

Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant

Xue Wang¹, Leonid Yurkovetskiy², Kuang Shen², Jeremy Luban², Natalya Dudkina¹, Kristen Pascal³, Christopher Tomkins-Tinch⁴, Thomas Nyalile², Yetao Wang², Alina Baum⁵, William Diehl², Ann Dauphin², Claudia Carbone², Shawn Egri², Kristen Veinotte², Stephen Schaffner⁶, Jacob Lemieux⁶, James Munro², Ashique Rafique⁷, Abhi Barve¹, Pardis Sabeti⁸ and Christos Kyratsous³

¹Thermo Fisher Scientific, Eindhoven, Noord-Brabant, Netherlands, ²University of Massachusetts Medical School, United States, ³Regeneron Pharmaceuticals, United States, ⁴Harvard University, United States, ⁵3Regeneron Pharmaceutical, United States, ⁶4Broad Institute of Harvard and MIT, United States, ⁷Regeneron Pharmaceutical, United States, ⁸Broad Institute of Harvard and MIT, United States

The SARS-CoV-2 spike (S) protein variant D614G supplanted the ancestral virus worldwide, reaching near global fixation in June 2020. Here we investigated potential structural and functional consequences of this variant and proved its high infectivity.

Assessment of the S protein homotrimer by cryo-electron microscopy single particle analysis showed D614G spike adopts more open conformations compared with the published structure for its ancestral form. Four conformations were observed, corresponding to the open or close state of receptor-binding domain (RBD) in each protomer. However, only two conformations were detected in the published ancestral form structure, which are all three RBD in close state and one RBD in open state. The ratio of these conformations contrasted dramatically. Also, an interprotomer contact was found to be disrupted in the D614G spike and that the conformation is shifted toward an ACE2 binding-competent state, which is modeled to be on pathway for virion membrane fusion with target cells.

Consistent with the more open structure, virion containing D614G spike has higher infectivity on ACE2-positive cells. We found that D614G was more infectious than the ancestral form on human lung cells, colon cells, and on cells rendered permissive by ectopic expression of human ACE2 or of ACE2 orthologs from various mammals, including Chinese rufous horseshoe bat and Malayan pangolin. D614G did not alter S protein synthesis, processing, or incorporation into SARS-CoV-2 particles, but D614G affinity for ACE2 was reduced due to a faster dissociation rate. It was also proved that the neutralization potency of antibodies targeting the D614G spike protein RBD was not attenuated in spite of its higher infectivity.

This work was done in collaboration with University of Massachusetts Medical School, Thermo Fisher Scientific, Regeneron Pharmaceutical, Broad Institute of Harvard and MIT, Harvard University, Massachusetts General Hospital, Harvard T.H. Chan School of Public Health, Howard Hughes Medical Institute and Massachusetts Consortium on Pathogen Readiness.

