How an early mutation in the COVID-19 virus helped it spread so quickly

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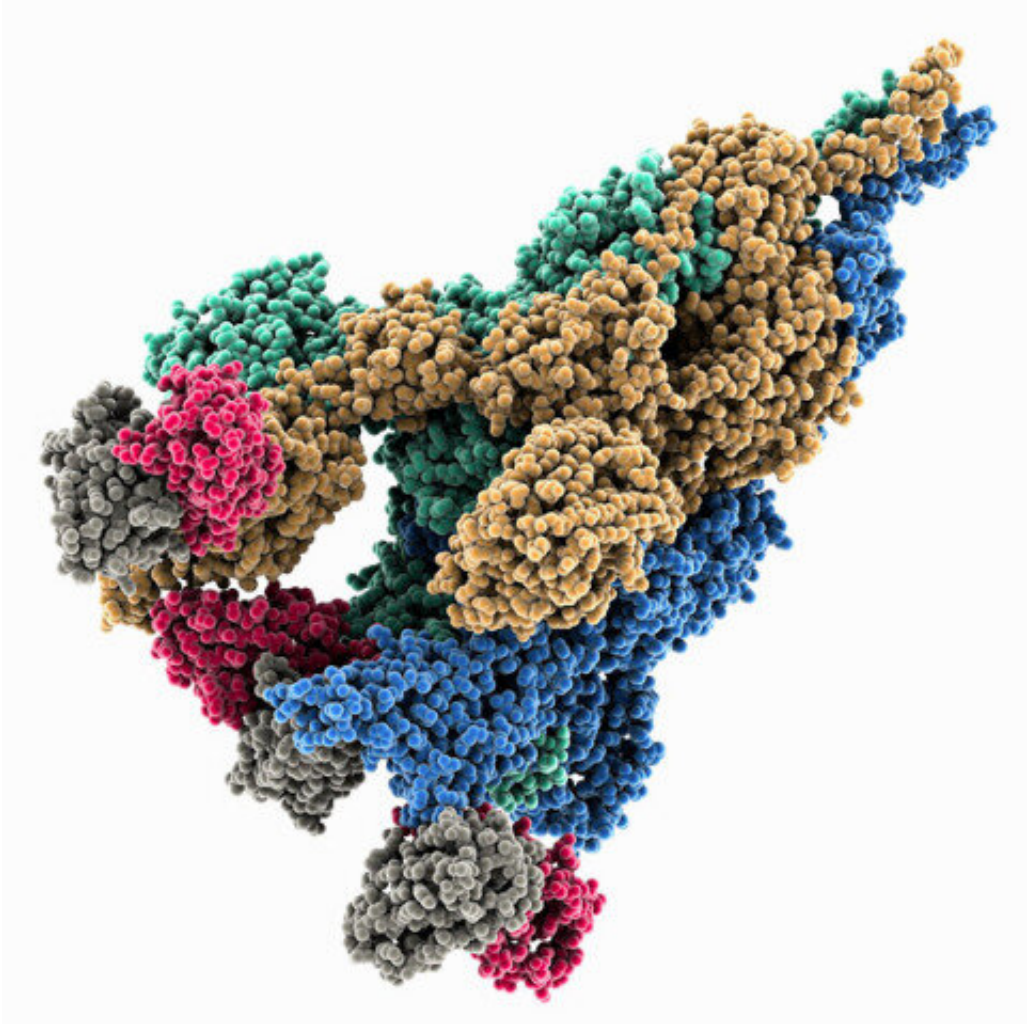

The spike caption of SARS-CoV2, the virus that causes COVID-19. RIKEN researchers have found that the D614G mutation restructures the Spike protein toward a state that is primed for infecting cells. Credit: Laguna Design/Science Photo Library

The rapid spread of COVID-19 may have been partly due to changes in the structure of the SARS-CoV-2 virus wrought by an early mutation in its genome, a detailed analysis by RIKEN researchers suggests. The finding, published in the *Biophysical Journal*, could help inform the development of next-generation vaccines and antiviral drugs.

Alpha, delta, omicron and other variants of concern have been making news throughout the COVID-19 pandemic. But the most significant mutation may have occurred in the early days of the pandemic, and it might have enabled the virus to spread so rapidly.

Yuji Sugita of the RIKEN Center for Computational Science (R-CCS) and Hisham Dokainish, who was at R-CCS at the time of the study, investigated the effect of mutations on viral structure. They did this by simulating the atomic positions of molecules found in different forms of the virus's important spike protein—a tool coronaviruses use to bind and enter human cells.

They found that the substitution of a single amino acid altered this protein's shape, helping SARS-CoV-2 to adapt to human hosts. This finding demonstrates how even tiny mutations—swapping a single amino acid in this case—can greatly affect protein dynamics.

To understand why the mutation proved so advantageous to the virus, the pair ran detailed simulations of the protein's structure and stability. Their analysis—done using the RIKEN Fugaku supercomputer, one of the fastest in the world—revealed how the mutation (known as D614G) breaks an ionic bond with a second subunit of the Spike protein. It also changes the shape of a nearby loop structure, which alters the orientation of the entire protein, locking it into a form that makes it easier for the virus to enter cells.

"A single and local change in an interaction within the molecule caused

by a single mutation could affect the global structure of the spike protein," explains Sugita, who is additionally affiliated with the RIKEN Center for Biosystems Dynamics Research. The resulting mutant proved better at replicating and transmitting between human hosts, and the D614G lineage quickly outcompeted its ancestral lineages and spread across the globe. It remains a fixture of every dominant variant that has followed.

Sugita's team is now performing similar investigations of adaptive viral mutations that arose later in the course of the pandemic, including those found in the omicron variant.

"Information obtained from our molecular dynamics simulations should help increase the opportunities for us to find effective drugs and other medicines," he says.

More information: Hisham M. Dokainish et al, Structural effects of spike protein D614G mutation in SARS-CoV-2, *Biophysical Journal* (2022). DOI: 10.1016/j.bpj.2022.11.025

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