Molecular Neuropathology of HACE1 Deficiency

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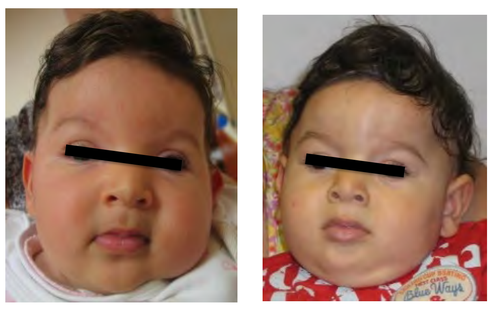
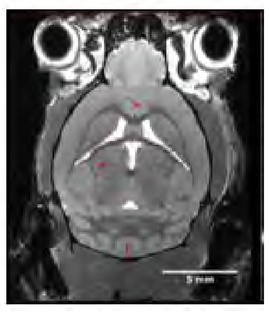
Introduction

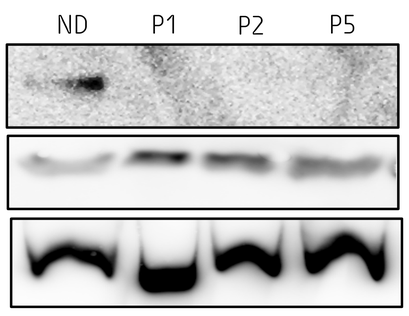
Spastic Paraplegia and Psychomotor Retardation with or without Seizures (SPPRS – OMIM #616756) is caused by mutations in the gene HACE1 (HECT Domain and Ankyrin Repeat Containing E3 Ubiquitin Ligase). Symptoms include severe **developmental delay** and **intellectual disability**. *Hace1* KO mice phenocopy SPPRS patients:

