Binding affinity improvement analysis of multiple-mutant Omicron on 2019-nCov to human ACE2 by In-silico predictions

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Abstract

Since the outbreak of COVID-19 in 2019, the 2019-nCov coronavirus has appeared diverse mutational characteristics due to its own flexible conformation. One multiple-mutant strain (Omicron) with surprisingly infective activity outburst, and affected the biological activities of current drugs and vaccines, making the epidemic significantly difficult to prevent and control, and seriously threaten health around the world. Importunately exploration of mutant characteristics for novel coronavirus Omicron can supply strong theoretical guidance for learning binding mechanism of mutant viruses. What's more, full acknowledgement of key mutated-residues on Omicron strain can provide new methodology of the novel pathogenic mechanism to human ACE2 receptor, as well as the subsequent vaccine development. In this research, 3D structures of 32 single-point mutations of 2019-nCov were firstly constructed, and 32-sites multiple-mutant Omicron were finally obtained based one the wild-type virus by homology modeling method. One total number of 33 2019-nCov/ACE2 complex systems were acquired by protein-protein docking, and optimized by using preliminary molecular dynamics simulations. Binding free energies between each 2019-nCov mutation system and human ACE2 receptor were calculated, and corresponding binding patterns especially the regions adjacent to mutation site were analyzed. The results indicated that one total number of 6 mutated sites on the Omicron strain played crucial role in improving binding capacities from 2019-nCov to ACE2 protein. Subsequently, we performed long-term molecular dynamic simulations and protein-protein binding energy analysis for the selected 6 mutations. 3 infected individuals, the mutants T478K, Q493R and G496S with lower binding energies − 66.36, -67.98 and − 67.09 kcal/mol also presents the high infectivity. These findings indicated that the 3 mutations T478K, Q493R and G496S play the crucial roles in enhancing binding affinity of Omicron to human ACE2 protein. All these results illuminate important theoretical guidance for future virus detection of the Omicron epidemic, drug research and vaccine development.

Introduction

Since the breakout of Coronavirus disease 2019 (Covid-19) reported on December 8th 2019, millions of people have been infected and more than 3.3 million people were killed, making this epidemic difficult to prevent and possessed health dangerous to the human beings [1]. Currently, numerous studies have been conducted on Covid-19, and significant scientific achievements including effective drugs (Molnupiravir and Paxlovid) [2–3] and vaccines [4–6] including have been authorized for emergency needs.

It is worth noting that the virus has shown multi-point mutational characteristics, and can significantly affect the coronavirus activity function, and even affect the current drug and vaccines function, significantly increasing the difficulty of epidemic prevention and control, and seriously threatening the human health and life safety of the world. One new variant of the novel coronavirus B.1.1 has been detected in South Africa, and trigger rapidly increase of testing positive cases [7]. Preliminary studies by British scientists found that compared with wild-type SARS-nCov, the local B.1.1.7 strain is 70% stronger infective, making the virus more difficult to prevent [8]. The new Delta variant AY.4.2 is highly contagious, more than 200% as contagious as previous variants [9]. In September 2020, the new SARS-CoV-2 variant in Denmark was detected that can reduce the neutralization and immune protection effects of vaccine, and may even abolish the current novel coronavirus vaccine [10]. The first B.1.617 double mutant (E484Q and L452R) found in India on March 2021 was more infective and able to evade neutralizing antibody recognition, reducing the effectiveness of existing vaccines [11].

What's more, one new mutant with > 50 mutations (Omicron) were first reported in South Africa. Moreover, 60% of these mutations occur on the spike region that play critical roles in binding to human cells [12]. Until December 16th, the Omicron strain has appeared in more than 89 countries and regions, presented significantly faster transmission spread than any existing mutants [13]. Researches conducted by HongKong university indicated that three doses of the BNT or Pfizer vaccine can not produce enough antibody levels to fight against the Omicron variant [14]. Further investigations of Omicron mutant own milder infective properties than that of Delta virus. As of 16 December 2021, the variant has been confirmed in more than 80 countries and in all continents except Antarctica [15]. The World Health Organization estimates that by mid-December Omicron likely was in most countries in the world, whether they had detected it or not [16]. The Omicron strain is more likely to cause respiratory infections, but not to the deep tissues of the lungs and therefore not easy to cause more harm to the body [17]. All these reports suggest that the Omicron was more harmful to human beings. Therefore, the study of novel coronavirus mutation characteristics can provide stronger theoretical guidance for the binding mechanism of Omicron, as well as the subsequent vaccine development.

Herein, one total number of 36 structures (34 single mutants affecting the spike protein and one multiple mutant with 34 mutations) were constructed by homology modeling method. We then investigated the interaction patterns and binding affinities between ACE2 and all 36 mutants by in silico analysis. Results indicated that 16 single point mutations including T95I, G142D, Δ211, S371L, S373P, K417N, G446S, S477N, E484A, Q498R, N501Y, Y505H, D796Y, Q954H and N969K possess better binding energy higher than − 55.18 kcal/mol. 6 mutants (G339D, Q493R, G496S, S375F, N440K and T478K) owns lower that − 60.00 kcal/mol and were selected for further binding modes analysis. Subsequently, > 180ns long time molecular dynamic simulations were operated and binding energy analysis for the 6 mutations indicated that T478K, Q493R and G496S play the crucial roles in enhancing binding affinity of Omicron to human ACE2 protein.

Materials And Methods

Homology modeling

Multiple-mutant with 34 mutations on 2019-nCov-Spike region based on wild-type Omicron and ACE2 complex was obtained by Homology modeling method. Homology models are useful to guide mutational experiments about the structure-functional relationship, and reliable in predicting the conformation of the insertion or deletion. The primary structure sequence of Omicron was compared with the target protein (PDB ID: 6VXX) for sequence blasting, and select the protein most similar to the target protein as the template for homology module construction. A high sequence similarity 95% was existed between wild-type Spike and Omicron strain. Homology modeling construction was executed by using MODERLLER module [18].

