

## **St. Dominic Middle School Smart Team**

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### **CHIP Is a Neuroprotective Ubiquitin Ligase**

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CHIP (C-terminus of Hsc interacting protein) is a neuroprotective ubiquitin ligase highly expressed in the brain. CHIP plays a crucial role in the ubiquitin proteasome system (UPS), a process that tags proteins with polyubiquitin chains targeting them for degradation. CHIP helps regulate protein quality control through its E3 ligase activity. As an E3 ligase, CHIP acts as a scaffold binding the E2 (ubiquitin conjugating enzyme) and the molecular chaperone Hsp90. CHIP aids the transfer of ubiquitins from E2 to a target protein bound to its chaperone, Hsp90. The polyubiquitin chain tags proteins for proteasomal degradation. The St. Dominic SMART Team (Students Modeling A Research Topic) modeled the homodimer CHIP using 3D-printing technology. Each monomer contains a tetratricopeptide repeat (TPR), helical hairpin (HH), and a U-Box domain. The N-terminal TPR domain binds the molecular chaperone Hsp90 using the sidechains Phe38, Lys73, Asn66, Leu69, Phe100, Lys96, Phe99, Phe132, and Asp135. The C-terminal U-Box binds E2 ubiquitin conjugates using Asp230, Phe238, Ile236, Val271, and Arg273. The HH domain is a long straight helix in one monomer but bends at a 90° angle in the other. Autosomal recessive mutations in the TPR, HH, and U-Box domains cause neurodegeneration in multiple areas of the brain leading to various combinations of symptoms such as ataxia, dementia, hypogonadism, seizures, and loss of language. Further research of CHIP's structure and function could also lead to new understanding more common neurodegenerative diseases such as Alzheimer's and Parkinson's.