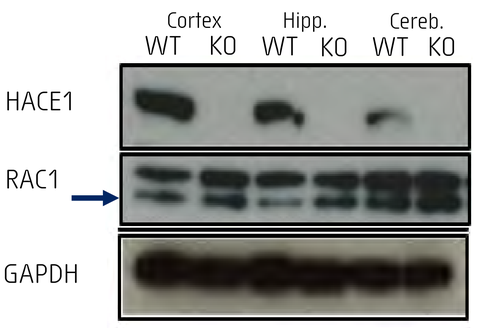
SPPRS Patients

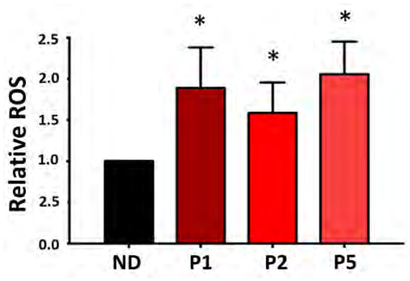


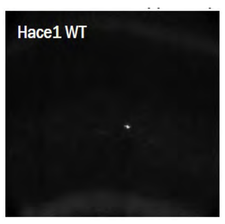
Hace1 KO Mouse

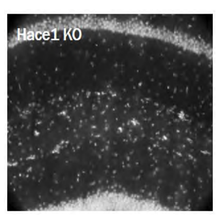




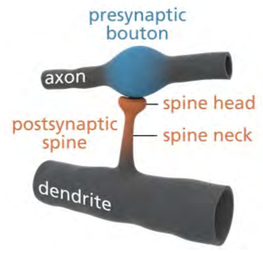


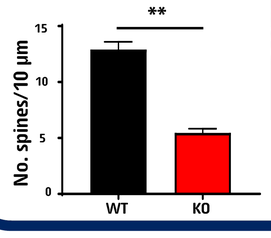


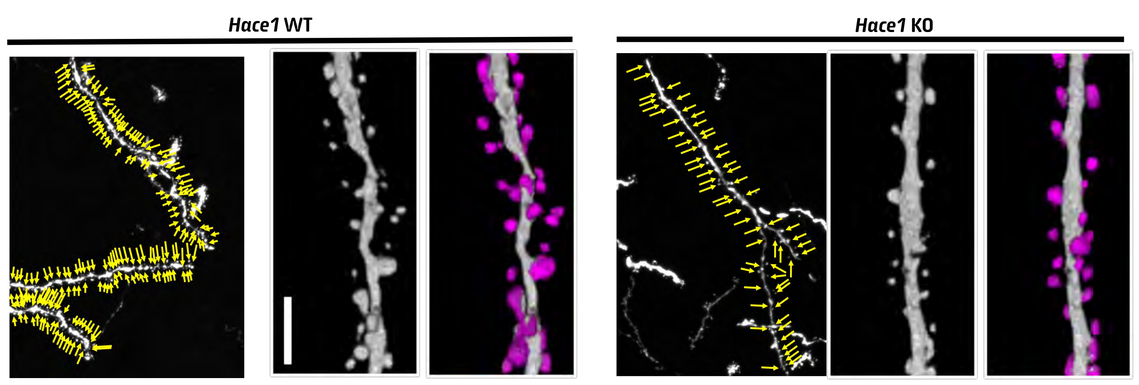




In Vivo Effects of HACE1-Deficiency

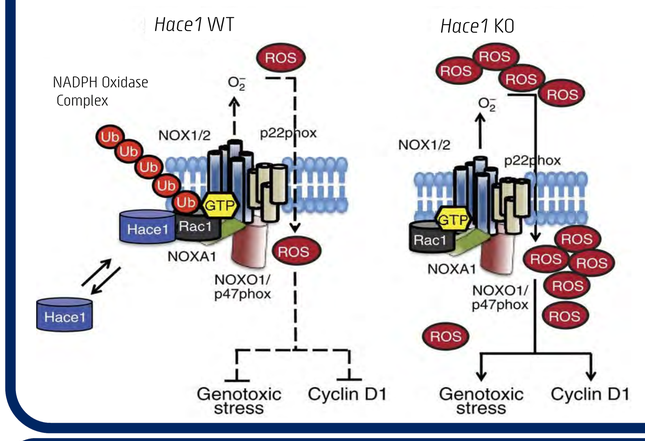






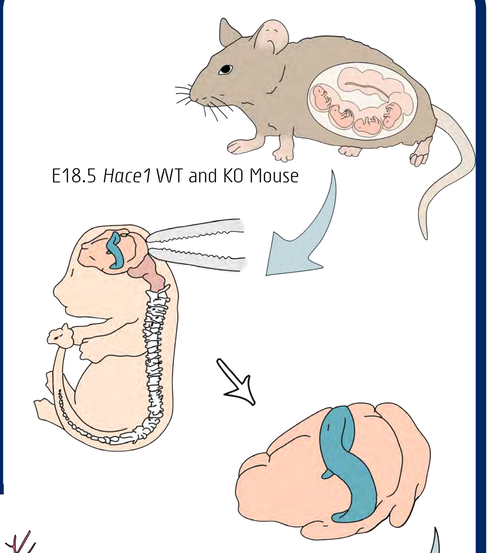
Thy1-GFP x HACE1 Mouse Hippocampus Ca1 region. Synapse spines are indicated by arrows and quantified (bottom left).
N = 3 ; 27 images per genotype.

