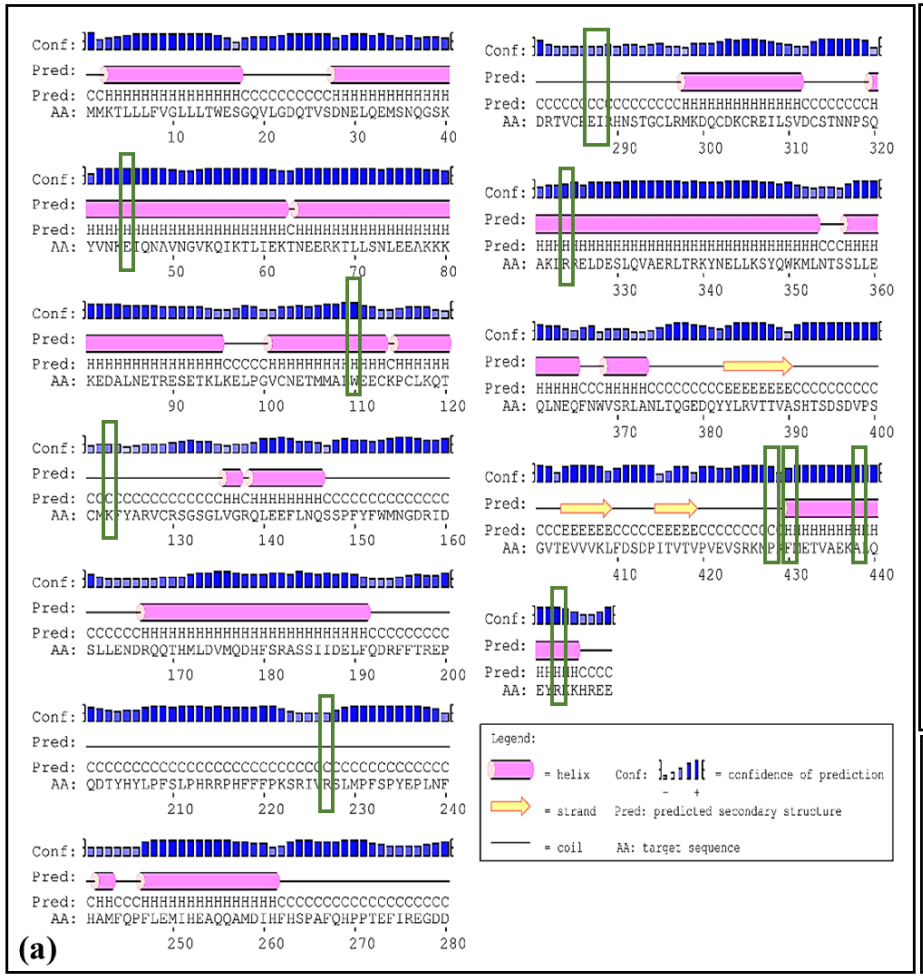
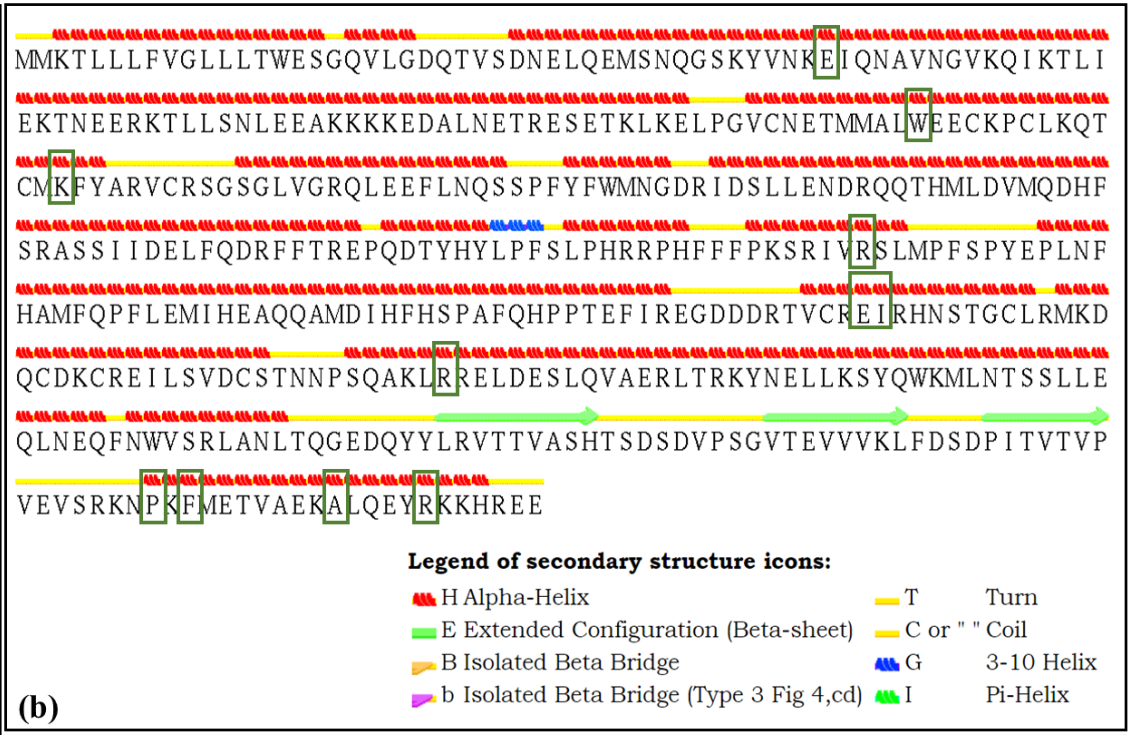
Supplementary figure 1: Correlation between **(a)** secondary structure prediction by PSIPRED and **(b)** secondary structure prediction of *ab initio* model structure by STRIDE. The evolutionarily conserved residues are highlighted by green boxes. **(c)** Percentage of α-helix, random coil, and β-sheet calculated by PSIPRED and STRIDE. Most parts of the secondary structure predicted by PSIPRED correlate well with the final model of psCLU. Coiled coil regions are usually unstable in nature and hence the degree of confidence in predicting them is lower, as indicated by the shorter blue bars in the PSIPRED prediction result. However, this gets resolved during model refinement, which ultimately generates a more stable structure. Therefore, some differences are observed in the coiled coil regions of the PSIPRED prediction and the final model.

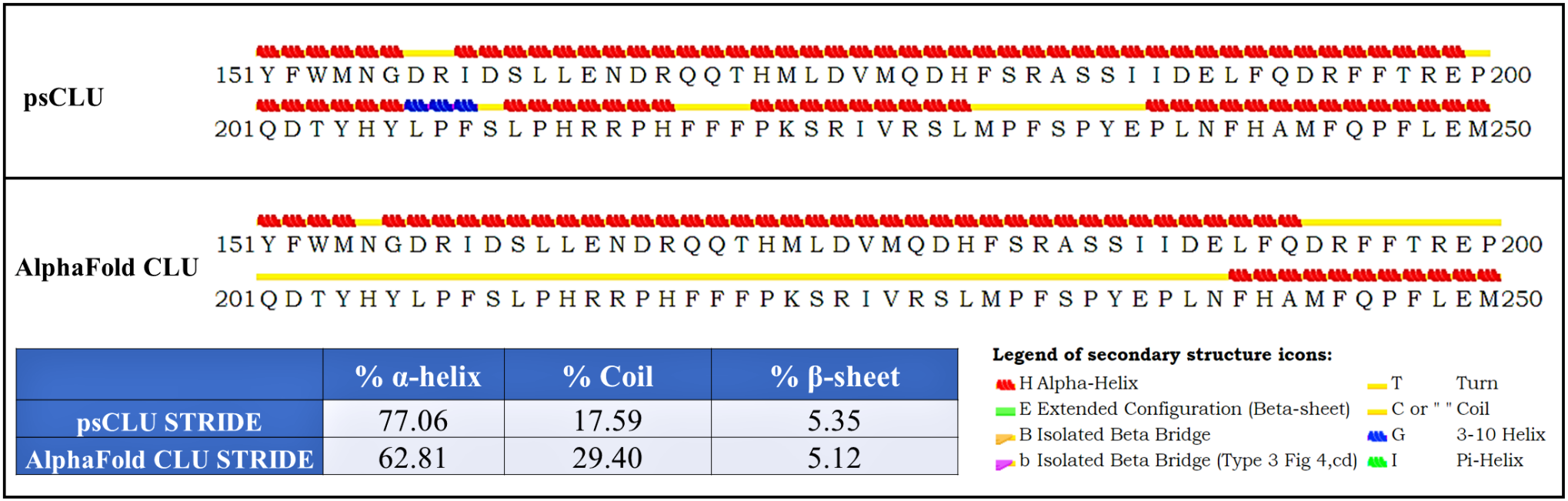




	% α-helix	% Coil	% β-sheet
PSIPRED	61.02	33.41	5.57
STRIDE	77.06	17.59	5.35

(c)

Supplementary Figure 2: Correlation between the low confidence region (Asp193 to Glu245) in the modelled psCLU and AlphaFold CLU structures. The modelled psCLU structure shows refinement of the previously predicted loop region as α-helices. STRIDE secondary structure predictions are indicated in tabular form.



