# Supporting Information

# Conformational dynamics and allosteric effect modulated by the unique zinc-binding motif in class IIa HDACs

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**Table S1.** The computational models and simulation time.

| Simulation Model | Time（ns） | Simulation Model | Time（ns） |
|---|---|---|---|
| HDAC4-WT | 1000ns | HDAC4-C669A/H675A | 1000ns |
| HDAC7-WT | 1000ns | HDAC7-C535A/H541A | 1000ns |
| HDAC4-WT-SMRT | 1000ns | HDAC4-C669A/H675A-SMRT | 1000ns |
| HDAC1-WT | 500ns | HDAC1-Y24A/H28A | 500ns |
| HDAC1-Y24A | 250ns | HDAC1-H28A | 250ns |
| HDAC1-WT-SAHA | 500ns | HDAC1-Y24A/H28A-SAHA | 500ns |
| HDAC2-WT | 500ns | HDAC2-Y29A/H33A | 500ns |
| HDAC2-WT-SAHA | 500ns | HDAC2-Y29A/H33A-SAHA | 500ns |
| HDAC3-WT | 700ns | HDAC3-Y18A/H22A | 500ns |
| HDAC3-WT-SAHA | 500ns | HDAC3-Y18A/H22A-SAHA | 500ns |

**Table S2.** The hydrogen bond analysis for Loop2 in HDAC4 and HDAC7 models.

| Model | Acceptor | Donor H | Donor | Distance (Å) | Occupancy (%) |
|---|---|---|---|---|---|
| HDAC4-WT | Glu764@OE1 | Arg730@HH12 | Arg730@NH1 | 2.8418 | 55.23 |
| | Glu764@OE2 | Arg730@HH22 | Arg730@NH2 | 2.8415 | 54.88 |
| | Glu764@OE2 | Trp762@HE1 | Trp762@NE1 | 2.8790 | 38.21 |
| | Glu764@OE1 | Arg730@HH22 | Arg730@NH2 | 2.8532 | 9.56 |
| | Glu764@OE2 | Arg730@HH12 | Arg730@NH1 | 2.8533 | 9.06 |
| | Glu764@OE1 | Trp762@HE1 | Trp762@NE1 | 2.8802 | 8.26 |
| HDAC7-WT | Glu631@OE2 | Arg611@HH22 | Arg611@NH2 | 2.8381 | 32.25 |
| | Glu631@OE1 | Arg611@HH22 | Arg611@NH2 | 2.8468 | 29.64 |
| | Glu631@OE1 | Arg611@HH12 | Arg611@NH1 | 2.8545 | 27.64 |
| | Glu631@OE2 | Arg611@HH12 | Arg611@NH1 | 2.8532 | 26.64 |
| | Glu631@OE1 | Trp629@HE1 | Trp629@NE1 | 2.8679 | 26.49 |
| | Glu631@OE2 | Trp629@HE1 | Trp629@NE1 | 2.8724 | 26.39 |
| HDAC4-C669A/H675A | Glu764@OE2 | Arg730@HH11 | Arg730@NH1 | 2.7916 | 81.50 |
| | Glu764@OE2 | Arg730@HH21 | Arg730@NH2 | 2.7878 | 57.66 |
| | Glu764@OE1 | Arg730@HH21 | Arg730@NH2 | 2.8081 | 35.43 |
| | Glu764@OE1 | Trp762@HE1 | Trp762@NE1 | 2.8445 | 24.52 |
| HDAC7-C535A/H541A | Glu631@OE2 | Arg611@HH22 | Arg611@NH2 | 2.8039 | 49.50 |
| | Glu631@OE1 | Arg611@HH22 | Arg611@NH2 | 2.8014 | 46.64 |
| | Glu631@OE2 | Arg611@HE | Arg611@NE | 2.8242 | 42.43 |
| | Glu631@OE1 | Arg611@HE | Arg611@NE | 2.8172 | 32.01 |
| | Glu631@OE1 | Trp629@HE1 | Trp629@NE1 | 2.8544 | 18.44 |
| | Glu631@OE2 | Trp629@HE1 | Trp629@NE1 | 2.8555 | 17.38 |

