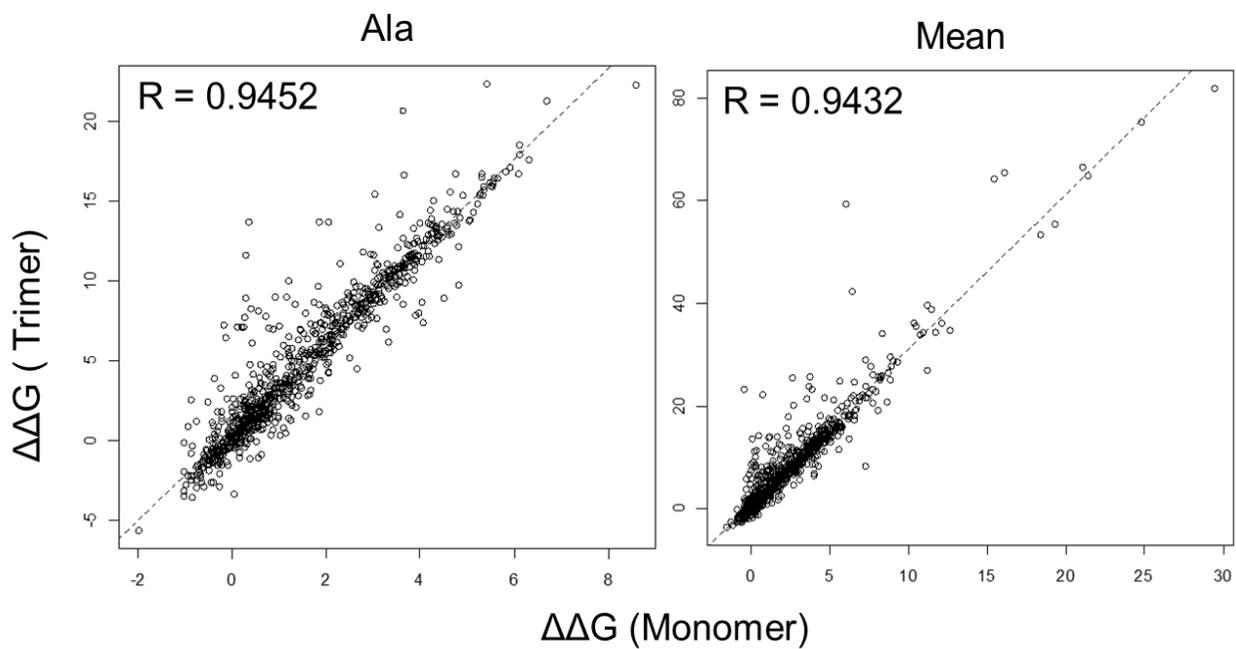
