Supplementary Information

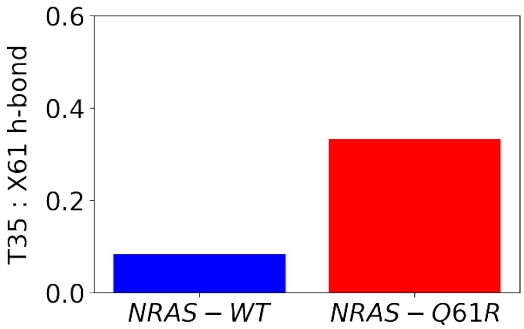
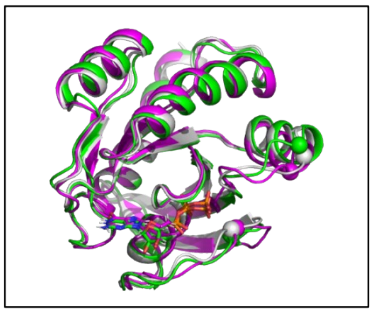
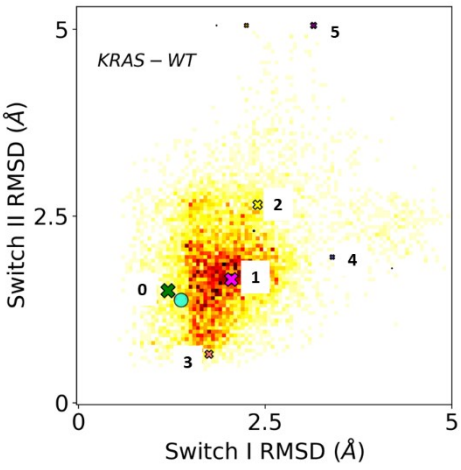


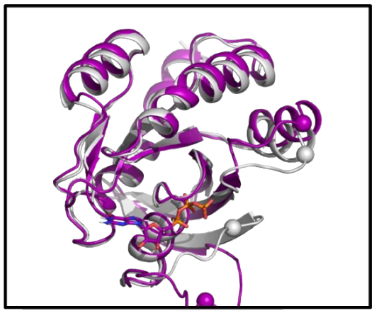
Figure S1: Frequency of hydrogen bond formation between Thr35 carbonyl oxygen and the Gln61/Arg61 side chain in molecular dynamics calculations.



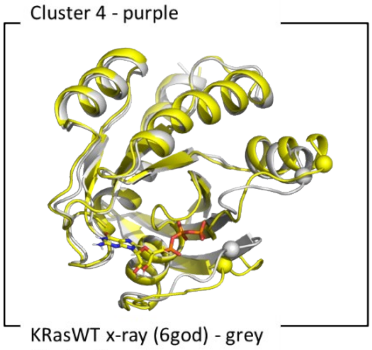
KRasWT x-ray (6god) - grey
Cluster 0 - green
Cluster 1 - magenta

Cluster	Pop (frac)
0	0.32
1	0.30
2	0.14
3	0.10
4	0.06
5	0.04





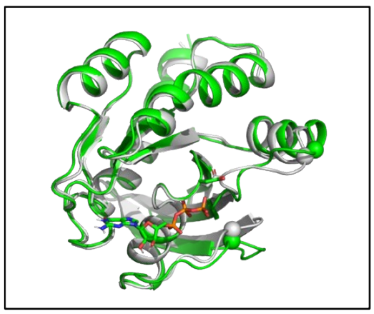
KRasWT x-ray (6god) - grey
Cluster 4 - purple



KRasWT x-ray (6god) - grey
Cluster 2 - yellow

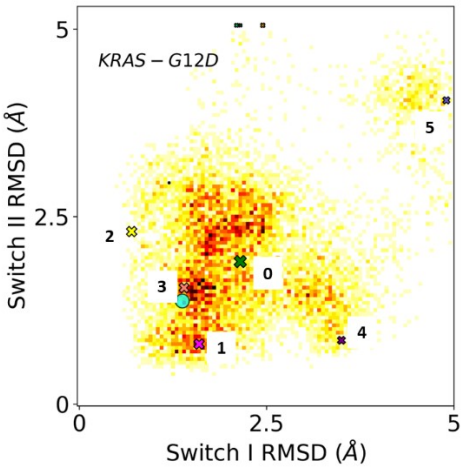
Figure S2: Molecular dynamics (MD) simulations of KRAS wt. The mobilities, seen as carbon-alpha RMSDs relative to the state-2 starting structures, of switch-1 and switch-2 are plotted on the horizontal and vertical axis, respectively. The typical RMSD of 1.3 Å after minimization of starting x-ray structures is shown as a cyan marker. Most populated cluster centres after full backbone RMSD clustering are projected onto the RMSD heatmap as crosses, with the marker size reflecting the cluster populations. Protein conformations for selected clusters are shown compared to starting conformations (in grey), with