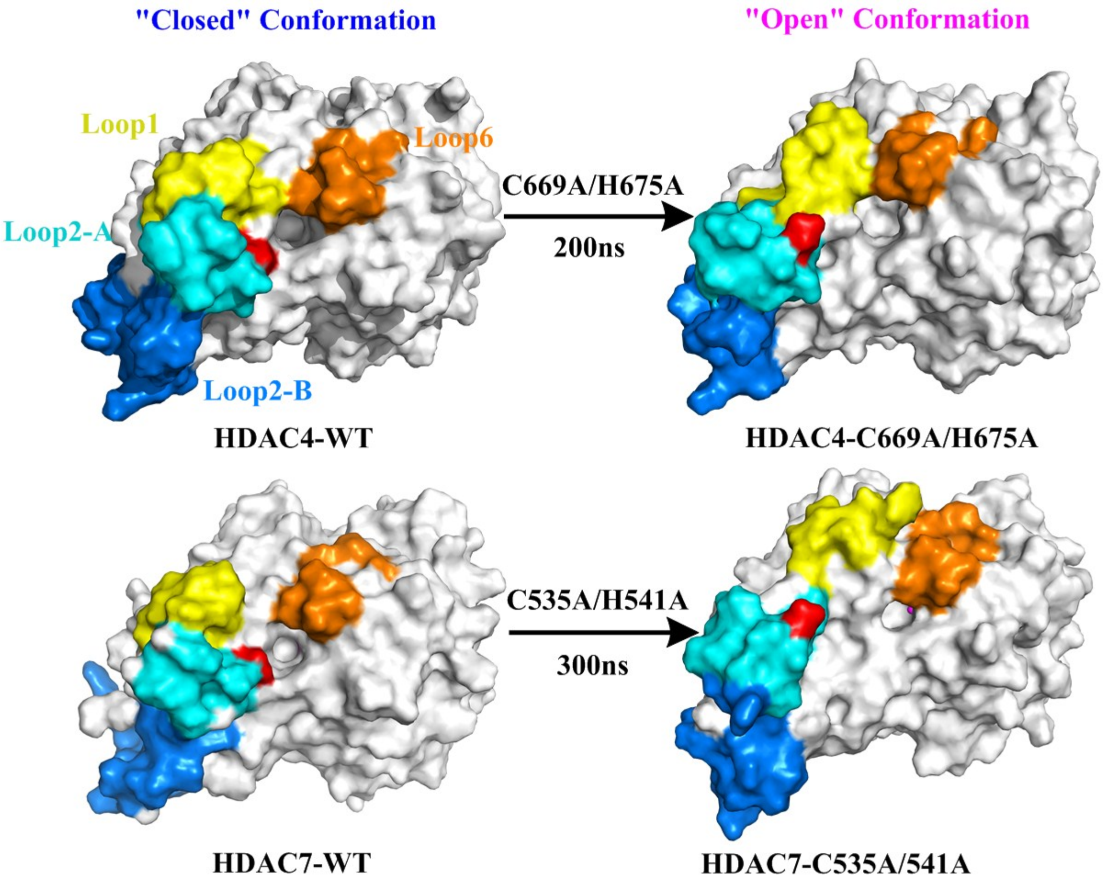
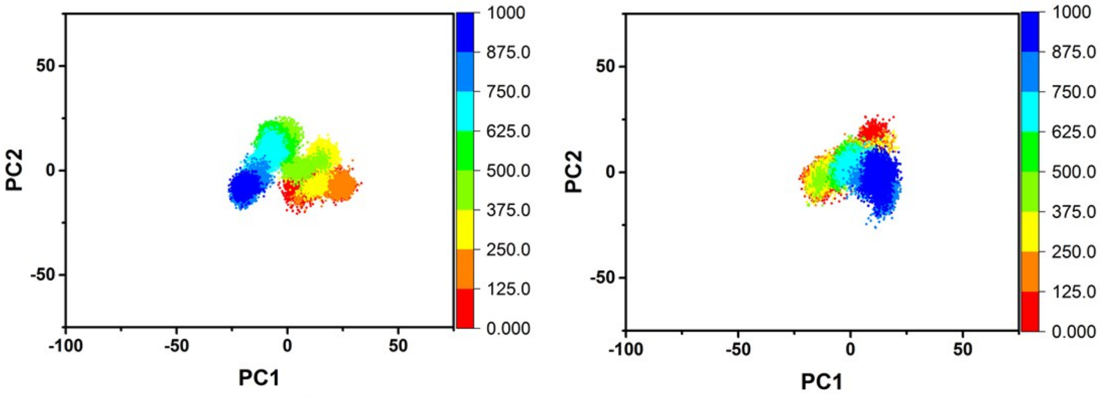
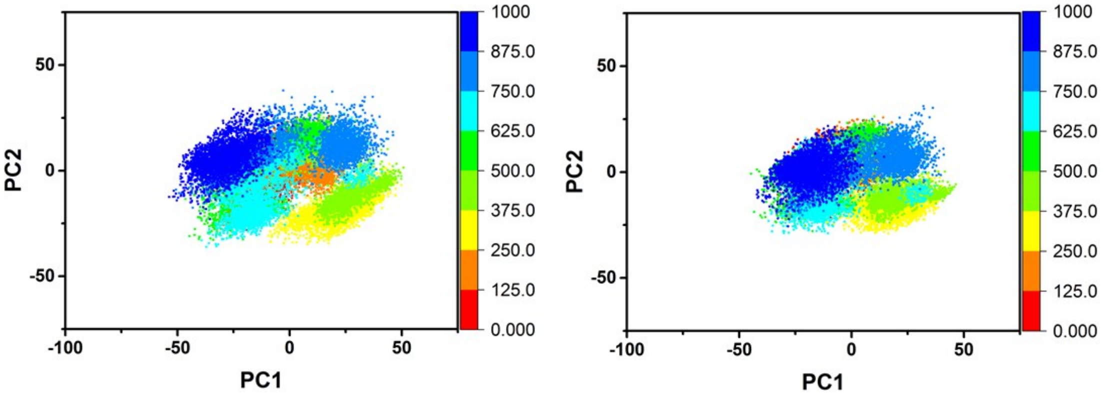


