Supporting Information

Structural dynamics of wild-type p53 DNA-binding domain and hotspot mutants reveal oncogenic conformational shifts

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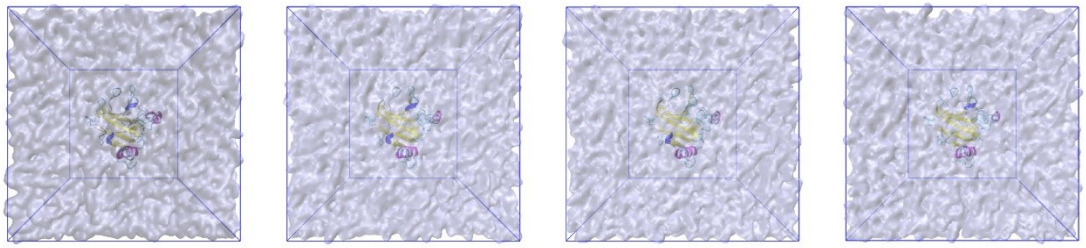

Fig. S1 Initial states of simulated systems. p53DBD molecules are drawn in New Cartoon method and secondary structures in different colors. Water solution is drawn in Quick Surface method.

Table S1 Simulation details of different systems

Simulated system	Box size (nm^3)	Simulation duration	Number of atoms
p53DBD-wt	8.57 × 8.57 × 8.57	1 μs × 10	61670
p53DBD-R273H	8.57 × 8.57 × 8.57	0.3 μs × 10	61659
p53DBD-R273C	8.57 × 8.57 × 8.57	0.3 μs × 10	61656
p53DBD-R175H	8.58 × 8.58 × 8.58	0.3 μs × 10	61680

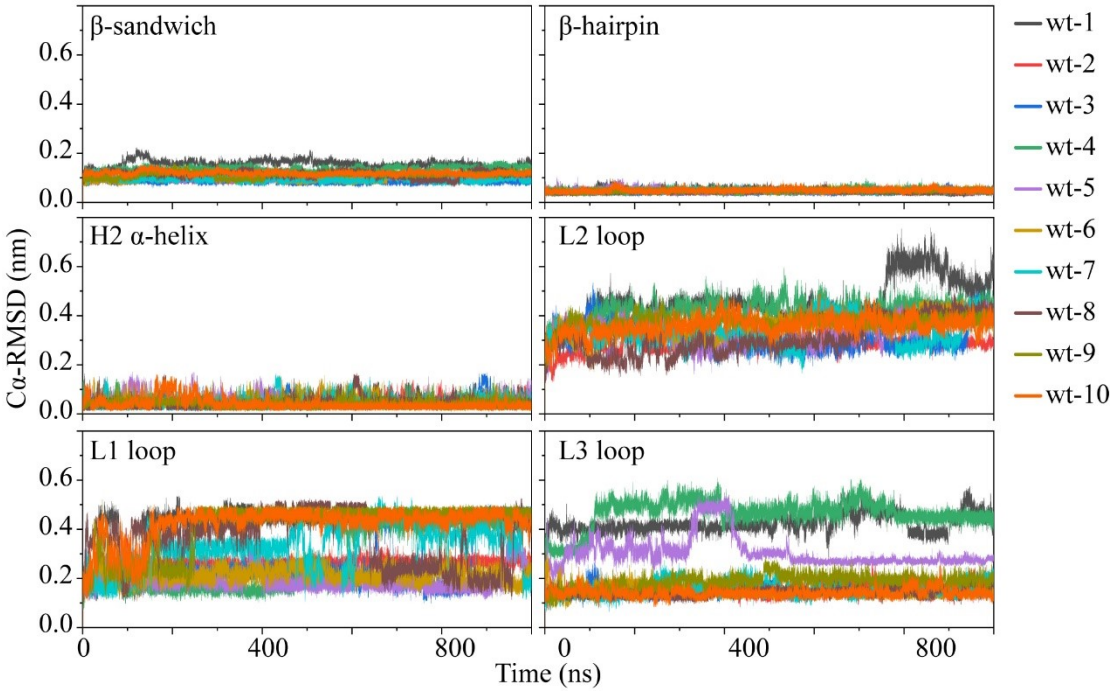

Fig. S2 Cα-RMSD of different fragments in p53DBD-wt system. Curves representing different trajectories are colored differently.

