Title: Hereditary Spastic Paraplegia 4: Mechanism and Therapy from a Microtubule-Biologist's Perspective

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Abstract

Mutations in more then 70 distinct loci and more than 50 mutated gene products have been identified in patients with hereditary spastic paraplegias, a diverse group of neurologic disorders characterized predominantly but not exclusively by progressive lower limb spasticity and weakness resulting from distal degeneration of corticospinal tract axons. Mutations in the *SPAST* gene that encodes the microtubule-severing protein called spastin are the most common cause of the disease. The etiology of the disease (termed Hereditary Spastic Paraplegia 4 or SPG4) is poorly understood, but partial loss of microtubule-severing activity resulting from inactivating mutations in one *SPAST* allele is the most postulated explanation. Microtubule severing is important for regulating various aspects of the microtubule array, including microtubule number, length, and mobility. In addition, higher numbers of dynamic plus ends of microtubules, resulting from microtubule-severing events, may play a role in endosomal tubulation and fission. Even so, there is growing evidence that decreased severing of microtubules does not fully explain HSP-SPG4. The presence of two translation initiation codons in *SPAST* allows synthesis of two spastin isoforms: a full-length isoform called M1 and a slightly shorter isoform called M87. M87 is more abundant in both neuronal and non-neuronal tissues. In rodents M1 is only readily detected in adult spinal cord, where nerve degeneration mainly occurs in the disease. Some mutated spastins may act in dominant-negative fashion to further lower microtubule-severing activity, but others have detrimental effects on neurons without lowering microtubule severing. It seems likely that the observed adverse effects on nerve degeneration may be caused not only by diminished severing of microtubules, but also by neurotoxicity of mutant spastin proteins, chiefly M1. Some large deletions in *SPAST* might also affect the function of the adjacent genes, further complicating the etiology of the disease. The evidence and controversy surrounding gain-of-function mechanisms versus loss-of-function mechanisms that contribute to nerve degeneration in Hereditary Spastic Paraplegia 4 (as well as the need to understand mechanism in order to develop appropriate therapies) are discussed from the point of view of a microtubule biologist.