A mutation of spastin is responsible for swellings and impairment of transport in a region of axon characterized by changes in microtubule composition.

Tarrade A[§1], Fassier C[§1], Courageot S[1], Charvin D[1], Vitte J[1], Peris L[2], Thorel A[3], Mouisel E[1], Fonknechten N[4], Roblot N[1], Seilhean D[5], Dierich A[6], Hauw JJ[5], Melki J[1].

[1]Molecular Neurogenetics Laboratory, INSERM U798, University of Evry, Evry, France
[2]INSERM U366, Grenoble, France
[3]Centre des Matériaux, Evry, France
[4]Genoscope, Evry, France
[5]Laboratoire de Neuropathologie, Groupe Hospitalier Pitié-Salpétrière, Paris, France
[6]IGBMC, Illkirch, France.
§ equal contribution

Mutations of the spastin gene (Sp) are responsible for the most frequent autosomal dominant form of spastic paraplegia, a disease characterized by the degeneration of corticospinal tracts. We show that a deletion in the mouse Sp gene, generating a premature stop codon, is responsible for progressive axonal degeneration, restricted to the central nervous system, leading to a late and mild motor defect. The degenerative process is characterized by focal axonal swellings, associated with abnormal accumulation of organelles and cytoskeletal components. In culture, mutant cortical neurons showed normal viability and neurite density. However, they develop neurite swellings associated with focal impairment of retrograde transport. These defects occur near the growth cone, in a region characterized by the transition between stable microtubules rich in detyrosinated alpha-tubulin and dynamic microtubules composed almost exclusively of tyrosinated alpha-tubulin. Here, we show that the Sp mutation has a major impact on neurite maintenance and transport both in vivo and in vitro. These results highlight the link between spastin and microtubule dynamics in axons, but not in other neuronal compartments. In addition, it is the first description of a human neurodegenerative disease which involves this specialized region of the axon. (Hum Mol Genet. 2006 Dec 15;15(24):3544-58)