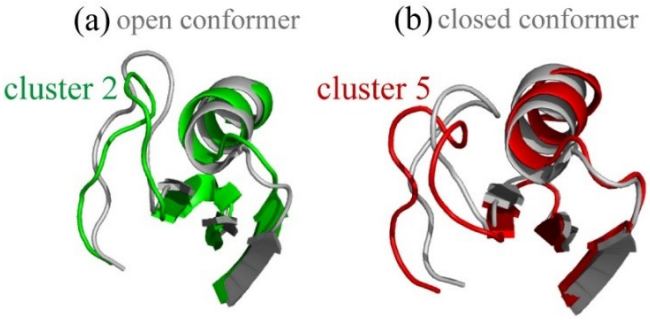

Fig. S3 The alignment of cluster 2 with the open conformer (a) and the alignment of cluster 5 with the closed conformer (b) in the crystal structure 2FEJ (grey) based on the Cα atoms of LSH motif.

Table S2 Contact numbers between A119-P278 sidechains and V122-P278 sidechains in top six clusters of p53DBD-wt

	V122-P278	A119-P278
cluster 1	0.1±1.5	0.0±0.0
cluster 2	36.9±15.9	0.0±0.1
cluster 3	60.1±14.3	0.0±0.0
cluster 4	5.6±5.8	0.0±0.0
cluster 5	18.4±16.9	20.6±12.4
cluster 6	22.8±17.8	0.0±0.0

Table S3 Mean and standard deviation of Cα-RMSD of H2 region over the entire 1.0 μs time duration in all the ten trajectories of the WT system.

Trajectory	Average of RMSD (nm)	Standard Deviation of RMSD (nm)	Trajectory	Average of RMSD (nm)	Standard Deviation of RMSD (nm)
wt-1	0.0512	0.01854	wt-6	0.04599	0.01958
wt-2	0.04584	0.01668	wt-7	0.04474	0.01897
wt-3	0.05087	0.01788	wt-8	0.04432	0.01835
wt-4	0.04494	0.01638	wt-9	0.04105	0.01319
wt-5	0.05366	0.02048	wt-10	0.04112	0.02219

Table S4 Mean and standard deviation of Cα-RMSD' of H2 region over the entire 1.0 μs time duration in all the ten trajectories of the WT system.

Trajectory	Average of RMSD′ (nm)	Standard Deviation of RMSD′ (nm)	Trajectory	Average of RMSD′ (nm)	Standard Deviation of RMSD′ (nm)
wt-1	0.17862	0.04349	wt-6	0.1971	0.04641
wt-2	0.18867	0.03705	wt-7	0.1977	0.04331
wt-3	0.19984	0.04451	wt-8	0.19141	0.04600
wt-4	0.15323	0.03920	wt-9	0.18514	0.03726
wt-5	0.16968	0.04300	wt-10	0.20171	0.04629

