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Brief Communication

Genomic Evolution of Severe Acute Respiratory Syndrome Coronavirus 2 in India and Vaccine Impact

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Abstract

Recent emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent containment procedures have impacted the world as never seen before. Therefore, there is considerable curiosity about the genome evolution related to the origin, transmission and vaccine impact of this virus. We have analysed genome sequences of SARS-CoV-2 isolated from Indian patients to gain an in-depth understanding of genomic evolution and transmission in India. Phylogenetic analysis and mutation profiling revealed major lineages being evolved by characteristic mutations. As the mutation frequency in spike protein is comparatively lesser, the candidate vaccines expected to have wide coverage worldwide including India.

Keywords: COVID-19, evolution, India, severe acute respiratory syndrome coronavirus 2, transmission, vaccine

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, and its subsequent international spread is unprecedented and generated a global health emergency. To slow the chain of transmission of coronavirus disease (COVID-19), India too responded with containment procedures such as travel bans, lockdowns and social distancing. As the virus transmission and subsequent lockdown have impacted the living habits and social behaviour of general public, there has been considerable curiosity on the genome evolution related to the origin, transmission and vaccine impact with special reference to India. Hence, this work was carried out.

Materials and Methods

The genomic analysis of the Indian genome sequences of SARS-CoV-2 was gathered from GISAID (https://www.gisaid.org/). The genomes containing sampling time and location were chosen for the study. A multiple genome sequence alignment performed with MAFFT (https://mafft.cbrc.jp/alignment/software/). The isolate Wuhan-Hu-1 (MN908947) was used as the reference genome. Maximum likelihood tree was generated using Fasttree (http://www.microbesonline.org/fasttree/). The phylogenetic trees and the geographical distribution are interactively depicted using Microreact (https://microreact.org).

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Results and Discussion

Origin and evolution

The origin of the SARS-CoV-2 is one of the most mysterious and controversial questions of the recent times as there are arguments for and against the natural selection hypothesis. Currently, much of the research related to SARS-CoV-2 is revolving around the likely recombination and mutation that led to the origin of the virus. The initial report on evolution of SARS-CoV-2 from a closely related BatCoV RaTG13 as a result of a recent recombination event seems to be not true.[1] The latest phylogenetic data estimate that the timing of the most

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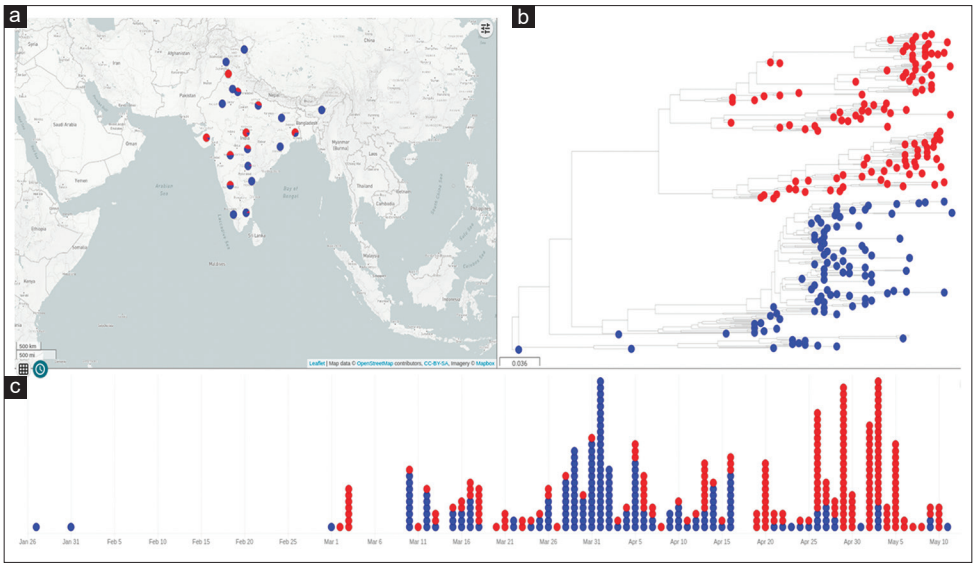

Figure 1: Tracing the genomic evolution and spread of severe acute respiratory syndrome coronavirus 2 in India visualisation of severe acute respiratory syndrome coronavirus 2 genomic evolution and transmission events on Microreact. (a) Geographical distribution of genomes across India. (b) The phylogenetic tree representing two major lineages. (c) The bottom view panel shows the distribution of isolates with respect to its collection time

recent common ancestor of SARS CoV-2 and RaTG13 suggests the strains diverged 40–70 years ago and the emergence is not a recent recombination event.[2] Since coronaviruses in bats and other species are particularly undersampled, more viral sequences from animal sources would decode the mystery of the origin of SARS-CoV-2.

