Modeling Gain-of-Function and Loss-of-Function Components of *SPAST*-based Hereditary Spastic Paraplegia using Transgenic Mice

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Abstract

Hereditary Spastic Paraplegia (HSP) is a disease in which dieback degeneration of corticospinal tracts, accompanied by axonal swellings, leads to gait deficiencies. *SPG4*-HSP, the most common form of the disease, results from mutations of *SPAST*, which is the gene that encodes spastin, a microtubule-severing protein. The lack of a vertebrate model that recapitulates both the etiology and symptoms of *SPG4*-HSP has stymied the development of effective therapies for the disease. h*SPAST*-C448Y mice, which express human mutant spastin at the *ROSA26* locus, display corticospinal dieback and gait deficiencies, but not axonal swellings. On the other hand, *Spast*-knockout mice display axonal swellings but not corticospinal dieback or gait deficiencies. One possibility is that reduced spastin function, resulting in axonal swellings, is not the cause of the disease, but exacerbates the toxic effects of the mutant protein. To explore this idea, *Spast*-knockout and h*SPAST*-C448Y mice were crossbred, and the offspring were compared to the parental lines via histological and behavioral analyses. The crossbred animals displayed axonal swellings, as well as earlier onset, worsened gait deficiencies and corticospinal dieback compared to the h*SPAST*-C448Y mouse. These results, together with observations on changes in HDAC6 and tubulin modifications in the axon, indicate that each of these three transgenic mouse lines is valuable for investigating a different component of the disease pathology. Moreover, the crossbred mice are the best vertebrate model to date for testing potential therapies for *SPG4*-HSP.