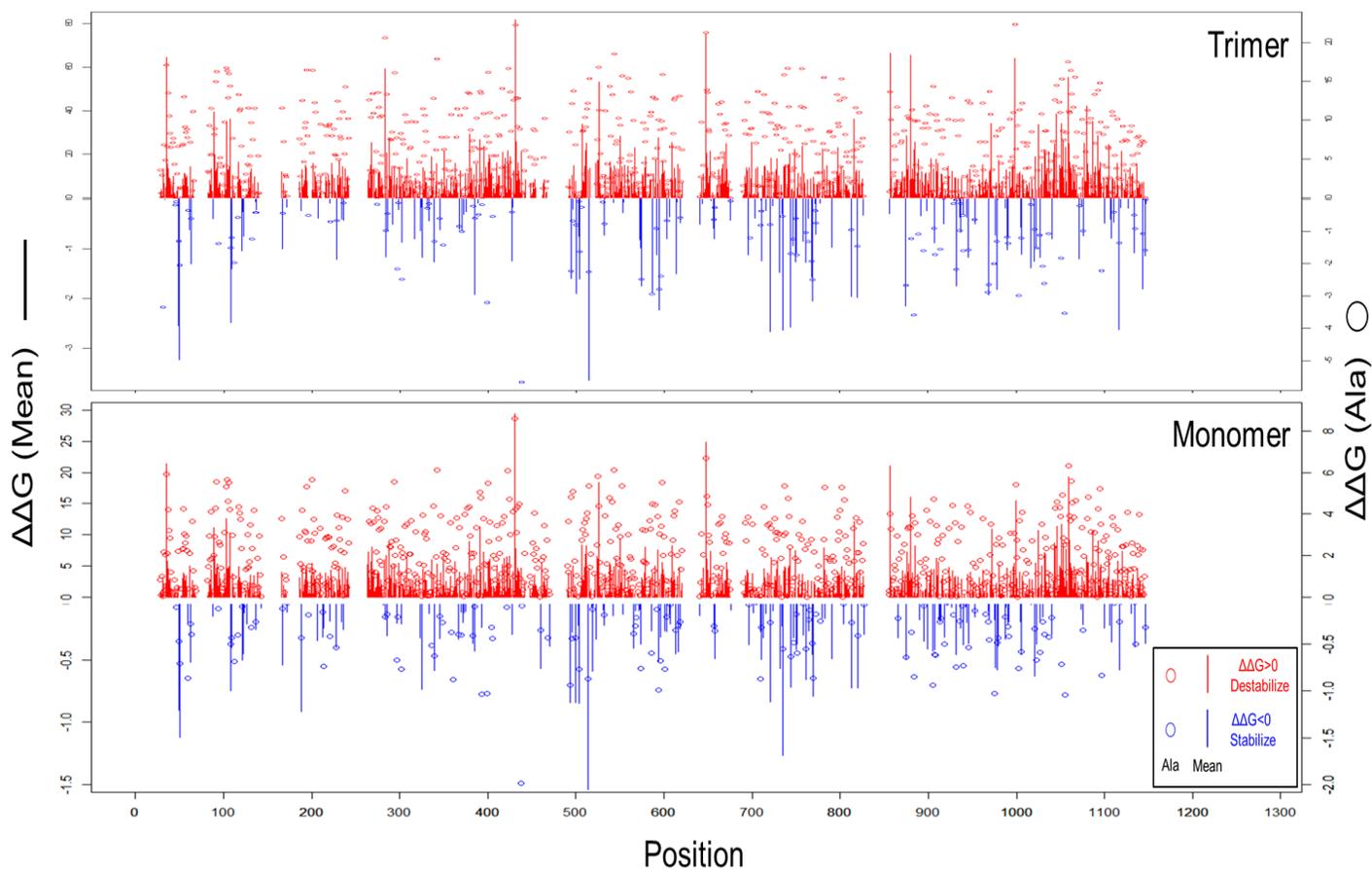
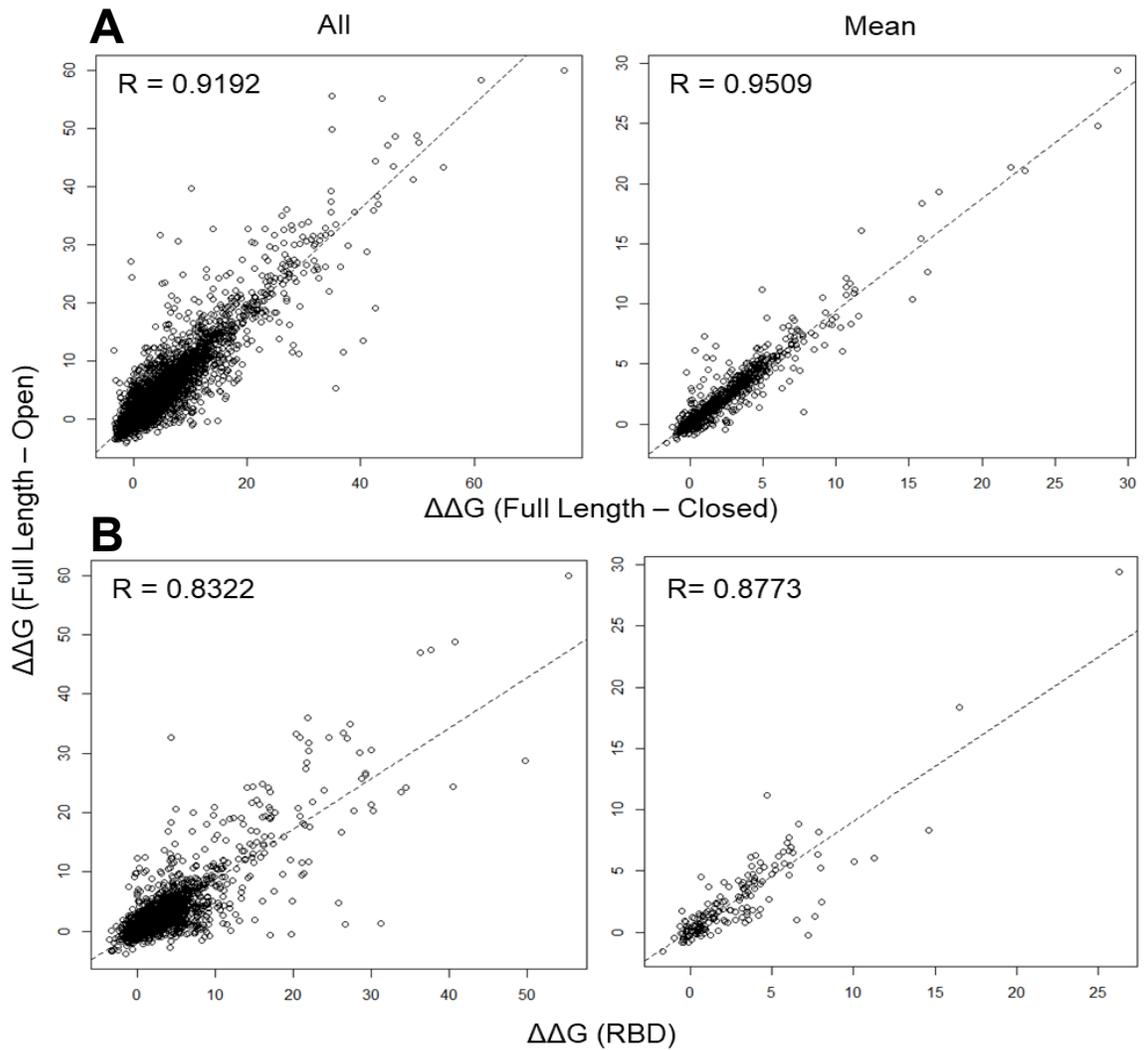
