

How fast does the COVID-19 virus change?

Researchers quantify, for the first time, the mutations generated in a single infection with SARS-CoV-2

Oeiras, April 6, 2022 – The Instituto Gulbenkian de Ciência (IGC) and the Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA) are the first to quantify and to characterize the mutations that can be generated by SARS-CoV-2 when it infects cells. The experimental data provides valuable information to understand how the virus evolves in the human population and for the development of antiviral strategies.

Each time a virus makes copies of itself inside an infected cell, some letters of its genetic code can be mistakenly replaced by others, creating errors (mutations). Some mutations change important characteristics of the virus, such as its transmissibility and severity, which in turn can give rise to more successful versions (strains). This process of change and selection of strains that thrive more easily in their environment is called evolution.

To fully grasp how the COVID-19 virus evolves and gives rise to new variants, researchers first need to understand how mutations in its genetic code emerge when it multiplies inside the cells of its host, and at what rate. But it was not until now that this was achieved: efforts prior to IGC and INSA's were based on estimates from other coronaviruses and on small scale studies with little power to detect the large spectrum of mutations that can emerge.

In this study, published in the **Evolution, Medicine, and Public Health** journal, researchers infected cells isolated from monkey kidneys with two SARS-CoV-2 strains: one carrying the originally described spike protein and the other carrying a mutated form that is prevalent worldwide. After letting the virus multiply for several cycles, they sequenced it and looked for emerging alterations and any evidence of evolution.

The team confirmed that SARS-CoV-2 has a remarkable ability to adapt to new environments, particularly through the evolution of the spike protein. The gene coding for this protein accumulated five times more alterations than other regions, as a result of the selection of beneficial mutations. Genes encoding for components of the viral nucleocapsid, envelope and membrane also showed signs of adaptation. Importantly, several of the identified mutations have also been observed in the natural population of the virus, particularly in the Beta, Gamma, and Omicron variants.

However relevant, “the experimental evolution of the virus poses an extra challenge for researchers. And that is because the selection of successful variants can shape the way mutations accumulate”, explains Massimo Amicone, researcher at the IGC and co-author of the study. Since they wanted to quantify SARS-CoV-2's spontaneous mutation rate, the researchers had to distinguish targets of selection from targets that did not alter the virus' fitness.

Taking this into consideration, the researchers obtained a more realistic estimation: with each infection, the probability that any letter of SARS-CoV-2's genetic code will be mistakenly replaced is around 1,3 in a million, lower than that of the flu virus. "Given that the genetic code of SARS-CoV-2 is composed of approximately 30.000 letters, this means that each time it makes a copy of itself, 1 in 10 will have a new mutation", explains Isabel Gordo, principal investigator at the IGC who co-authored the publication. The authors also concluded that the most common "typos" replaced the letter C for a T in both strains used to infect the cells. Besides sharing many of the new alterations, the strains also displayed similar mutation rates, suggesting that their mutational path was not substantially altered due to their initial differences. Despite the similarities, the strain carrying the mutated form of the spike protein accumulated less beneficial mutations than the original one, which is consistent with the hypothesis that fitter strains adapt at a slower pace.

There were, however, some viruses, called mutators, that accumulated a larger number of mutations when compared to others. The faster rate at which these viruses accumulated errors was probably linked to the impairment of genes involved in the replication or the correction of errors in the genetic code. This is the first time that it is shown that it is possible for SARS-CoV-2 to substantially increase its mutation rate and still survive. This could have implications for the development and success of new antivirals that rely on the increase of mutation load beyond a tolerable limit for the pathogen, especially if these are being tested against SARS-CoV-2 grown in the type of cells used in this study.

Although these cells do not reflect exactly what happens in SARS-CoV-2's natural environment, the findings of this study provide valuable information regarding the basic biology of the virus and on how it can shape its genetic code to adapt to new environments.

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Original Study: Amicone et al. **Mutation rate of SARS-CoV-2 and emergence of mutators during experimental evolution.** *Evolution, Medicine, and Public Health* (2022).

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