Electronic Supplementary Material (ESI) for Molecular BioSystems.


*Electronic Supplementary Information*

*for*

# Perturbations in inter-domain associations may trigger onset of pathogenic transformations in $PrP^C$: insights from atomistic simulations

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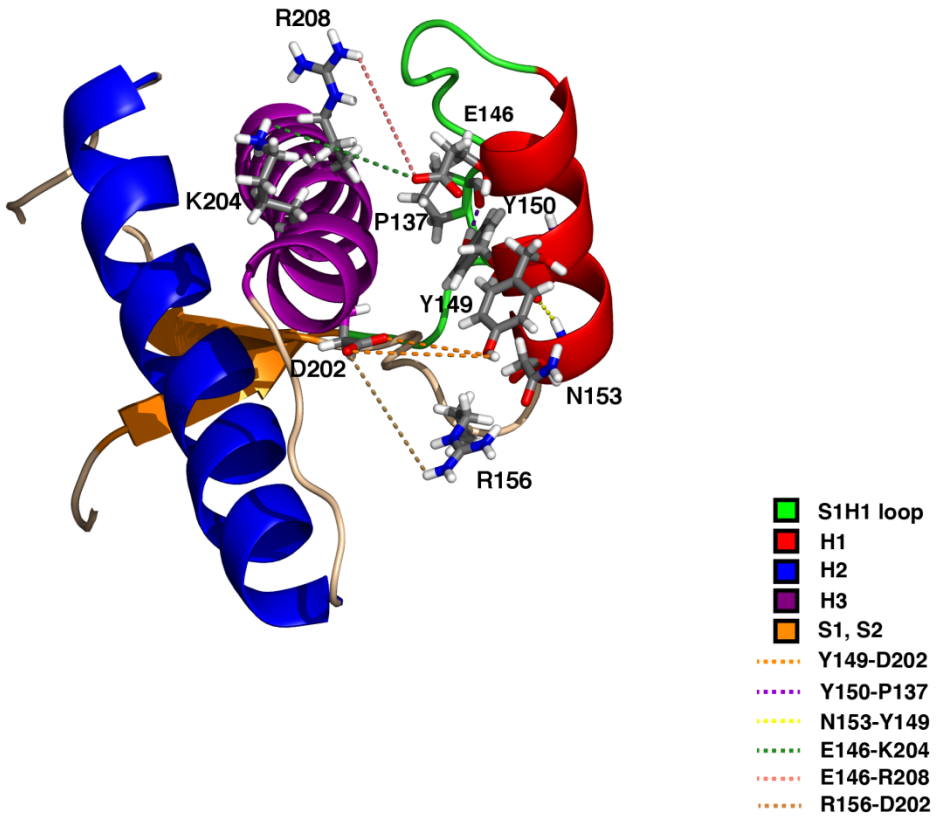


**Figure S1.** Charged interactions of helix H1 residues with H3 and the S1H1 loop. These include hydrogen bond interactions: Y149-D202, Y150-P137 and N153-Y149; and salt bridge interactions: E146-K204, E146-R208 and R156-D202. The residues are represented as sticks and the interactions as dashed lines.

