Structural disorder promotes functional diversity in human ubiquitin pathway

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Ubiquitin System

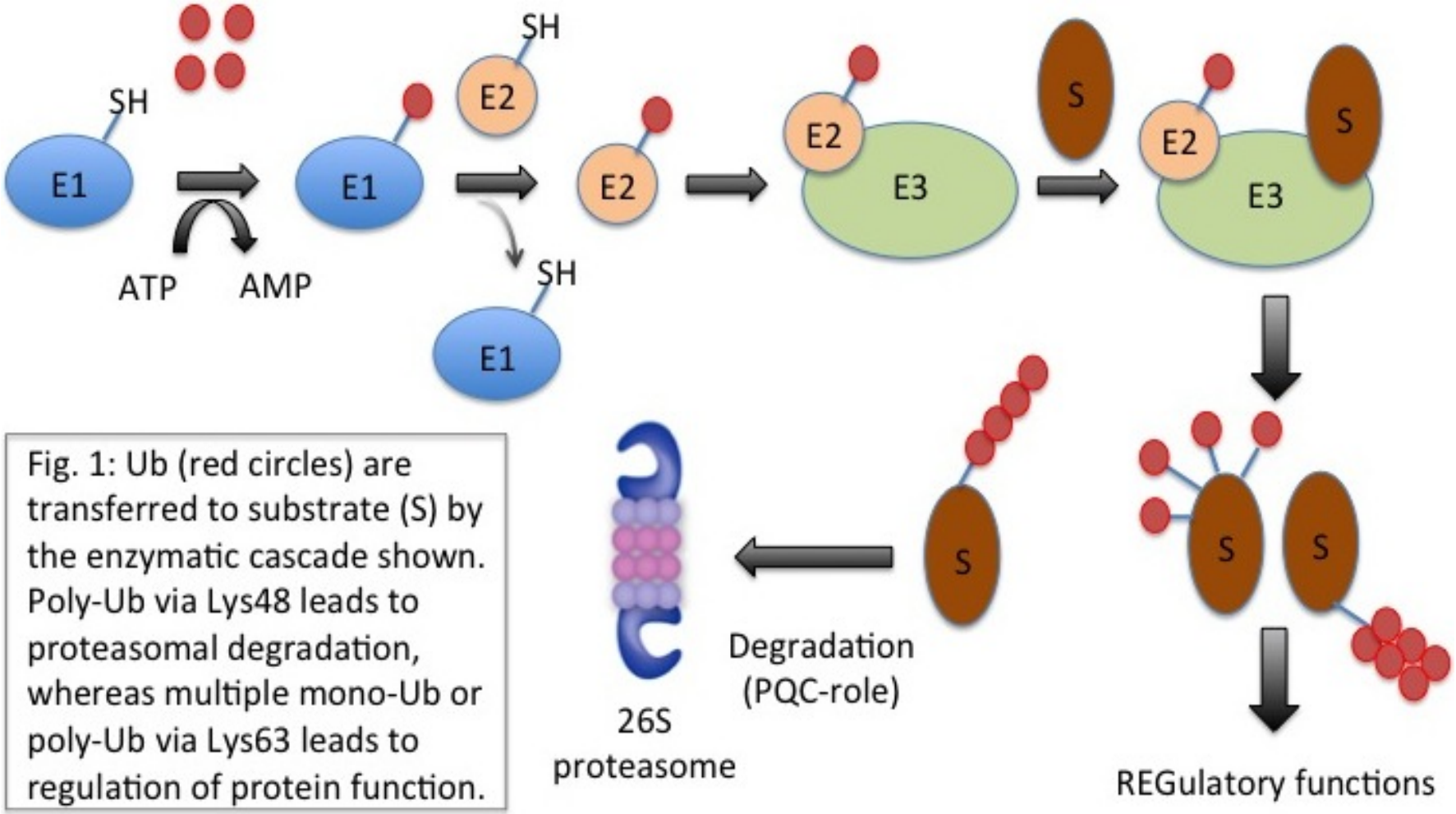

Fig. 1: Ub (red circles) are transferred to substrate (S) by the enzymatic cascade shown. Poly-Ub via Lys48 leads to proteasomal degradation, whereas multiple mono-Ub or poly-Ub via Lys63 leads to regulation of protein function.