Structure preparation of 184 multiple-mutants and MD simulation

Mutational process of the 3-dimensional multiple-mutant structures was performed using the Pymol software. Molecular dynamics simulations were performed to explore the dynamic and binding differences of the tertiary changes associated with the mutations. 1500 kcal/mol force was applied to all the heavy atoms on the Spike and ACE2 proteins during the MD simulations.The root mean square deviation (RMSD) of the heavy atoms of each multiple mutant was examined until the MD simulations reached equilibrium.Binding free energies of the 2019-nCoV-Spike / ACE2 mutants were extracted for differential analysis.

Results

Mutation sites on Omicron strain

The variant Omicron owns 60 mutations compared with the original Wuhan variant (Table 1 and Fig. 1). Among the mutations, 50 non-synonymous mutations, 8 synonymous, 2 non-coding mutations were detected on the 2019-nCov virus and 34 mutations were found to be distributed on the spike region. Interestingly, 3 small deletion mutations and 1 small insertion mutation and 15 single mutation are located in the 2019-nCov-Spike/ACE2 receptor-binding interface domain. It also carries some changes and deletions in other genomic regions. Interestingly, only one mutation was distributed in the Envelope domain. In addition, this variant has 3 mutations on the Membrane site. The ORF1b and Nucleocapsid region also have 11 and 4 mutation sites respectively [19].

Table 1
Distributions of mutation sites on Omicron variant

Region	Mutations
Spike	A67V, Δ69–70, T95I, G142D, Δ143–145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
ORF1ab	nsp3 (K38R, V1069I, Δ1265, L1266I, A1892T), nsp4 (T492I), nsp5 (P132H), nsp6 (Δ105–107, A189V), nsp12 (P323L), nsp14 (I42V)
Envelope	T9I
Membrane	D3G, Q19E, A63T
Nucleocapsid	P13L, Δ31–33, R203K, G204R

The Spike protein play a critical role in identifying and binding the host cell surface receptors, and mediating the fusion of viral envelope to the cell membrane. The spike protein is like a "key" and the ACE2 receptor on the cell is like a "lock". The key is locked for the virus to enter the cell. The main goal of developing the COVID-19 vaccine is also to prevent keys from opening locks to prevent the virus from infecting cells. Thus, learning mutation sites on Omicron spike proteins will supply an extremely important driving role for drug and vaccine development.

Currently, multiple crystal structures of the 2019-nCov-Spike/ACE2 complex have been resolved in the RCSB PDB database. In this paper, structure of the SARS-nCov-2 spike glycoprotein (closed state) with RCSB PDB ID: 6VXX [20] was selected, and excess elements including waters, ions and peptides were deleted for structural studies. Spike protein belongs to the trimer with the top region on each monomer, which was capable of tightly binding to ACE2. All amino acids on each protein between the 2019-nCov-Spike protein and ACE2 within the 15nm distance from each other were set as the binding interface.

As shown in Fig. 1, amino acid mutation sites on the Spike region were uniformly distributed over the Spike region. Among them, the mutation sites which were adjacent to the ACE2 binding interface, is more important for the stability of 2019-nCov/ACE2 complex due to the strong structural interference on the complex system. Here, we selected the 32 amino acid mutation sites on the Spike region for subsequent analyses.

Structure Constructions Of 34 Single-mutants And 1 Multiple-mutant

The 3D structures of the wild-type 2019-nCov/ACE2 complex system was directly extracted from the crystal structure with PDB ID: 6VXX. Subsequently, single-point mutants based on the wild-type Spike protein were constructed by using the mutated wizard module on Pymol software [21]. One total number of 34 single point mutations were obtained.

Binding Energies Of 35 Mutants

Mutation of an amino acid on protein often causes the variation of biological function. We firstly performed primary molecular simulations for 34 single-point mutant and 1 multiple mutant. We used the molecular dynamics software Amber 16 [22] to conduct structural optimization for each 2019-nCov-Spike/ACE2 mutant complex. The whole protein system was parameterized with gaff and AMBER ff99SB force fields. The whole protein complex was geometrical centered with a 10Å plus cubic water box, and electrically neutralized by adding Na + ions. The first step was heating balance process which the whole system was balanced by using the temperature control method of 100ps. The boost balancing process was then balanced for 100ps, and an isotropic Berendsen pressure control method was added. An unrestricted molecular dynamics simulations for free simulation phase was conducted. Temperature and pressure control method is the same as in the previous stage. One 10Å cut-cutoff distance between 2019-nCov and ACE2 protein was used for van der Waals and short-range electrostatic energy calculation, and the long-range electrostatic energy was calculated using the PME method. During molecular dynamics simulations, we force 1500 kcal/mol on all heavy atoms for each protein. Each positional optimization time was at least 6ns per system. Binding energy between the ACE2 protein and the 2019-nCov-Spike mutation system was calculated by using the MMPBSA module based on the 6ns molecular dynamic simulation, as shown in Table 2.

Table 2
Binding energies (Kcal/mol) of 35 mutants 2019-nCov-Spike/ACE2 complex.

