SARS-CoV-2 Omicron BA.2.75 variant may be much more infective than preexisting variants

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Abbreviations: spike protein gene, S gene; angiotensin-converting enzyme 2, ACE2; receptor-binding domain, RBD

ABSTRACT

Objectives: In our previous research, we have reported mathematical model with molecular simulation analysis to predict the infectivity of seven SARS-CoV-2 variants. In this report, we aimed to predict the relative risk of the recent new variants of SARS-CoV-2 based on our previous research.

Methods: We subjected Omicron BA.4/5 or BA.2.75 variant of SARS-CoV-2 to the analysis for the evolutionary distance of the spike protein gene (S gene) to appreciate the changes of the spike protein. We performed the molecular docking simulation analyses of the spike protein with human angiotensin-converting enzyme 2 (ACE2) to understand the docking affinity in these variants. We then compared the evolutionary distance and the docking affinity of these variants with that of the seven variants which were analyzed in our previous research.

Results: The evolutionary distance of the S gene in BA.4/5 or BA.2.75 from the Wuhan variant were longer than the other variants. The highest docking affinity of the spike protein with ACE2 (ratio per Wuhan variant) was observed in BA.2.75.

Conclusion: It is important to note that BA.2.75 has both the highest docking affinity and the longest evolutionary distance of the S gene. These results suggest that the infection of BA.2.75 can be spread further than preexisting variants.

Introduction

In Japan, Omicron BA.5 variants of SARS-CoV-2 is being epidemic as of July in 2022. In addition, Omicron BA.2.75 is discovered and concerned as the coming epidemic. We have previously constructed a mathematical model to predict the infectivity of SARS-CoV-2—Wuhan, Alpha, Beta, Gamma, Delta, Omicron BA.1and BA.2 variants (Takaoka et al., 2022). In this research, we report the predicted risk of Omicron BA.4/5, and BA.2.75 which are recently being epidemic, by using our methodology in the previous report (Takaoka et al., 2022).

Materials and methods

Determination of the evolutionary distance between Wuhan variant and variant S genes, docking affinity of each spike protein with ACE2

We analyzed the evolutionary distance of S gene between the Wuhan variant and Omicron BA.4/5, or BA.2.75 according to our previous method (Takaoka et al., 2022). The sequences of the S gene were obtained by searching EpiCoV database of GISAID for the one with complete sequence in S gene: Accession IDs for Omicron BA.4/5, EPI_ISL_13410397; BA.2.75, EPI_ISL_13438754 respectively (Elbe et al., 2017; Khare et al., 2021).

The docking affinity of the receptor binding domain (RBD) of each spike protein

of these variants with ACE2 was analyzed by docking simulation and cluster analysis as in our previous report (Takaoka et al., 2022). The docking affinity is calculated by the following expression:

$$\frac{A}{A_{Wuhan}}^{\left(\frac{B}{B_{Wuhan}}\right)}$$

where A is the average score of the most stable cluster and B is the score of the most stable complex in the docking result.

The amino acid sequences of spike proteins were obtained from CoVariants website which classifies the variants by Nextstrain clades: 22A (Omicron, BA.4), 22B (Omicron, BA.5) and 22D (Omicron, BA.2.75) (Hadfield et al., 2018; Hodcroft 2021). BA.4 and BA.5 have the identical spike proteins and thus the sequence of the S gene or amino acid sequence were grouped together in this research.

Results

Evolutionary distances for S gene variants and results of docking of RBD with ACE2 protein

Table 1 shows the S gene evolutionary distances between the Wuhan variant and each of the other variants, as well as the docking affinities of RBD of the spike protein with ACE2 (ratio per Wuhan variant) which are resulted from the docking

simulation. The variants with longer evolutionary distance from the Wuhan variant had a tendency toward more epidemic. Omicron BA.2.75 variant was observed the highest docking affinity of the spike protein with ACE2 protein.

In comparison with BA.2, BA.4/5 has longer S gene evolutionary distance but showed lower docking affinity. Meanwhile, BA.2.75 showed not only longer evolutionary distance but also much higher docking affinity than that of BA.2.

Discussion

In this report, we analyzed the evolutionary distance of the S gene and the docking affinity with ACE2 of the recent new variants, BA.4/5 and BA.2.75. We focused on only the S gene sequence to calculate the evolutionary distance, not using genome sequence as in the phylogeny provided by Nextstrain (Hadfield et al., 2018).

We consider that the following two factors play important roles for the infectivity: the ability of virus to enter into human cells and the effect of neutralizing antibody in human or the effect of vaccines. The former is shown by the docking affinity of each RBD in the spike protein with ACE2, which is the higher, the greater. The latter is shown by the evolutionary distance of the S gene: The longer the distance is, the weaker the effect would be. It is based on the fact that the currently

117 available vaccines are developed based on Wuhan variant (Hassine 2022).
118 However, it should be kept in mind that the risk for the exacerbation of SARS-
119 CoV-2 cannot be appreciated in this method.
120 Omicron BA.2.75 showed the highest docking affinity of the spike protein with
121 ACE2 protein among the other seven variants (ratio per Wuhan). In addition, the
122 S gene evolutionary distance of BA.2.75 was the longest from the Wuhan variant.
123 Therefore, BA.2.75 has high ability to enter into human cells and simultaneously
124 the current vaccines are much less effective to this variant. These results suggest
125 that the infection of BA.2.75 can be spread further than preexisting variants and
126 the need for a strong note of caution.
127
128
129 **Conclusion**
130 We demonstrated that Omicron BA.2.75 variant of SARS-CoV-2 is very high by
131 our results of the evolutionary distance of S gene and the docking simulation for
132 spike protein with ACE2. Our results indicates that Omicron BA.2.75 has a
133 greater risk to global health than the other ten variants. and there is a need for
134 paying close attention to the infection trends of Omicron BA.2.75.
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Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request, except publicly available data source.

Conflict of Interest Disclosures

Authors declare no conflict of interest.

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Author contributions

Y.T. conceived and designed this research. Y.T. and A.S. preformed the analyses and acquired the data. Y.T., A.S., and M.O. interpreted the data. Y.T. and A.S. wrote the draft, and all authors reviewed and approved the manuscript.

Ethical approval statement

This research is not applicable because we performed computer analyses by using sequence data obtained from public database.

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Table 1 The evolutionary distance of the S gene and the docking affinity of spike protein with ACE2 (ratio per Wuhan variant)

	Wuhan	Alpha	Beta	Gamma	Delta	Omicron BA.1	Omicron BA.2	Omicron BA.4/5	Omicron BA.2.75
Evolutionary Distance of S gene (from Wuhan) x 10^-3	-	4.2	4.5	10.8	12.1	14.3	25.6	41.2	46.8
Docking affinity (Ratio per Wuhan)	1	1.15	1.23	1.32	2.40	3.00	7.91	4.82	21.05