Dataset creation

KEGG BRITE database (manually curated)
Literature Mining (based on sequence similarity).
[van Wijk ,et al(2009) A comprehensive framework of E2-RING E3
interactions of the human ubiquitin-proteasome system. Mol Syst Biol.
doi:10.1038/msb.2009.55]

Name of Enzymes	E1	E2	E3
Number of Enzymes	2	29	563

Predicted disorder tendency of ubiquitin system using different predictors

	IUPred	VSL2	FoldIndex
E1	5.97	18.10	20.10
E2	17.74	37.51	32.90
E3	20.03	39.59	33.02

Increasing level of structural disorder in the system E1<E2<E3

The main classes of human E3 ubiquitin ligases

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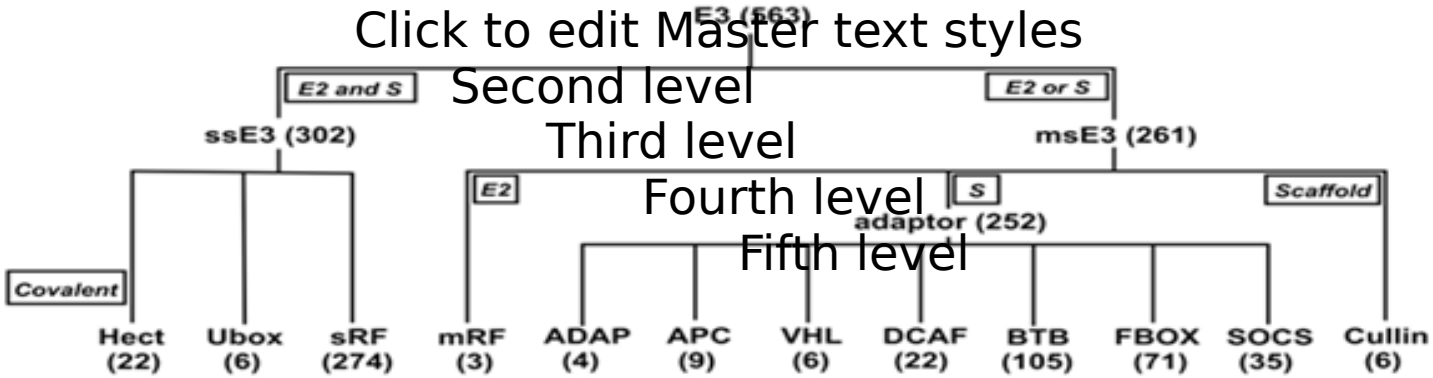
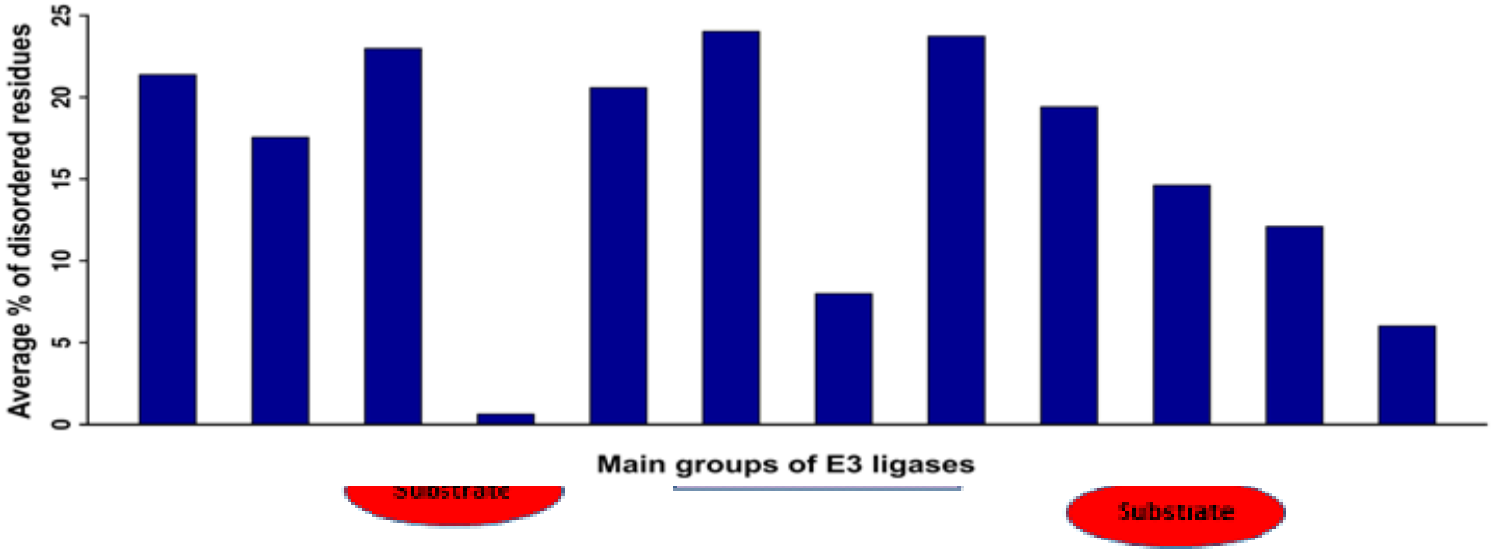
Fourth level
Fifth level