Mutations	Energy	Mutations	Energy	Mutations	Energy	Mutations	Energy
Q498R	-47.26	G142D	-52.09	N679K	-56.03	Δ143–145	-57.23
G446S	-47.98	N969K	-52.45	A67V	-56.03	P681H	-58.25
D796Y	-49.06	T95I	-53.11	L212I	-56.08	T478K	**-60.09**
E484A	-50.37	S477N	-53.21	T547K	-56.24	N440K	**-60.40**
N501Y	-50.69	Q954H	-54.89	ins214EPE	-56.38	Q493R	**-61.08**
K417N	-50.82	Δ211	-55.10	N856K	-56.38	S375F	**-61.72**
Y505H	-51.27	**Wild**	**-55.18**	H655Y	-56.80	G339D	**-62.21**
S373P	-51.28	Δ69–70	-55.21	D614G	-57.10	G496S	**-65.31**
S371L	-51.32	L981F	-55.77	N764K	-57.19	34-mutations	-83.29

6 Mutations Triggered Lower Binding Affinity Of 2019-ncov-spike To Ace2

The binding free energy of wild-type 2019-nCov-Spike/ACE2 protein complex was − 55.18 kcal/mol. Among the 34 single point mutant systems, a total of 16 single point mutations with energy higher than >-55.18 kcal/mol were T95I, G142D, Δ211, S371L, S373P, K417N, G446S, S477N, E484A, Q498R, N501Y, Y505H, D796Y, Q954H and N969K. This result indicated that mot all mutation appeared in Spike region on 2019-nCov virus can lead to increased binding capacity with human ACE2 protein. For 12 mutations, the energy is almost unchanged compared with that of the wild-type complex, indicating that these mutation sites, do not affect much of the binding patterns between the virus and human beings. In addition, 6 complexes (G339D, Q493R, G496S, S375F, N440K and T478K) owns lower that − 60.00 kcal/mol, accounting for 17.14%, indicating that the Omicron COVID-19 mutant have a high frequency that improve the viral infectivity. Notably, for both mutations at G496S and G339D, the binding energies of simulated system were − 65.31 kcal/mol and − 62.21 kcal/mol respectively. Crucially, the multiple mutant system with 32 mutations on the Spike protein has a minimum energy of -83.29 kcal/mol, which is completely consistent with the expected results, because the Omicron virus has an extremely strong infectious capacity.

It can be seen from the Fig. 2 that there being basic rules of the predicted energy distribution in the protein structure. Among them, the mutation sites possessing lower energies were almost close to the 2019-nCov-Spike/ACE2 binding interface. Mutation sites owning similar binding energies with that of wild-type Spike proteins are generally far away from the binding interface. More importantly, the 6 mutation sites with lower energy than − 60.00 kcal/mol were all located on the Spike region, spread from G339 to Y505. Among which, the Q493R and G496S were directly involved in forming binding interface of 2019-nCov-Spike/ACE2 complex. All these results prompted us one deeper insights into the effects of mutations on the entire Spike protein structure and binding mode difference of 6 mutants (<-60.00 kcal/mol) and the multiple mutant.

400ns Md Simulations For 6 Single-mutant And 1 Multiple-mutant

For the selected 6 single-point mutations (T478K, N440K, Q493R, S375F, G339D and G496S) and 34-point mutation system, one 400ns long time molecular dynamics simulations were conducted. Molecular dynamics were carried out by using the software Amber 16. Binding analysis and binding free energies were calculated for protein-protein 2019-nCov-Spike/ACE2 complex after equilibrium phase based on the molecular dynamics trajectories for each system.

The root mean variance (RMSD) represents the dispersion of centroid coordinates means, which can reflect the structural changes of the protein. During the molecular dynamics process, the RMSD trend between initial structure and each time are monitored in real time, and the molecular dynamics simulation is stopped until the RMSD value is stable.

As shown in Fig. 3, RMSD values for all the six single-point mutants exhibited large and drastic fluctuations, indicating the instability of virus to the human receptor ACE2. Each mutation can cause the apparently initial structural changes for 2019-nCov/Spike complex within the starting 1 ~ 30ns time range, and the RMSD vales

keeps floating up and down, indicating the conformation changes when the virus binds to the human ACE2 protein. Within the 30 ~ 190ns range, RMSD values for 6 single-point mutations (T478K, N440K, Q493R, S375F, G339D and G496S) maintained smoothly between 10Å and 14Å, indicating that the relatively stable binding modes between Spike and the human ACE2 protein. Notably, compared with 6 single point mutant systems, the multiple-mutant Omicron possessed relatively lower RMSD value. RMSD value for the multiple-mutant with 34-point mutations finally fluctuated from 6Å to 8Å. Relatively lower RMSD value, meaning the smaller structural alteration, also indicates the weaker conformation change of multiple-mutant system itself. All results imply the smaller swing of multiple-mutant system 2019-nCov-Spike/ACE2. It's interestingly to note that the co-existing 34 mutations for Omicron strain does not trigger larger conformation change, but made itself relatively more stable to bind with human ACE2.

Table 3 Binding free energies (Kcal/mol) between each mutant and ACE2 protein.

System	$\Delta E_{VDWAALS}$	ΔElectronic	ΔE_{GB}	$\Delta E_{SURFACE}$	ΔE_{GAS}	ΔE_{SOL}	ΔE_{TOTAL}
T478K	-95.2880	-1308.6568	1351.4505	-13.8726	-1403.9448	1337.5779	-66.3669
N440K	-90.7503	-1536.1082	1573.4960	-13.4663	-1626.8585	1560.0297	-66.8288
Q493R	-88.6793	-1088.8846	1123.6100	-14.0337	-1177.5639	1109.5763	-67.9876
S375F	-89.2105	-857.6900	893.8887	-13.3961	-946.9005	880.4927	-66.4079
G339D	-87.3446	-1143.4603	1177.7766	-13.7657	-1230.8049	1164.0109	-66.7940
G496S	-95.4827	-770.1586	812.1509	-13.6003	-865.6413	798.5506	-67.0907
34-mutations	-98.7460	-962.5140	990.7028	-15.2413	-1061.2599	975.4614	-85.7985

VDWAALS = van der waals contribution from MM.

EEL = electrostatic energy as calculated by the MM force field.

EGB = the electrostatic contribution to the solvation free energy calculated by GB respectively.

ECAVITY = nonpolar contribution to the solvation free energy calculated by an empirical model.

DELTA G binding = final estimated binding free energy calculated from the terms above. (kCal/mol).

