The recently announced discovery of a new ALS gene, called NEK1, focuses renewed attention on the “cytoskeletal” proteins that give neurons shape and promote transport of important materials within them. The discovery also highlights the power of whole genome sequencing combined with analysis of huge data sets, both recent developments that are reshaping the landscape of gene hunting in ALS. The discovery, and the groundwork and infrastructure that made it possible, were funded in part by The ALS Association, and are a direct benefit of Ice Bucket Challenge funds raised in the summer of 2014.

“That fundraising effort is now producing large, tangible benefits in ALS research,” said Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The Association. The story of how NEK1 was found was recounted in a recent Association-sponsored webinar by co-discoverer John Landers, Ph.D., Professor of Neurology at University of Massachusetts Medical School in Worcester.

“People are 99% identical on the DNA level,” Dr. Landers pointed out, so that in our three billion base pairs, or letters of the DNA code, there are on average three million differences between any two individuals. These differences take the form of letter changes in specific spots within gene; for instance, where one person has an “A,” another might have a “T,” while a third might have a “C.” These variations can make subtle or dramatic differences in the function of the protein made from the gene. Within the human population as a whole, over 100 million differences have been identified to date.

A powerful new way to find an ALS risk gene, Dr. Landers said, is to sequence the entire genome of many individuals, some of whom have ALS and some of whom don’t (called controls). “We compare variants between ALS patients and controls,” he said. “We hope to identify genes with more variants in ALS patients than in control populations.”

With the sequences in hand, computers compare the specific letters at each position in all the genes in the genome, 25,000 genes in all. For instance, if in gene #1, people with ALS tend to have three variants, while controls have four, that gene is of little interest. On the other hand, if in gene #2, people with ALS tend to have four variants while controls have only one that may mean that the variants in people with ALS contribute to disease risk. By comparing the genomes of thousands of people with ALS to thousands of controls, a few genes emerge as being potentially significant. In a recent study led by Dr. Landers, a gene called NEK1 was identified as the strongest candidate.

With this discovery in hand, Dr. Landers wanted to confirm the importance of the gene. He turned to colleagues in The Netherlands, and found that Jan Nelink, Ph.D., of the University of Utrecht, had recently identified the same gene by analyzing a large family from an isolated village in the country.
“Whenever you have two independent approaches leading to the same result, it strengthens your confidence that this is the real gene. But replication is still important for confirming the result,” Dr. Landers said, and so he and his colleagues repeated the analysis on a second large sample population, and again NEK1 was revealed as a contributor to ALS risk. “We saw an increase in percent of cases with this variant versus controls,” he said. It was more than twice as common, and depending on the country, up to 5 times as common in familial ALS as in controls. “This gave us very strong support that this was a risk factor for ALS.”

The NEK1 protein is important for the function and stability of microtubules, part of the cytoskeleton of all cells, including neurons. It also plays a role in neuronal shape and repairing DNA damage. It is not yet clear which of these functions is impaired in the disease-related variants, but research to determine that has begun. Other cytoskeletal genes have also emerged as important in ALS, and the discovery of NEK1 is likely to spur new research in this area.

A risk factor gene increases the likelihood of disease, but most people carrying the risk factor variants will not develop ALS, Dr. Landers stressed. “We do not think it is a good gene for diagnostic testing, because different variants likely convey different levels of risk, and some may even be benign. We don’t have enough information on each variant to assign risk. We think that fewer than 20% of NEK1 variant carriers will actually develop ALS.”

And because there are no gene-specific treatments available, there is not a direct medical benefit from genetic testing to the person undergoing the test. Diagnosis still relies mainly on clinical tests, including electromyography.

Part of the effort in discovering the NEK1 gene was done through Project MinE, led internationally by Dr. Leonard van den Berg of The Netherlands, and in the United States by Dr. Landers and Jonathan Glass, MD, of Emory University, with funding from The ALS Association. The goal of Project MinE is to sequence 15,000 people with ALS and 7,500 controls; it is approximately 35% completed, and funding is currently in place for 7850 samples. Those wishing to donate or to contribute samples can find more information at the website.

The Association is also funding development of a mouse model of NEK1 in order to better understand how it causes disease. “Even though it is a rare cause of disease,” Dr. Landers said, “this opens up new ideas in pathways and therapy development that may be relevant for all ALS.”

“This discovery, and Project MinE as a whole, is a real testament to collaboration on the global level to spur new discoveries in ALS,” Dr. Bruijn said.