Predicted disorder of the main classes of human E3 ubiquitin ligases

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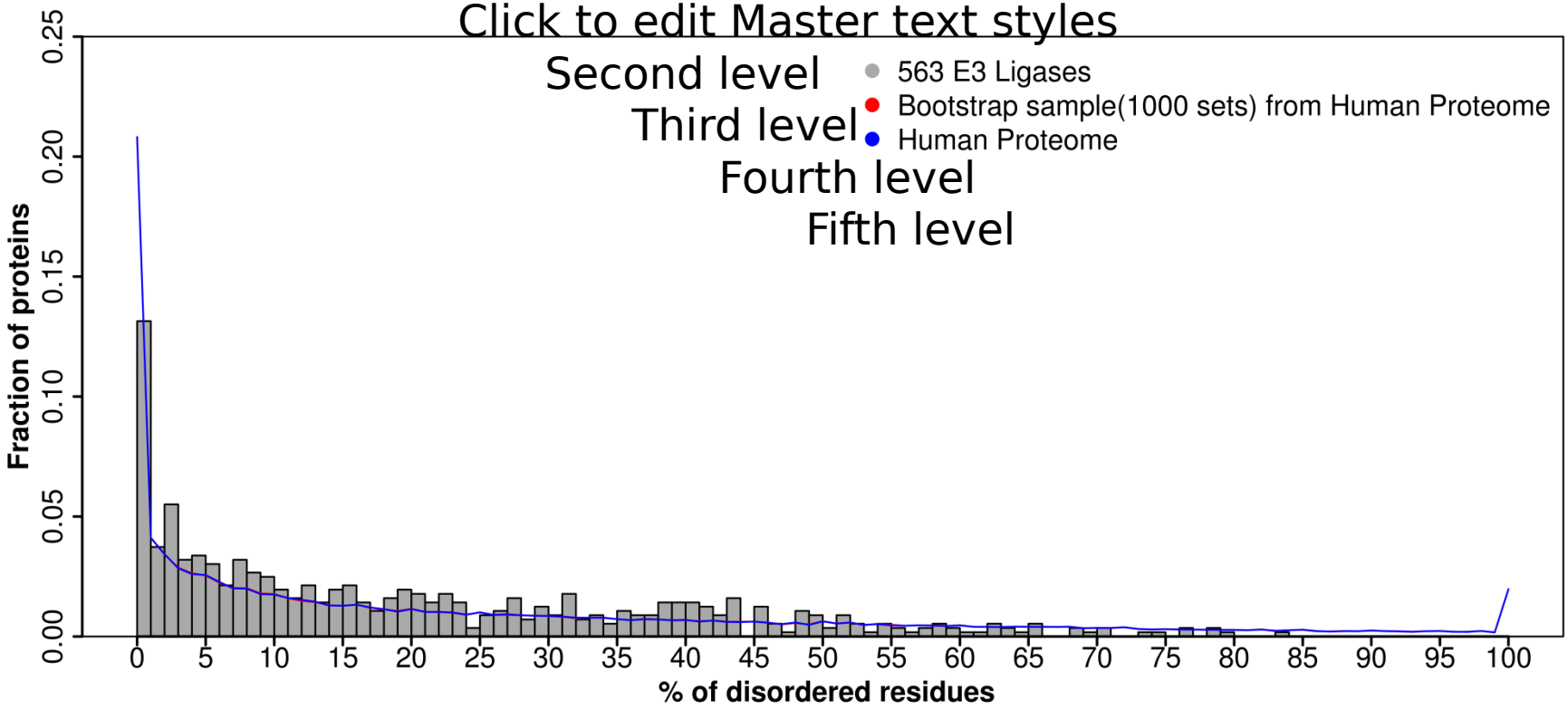