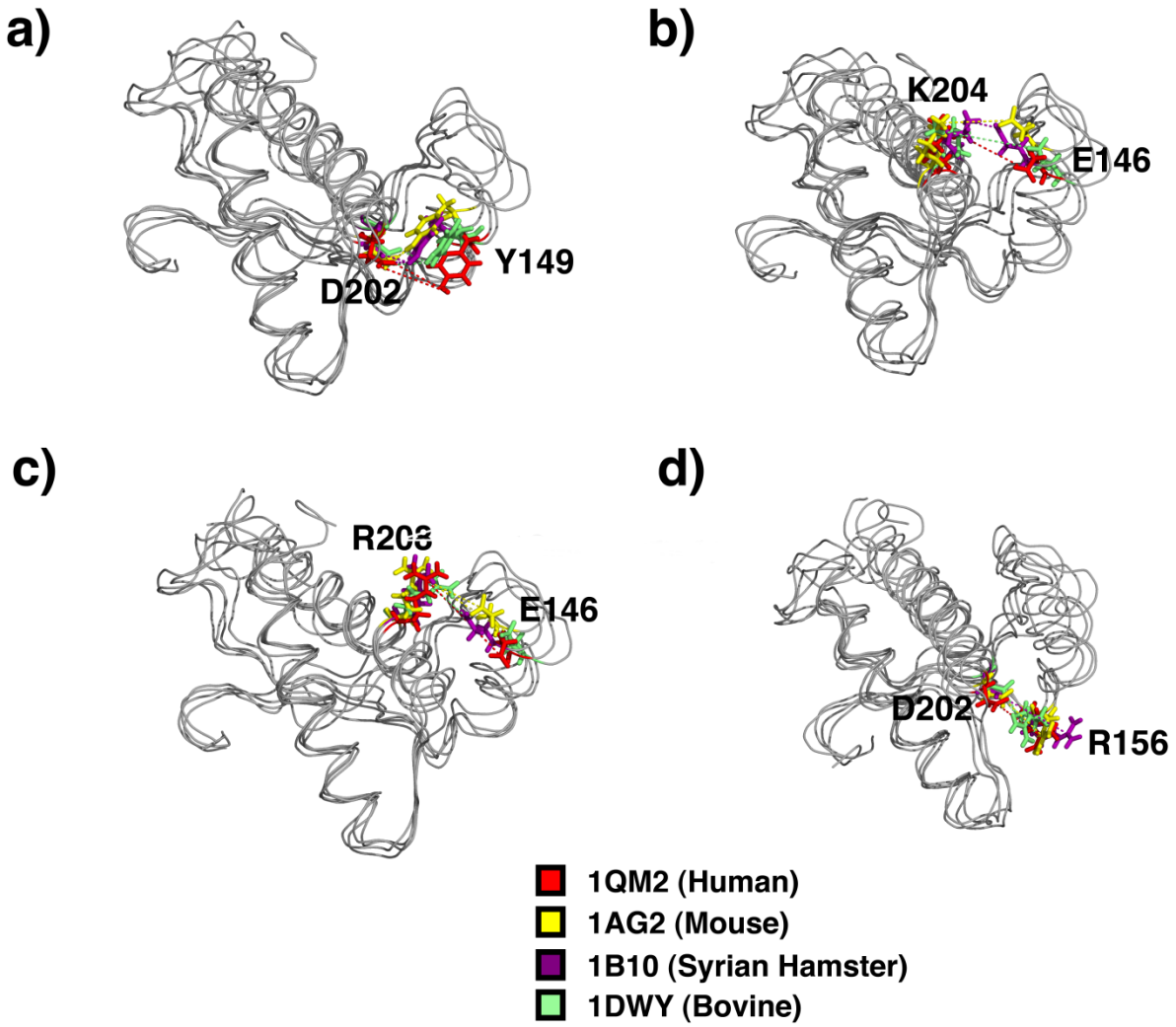


**Figure S2.** Interactions between H1 and H3, in the superimposed structures of prion protein from four different species: Human, Mouse, Syrian Hamster and Bovine PrP. The interactions include hydrogen bond (a) Y149-D202 and salt-bridges (b) E146-K204, (c) E146-R208 and (d) R156-D202. The residues involved are represented as sticks, with the color for each structure given as legend. The superimposed structures are rendered as ribbon in grey.