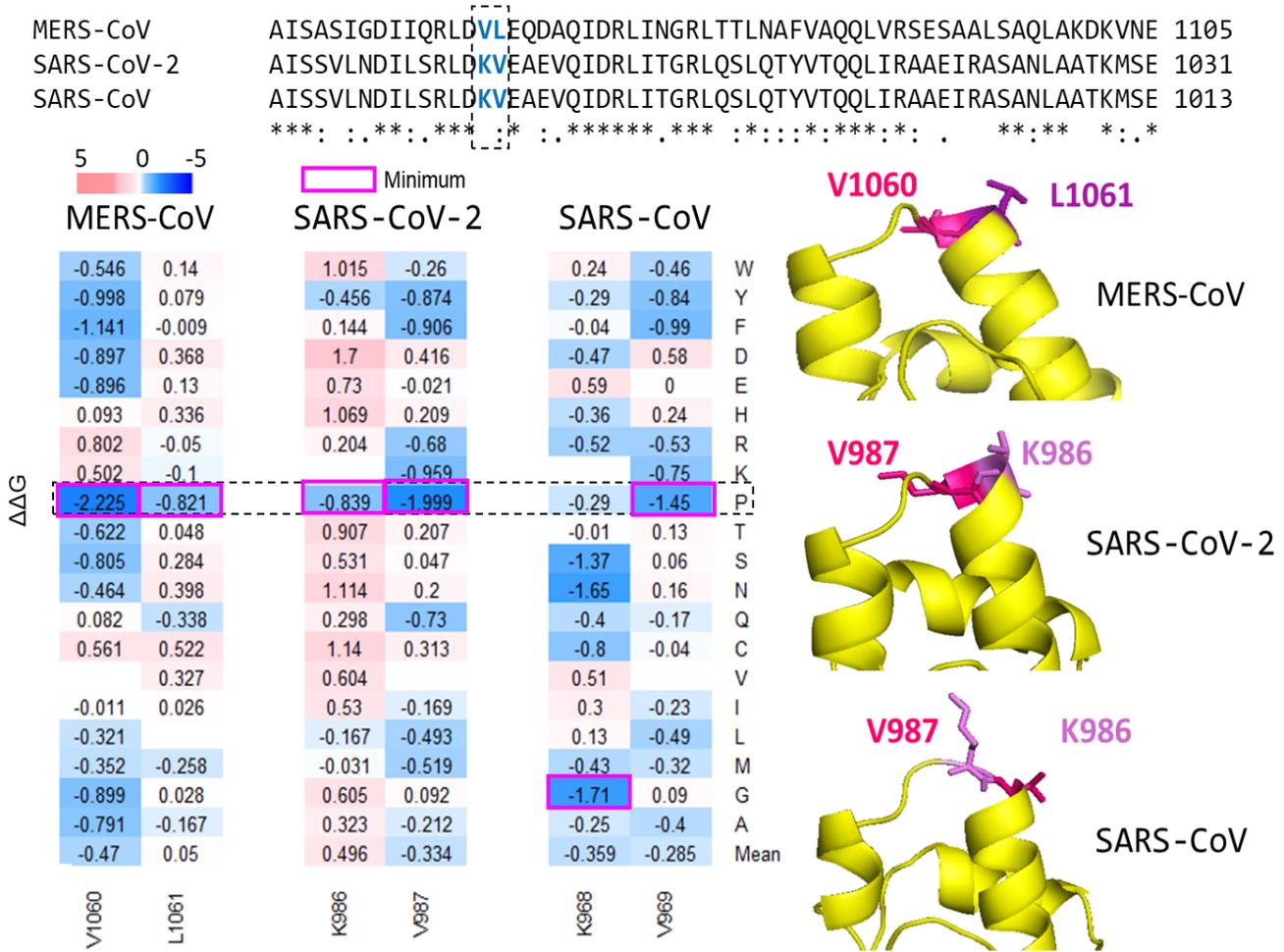


