Supplementary information

How do Parkinson's disease-related mutations disrupt the dimerization of WD40 domain in LRRK2: a comparative molecular dynamics simulation study

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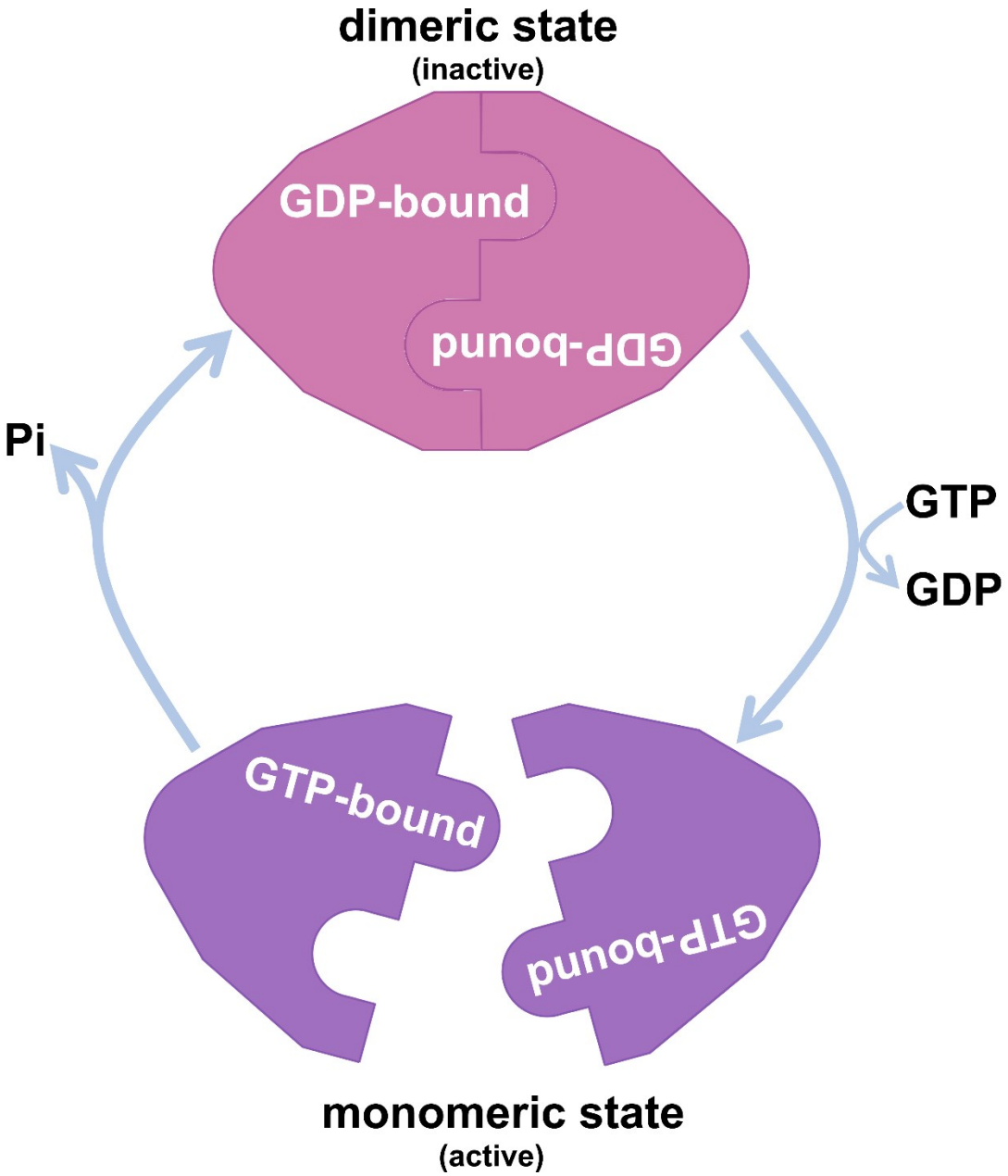

Figure S1: Schematic representation of LRRK2 dimerization-based activation cycle.