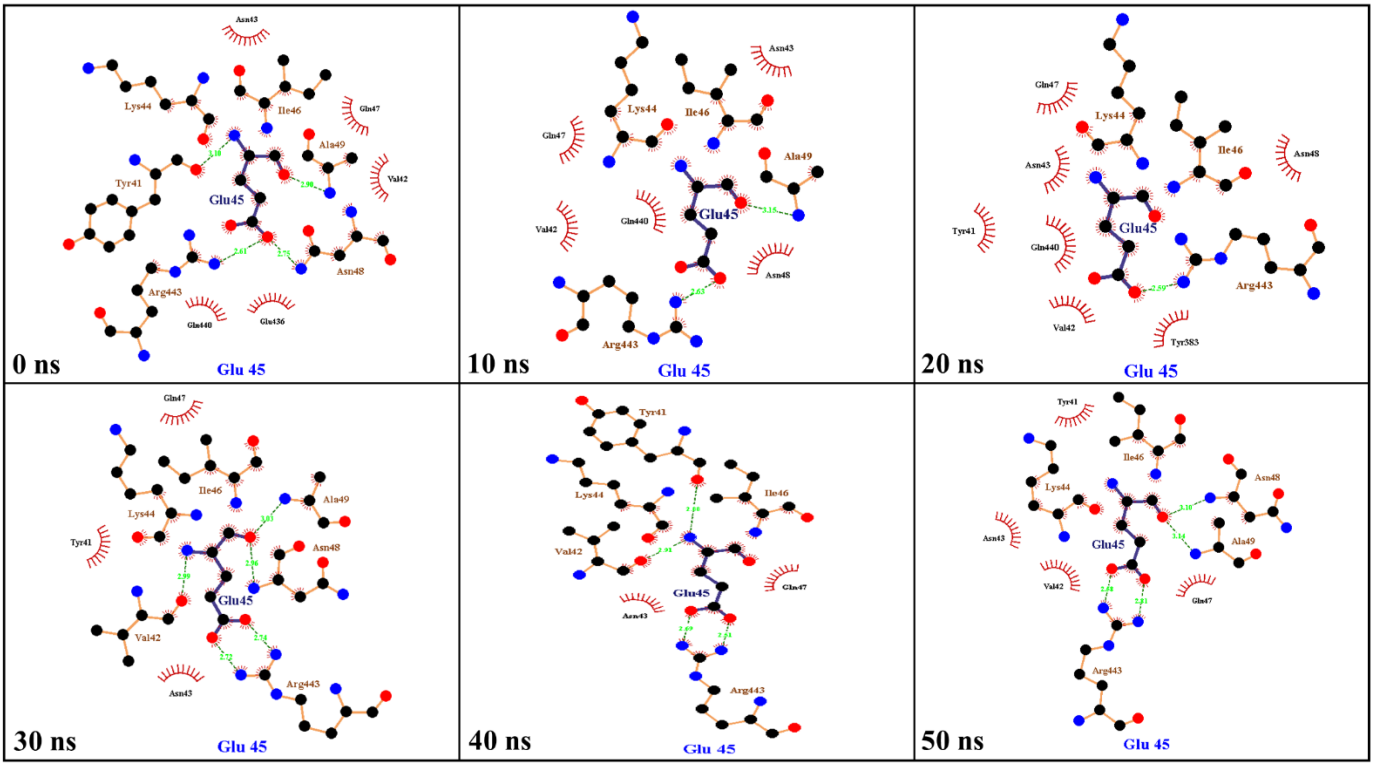
	% α-helix	% Coil	% β-sheet
psCLU STRIDE	77.06	17.59	5.35
AlphaFold CLU STRIDE	62.81	29.40	5.12

Legend of secondary structure icons:

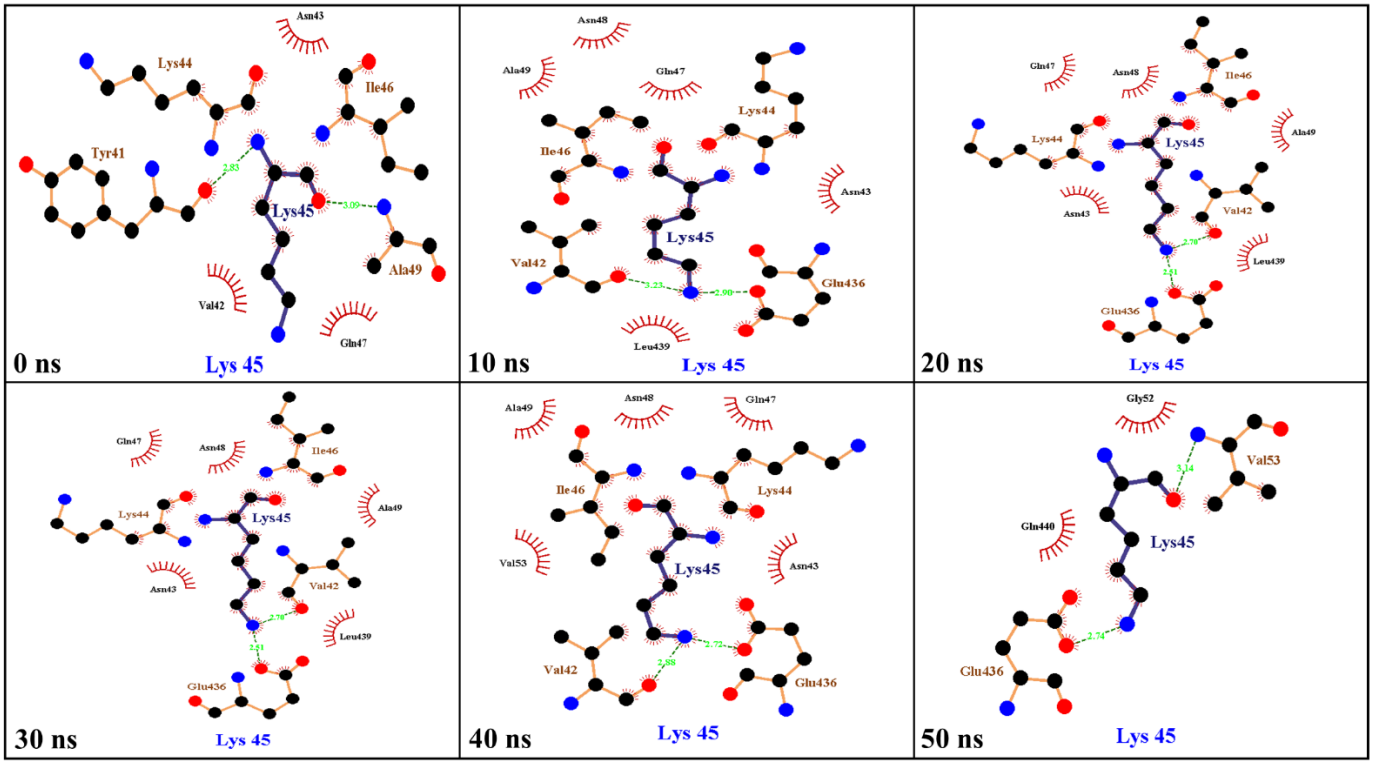
H	Alpha-Helix	T	Turn
E	Extended Configuration (Beta-sheet)	C or " "	Coil
B	Isolated Beta Bridge	G	3-10 Helix
b	Isolated Beta Bridge (Type 3 Fig 4,cd)	I	Pi-Helix

Supplementary Figure 3: Weak intramolecular interactions observed in psCLU mutations located in the functionally conserved regions. Protein structures have been captured at every 10ns of MD simulation. Panel **(a)** depicts the interactions observed in the wild type psCLU structure and panel **(b)** depicts the interactions in the mutant structure. Hydrogen bonds are depicted in green colored dotted lines. Hydrophobic interactions are denoted by red half circles.

Glu45Lys mutation

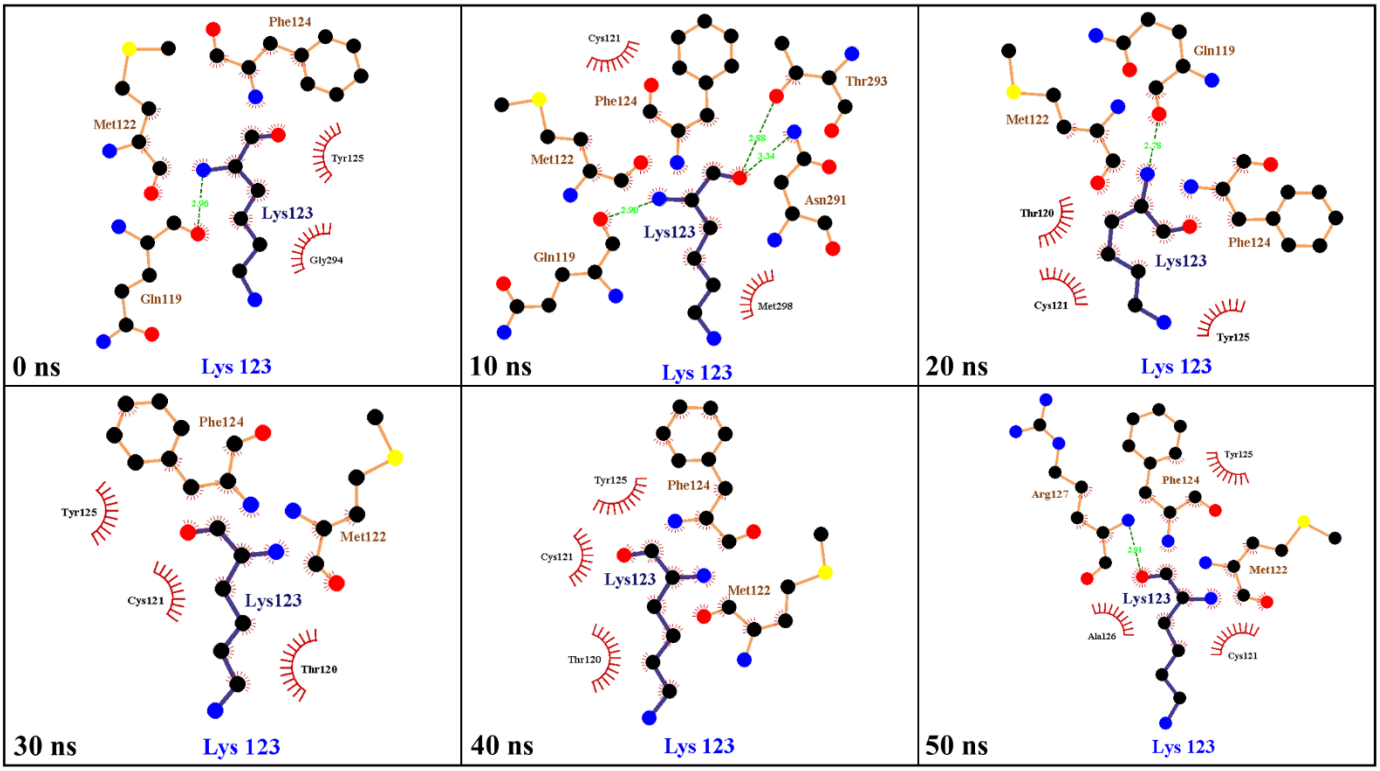


(a)