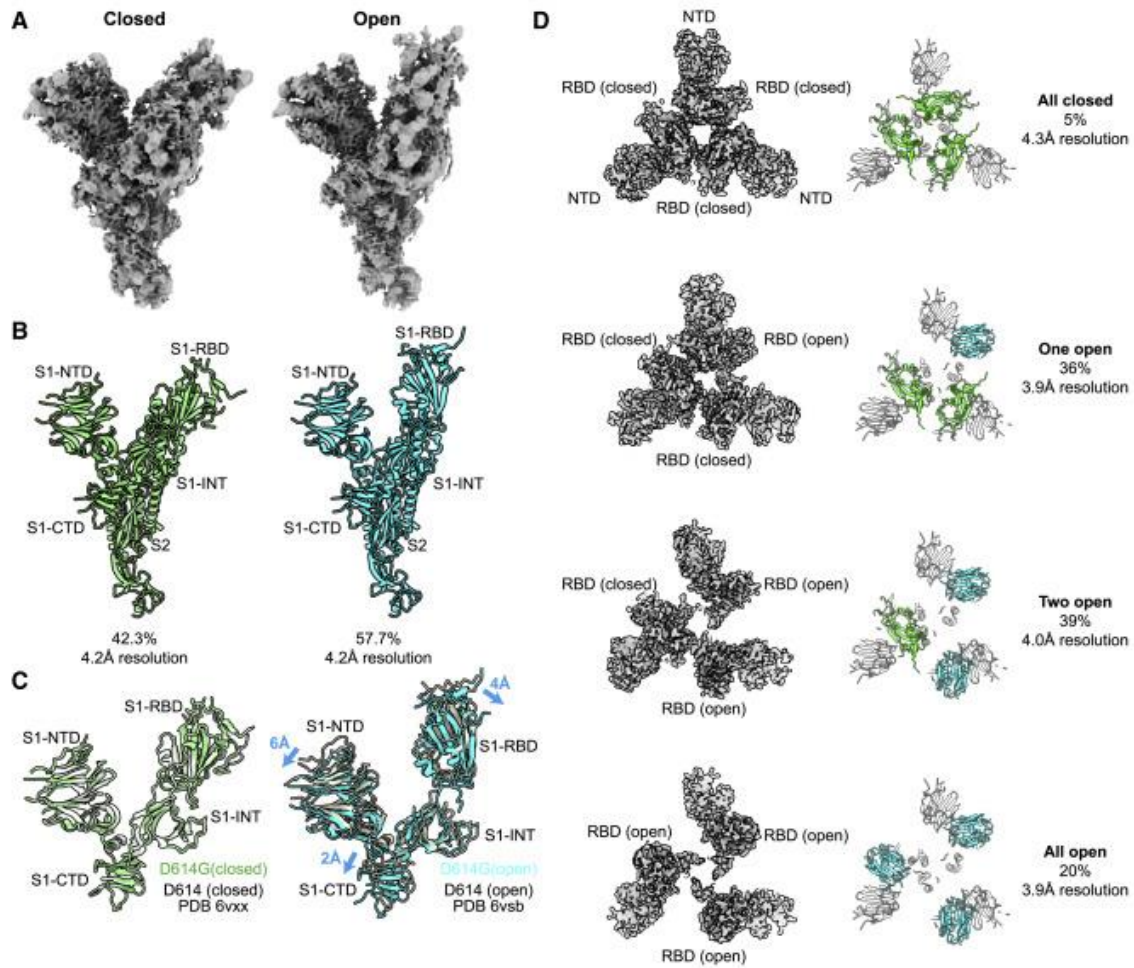


Figure 1. D614G Populates More Open Conformations Than Does the Ancestral S Protein

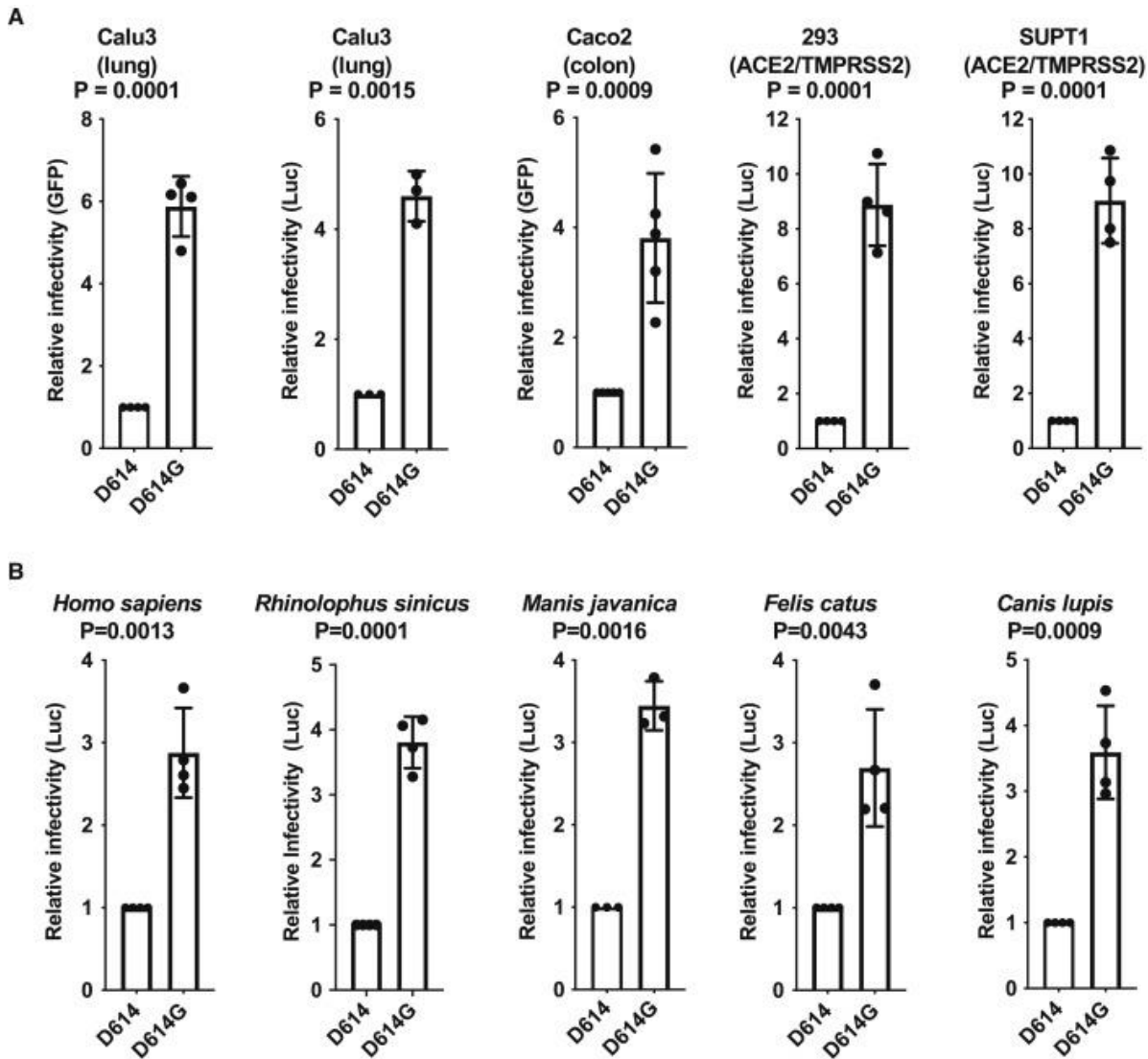


Figure 2. SARS-CoV-2 D614G S Protein Variant Enhances Infectivity of Pseudotyped Lentiviruses in Cell Culture

References

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