Received: 8 March 2023 | Accepted: 27 March 2023

DOI: 10.1002/jmv.28714

COMMENTARY

JOURNAL OF MEDICAL VIROLOGY WILEY

Genome-based survey of the SARS-CoV-2 BF.7 variant from Asia

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Funding information
Stefano Pascarella is in part supported by the Sapienza, Grant/Award Number: RP12117A7670A1E8; FONDAZIONE DI SARDEGNA bando 2022-2023 for the Dipartimento di Scienze Biomediche - UNISS (to Fabio Scarpa and Daria Sanna); Marta Giovanetti is funded by PON "Ricerca e Innovazione" 2014–2020 and by the CRP—ICGEB RESEARCH GRANT 2020 Project CRP/BRA20-03, contract CRP/20/03, Oswaldo Cruz Foundation

Abstract

The SARS-CoV-2 BF.7 variant represents one of the most recent subvariant under monitoring. At the beginning of the 2023 it caused several concerns especially in Asia because of a resurge in COVID-19 cases. Here we perform a genome-based integrative approach on SARS-CoV-2 BF.7 to shed light on this emerging lineage and produce some consideration on its real dangerousness. Both genetic and structural data suggest that this new variant currently does not show evidence of an high expansion capability. It is very common in Asia, but it appears less virulent than other Omicron variants as proved by its relatively low evolutionary rate (5.62×10^{-4} subs/sites/years). The last plateau has been reached around December 14, 2022 and then the genetic variability, and thus the viral population size, no longer increased. As already seen for several previous variants, the features that may be theoretically related to advantages are due to genetic drift that allows to the virus a constant adaptability to the host, but is not strictly connected to a fitness advantage. These results have further pointed that the genome-based monitoring must continue uninterruptedly to be prepared and well documented on the real situation.

Daria Sanna and Massimo Ciccozzi contributed equally to this work.

KEYWORDS
BF.7, classification, molecular epidemiology, SARS coronavirus, SARS-CoV-2, virus evolution

"*It is not the strongest species that survive, nor the most intelligent, but the ones who are most responsive to change*". In his famous sentence, Charles Darwin clearly explained the essence of evolution. Changes have always been in DNA, and viruses represent the biological entities able to perform the best complex strategy, host adaptation and survival tactics. In such a context, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proved to be a great interpreter of all these biological features by significantly mutating over the course of the pandemic,[1] producing many lineages and sub-lineages and showing different levels of expansion capabilities.[2] The SARS-CoV-2 BF.7 variant represents one of the most recent results of this phenomenon and, as all emerging lineage, requires an in-depth study on its capacity for expansion and contagiousness. As of February 22, 2023 the World Health Organization (WHO) indicated seven (BF.7, BQ.1, BA.2.75, XBB, XBB.1.5, XBF, and CH.1.1) Omicron lineages as subvariants under monitoring (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—22-february-2023) because of their observed transmission advantage relative to other circulating variants and additional amino acid changes that are known (or suspected) to confer increase transmissibility. Anyhow, it is interesting to note that recent research works pointed out that BA.2.75, BQ.1, XBB, and XBB.1.5[3–6] actually do not represent a real global threat but only newly developed lineages that, due to genetic drift accumulated features that may be theoretically related to improvement in fitness but do not confer such fitness advantage. As further confirmation of this condition, in several cases, these variants appeared to spread even more slowly than other sub-variants that have caused concerns in 2022.[5,6] From what BF.7 variant is concerned, it is one of the most recent attentioned lineages that caused several concerns at the beginning of 2023, especially in Asia. In such a context, here we perform a genome-based integrative approach on SARS-CoV-2 BF.7 to shed light on this emerging lineage and produce some consideration on its real dangerousness.

The genomic epidemiology of SARS-CoV-2 with a subsampling focused globally on the Omicron GSAID CLADE 21 M (Figure S1) indicates that genomes of BF.7 (belonging to the GSAID CLADE 22B) are placed within the main clade as an evolutionary blind background with no descendant. The same condition has been recently detected also in other variants, which at last have proved to be not particularly dangerous (i.e., BA.2.75, BQ.1, XBB, and XBB.1.5),[3–6] indicating the lack of rapid diversification.