Residue-level structural disorder in 563 human E3 ligases, Human Proteome and Bootstrap
sample with sample size 563 were predicted by IUPred, from which the
age percent of
rdered residues was calculated for the entire protein.

nduced folding in the interaction of human E3 igases and their partner molecule and their substrates

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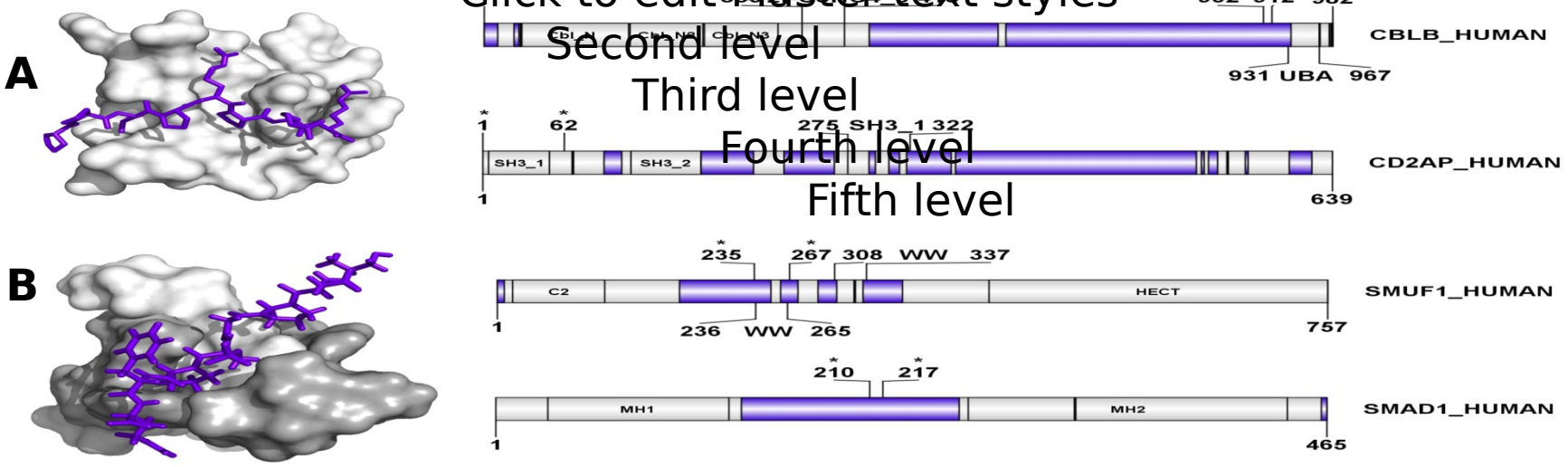