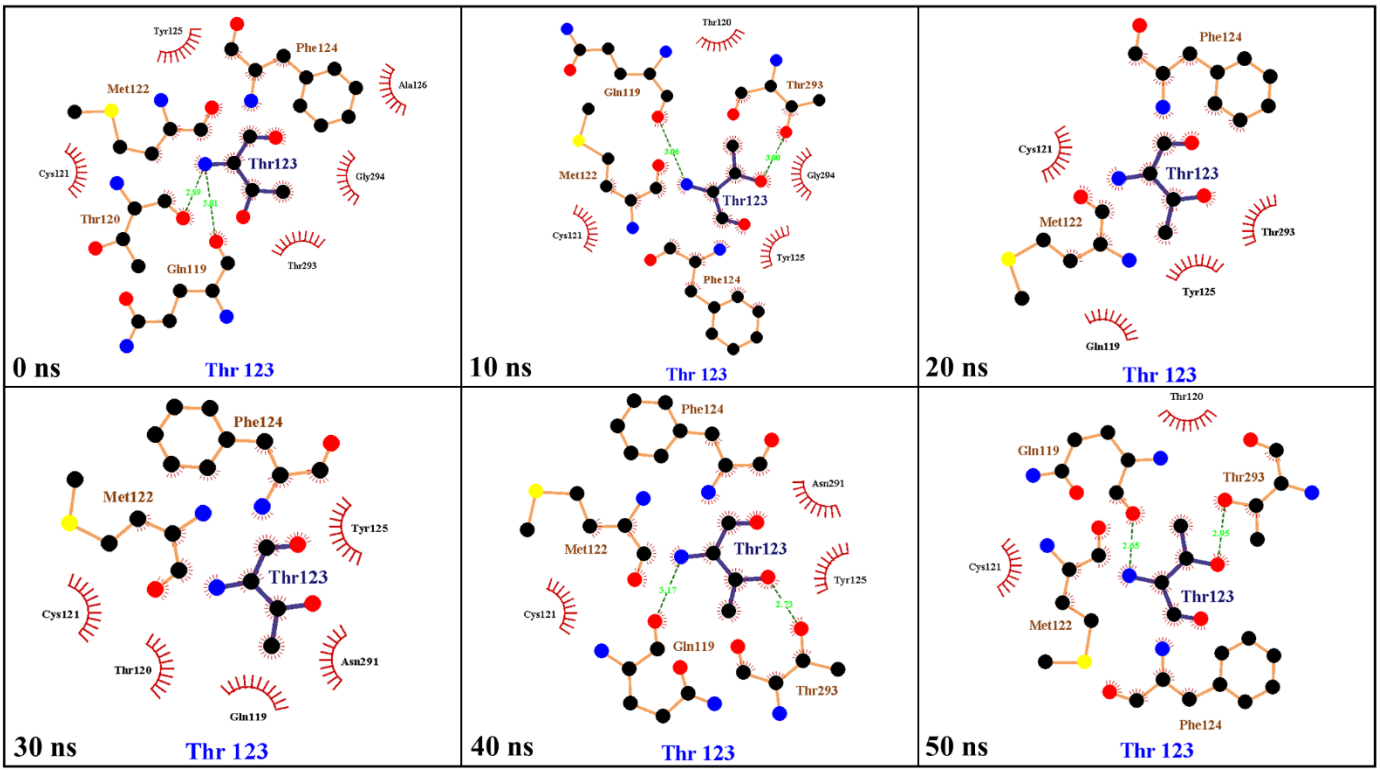


(b)

Lys123Thr mutation

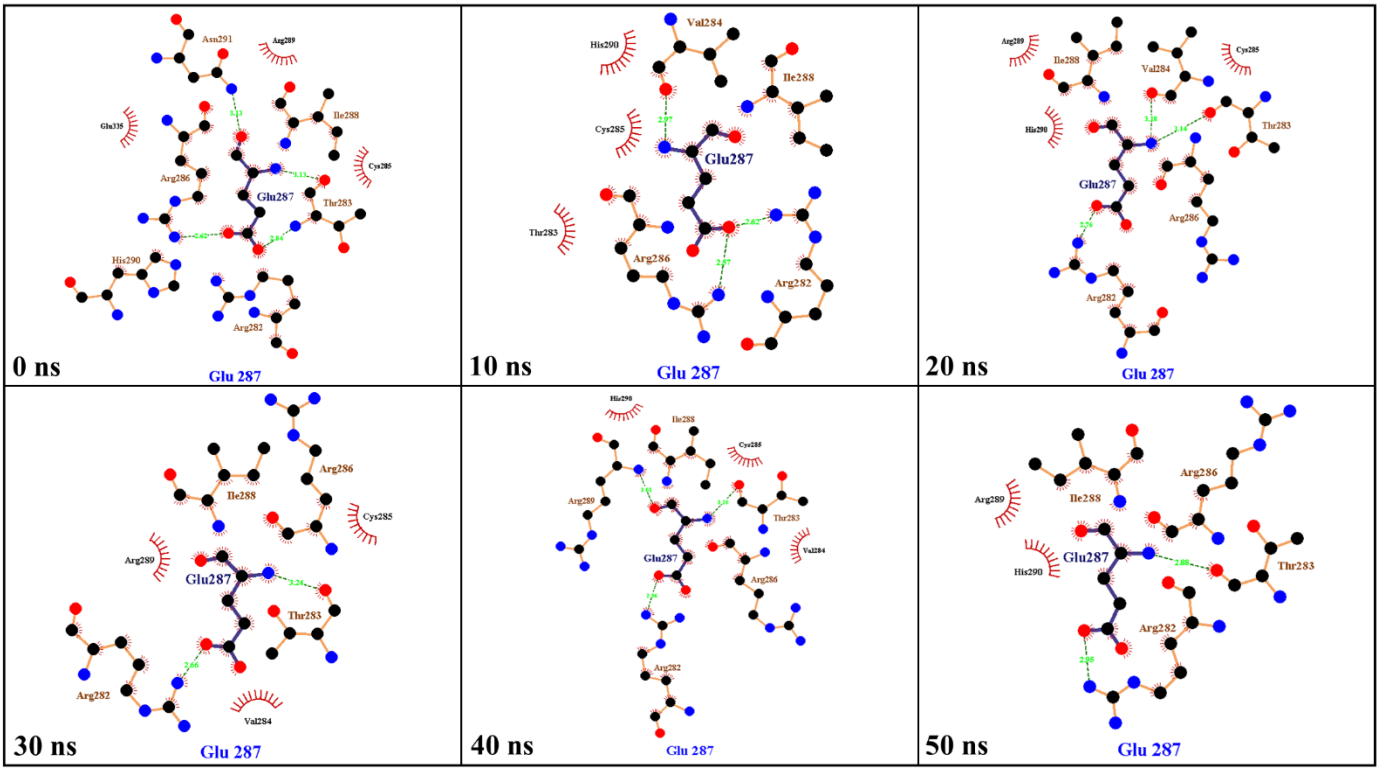


(a)

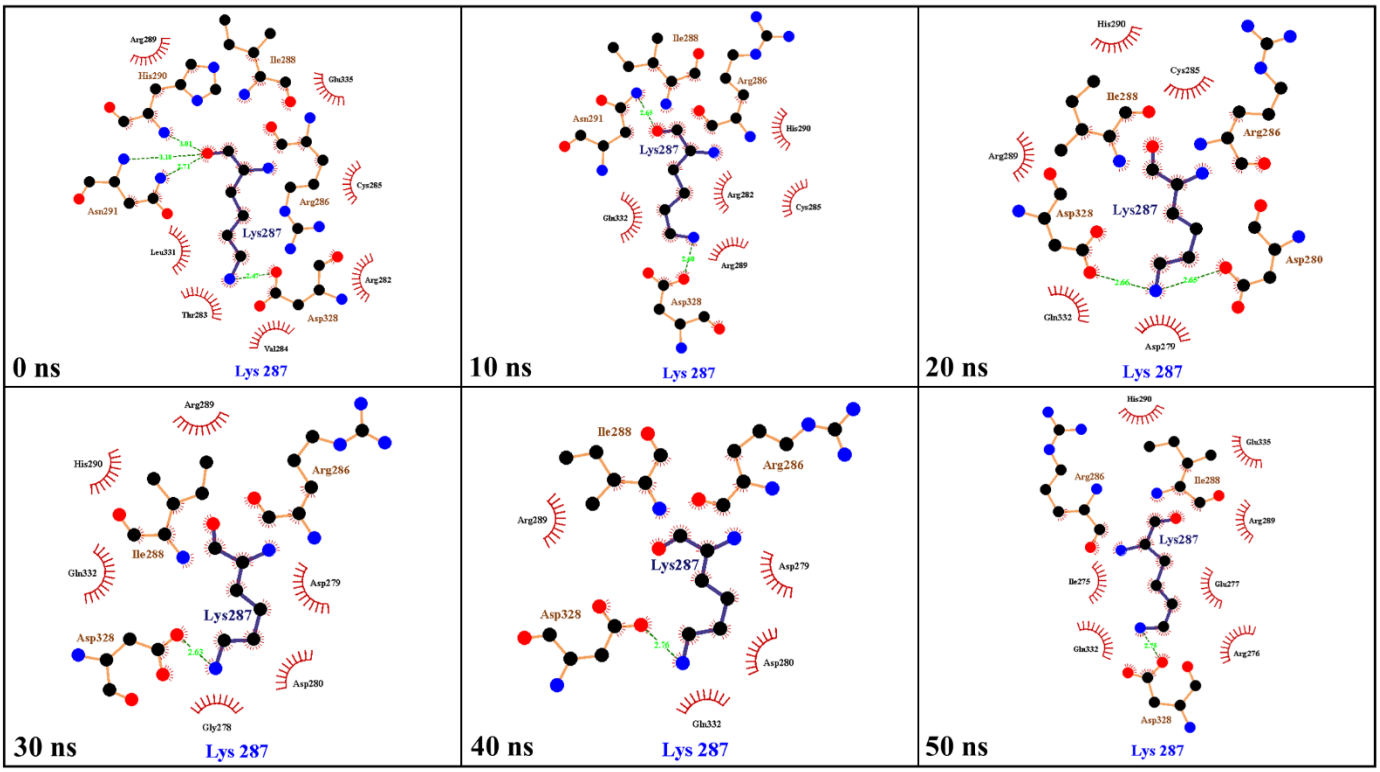


(b)

