Whole-Exome Sequencing Turns Up New ALS Gene, and That’s Just the Start

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Speaker: John Landers, Ph.D.

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New gene-hunting techniques are providing important new insights into the causes of ALS, according to John Landers, Ph.D., Professor of Neurology at the University of Massachusetts Medical Center in Worcester. Dr. Landers presented an update of new approaches and the latest genetic discoveries in a webinar hosted by Lucie Bruijn, Ph.D., Chief Scientist for The ALS Association.

Familial ALS, in which more than one family member is affected, makes up about 10 percent of all cases of the disease. “We know the causes of about two-thirds of these cases,” Dr. Landers said, “including the C9orf72 gene, SOD1, TDP-43, and FUS.”

However, there is likely much more to find, not only for the remaining familial cases, but also in sporadic disease, in which there is not a family history. Researchers are increasingly recognizing that some portion of sporadic cases also have an underlying genetic basis.

Dr. Landers uses an approach called “exome-wide rare variant analysis.” A gene is a “recipe” for a protein. Genes are divided into exons and introns. The exons encode the protein, while the introns provide spacers between the exons. Analyzing the exons, therefore, is the quickest route to finding likely disease-causing changes in the gene.

Looking at all the exons of all the genes—collectively known as the exome—is possible because of advances in technology unavailable even 10 years ago. Whole genome sequencing—looking at all 19,000 genes, and all the non-coding DNA in between—is beginning to be feasible as well.

However, simply sequencing the exome of an affected individual is not enough to identify a genetic cause of disease, Dr. Landers said. “All of us have about 800 rare sequence variants, including about 80 that change the encoded protein,” any one of which might be at fault.

To find true disease-associated variants, Dr. Landers and his colleagues look for rare variants that are more frequent in people with ALS than in unaffected controls. “We identify all the variants present, then look gene by gene, and count up the number of variants in cases and in controls,” he said. A gene with significantly more variants in ALS cases than in controls “tells us the gene is somehow associated with the disease.”
The challenge, he said, is that while you don’t need other affected family members (as you would for a typical gene search), “you need very large sample sizes,” with hundreds to thousands of ALS cases.

In Dr. Landers’s study, he examined the exomes of 363 people with ALS and 4300 controls. The gene showing the strongest connection to ALS was tubulin 4A, a protein that forms part of the “cytoskeleton,” or internal structure and transportation system, for neurons and other cells. Four of the five sequence variants he found are likely to cause a deleterious change in the tubulin 4A protein. The mutant proteins appear to have a diminished ability to link together, a key part of their function. Other tests also supported the causative role of the variants. “All this gave us confidence that this gene is indeed somehow involved in familial ALS,” Dr. Landers said.

There are more familial genes to find, but the biggest challenge will be understanding genetic contributions to non-familial, or sporadic, ALS. To that end, with major support from the ALS Association, Dr. Landers is helping to spearhead Project MinE www.projectmine.com, an international collaboration whose goal is to sequence the entire genome of 15,000 people with sporadic ALS. “Once we know what those genes are, it will help us understand the pathways that lead to disease and point to treatments to fix these pathways. This is the largest collaborative ALS study ever.”

Those who want to get involved in Project MinE can contact researchgrants@alsa-national.org.

“We are extremely excited to be supporting Project MinE and other large-scale genomic efforts to understand ALS,” said Dr. Bruijn. “There is still much to learn about the genetic basis of all forms of ALS, and that information should provide us with deep insights into development of new treatments.”

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