What makes SARS-CoV-2 different from other endemic coronaviruses is the efficient human-human transmission in a short time period. This can be attributed to two notable features in the viral genome (i) mutations in the receptor-binding domain (RBD) and (ii) the furin cleavage site at the S1/S2 boundary of the spike protein.[3] In brief, SARS-CoV-2 is a SARS like lineage B β-CoV carrying RBD identical to Pangolin-β-CoV and furin recognition motif (PRRAR ↓ SV) similar to lineage A and C β-CoV.[4,5]

Up to date globally, 46,570 (as on 15 June 2020) genome sequences of SARS-CoV-2 were in public domain. Tools for real-time tracking, mutation mapping and assigning nomenclature were formulated to support the epidemiological understanding and improve outbreak response (https://nextstrain.org/, http://cov-glue.cvr.gla.ac.uk/#/home). In India, a total of >600 high-quality genome sequences were available in the public domain. The mutation profile suggests increase in genetic diversity within a short period of 5 months. The global phylogenetic distribution shows six high-level phylogenetic groupings (S, L, V, G, GH and GR) classified on the basis of marker mutations. The GISAID lineages were further subclassified using Phylogenetic Assignment of Named Global Outbreak LINeages (PANGOLIN) tool (https://github.com/hCoV-2019/pangolin). Genomic analysis of India isolates showed lineage PANGOLIN lineage B.1/B.1.1/B.1.36 (previously A2a) with D614G mutation being dominant with a possibility of more efficient transmission.[6] The second common lineage B.6 (previously A3/A3i)[7] in India is less transmissible may be due to the lack of mutation in the spike protein.[8] Phylogeography of Indian SARS-CoV-2 [Figure 1] showed that lineage A isolates are imported cases from central Asia (China) while lineage B.6 and B.1.36 were imported from Southeast Asia and Europe, respectively (Unpublished data). Interestingly, linage B.1.36 dominant in Gujarat possesses 1–3 mutation (D614G, R78M and L54F) in S protein, which may contribute to increased infectivity.

Transmission

Identification of R0 can efficiently predict the spread of virus and also helps in disease containment during outbreak. Studies from 13 different research groups predict the 'R0' value to be ranged between 2 and 7.23.[9] The variation in the 'R0' estimate can be attributed to the differences in mathematical transmission modelling and assumptions methods followed by the authors. In India where the epidemic growth trajectory was slow, the R0 value is estimated to be 1.22–1.85.[10] This can be attributed to the strict control measures and lockdown. After the recent relaxations in restrictions and increase rate of testing, India could register an explosion of cases where local cluster transmissions occur. Hence, the 'R0' are expected to rise further. According to Nation Institute of Epidemiology, Chennai, the projected R0 estimate can reach up to a maximum of 4 without proper containment measures.

Prevention and treatment

A vaccine can be the best way to protect the world from this likely catastrophe on an affordable basis. Although it may take 12–18 months for a vaccine roll out, 10 candidate vaccines are in clinical evaluation and 126 are in pre-clinical evaluation (As of 9 June 2020). In India, three major groups have started the pre-clinical evaluation of candidate vaccine in collaboration with leading vaccine groups. The landscape of four COVID-19 candidate vaccines in pipeline is listed in

Table 1: Landscape of coronavirus disease-19 candidate vaccines (as on 9 June 2020)

Type of candidate vaccine	Indian developer	Foreign collaborator	Current status
Codon-deoptimised live-attenuated vaccines	Serum Institute of India	Codagenix	Pre-clinical
Codon-deoptimised live-attenuated vaccines	Indian Immunologicals Ltd	Griffith University	Pre-clinical
Recombinant deactivated rabies virus containing S1	Bharat Biotech	Thomas Jefferson University	Pre-clinical
M2SR influenza vector	Bharat Biotech	UW-Madison/FluGen	Pre-clinical

M2SR: M2-deficient single replication

Table 1. Since many of the candidate vaccines are targeting the S protein, accumulation of missense mutations could possibly affect the vaccine coverage. However, the presence of low mutation rate in S protein makes it a good target for an effective vaccine candidate. Due to the increased mutation frequency in the Orf1a, N proteins make them a less preferable vaccine targets. However, these genes can be used as confirmatory targets for laboratory diagnosis.

The current ICMR recommended treatment strategy in India, allow the use of hydroxychloroquine in patients with mild illness and remdesivir in moderate and severe illness. Tocilizumab is recommended in patients with moderate illness after monitoring the inflammatory markers. Though, hydroxychloroquine emerged as a front runner with high hope, hype and politicisation three major studies failed to show significant evidence in using this drug.[11] The use of remdesivir in COVID-19 patients can prevent progression to pneumonia if initiated early.[12] Steroids (dexamethasone) appear to be a promising rescue therapy in management of those with moderate to severe illness. Early administration of tocilizumab as rescue therapy may benefit patients with increased inflammatory response with no evidence of secondary bacterial infection.[13] Moreover low-molecular-weight heparin appears to be associated with better prognosis in severe COVID-19 patients or among those with markedly elevated D-dimer.[14]

Conclusion

Genome analysis of Indian isolates indicates that PANGOLIN lineage B.1/B.1.1/B.1.36 (previouslyA2a) with D614G mutation being dominant with a possibility of more efficient transmission. The second common lineage B.6 (previously A3/A3i)[7] in India is less transmissible may be due to the lack of mutation in the spike protein. As the mutation frequency in S protein is comparatively lesser, the candidate vaccines expected to have a wide coverage worldwide including India.

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Conflicts of interest

There are no conflicts of interest.

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