Prediction of infectivity of SARS-CoV2: Mathematical Model with Docking Simulation analysis between Spike Protein and ACE2

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Keywords:
SARS-CoV2, COVID-19, infectivity, spike protein, binding affinity, mathematical model

Abstract

Variants of coronavirus (SARS-CoV-2) have been spreading in a global pandemic. It is important to understand quick the infectivity of future new variants for effective countermeasure against them. In this research, we aimed to investigate the prediction of infectivity of SARS-CoV-2 by using mathematical model with molecular simulation analysis and the evolutionary distance of spike protein gene (S gene) of SARS -CoV-2 in the phylogenetic analysis. We subjected the six variants and wild type (WT) of spike protein and Angiotensin-Converting Enzyme 2 (ACE2) of human to molecular docking simulation analyses in order to understand the binding affinity. Then the regression analysis of the coefficient from our mathematical model and the infectivity of SARS-CoV-2 were investigated for the prediction of infectivity.

The evolutionary distance by S gene (spike protein) correlated to the infectivity of SARS-CoV-2 variants. And the coefficient of mathematical model by using the results of molecular docking simulation correlated to the infectivity of SARS-CoV-2 variants, too.

These results suggests that the provided data from the docking simulation for Receptor Binding Domain (RBD) of variant spike protein and ACE2 of human were valuable to the prediction of SARS-CoV-2 infectivity. Finally, we established the mathematical model for the prediction of infectivity in the SARS-CoV-2 variant by using the binding affinity under the molecular docking experiment and evolutionary distance by S gene.

1. Introduction

Novel coronavirus (SARS-CoV-2) in the world-wide pandemic have caused difficulty in doing the countermeasure of infection, because many variants are occurring in succession [1]. Infection control methods for Cov-19 are mainly face wearing of mask, avoidance of close contact (ex. lockdown for urban area), and vaccination [2]. SARS-CoV-2 have been rapidly evolving in infectivity, so the understanding of—infectivity for new variant is important for initial response of pandemic [3].

As a result of evolution, new variant of SARS-CoV-2 is characterized by higher infectivity than the past variant [4-9]. These alteration of infectivity in variant indicates that the infectivity of new coronavirus may be estimated by the evolutionary distance of the S gene (spike protein) between wild-type and variants.

Previously, we reported the mathematical model using docking simulation results for prediction of the UDP-glucuronosyltransferase 1A1 conjugation capacity [10]. And we found the plant leaf extract which is inhibits the binding of SARS-CoV-2 spike protein to ACE2 based on the molecular simulation analyses [11]. Similarly, in silico docking data for the variant form of SARS-CoV-2 spike protein and ACE2 may estimate the infectivity of new variant, too. In

this research, we choose these two approaches with mathematical models for the rapid and deeper understanding of the infectivity of new SARS-CoV-2 variant.

2. Material and methods

2.1 Evolutionary distance from variant S genes and these infectivity

Six variants of SARS-CoV-2, alpha [12], beta [13], gamma [14], delta [15], omicron BA.1 [16], and omicron BA.2 [17], were chosen for this research. Multiple sequence alignment for S gene (spike protein) of the SARS-CoV-2 variants, whose nucleotide sequences of each variant were obtained from NCBI, was analyzed by Clustal W program [18]. Then FastTree [19] with default parameters provided phylogenetic tree and evolutionary distances between each mutant. The infectivity of SARS-CoV-2 variants were obtained from previous research to summarize them as the infectivity index for our research [4-9].

2.2 Analysis of the 3-D structures of SARS-CoV-2 spike protein, docking analysis for RBD and ACE2 protein, and a derivation of mathematical model

The amino acid sequence of wild-type SARS-CoV-2 spike protein was obtained from Uniprot (UniProt ID: P0DTC2). The 3-D structure of SARS-CoV-2 spike protein (PDB ID: 6ZGG), which is an open state trimer was used as the template for homology modeling for wild-type and each variant of SARS-CoV-2 spike protein. The homology modeling was performed by using Molecular Operating Environment (MOE) software (Chemical Computing Group, Montreal, Quebec, Canada). The model structures were then subjected to structural optimization with molecular dynamics (MD) simulation as described in our previous research [20]. After 10000 ps MD simulation of each spike protein, the docking analysis with ACE2 was performed as described below: The ACE2 structure was obtained from PDB (PDB ID: 6M0J). To reduce the search space for docking, the partial structure of the RBD in up conformation was cut out from our simulated structure of SARS-CoV-2 spike protein trimer. Docking sites were defined based on the crystal structure of SARS-CoV-2 spike protein RBD bound with ACE2 (PDB ID: 6M0J). Two thousand docking runs were carried out by using ZDOCK software (University of Massachusetts Medical School, MA). To determine the stable complex group among the docking runs, the ZDOCK scores for the resulting complexes were clustered using the group average clustering algorithm. The upper tail rule [21] was applied to determine the number of