Glu287Lys mutation

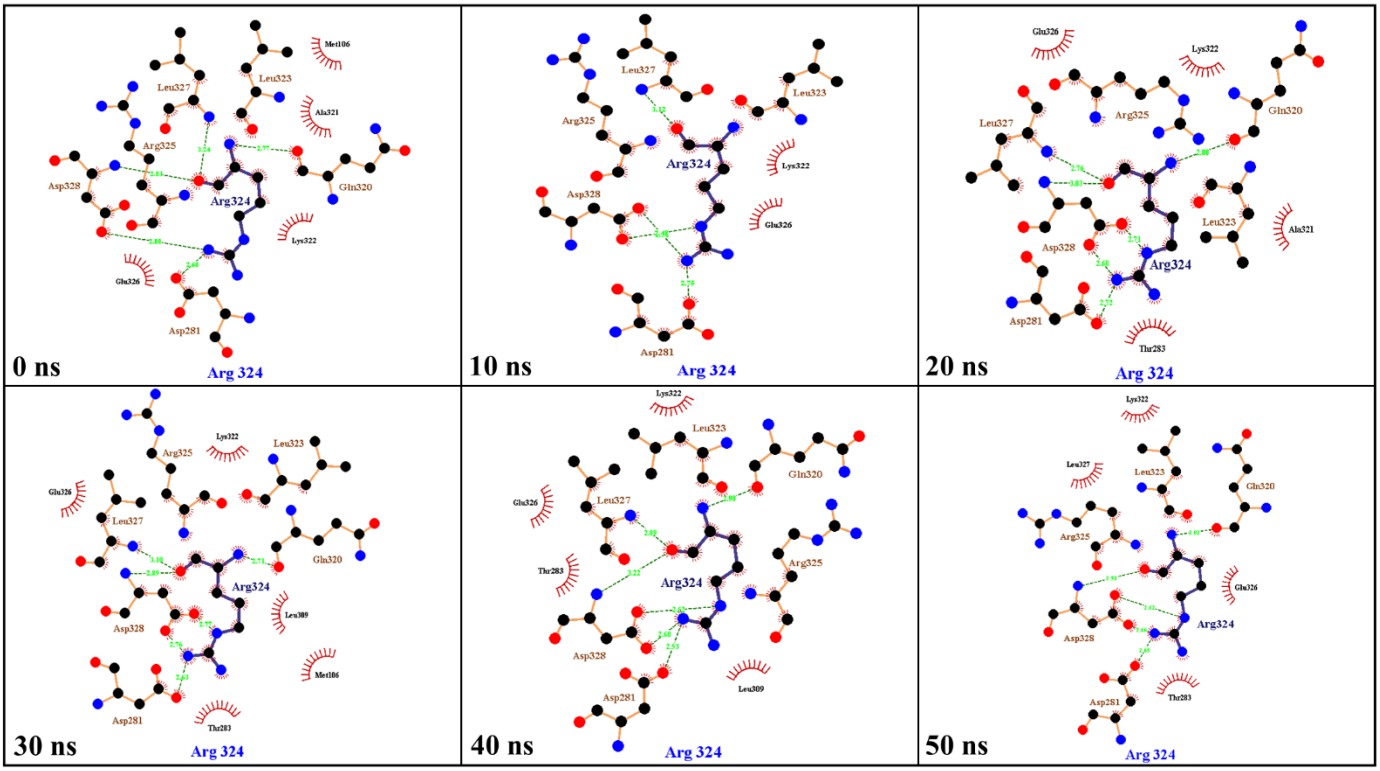


(a)

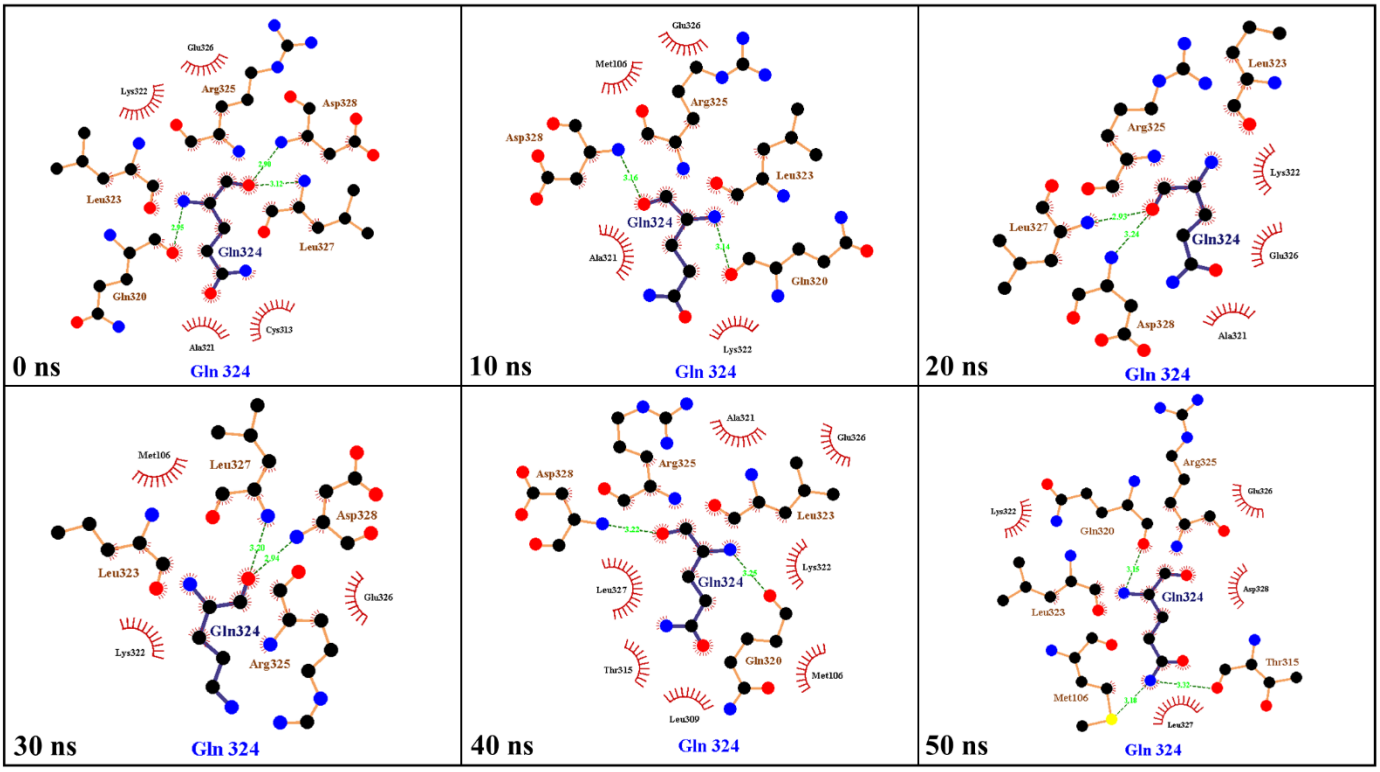


(b)

Arg324Gln mutation

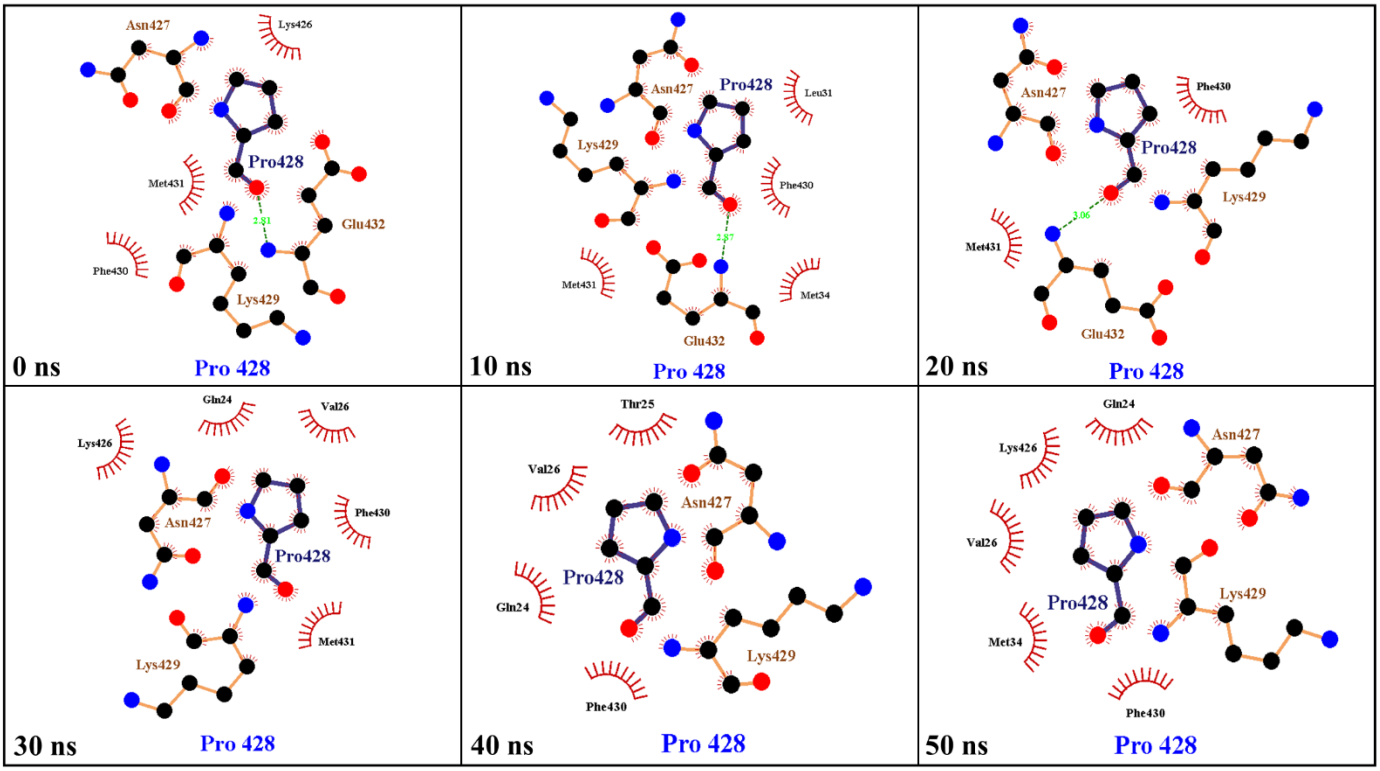


(a)

