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

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Niemann-Pick Disease, Type C (NPC) is a progressive neurodegenerative disorder with onset in early childhood that is rapidly fatal, often before the second or third decade. Symptoms include motor-coordination difficulties, abnormal gait, and cognitive decline. Amazingly, great clinical variability is seen, even between siblings affected with this disease, suggesting that multiple genetic and/or environmental factors affect the onset and progression of neurodegeneration. Two genes (NPC1 and NPC2) have been shown to cause NPC in humans. Mutation in either gene is associated with accumulation of cholesterol in the lysosome and abnormalities in sphingolipid metabolism. Progression of NPC is associated with loss of purkinje cells in the cerebellum, leading to progression of neurologic symptoms. Mice lacking NPC2 mirror the symptoms seen in humans with NPC. Like humans, mice lacking NPC2 have been studied and also show great variability in disease onset and progression, depending on the genetic background. We have shown that NPC2 null mice on an FVB/N background show an increase in lifespan and decrease in disease progression compared to NPC2 null mice on the 129P2 background. Using a standard genetic approach, we have begun analyzing genetic modifiers of neurodegeneration in NPC2 deficient mice through intercrosses of NPC2 null mice on the FVB/N and 129P2 background. Using standard histological techniques to assess loss of cerebellar purkinje cells and a behavioral test for motor coordination and learning, we plan to map genetic modifiers of the onset and progression of neurodegeneration in NPC2 null mice.