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HACE1 deficiency leads to structural and functional neurodevelopmental defects

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HECT Domain and Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase (*HACE1*) was initially identified in Wilms tumor, and subsequently characterized as a tumor suppressor. Recently, mutations in *HACE1* were shown to be associated with an autosomal recessive neurodevelopmental syndrome called Spastic Paraplegia and Psychomotor Retardation with or without Seizures (SPPRS; OMIM#616756). The causality and molecular and functional underpinnings of *HACE1*-deficiency in neurodevelopment are not known. Here, we identify two novel homozygous truncating mutations in *HACE1* in three patients from two families, p.Q209* and p.R332*. To gain insight into the molecular pathophysiology of SPPRS, we performed detailed molecular and phenotypic analyses of *HACE1* Knock-Out (KO) mice and SPPRS patient fibroblasts. We show that *HACE1* KO mice display many clinical features of SPPRS including enlarged ventricles, hypo-plastic corpus callosum, as well as locomotion and learning deficiencies. Mechanistically, loss of *HACE1* results in altered abundance and activity of the small GTPase, RAC1, and a loss of hippocampal spine number, which presumably underlies abrogated Long-Term Potentiation (LTP). Similarly, in fibroblasts from SPPRS patients, carrying disruptive *HACE1* mutations, resembling loss of *HACE1* in the KO mice, we observed significant up-regulation of the total and active, GTP-bound, form of RAC1, along with an induction of RAC1-regulated downstream pathways. Our results provide a first animal model to dissect this complex human disease syndrome, establishing the first causal proof that a *HACE1* mutation results in altered synapse formation and structural and behavioral neuropathological features that resemble SPPRS patients.

Biography

Vanja Nagy has completed her PhD from Icahn School of Medicine at Mount Sinai (MSSM), New York, USA and Postdoctoral studies from Institute of Molecular Biotechnology (IMBA), Vienna, Austria. She is a Group Leader at Ludwig Boltzmann Institute for Rare and Undiagnosed Disease, Vienna, Austria, dedicated to the identification and characterization of genetic variants of rare neuropathologies. She has published numerous highly cited papers, and has earned a number of awards and recognitions for her work.

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