Two recent gene discoveries in ALS have greatly accelerated research into the causes of the disease. The genes, called TDP43 and FUS, have enough similarity in function that researchers hope they may point to one or a few important pathways leading to the death of motor neurons.

Background about these genes and strategies for understanding how they lead to disease, were the focus of a recent webinar featuring Tom Maniatis, Ph.D. Dr. Maniatis is Professor of Biochemistry and Molecular Biophysics at Columbia University in New York. He also serves as Chair of The ALS Association Scientific Advisory Board.

“The field of ALS has really changed over the past few years with the discovery of these two new genes,” said ALS Association Chief Scientist Lucie Bruijn, Ph.D., who hosted the webinar. “The field is really exploding.”

Dr. Maniatis began by noting that while mutations in the two genes account for only a small number of cases of disease, they are likely far more important to the understanding of ALS than their numbers imply.

“We hope that by studying these genes we will be able to gain insight into the causes of the disease,” Dr. Maniatis said, “including sporadic disease,” or disease caused by no known genetic or environmental factors.

The potential importance of TDP43 and FUS stems from the normal function of their proteins. Both of them bind to “messenger RNA,” the molecule used by the cell to transmit genetic information from the nucleus, where it is stored, to the cytoplasm, where it is used to make proteins. A cell makes many thousands of types of messenger RNA, and many copies of each type.

RNA binding proteins such as TDP43 and FUS bind to messenger RNA, and regulate their activities. “This is the fundamental thing to understand about these genes,” Dr. Maniatis said.

The “big breakthrough” came a few years ago with the discovery that the dying motor neurons of patients with sporadic ALS contained aggregations of TDP43. While the consequence of these aggregates is still unknown, their presence indicated that RNA regulation was likely to be upset in ALS. Soon after, FUS was also discovered in aggregates. Because they are found even in patients with sporadic ALS, studying them they may be valuable for understanding sporadic disease.

Both proteins have been implicated in “splicing” of messenger RNA, Dr. Maniatis explained. Genes have “nonsense information,” called introns, which must be removed from the RNA copy before it can be used to make protein. The process of removing the nonsense and joining the useful parts is called splicing, and both TDP43 and FUS play a role in the process.

It is still too early to say exactly how mutations in the two genes cause disease. But Dr. Maniatis outlined how his lab and others are attacking the problem. They are creating human motor neurons from patient skin cells, using the techniques explained in a previous webinar by Dr.
The skin cells are treated to turn them into stem cells, and then allowed to differentiate into motor neurons. “The goal is to find important differences between motor neurons generated from patients and those from persons unaffected by the disease,” Dr. Maniatis explained.

The difference he is looking for is a “gene signature,” a change in the activity of a set of genes that is linked to disease. RNA holds the key here, as well. Dr. Maniatis analyzes all of the thousands of messenger RNAs created by the motor neurons to see which are more common, and which less common, in ALS patients. This process of “transcriptional profiling” generates a list of genes whose expression is altered, he said. “There are hundreds of such changes, and we need to go through them to understand which are important for ALS.”

Mutation in TDP43, for instance, causes an increase in the activity of genes for ion channels and neurotransmitters. Both are vital for neuronal activity, but excesses may lead to too much activity, and hasten neuron death. The investigation of such changes is just beginning and has required new tools and new approaches to gene analysis.

Motor neurons express thousands of genes, and mutations cause hundreds of gene expression changes. “When you begin to look at hundreds of genes and how they are regulated, it requires a new science, called systems biology,” Dr. Maniatis said. The focus of systems biology is on understanding the interactions of many different genes. Many researchers think this type of approach will be vital to understanding a complex disease such as ALS. “We are hoping to identify a disease signature for ALS.”

“If successful, it should be possible to use these same methods to understand sporadic ALS, where there is no mouse model. If we understand what goes wrong, we may be able to develop strategies for drug design.”

Progress in ALS depends on cooperation among many labs, Dr. Maniatis said. “Everyone realizes it is far too complex to study as individual labs, and only by working together can we hope to make progress in this disease.”

Dr. Bruijn echoed this thought: “Over the past ten years, the field has become enormously more cooperative. There is no one lab that can do it all. Building a partnership, through meetings or through our organization, is fundamental.”

To view the webinar in its entirety, please go to www.alsa.org, or https://alsa.webex.com/alsa/lsr.php?AT=dw&SP=MC&rID=62860127&rKey=4aa6da4d269f9b30