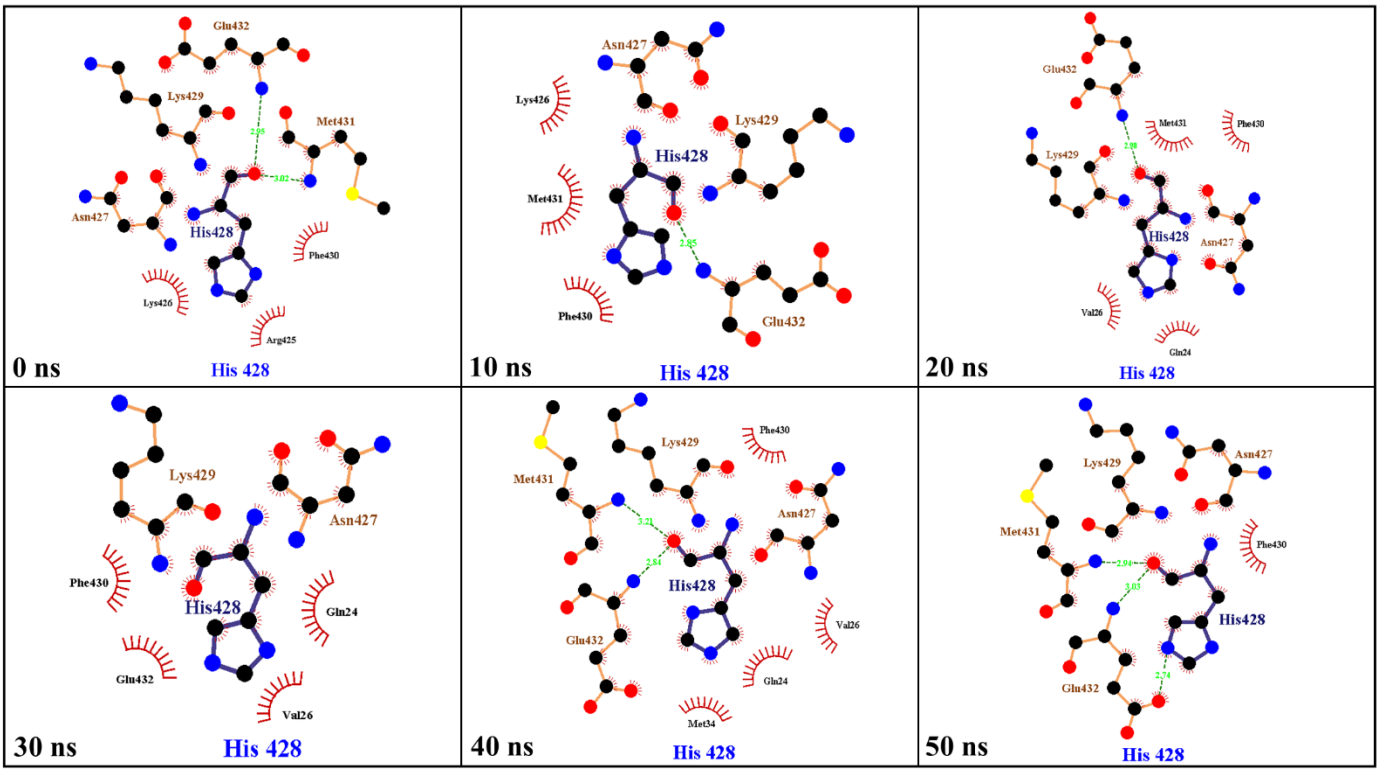


(b)

Pro428His mutation

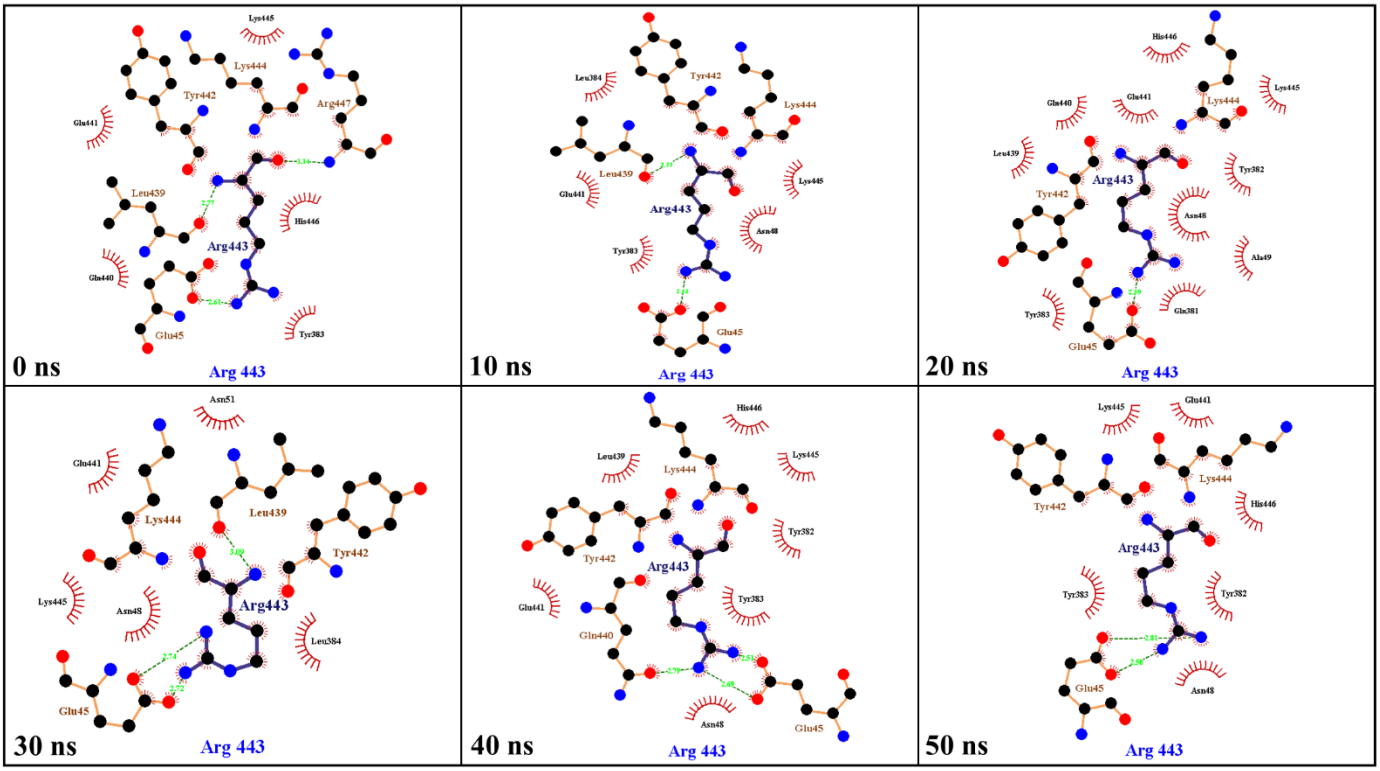


(a)