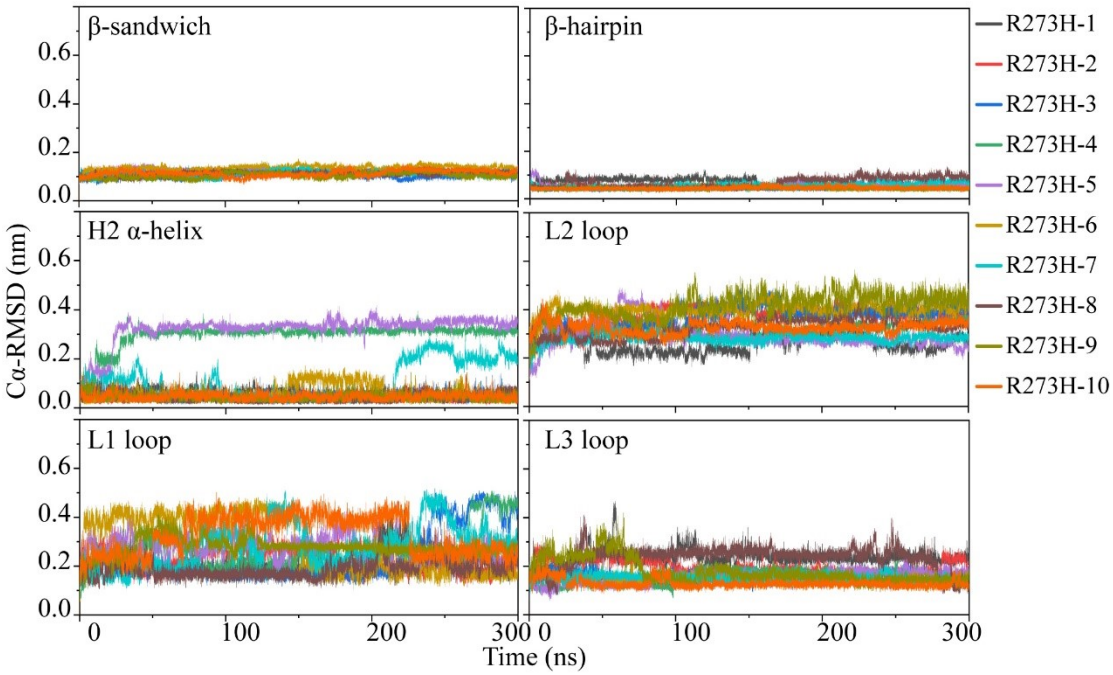

Fig. S4 Cα-RMSD of different fragments in p53DBD-R273H system. Curves representing different trajectories are colored differently.

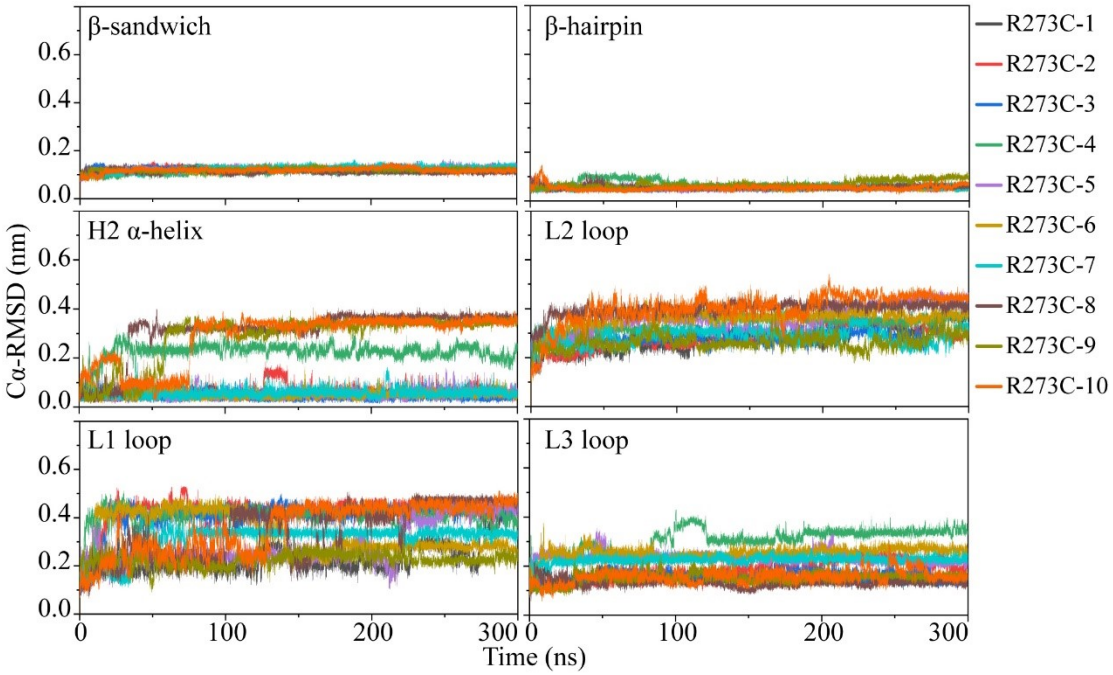

Fig. S5 Cα-RMSD of different fragments in p53DBD-R273C system. Curves representing different trajectories are colored differently.

