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RESEARCH ARTICLE
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Comparative Genomic Analysis of Rapidly Evolving SARS-CoV-2 Reveals Mosaic Pattern of Phylogeographical Distribution

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ABSTRACT The outbreak of coronavirus disease 2019 (COVID-19) that started in Wuhan, China, in December 2019 has spread worldwide, emerging as a global pandemic. The severe respiratory pneumonia caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has so far claimed more than 0.38 million lives and has impacted human lives worldwide. However, as the novel SARS-CoV-2 virus displays high transmission rates, the underlying genomic severity is required to be fully understood. We studied the complete genomes of 95 SARS-CoV-2 strains from different geographical regions worldwide to uncover the pattern of the spread of the virus. We show that there is no direct transmission pattern of the virus among neighboring countries, suggesting that its spread is a result of travel of infected humans to different countries. We revealed unique single nucleotide polymorphisms (SNPs) in nonstructural protein 13 (nsp13), nsp14, nsp15, and nsp16 (ORF1b polyproteins) and in the S-protein within 10 viral isolates from the United States. These viral proteins are involved in RNA replication and binding with the human receptors, indicating that the viral variants that are circulating in the population of the United States are different from those circulating in the populations of other countries. In addition, we found an amino acid addition in nsp16 (mRNA cap-1 methyltransferase) of a U.S. isolate (GenBank accession no. MT188341.1) leading to a shift in the amino acid frame from position 2540 onward. Through comparative structural analysis of the wild-type and mutant proteins, we showed that this addition of a phenylalanine residue renders the protein in the mutant less stable, which might affect mRNA cap-1 methyltransferase function. We further analyzed the SARS-CoV-2–human interactome, which revealed that the interferon signaling pathway is targeted by orf1ab during infection and that it also interacts with NF-κB-repressing factor (NKRF), which is a potential regulator of interleukin-8 (IL-8). We propose that targeting this interaction may subsequently improve the health condition of COVID-19 patients. Our analysis also emphasized that SARS-CoV-2 manipulates spliceosome machinery during infection; hence, targeting splicing might affect viral replication. In conclusion, the replicative machinery of SARS-CoV-2 is targeting interferon and the notch signaling pathway along with spliceosome machinery to evade host challenges.

IMPORTANCE The COVID-19 pandemic continues to storm the world, with over 6.5 million cases worldwide. The severity of the disease varies with the territories and is

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