LEONARD PETRUCELLI: My name's Dr. Leonard Petrucelli. I'm the chair of the Department of Neuroscience at Mayo Clinic in the Jacksonville campus in Florida. I'm also the Ralph and Ruth Abrams professor. My laboratory has been at the forefront of understanding how a genetic mutation called chromosome 9ORF72 has been involved in ALS and frontotemporal dementia.

A couple of years ago, we identified, as a result of this genetic mutation, that a novel protein can abnormally accumulate in the brains of these individuals. Subsequent to that, we've now recently shown that if you take this genetic mutation and overexpress it in a mouse, you can mimic the disease features including neuronal loss, behavioral deficits, and the neural pathology that is found in individuals with this genetic mutation. So we feel now that we are capable of testing the drug discovery efforts that will soon to emerge for chromosome 9 treatment in this novel mouse model.

And so we're particularly very excited about the opportunities that this will have not only for our laboratory, but also the scientific community as well. The overview of our study today that was recently published in the journal *Science* develops a novel model of ALS and frontotemporal dementia by specifically looking at a very common genetic mutation that is found in these patients and how we can potentially provide not only a working model for future therapeutic trials, but also understanding the disease mechanism that's associated with these devastating disorders.

ALS and frontotemporal dementia are two neurodegenerative diseases. ALS, in particular, typically influences individuals in their mid-adulthood, whereas frontotemporal dementia influences or affects individuals in their late adulthood. They're two separate, but there's also overlapping pathologies between them.

ALS is a disease where there's rapid motor neuron loss in the spinal cord, both upper and motor spinal cord. And these individuals begin to lose the ability to move, ultimately succumbing to the inability to swallow and breathe, whereas frontotemporal dementia is more of a disorder that not only influences cognitive decline, but also the individuals also present with behavioral and language deficits.

At Mayo Clinic, we're very translationally minded. And what that means is that, for a basic scientist such as myself, is to form and develop studies as well as collaborations that will allow us to utilize this mouse model to improve patient care, especially for those individuals that have the genetic mutation. And so that's what our lab is going to be doing.

And as our next step is to form collaborations, which we have, to test small molecules, which are in development ultimately in our animal model. And if proven to be successful, I think it would continue the acceleration and the development of small molecules and therapies towards this genetic mutation. When the gene was identified by Dr. [INAUDIBLE] in 2011, we became very interested in studying this disease.

One of the things that Mayo Clinic has a rich history of doing is modeling-- not only identifying these genes, but also modeling them in cell culture as well as in animal models. And fundamentally, that's what we did. We took-- this gene is a result of a repeat expansion, a genetic mutation. And it repeats itself over and over again.

And so what we did was use a combination of molecular cloning as well as viral approaches to overexpress this mutant gene in animals with the hope that we would perhaps be able to model it from a neural pathological perspective, a behavioral perspective-- and understanding once again the implications that this may have from a mechanistic perspective, as well as with our overall goal of developing a preclinical model, something that we could potentially utilize for upcoming and emerging small molecule therapies that will allow us to eventually test before they will proceed to clinical trials.

The significance of our study is the fact that we were able to model the disease pathology by overexpressing this genetic mutation. And this is incredibly important because as therapies will emerge for targeting this repeat expansion, we become now incredibly hopeful that not only can you target the pathology that is really associated with the chromosome 9 repeat expansion, but also the underlying pathology called TDP-43 that also exists in these patients as well sporadic.

So in short, the therapy now will be able to target not only the pathology associated with the mutation, but also what is linked to it, downstream of it. And that's TDP-43. And this is very, very significant. In the absence of this unexpected finding, the TDP-43 neuropathology, I think we would have been a little bit skeptical whether or not we would have been able to target both pathologies. Now in light of this data, which the model is indicating to us, I think we will now be able to really understand and believe that we can perhaps target both of these pathologies that do exist in these patients.