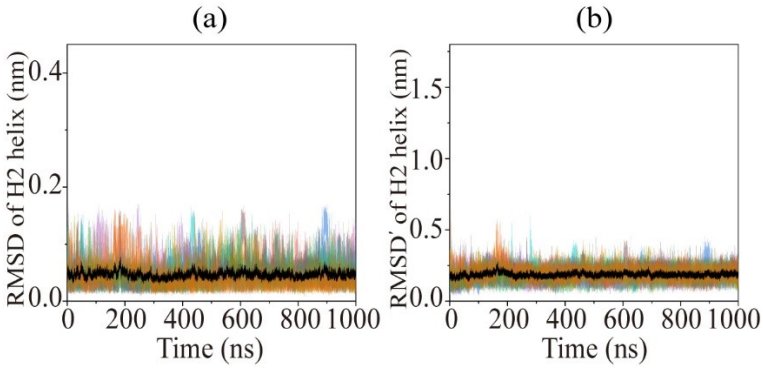

Fig. S6 (a) Time evolutions of Cα-RMSD of H2 region for the WT system after least square fitting with the Cα atoms of H2 region. (b) Time evolutions of Cα-RMSD' of H2 region for the WT system after least square fitting with the Cα atoms of β-hairpin. The ranges of y-axis are consistent with those in the main text.

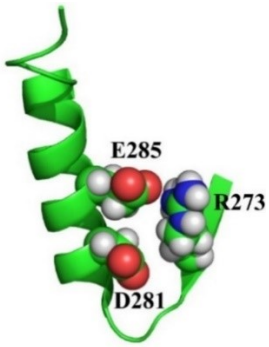

Fig. S7 Representative snapshot of the salt bridge formed by positively charged R273 and negatively charged D281 or E285 in the H2 region for the WT system.

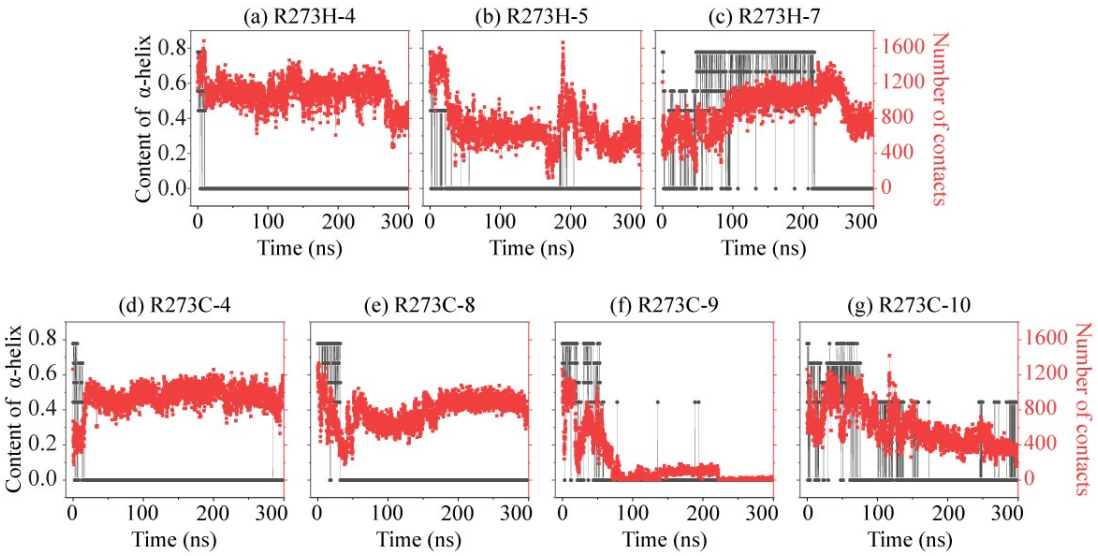

Fig. S8 Content of α-helix in the H2 region and number of contacts between H2 and β-sheet in LSH motif as a function of time for the R273H* and R273C* systems.