A**B**

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



Supplementary Figure 2. Folding energy changes for $\Delta\Delta G$ of substitutions to Alanine (left) and $\Delta\Delta G$ 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 ($\Delta\Delta G$) is computed based on the A chains of 6VYB and 6VXX.

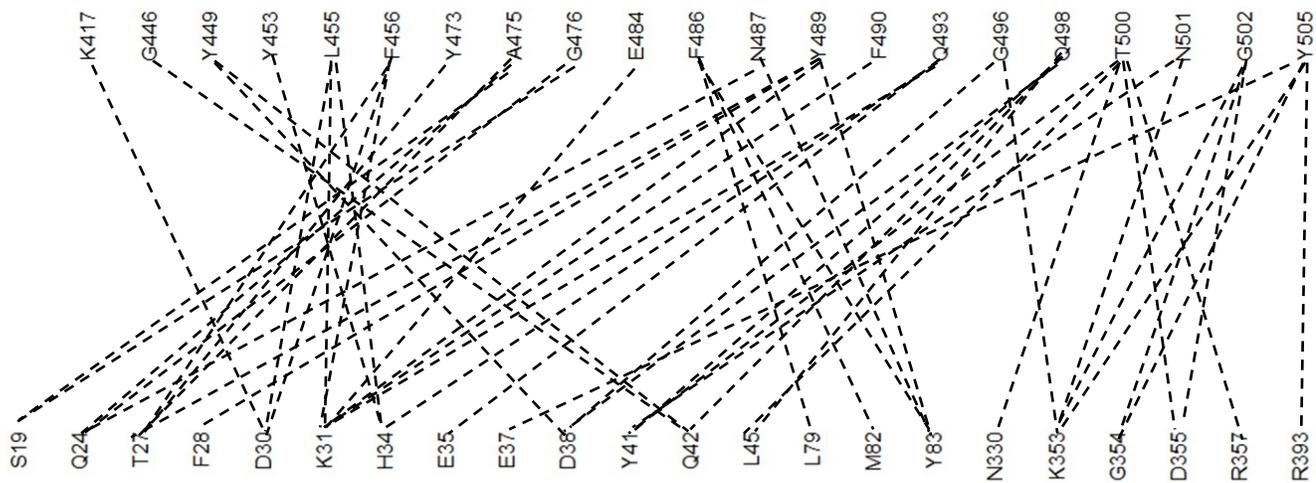


Supplementary Figure 3. Comparisons of 2P mutations among MERS-CoV, SARS-CoV-2 and SARS-CoV. The folding energy change ($\Delta\Delta G$) is computed based on the monomer.

