Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Common cancer mutations R175H and R273H drive p53 DNA-binding domain towards aggregation-prone conformations

Le Li, Xuhua Li, Yiming Tang, Zenghui Lao, Jiangtao Lei and Guanghong Wei*

Department of Physics, State Key Laboratory of Surface Physics, and Key Laboratory for Computational Physical Sciences (Ministry of Education), Multiscale Research Institute of Complex Systems, Fudan University, Shanghai 200438, People's Republic of China.

This supporting material contains one supplemental table and eight supplemental figures (Figs. S1-S8).

Table 1. The values of distance and the force constant between Zn^{2+} ion and the four coordinated atoms.

Residue	r_0 (nm)	r_1 (nm)	r_2 (nm)	Force constant kcal/mol·Å^2
C176	0.135	0.335	1.335	60
C238	0.140	0.340	1.340	60
C242	0.141	0.341	1.341	60
H179	0.133	0.333	1.333	26

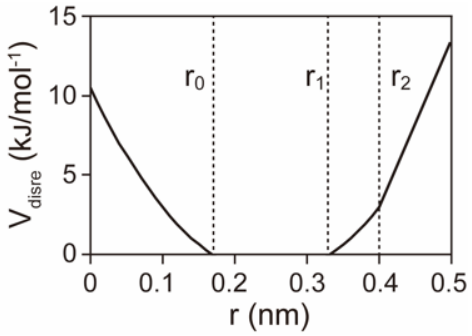

Fig. S1 The distance restraint potential for Zn^{2+} ion.

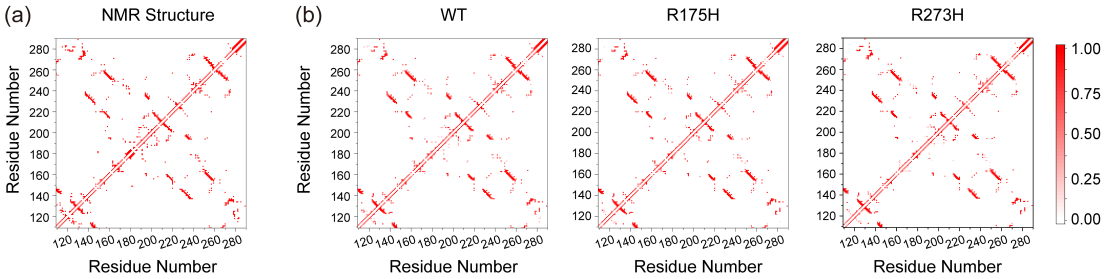

Fig. S2 Comparison of native residue contacts in WT p53C with those in R175H and R273H mutants. The residue contacts in NMR structure are defined as native contacts. (a) Native residue contacts in NMR structure, where red dots represent the residue pairs that have atomic contacts in NMR structure. (b) The native contact probability maps of WT, R175H and R273H mutants calculated using simulation data (the last 160 ns data were used for MD-2 and MD-3 of R273H mutant as the simulation reached equilibrium after t=440 ns). The contact pattern in WT is quite similar to that in NMR structure, indicating CHARMM force field is suitable for p53C.