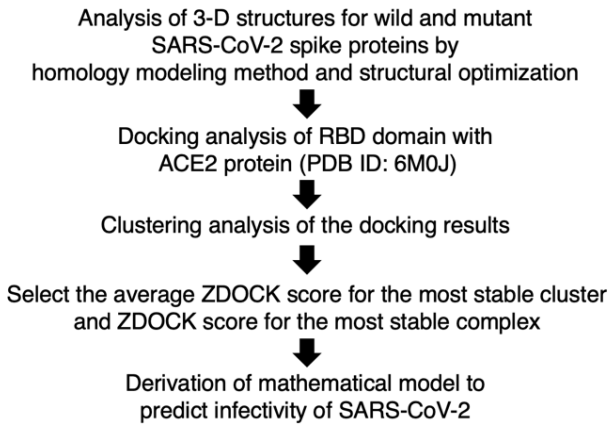

Figure 1. The method used for the molecular simulation analysis.

clusters. The most stable ZDOCK score in the docking runs and the average ZDOCK score of the most stable complex group were used to derive a mathematical model according to our previous research [10]. Figure 1 shows schematic diagram of this research.

3. Results

3.1 Evolutionary distance from variant S gene and docking results of RBD with ACE2 protein

Table 1 shows the evolutionary distance between wild and each variant and docking affinity of RBD with ACE2. After multiple alignment of wild and variant S genes by Clustal W program, FastTree was used to determine phylogenetic tree (data not shown) and evolutionary distance. Binding affinity of SARS-CoV-2 spike protein RBD and ACE2 was defined by ZDOCK score as an indicator. ZDOCK scores were provided to cluster analysis to determine the average ZDOCK scores for the most stable clusters, and the most stable ZDOCK scores. These results were provided for the derivation of mathematical model to predict the infectivity of SARS-CoV-2 variants.

Table 1. Evolutionary distance and binding affinity of SARS-CoV-2 spike protein with ACE2

	Wild	Alpha	Beta	Gamma	Delta	Omicron BA.1	Omicron BA.2
Evolutionary distance	0	0.00420	0.00446	0.01077	0.01209	0.01426	0.02600
The ZDOCK score for the most stable complex	216.076	253.965	264.905	282.820	454.240	509.856	615.442
ZDOCK score for the most stable cluster (Mean±SD)	219.633 ±50.513 (n=10)	247.478 (n=1)	260.243 (n=1)	270.947 (n=1)	428.721 (n=1)	417.824 ±4.936 (n=5)	595.340 ±4.736 (n=3)

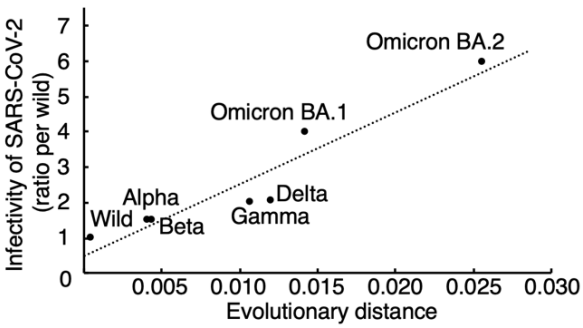

Figure 2. Correlation between evolutionary distance and infectivity of SARS-CoV-2
There were collinearity between the evolutionary distance and infectivity. The Regression line was indicated by dotted line as an equation of "y = 88.812x + 0.6518".