The Bayesian Skyline Plot (BSP) reconstruction (Figure 1A) indicates that the genetic variability of BF.7 lineage has undergone several slight fluctuations over time, and thus, its viral population size has expanded and contracted several times. However, such fluctuations do not correspond to the occurrence of epidemic events but only reflect limited increases in infections. More specifically, the viral genetic variability and the population size peaked for the first time around August 25, 2022, and after that, a plateau phase began. After a few months, the genetic variability decreased until around December 5, 2022, when started a new slight increase peaked around December 14, 2022. This last expansion corresponds to the great pressure on the healthcare system put by BF.7 in Asia, especially in several localities of China.[8] The LTT plot (Figure 1B) suggests a linear growth of the number of lineages during time with a quite mild curve, also confirming the lack of a high level of genetic variability. In addition, the evolutionary rate of BF.7 here estimated to amount to 5.62×10^{-4} [95% HPD: 4.84×10^{-4} to 6.37×10^{-4}] subs/sites/years, further accounts for the low level of genetic variability and for the limited capacity for strong demographic expansion. Indeed, this evolutionary rate is fully consistent with recent subvariants that caused concerns only at the beginning, while it is 10 times lower than SARS-CoV-2 Wuhan-Hu-1.[9]

For as the spike protein is concerned, BF.7 differs from its direct progenitor (BA.5) for the mutation R346T in receptor binding domain (RBD) while the two *N*-terminal domains (NTDs) are identical. The impact of the single mutation on RBD properties of BA.7 has been analyzed. Alteration of surface electrostatic potential has been tested as it is an important factor guiding electrostatic interactions between macromolecules and molecules. The overall dominant charge (positive or negative) of the electrostatic potential may be indirectly approximated by calculating the net charge at a given pH, usually 7.0 set as a reference value.[10] Calculations have been carried out following Pascarella et al.[10] BF.7 and BA.5 RBDs display a net charge equal to 5.18 ± 0.01 and 4.19 ± 0.01, respectively, which is in line with the removal of the positive charge of R346. However, the decrease of the positive charge does not involve directly the RBD interface to the ACE2 receptor. Indeed, mapping of the surface electrostatic potential shows that the interface has a similar electrostatic pattern in BF.7 and BA.5 (Figure 1C). In fact, the substitution R346T occurs beside the interface, and it does not contact ACE2 residues (Figure S2). Interface interaction energies predicted are similar for BA.5 and BF.7: -4.67 ± 0.28 and -4.42 ± 0.32 kcal/mol, respectively. However, it cannot be ruled out that the R346T substitution can alter the interactions of BF.7 with other molecules.

In conclusion, genetic and structural data on SARS-CoV-2 BF.7 here presented suggest that this new variant currently does not show evidence of a likely high expansion capability. It is very common in Asia, but it appears less virulent than other Omicron variants.[11] Although BF.7 (and in particular the R346 mutation) has been associated to the immune escape capability to neutralize antibodies (https://www.cbsnews.com/news/bf7-new-omicron-coronavirus-variant-covid/), as of now, it does not show evidence of its particular dangerous or high expansion capability. Also, in this case, the features that may be theoretically related to advantages are due to genetic

