Evolutionary insight into the emergence of SARS-CoV-2 variants of concern

Analysis of SARS-CoV-2 evolution during chronic infection reveals that in this setting, the virus evolves to bear mutations similar to those seen in variants of concern, and that many of these mutations are associated with antibody evasion. However, as mutations associated with high SARS-CoV-2 transmissibility are not observed, the emergence of variants of concern during chronic infection might be rare.

This is a summary of:
Harari, S. et al. Drivers of adaptive evolution during chronic SARS-CoV-2 infections. *Nat. Med*. https://doi.org/10.1038/s41591-022-01882-4 (2022).

Published online:
8 July 2022

The mission

Over the past 2 years, the world has witnessed waves of SARS-CoV-2 infection, often associated with the emergence of new viral variants called 'variants of concern' (VOCs). How these VOCs, which are often highly mutated forms of the virus, arise within the population is unclear. One hypothesis is that VOCs evolve due to selection pressure created during chronic viral infection. Indeed, most patients with chronic SARS-CoV-2 infection have a suppressed immune system, which is thought to allow the virus to persist for months[1]. However, the evolutionary patterns of SARS-CoV-2 across chronic infections are dynamic and vary between patients[2–5]. Moreover, the selective pressures and evolutionary processes that act during chronic infection remain unknown. We set out to consolidate the evolutionary patterns in SARS-CoV-2 found across a large set of patients with chronic infection, focusing on identifying correlates of adaptive evolution, with the hope of better understanding how and if future VOCs will emerge.

The observation

We generated a cohort of 27 patients with chronic SARS-CoV-2 infection; the viral genomes from 21 patients were previously published, and we sequenced those of the remaining 6 patients here. We examined the accumulation of viral mutations for each patient and summarized their medical backgrounds, with emphasis on immunosuppressive and COVID-19 treatments. We established a high degree of similarity between the mutational landscape of SARS-CoV-2 in patients with chronic infection and that observed during the emergence of VOCs (Fig. 1a), with many antibody-evasion-associated mutations common to both. In contrast, we noted a stark difference between mutations observed during chronic infection and in VOCs, versus those observed in globally circulating viruses. This finding suggests that evolutionary pressures in chronic infection might allow a VOC to emerge.

Our physician collaborators noted that many patients with SARS-CoV-2 experienced dramatic fluctuations in viral load, often 'clearing' the virus for a few days before becoming positive again. We found that this viral rebound was highly correlated with the accumulation of antibody-evasion-related mutations. Surprisingly, use of anti-viral antibody treatment was not correlated with these mutations. Finally, we observed highly polymorphic viral populations across several types of samples (that is, niches), including those from the upper and lower respiratory tracts and plasma. Putting our results together, we suggest that selection for SARS-CoV-2 antibody evasion might occur in niches in the lungs, leading to the migration of new resilient variants and viral rebound in the upper airways.

Finally, it is notable that key mutations associated with high SARS-CoV-2 transmissibility were not observed in chronic infection. This observation suggests that higher transmissibility is not selected for during chronic infection, and thus that the emergence of a new VOC during chronic infection might be rare.

The interpretation

We have identified both links and discrepancies between SARS-CoV-2 evolution in chronic infection and VOCs, and our findings highlight the importance of constantly monitoring chronic SARS-CoV-2 infection in immunosuppressed patients. Indeed, a negative PCR result might not indicate clearance of the virus, and viral rebound might suggest that a more 'fit' virus has emerged and that constant monitoring of the patient is required. Furthermore, genomic analysis of chronic infection is one key route to understanding how VOCs emerge. As immunosuppressed patients are at high risk for COVID-19 complications and might serve as a background for the virus to thrive and evolve, these people should be protected from SARS-CoV-2 infection.

This study has several limitations, including a relatively small sample size, and it might have some biases for age, sex and medical background. Also of note, all of the sequencing data analyzed in this study were obtained before the emergence of most VOCs. Additionally, large proportions of the global community are now vaccinated against, and/or have recovered from infection with, SARS-CoV-2, and new treatments are available. These developments might generate a new set of selective pressures for the virus. We intend to continue our investigations by examining a new cohort of patients with suppressed immune systems and chronic infection with the current VOC, Omicron. Results from such research might allow us to forecast, and be prepared for, new VOCs.

