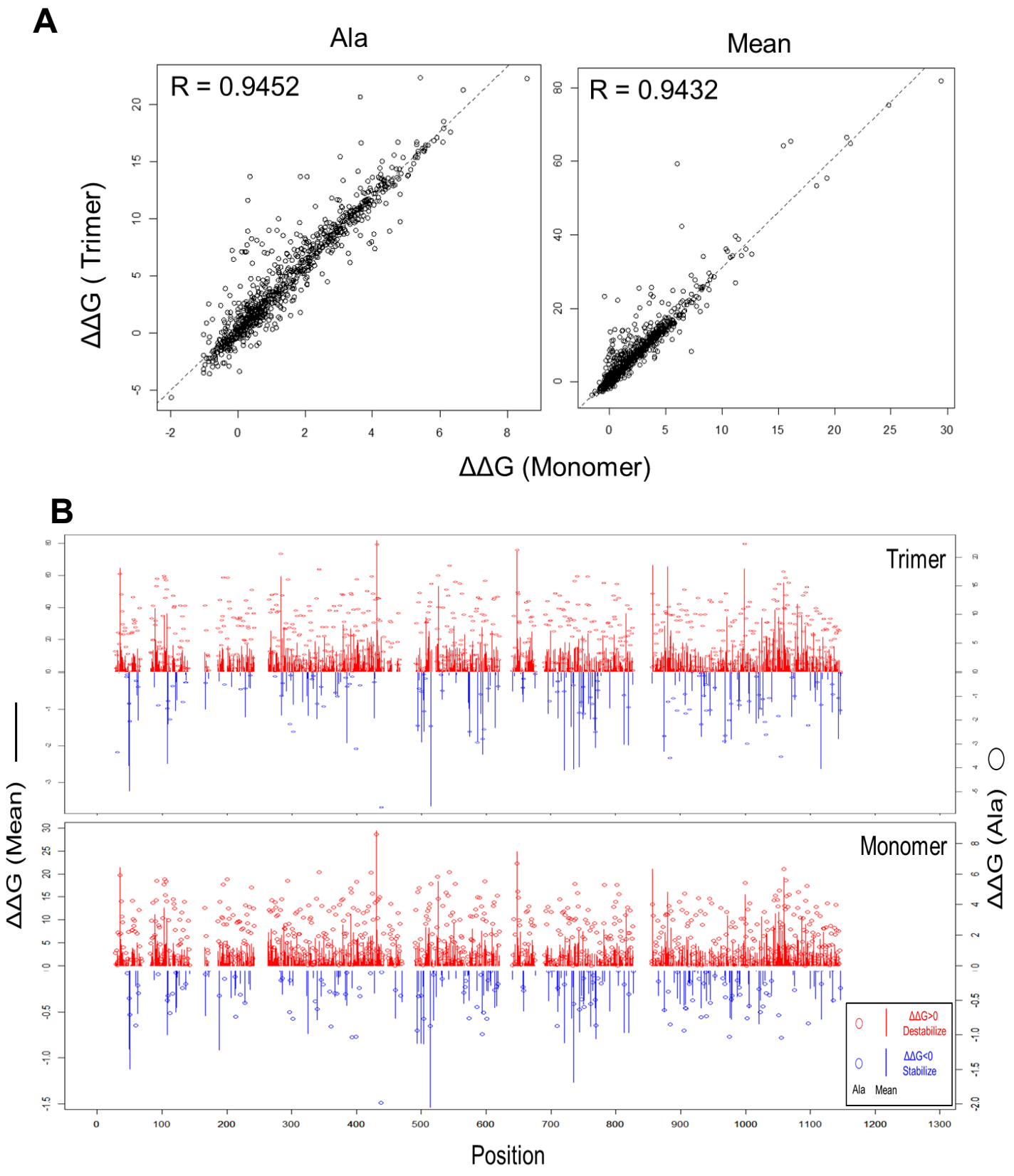
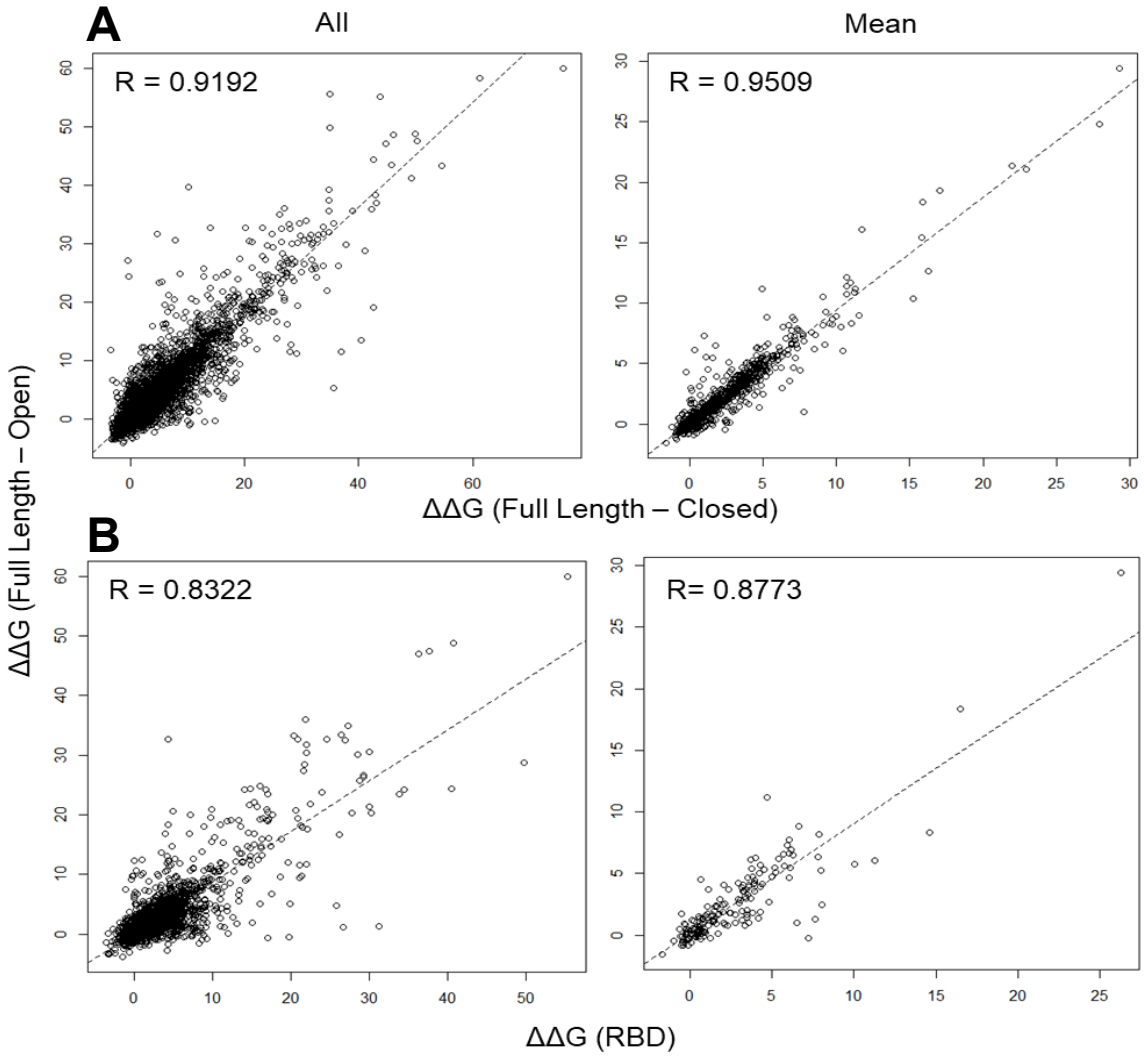
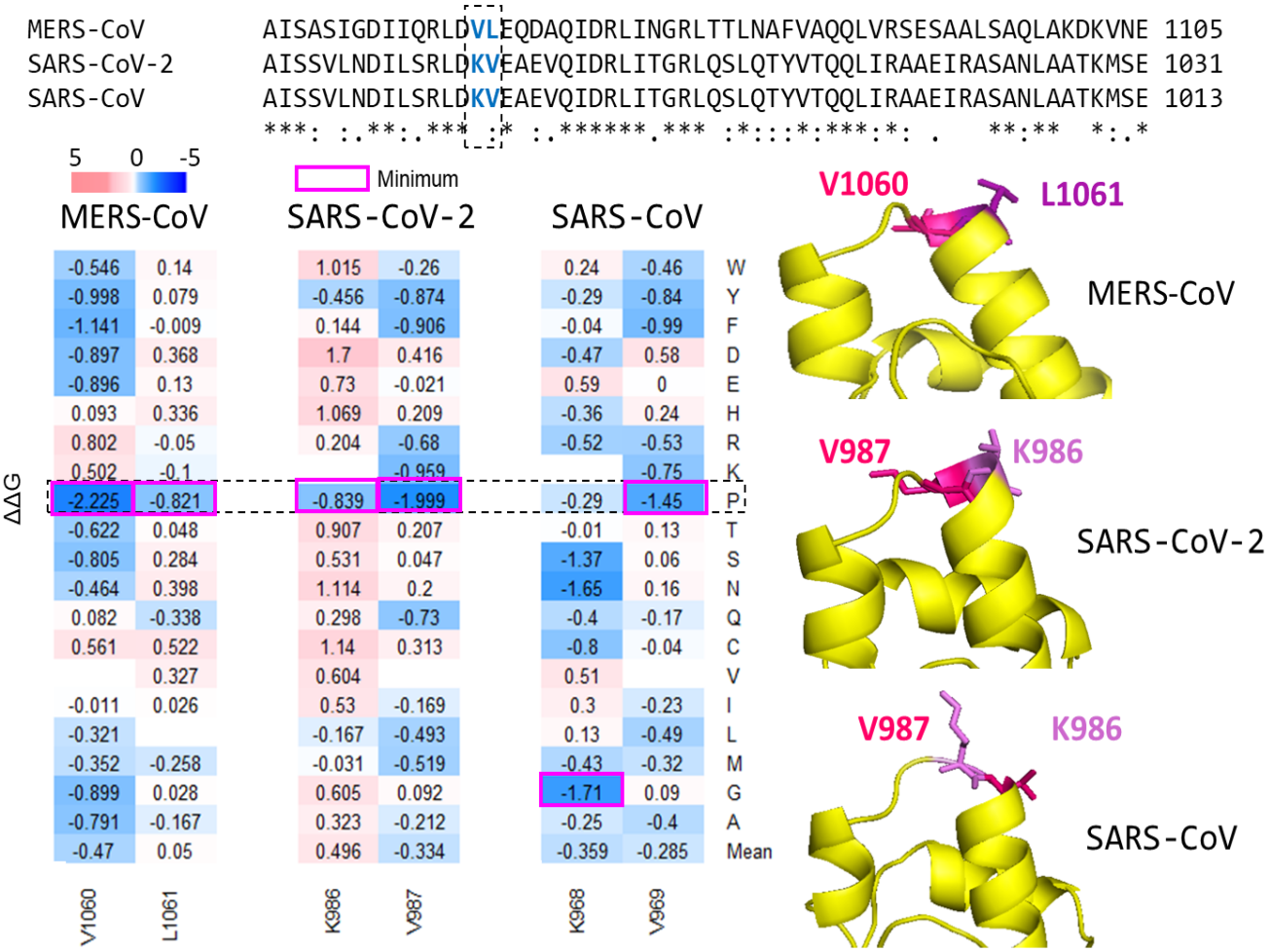