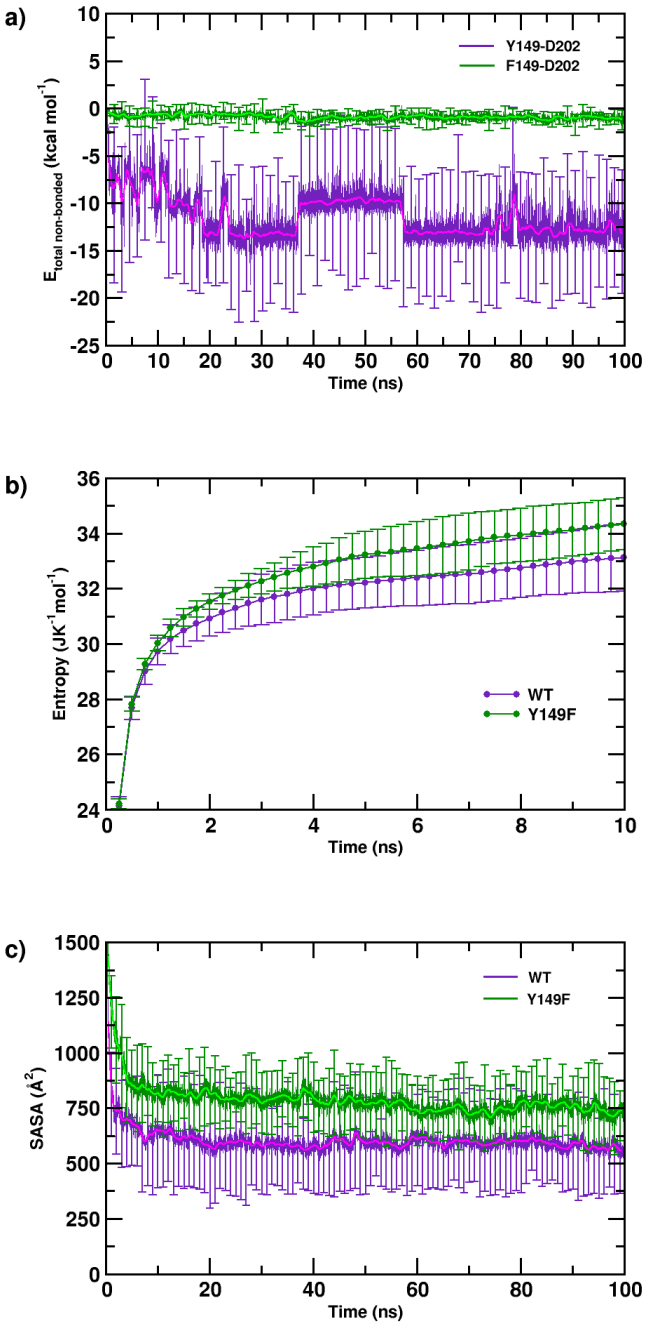


**Figure S3.** (a) Mean interaction energy strength between residues Y149-D202 in WT and F149-D202 in Y149F system, as a function of simulation time. (b) Cumulative configurational entropy per $C_\alpha$ atom of the WT and Y149F systems, averaged over the five trajectories of each system. (c) Mean SASA of the hydrophobic core residues, calculated over simulation time. The standard deviations show the spread of the values among multiple trajectories.