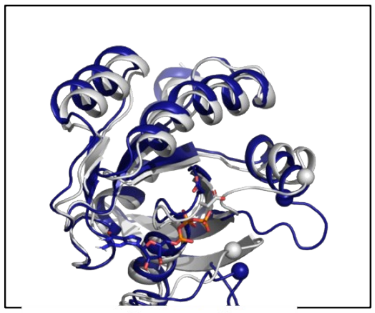
protein colouring matching those of the cross markers. The carbon-α atoms of T35 (switch-1) and Y64 (switch-2) are shown in spheres.



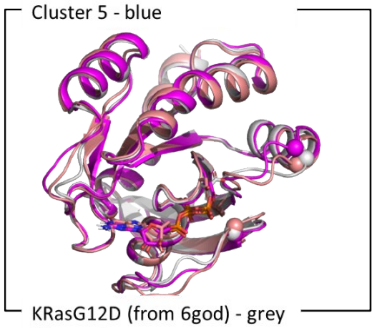
KRasG12D (from 6god) - grey
Cluster 0 - green

Cluster	Pop (frac)
0	0.24
1	0.17
2	0.17
3	0.16
4	0.10
5	0.08



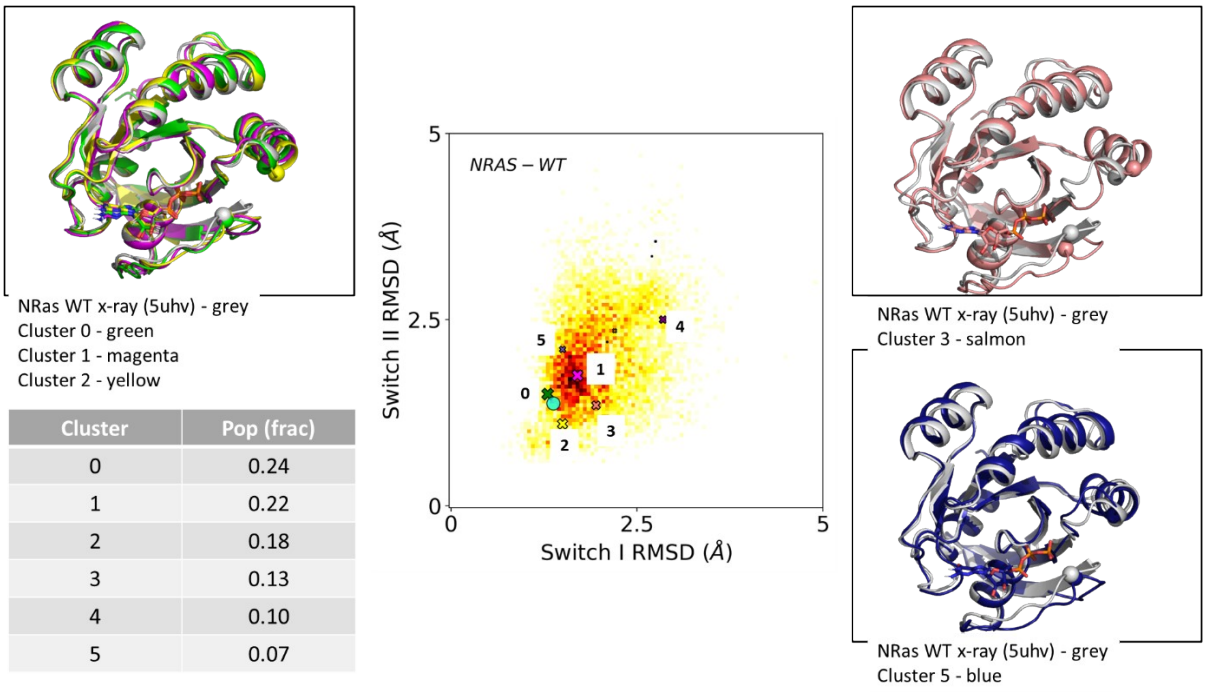


KRasG12D (from 6god) - grey
Cluster 5 - blue



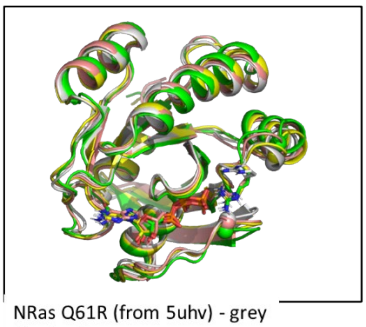
KRasG12D (from 6god) - grey
Cluster 1 - magenta
Cluster 3 - salmon