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EXPERT OPINION

"This is an interesting study that aggregates data across multiple studies of chronic SARS-CoV-2 infections and compares them to global evolution. The work is of both medical and evolutionary interest, and is one of the best aggregated meta-analyses (plus it also sequences some new patients) that I've seen." **Jesse Bloom, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.**

FIGURE

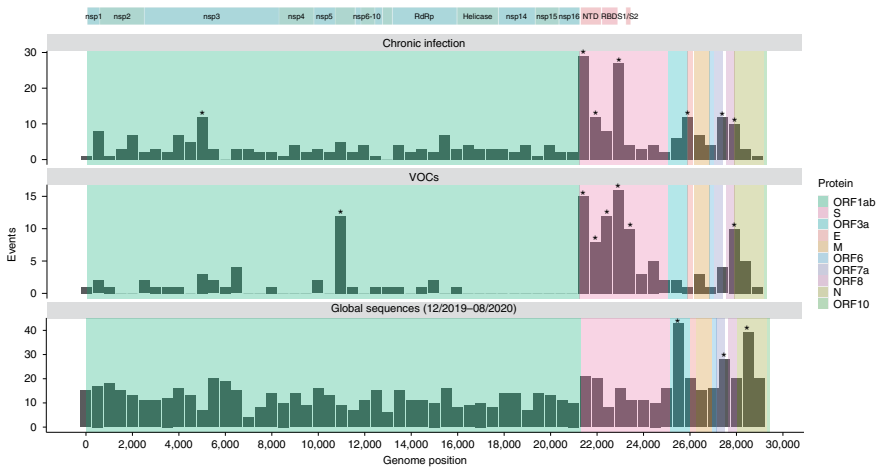

Fig. 1 | Mutational landscape of SARS-CoV-2 in patients with chronic infection. The number of substitution events observed along the SARS-CoV-2 genome in patients with chronic infection compared with mutations that define VOCs and with dominant substitutions in globally dispersed acute infections between December 2019 and August 2020. Asterisks indicate bins enriched for substitutions ($P < 0.05$; one-tailed binominal test). Shading colors (key) indicate SARS-CoV-2 proteins encoded along the genome; individual proteins encoded by open reading frames 1a and 1b (ORF1ab) and spike protein (S) domains are noted at the top of the figure, over the corresponding genome positions. nsp, non-structural protein; RdRp, RNA-dependent RNA polymerase; NTD, N-terminal domain; RBD, receptor-binding domain; E, envelope; M, membrane; N, nucleocapsid.

BEHIND THE PAPER

The COVID-19 pandemic placed us, a laboratory investigating viral evolution, in a unique position as the world became our scope of research. About a year ago, two physicians contacted us with interesting cases of chronic infection, with conflicting PCR results for the presence of SARS-CoV-2. They asked us to investigate the genetics behind this phenomenon. We were surprised to discover that although SARS-CoV-2 from some patients displayed dramatic evolution, SARS-CoV-2 from others showed limited or no evolution. We gathered all existing data on chronic infections and initially gained more questions than answers. Gradually we found the medical parameters that correlate with the evolutionary track of the virus and began to understand the settings that allow the virus to evolve to a VOC. We are still working on this puzzle, but hope a better understanding of how VOCs emerge will enable us to block their emergence. **S.H. and M.T.**

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FROM THE EDITOR

"The evolutionary origins of SARS-CoV-2 VOCs are unknown, but one possibility is that they emerge in infected and immunocompromised people. Comparing SARS-CoV-2 mutations in globally circulating strains with those of the variants that evolve over time in immunocompromised patients uncovers fascinating hypotheses on the selective pressures driving chronic infection in an individual versus transmission in a population." **Alison Farrell, Senior Editor, *Nature Medicine***