Elucidating the molecular function of *Zfyve27*, the gene mutated in hereditary spastic paraplegia (SPG33)

Ashraf U. Mannan, Krishna Pantakani, Loukas Argyriou and Wolfgang Engel
Institute of Human Genetics, University of Goettingen, Goettingen, Germany

Hereditary spastic paraplegias (HSP) are a group of neurodegenerative disorders, which are clinically characterized by progressive spastic paralysis of the legs, usually caused by a length-dependent distal degeneration of the corticospinal tract axons. HSP are genetically heterogeneous and till now 35 loci have been identified. Recently, we reported a mutation in a novel endosomal protein ZFYVE27 (SPG33) in a German family with autosomal dominant HSP. ZFYVE27 was identified as a spastin interacting protein and we have characterized the interaction between these two proteins in mammalian cells. Moreover, our studies revealed that the mutated ZFYVE27 protein shows aberrant intracellular pattern in tubular structure of cells and its interaction with spastin is severely affected. Intracellular distribution studies revealed that ZFYVE27 is expressed in punctate vesicles which were both of endosomal and endoplasmic reticulum origin. A comprehensive expression analysis of Zfyve27 was evaluated in mouse by Western blot analysis and high level of Zfyve27 was detected primarily in the HSP affected tissues such as brain, cerebellum and spinal cord. To gain mechanistic insights in murine Zfyve27 function, currently, generation of loss of function mouse models by using both gene-trap and knockout strategy are in progress.Conceivably the phenotype of these mouse models might mimic the pathological features of HSP, therefore will provide us with a valuable model system to elucidate the underlying cause for HSP etiology.