



2016-2017 Research and Design Model

St. Dominic Middle School Smart Team

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CHIP Is a Neuroprotective Ubiquitin Ligase

PDB: 2C2L

Primary Citation: Zhang, M., Windheim, M., Roe, S.M., Peggie, M., Cohen, P., Prodromou, C., Pearl, L.H. Chaperoned Ubiquitylation-Crystal Structures of the Chip U Box E3 Ubiquitin Ligase and a Chip-Ubc13-Uev1A Complex. (2005) *Molecular Cell*. 20: 525-538.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description: 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.



Specific Model Information:

TPR domain (amino acids 24-133; 1-23 are missing from file)

- Backbone is colored medium slate blue.

HH (helical hairpin) domain (amino acids 134-224)

- Backbone is colored green yellow.

U-box domains (amino acids 225-304)

- Backbone is colored aquamarine.

Hsp90 fragments (chain e and chain f)

- Backbone is colored hot pink.

Displayed sidechains are colored cpk.

TPR domain binding site for Hsp90

- Asn35, Phe38, Lys73, Asn66, Leu69, Phe100, Lys96, Phe99, Phe132, and Asp135

U-Box domain binding site for ubiquitin conjugating enzymes

- Asp230, Phe238, Ile236, Val271, and Arg273

Struts are colored white.

H-bonds in sheets are colored yellow.

C-terminus is colored dark red.

N-terminus is colored dark blue

Note: CHIP is a homodimer so there are two of everything.

<http://cbm.msos.edu/smartTeams/smartTeamsLocal.php>