Difference Analysis Of Binding Modes

In order to elucidate the binding patterns of 2019-nCov-Spike to ACE2 protein in different mutants (6 single point mutants and 34-point mutant), we performed a comparative analysis of their structural difference especially the binding interfaces. Assessing the binding surface areas between these possible interfaces indicates that wild-type 2019-nCov-Spike wrap over ACE2 on the lowest level. The predicted interface here was consistent with the crystal structure of 2019-nCov-Spike/ACE2 (PDB ID 6VXX). According to the combined surface area values between 2019-nCov-Spike and human ACE2 protein, the wild-type mutant owns the minimum contacting surface area 206$Å^3$ (ACE2) and 164$Å^3$ (Spike), which was in corresponding with the lowest binding free energies of -55.18 kcal/mol. Whereas for 6 single-point mutants T478K, N440K, Q493R, S375F, G339D and G496S, the

contacting surface areas were 179Å^3 (ACE2)-237Å^3 (Spike), 180Å^3 (ACE2)-240Å^3 (Spike), 179Å^3 (ACE2)-228Å^3 (Spike), 179Å^3 (ACE2)-226Å^3 (Spike), 186Å^3 (ACE2)-232Å^3 (Spike), 179Å^3 (ACE2)-237Å^3 (Spike) and 202Å^3 (ACE2)-260Å^3 (Spike). Interestingly, the six single-point mutants possessed the lower binding energies within −66.3669~-67.9876 kcal/mol. Residues of the single-point mutant 2019-nCov-Spike protein forms more intensive binding interface than that of wild-type virus. What's more, among all mutants, the Spike protein of Omicron has the lowest binding capacity to the human ACE2 at -85.7985 kcal/mol. As shown in Fig. 4, we extracted two surface area difference for both Spike and ACE2 the binding patterns when compared to humans.

Binding Modes Difference Between Human Ace2 And Mutants

We next investigated how the mutation sites influence the regional structure of 2019-nCov-Spike to the human ACE2 protein, and analyzed the important residues of 7 mutants which disturb the physicochemical properties of binding interface. The 6 single-point mutants were divided into two categories according to the distance from binding interface: (1) mutation sites not directly form the binding interface (G339D, S375F and N440K); (2) mutation sites formed direct interactions with ACE2 (T478K Q493R and G496S).

As shown in Fig. 5, the mutation sites G339D, S375F and N440K were located far from the binding interface, and weakly changes of mutation resulted in the conformation fluctuation near the mutation site. In mutant G339D, the system possessed relatively stronger binding capacity − 66.7940 kcal/mol than that of wild-type complex with − 55.18 kcal/mol. The binding modes of ACE2 and 2019-nCoV-Spike were shown in Fig. 5A. Typical hydrogen bond interactions including N343-R509 and N343-D339 play significant roles in maintaining structural stability for mutant G339D. Figure 6 mapped the conformation differences at the same position S375/F375 between wild-type and mutant S375D. From Fig. 6, we can see that one weak hydrogen bond interaction was formed between the hydroxyl group of Y508 to S375 on Spike protein. Binding affinities for mutant S375F decrease obviously was − 66.4079 kcal/mol. This obviously conformation variation resulted the intensive contacting between mutant Spike and human ACE2 protein. A relatively higher energy variation (N440K: -66.8288, wild-type: -55.18 kcal/mol) occurred due to the different binding modes for residues near mutation N440K. Binding modes data indicated that atoms on chemical group amin -NH3 from residue K440 make new hydrogen bonds with residue N437, as shown in Fig. 5C.

Similar results were also observed for mutants T478K, Q493R and G496S. These three mutation site are all located at the binding interface, and directly structural perturbations on the protein structure were observed in all 3 mutants. In mutant G496S, amino acid S496 of Spike region formed good hydrogen bonds with the adjacent residues K353 and D38 on ACE2. In wild-type coronavirus, only normal hydrogen bonds were formed between Q493(Spike) and E35-K31(ACE2). However, mutated residue R493 from the mutant Q493R formed stronger salt-bridging interaction with opposite E35 amino acid. The same situations were also detected in mutant T478K, as new polar interactions were formed between the mutated K478 and Q42-S19 on human ACE2 protein. The key point was that the residues K478, R493 and S496 on 34-points' multiple mutant Omicron strain simultaneously formed the same interactions as shown in single point mutants T478K, Q493R and G496S. Thus, the new mutated residues K478, R493 and S496 formed intensive polar interactions significantly affect the structural stability of the mutant. Thus, we can infer that these three amino acids K478, R493 and S496 are crucial for high viral infection rates for mutant Omicron strain.

Conclusions

The binding interface of novel coronavirus Omicron and human ACE2 plays the important role in the viral infection. Various mutations, especially those mutations between 2019-nCoV-Spike and ACE2 can result in dramatic changes in viral transmission. Structural investigations of mutations on Omicron strain affect the binding affinity of 2019-nCoV-S1/ACE2 complex can supply significant roles in drug and vaccine study and development. In this paper, we constructed protein-protein complex of 34 single point mutations participating forming Omicron strain, and then optimized the mutant systems by using molecular dynamics simulations. Comparing with the binding free energies of wild-type coronavirus Spike/ACE2 complex (-55.18 kcal/mol), 6 single point mutations G339D, S375F, N440K, T478K Q493R and G496S possessed relatively lower energy values. Binding modes difference analysis residues K478, R493 and S496 on 34-points' multiple mutant Omicron strain played the key roles in forming intensive polar interactions that maintaining structural stability of the mutant. Thus, we can infer that these three amino acids K478, R493 and S496 are crucial for high viral infection rates for mutant Omicron strain.

Declarations

Data Availability

The data used to support the findings of this study are included within the article.

