SPG3: Towards Understanding the Function of the Disease Protein Atlastin 1

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Approximately 10% of all autosomal dominant spastic paraplegia cases are caused by mutations in the large GTPase atlastin 1. Atlastin 1 is a 558 aa transmembrane protein localized to the Golgi apparatus with both the large N-terminal GTPase domain and the short C-terminus being directed towards the cytoplasm. To date 19 missense mutations distributed throughout the protein and one frameshift mutation have been identified, yet the function of atlastin1 in motoneurons and the disease mechanism are still poorly understood. For this reason we are interested in 1) identifying physiological interactors of atlastin; 2) the influence of different mutations on the enzyme activity and guanine nucleotide affinity of this enzyme. In a Y2H screen with the 63 aa long C-terminal domain we have identified a weak interactor, which is possibly involved in neuronal mRNA processing. Besides a similar expression profile, our confocal microscopy studies in cos-7 cells transfected with HA-tagged atlastin showed partial colocalization of atlatin 1 with this endogeneously expressed interactor in the Golgi apparatus. We also have purified both wildt-ype and mutated atlastin 1 as GST fusion protein, and will present preliminary data on GTP hydrolysis and binding assays performed in a collaborative effort.