Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by a polyglutamine (polyQ) expansion in the huntingtin (HTT) protein (HDCRG, Cell 1993). Dysfunction of the synapse and concomitant alterations in cortico-striatal circuitry represent a hallmark of HD pathogenesis. Several components of the cortico-striatal synapse are impaired in the disease but the initial events that trigger synaptic defects as well as neuroprotective compounds able to prevent synaptic abnormalities, delay disease onset and slow down its progression have yet to be identified.

ADAM10, a member of the large ADAM transmembrane protein family, is expressed at high level in the brain, resides in the post-synaptic densities (PSDs) of the glutamatergic synapse and regulates synaptic cell adhesion and neurotransmission by shedding post-synaptic substrates including N-cadherin, APP, Nectin-1, PrP, Neuroligin 1, L1-NCAM, Ephrin A2 and A5 (Saftig, Prog Neurobiol 2015). Dendritic spine development, synapse plasticity, memory, and learning all rely on ADAM10 activity (Saftig, Prog Neurobiol 2015). Consequently, impairments in ADAM10 level and/or enzymatic activity as well as in the cleavage of its synaptic substrates are detrimental for the human brain and ADAM10 has been linked to epilepsy, Alzheimer’s disease (AD), and, more recently, to Fragile X syndrome.

We previously reported that catalytically active ADAM10 levels are increased in the brain of adult mice, in which the Huntington gene (Hdh) has been conditionally inactivated throughout the neural lineage, indicating that wild-type HTT controls ADAM10 activity in the adult brain (Lo Sardo, Nat Neurosci 2012).

Here I will show recent data indicating that ADAM10 can be a novel target of mutant HTT activity in the HD brain and a relevant component of synaptic dysfunctions typically observed in the disease.