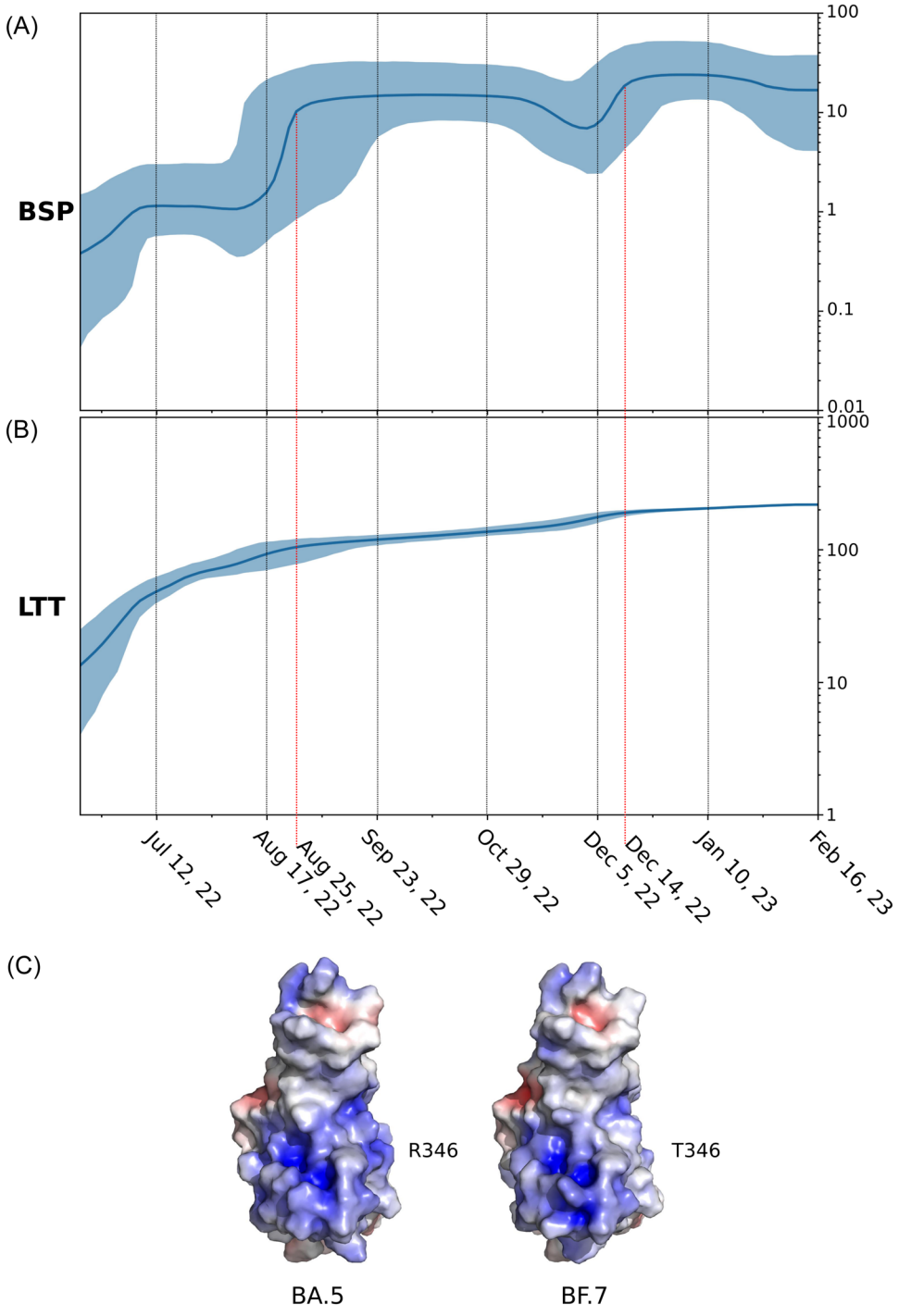

FIGURE 1 (A) Bayesian Skyline Plot and (B) Lineages Through Time of SARS-CoV-2 BF.7 variant. The viral effective population size and the number of lineages (y-axis) are shown as a function of days (x-axis). The solid areas represent the 95% high posterior density (HPD) region. These plots have been reconstructed following Mugosa et al.,[7] using all of the available genomes from Asia for which the sampling data was indicated (n = 5104). See Table S1 for details on the used genomes and authorship. (C) Comparison of the electrostatic potential surfaces of BF.7 and BA.5 RBDs. Red and blue colors indicate negative and positive potential, respectively. The color scale ranges from −5.0 (red) to +5.0 (blue) kT/e. The RBD is represented with the ACE2 interface oriented toward the viewer. The positions of R and T346 are denoted by labels. ACE2, angiotensin-converting enzyme 2; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

drift that allows to the virus a constant adaptability to the host but is not strictly connected to a fitness advantage. Of course, this must not be understood as a reason to let our guard down against the pandemic, but the fear must not cloud the judgment, and decisions must be made based on data.[12] As pointed out by Akif et al.[11] "… *we should not give the virus any chance to control our lives*." Indeed, genome-based monitoring must continue uninterruptedly to be prepared and well-documented on the real situation.

AUTHOR CONTRIBUTIONS

Conceptualization: Fabio Scarpa and Massimo Ciccozzi. *Data analyses*: Fabio Scarpa and Stefano Pascarella. *Writing-original draft preparation*: Fabio Scarpa. *Writing-review and editing*: Fabio Scarpa, Marta Giovanetti, Ilenia Azzena, Chiara Locci, Marco Casu, Pier Luigi Fiori, Alessandra Ciccozzi, Elena Imperia, Liliana Bazzani, Alessandra Borsetti, Antonello Maruotti, Stefano Pascarella, Daria Sanna, and Massimo Ciccozzi.

ACKNOWLEDGMENTS

This research was funded from by FONDAZIONE DI SARDEGNA bando 2022-2023 for the Dipartimento di Scienze Biomediche - UNISS (to Fabio Scarpa and Daria Sanna). Marta Giovanetti is funded by PON "Ricerca e Innovazione" 2014–2020 and by the CRP—ICGEB RESEARCH GRANT 2020 Project CRP/BRA20-03, contract CRP/20/03, Oswaldo Cruz Foundation. Stefano Pascarella is in part supported by the Sapienza grant no. RP12117A7670A1E8. We also would like to thank all the authors who have kindly deposited and shared genomes on GSAID. Open Access Funding provided by Universita degli Studi di Sassari within the CRUI-CARE Agreement.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Genomes analyzed in the present study were taken from the GSAID database and are available at https://gisaid.org/.

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SUPPORTING INFORMATION

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How to cite this article: Scarpa F, Giovanetti M, Azzena I, et al. Genome-based survey of the SARS-CoV-2 BF.7 variant from Asia. *J Med Virol*. 2023;95:e28714. doi:10.1002/jmv.28714