Disease models are the key to understanding ALS and developing new treatments. Rodent models can be especially useful, since their complex physiology and behavior can reflect many aspects of human disease. In ALS, the only mouse model that replicates both the pattern of neurodegeneration and the paralysis of ALS has been based on mutations in the SOD1 gene. But that model doesn’t develop a specific cellular pathology, called TDP-43 aggregation, which is seen in 97% of ALS cases, and researchers have been concerned that without that aspect of the disease, they may be missing some important clues to developing new treatments.

Now, a new mouse model of ALS has been developed that exhibits this pathology, as well as the neurodegenerative and motor aspects of the disease. The model was the topic of a recent webinar given by its creator, Mervyn Monteiro, Ph.D., Professor at the Maryland School of Medicine, and hosted by Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The ALS Association, which supports Dr. Monteiro’s work. The new model “is an excellent tool that mimics many of the components of ALS,” Dr. Bruijn said, “and in combination with other models, is likely to help us develop new therapies.”

The model Dr. Monteiro created incorporates mutations in the ubiquilin 2 gene, a rare cause of ALS. The ubiquilin 2 protein plays a role in “protein homeostasis,” or protein quality control. Proteins must be folded properly in order to function, and when the folding process goes wrong, the resulting protein can aggregate, or form insoluble clumps. These aggregates can interfere with multiple cell processes and may contribute to development of disease. Ubiquilin 2 ferries misfolded proteins to one of two protein recycling systems in the cell, called the proteasome and the autophagy systems.

Dysfunction of protein homeostasis is a factor in multiple neurodegenerative diseases beside ALS, including Alzheimer’s disease, Parkinson’s disease and Huntington’s disease. Aging and environmental factors can accelerate dysfunction, which may explain how both contribute to risk for ALS.

One consequence of defects in protein homeostasis in ALS is the development of aggregates of the protein TDP-43, which occur in virtually all ALS cases. The consequences of these aggregates are not yet clear, but the SOD1 mouse has not provided insights, since they don’t develop these aggregates. “There is a dire need for models that have TDP-43 pathology,” Dr. Monteiro said, “because it is implicated in ALS pathogenesis.”

Working with a small but highly dedicated team, Dr. Monteiro has created a mouse model carrying the mutated human ubiquilin 2 gene that exhibits TDP-43 pathology, as well as the
other major aspects of the disease. The mice develop a progressive weakness and ultimately paralysis, and have shorter lifespans than mice that do not carry the human gene. They are also weaker and shorter-lived than mice that express a normal, un-mutated form of the human protein. This second kind of control is vital to test the validity of the model, he said, to show that it is the mutation, not simply having any human form of the protein that is toxic.

The mutation-carrying mice also display other aspects of ALS, including muscle atrophy and degeneration of the axons, the long extensions of motor neurons used to send signals to muscle. Finally, the mice develop cognitive defects as well as motor dysfunction, which is common in several forms of ALS.

“It has taken some time to get a second ALS mouse model, and one with the TDP-43 pathology, and I am very excited about that,” Dr. Bruijn commented. “The model can now be used to learn more about how defects in protein homeostasis contribute to ALS, and whether and how TDP-43 aggregates independently contribute to the disease process.” “If we can enhance the protein clearance pathways, we might be able to alter the disease,” Dr. Monteiro said.