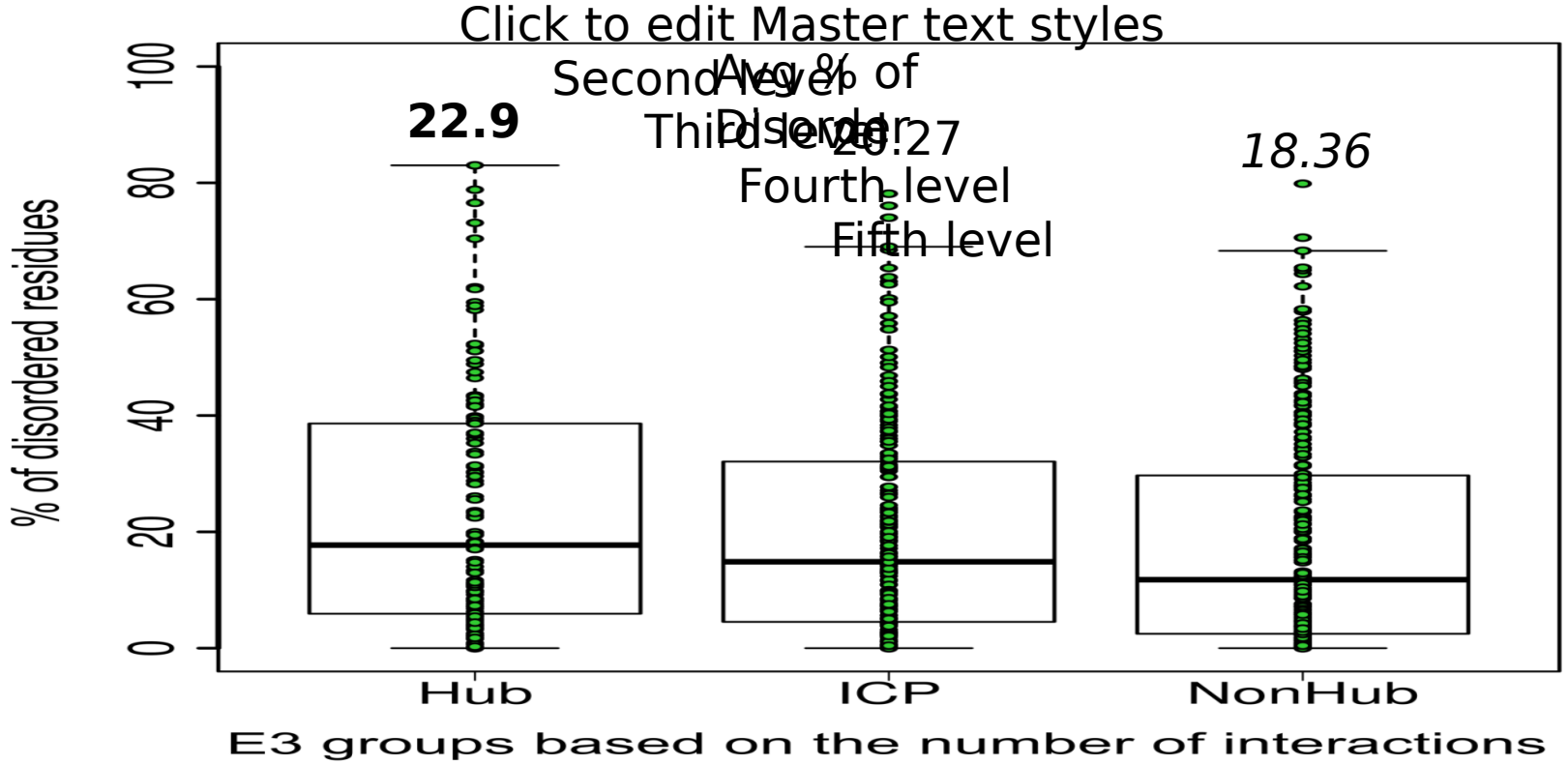


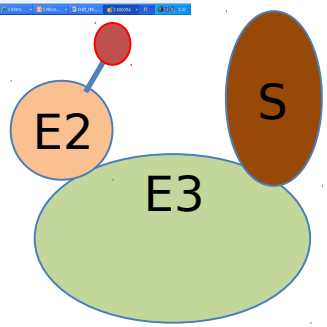
A)Interaction between E3 ligase CBL-B (CBLB) and CD2-associated protein (CD2AP; PDB 2J6F). B)Interaction between E3 ligase SMURF1 and its substrate SMAD1 (SMA and mothers against decapentaplegic homolog 1; PDB 2LAZ) is a case of cofolding of the two disordered regions.