RBD

Maximum Minimum

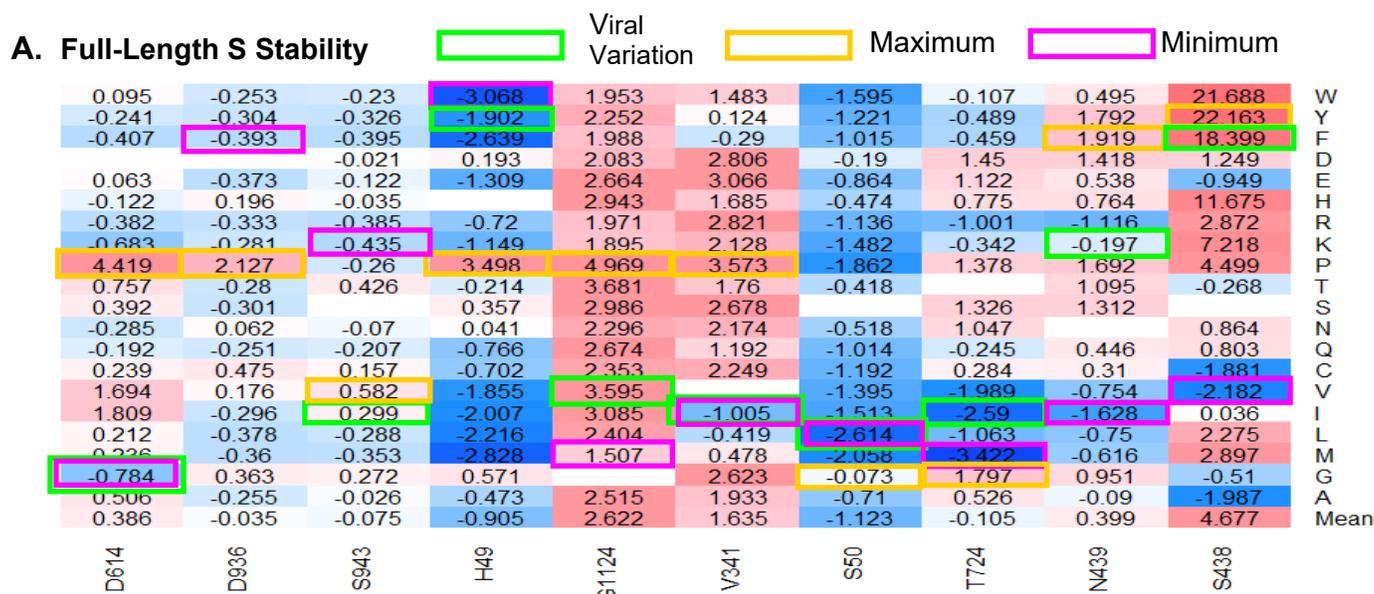
0.628	-0.229	1.816	0.81	6.491	2.11	0.002	8.731	1.071	-0.022	1.83	2.198	-0.377	0.017	0.365	17.418	-0.465	-0.459	3.118	2.394	-0.74	W	
-1.268	-0.157			4.23	1.672		7.663	0.173	-0.017	-0.06	0.826		-0.013	3.314	13.42	0.627	-0.181	4.55	1.707		Y	
0.152	0.013	1.539	0.812	2.494			-0.308	2.832	0.092	-0.012		0.637	-0.597		0.193	1.037	0.411	-0.4	3.986	1.744	-0.529	F
1.09	0.139	1.922	1.849	2.618	3.579	0.27	0.633	2.273	0.052	2.998	-1.484	3.271	0.032	1.441	3.104	1.843	0.371	-0.346	3.8	1.02	D	
0.667	0.051	1.917	1.408	2.53	3.417	0.128	1.706	0.634		3.5	0.461	3.116	0.048	2.167	7.278	1.358	1.188	2.49	3.628	0.676	E	
0.177	0.077	0.036	1.575	2.802	2.513	-0.018	1.422	0.513	-0.009	3.358	0.479	1.038	-0.015	0.645	5.654	0.402	0.043	0.949	2.428	1.096	H	
0.183	-0.905	0.961	-0.488	2.541	2.091	0.248	5.046	0.276	-0.101	3.166	-0.038	2.042	-0.017	-0.571	3.781	0.373	0.795	2.094	1.653	-0.166	R	
	-0.01	1.114	1.059	1.914	1.767	-0.146	3.266	0.834	-0.059	2.791	0.128	1.956	0.021	0.704	4.1	0.313	0.79	-2.134	1.641	0.474	K	
0.492	-0.025	1.889	1.556	2.425	2.88	0.555	0.282	0.291	0.002	3.261	0.755	2.593	0.082	0.791	-0.119	-0.56	0.436	-1.04	11.767	-0.051	P	
0.543	0.069	1.763	1.562	1.341	2.9	0.168	-0.075	0.603	-0.008	3.302	-0.075	2.567	0.019	0.892	3.411	0.592		-1.346	3.856	0.517	T	
0.481	0.038	1.777	1.636	2.427	3.814	0.195	0.808	0.751	-0.023	3.055	0.579	2.81	0.029	1.182	1.451	-0.221	0.516	-0.413	2.528	0.994	S	
0.481	0.041	1.7	1.568	1.889	3.145	0.223	1.119	0.777	-0.019	3.615		2.73	0.011	0.679	4.164	0.681	0.551		2.322	-0.083	N	
0.418	0.05	1.876	1.157	0.968	3.124	0.118	1.456	0.503	-0.01	3.323	-0.032	2.104	0.037		5.502		0.069	-1.528	2.401	0.158	Q	
0.465	0.028	1.758	1.573	1.169	2.891	0.108	-0.031	0.425	-0.019	3.245	0.247	2.101	0.031	0.956	3.578	0.942	0.556	-1.041	2.233	0.382	C	
0.506	0.052	1.762	1.271	0.966	2.414	0.104	0.288	0.237	-0.014	3.046	-0.075	1.121	-0.007	0.621	4.593	-1.527	0.078	-1.29	3.136	-0.188	V	
0.456	0.057	1.763	1.025	0.192	2.289	0.111	1.568	0.494	-0.014	2.672	0.263	2.269	0.041	0.766	5.082	1.845	0.073	-0.423	3.08	0.168	I	
0.512	0.024	1.732	1.477		1.522	-0.004	0.99	0.779	-0.015	1.216	-0.362	0.581	-0.014	0.477	2.665	-1.561	-0.328	-2.397	1.601	-0.341	L	
0.606	-0.199	1.533	1.266	0.458	0.792	-0.28	0.651	0.465	0.004	1.204	-0.106	0.117	-0.006	-0.3	2.305	0.057	-0.304	-2.273	1.709	-0.571	M	
0.597		1.821	1.243	2.667	3.288	0.301	0.521		0.006	3.924	0.805	2.913	0.043	1.19		1.284	1.209	-0.149		1.741	G	
0.483	0.251	1.805	1.641	2.612	3.31	0.191		0.109	-0.025	3.903	0.513	2.559	0.009	0.957	0.756	0.727	0.683	-0.68	1.881	0.569	A	
0.404	-0.033	1.601	1.263	2.249	2.606	0.103	2.046	0.595	-0.016	2.808	0.301	1.838	0.01	0.867	4.694	0.181	0.299	-0.15	2.922	0.27	Mean	



