The TAR DNA-binding protein 43 (TDP-43) is a highly conserved DNA/RNA binding protein that is the major disease protein in most sporadic forms of amyotrophic lateral sclerosis (ALS) and familial ALS caused by TARDBP mutations, as well as the most common subtype of frontotemporal lobar degeneration (FTLD-TDP). However, the mechanisms leading to accumulation of abnormal TDP-43 and its consequences (loss-of-function vs. toxic-gain-of-function) remain unclear. In order to elucidate pathomechanisms in TDP-43 proteinopathies, we generated transgenic mice expressing either the human wildtype TDP-43 or ALS-associated pathogenic mutations (M337V and G348C) under the control of the mouse PrP promoter. Mice were characterized by a battery of behavioral tests for motor and learning/memory functions and by histological and biochemical analyses.

Wildtype and mutated TDP-43 lines showed a pan-neuronal transgenic TDP-43 expression throughout the brain and spinal cord, with a predominantly nuclear localization. Overexpression of wildtype TDP-43 led to premature death (~3-5 months) with rapid disease progression, while expression of similar amounts of mutant TDP-43 was associated with a less severe phenotype with signs of motor impairment and learning/memory dysfunctions at around 15-18 months. However, histological and biochemical hallmarks of human TDP-43 proteinopathies, such as formation of cytoplasmic TDP-43 inclusions and abnormal phosphorylation or truncation of TDP-43 were not recapitulated in these mice.

In summary, our data suggest that perturbation of the physiologically highly regulated TDP-43 level is not well tolerated by neurons most likely by changes in downstream gene regulatory pathways and moreover argue against a toxic-gain-of-function mechanism for ALS associated TARDBP mutations.