Trends in Medical Research

ISSN 1819-3587

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Gene That Causes Some Cases of Familial Amyotrophic Lateral Sclerosis Discovered

Using a new gene sequencing method, a team of researchers led by scientists from Johns Hopkins and the National Institutes of Health has discovered a gene that appears to cause some instances of familial Amyotrophic Lateral Sclerosis (ALS). The finding could lead to novel ways to treat the more common form of this fatal neurodegenerative disease, which kills the vast majority of the nearly 6,000 Americans diagnosed with ALS every year.

Researchers don't know exactly what causes ALS, which destroys the motor neurons that control the movement of all the body's muscles, including those that control breathing. However, studies into the familial form of the disease, which affects 5 percent to 10 percent of those diagnosed with the disease, could shed some light on why motor neurons die in all types of ALS, says study leader Bryan J. Traynor, M.D., an Assistant Professor in the Department of Neurology at the Johns Hopkins University School of Medicine and chief of the Neuromuscular Diseases Research Group at the National Institutes of Health.

"If you look at the spectrum of diseases caused by dysfunctional genes, our knowledge of almost all of them has grown out of the familial form of those diseases," Traynor says. By finding the genes associated with those diseases, he says, researchers can insert the causative genes in animals, creating models that can help them decipher what takes place to cause pathologies and develop ways to stop them.

Scientists were already aware of a handful of genes that appear to cause some cases of familial ALS. In the new study, published in the Dec. 9 issue of the journal Neuron, Traynor and his colleagues used a new technique known as exome sequencing to search for more. This new technique differs from the more common type of gene sequencing since it focuses only on the 1 percent to 2 percent of the genome that codes for proteins and ignores the remaining, non-coding DNA. Exome sequencing also sequences thousands of genes at the same time, rather than the step-by-step sequencing of the more traditional method, making exome sequencing significantly faster.

Traynor's team worked with two affected members of an Italian family discovered by colleague Adriano Chiò, M.D., of the University of Turin, an ALS specialist who maintains a registry of all cases of the disease in northern Italy, and by Jessica Mandrioli, M.D., of the University of Modena. Using exome sequencing on these two ALS patients and 200 people without the disease, the scientists looked for gene differences that the ALS patients had in common that differed from the other samples. Their search turned up a gene called VCP, short for valosin-containing protein.

When the researchers looked for other instances in which this gene was mutated in 210 additional ALS patients, they found four different mutations that affect VCP in five individuals. None of these mutations were found in the genomes of hundreds of healthy controls, suggesting that VCP is indeed the cause for some of the ALS cases.

Though the scientists still don't know exactly how mutated VCP might lead to ALS, they do know that this gene plays a role in a process known as ubiquination, which tags proteins for degradation. A glitch in this process could lead to too much or too little of some proteins being present in motor neurons, leading to their death. Eventually, Traynor says, scientists may be able to develop drugs that could transform this pathological process into a healthy one in ALS patients, saving motor neurons that otherwise would have died.

This work was supported in part by the Intramural Research Programs of the NIH, National Institute on Aging, and National Institute on Neurological Diseases and Stroke. The work was also funded by the Packard Center for ALS Research at Johns Hopkins, the Fondazione Vialli e Mauro for ALS Research Onlus, Federazione Italiana Giuoco Calcio, the Ministero della Salute, the Muscular Dystrophy Association, and the Woodruff Health Sciences Center at Emory University.

Jeffrey Rothstein, M.D., also of Johns Hopkins, participated in this study.

Janel O. Johnson et al. Exome Sequencing Reveals VCP Mutations as a Cause of Familial ALS. Neuron, Volume 68, Issue 5, 857-864, 9 December 2010 DOI: 10.1016/j.neuron.2010.11.036