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Omicron SARS Co-V2 Sub Variants BA.2 and BA.3 have Lower Free Binding Energy than BA.1

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Abstract: COVID-19 is currently a major global public health concern. The newest dangerous type, Omicron, comes in late 2021 and spreads quickly from Africa. There have already been new omicron subvariants discovered. Mutations inside the molecular structure of omicron subvariant induce intriguing molecular changes. The authors undertook a study to examine the effects of mutations in important COVID-19 omicron subvariants, including BA.1, BA.2, and BA.3, based on free binding energy alterations. According to molecular study findings, each studied subvariant has a different free binding energy. The BA.3 has undergone the most changes. As a result, the binding of ACE-2 may be affected. This suggests that the new subvariant may be linked to a higher likelihood of transmission.

Keywords: Omicron, Variant, Subvariant, COVID-19, Binding Energy

Introduction

COVID-19 is a worldwide public health concern. The pandemic has lasted without being fully suppressed since its first appearance in late 2019 (Hsia, 2020). Countless COVID-19 cases have already been collected from around the world. As of December 2021, there is still no effective COVID-19 treatment (Tsai *et al*., 2021). Despite the availability of the COVID-19 vaccine, its efficacy in outbreak management remains a public health concern. There have already been more than 540 million infections worldwide since the first appearance of COVID-19 in 2019. The emergence of a new mutant form of SARS Co-V2 is a critical consideration. Many new hazardous variants are expected to pose a serious threat to public health. The Delta strain is a well-known problematic strain that has caused worldwide outbreaks (Jhun *et al*., 2021). In late 2021, the World Health Organization (WHO) announced the newest dangerous strain, omicron (Callaway, 2021a). The molecule of the omicron version has several modifications.

The omicron version, the most serious type of concern, was discovered in South Africa in November 2021 (Torjesen, 2021; Jhun *et al*., 2021; Callaway, 2021a; Rahimi and Abadi, 2022). This new molecular version has several structural alterations. The World Health Organization identified the omicron variant, also known as lineage B.1.1.529, as a variety of concerns on November 26, 2021. This version has various changes, some of which may be detrimental. The number of cases with the B.1.1.529 lineage is increasing in South Africa. This variance has been linked to an increased risk of reinfection in several studies (Torjesen, 2021; Jhun *et al*., 2021; Callaway, 2021b). WHO is tracking the Pango lineages BA.1/B.1.1.529.1, BA.2/B.1.1.529.2, and BA.3/B.1.1.529.3 under the omicron umbrella. The three primary omicron subvariants now circulating the world are BA.1, BA.2, and BA.3 (Rahimi and Abadi, 2022).

There have already been new omicron subvariants discovered. Following the classification of the initial Omicron version as a Variant of Concern (VoC), a specific inquiry is required to collect data on the implications of novel omicron subvariants. It is still unclear whether omicron subvariants cause more disease than the original omicron or other variants like a delta. Some new data suggests that some parameters may be linked to changes in the transmissibility and virulence of omicron subvariants. For example, a recent study on structural modeling of the Omicron spike protein and its complex with the human ACE-2 receptor revealed that the complex of the Receptor Binding Domain (RBD) with the human ACE-2 receptor contains seven mutations at the interacting interface, which includes two ionic interactions, eight hydrogen bonds, and seven Van der Waals interactions (Koley *et al*., 2022). The RBD domain is more potent to the receptor than its wild-type counterpart based on the frequency and quality of these contacts, as well as other binding biophysical properties (Koley *et al*., 2022).

Furthermore, according to a cryo-electron microscopy investigation, the Omicron RBD alterations may result in novel salt bridges and hydrogen bonds, improved electrostatic surface characteristics, and a stronger spike protein-ACE2 interaction (Hong *et al*., 2022). Furthermore, neutralizing epitopes are severely changed in Omicron, implying that current vaccinations will likely provide limited protection against this form (Fantini *et al*., 2022).

