The pace of ALS research has been accelerating in the past several years with new gene discoveries shining light in unexpected new places in the search for the causes of ALS. The newest discovery has intensified that acceleration and has caused “incredible excitement” in the field since it was announced in late 2011. “We really feel there has been a shift in the field,” said ALS Association Chief Scientist Lucie Bruijn, Ph.D., as she introduced the co-discoverers of the new gene at a recent Association webinar.

The two scientists are Bryan Traynor, M.D., and Rosa Rademakers, Ph.D. Dr. Traynor is Investigator and Chief of the Neuromuscular Diseases Research Group in the Laboratory of Neurogenetics at the National Institute of Aging. Dr. Rademakers is Associate Professor in the Department of Neuroscience at the Mayo Clinic in Jacksonville, Florida.

They independently discovered the identity of a long-sought gene mutation on chromosome 9. The mutation causes a larger proportion of familial ALS than all other identified genes combined along with a smaller but still significant number of cases of sporadic ALS.

Both scientists lauded The ALS Association for its pivotal role in funding the research that led to the gene discovery.

The gene is called C09ORF72, a label that indicates it is on chromosome 9, and that it occurs at the 72\textsuperscript{nd} “open reading frame” or DNA segment available for reading by the genetic machinery. The name was chosen because nothing else about the gene’s function is currently known.

The mutation occurs in a section of DNA with multiple units of six DNA bases, GGGGCC (hence, a “hexanucleotide” repeat). The normal gene carries between 2 and 22 of these units. The mutation, in contrast, includes hundreds or even thousands of them. “It doesn’t look like anything we have studied before in ALS,” Dr. Rademakers said. “It’s really a challenge to understand how it functions and causes disease.”

The mutation actually occurs just “upstream” of the C09ORF72 gene at a position that usually affects how much of the gene’s protein is made. It is not yet clear whether the mutation does in fact cause a change in the amount of protein produced, and if so, whether this contributes to disease. Another possibility, which Dr. Rademakers outlined during the webinar, has to do with the RNA made from the mutation.

The hexanucleotide repeat, whether normal or mutated, is “transcribed,” used to make an RNA copy of the gene and its surroundings. Any excess material, including the repeat, is snipped off, before the RNA is used to make protein. It is possible that the very long RNA copy of the repeat interferes with normal cell functions, instead of being degraded and recycled. “RNA
accumulation inside cells may have detrimental effects,” Dr. Rademakers said. “The RNA may attract other RNAs, or proteins, and stick to them.” A similar mechanism has recently been found to operate in an unrelated neurologic disease called myotonic dystrophy.

Determining how the mutation causes ALS will now be the focus of intense research in labs around the world. That focus will be especially acute because of how common the C09ORF72 gene mutation is in ALS.

Dr. Rademakers discovered the gene in a single large family, then scanned the genes of all familial ALS cases seen at the Mayo Clinic in Jacksonville over a 20-year period. She found the gene mutation in 23% of familial ALS patients and 4% of sporadic ALS patients. She also looked at patients with frontotemporal dementia (FTD), a neurodegenerative disease also found in many ALS families, including her original C09ORF72 family. She found mutations in 12% of all familial FTD patients and 3% of all sporadic FTD patients. The results, she said, “are astonishing: the mutations in this new gene are the most common cause of FTD and ALS known today.”

“This discovery is going to influence the entire field as we determine how to move forward over the next several years,” Dr. Traynor added.

Dr. Traynor’s own search for the gene began in Finland. This was for two reasons, he explained: The Finns are a relatively homogenous population, genetically speaking, and they have the highest incidence of ALS in the world. This suggested to him that if the chromosome 9 gene could be found, Finland would be a great place to look. The “Eureka moment” in the two-year search, he said, came when he took over for the computers for a few days to analyze some of the DNA sequences by hand. What he noticed, which the computers had missed, was an unusual amount of a six-base pair repeating section in some of the samples. When he reanalyzed some of the samples from the Finnish patients, “my jaw dropped,” he said. Half of them contained the same expanded repeat. “I never thought I would see a gene in ALS that would have that high a frequency.”

Worldwide, the C09ORF72 gene is likely responsible for about 40% of all familial ALS cases, compared to about 15% for SOD1 and 4% each for TDP43 and FUS. With all four genes, “we can now explain two-thirds of familial ALS,” he said.

Much remains to be learned. It is thought that almost every person who carries the gene mutation will develop ALS, but the age of onset ranges from the early 30s to the 80s, Dr. Rademakers said. The gene appears to be inherited in a dominant manner (meaning inheritance of a single copy is enough to cause disease). However, given that, it is not clear why the mutation occurs in patients with sporadic ALS who report no family history despite having inherited the gene. A gene test is currently being developed but is not yet available.

Most importantly, researchers will now be determining how to use this new knowledge to understand ALS better and to develop treatments. It is too soon to know whether blocking production of the RNA, for instance, would be helpful or not. “Everybody is very excited,” Dr.
Traynor said, “but we need to be realistic. From the gene to a drug trial is long road. Ultimately we will have a treatment, but it won’t happen tomorrow.”

Meanwhile, he said, his group is actively seeking DNA samples from ALS patients for testing. Those who are interested in more information can contact his assistant Cynthia Crews at ccrews@nia.nih.gov or 301-451-3826.

To view the presentation in its entirety, please visit: https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=64305412&rKey=9a0488f8075ba99d