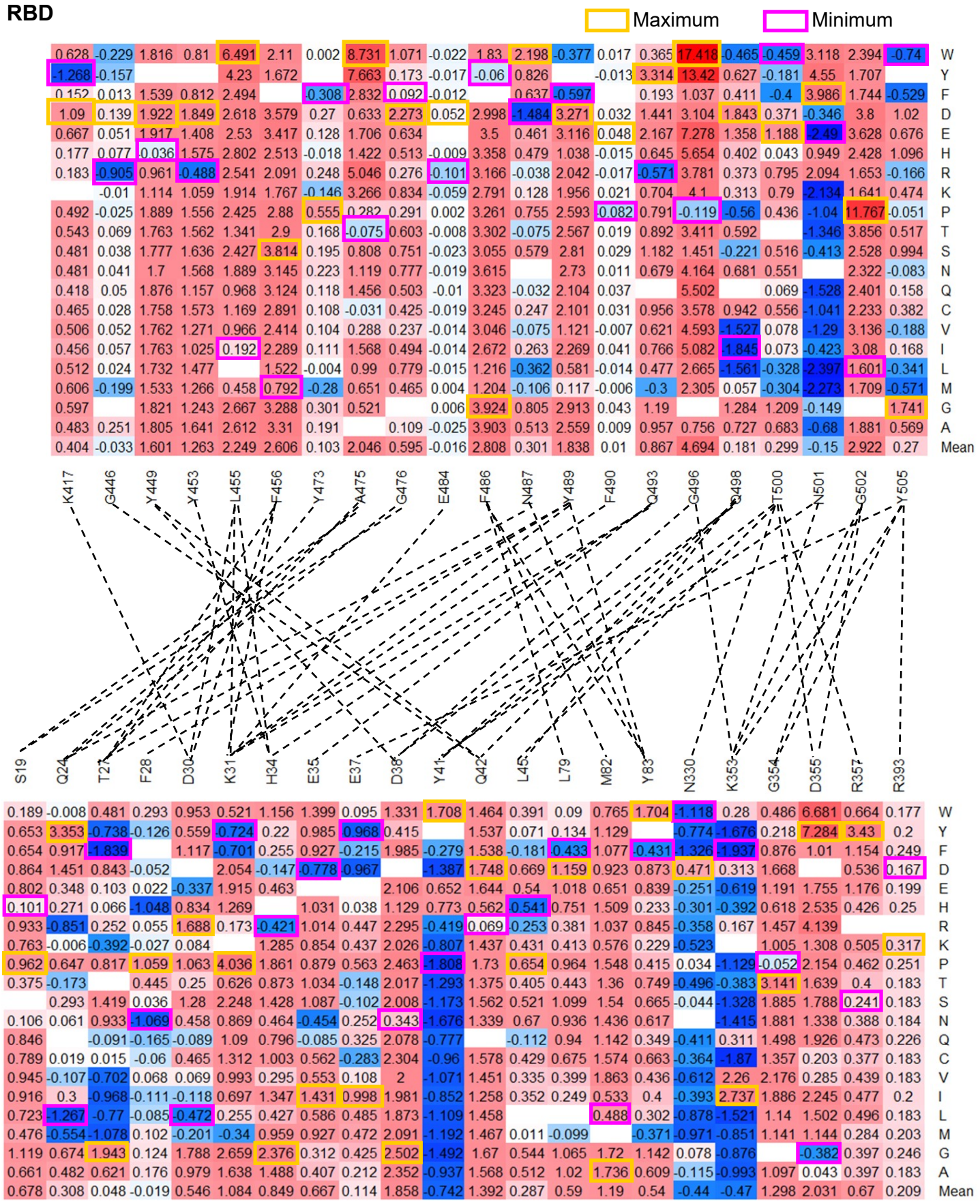
Supplementary Figure 1. (**A**) Folding energy changes for ΔΔG of substitutions to Alanine (left) and ΔΔG mean of residues (right) in SARS-CoV-2 S trimer and monomer. (**B**) Line charts summarize the folding energy changes for ΔΔG mean of residues (bar) and ΔΔG of substitutions to alanine (circle) in SARS-CoV-2 S trimer and monomer.



