# Neuronal function of huntingtin associated protein

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**Principal Investigators**

LI, XIAO-JIANG

**Institution**

EMORY UNIVERSITY

**Contact information of lead PI**
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Neuronal function of huntingtin associated protein

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Huntington gene, Neurons, Endocytosis, Proteins, neuropathology

**Research Abstract**

DESCRIPTION (provided by applicant): Neuronal function of huntingtin associated protein Huntingtin-associated protein-1 (Hap1) was first identified as a cytoplasmic protein that interacts with the Huntington disease protein huntingtin. Like huntingtin, which is critical for embryonic development, Hap1 is also essential for animal survival, as deletion of the Hap1 gene in the mouse leads to a retarded growth and early postnatal death. However, unlike huntingtin, which is ubiquitously expressed, Hap1 is enriched in the brain and is expressed at different levels in

various types of neurons, suggesting that Hap1 may function differently in different brain regions. Our recent studies also show that Hap1 forms a stable complex with Ahi1, a protein whose mutations cause Joubert syndrome, which is a brain developmental disorder. Growing evidence has demonstrated that Hap1 associates with microtubule-dependent transporters and that both huntingtin and Hap1 participate in intracellular trafficking. More importantly, mutant huntingtin can affect Hap1-mediated transport of vesicles and membrane receptors. While these findings have proved our previous hypothesis that Hap1 is involved in intracellular trafficking, the mechanism underlying the trafficking function of Hap1 remains to be investigated. Understanding this mechanism is important for unraveling the complex regulation of intracellular transport of membrane receptors and the neuropathology related to impaired intracellular trafficking. We hypothesize that Hap1 dysfunction may cause neuropathology in an age- and/or brain regional dependent manner and that phosphorylation of Hap1 regulates its function in endocytosis of membrane receptors. In Aim 1, we will utilize the conditional Hap1 knockout mice to selectively deplete Hap1 expression in different brain regions and at different ages. We will then examine the neuropathology and behavioral phenotypes of Hap1 mutant mice to determine the critical function of Hap1. In Aim 2, we will investigate how Hap1 participates in the endocytosis and recycling of neurotrophic receptors and whether mutant huntingtin affects Hap1-associated endocytosis of Trk receptors in an age-dependent manner. The studies aim to provide mechanistic insight into intracellular trafficking and endocytosis of membrane receptors and also offer a therapeutic target for the neuropathology caused by impaired endocytosis of neurotrophic receptors.

**Further information available at:**

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