Figure S3: Molecular dynamics (MD) simulations of KRAS G12D. The mobilities, seen as carbon-alpha RMSDs relative to the state-2 starting structures, of switch-1 and switch-2 are plotted on the horizontal and vertical axis, respectively. The typical RMSD of 1.3 Å after minimization of starting x-ray structures is shown as a cyan marker. Most populated cluster centres after full backbone RMSD clustering are projected onto the RMSD heatmap as crosses, with the marker size reflecting the cluster populations. Protein conformations for selected clusters are shown compared to starting conformations (in grey), with protein colouring matching those of the cross markers. The carbon-α atoms of T35 (switch-1) and Y64 (switch-2) are shown in spheres. Residue Asp12 is shown in sticks.



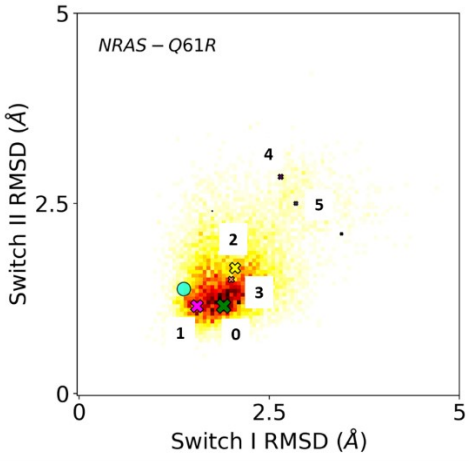
Cluster	Pop (frac)
0	0.24
1	0.22
2	0.18
3	0.13
4	0.10
5	0.07

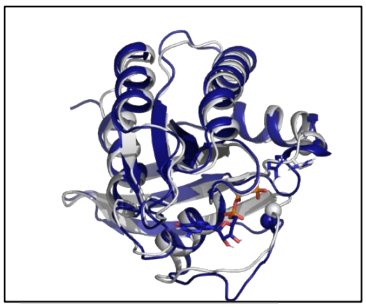
Figure S4: Molecular dynamics (MD) simulations of NRAS wt. The mobilities, seen as carbon-alpha RMSDs relative to the state-2 starting structures, of switch-1 and switch-2 are plotted on the horizontal and vertical axis, respectively. The typical RMSD of 1.3 Å after minimization of starting x-ray structures is shown as a cyan marker. Most populated cluster centres after full backbone RMSD clustering are projected onto the RMSD heatmap as crosses, with the marker size reflecting the cluster populations. Protein conformations for selected clusters are shown compared to starting conformations (in grey), with protein colouring matching those of the cross markers. The carbon-α atoms of T35 (switch-1) and Y64 (switch-2) are shown in spheres.



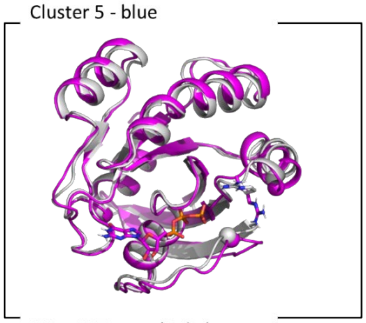
NRas Q61R (from 5uhv) - grey
Cluster 0 - green
Cluster 2 - yellow
Cluster 3 - salmon

Cluster	Pop (frac)
0	0.35
1	0.28
2	0.20
3	0.07
4	0.04
5	0.03





NRas WT x-ray (5uhv) - grey
Cluster 5 - blue



NRas WT x-ray (5uhv) - grey
Cluster 1 - magenta

Figure S5: Molecular dynamics (MD) simulations of NRAS Q61R. The mobilities, seen as carbon-alpha RMSDs relative to the state-2 starting structures, of switch-1 and switch-2 are plotted on the horizontal and vertical axis, respectively. The typical RMSD of 1.3 Å after minimization of starting x-ray structures is shown as a cyan marker. Most populated cluster centres after full backbone RMSD clustering are projected onto the RMSD heatmap as crosses, with the marker size reflecting the cluster populations. Protein conformations for selected clusters are shown compared to starting conformations (in grey), with protein colouring matching those of the cross markers. The carbon-α atoms of T35 (switch-1) and Y64 (switch-2) are shown in spheres. Residue Arg61 is shown in sticks.