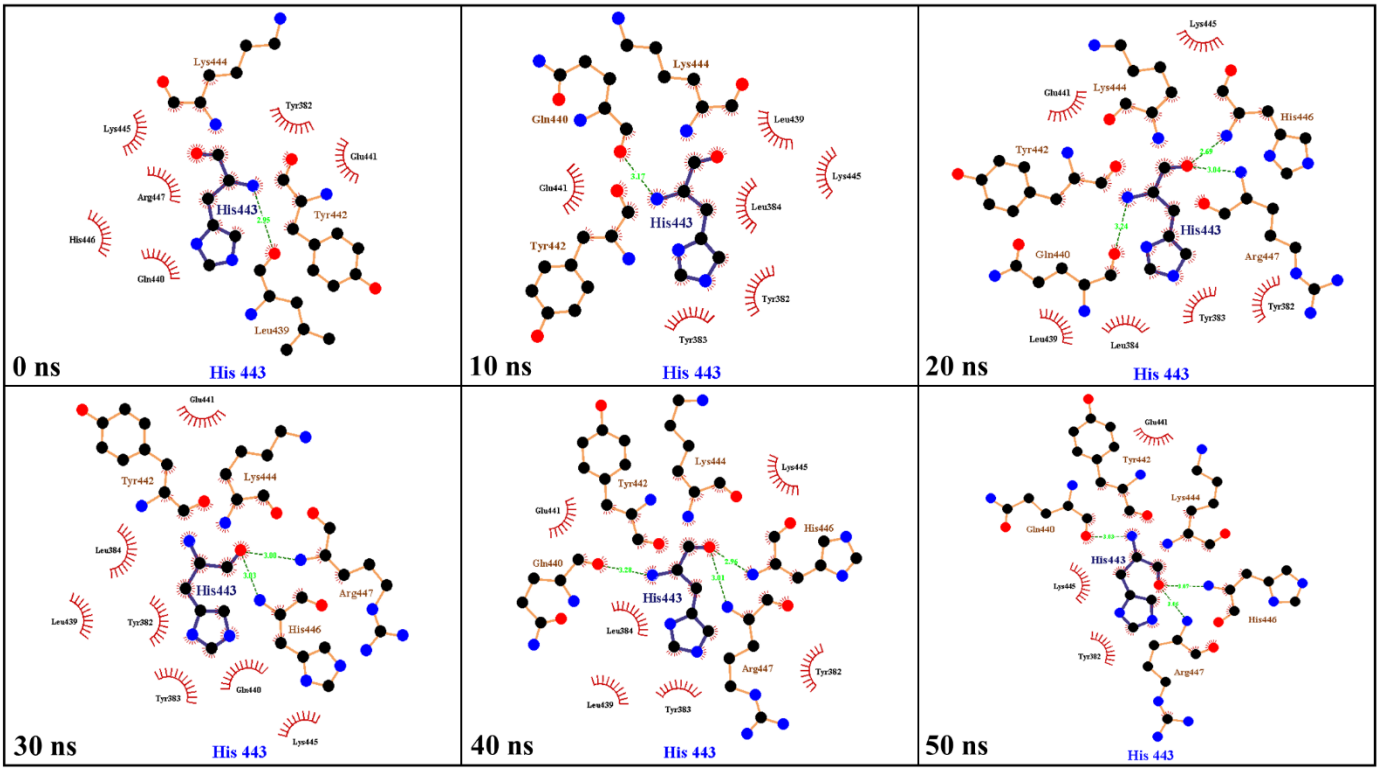


(b)

Arg443His mutation



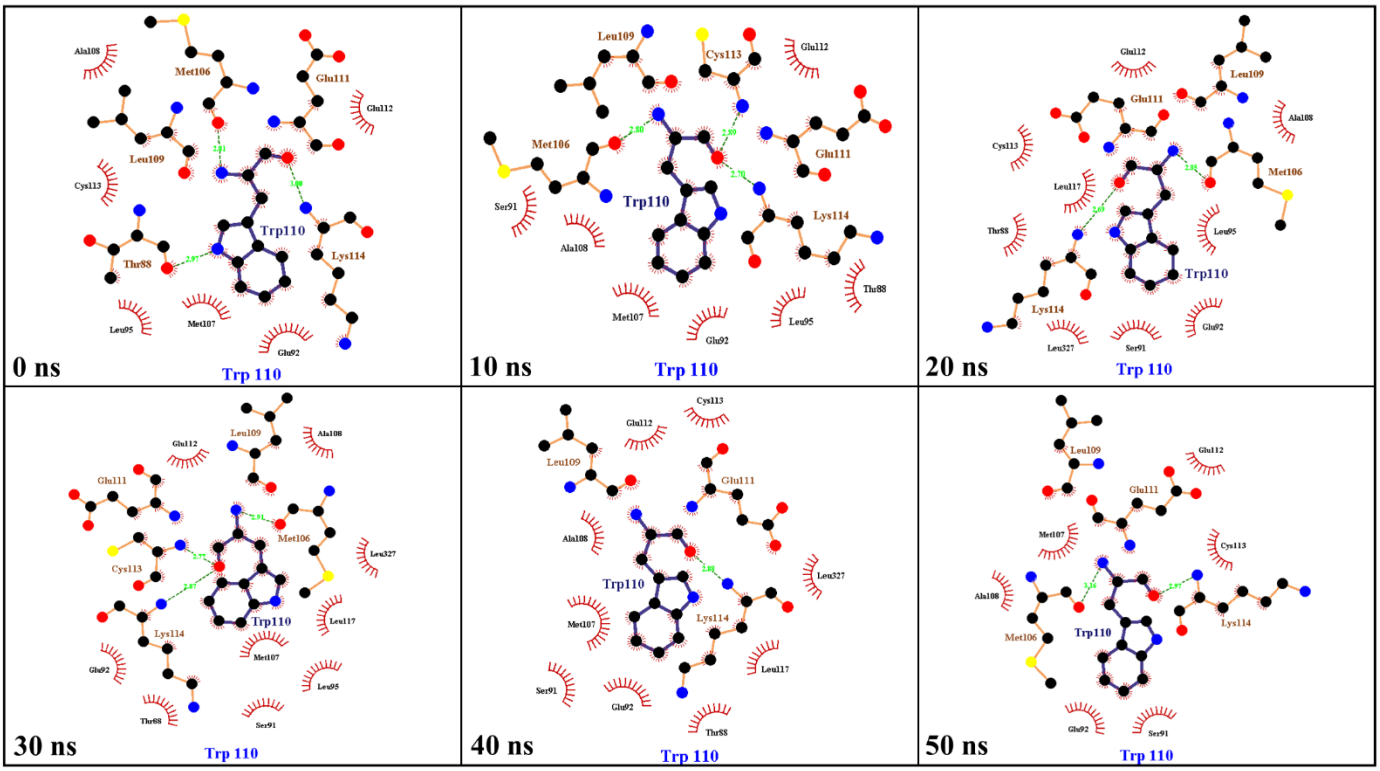
(a)



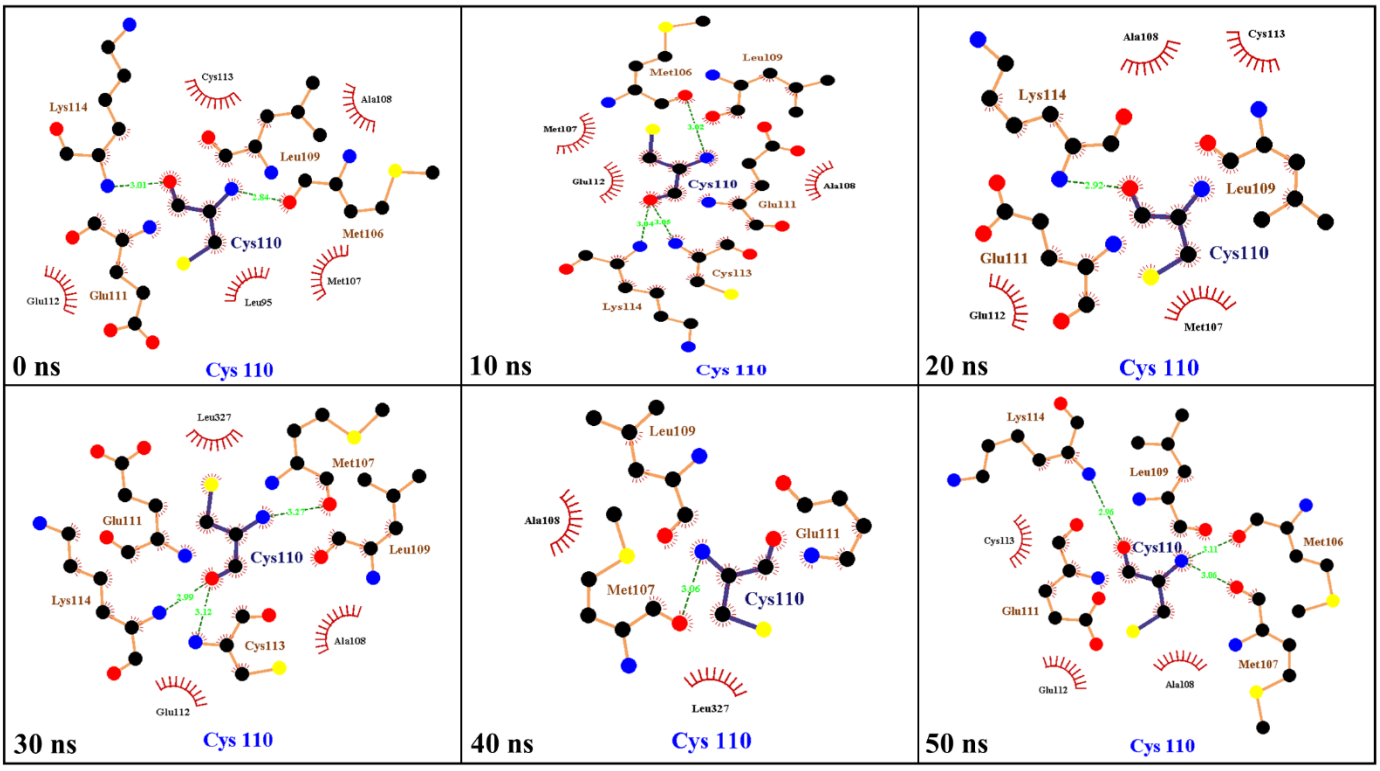
(b)

Supplementary figure 4: Weak intramolecular interactions observed in psCLU mutations located in the structurally conserved regions. Protein structures have been captured at every 10ns of MD simulation. Panel **(a)** depicts the interactions observed in the wild type psCLU structure and panel **(b)** depicts the interactions in the mutant structure. Hydrogen bonds are depicted in green colored dotted lines. Hydrophobic interactions are denoted by red half circles.