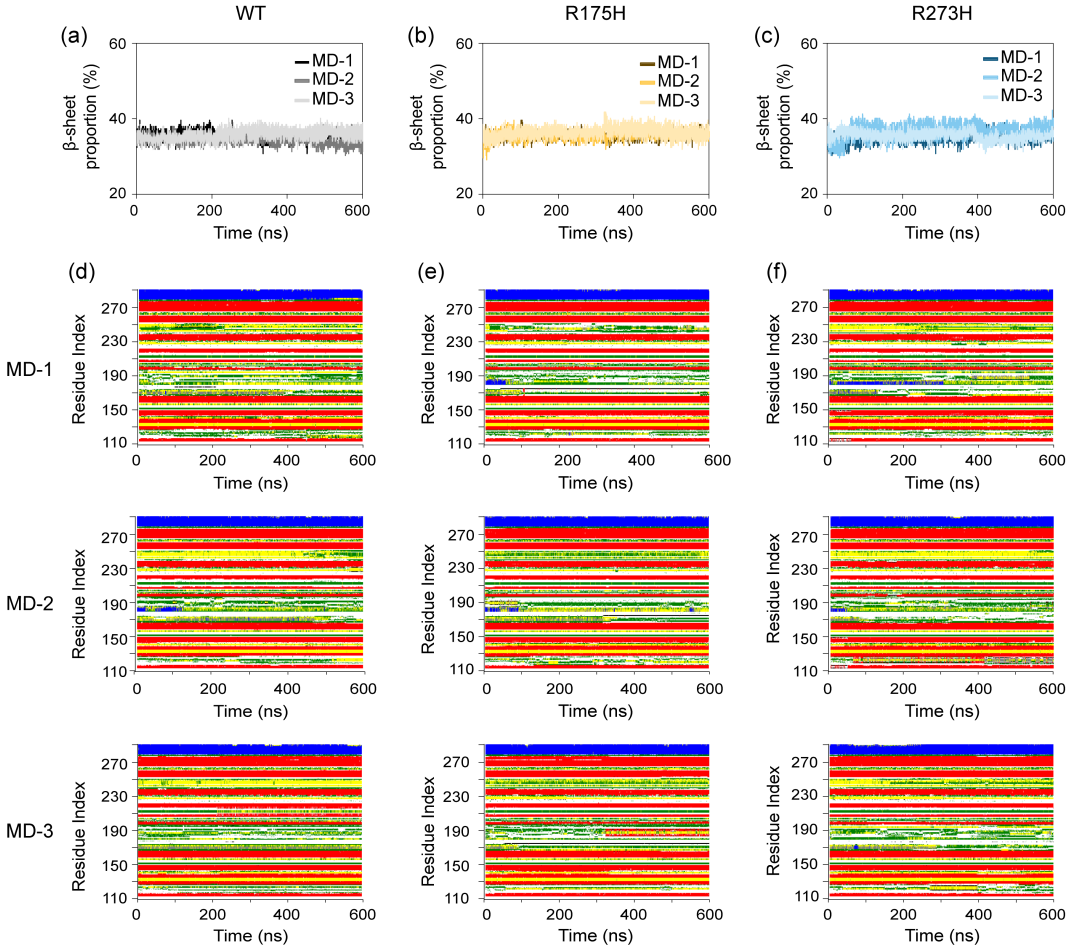

Fig. S3 The effect of R175H and R273H mutations on the secondary structure of p53 DBD. The time evolution of the proportion of β-sheet of (a) WT, (b) R175H mutant and (c) R273H mutant. Secondary structure profiles of (d) WT, (e) R175H mutant and (f) R273H mutant.