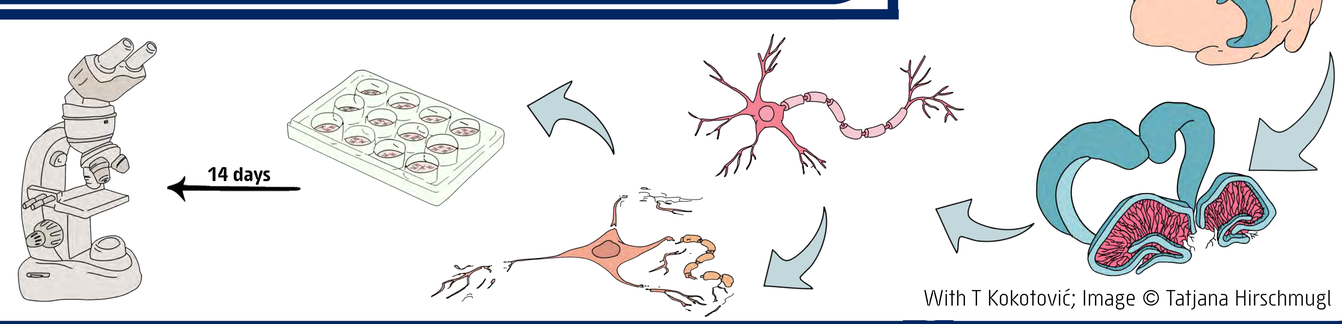
RAC1 is the Main Effector of HACE1-Deficiency



1. Actin Polymerisation

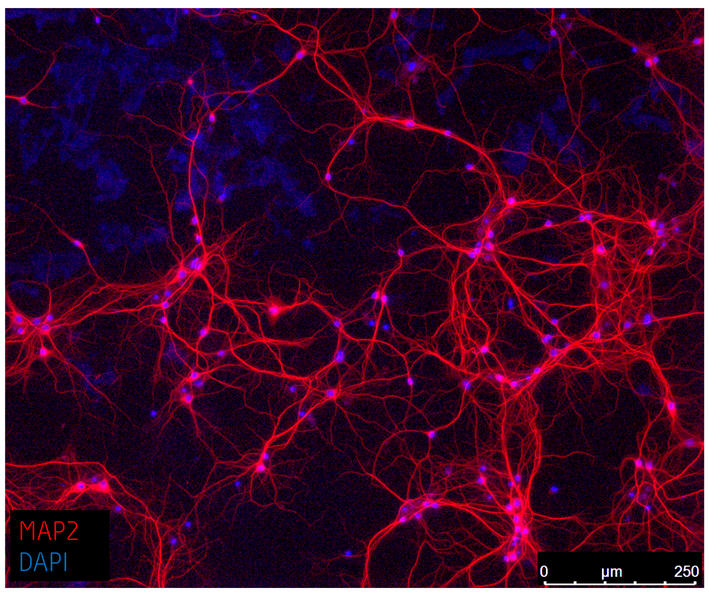
2. High ROS levels (Left)
   - Oxidative stress?
   - DNA damage?
   - Microglia activation?