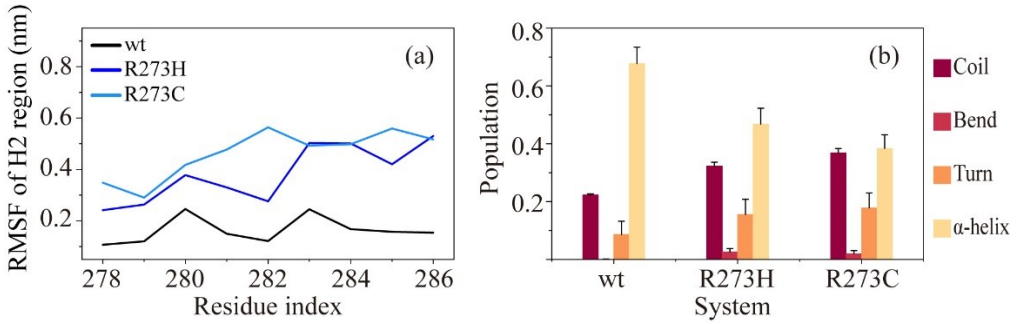

Fig. S9 (a) Residue-based RMSF of H2 region in p53DBD-wt, R273H and R273C systems. (b) Population of different secondary structures for H2 region in final states of the p53DBD-wt, R273H and R273C systems.

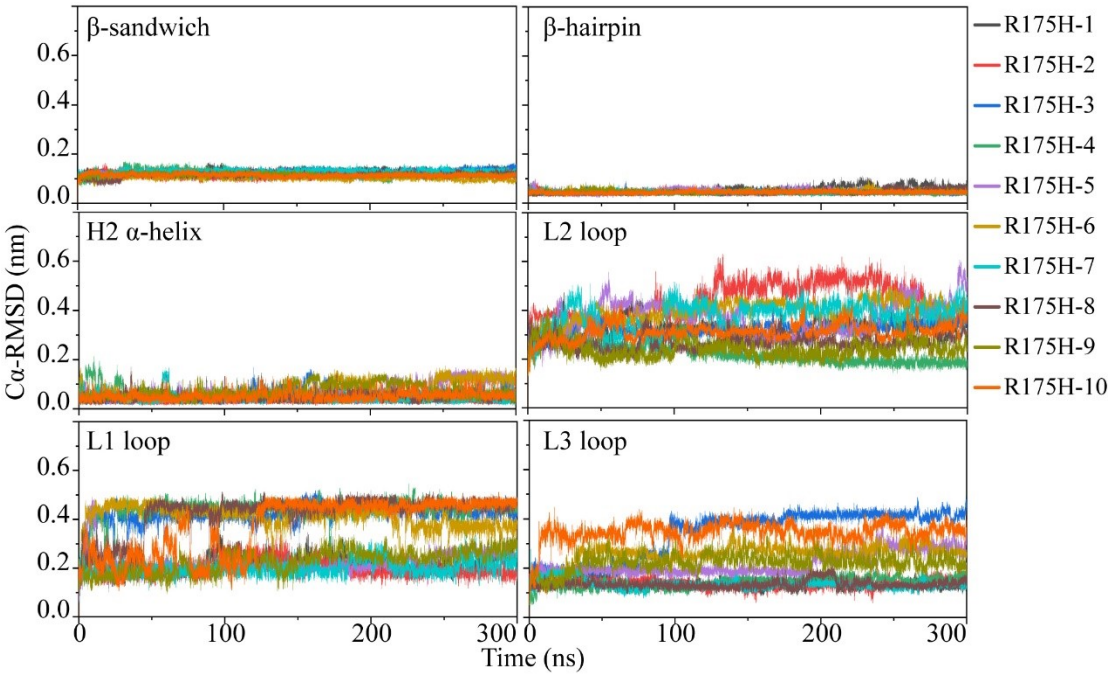

Fig. S10 Cα-RMSD of different fragments in p53DBD-R175H system. Curves representing different trajectories are colored differently.

Table S5 Gibbs free energy (kcal/mol) between individual residues from residue 176-179 and residue 238-242 (corresponding to the region of zinc ion ligands)

System	ΔE_{vdW}	ΔE_{elec}	ΔG_{apol}	ΔG_{pol}	ΔG_{total}
wt	−0.55±0.54	0.98±0.76	1.29±0.08	−16.75±1.11	−15.03±1.12
R175H	−1.23±0.61	−0.67±1.03	1.33±0.08	−16.91±1.06	−17.47±1.20