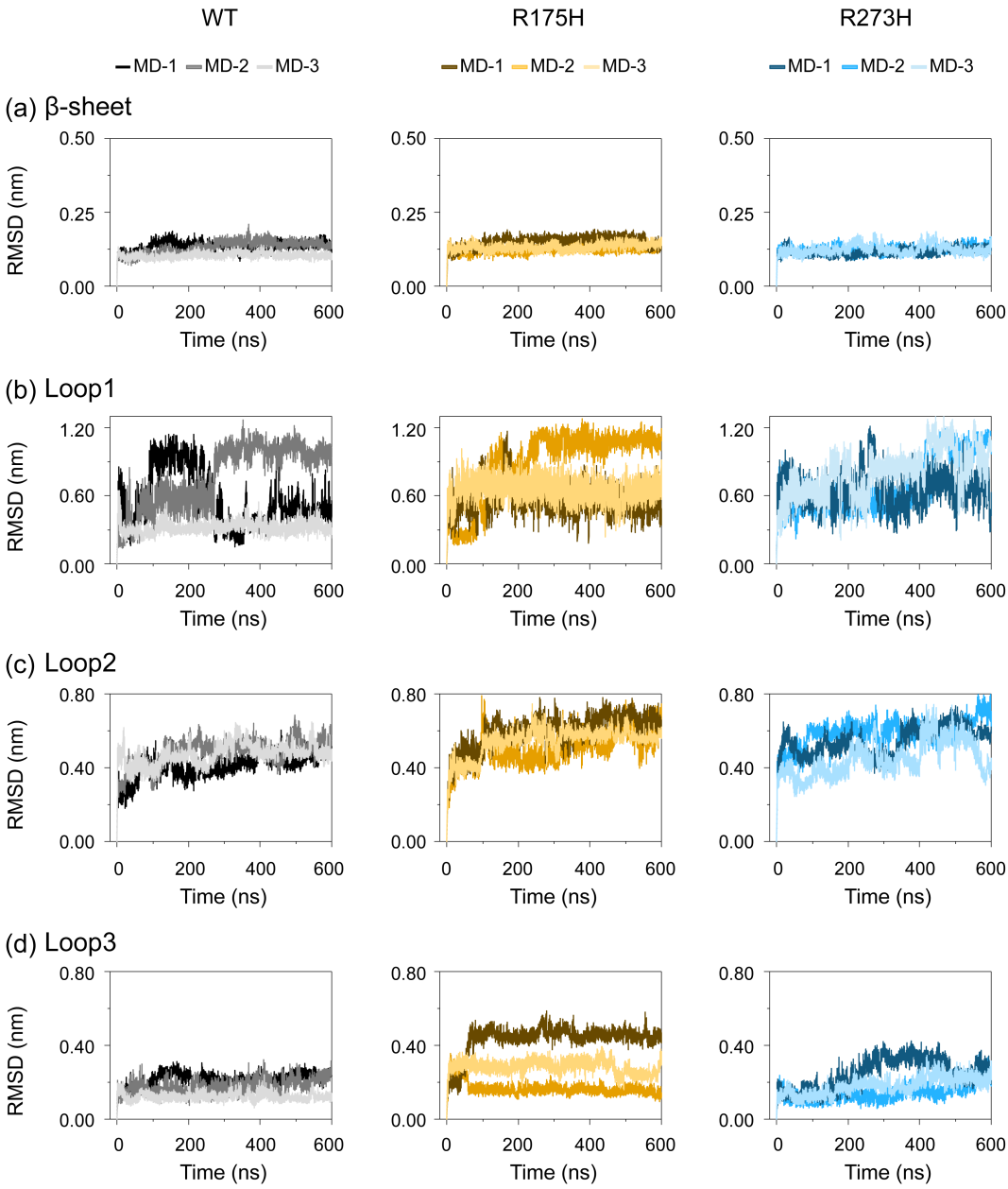

Fig. S4 Time evolution of root-mean-square-deviation (RMSD) values of the following regions relative to their initial conformation: (a) β-sheet, (b) loop1, (c) loop2, and (d) loop3 for each system.

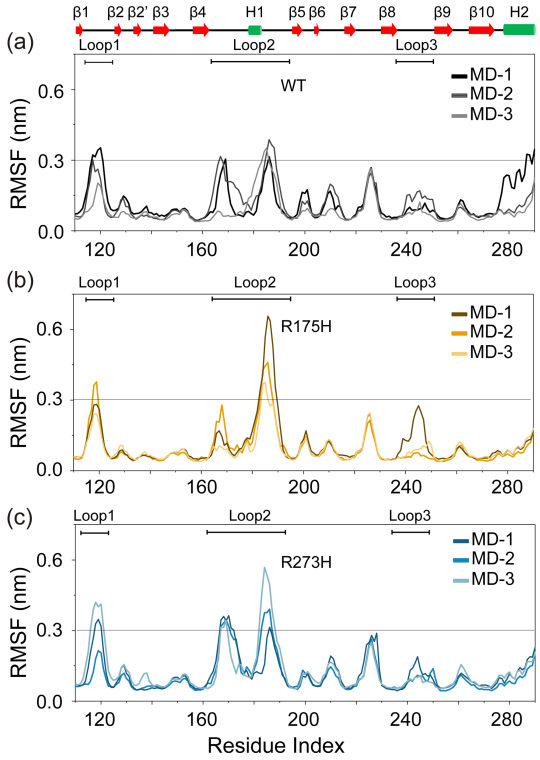

Fig. S5 Root-mean-square-fluctuation (RMSF) of (a) WT, (b) R175H mutant and (c) R273H mutant for each of the three MD runs (the last 160 ns data were used for MD-2 and MD-3 of R273H mutant as the simulation reached equilibrium after t=440 ns).

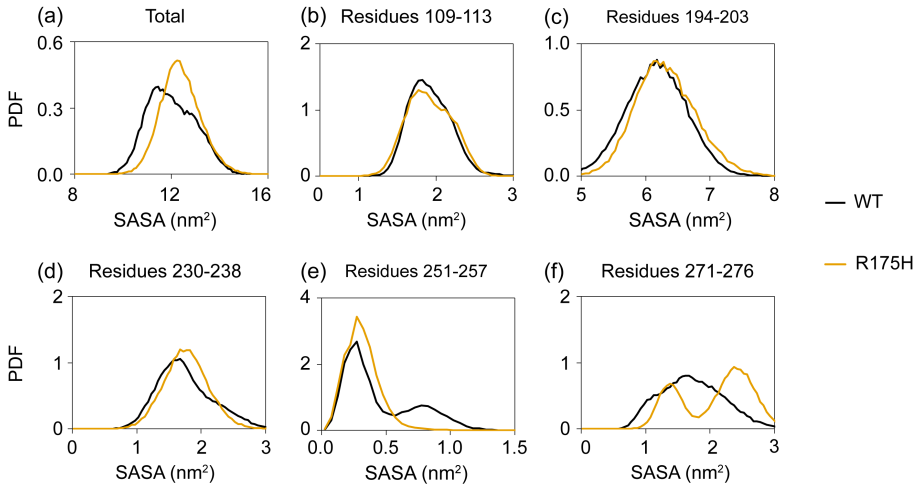

Fig. S6 The effect of mutation R175H on solvent exposure of five effective amyloidogenic sequences (including residues 109-113, 194-203, 230-238, 251-257 and 271-276). Probability density function (PDF) of (a) total SASA of the five amyloidogenic sequences and SASA of each individual amyloidogenic sequence: (b) residues 109-113, (c) residues 194-203, (d) residues 230-238, (e) residues 251-257, and (f) residues 271-276. All the results are obtained using the data from the three MD simulations (the last 160 ns data were used for MD-2 and MD-3 of R273H mutant as the simulation reached equilibrium after t=440 ns).

