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Title	**Behavioural validation of the rNLS8 TDP-43 mouse model on a pure C57BL/6J background**
Abstract (max 300w)	rNLS8 TDP-43 mice recapitulate TDP-43 pathology and disease progression similar to ALS/FTLD-TDP. In rNLS8 mice, expression of cytoplasmic human TDP-43 protein in brain and spinal cord neurons is suppressed by the drug doxycycline (Dox). As a model for ALS/FTLD-TDP, these mice display features including neuron loss, muscle denervation/atrophy, and a progressive motor phenotype. These mice were generated and maintained on a mixed C57BL/6JxC3HeJ genetic background, which produces progeny with ~50% unnecessary genotype and presents a potential risk of variability. To bypass these problems, we have completed congenic backcrossing to pure C57BL/6J background with multiple rounds of speed congenics selection and over 10 generations of breeding, and also established the NLS4 subline at homozygosity. To ensure replication of the previous phenotypes on this new background, we designed the present study as a behavioural validation of C57BL/6J rNLS8 mice. We evaluated performance on rotarod, wirehang test of grip strength, and activity monitor. The new C57BL6/J rNLS8 mice displayed progressive loss of grip strength and deterioration in coordinated movement and balance as measured by the rotarod test over a timeframe similar to previous C57BL/6JxC3HeJ rNLS8 mice. Additionally, C57BL6/J rNLS8 mice showed rapid functional improvement upon return of Dox to mouse feed after disease onset, as expected. However, C57BL6/J rNLS8 mice showed lower penetrance of hindlimb and forelimb tremor than previous C57BL/6JxC3HeJ rNLS8 mice. Overall, the C57BL6/J rNLS8 model recapitulates the same predictable course of disease as the original mixed background, making it a viable model for ALS/FTLD-TDP whilst reducing production of unneeded animals.

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