Funding statement

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Author Contributions

Bo Li collected the data and performed the data analysis. Jindan Guo drafted the manuscript. Wenxiang Hu verified the analytical methods. Chuan Qin, Jiangning Liu and Yubao Chen designed the study. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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Figures

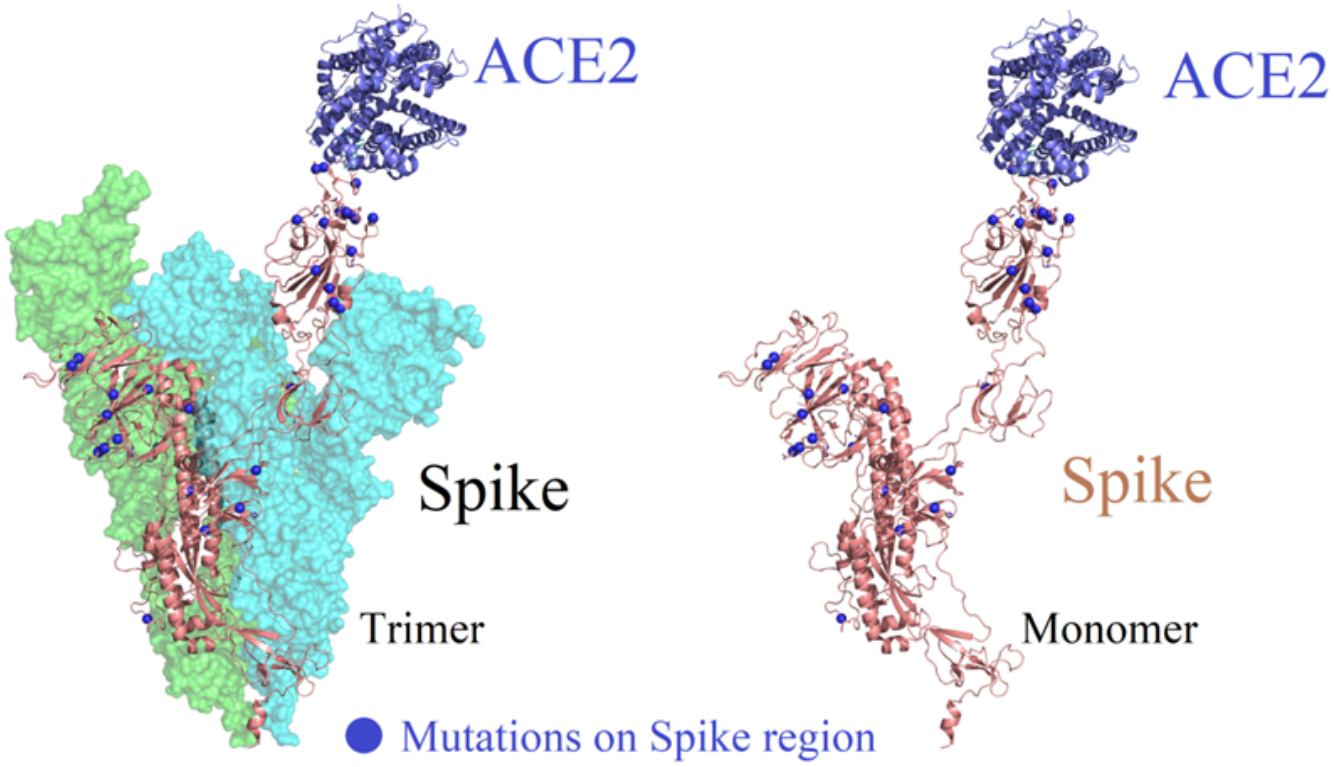

Figure 1

Distribution of 34 mutations on Omicron variant. (A) Overall structure of the Spike with human receptor ACE2. Schematic of 34 mutation sites on the Spike region were shown as shpere. (B) Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2.

