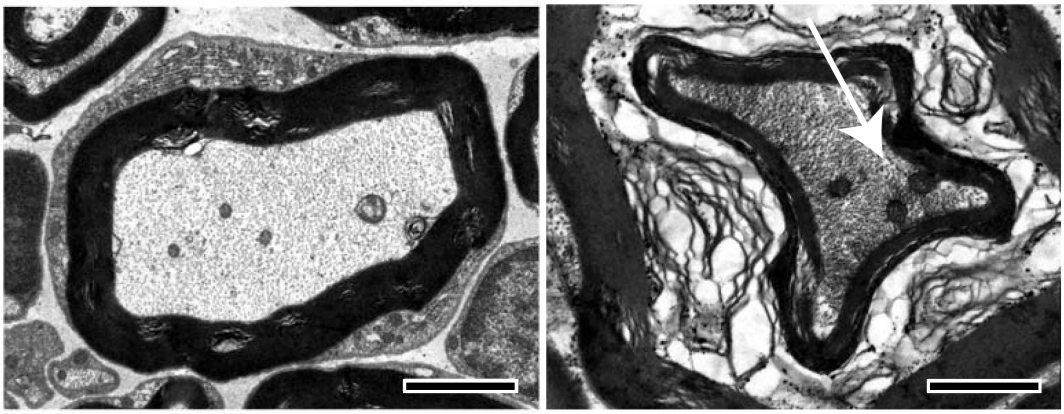
“Merlin isoform 2 in neurofibromatosis type 2-associated polyneuropathy”

The autosomal dominant disorder neurofibromatosis type 2 (NF2) is a hereditary tumor syndrome caused by inactivation of the NF2 tumor suppressor gene, encoding merlin. Apart from tumors affecting the peripheral and central nervous systems, most NF2 patients develop peripheral neuropathies. This peripheral nerve disease can occur in the absence of nerve-damaging tumors, suggesting an etiology that is independent of gross tumor burden. We discovered that merlin isoform 2 (merlin-iso2) has a specific function in maintaining axonal integrity and propose that reduced axonal NF2 gene dosage leads to NF2-associated polyneuropathy. We identified a merlin-iso2-dependent complex that promotes activation of the GTPase RhoA, enabling downstream Rho-associated kinase to promote neurofilament heavy chain phosphorylation. Merlin-iso2-deficient mice exhibited impaired locomotor capacities, delayed sensory reactions and electrophysiological signs of axonal neuropathy. Sciatic nerves from these mice (*nf2* iso2$^{-/-}$) and sural nerve biopsies from NF2 patients revealed reduced phosphorylation of the neurofilament H subunit, decreased interfilament spacings and irregularly shaped axons.



nf2 iso2 $^{+/+}$ *nf2* iso2 $^{-/-}$

Schulz A, Baader SL, Niwa-Kawakita M, Bauer R, Garcia C, Zoch A, Jung MJ, Gutmann DH, Hagel C, Mautner VF, Hanemann CO, Weis J, Schröder JM, Giovannini M, Morrison H. The role of merlin isoform 2 in neurofibromatosis type 2-associated polyneuropathy. Nat. Neurosci. 2013. 4:426-33.

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