Hospitalization rates for the original omicron form are increasing in South Africa however this could be due to an increase in the overall number of infected patients (Torjesen, 2021; Jhun *et al*., 2021; Callaway, 2021b; Rahimi and Abadi, 2022). A specific inquiry is required to collect data on the implications of novel omicron subvariants. It is unknown whether omicron subvariants are more transmissible than others in terms of transmissibility. Regular universal respiratory transmittable virus prophylaxis is still required to prevent the omicron type. The COVID-19 vaccine, which is currently available, is ineffective against the omicron type. As a result, research into molecular change and its effects are immensely valuable.

Mutations in the omicron molecular level of the variant are thought to induce clinically important molecular structural changes (Torjesen, 2021). It is reported that the omicron is rapidly spreading. The clinical significance of the omicron mutation is an intriguing clinical question. Although there is some information about the original omicron variant, there is little information about the new omicron subvariants. A mutation in the SARS Co-V2 variant could cause a significant change in the receptor-binding region of the free binding energy of the spike protein (Pascarella *et al*., 2021). The influence of the SARS Co-V2 variant on free binding energy modifications could reveal fresh information about the pathobiological mechanism of the virus. The authors conducted a study to investigate the effects of mutations in omicron subvariants based on free-binding energy variants.

Materials and Methods

The objective of the Study

The current research is a molecular genetics bioinformatics study. The authors analyze free binding energy change using a common informatics technique based on a recent reference study (Koley *et al*., 2022). The three-dimensional structure of crystal structure of the SARS CoV-2 spikes receptor-binding domain bound with ACE-2 (PDB code: 6M0J) (Fig. 1), is the primary template for analysis.

Bioinformatics Analysis

Tool

DynaMut is common in silico computational method for predicting the impact of mutations on the stability of molecular complexes (Hong *et al*., 2022).

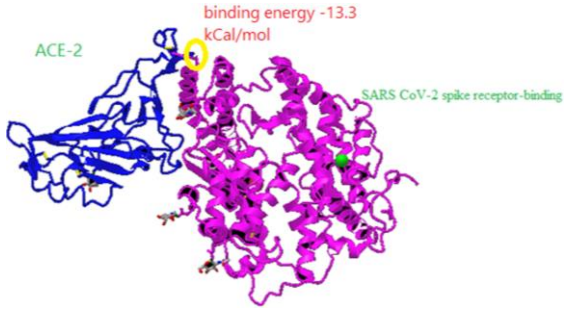

Fig 1: The three-dimensional structure of crystal structure of the SARS CoV-2 spikes receptor-binding domain bound with ACE-2. The yellow circle indicated bonding part *calculation for bonding energy change (ΔΔG) is according to the equation "ΔΔG = bonding energy in subvariant – bonding energy in the original variant"

DynaMut is a web service that implements two well-known normal mode methodologies for researching and visualizing protein dynamics by sampling conformations and assessing the impact of mutations on protein dynamics and stability due to changes in vibrational entropy. The SARS Co-V2 nave wild type is represented by the main template. Then, to execute the in-silico mutation assignment, PyMol (PyMol, version 2.4) is utilized (Rodrigues *et al*., 2018; Seeliger and de Groot, 2010). PyMOL is one of the few open-source structural biology model visualization tools available.

Studied SARS CoV2 Type

The omicron variant and its three main subvariants, BA.1, BA.2, and BA.3, were among the variants investigated. The PyMol was used to assign the mutation into the SARS Co-V2 nave wild-type coding to eventually generate the three focused omicron subvariants.

Outcome Measurement

Electrostatic interactions between proteins influence their stability and function. Calculations of free binding energy can be used to predict electrostatic free energy in molecules. The previously published bioinformatics tool analyses the distribution of free binding energy within and around the molecule to determine free energy.

The change in free binding energy is calculated using the free energy difference (G) between the original micron variant and the omicron subvariant structure. The free energy difference is a measure of the stability of a molecular complex. A lower free binding energy suggests easier binding to ACE-2 formation and a higher likelihood of transmissibility.