Trp110Cys mutation

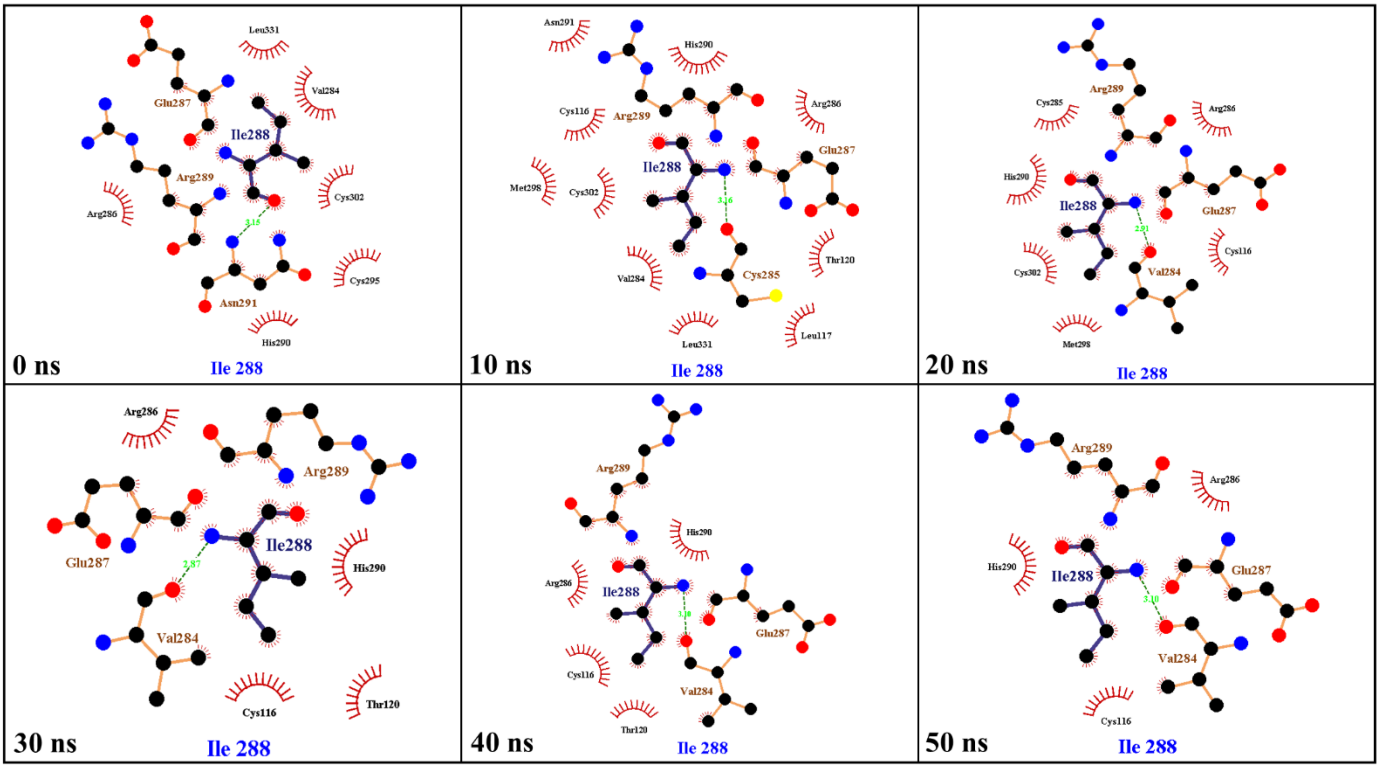


(a)

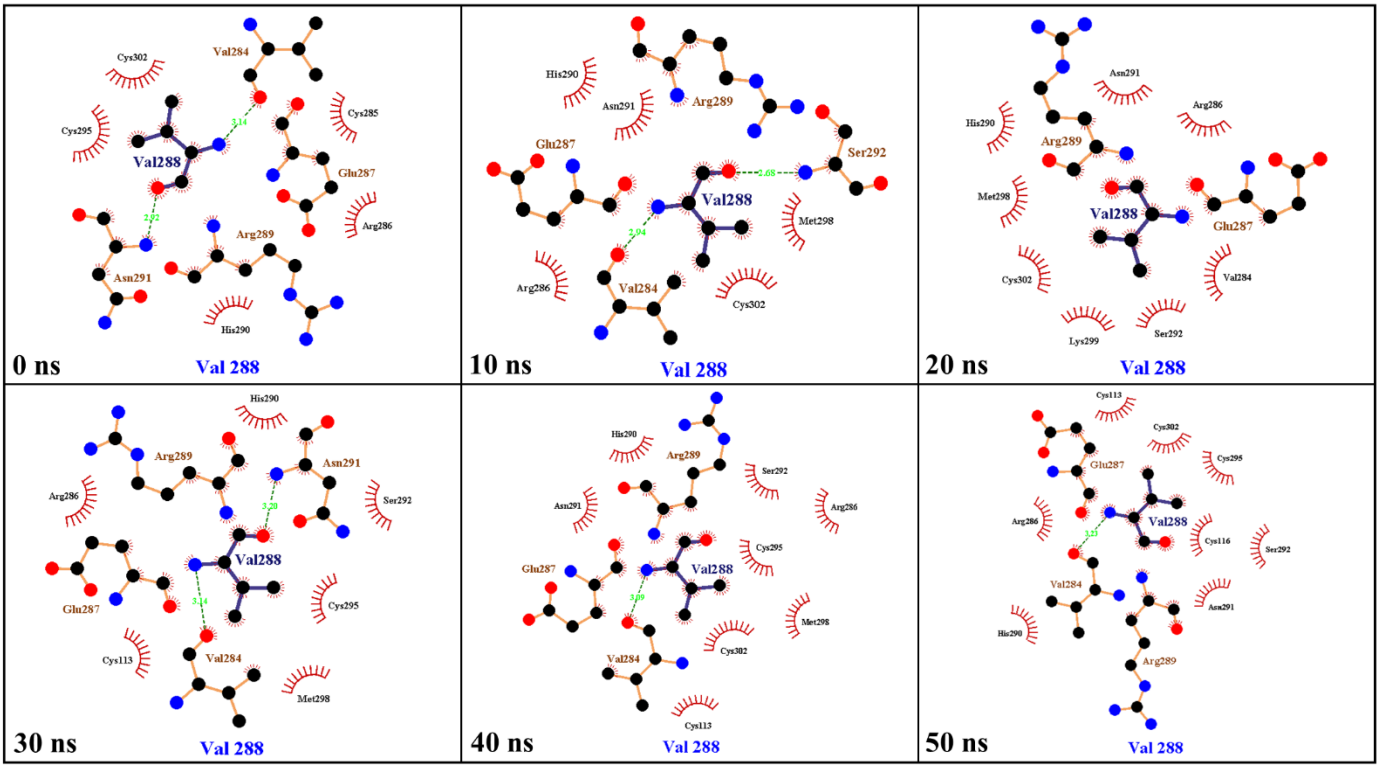


(b)

Ile228Val mutation

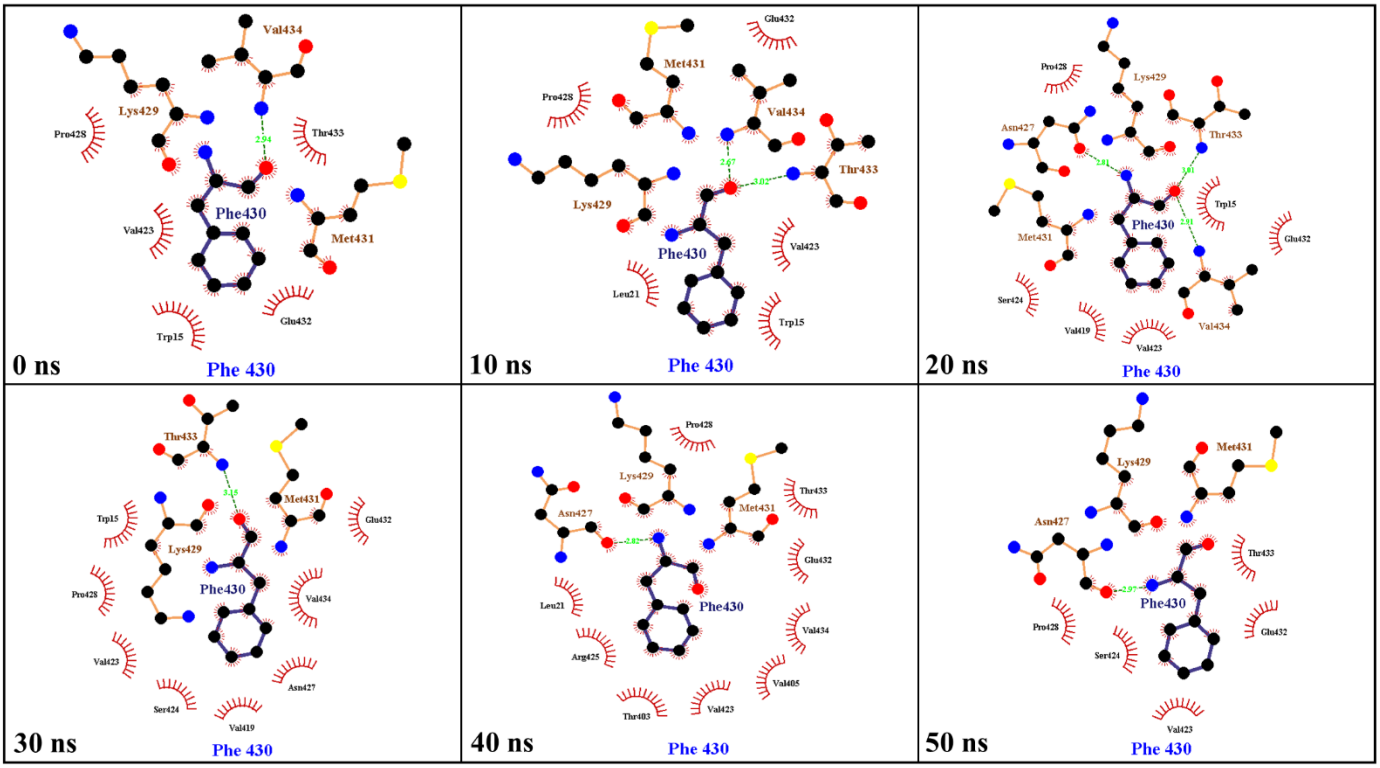


(a)