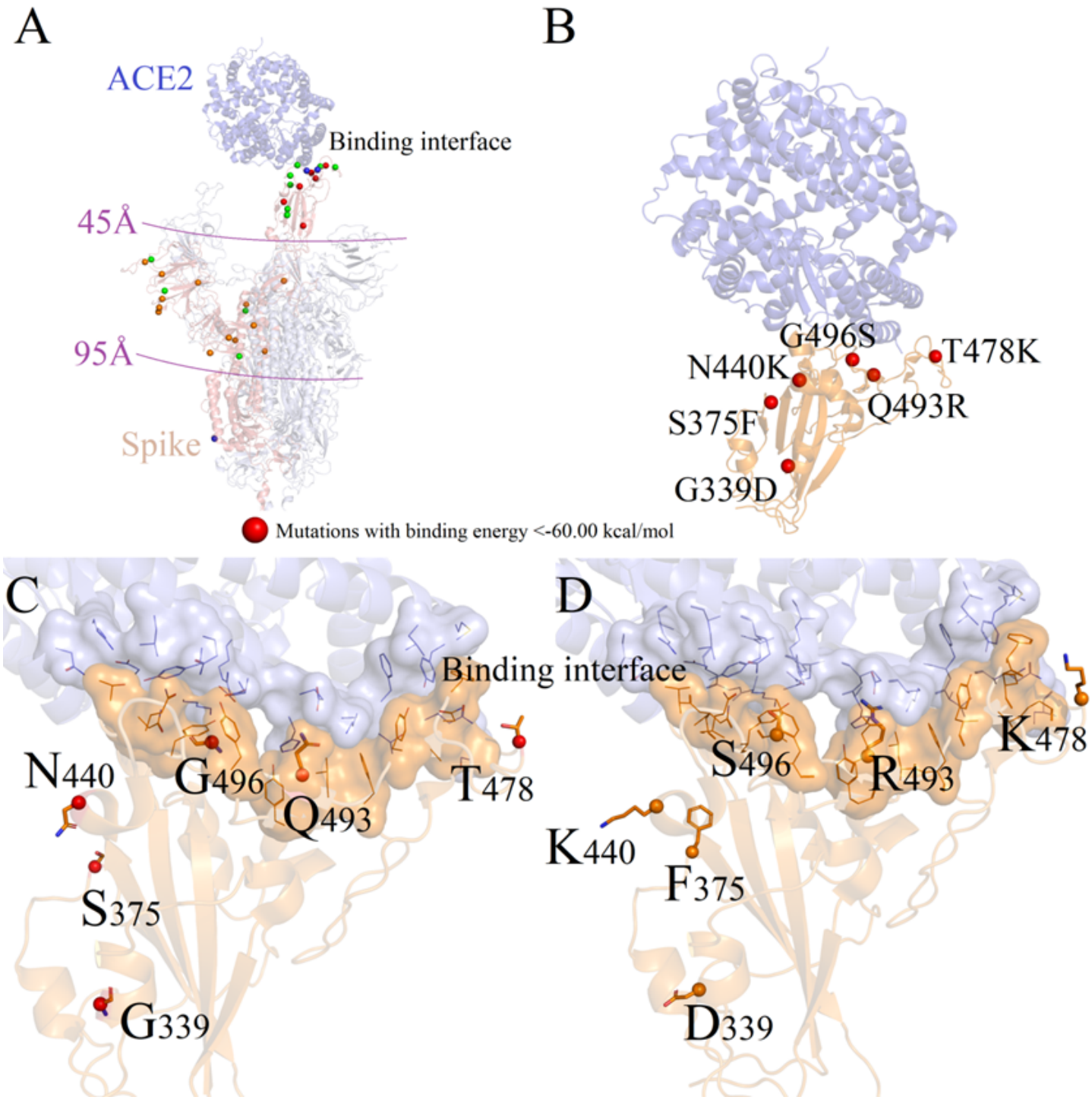

Figure 2

Positions of mutations with binding energies lower than -60.00 kcal/mol on Omicron variant.