**Fig. S1** The surface maps of the wild type and mutant HDAC4/7. Loop1 is rendered in yellow, Loop2-A is rendered in cyan, Loop2-B is shown in blue, Loop6 is shown in orange, the Asp in binding rail is shown in red. Refer to Fig. 3 in main text.



**(a) HDAC4-WT** **(b) HDAC4-WT-Loop2**



**(c) HDAC7-WT** **(d) HDAC7-WT-Loop2**

**Fig. S2** The PCA analysis for the whole protein and Loop2 in wild type HDAC4 (a, b) and HDAC7 (c, d). As the Loop2-A is located by the second zinc ion, so the primary protein motion is coming from the wiggle of Loop2-B, but the motions of Loop2-B in HDAC7-WT model is more notable than HDAC4-WT model.

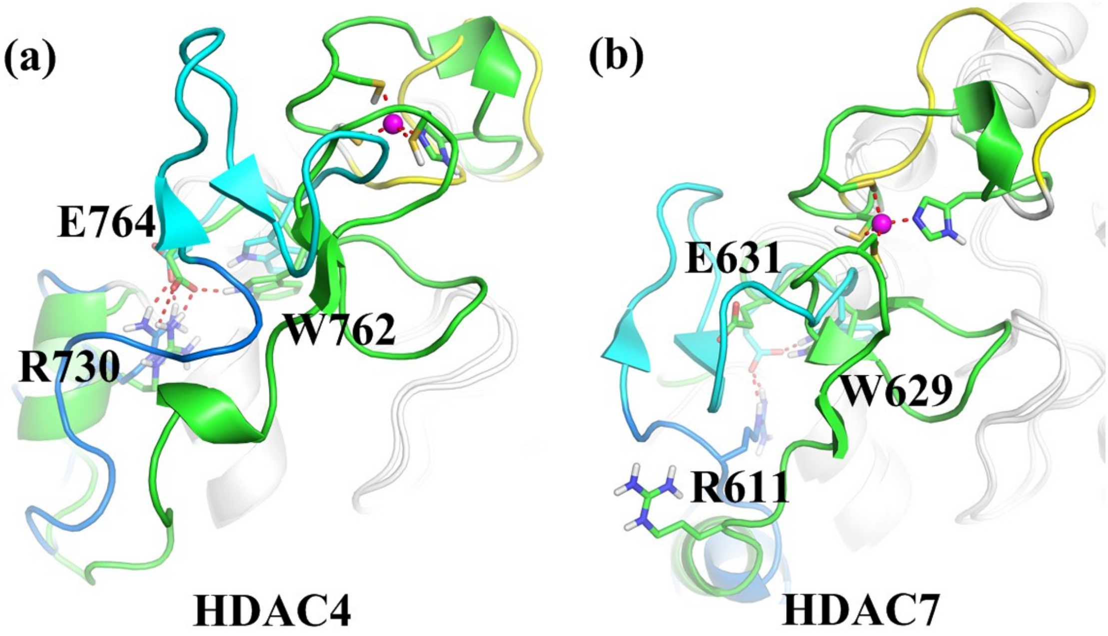


**Fig. S3** Superimposition of the mutant model ("open" conformation) and crystal structure ("closed" conformation) for HDAC4 (a) and HDAC7 (b). The crystal structure is shown in green, while in mutant models, the Loop1 is shown in yellow, the Loop2-A is shown in cyan, the Loop2-B is shown in blue.

