Mice expressing a mutant dynactin gene (DCTN1) identified in sporadic ALS exhibit evidence of motor neuron disease

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The dynactin p150 subunit, encoded by the gene DCTN1, is part of the dynein-dynactin motor protein complex responsible for the retrograde axonal transport in nerve cells, including motor neurons. DCTN1 is a candidate gene for neurodegenerative diseases, in particular motor neuron and extrapyramidal diseases. Based on an extensive screening effort of all 32 exons in more than 2500 ALS/MND patients and controls as well as cell-based studies, we tested the hypothesis that some of these DCTN1 variants identified in sporadic ALS cause motor neuron disease in mice.

Here, we generated several lines of mice expressing a DCTN1 variant for which the mutation is located in the microtubule binding motif of p150 subunit. As the DCTN1 transgene is driven by the neuron-specific promoter (Thy1.2), we first confirmed that the mutant p150 protein is exclusively expressed in neurons, including spinal motor neurons of these mice.

Clinically, these transgenic mice showed a distinct hind limb clasping as early as four weeks of age and exhibited evidence of weakness as judged by their ability to hang on a wire grid by three months of age. Finally, these mice showed a severe gait disturbance and eventually paralysis of the hindlimbs between seven to eight months of age.

Pathological analysis of mutant p150 mice revealed evidence of loss of spinal motor neurons near end-stage disease accompanied by a severe neurogenic degeneration of the skeletal muscles (e.g., quadriceps) characterized by typical hallmarks as angular muscle fibers and grouped muscle atrophies.

Our preliminary results strongly suggest that at least one of these DCTN1 variants identified in sporadic ALS can cause motor neuron disease in mice, supporting the view that this new experimental animal mouse model would be useful for clarifying disease mechanism and testing of therapeutic strategies in this devastating disease of the elderly for which no effective therapy is currently available.