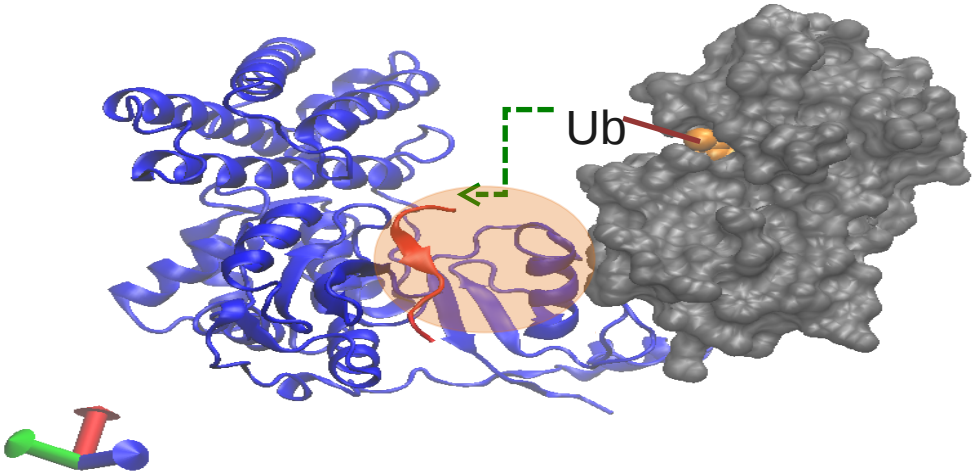
Structural disorder of E3 ligases as a function of their connectivity in the interactome



Disorder content for the three connectivity groups of human E3s (hub: $k \geq 25$, ICP: $4 \leq k \leq 24$, non-hub: $k \leq 3$) classified by their number of partners in the STRING database. Green circles represent individual proteins.

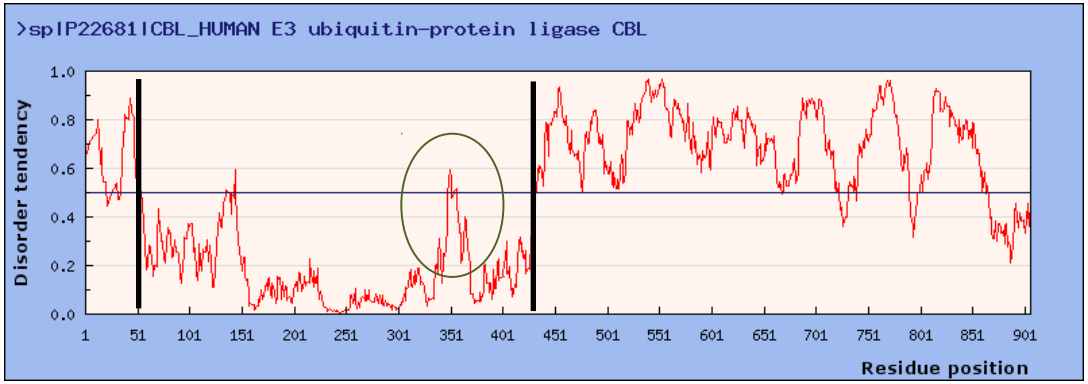
e E3 ligase: structure, function, and conformational dynamics



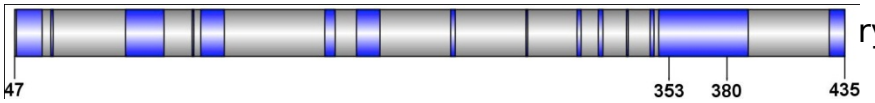


PDBid: 4a4c
E2 (UbcH5B)
E3 ligase (CBL)
Substrate (Tyr kinase ZAP-70)