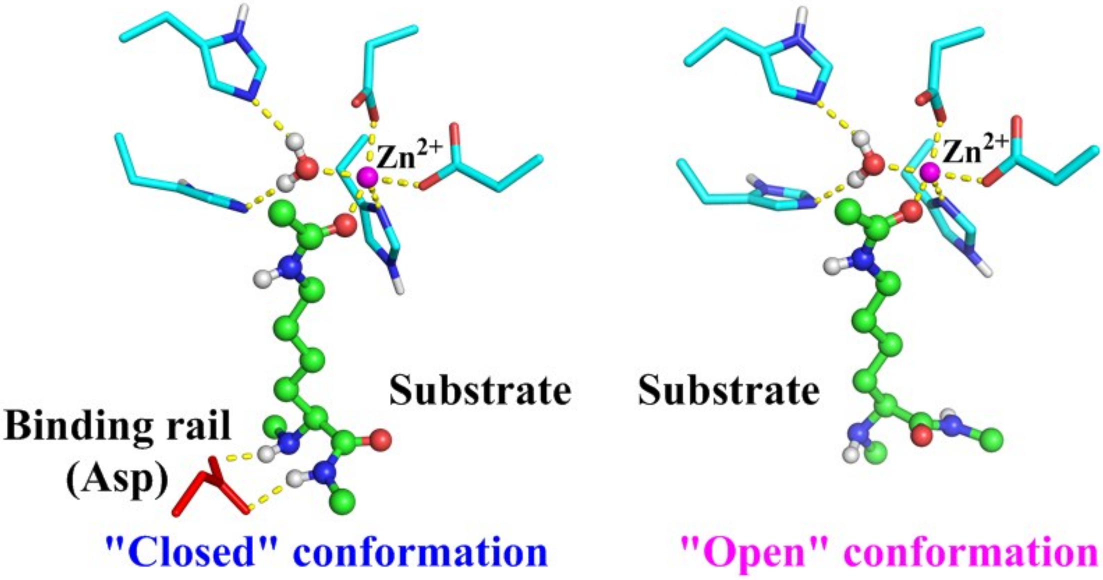


**Fig. S4** The representative binding modes of the substrate in class IIa HDACs. In the "open" conformation, the Asp residue will leave away from the substrate binding pocket to the solvent.