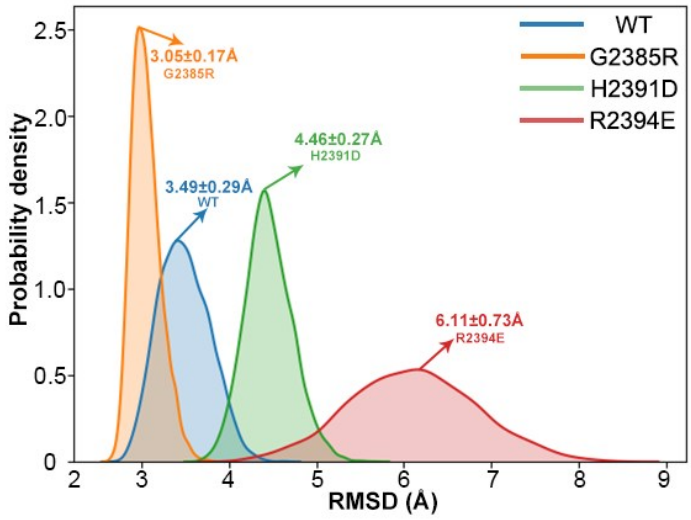

Figure S2: The probability density distribution map of Cα RMSD values in WT (black), G2385R (red), H2391D (blue) and R2394E (green).