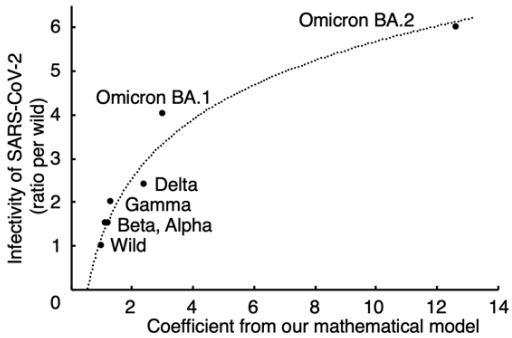

Figure 3. Correlation between infectivity of SARS-CoV-2 and mathematical model based on molecular simulation analyses
Coefficient from our mathematical model with the data of molecular simulation analyses can predict the infectivity of SARS-CoV-2 variants. The Regression curve was indicated by dotted line as an equation of "y = 1.9436ln(x) + 1.2257".

3.2 Derivation of a mathematical model for estimating the infectivity of SARS-CoV-2

A mathematical model to predict the infectivity of SARS-CoV-2 was derived according to our previous research [10]. As shown in Figure 2, the relationship between the evolutionary distance and infectivity of each variant can be represented by the following equation:

$$F = px + q$$

Where x is the evolutionary distance between wild and mutant SARS-CoV-2 spike protein. Constant values p and q were estimated by minimizing the sum of squared error between the calculated infectivity and the reported infectivity (ratio per wild) [4-9].

Then the mathematical model for binding affinity of RBD and ACE2 was derived using the results of docking analyses. Coefficient was derived from the following equation:

$$\frac{B}{B_{wild}} \log\left(\frac{A}{A_{wild}}\right)$$

Where A is the average docking score of the most stable cluster and B is the docking score for the most stable complex. Relationship between the coefficient of variant and the reported infectivity can be described in Figure 3 and represented by the following equation:

$$G = s \times \frac{B}{B_{wild}} \log\left(\frac{A}{A_{wild}}\right) + t$$

Constant values s and t were estimated by minimizing the sum of squared error between the calculated infectivity and reported infectivity (ratio per wild) [4-9]. The infectivity of SARS-CoV-2 (P) is defined by the evolutionary distance and the docking result with ACE2:

$$P = uF + vG + w = u(px + q) + v\left(s \times \frac{B}{B_{wild}} log\left(\frac{A}{A_{wild}}\right) + t\right) + w$$

Constant values u, v and w were estimated by minimizing the sum of squared error between calculated infectivity P and reported infectivity of each SARS-CoV-2 variant V:

$$(u, v, w) = argmin\left\{\sum_{M} (P - V)^2\right\}$$

Where set M represents the SARS-CoV-2 variants whose infectivity are reported. A correlation was shown between the coefficient of mathematical model and the evolutionary distance of SARS-CoV-2 spike protein (data not shown). These results suggest that our mathematical model can predict infectivity of SARS-CoV-2.

Finally, the infectivity of SARS-CoV-2 variants is defined by following equation:

$$P = 0.3074869 \times \frac{B}{B_{wild}} log\left(\frac{A}{A_{wild}}\right) + 1.18598 \times x + 1.3879845$$

4. Discussion

Reported infectivity of SARS-CoV-2 variants were correlated with both evolutionary distance by S gene and coefficient by our *in silico* docking (Figure 2 and 3). For our mathematical model, these two factors could reproduce the reported infectivity better than the model using either factor only in the coefficient of determination (data not shown).

In other previous research, only RBD domain of spike protein were used for the analysis of binding affinity with ACE2 as below: no MD analysis for the structure optimization [22-26] and/or local optimization of only RBD domain [22-28] of spike protein. However, we choose 3-D structure of whole trimer spike protein (PDB ID: 6ZGG) for homology modeling in this research. After MD analysis, we confirmed the trajectory of root mean square deviation (RMSD) and the disallowed regions of the Ramachandran plot for the quality of each variant spike protein structure. Then the RBD domain of trimer variant spike protein structures were provided for the docking analyses with ACE2. So, our experimental strategy can achieve high accuracy because we used imitated molecular simulation method for the behavior of biomolecule. In addition, our previous research [29-34] suggest the usefulness of this prediction by using our molecular simulation methods.

Additional analyses of binding affinity for other spike protein of SARS-CoV-2 variants with ACE2 may provide higher accuracy, and such experiments are now in progress.

Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Autohor contributions

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

Competing interest

Authors declare no conflict of interest.

Acknowledgements

This work was supported by JSPS Grant-in-Aid for Scientific Research grant numbers 21K12110 to Y.T., and 19K12202 to S.A.

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