Linker 'helix' region



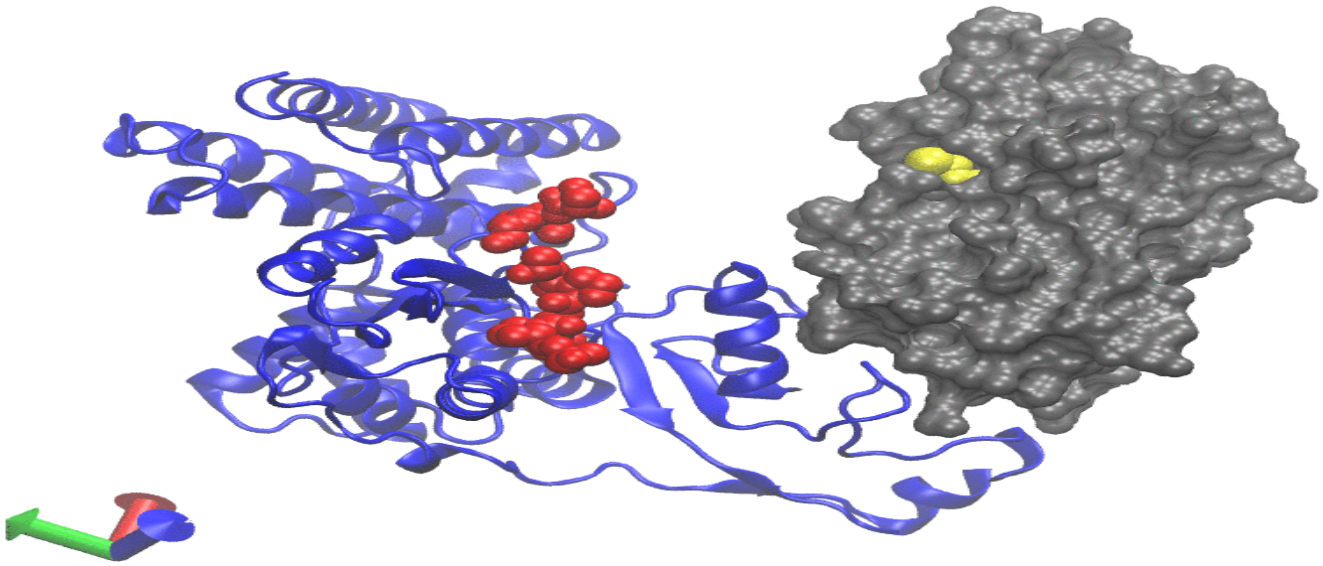
Predicted disorder (IUPred)

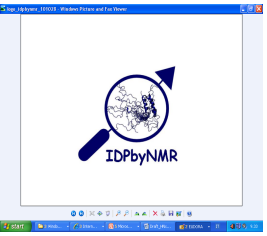


rystal B-factors

Linker

e E3 ligase: structure, function, and conformational dynamics



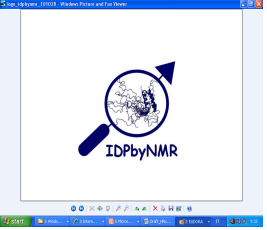


Conclusion

Due to the extreme heterogeneity and complexity of the system, it is difficult to draw general conclusions.
Disorder increases from E1s through E2s to E3s, and show that disorder is highest in single subunit E3s that function in both E2 and substrate binding.
The level of disorder correlated with connectivity (using the STRING database of known PPIs). They show that mean disorder increases with 'hubness'.
Disorder region of ligase responsible to bind with their partner.
Disorder flexible linker region allows inter-domain closure .This brings the Ub close to the substrate making Ub-transfer possible

Future Tasks

How can we recognize the substrates of E3s?
What distinguishes quality control (PQC) and regulatory (REG) roles of E3s?



Acknowledgement

Peter Tompa(Supervisor)
Mainak Guha Roy (Co-Supervisor)
Rita Pancsa (Project Collaborator)
Angela Bekesi
Simone Kosol
Denes Kovacs
Pierre Lebrun
Kris Pauwels
Thu Tran Thanh
Maksym Tsytlonok
Cesyen Cedeño
Sara Contreras Martos
Misi Váradi
Karolien Van Belle