In-vivo interactor and pathway analysis of CLN3, CLN6, and CLN8 using proximal biotinylation

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For many years, scientists have sought common, overlapping mechanisms for the proteins mutated in Batten disease with little success. Three of these proteins, CLN3, CLN6, and CLN8, are transmembrane proteins suggested to be involved with intracellular trafficking, though the relevance of these roles for neuron-specific functions remains largely unknown. Here we employ BioID to label interacting and associated proteins of these CLN proteins. Initial data was generated using a neuroblastoma cell line, validating this approach with these proteins and generating an initial interactome. To refine this interactome to CNS specific interactions, we next performed BioID in mouse cortices transduced with AAV9 expressing the CLN-BioID constructs. This proteomic screen reveals many novel interactors for these proteins, providing strong evidence of neuron-specific functions. CLN3 shows enrichment for SNARE interacting proteins, anterograde axonal transport proteins, and vesicular transport proteins. CLN6 and CLN8 interactors also have strong enrichment for proteins involved in vesicle-mediated transport, dendritic morphogenesis, axodendritic trafficking, and potential interactions with mitochondrial proteins. Combining these analyses implies a broader function held in common by these CLN proteins to direct heterotypic membrane fusion such as that involved in synaptic vesicle release. Aberrations in this vesicular trafficking would be especially detrimental to neurons with far-reaching arbors, giving a possible explanation for the neuronal etiology of Batten disease. This work gives insight to the pathways affected by CLN3, CLN6, and CLN8 proteins and may provide an understanding of the primarily neurodegenerative presentation of Batten disease pathology.