Jon Audhya: Roles for TFG in protein trafficking, ER structure, and neuronal maintenance

Hereditary spastic paraplegias (HSPs) are a clinically and genetically heterogeneous group of gait disorders characterized by progressive weakness (paraplegia) and stiffness (spasticity) of the legs. Treatment consists of physical therapy, but no intervention is currently available to slow or alter the progression of the disease. The pathological hallmark of HSPs is a length-dependent distal axonopathy of nerve fibers in the corticospinal tract. Involvement of other neurons, including the optic nerve, can cause additional neurological symptoms, which define a diverse set of complex HSPs. We identified two children, who suffer from a combination of early onset spastic paraplegia, optic atrophy, and neuropathy. Genome-wide SNP-typing, linkage analysis and exome sequencing revealed a homozygous c.316C>T (p.R106C) variant in Trk-fused gene (TFG) as the only plausible mutation. Biochemical characterization of the mutant protein demonstrated a defect in its ability to self-assemble into an oligomeric complex, which is critical for normal TFG function. In cell lines, TFG inhibition slowed protein secretion from the endoplasmic reticulum (ER) and altered ER morphology, disrupting organization of peripheral ER tubules and causing collapse of the ER network onto the underlying microtubule cytoskeleton. These findings provide a new link between altered ER architecture and neurodegeneration.