALS have mutations linked to the illness but no family history of the disorder. Researchers don't know if these patients are the first in their families to develop these mutations, or if these altered genes are present in other family members but do not cause the disorder. Harms noted that some of the mutations they identified might not contribute to disease at all.

"It's also possible that these mutations could be combining with environmental factors linked to ALS," said co-senior author Robert Baloh, MD, PhD, associate professor of neurology at Cedars-Sinai Medical Center. "Those factors might coincide in an individual family member and cause disease, while other family members who have the mutation but not the environmental exposures remain unaffected."

The study also shows that having mutations in more than one ALS gene can accelerate the onset of symptoms. In patients with only one mutation, the average age of onset was 61, but in those with more than one mutation, the average age of onset was 51.
The scientists are analyzing genetic data from additional patients with ALS to confirm their findings.

The ALS Association estimates that 30,000 Americans have ALS at any given time. Riluzole, the sole medication approved to treat the disease, has only marginal benefits in patients.

More information: Cady J, Allred P, Bali T, Pestronk A, Goate A, Miller TM, Mitra R, Ravits J, Harms MB, Baloh RH. ALS onset is influenced by the burden of rare variants in known ALS genes. *Annals of Neurology*. Online Nov. 11, 2014.
ttp://www.ncbi.nlm.nih.gov/pubmed/25382069