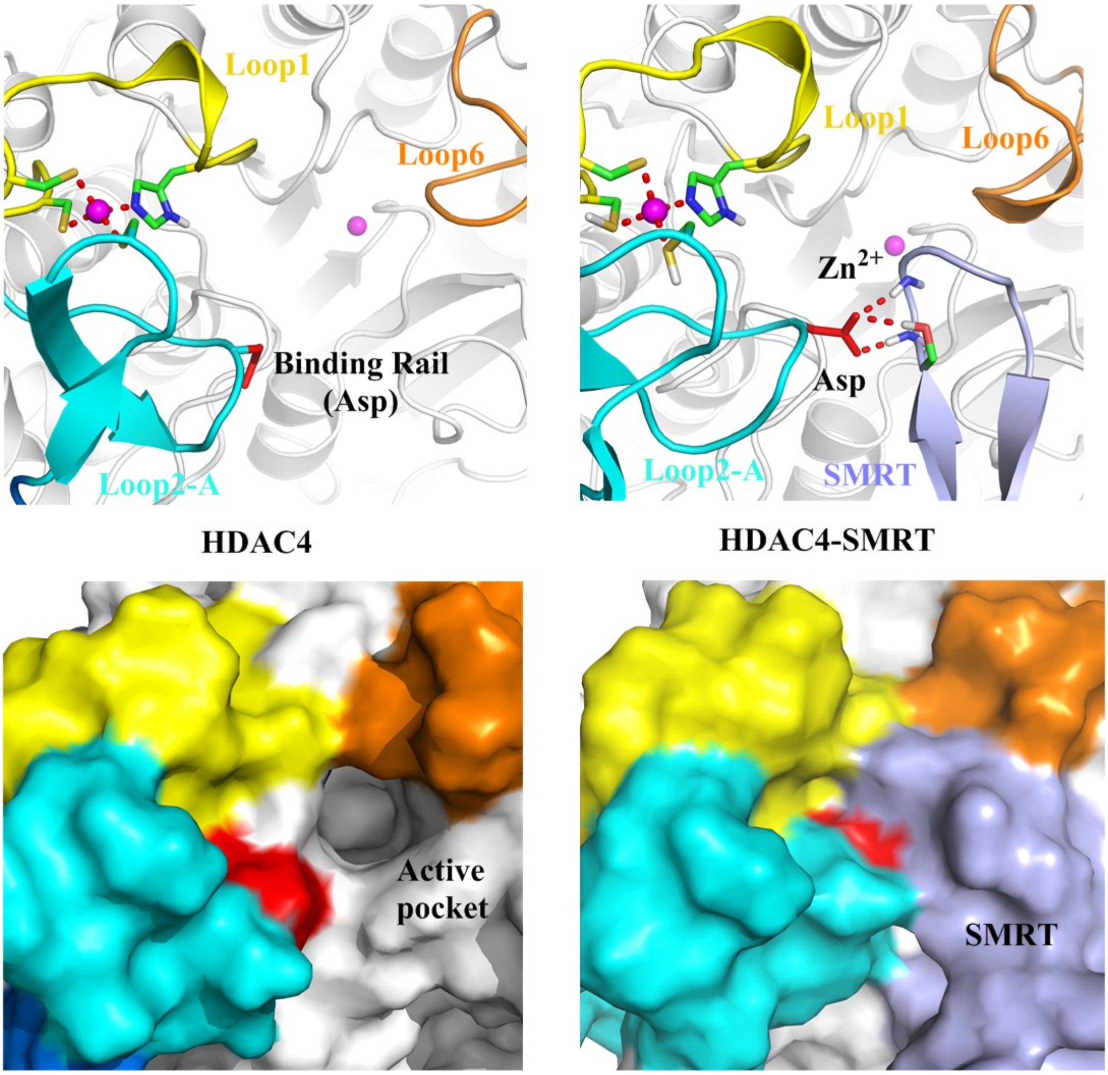


**Fig. S5** The crystal structure and surface map of HDAC4 (PDB code 4CBY) and HDAC4-SMRT (PDB code 5ZOP).

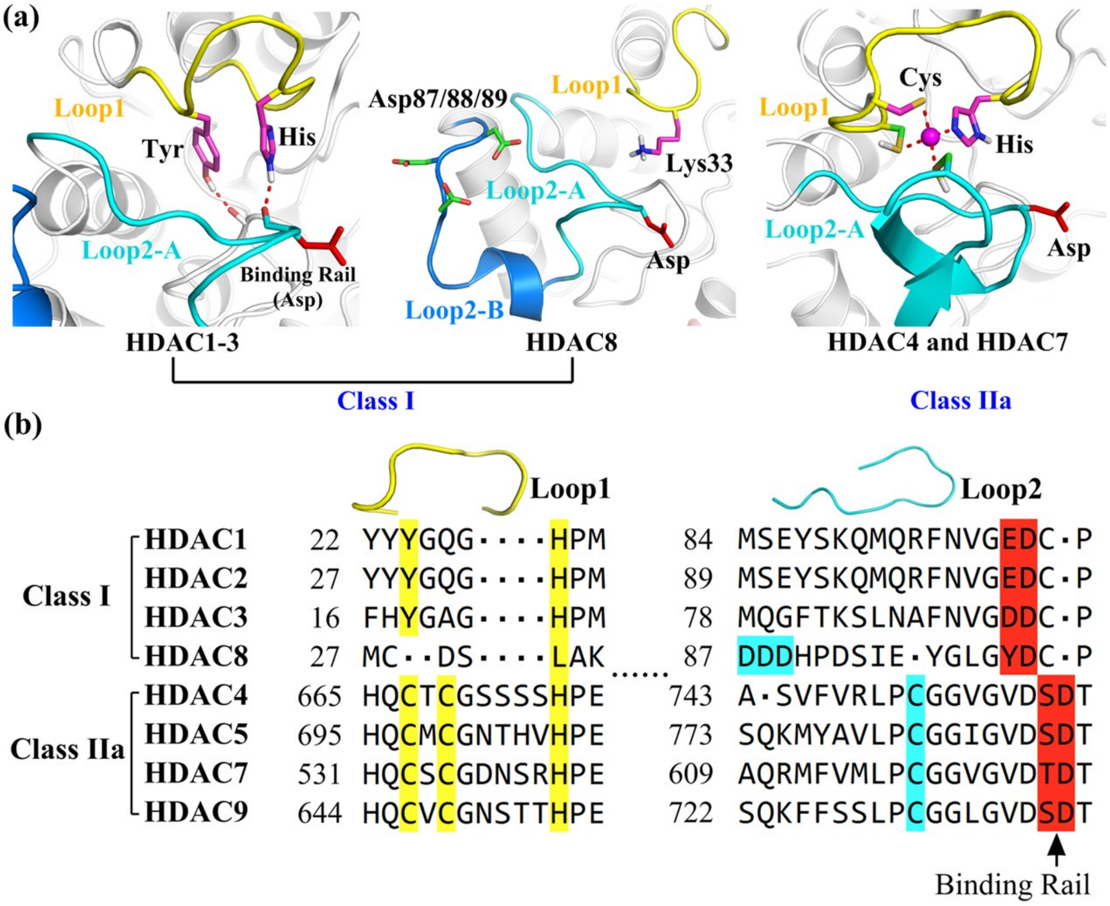


**Fig. S6** (a) The representative Loop1 and Loop2 interactions in the class I and class IIa HDACs. (b) Sequence alignment of Loop1/Loop2 among the class I and class IIa HDACs. The binding rail is conserved and the key residues are shown in yellow (Loop1) and cyan (Loop2).