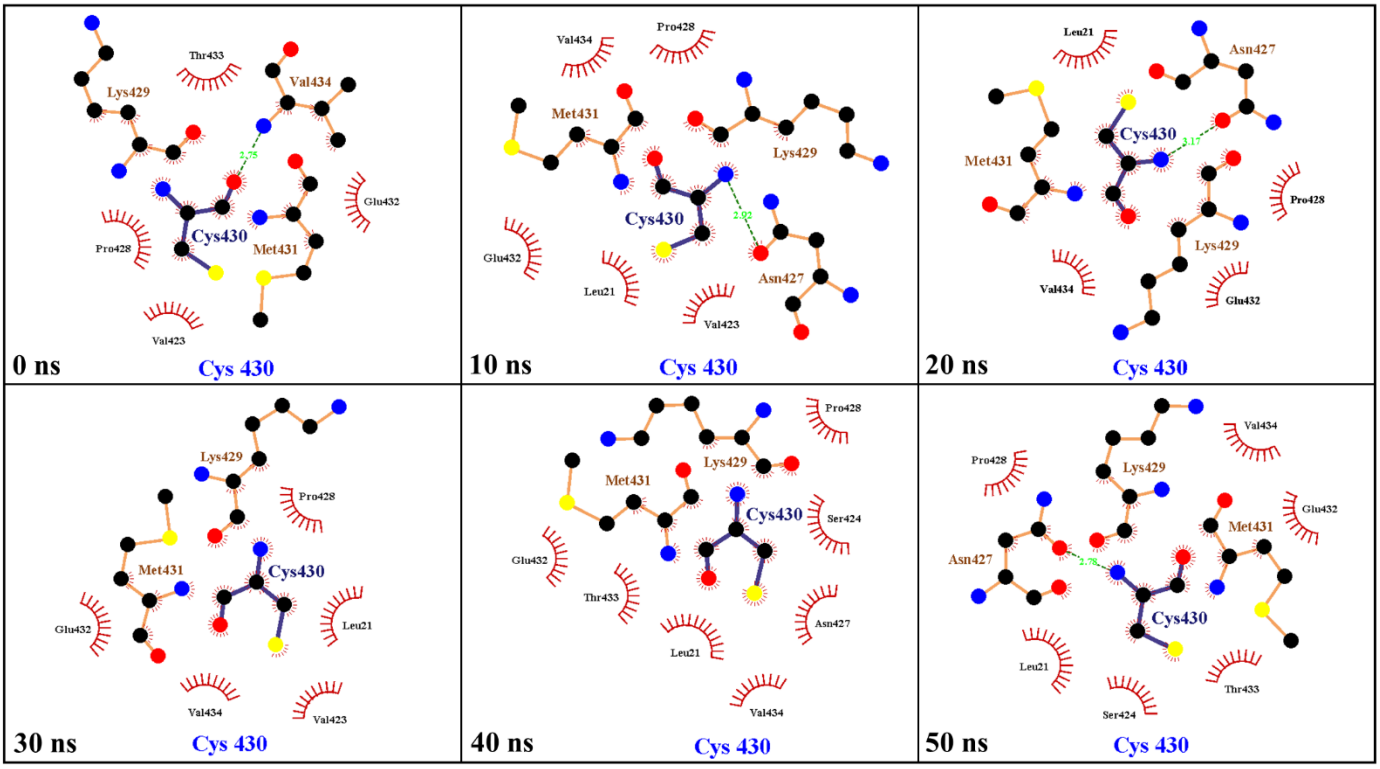


(b)

Phe430Cys mutation

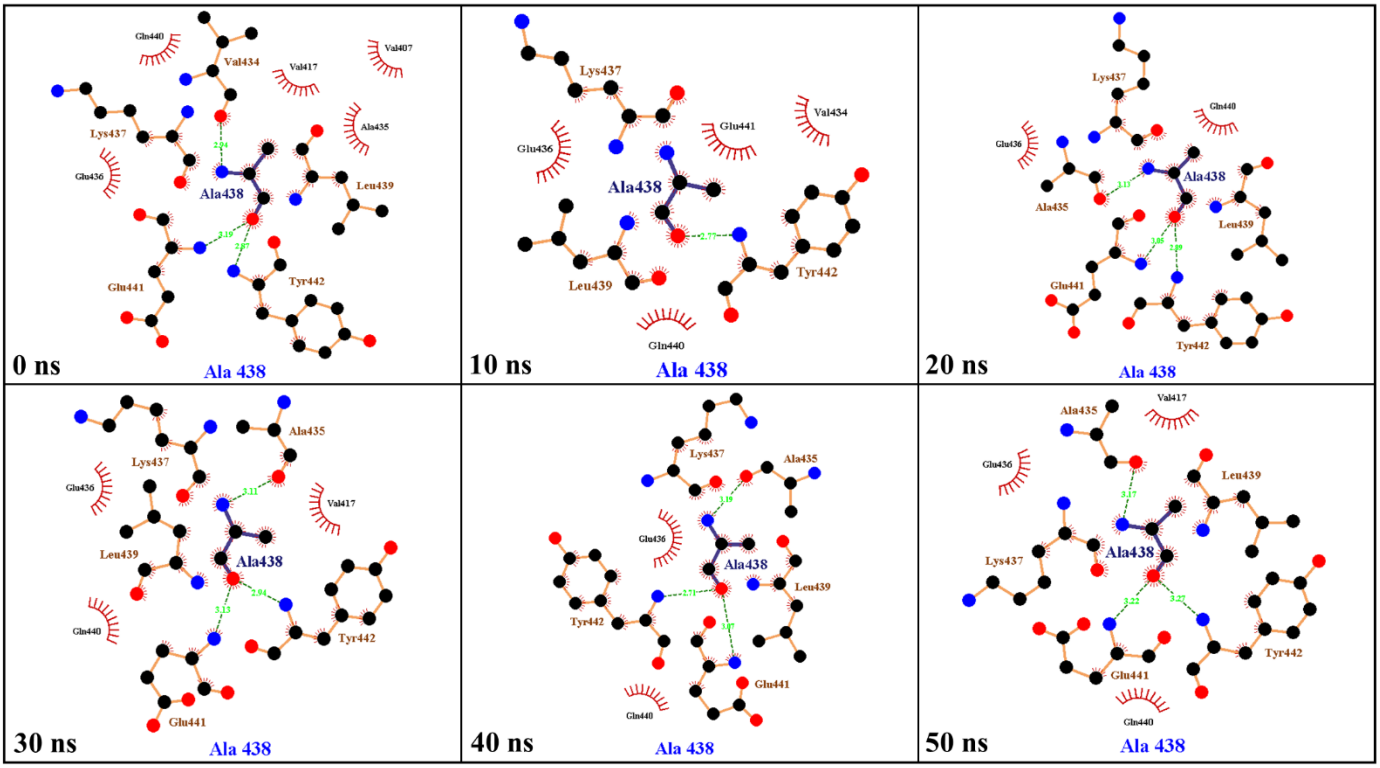


(a)

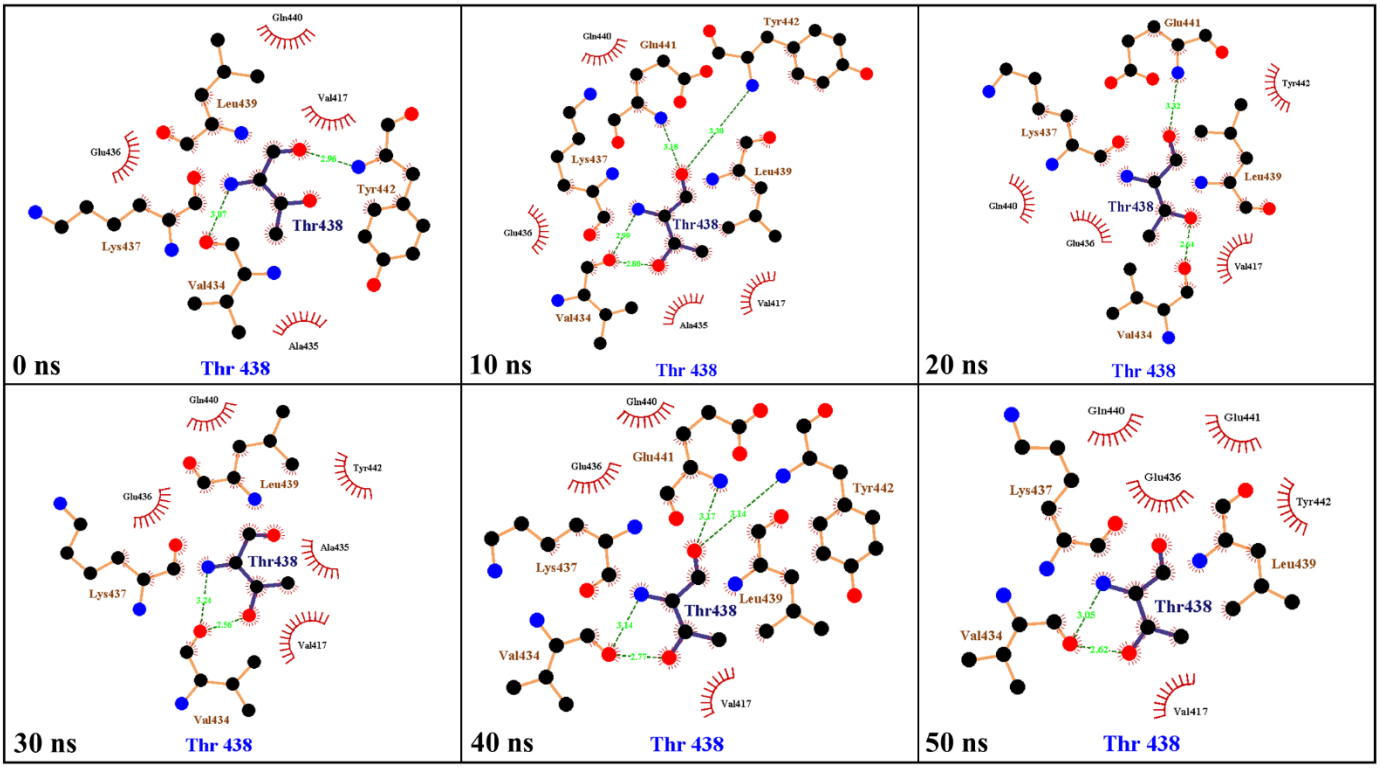


(b)

Ala438Thr mutation



(a)



(b)

Supplementary Figure 5: Occupancy analysis of mutated residues across all trajectories as visualized in VMD. The differently colored spheres indicate the volume occupied by the atom during the simulation. Blue- maximum volume; Green-medium volume; Red-minimum volume.