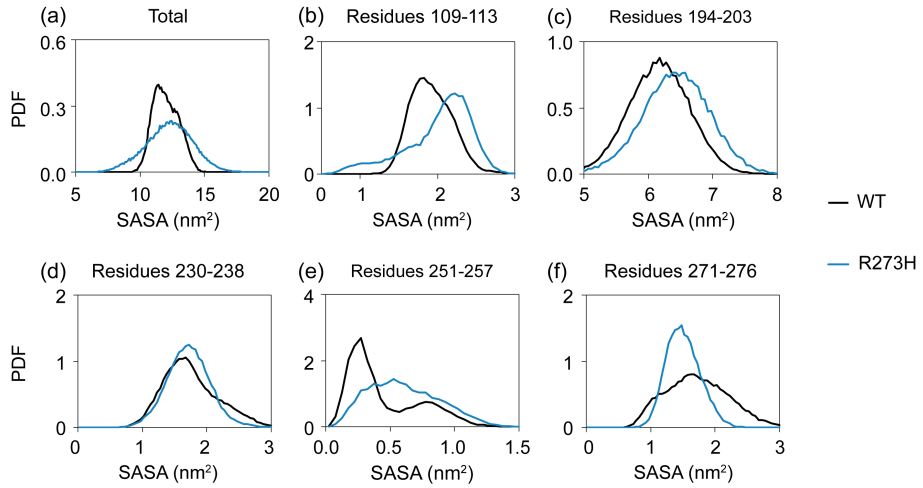

Fig. S7 The effect of mutation R273H on solvent exposure of five effective amyloidogenic sequences (including residues 109-113, 194-203, 230-238, 251-257 and 271-276). Probability density function (PDF) of (a) total SASA of the five amyloidogenic sequences and SASA of each individual amyloidogenic sequence: (b) residues 109-113, (c) residues 194-203, (d) residues 230-238, (e) residues 251-257, and (f) residues 271-276. All the results are obtained using the data from the three MD simulations (the last 160 ns data were used for MD-2 and MD-3 of R273H mutant as the simulation reached equilibrium after t=440 ns).

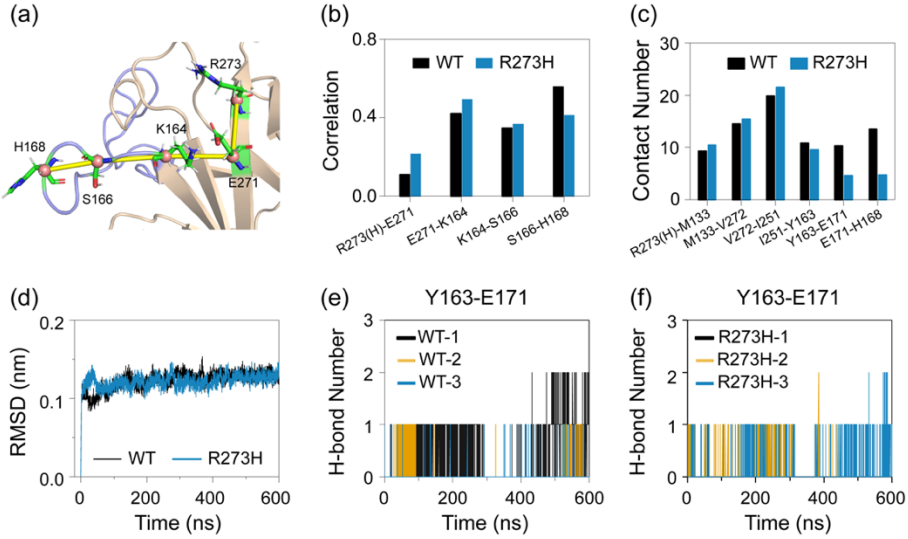

Fig. S8 The Dynamical Network Analysis of optimal allosteric path from R273 to H168 in WT p53 and R273H mutant. (a) The snapshot of WT p53 showing the optimal allosteric path from R273 to H168. (b) Correlation values of four residue pairs involved in the optimal path. (c) Contact number of six residue pairs involved in the sub-optimal path in WT p53 and R273H mutant. (d) The average backbone Root-mean-square-deviation (RMSD) of β-sheet relative to its initial conformation in WT and R273H mutant. The time evolution of H-bond number of Y163-E171 in (e) WT p53 and (f) R273H mutant. All the results are obtained using the data from the three MD simulations.