

CLN3 Modulates the Function of an Ion Channel

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Juvenile neuronal lipofuscinosis, or JNCL, results from inherited mutations in CLN3. JNCL is a progressive neurodegenerative disease with symptoms of visual loss, seizures, and motor skill decline. The function of CLN3 and the pathogenesis of JNCL remain obscure. Our lab has been investigating the hypothesis that CLN3 modulates a potassium ion channel that is abundant in the brain and is important for regulating neuronal firing. This channel is a multimeric complex composed of the main pore-forming protein as well as other various interacting proteins. By using a fibroblast culture system we found that CLN3 expression substantially reduced the potassium ion current, suggesting that CLN3 influences the trafficking of the channels to or from the cell surface. Using neuronal cultures, we determined that in the absence of CLN3, the channels transitioned more readily into a closed state. Together these results suggest that CLN3 interacts with channel complexes, and in this way participates in the regulation of neuronal firing. Using co-immunoprecipitation and immunofluorescent experiments, we confirmed that CLN3 associates with a channel-interacting protein, which in turn may link CLN3 to the channel complexes. Further experiments will address whether mutant forms of CLN3 alter channel localization and function, and whether gene transfer of native CLN3 can restore a normal phenotype to CLN3-deficient neurons. We hope that a better understanding of the molecular roles of CLN3 in neurons will lead to the design of effective therapies for JNCL.