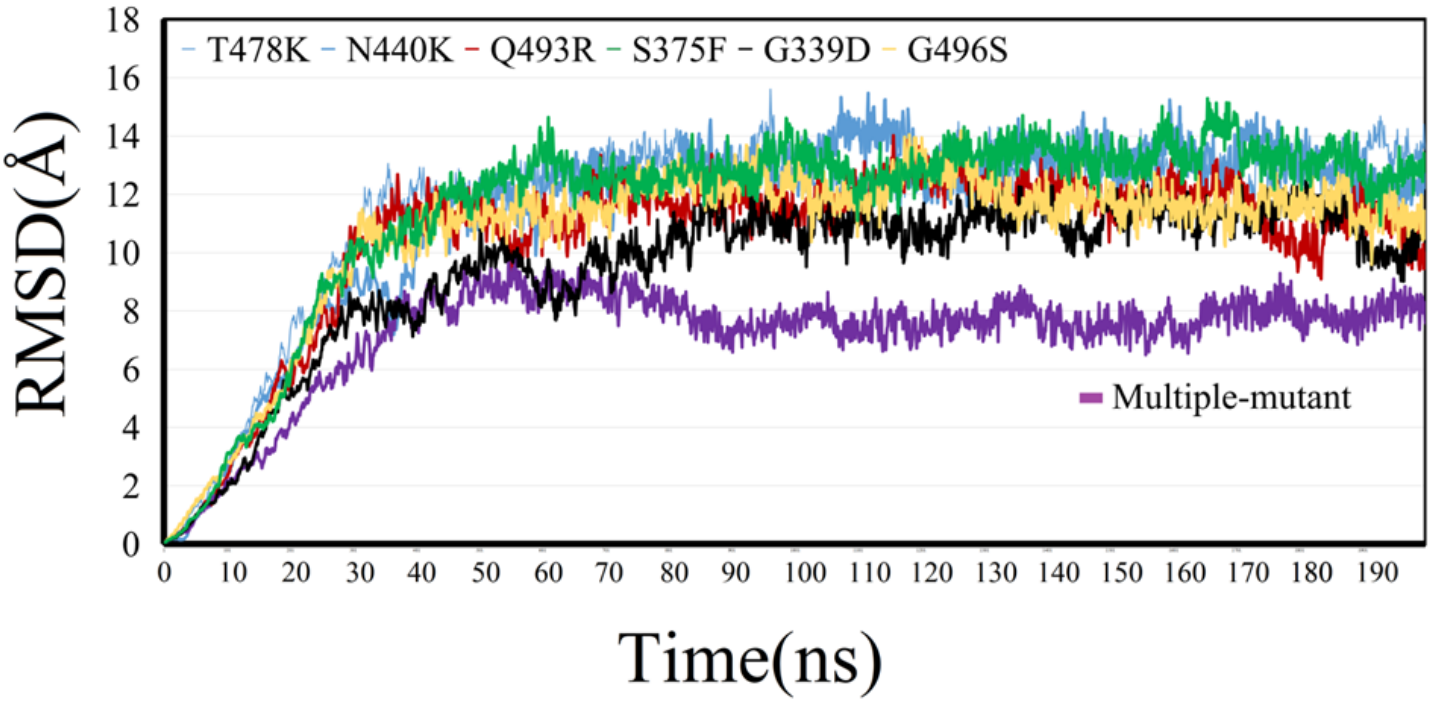

Figure 3

RMSD values for each single-mutant and multiple-mutant

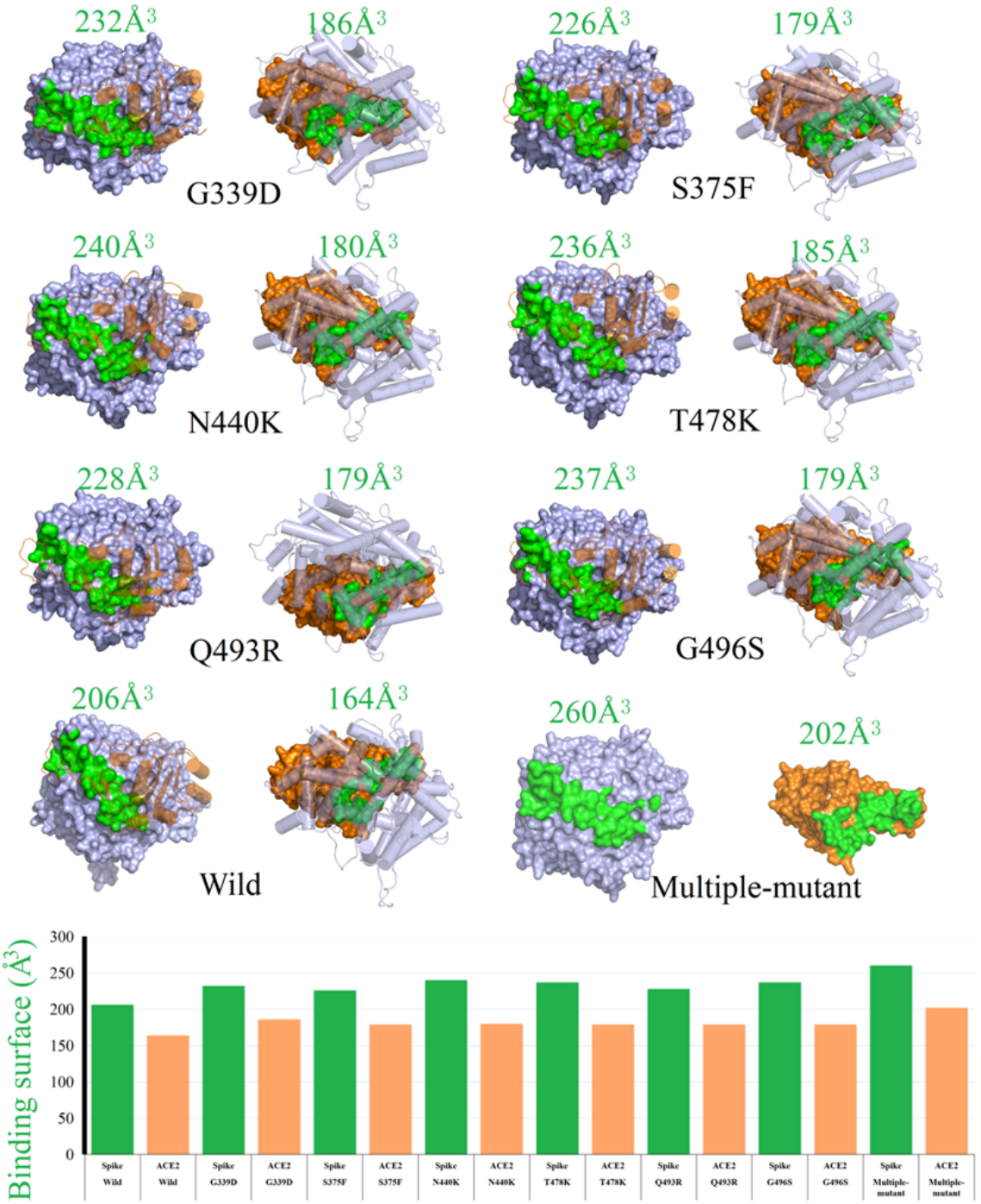

Figure 4

Identifying potential 2019-nCov-Spike/ACE2 binding interfaces. Binding interface are obtained on the surface of 2019-nCov-Spike (left) and ACE2 (right) for wild-type and each mutant complex. Binding surface of Spike and ACE2 were both colored as green. Bindig surface area were counted.