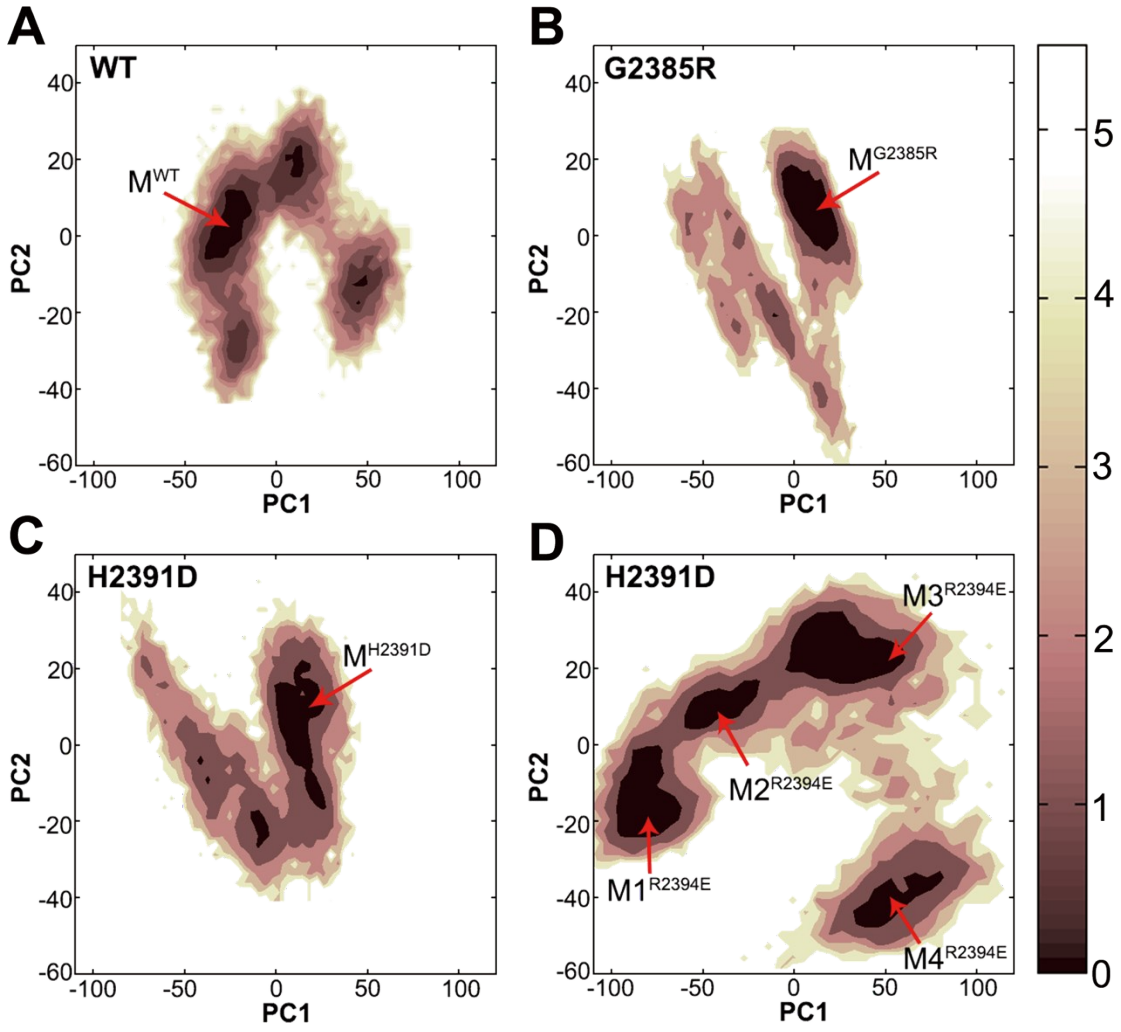

Figure S3: Overall conformational free energy landscapes of the first two PCs in (A) WT, (B) G2385R, (C) H2391D and (D) R2394E systems. The corresponding colormap was shown on the right.