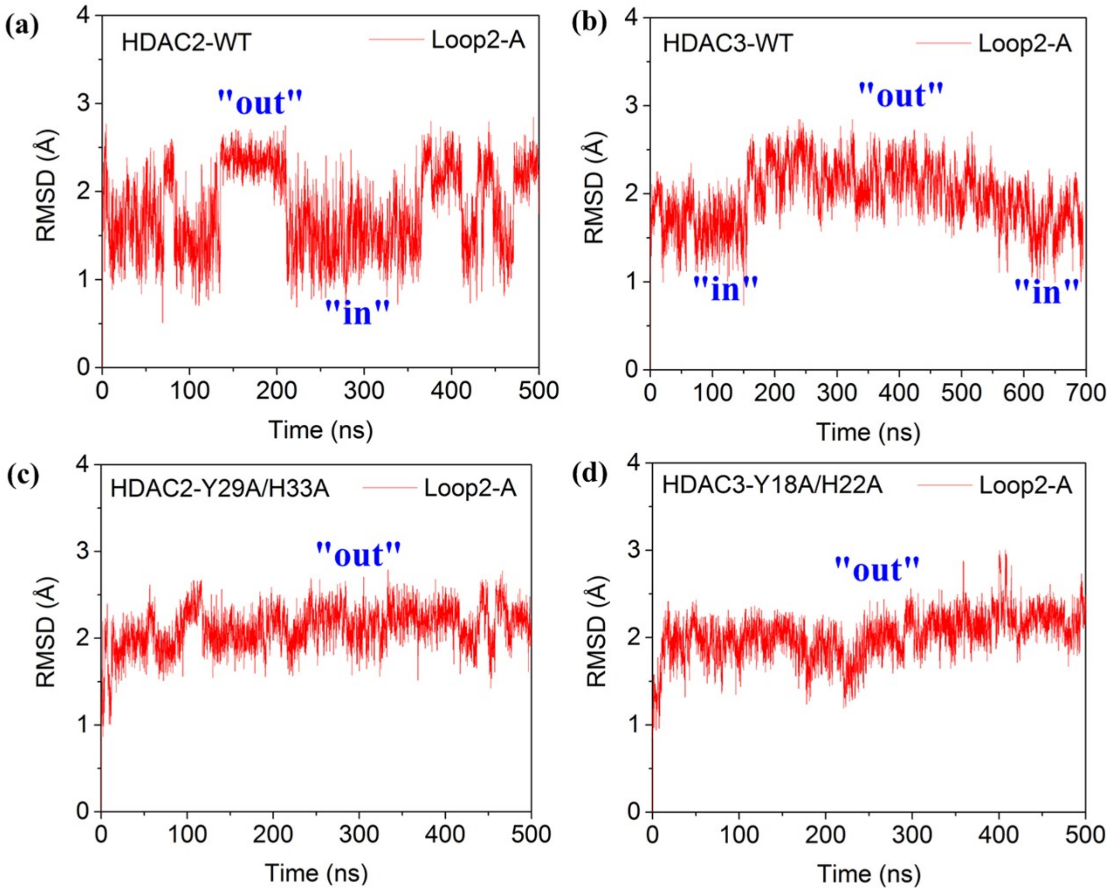


**Fig. S7** The RMSD of Loop2-A in wild type and mutant HDAC2 (a, c) and HDAC3 (b, d).

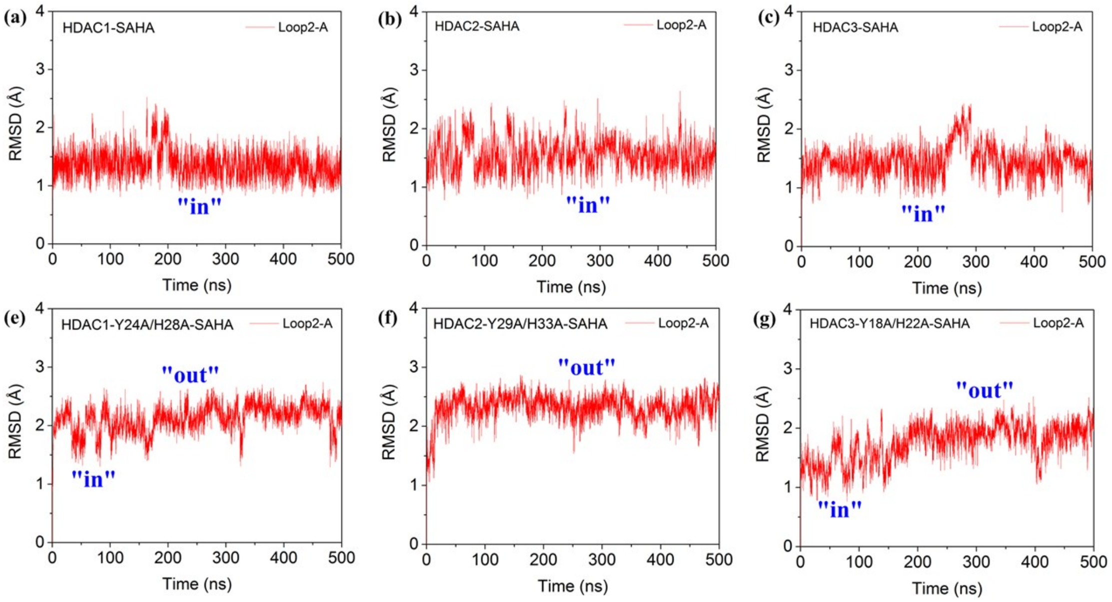


**Fig. S8** The RMSD of Loop2-A in HDAC1 (a, e), HDAC2 (b, f) and HDAC3 (c, g), with the inhibitor SAHA in the active pocket.

