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Poster P9

Motor neuropathy gene FAM169A interacts with other neuropathy-causing genes at the nuclear envelope

A. Blum (1,2), W. Antonin (1), H. Lue (1), M. Dohrn (2)

(1) Institute of Biochemistry and Molecular Cell Biology, RWTH Aachen University, Aachen, Germany
(2) Department of Neurology, Medical Faculty RWTH Aachen University, Aachen, Germany

Heterozygous loss-of-function mutations in FAM169A were identified in six unrelated families with autosomal dominant inheritance, manifesting as early adult-onset, progressive distally pronounced muscle atrophy, gait abnormalities, and upper motor neuron signs. These mutations are absent from the general population, suggesting FAM169A is prone to haploinsufficiency and likely acts as a disease gene.

FAM169A encodes the nuclear envelope protein SLAP75 (soluble lamin-associated protein, 75 kDa), whose biological function remains to be discovered.

Upon western blot, SLAP75 appeared to form a dimer of 150 kDa. Immunofluorescence in HEK293T cells and stable expression of EGFP-FAM169A in HeLa cells confirmed its nuclear envelope localization. siRNA-mediated knockdown of SLAP75 reduced its signal, whereas the nuclear shape still remained intact, suggesting FAM169A is not essential for nuclear envelope integrity.

Mass spectrometry-based pull-down analyses of tagged FAM169A revealed interactions between SLAP75 and several nuclear envelope components, notably Lamin-A/C—linked to neuropathy and myopathy—and NUP50, an ALS-associated nuclear pore protein.

LMNA (encoding Lamin-A/C) and NUP50 knockdown did not affect SLAP75 localization. Vice versa, knockdown of SLAP75 did not have an influence on the localization of LMNA and NUP50. However, FAM169A band size decreased in LMNA- and NUP50-depleted cells, requiring further quantification.

We are generating dTAG-based HEK293T cell lines for more rapid, reversible SLAP75 degradation, enabling detailed assessment of loss- and gain-of-function phenotypes. The dTAG and EGFP cell lines will allow live-cell imaging to directly observe FAM169A dynamics, interactions, and functional consequences of acute or reversible depletion.

By the time of the conference, we anticipate providing more insights into FAM169A function and dysfunction and discussing the importance of the nuclear envelope for future treatment developments.