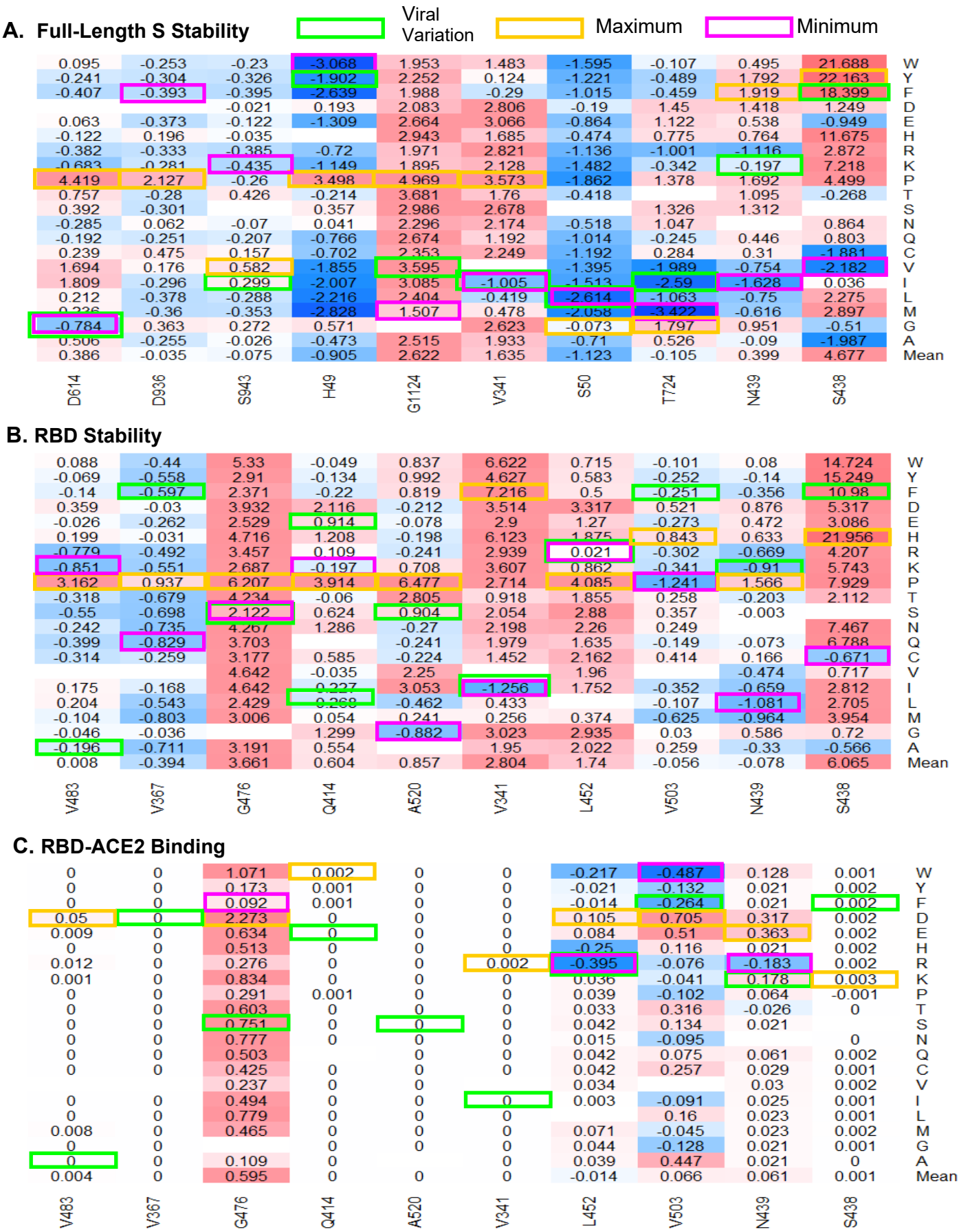
Supplementary Figure 2. Folding energy changes for ΔΔG of substitutions to Alanine (left) and ΔΔG mean of residues (right) in (**A**) the cryo-EM structures of SARS-CoV-2 S in closed state and open state and (**B**) the crystal structure of RBD and cryo-EM structure of SARS-Cov-2 S RBD. The folding energy change (ΔΔG) is computed based on the A chains of 6VYB and 6VXX.



