2nd European CMT Specialists Conference
Antwerp, 23-25 October 2025

Presentation PL3-06

Loss of ARHGAP19 function disrupts RhoA regulation in Charcot-Marie-Tooth disease: mechanisms and therapeutic targets

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Charcot-Marie-Tooth Disease is a clinically and genetically heterogeneous group of hereditary neuropathies. Using next-generation sequencing, we identified biallelic variants in ARHGAP19, encoding for a RhoA-specific GTPase-activating protein, in 25 individuals from 20 unrelated families presenting with motor-predominant neuropathy.

In-vitro biochemical and cellular assays revealed that patient variants impair the GTPase-activating protein (GAP) activity of ARHGAP19 and reduce ARHGAP19 protein levels. Parallel in-vivo studies using Drosophila and zebrafish models revealed a conserved role for ARHGAP19 orthologs in regulating locomotor function, motoneuron axon length and branching, and neuromuscular junction morphology.

Leveraging these models and to address the limited therapeutic options, we established an in vivo movement-based drug screen to identify novel therapies, using a Drosophila model of ARHGAP19 ortholog, RhoGAP54D, loss of function. RhoGAP54D knock out flies exhibit motor defects that recapitulate patient phenotypes. To date, we have acutely fed the flies 120 drugs from a library of FDA-approved compounds and screened for drugs that rescued locomotor dysfunction. Any candidate compounds will be validated in patient-derived tissues to assess their clinical potential. This screening algorithm is adaptable and may accelerate therapeutic discovery across diverse CMT subtypes.

Our findings reveal ARHGAP19 loss-of-function as a novel driver of inherited neuropathy and support integrated Drosophila and cell-based studies as a means to enable drug repurposing in CMT.