



Antigenic minimalism of SARS-CoV-2 is linked to surges in COVID-19 community transmission and vaccine breakthrough infections

A.J. Venkatakrisnan, Praveen Anand, Patrick Lenehan, Pritha Ghosh, Rohit Suratekar, Abhishek Siroha, Dibyendu Roy Chowdhury, John C. O'Horo, Joseph D. Yao, Bobbi S. Pritt, Andrew Norgan, Ryan T. Hurt, Andrew D. Badley, John D. Halamka, Venky Soundararajan

doi: <https://doi.org/10.1101/2021.05.23.21257668>

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.

[Abstract](#)[Full Text](#)[Info/History](#)[Metrics](#)[Preview PDF](#)

Abstract

The raging COVID-19 pandemic in India and reports of “vaccine breakthrough infections” globally have raised alarm mandating the characterization of the immuno-evasive features of SARS-CoV-2. Here, we systematically analyzed 1.57 million SARS-CoV-2 genomes from 187 countries/territories and performed whole-genome viral sequencing from 53 COVID-19 patients, including 20 vaccine breakthrough infections. We identified 89 Spike protein mutations that increased in prevalence during at least one surge in SARS-CoV-2 test positivity in any country over a three-month window. Deletions in the Spike protein N-terminal domain (NTD) are highly enriched for these ‘surge-associated mutations’ (Odds Ratio = 41.8, 95% CI: 6.36-1758, p-value = 7.7e-05). In the recent COVID-19 surge in India, an NTD deletion (Δ F157/R158) increased over 10-fold in prevalence from February 2021 (1.1%) to April 2021 (15%). During the recent surge in Chile, an NTD deletion (Δ 246-253) increased rapidly over 30-fold in prevalence from January 2021 (0.86%) to April 2021 (33%). Strikingly, these simultaneously emerging deletions associated with surges in different parts of the world both occur at an antigenic supersite that is targeted by neutralizing antibodies. Finally, we generated clinically annotated SARS-CoV-2 whole genome sequences and identified deletions within this NTD antigenic supersite in a patient with vaccine breakthrough infection (Δ 156-164) and other deletions

from unvaccinated severe COVID-19 patients that could represent emerging deletion-prone regions. Overall, the expanding repertoire of Spike protein deletions throughout the pandemic and their association with case surges and vaccine breakthrough infections point to antigenic minimalism as an emerging evolutionary strategy for SARS-CoV-2 to evade immune responses. This study highlights the urgent need to sequence SARS-CoV-2 genomes at a larger scale globally and to mandate a public health policy for transparent reporting of relevant clinical annotations (e.g. vaccination status) in order to aid the development of comprehensive therapeutic strategies.

Competing Interest Statement

AJV, PA, PL, PG, RS, AS, DRC, and VS are employees of nference and have financial interests in the company and in the successful application of this research. nference collaborates with bio-pharmaceutical companies on data science initiatives unrelated to this study. These collaborations had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. JCO receives personal fees from Elsevier and Bates College, and receives small grants from nference, Inc, outside the submitted work. ADB is a consultant for Abbvie and Flambeau diagnostics, is a paid member of the DSMB for Corvus pharmaceuticals, Equilibrium, and Excision biotherapeutics, has received fees for speaking for Reach MD, owns equity for scientific advisory board positions in nference and Zentalis, and is founder and President of Splissen therapeutics. JH, JCO, GJG, AWW, AV, MDS, and ADB are employees of the Mayo Clinic. The Mayo Clinic may stand to gain financially from the successful outcome of the research. nference and Mayo Clinic have filed a provisional patent application associated with this study. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies.

Funding Statement

This study was funded by nference. No other external funding was received for this study.

Author Declarations

I confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.

Yes

The details of the IRB/oversight body that provided approval or exemption for the research described are given below:

This is a retrospective study of individuals who underwent polymerase chain reaction (PCR) testing for suspected SARS-CoV-2 infection at the Mayo Clinic and hospitals affiliated to the Mayo health system. This study was reviewed by the Mayo Clinic Institutional Review Board (IRB) and determined to be exempt from human subjects research. Subjects were excluded if they did not have a research authorization on file.

All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Yes

I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).

Yes

I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.

Yes

Paper in collection COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

Copyright

The copyright holder for this preprint is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license.

Blog posts linking to this article:

Front Line Genomics, 25 Jun 2021

We have summarised all of the most recent news and research surrounding the novel coronavirus and put it here in one place! ...

Tweets referencing this article:

DocMinarchist-TRUMP WON

@3GHtweets

@celinegounder @KellyMDoran There is a pronounced decline in protection against infection with time. <https://t.co/ek3UQNY2qh> Immune escape is at least partly to blame. <https://t.co/NfNiktNjD0> <https://t.co/w6iAZoMYFp> Boosters against yesterday's SI wi

02:49PM

Fernando vs Mr conejo

@ferdevill

<https://t.co/8r6symhrzI> <https://t.co/wNcaqoflvH>

23 Sep 2021

I.min

medRxiv Comment Policy

Comments are moderated for offensive or irrelevant content (can take ~24 hours). Duplicated submission is unnecessary.

Please read our [Comment Policy](#) before commenting.



0 Comments medRxiv Disqus' Privacy Policy

1 Login ▾

Recommend Tweet Share

Sort by Newest ▾



Start the discussion...

LOG IN WITH

OR SIGN UP WITH DISQUS

Name

Be the first to comment.

Subscribe Add Disqus to your site Add DisqusAdd Do Not Sell My Data

Back to top

Previous

Next

Posted June 14, 2021.

Download PDF

Author Declarations

Data/Code

XML

Revision Summary

Email

Share

Citation Tools

Tweet

Like 40

COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

Subject Area

Infectious Diseases (except HIV/AIDS)

Subject Areas

All Articles

Addiction Medicine
Allergy and Immunology
Anesthesia
Cardiovascular Medicine
Dentistry and Oral Medicine
Dermatology
Emergency Medicine
Endocrinology (including Diabetes Mellitus and Metabolic Disease)
Epidemiology
Forensic Medicine
Gastroenterology
Genetic and Genomic Medicine
Geriatric Medicine
Health Economics
Health Informatics
Health Policy
Health Systems and Quality Improvement
Hematology
HIV/AIDS
Infectious Diseases (except HIV/AIDS)
Intensive Care and Critical Care Medicine
Medical Education
Medical Ethics
Nephrology
Neurology
Nursing
Nutrition
Obstetrics and Gynecology
Occupational and Environmental Health
Oncology
Ophthalmology
Orthopedics
Otolaryngology
Pain Medicine
Palliative Medicine

Pathology

Pediatrics

Pharmacology and Therapeutics

Primary Care Research

Psychiatry and Clinical Psychology

Public and Global Health

Radiology and Imaging

Rehabilitation Medicine and Physical Therapy

Respiratory Medicine

Rheumatology

Sexual and Reproductive Health

Sports Medicine

Surgery

Toxicology

Transplantation

Urology

Supported by **Chan
Zuckerberg
Initiative** 