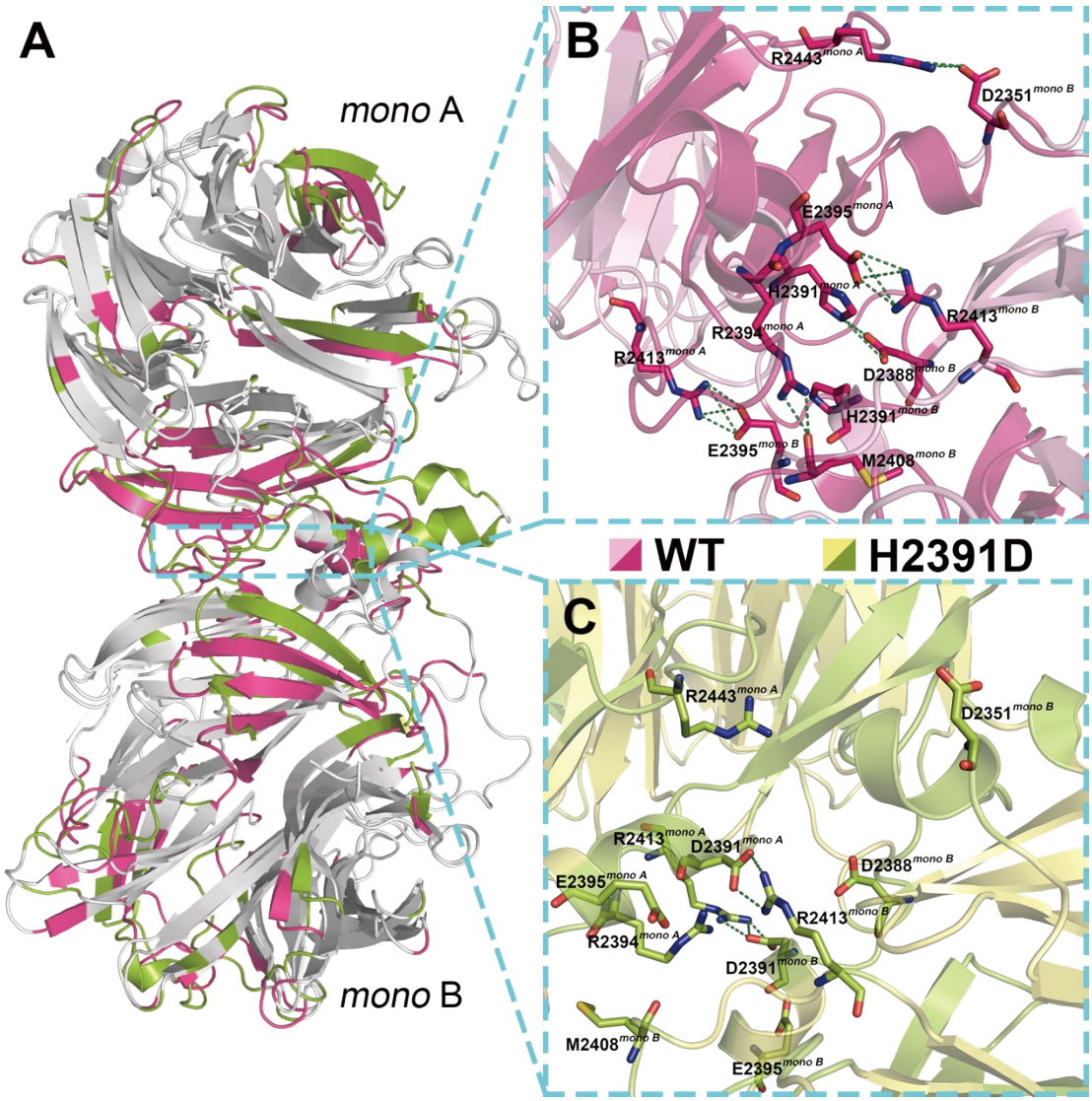

Figure S4: (A) Cartoon diagram of WT and H2391D WD40 dimer structural superposition, regions with significant structural deviations were highlighted with hotpink (WT) and green (H2391D). Bonds formed between the representative residue pairs (shown as sticks) in (B) WT and (C) H2391D systems on the dimerization interface. Bonds were displayed with green dashed lines.

