Aaron Gitler's lab at Stanford University is focused on understanding neurodegenerative diseases, including ALS. Recently, their work has gone in two different and potentially highly important directions: understanding a genetic risk factor possessed by 5% or more of people with ALS, and developing a new treatment approach for people carrying the C9orf72 mutation.

“All the common neurodegenerative diseases share a theme of protein aggregation, in which misfolded proteins accumulate,” he said, including in ALS, where the protein TDP-43 misfolds and accumulates in most people with the disease. “The goal of my lab is to try to understand why these proteins aggregate, and to figure out ways to protect neurons from these aggregates.”

Much of his work is done in yeast, the single-celled organism responsible for rising bread and bubbling champagne. “In yeast, we can see aggregates form in a couple of hours, rather than years,” Dr. Gitler said. That means that the effects of gene mutations, or correction of mutations, can be observed far quicker than in many other model systems.

Dr. Gitler’s lab has used yeast to find genes that promote or prevent TDP-43 aggregation, by ramping up the production of each of the yeast's approximately 6000 genes, one at a time. That work revealed 41 genes that either suppressed or enhanced the toxicity of TDP-43 aggregates.

Of special interest was the yeast version of a human gene called ataxin-2. The precise function of the normal gene is unknown, but when a mutation expands the portion of the gene encoding the amino acid glutamine, the resulting protein is toxic to cells, and causes the disease spinocerebellar ataxia type 2.

Working next in flies, Dr. Gitler found that expressing the ataxin-2 gene in the fly eye alone caused no problems, but when it was co-expressed with TDP-43, it caused much worse neurodegeneration alone than TDP-43 by itself. That led him to ask whether people with ALS might harbor an abnormal ataxin-2 gene. He found that 5% of people with ALS indeed have an expansion in the gene, not enough to cause spinocerebellar ataxia, but potentially enough to increase the risk of ALS, similar to the effect he saw in the flies.

“We think this a powerful new genetic risk factor for ALS,” he said, a finding that has been replicated in other ALS labs throughout the world. Work is underway to better understand how the expanded ataxin-2 might contribute to disease, and how best to reduce its effects. “I would love to come up with a way to lower ataxin-2 levels in ALS,” he said. “We are working on that.”
The second ALS discovery coming from his lab, in collaboration with the labs of Leonard Petrucelli at Mayo Clinic in Jacksonville, Fla., and Nancy Bonini at the University of Pennsylvania in Philadelphia, concerns the C9orf72 gene, the most common genetic cause of ALS.

Mutation of the gene causes enormous expansion of a six-nucleotide sequence, leading to the production of excessive and repetitive messenger RNA from the gene, and production of unusual proteins, called dipeptide repeats, from the messenger RNA. While it is unclear which of these is most toxic, a promising therapeutic strategy is to shut down gene expression using antisense oligonucleotides (ASOs).

But there may be a problem with this approach. Most genes are “read,” and messenger RNA is made, from only one side of the DNA, and so an ASO is created to bind to and inactivate the RNA made from that one side. But for reasons that are unclear, the C9orf72 gene is read from both sides, and so messenger RNA is made from both sides. That is likely to mean that a possible effective ASO strategy is to target them both, potentially doubling the challenge of developing treatment.

Working in Dr. Gitler’s lab, post-doctoral fellow Dr. Nick Kramer has shown that a protein called Spt4 plays a special role in reading DNA with a very long repeated region, such as that in the mutant C9orf72 gene. “Spt4 acts like a clamp” to keep the RNA-making machinery chugging through the long repeat, Dr. Gitler explained. Spt4 does not seem to be required to read the normal gene, but his experiments have shown that without it, the mutant gene is not read effectively, reducing the amount of messenger RNA produced from both sides of the DNA, and therefore the amount of dipeptide repeat protein created.

“This is very exciting, because it means we may be able to selectively affect the disease-causing repeats, without altering expression of the normal gene,” he said. People with ALS due to the C9orf72 mutation also carry one normal version of the gene.

“This exciting work from Dr. Gitler’s lab has the potential to drive the development of new understanding of the disease process, and the development of new treatments,” commented ALS Association Chief Scientist Lucie Bruijn, Ph.D., MBA, who hosted the webinar. “It may be possible to reduce Spt4 activity with drugs, which would give us a treatment option in addition to antisense therapy. And understanding the role of ataxin-2 in increasing ALS risk could provide insights into the disease process that may be useful in developing treatments for all forms of ALS.”

Learn more about Dr. Gitler’s exciting project [here](#).