

Description of Additional Supplementary Files

File Name: Supplementary Data 1

Description: **PPIs with aligned PDB chain pairs**

PPIs in the human reference interactome with at least one pair of chains in the same PDB structure jointly aligned with significant E-value ($<10^{-10}$).

(A) HI-II-14 interactome

(B) IntAct interactome

File Name: Supplementary Data 2

Description: **Human structural interactome with resolved PPI interfaces**

(A) HI-II-14 structural interactome (Y2H-SI)

(B) IntAct structural interactome (IntAct-SI)

File Name: Supplementary Data 3

Description: **Mutations with geometry-based edgotype predictions**

(A) Non-disease mutations in Y2H-SI

(B) Disease mutations in Y2H-SI

(C) Non-disease mutations in IntAct-SI

(D) Disease mutations in IntAct-SI

File Name: Supplementary Data 4

Description: **Change in PPI binding free energy calculated using BindProfX**

Change in binding free energy ($\Delta\Delta G$) of PPIs upon mutation at the interface, calculated on PPI structural models using BindProfX.

(A) PPIs with non-disease mutations in Y2H-SI

(B) PPIs with disease mutations in Y2H-SI

(C) PPIs with non-disease mutations in IntAct-SI

(D) PPIs with disease mutations in IntAct-SI

File Name: Supplementary Data 5

Description: **Mutations with physics-based edgotype predictions**

(A) Non-disease mutations in Y2H-SI

(B) Disease mutations in Y2H-SI

(C) Non-disease mutations in IntAct-SI

(D) Disease mutations in IntAct-SI

File Name: Supplementary Data 6

Description: **Change in PPI binding free energy calculated using FoldX**

Change in binding free energy ($\Delta\Delta G$) of PPIs upon mutation at the interface, calculated on PPI structural models using FoldX.

(A) PPIs with non-disease mutations in Y2H-SI

(B) PPIs with disease mutations in Y2H-SI

(C) PPIs with non-disease mutations in IntAct-SI

(D) PPIs with disease mutations in IntAct-SI