Statistical Analysis

In this study, basic descriptive statistical analysis is used. The omicron variant G and the three subvariants are directly compared by a direct arithmetic comparison. The magnitude of change is calculated. A simple degree of change comparison is also carried out.

Table 1: Free binding energy change due to omicron variant and its three important subvariant

SARS CoV2 type	$\Delta\Delta G$ (kcal/mol)
Original omicron variant	0.00
BA.1 omicron subvariant	+1.04
BA.2 omicron subvariant	-1.20
BA.3 omicron subvariant	-1.99

Results

Each omicron analyzed had a different free binding energy change. The differences in free binding energy in omicron variants and their three subvariants are shown in Table 1. The BA.3 is the one that has changed the most. As a result, the binding of ACE2 may be affected.

When compared to the conventional omicron variant, the BA.2 and BA.3 subvariants have a negative change, whereas the BA.1 subvariant have a positive change. As a result, in the case of BA.1, greater energy for binding to ACE2 should be predicted, while in both BA.2 and BA.3, less energy for binding to ACE2 should be expected.

Discussion

Understanding the pathogenesis of COVID-19 remains a key clinical concern as a newly emerging disease. The therapeutic significance of a novel COVID-19 variant is typically questioned when it is identified. Omicron is a newly discovered SARS Co-V2 variant with many mutations. The mutation is expected to alter the severity and transmissibility (Vaughan, 2021; Russell, 2021; Thakur and Ratho, 2022), although clinical evidence on the new variant is currently lacking. It is the most recent omicron type to be recognized for its high transmission rate potential (Tsai *et al*., 2021). Changes in molecular genetics are assumed to be linked to the ease of transmission.

The chemical structure of the omicron version has been altered significantly. Changes in molecular characteristics can be caused by mutations. This study focuses on an important property called electrostatic potential. The pathomechanism generating changes in transmission rate and antibody response has been identified as free binding energy. The transmission of the original omicron variant is undeniably quick (Callaway, 2021a), but the specific phenomena in the new subvariants remain a myth.

The glycoprotein of SARS-spike CoV-2 essentially mediates entry into host cells, and ACE-2 has been identified as a cellular receptor (Yang *et al*., 2020). The ACE-2 receptor and the S-glycoprotein serve as the binding interface for the RBD, which also extracts the kinetic and thermodynamic characteristics of this binding pocket (Yang *et al*., 2020). An essential stage in pathogenesis is the binding process (Yang *et al*., 2020). As a result, examining the shift in binding to the ACE2 can provide useful information for dealing with the introduction of new omicron subvariants. According to this study, the free binding energy has changed significantly. Alterations in free binding energy could indicate ACE-2 binding changes. According to this study, changes in binding occur, which could have an impact on the transmissibility of the new omicron subvariants. According to this research, B.A2 and B.A3 have a higher risk of transmission. This could explain why the new omicron subvariants have spread so quickly over the world (Callaway, 2022).

The authors believe that a mutation within the virus molecule caused the clinical features of the virus to shift. This could be accomplished by altering a molecular biological process. This research identified a shift in free energy binding, which may explain the new clinical characteristics of the subvariants. It is important to remember that this is a bioinformatics study. It can give a preliminary indication based on an in-silico experiment. To reach a definitive judgment on the exact effect of the omicron subvariant, more in vitro and in vivo research is required.

In addition to the free energy, which has already been mentioned, various other parameters that influence the transmissibility and pathogenicity of omicron subvariants are also discussed. In addition to free energy, those variables/descriptors that are responsible for the increased transmissibility of the omicron subvariant must be highlighted. More research is needed to determine the impact of several factors on the transmissibility of the omicron subvariant.

Conclusion

The current preliminary study on free binding energy change in the omicron subvariants reveals that the magnitude of change is greater than that of the well-known original omicron variant. Because of the novel omicron subvariants, there may be issues with increased transmissibility of the new subvariants.

Author's Contribution

Rujittika Mungmunpuntipantip: 50% ideas, writing, analyzing and approval for final submission.

Viroj Wiwanitkit: 50% ideas, supervising and approval for final submission.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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