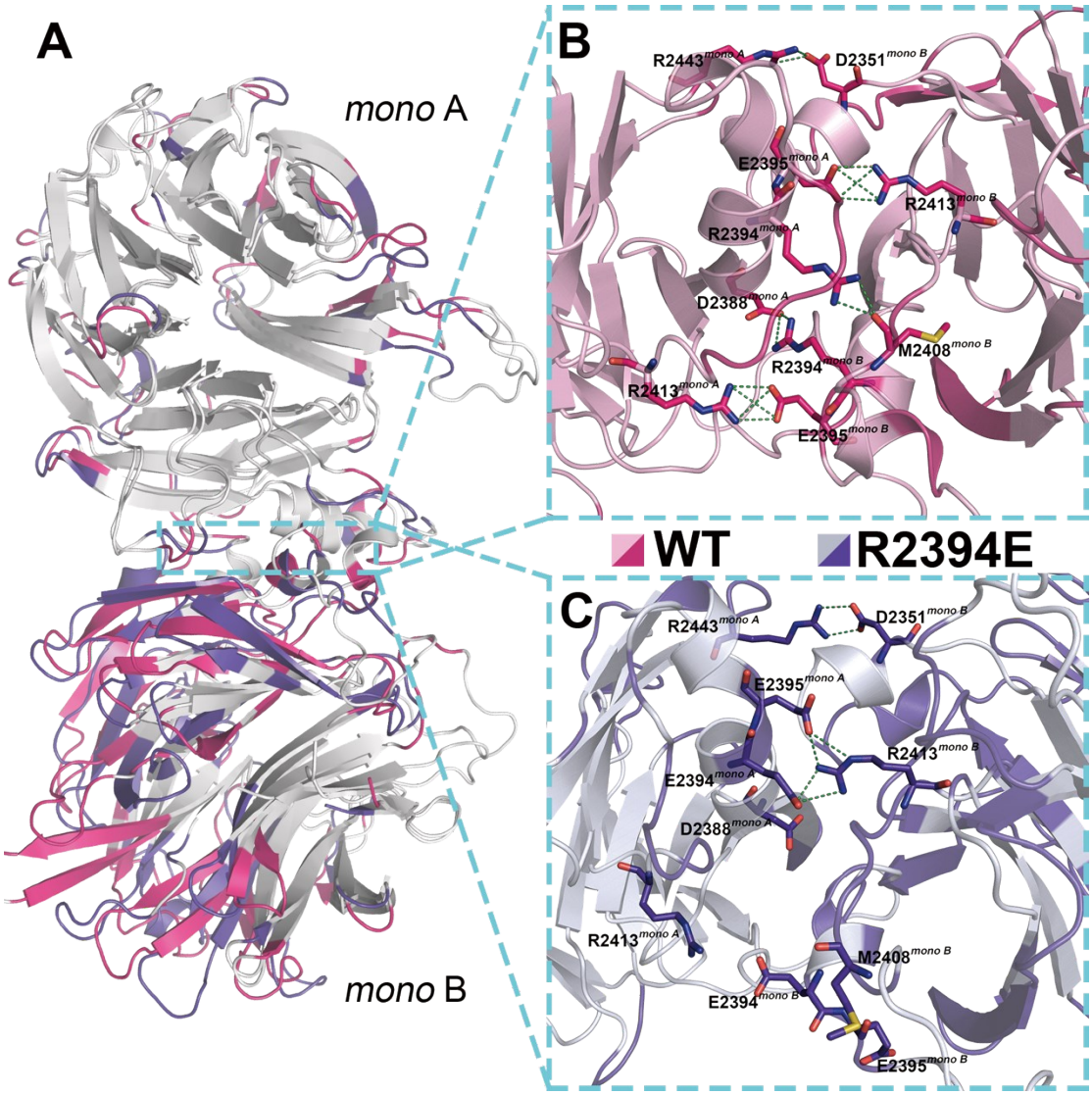

Figure S5: (A) Cartoon diagram of WT and R2394E WD40 dimer structural superposition, regions with significant structural deviations were colored with hotpink (WT) and purple (R2394E). Bonds formed between the representative residue pairs (shown as sticks) in (B) WT and (C) R2394E systems on the dimerization interface. Bonds were displayed with green dashed lines.

Table S1: Detailed energy contributions in MM/PBSA calculation*

	M_{W1}	M_{W2}	M_{W3}	M_G	M_H	M_R
$^1\Delta E_{vdW}$	-127.14 (8.68)	-127.30 (7.75)	-132.58 (7.71)	-140.83 (7.41)	-85.17 (7.29)	-72.93 (6.27)
$^2\Delta E_{ele}$	726.13 (59.61)	736.63 (55.99)	681.02 (57.36)	936.54 (60.61)	536.48 (43.90)	404.08 (23.78)
$^3\Delta E_{PB}$	-689.87 (53.75)	-680.86 (50.45)	-633.21 (52.39)	-851.23 (55.85)	-499.77 (43.13)	-374.43 (21.85)
$^4\Delta E_{nonpolar}$	-14.40 (0.66)	-18.10 (0.99)	-19.07 (0.94)	-14.95 (0.52)	-10.38 (0.59)	-7.77 (0.57)
$^5\Delta G_{gas}$	598.99 (62.44)	609.33 (57.28)	548.44 (57.92)	795.71 (60.56)	451.31 (45.17)	331.15 (24.30)
$^6\Delta G_{solv}$	-704.27 (53.43)	-698.96 (49.99)	-652.28 (51.95)	-866.19 (55.89)	-510.15 (42.88)	-382.2 (21.84)

* Numbers in the parentheses represent standard deviations; $^1\Delta E_{vdW}$: van der Waals force energy contribution; $^2\Delta E_{ele}$: electrostatic force energy contribution; $^3\Delta E_{PB}$: Poisson Boltzmann energy contribution; $^4\Delta E_{nonpolar}$: nonpolar energy contribution; $^5\Delta G_{gas}$: gas free energy contribution; $^6\Delta G_{solv}$: solvation energy contribution.