0.189	-0.008	0.481	0.293	0.953	0.521	1.156	1.399	0.095	1.331	1.708	1.464	0.391	0.09	0.765	1.704	-1.118	0.28	0.486	6.681	0.664	0.177	W
0.653	3.353	-0.738	-0.126	0.559	-0.724	0.22	0.985	0.968	0.415		1.537	0.071	0.134	1.129		-0.774	-1.676	0.218	7.284	3.43	0.2	Y
0.654	0.917	-1.839		1.117	-0.701	0.255	0.927	-0.215	1.985	-0.279	1.538	-0.181	0.433	1.077	-0.431	1.326	-1.937	0.876	1.01	1.154	0.249	F
0.864	1.451	0.843	-0.052		2.054	-0.147	0.778	0.967		-1.387	1.748	0.669	1.159	0.923	0.873	0.471	0.313	1.668		0.536	0.167	D
0.802	0.348	0.103	0.022	-0.337	1.915	0.463			2.106	0.652	1.644	0.54	1.018	0.651	0.839	-0.251	-0.619	1.191	1.755	1.176	0.199	E
0.101	0.271	0.066	1.048	0.834	1.269		1.031	0.038	1.129	0.773	0.562	0.541	0.751	1.509	0.233	-0.301	-0.392	0.618	2.535	0.426	0.25	H
0.933	-0.851	0.252	0.055	1.688	0.173	-0.421	1.014	0.447	2.295	-0.419	0.069	0.253	0.381	1.037	0.845	-0.358	0.167	1.457	4.139			R
0.763	-0.006	-0.392	-0.027	0.084		1.285	0.854	0.437	2.026	-0.807	1.437	0.431	0.413	0.576	0.229	-0.523		1.005	1.308	0.505	0.317	K
0.962	0.647	0.817	1.059	1.063	4.036	1.861	0.879	0.563	2.463	-1.808	1.73	0.654	0.964	1.548	0.415	0.034	-1.129	-0.052	2.154	0.462	0.251	P
0.375	-0.173		0.445	0.25	0.626	0.873	1.034	-0.148	2.017	-1.293	1.375	0.405	0.443	1.36	0.749	-0.496	-0.383	3.141	1.639	0.4	0.183	T
	0.293	1.419	0.036	1.28	2.248	1.428	1.087	-0.102	2.008	-1.173	1.562	0.521	1.099	1.54	0.665	-0.044	-1.328	1.885	1.788	0.241	0.183	S
0.106	0.061	0.933	-1.069	0.458	0.869	0.464	-0.454	0.252	0.343	-1.676	1.339	0.67	0.936	1.436	0.617		-1.415	1.881	1.338	0.388	0.184	N
0.846		-0.091	-0.165	-0.089	1.09	0.796	-0.085	0.325	2.078	-0.777		-0.112	0.94	1.142	0.349	-0.411	0.311	1.498	1.926	0.473	0.226	Q
0.789	0.019	0.015	-0.06	0.465	1.312	1.003	0.562	-0.283	2.304	-0.96	1.578	0.429	0.675	1.574	0.663	-0.364	-1.87	1.357	0.203	0.377	0.183	C
0.945	-0.107	-0.702	0.068	0.069	0.993	0.295	0.553	0.108	2	-1.071	1.451	0.335	0.399	1.863	0.436	-0.612	2.26	2.176	0.285	0.439	0.183	V
0.916	0.3	-0.968	-0.111	-0.118	0.697	1.347	1.431	0.998	1.981	-0.852	1.258	0.352	0.249	0.533	0.4	-0.393	2.737	1.886	2.245	0.477	0.2	I
0.723	-1.267	-0.77	-0.085	-0.472	0.255	0.427	0.586	0.485	1.873	-1.109	1.458			0.488	0.302	-0.878	-1.521	1.14	1.502	0.496	0.183	L
0.476	-0.554	-1.078	0.102	-0.201	-0.34	0.959	0.927	0.472	2.091	-1.192	1.467	0.011	-0.099		-0.371	-0.971	-0.851	1.141	1.144	0.284	0.203	M
1.119	0.674	1.943	0.124	1.788	2.659	2.376	0.312	0.425	2.502	-1.492	1.67	0.544	1.065	1.72	1.142	0.078	-0.876		-0.382	0.397	0.246	G
0.661	0.482	0.621	0.176	0.979	1.638	1.488	0.407	0.212	2.352	-0.937	1.568	0.512	1.02	1.736	0.609	-0.115	-0.993	1.097	0.043	0.397	0.183	A
0.678	0.308	0.048	-0.019	0.546	1.084	0.849	0.667	0.114	1.858	-0.742	1.392	0.287	0.59	1.19	0.54	-0.44	-0.47	1.298	2.031	0.67	0.209	Mean