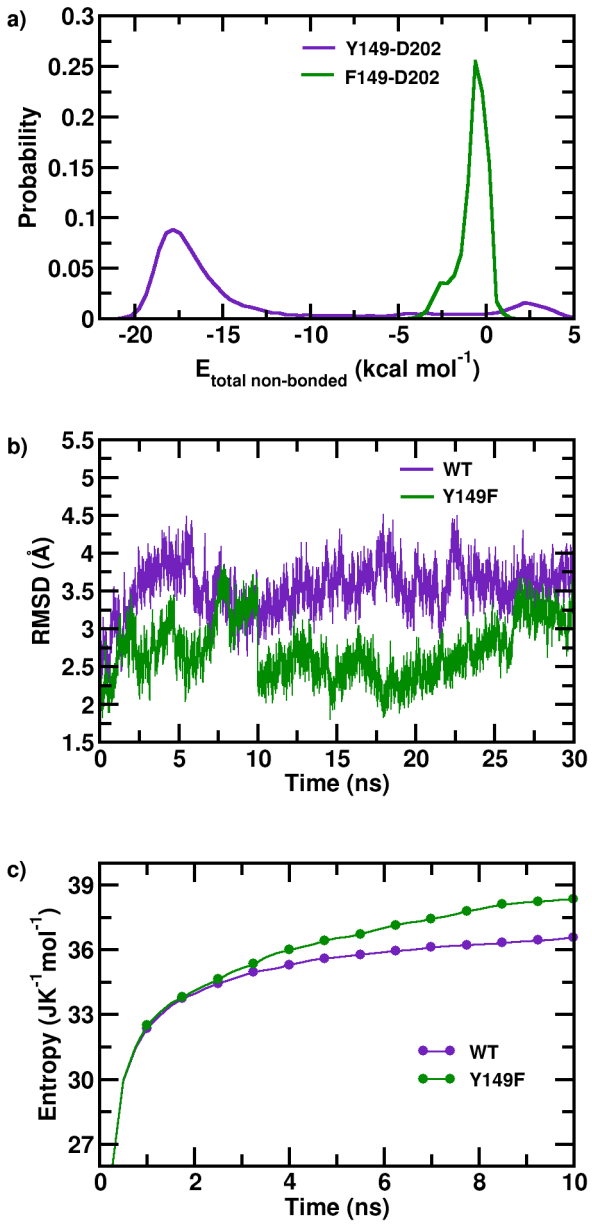


**Figure S4.** Control simulation, using the AMBER force field. (a) Probability distributions of interaction energy strength between residues Y149-D202 in WT and F149-D202 in Y149F system. (b) Backbone RMS deviations from the starting structure as a function of simulation time (c) Cumulative configurational entropy per $C_\alpha$ atom of the WT and Y149F systems.

