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## Genetic Modifiers of Neurodegeneration in a Mouse Model of Niemann-Pick Type C Disease

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Niemann-Pick Type C Disease is a juvenile-onset progressive neurodegenerative disease characterized by accumulation of cholesterol and gangliosides in the brain and peripheral tissues. The cerebellum is particularly affected and patients show ataxia, with massive loss of Purkinje neurons. The disease is caused by mutation in one of two genes NPC1 or NPC2, giving essentially an indistinguishable clinical phenotype in humans and mouse models. We have produced NPC2 hypomorphic mice with a ~1000 fold decrease in NPC2 mRNA and protein. These mice develop ataxia, tremors, cachexia, Purkinje neuron loss, and decreased lifespan; similar to previously published NPC2 hypomorphic mice. When the mutation is placed on a mixed genetic background (129P2 x FVB/N F2) mice show an increase in the range of lifespan compared to NPC2 hypomorphic mice on the 129P2 background, suggesting the presence of disease modifying alleles in FVB/N genome. We plan to map genes that modulate neurodegeneration in NPC2 hypomorphic mice. We are interested in dissecting the genes, cell types, and pathways that are altered by modifying genes that modulate disease severity. NPC2 hypomorphic mice show decreased performance on the rotating rod assay, a quantitative, objective measure of cerebellar function. This assay has been shown to correlate well with Purkinje neuron loss in other cerebellar mutant mice. Pre-symptomatic mice have a deficit in rotorod performance versus controls and this correlates reasonably well with lifespan. Using the rotorod assay as a predictive test for lifespan and severity of Purkinje neuron loss, we will identify genetic differences that modulate disease severity.