

Characterisation of a novel HSP mouse model

Christian Beetz, Institut für Klinische Chemie und Laboratoriumsdiagnostik,
Universitätsklinikum Jena, Germany

SPG31 is an autosomal dominant, clinically pure form of HSP. It is caused by truncating mutations in REEP1 which likely confer haploinsufficiency. To gain insight into the cellular pathomechanisms underlying SPG31, we investigated the expression as well the physiological and the pathological roles of REEP1 and its protein product.

During embryonic development, REEP1 is expressed throughout the nervous system. Expression is also detected in adult brain and spinal cord. Moreover, analysis of primary cell cultures suggests REEP1 expression to be neuron-specific. REEP1 protein is found in the membrane fraction of brain homogenates where it is enriched in the subfraction containing the endoplasmic reticulum (ER) but absent from the mitochondrial subfraction. *In silico* analyses along with overexpression approaches further support a localisation to the ER but not to mitochondria. Another HSP protein localising to the ER, i.e. atlastin-1, is a direct physical interactor of REEP1. Mice with the REEP1 gene knocked out are viable and fertile. Starting at around 4 months of age, homozygous animals develop a progressive gait abnormality that is consistent with the presence of hindlimb spasticity and weakness, i.e. the hallmarks of HSP in man. Heterozygous animals are less severely affected and symptoms start about one month later. Degenerating axons are found at the lumbar but not the thoracal spinal cord levels of mutant mice. Electrophysiological analyses argue against an involvement of the lower motoneuron.

Our data suggest a common pathway for at least SPG31 and SPG3A (atlastin-1) which involves some ER-related function. Our REEP1 knockout mouse is a valid disease model and should be useful for a better understanding of the malfunctions in SPG31 and HSP in general.