ZFYVE27, a novel spastin binding protein is mutated in hereditary spastic paraplegia (SPG30)

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Mutation in spastin is the principal cause for autosomal dominant form of hereditary spastic paraplegia (AD-HSP). Spastin is suggested to be involved in vesicular cargo trafficking processes by interacting with microtubule and components of vesicles transport machinery, however a comprehensive function of spastin is not yet elucidated. To characterize the molecular function of spastin, we used the yeast two-hybrid approach to identify new interacting partners of spastin. Here, we report ZFYVE27, a novel member of FYVE finger family of protein as a specific binding partner of spastin. *In vivo* co-immunoprecipitation experiments in mammalian cells validated the interaction between spastin and ZFYVE27 as observed in yeast. Our intracellular studies revealed a striking co-localization of ZFYVE27 with spastin in vesicle like structures. Spastin mediates its interaction with ZFYVE27 through its N-terminal region containing a MIT domain. More importantly, we report a German family with AD-HSP (SPG30) in which ZFYVE27 is mutated. Sequence analysis of this gene in affected and unaffected members of this family revealed segregation of a missense mutation G105V in all affected patients. The mutated ZFYVE27 protein shows aberrant intracellular pattern in tubular structure and its interaction with spastin is severely affected. We postulate that this specific mutation in ZFYVE27 affects neuronal intracellular trafficking in the longest axons of the CNS, which is consistent with the pathology of HSP.

Note: In the symposium exciting result on molecular mechanism of spastin and preliminary characterization of other spastin binding proteins will also be presented.