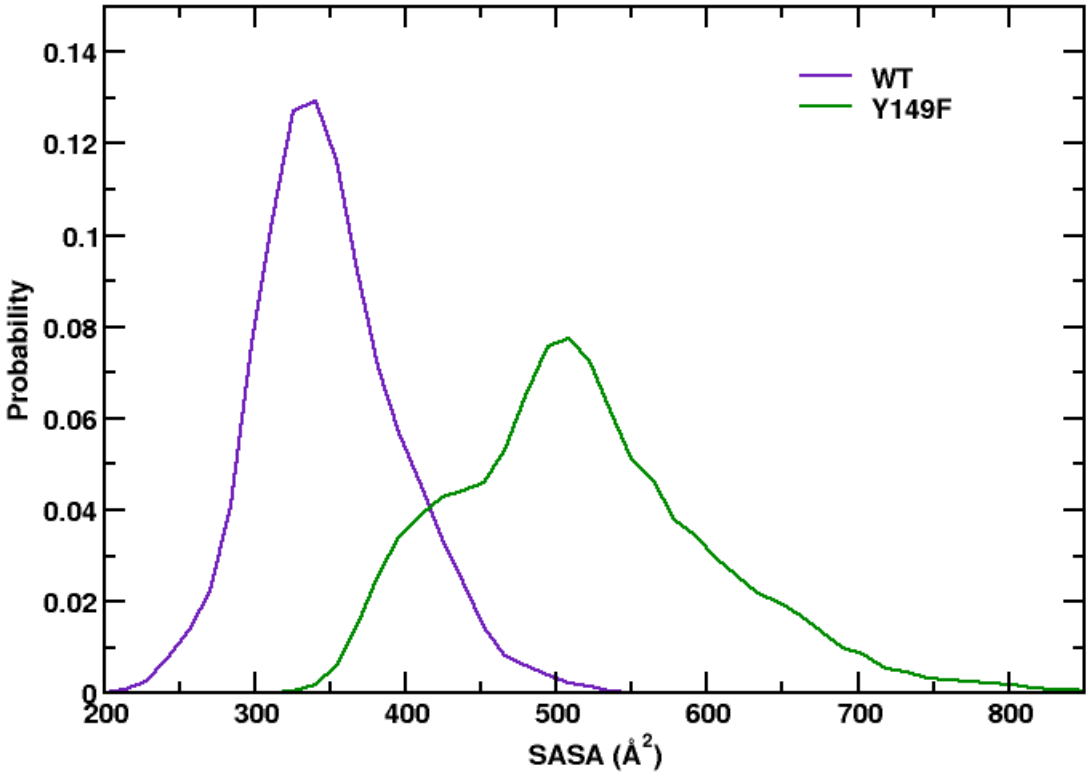


**Figure S5.** Probability distributions of SASA of hydrophobic core residues calculated from the AMBER simulations.

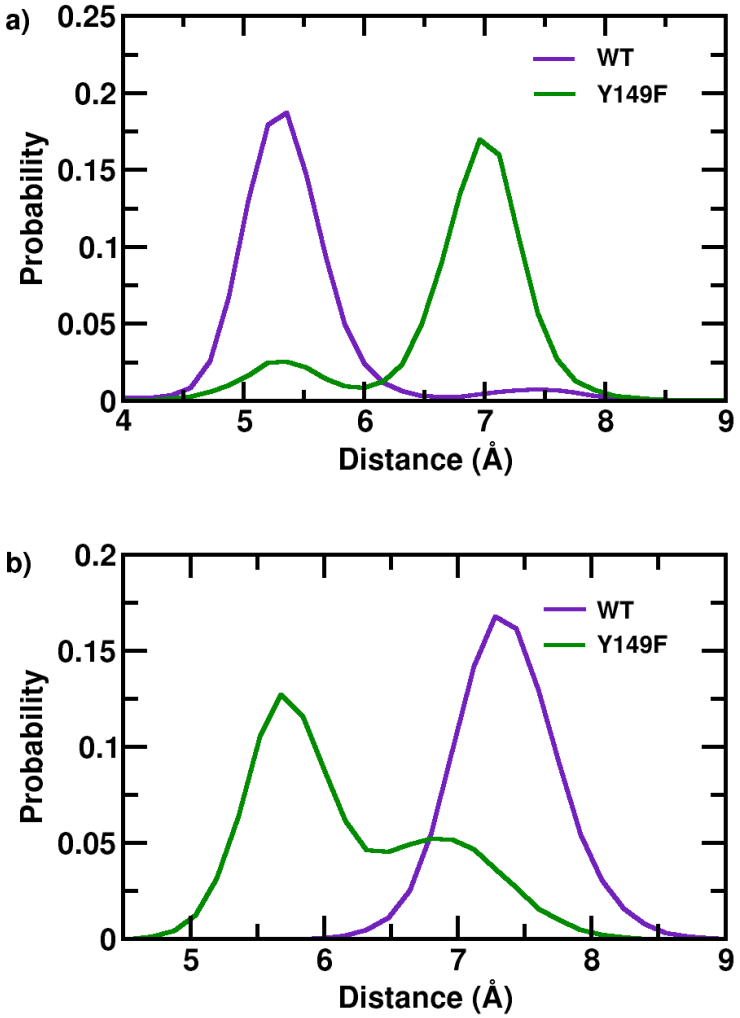


**Figure S6.** Probability distance distributions of atoms (a) S132:O - V161:N and (b) F175:O - R164:N belonging to hydration Site 1 and Site 2, respectively.

| PDB ID | 1QM2 | 1AG2 | 1B10 | 1DWY |
|---|---|---|---|---|
| **1QM2** | - | 2.612 | 2.156 | 1.371 |
| **1AG2** | 80.73 | - | 2.065 | 2.007 |
| **1B10** | 85.58 | 86.11 | - | 1.614 |
| **1DWY** | 91.43 | 83.33 | 86.67 | - |

**Table S1.** Structural superimposition of mammalian prion proteins of four species 1QM2: Human, 1AG2: Mouse, 1B10: Syrian Hamster, 1DWY: Bovine PrP. The upper triangular half of the matrix is RMSD (Å) and the lower triangular half is percent identity among pairwise PrP structures.

| PDB ID | Distance (Å) | | | | | |
|---|---|---|---|---|---|---|
| | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_5$ | $d_6$ |
| **1QM2** | 5.96 | 1.7 | 2.8 | 10.2 | 10.9 | 8.4 |
| **1AG2** | 1.62 | 1.7 | 2.6 | 7.1 | 8.2 | 7.1 |
| **1B10** | 1.52 | 5.2 | 2.4 | 3.0 | 5.9 | 9.2 |
| **1DWY** | 4.65 | 1.7 | 3.8 | 10.3 | 7.8 | 3.6 |

**Table S2.** Inter-residue distances of charged interactions in different mammalian prion proteins.

$d_1$ : Y149-D202 $d_4$ : E146-K204

$d_2$ : Y150-P137 $d_5$ : E146-R208

$d_3$ : N153-Y149 $d_6$ : R156-D202