Elucidating the Role of C19ORF12 in Triglyceride Homeostasis

Mitochondrial membrane protein associated neurodegeneration (MPAN) is a familial neurodegenerative disorder associated with functional deficits and neuronal loss involving various brain regions, most prominently basal ganglia. Like other variants of Neurodegeneration with Brain Iron Accumulation (NBIA), patients with MPAN also show accumulation of iron in basal ganglia. MPAN is caused by mutations in a poorly understood gene – c19orf12. Using the model system *Drosophila melanogaster*, we have demonstrated that Nazo, one of the fly homologs of c19orf12 is involved in lipid homeostasis. Nazo is a lipid droplet associated protein and its disruption leads to extensive loss of lipid droplets in gut. *nazo* mutants have diminished whole body triglyceride reserves, due to which these mutants are sensitive to starvation and oxidative stress. Nazo is required for maintaining normal levels of Perilipin-2, an inhibitor of the lipase-Brummer. Overexpression of Perilipin-2 or knockdown of Brummer rescues the *nazo* loss of function phenotype. This suggests that gut LD depletion in *nazo* mutants may arise, at least in part, from diminished Perilipin-2 on lipid droplets leading to aberrant Brummer-mediated lipolysis. Nazo-related gut defects have profound cell nonautonomous impacts on the brain, as evidenced by significant proteomic alterations, particularly related to lipid metabolism, in the heads of *nazo* mutants. Our findings provide novel insights into the role of c19orf12 as a possible link between lipid dyshomeostasis and neurodegeneration, particularly in the context of NBIA.