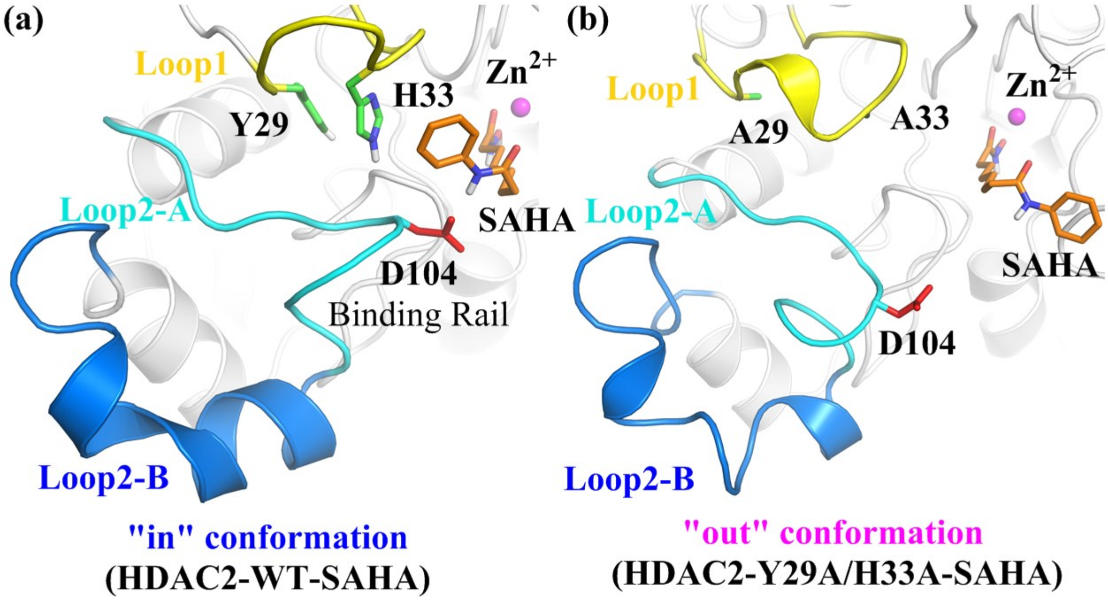


**Fig. S9** Representative structure observed in wild type (a) and mutant (b) HDAC2-SAHA.

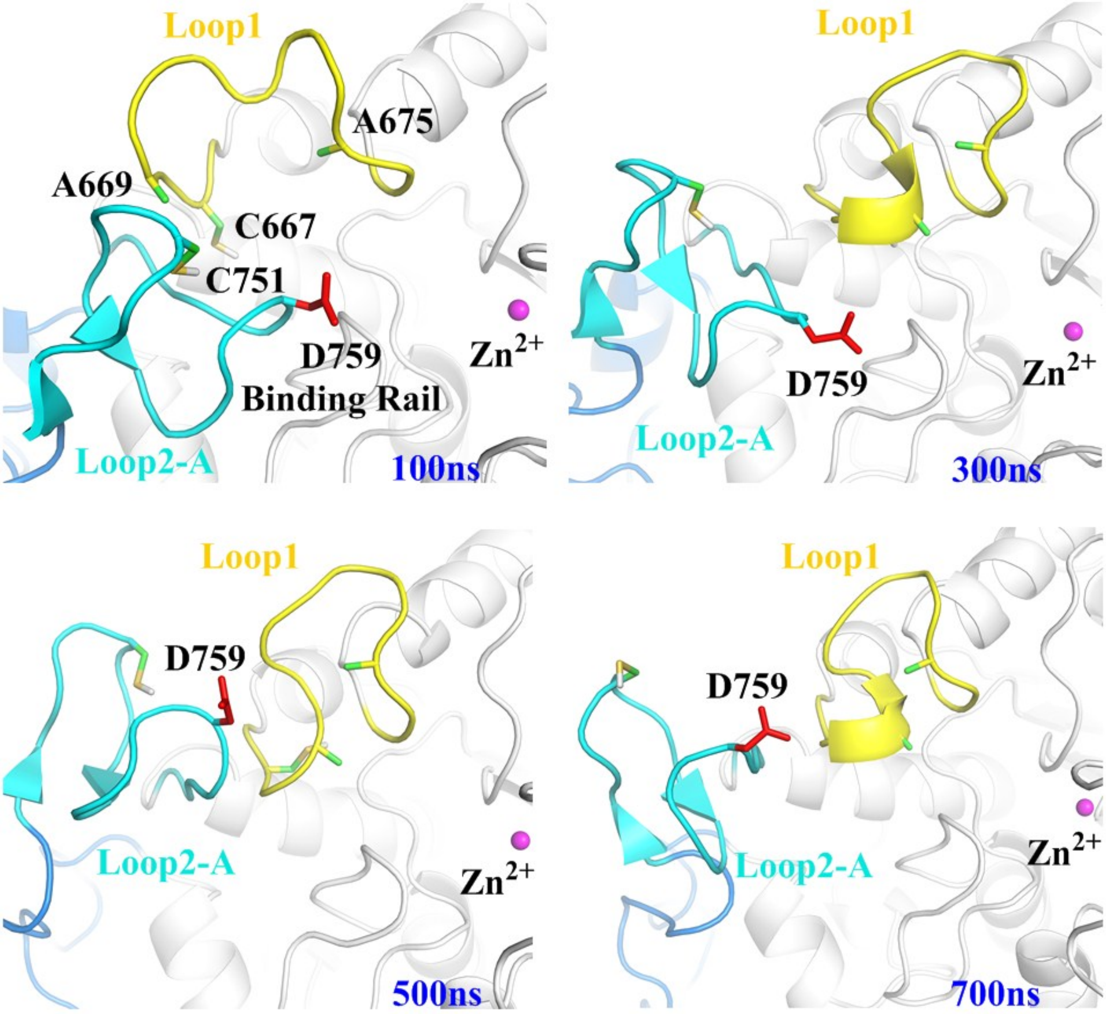