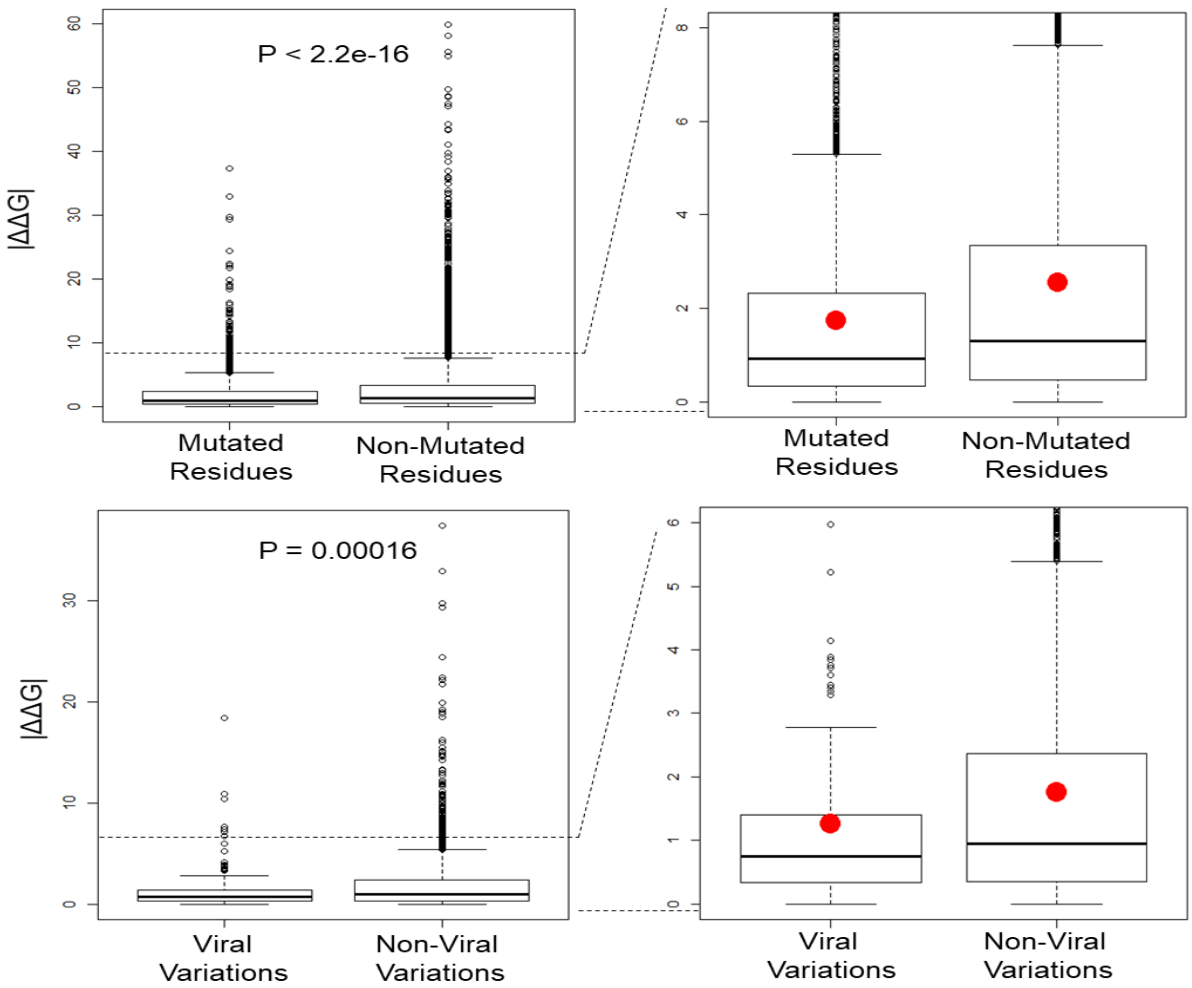
Supplementary Figure 3. Comparisons of 2P mutations among MERS-Cov, SARS-Cov-2 and SARS-Cov. The folding energy change (ΔΔG) is computed based on the monomer.



Supplementary Figure 4. Heatmaps show the ΔΔΔG of the mutations in RBD residues and ACE2 residues that make van der Waals contacts. Maximum (yellow) and Minimum (magenta) ΔΔΔG values are labelled for each residue position.



Supplementary Figure 5. Heatmaps of viral mutations (green) for (**A**) Full-length S stability (ΔΔG), (**B**) RBD stability ΔΔG and (**C**) RBD-ACE2 binding affinity (ΔΔΔG). Maximum (yellow) and Minimum (magenta) ΔΔG /ΔΔΔG values are labelled for each residue position. The folding energy change (ΔΔG) is computed based on the monomer.



Supplementary Figure 6. Boxplots for the |ΔΔG| of mean of residues with and without viral mutations (upper) and |ΔΔG| of viral mutations and other computationally predicted mutations in the same positions (lower). The mean values are shown as red dots. The folding energy change (ΔΔG) is computed based on the monomer.