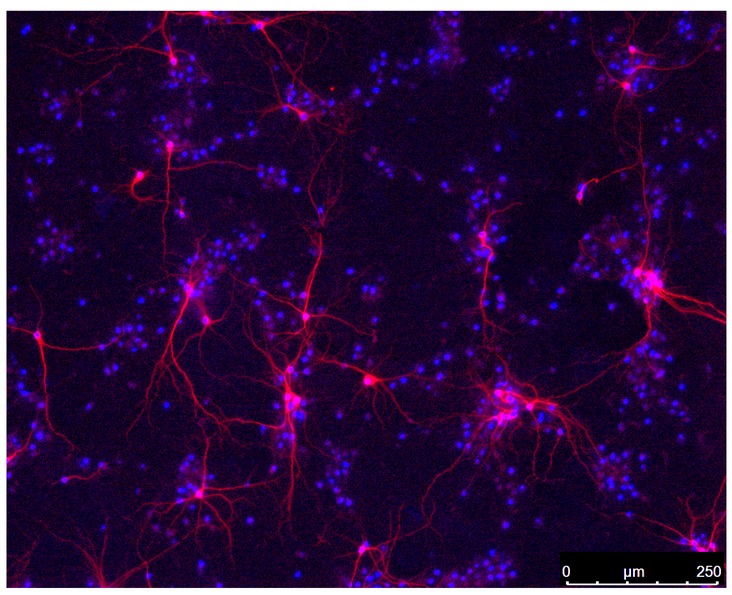


With T Kokotović; Image © Tatjana Hirschmugl

Mouse Primary Culture Model of SPPRS Shows Morphological Abnormalities



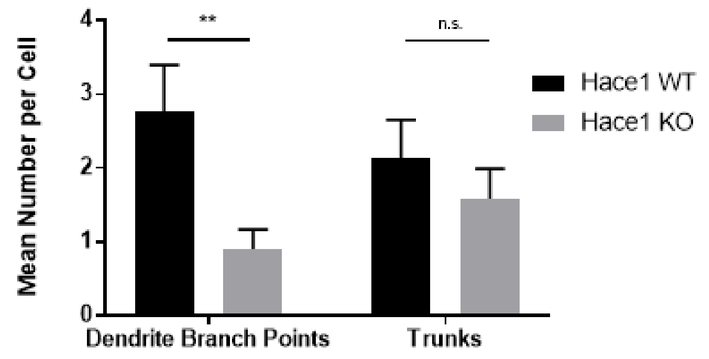
Hace1 WT



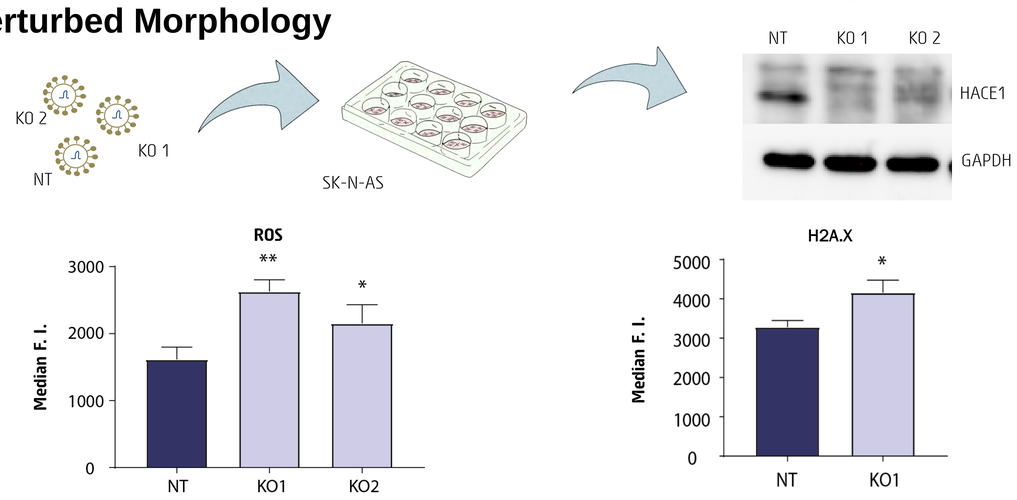
Hace1 KO

Left: Primary hippocampal cultures from *Hace1* WT (left) and *Hace1* KO (right) mice, cultured for 14 days and stained against MAP2 (red) and DAPI (blue)

Below: Quantification of mean dendritic branch points and dendritic trunks of the *Hace1* WT and KO neurons (Student's two-tailed t-test). N (mice) = 2 (WT); 2 (KO). N (pups) = 10 (WT); 9 (KO).



Hace1 KO Cell Lines Have Increased ROS, DNA Damage and Perturbed Morphology



Outlook:

1. Confirm increased levels of RAC1 in primary culture model and in iNs
2. Develop cell line model of SPPRS (in neuroblastoma?)
3. Inhibit RAC1, NADPH oxidase complex, HACE1 ubiquitination and scavenge ROS for rescue of disease phenotype
4. Explore contribution of microglia to SPPRS pathology in primary culture model

References:

Nagy et al., *Neurol. Genet.* 2019; Hollstein et al., *J. Med. Gen.*, 2015; Akawi et al., *Nat. Genet.*, 2015; Tortola et al., *Cell Rep.* 2016; Takahasi et al., *Cell* 2007; Platt et al., *Cell* 2014; Tanabe et al., *PNAS* 2018