**Fig. S10** Representative structures along the MD simulation for the mutant HDAC4.

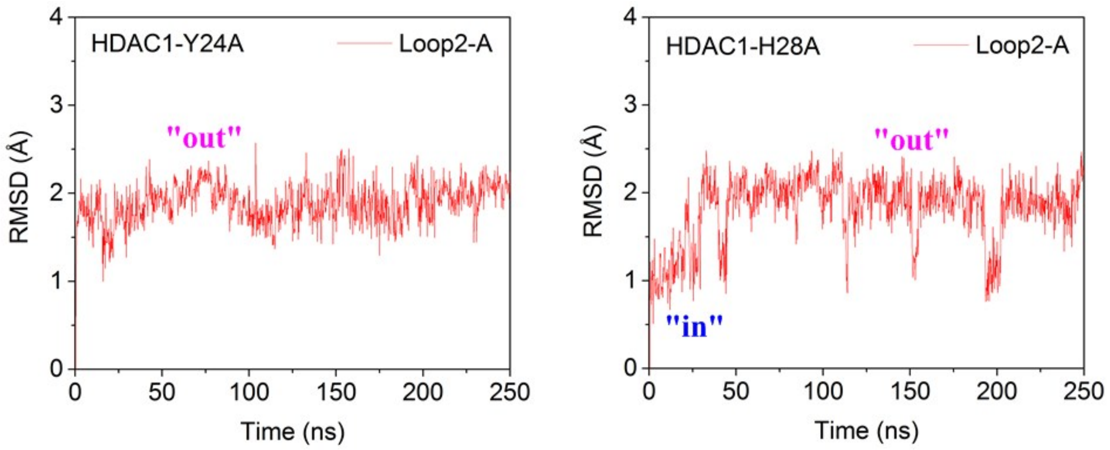


**Fig. S11** The RMSD curve due to the single mutation of HDAC1 (Y24A or H28A).