

Development of a New ALS Mouse Model that Targets Profilin1 and Actin Filaments

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Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a devastating, lethal, motor neuron disease and, despite the fact that it has been identified for 140 years, there is no therapeutic intervention. The mechanisms causing the neurodegeneration are not known and animal models of the disease are limited. The need for additional animal models is tremendous and could further define mechanisms of disease and facilitate development of novel

therapies for ALS. The recent breakthrough identifying profilin1 (PFN1) mutations in human familial ALS (fALS), presents us with the opportunity to develop a novel ALS model. Mutations in PFN1 disrupt the cytoskeleton by inhibiting polymerization of actin filaments. The consequences of this include disruption of key structures in neurons including the cytoskeleton, formation of axonal growth cones, inhibition of axon and dendrite outgrowth, and activities dependent on the actin cytoskeleton such as vesicle and mitochondria transport. To address the need for a mouse model of mutant PFN1 ALS that is expected to disrupt the cytoskeleton, we have produced transgenic mice overexpressing one of the mutations identified in familial ALS, a glycine118>valine substitution in the human PFN1 gene (hPFN1G118V). This model will provide an important opportunity to discover new, yet unknown cellular and molecular mechanisms that underlie neurodegeneration in ALS. Discoveries in this new mutant PFN1 ALS model will offer fundamental insights into pathogenic mechanisms and therapeutic intervention in ALS. We will use this model to test the hypothesis that expression of hPFN1G118V mutant protein in mice will cause cardinal phenotypes and pathologies that resemble those in ALS patients. Our hypothesis is based on preliminary characterization of hPFN1G118V transgene- expressing progeny. These mutant mice present degeneration and loss of motor neurons in the spinal cord, hindlimb tremor, clasping, muscle weakness and atrophy, reduced stride length, reduced general mobility, lower gait, hunched back, droopy tail, reduced motor performance, weight loss, and premature death. In this study, we propose to further characterize the ALS phenotype and neurodegenerative pathology in the hPFN1G118V model and investigate the cellular and molecular mechanisms of neurodegeneration caused by hPFN1G118V. Aim 1: Demonstrate that the functional phenotype and pathology of mutant hPFN1G118V transgenic mice resemble that of ALS patients. Aim 2: Define the mechanisms of mutant hPFN1G118V activity that underlie degeneration of motor neurons. This study will provide proof-of-principle that mouse models of mutant hPFN1 identified in ALS patients exhibit the phenotypes and pathologies of ALS. This will have significant impact because these models may unveil new mechanisms of ALS neurodegeneration applicable beyond the subset of familial ALS patients, providing new targets for therapeutic intervention. Further, these mice will provide a new model for therapeutic testing to stop progression of ALS-like neurodegeneration that may be translatable for human use.

Further information available at:

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