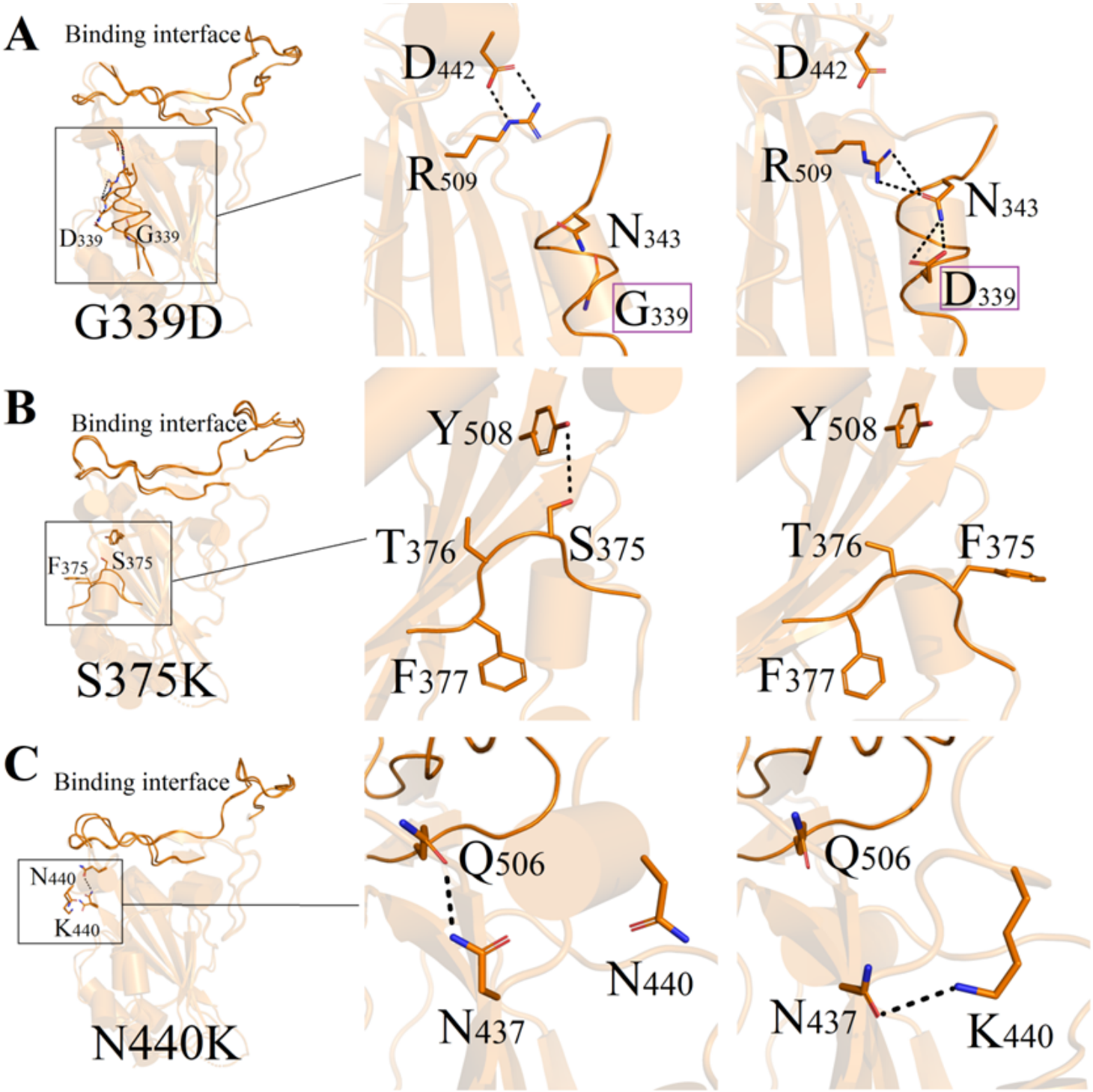

Figure 5

Binding difference of mutation sites between mutants (G339D, S375F, N440K) and wild-type coronavirus. Binding interface of 2019-nCov-Spike (left) and ACE2 (right) for wild-type and each mutant complex. Binding surface were shown as ribbon. Amino acid near mutation site were shown as sticks.

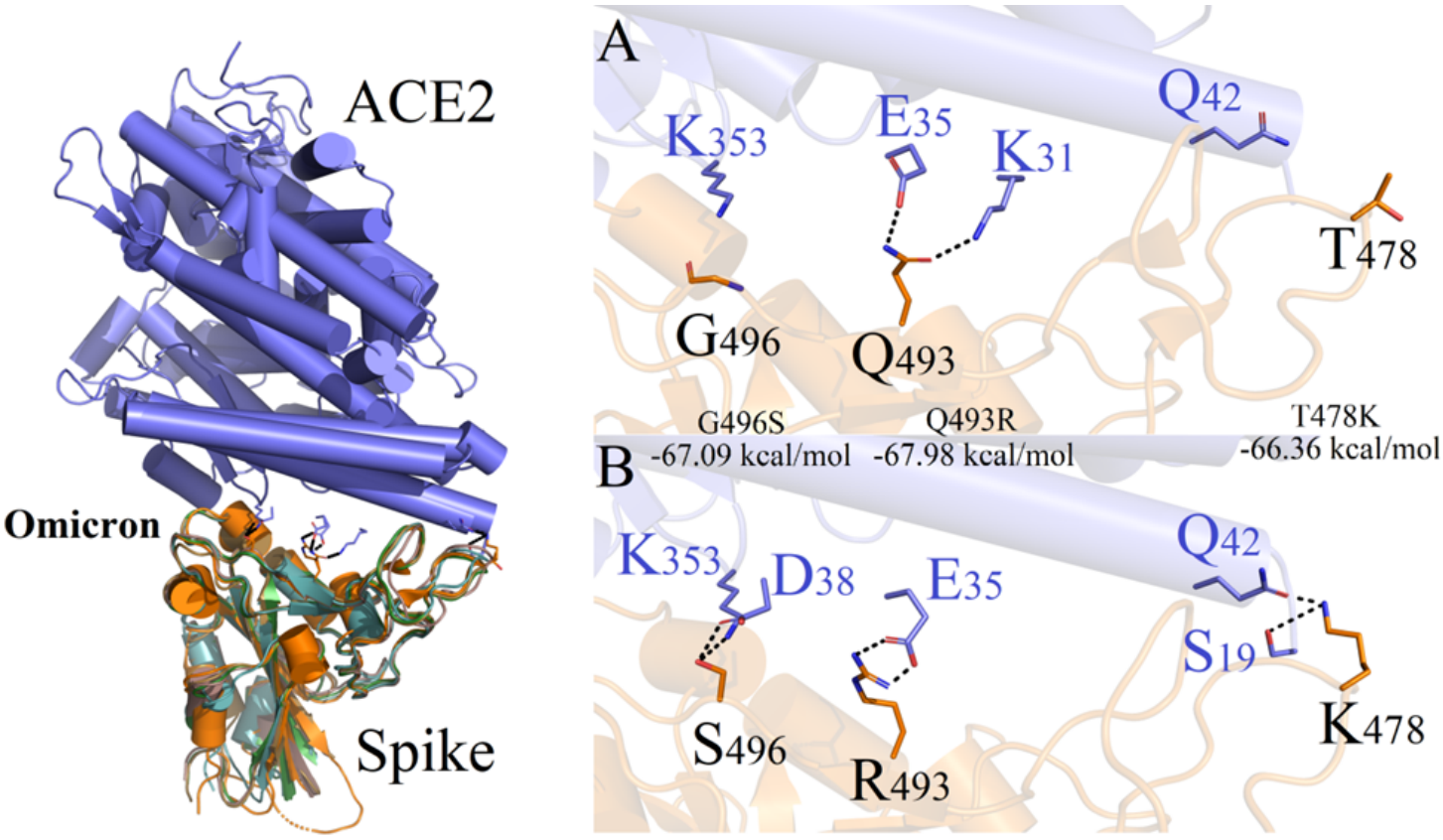

Figure 6

Binding difference of mutation sites between mutants (T478K, Q493R, G496S and Omicron) and wild-type coronavirus. Binding interface of 2019-nCov-Spike (left) and ACE2 (right) for wild-type and each mutant complex. Amino acid near mutation site were shown as sticks.