ACE2

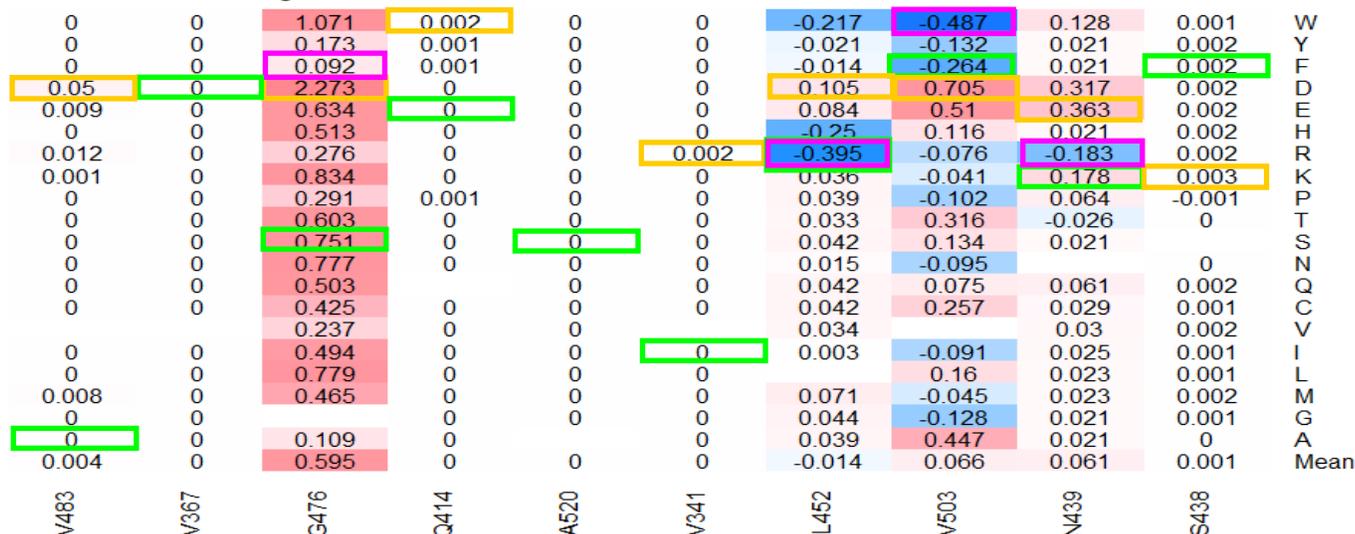
Supplementary Figure 4. Heatmaps show the $\Delta\Delta\Delta G$ of the mutations in RBD residues and ACE2 residues that make van der Waals contacts. Maximum (yellow) and Minimum (magenta) $\Delta\Delta\Delta G$ values are labelled for each residue position.