Table S2: Hydrogen bonds and salt bridges in the representative conformations*

	Hydrogen bonds	Salt bridges
M_{W3}	A:L2343[O] 2.32 B:L2386[H] A:L2386[O] 2.22 B:S2345[H] A:D2388[OD1] 2.33 B:R2394[HH22] A:D2388[OD2] 1.81 B:R2394[HH12] A:E2395[OE1] 1.88 B:R2413[HH22] A:E2395[OE2] 1.83 B:R2413[HH12] A:S2409[O] 2.12 B:K2407[HZ3] A:L2386[H] 2.19 B:L2343[O] A:R2443[HH12] 1.88 B:D2351[OD1] A:R2443[HH22] 1.79 B:D2351[OD1] A:R2413[HH22] 1.79 B:E2395[OE1] A:R2413[HH12] 1.79 B:E2395[OE2] A:R2394[HH12] 2.16 B:K2407[O] A:R2394[HH12] 1.94 B:M2408[O] A:R2394[HH22] 1.78 B:M2408[O] A:Y2346[HH] 1.71 B:L2444[O]	A:D2388[OD1] 3.55 B:R2394[NH1] A:D2388[OD1] 3.22 B:R2394[NH2] A:D2388[OD2] 2.80 B:R2394[NH1] A:D2388[OD2] 3.25 B:R2394[NH2] A:E2395[OE1] 2.85 B:R2413[NH2] A:E2395[OE1] 3.78 B:R2413[NH1] A:E2395[OE2] 3.24 B:R2413[NH2] A:E2395[OE2] 2.81 B:R2413[NH1] A:R2443[NH1] 2.78 B:D2351[OD1] A:R2443[NH2] 2.68 B:D2351[OD1] A:H2391[NE2] 2.82 B:D2388[OD1] A:H2391[NE2] 3.69 B:D2388[OD2] A:R2413[NH1] 3.82 B:E2395[OE1] A:R2413[NH2] 2.77 B:E2395[OE1] A:R2413[NH1] 2.80 B:E2395[OE2] A:R2413[NH2] 3.23 B:E2395[OE2]
M_G	A:L2343[O] 1.97 B:L2386[H] A:L2386[O] 1.94 B:S2345[H] A:K2402[O] 2.19 B:R2413[HE] A:E2403[OE1] 1.84 B:K2478[HZ1] A:S2345[H] 1.89 B:L2386[O] A:R2413[HH12] 2.04 B:E2395[OE1] A:R2413[HH22] 2.03 B:E2395[OE2] A:R2394[HH12] 1.83 B:Y2410[O] A:R2394[HH22] 1.90 B:Y2410[O]	A:E2403[OE1] 2.82 B:K2478[NZ] A:E2403[OE2] 3.87 B:K2478[NZ] A:R2413[NH1] 2.96 B:E2395[OE1] A:R2413[NH2] 3.54 B:E2395[OE1] A:R2413[NH1] 3.39 B:E2395[OE2] A:R2413[NH2] 2.78 B:E2395[OE2]
M_H	A:Q2342[O] 2.18 B:L2386[H] A:Q2342[OE1] 2.49 B:R2442[HH12]	A:D2391[OD1] 2.96 B:R2413[NH2] A:D2391[OD1] 3.62 B:R2413[NH1]

	A:S2345[O] 1.98 B:D2388[H]	A:D2391[OD2] 3.08 B:R2413[NH2]
	A:D2388[OD1] 2.15 B:Y2346[HH]	A:D2391[OD2] 2.90 B:R2413[NH1]
	A:D2391[OD1] 1.93 B:R2413[HH22]	A:R2413[NH1] 2.89 B:D2391[OD1]
	A:D2391[OD2] 1.87 B:R2413[HH12]	A:R2413[NH2] 3.34 B:D2391[OD1]
	A:R2413[HH12] 1.78 B:D2391[OD1]	A:R2413[NH1] 3.71 B:D2391[OD2]
	A:R2413[HH22] 1.86 B:D2391[OD2]	A:R2413[NH2] 2.91 B:D2391[OD2]
M_R	A:S2345[O] 2.31 B:D2388[H]	A:E2394[OE2] 3.47 B:R2413[NH1]
	A:E2394[OE2] 2.12 B:R2413[HH22]	A:E2394[OE2] 2.91 B:R2413[NH2]
	A:E2395[OE1] 1.82 B:R2413[HH21]	A:E2395[OE1] 3.41 B:R2413[NE]
	A:L2386[H] 2.14 B:L2343[O]	A:E2395[OE1] 2.80 B:R2413[NH2]
	A:R2443[HH22] 1.83 B:D2351[OD1]	A:R2443[NH1] 3.53 B:D2351[OD1]
	A:R2443[HH12] 1.73 B:D2351[OD2]	A:R2443[NH2] 2.78 B:D2351[OD1]
		A:R2443[NH1] 2.74 B:D2351[OD2]
		A:R2443[NH2] 3.41 B:D2351[OD2]

*The atoms for bonding are denoted in the parentheses; the numbers between bonding residues indicate the average distance between the bonding atoms throughout simulations.

Table S3: Interfacial and structural communities in each system

	Interfacial communities	Structural communities
WT	B, C, E, I	A, D, D', F, G, H
G2385R	B, C, E	A, D, F, G, H
H2391D	B, C, E, I'	A, D, F, G
R2394E	B, C, E, I'	A, D, D', F, G