Possible host-adaptation of SARS-CoV-2 due to improved ACE2 receptor binding in mink

Matthijs R.A. Welkers[1,2], Alvin X. Han[1], Chantal B.E.M. Reusken[2] and Dirk Eggink[1,2]

1) Department of Medical Microbiology & Infection Prevention, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands

2) National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Corresponding author: Dirk Eggink (dirk.eggink@rivm.nl)

Supplementary Material & Methods

Molecular dynamics

To estimate the binding energy changes between the mink ACE and Spike mutations relative to those found in humans, we applied simulated annealing energy minimizations through short molecular dynamics (MD) simulations in YASARA (Krieger and Vriend 2014),which was previously shown to produce a robust linear correlate between computationally predictive and experimentally measured receptor preference of influenza haemagglutinin protein (Guarnaccia et al. 2013). Here, we used the recently published structural complex of SARS-CoV-2 spike receptor-binding domain (RBD) bound to human ACE2 (PDB: 6M0J; Lan et al. 2020) and performed the minimization analysis as follows: First, the structure complex was energy-minimized to remove conformational stress by a short steepest descent minimization. We used the YASARA2 force field with a force cut off of 7.864Å and the Particle Mesh Ewald algorithm (York et al. 1994) to treat long-range electrostatic interactions. We then performed simulated annealing until convergence was reached. The MD simulations proceeded in time step of 2 fs with atom velocities scaled down by 0.9 in every 10^{th} step. Convergence was met if improvements in energy minimization were less than 0.05kJ/mol per atom for 200 steps. Counterions and solvation were both considered implicitly: For the former, net charges were set to zero while solvation was defined by a term that is proportional to accessible surface area. The entropic cost of expositing $1Å^2$ to solvent was estimated to be 1.3kJ/mol. To minimize potential complexities and bias arising from simulations of distant, unrelated atoms, only those within an 8Å radius from the mutated spike and

host-specific ACE2 residues were allowed to move while the rest of the complex were fixed in their respective positions. Finally, binding energy (E) was computed using a function that include standard potential energy terms and the aforementioned implicit solvation term. For each mutation, we performed three iterations of energy minimization for the set of wild-type (WT) and mutant (MT) residues in the viral spike and ACE2 proteins (i.e. three independent estimates of E_{WT} and E_{MT}). We then computed relative binding energy ($\Delta E = E_{MT} - E_{WT}$) and report the mean and standard deviation values across all three iterations.

To validate our approach, besides the RBD substitutions that we had identified in minks (i.e. Y453F, F486L and N501T) to be in contact with in ACE2 receptor, we have also selected substitutions with large affinity-enhancing as well as diminishing effects located at three sites (i.e. 493 486 and 501) that were found to be highly important to ACE2 receptor binding (Starr et al. 2020). We found a weak linear correlation between the predicted binding energy values and the measured average effect on binding (values obtained from Starr et al. 2020; Figure S1). Nonetheless, the estimated binding energies could still afford us to make qualitative inferences of binding affinity changes between Spike RBD the ACE2 receptor.

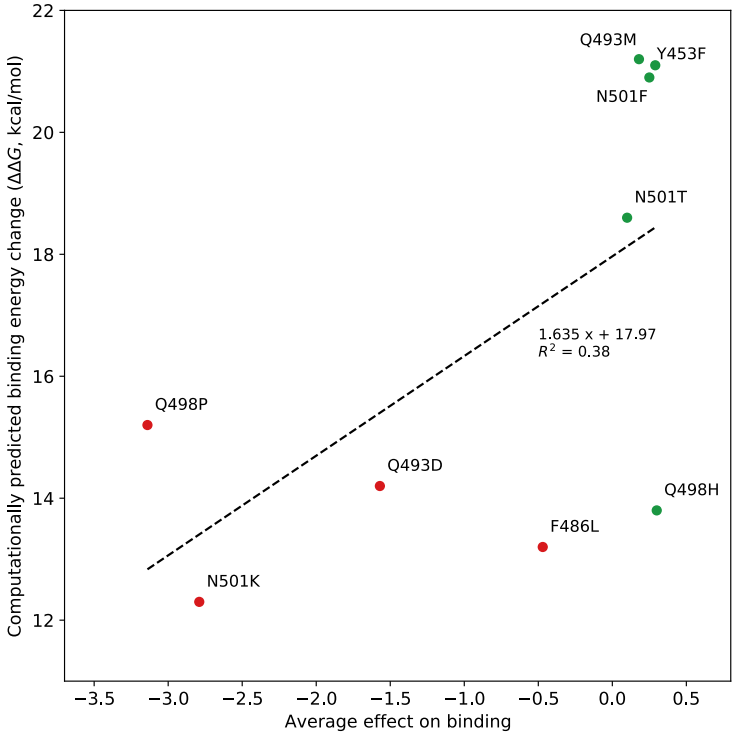

Figure S1. Correlation between computationally predicted binding energy changes and experimentally measured average binding effects of selected Spike protein amino acid substitutions and human ACE2 receptor from (Starr et al. 2020). Mutations found to have increased binding affinity to human ACE2 receptor are coloured in green while those with diminished binding effects are coloured in red.

Table S1. Binding energy changes

Spike mutation	Mean ΔE (S.D.) (kcal/mol)			
	Interacting human ACE2 residue		Interacting mink ACE2 residue	
Y453F	34H	20.9 (2.3)	34Y	22.3 (3.3)
F486L	79L	13.2 (0.8)	79H	22.5 (3.6)
F486L	82M		82T	22.4 (9.3)
N501T	354G	18.6 (1.8)	354R	22.5 (6.1)

References

Guarnaccia T, Carolan LA, Maurer-Stroh S, Lee RTC, Job E, Reading PC, Petrie S, McCaw JM, McVernon J, Hurt AC, et al. 2013. Antigenic Drift of the Pandemic 2009 A(H1N1) Influenza Virus in a Ferret Model. PLOS Pathog. 9(5):e1003354.

Krieger E, Vriend G. 2014. YASARA View—molecular graphics for all devices—from smartphones to workstations. Bioinformatics 30(20):2981–2982.

Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, et al. 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 581(7807):215–220.

Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, Navarro MJ, Bowen JE, Tortorici MA, Walls AC, et al. 2020. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell 182(5):1295-1310.e20.

York DM, Wlodawer A, Pedersen LG, Darden TA. 1994. Atomic-level accuracy in simulations of large protein crystals. Proc. Natl. Acad. Sci. 91(18):8715 LP – 8718.