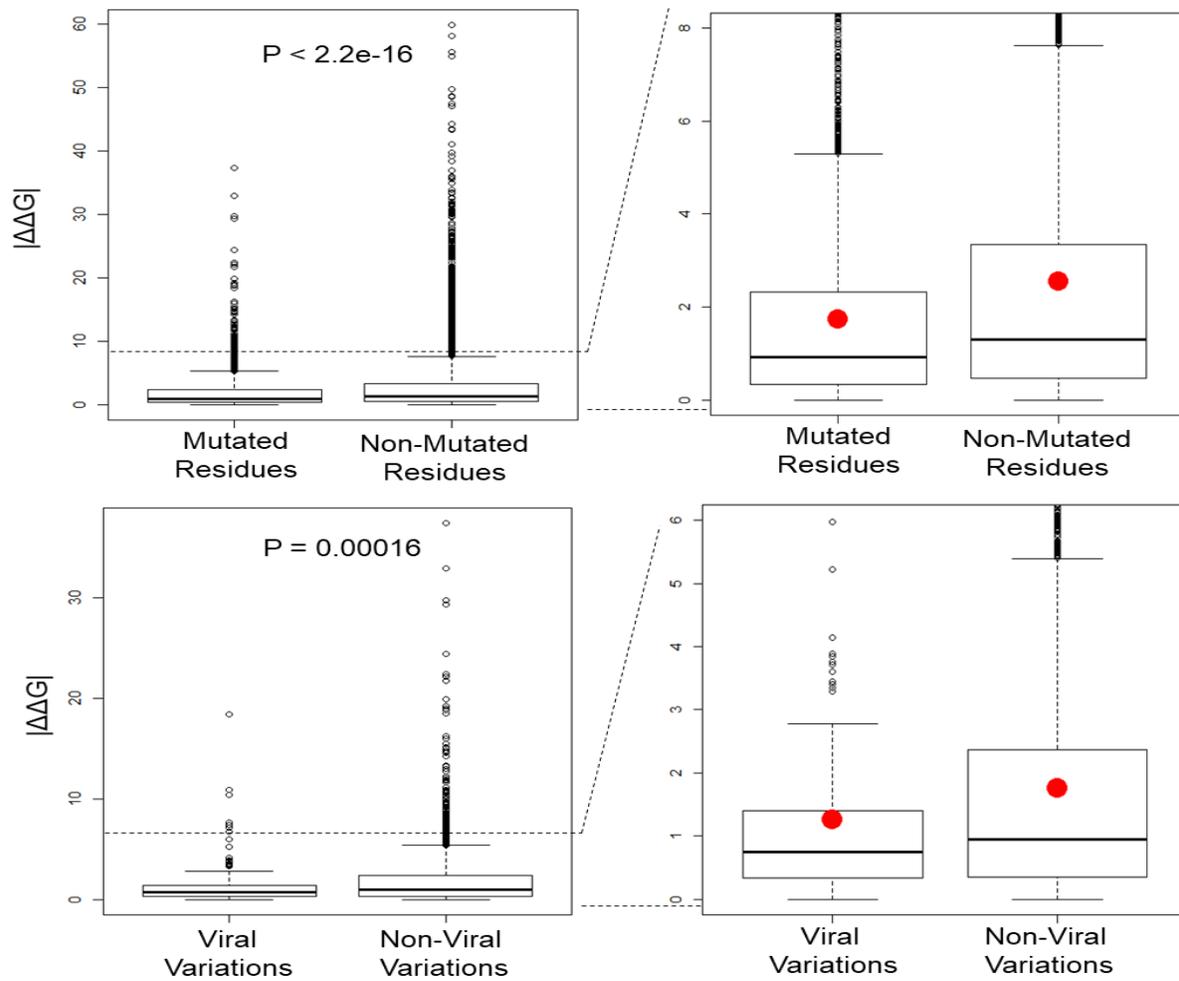
B. RBD Stability



C. RBD-ACE2 Binding



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



Supplementary Figure 6. Boxplots for the $|\Delta\Delta G|$ of mean of residues with and without viral mutations (upper) and $|\Delta\Delta G|$ 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 ($\Delta\Delta G$) is computed based on the monomer.