Genetic emergence of B.1.617.2 in COVID-19

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Abstract

Many proactive steps have been taken worldwide to fight against the SARS-CoV-2 pandemic and to prevent COVID-19 spread with realistic approaches. Recently, a novel variant B.1.617.2 has been identified in India, which is rapidly transmitting to other countries, challenging current therapeutics, wide vaccination and future research in COIVD-19.

Keywords: COVID-19 pandemic, delta variant, global initiative on sharing all influenza data (GISAID), Indian SARS-CoV-2 consortium on genomics (INSACOG), SARS-CoV-2
Original Submission: 9 July 2021; **Revised Submission:** 16 July 2021; **Accepted:** 19 July 2021
Article published online: 24 July 2021

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The Indian SARS-CoV-2 Consortium on Genomics (http://dbtindia.gov.in/insacog) includes 10 different national laboratories within the country, and this group is continuing the sequencing process to map the complete genetic code of the COVID-19 virus. COVID-19, a coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan, China [1]. The D614G was first identified in SARS-CoV-2, which was dominated later to other countries and across the world during the first wave of COVID-19.

Subsequently, many other variants of SARS-CoV-2 have been identified worldwide, and a few of them are classified as variants of concern (VOC), variants of interest (VOI), and variants of high consequence by the Centres for Disease Control and Prevention [2]. As of June 12, 2021, ~175 million cases of COVID-19 have been reported, with ~3.79 million total deaths and an increasing number of recovering cases of >94 million; perhaps, these numbers could be substantially underestimated.

Three different VOCs, namely B.1.1.7, B.1.351, and P.1 were initially prevalent within the United Kingdom (UK), South Africa, and Brazil, respectively, and subsequently worldwide [3]. In addition, VOIs such as B.1.617 and B.1.618 have emerged in India, and recently, B.1.617.2 (also known as the Delta variant), a sublineage of B.1.617, is continuously transmitting at a higher rate within the country and across the world [4]. Therefore, this is confirmed as a VOC by World Health Organization [5], and this could be possibly linked with the second wave of COVID-19 in India [6].

Nevertheless, E484Q mutation was seen first time in the B.1.351 and P.1, which was substituted later to E484K, and thus, this had emerged independently several times in other populations [7]. This simple process discloses that the virus mutates within its own family or creates new lineages to function as a VOC. The B.1.427/B.1.429 lineages have such VOC called L452R mutation (first identified in the USA), and this has been shown to be almost >20% higher transmissibility in comparison to pre-existing reported variants [8]. Besides, B.1.617.2 is transmitting much rapidly in the Indian population, and recently, this variant has been seen in many other countries [4]. A recent study has shown variant B.1.1.7 is 43% to 90% more transmissible in comparison to pre-existing lineages in the European population, as well as in other countries [9]. The initial GISAID data (https://www.gisaid.org/) explains B.1.617.2 variant has a reasonably higher transmissibility rate (Fig. 1). In addition, the latest findings from Public Health England (PHE) guidance, which show B.1.617.2 (Delta variant) is at least 40% to 50% more transmissible than the pre-existing B.1.1.7 variant in the UK [10,11]. At present, B.1.617.2 is speedily outcompeting B.1.1.7, which is a dominant lineage in the UK and the latest statistics (http://sars2.cvr.gla.ac.uk/cog-uk/#shiny-tab-vui_voc) show that B.1.617.2 is now accounting for 72.93% of all the new cases in the last 28 days. This observation further confirms a higher relative abundance of Delta variant worldwide.

Many studies have exhibited an amino acid change inside 438–506 position in the Spike protein (also called the receptor-binding domain) could be considerably associated with an increase in virus transmission, infection, or evade immunity [12]. Further, both E484Q and L452R amino acid substitutions are present within the receptor-binding domain (RBD) of the spike protein like most other VOCs [13]. For example, L452R mutation could be involved in enhanced interaction with the human angiotensin-converting enzyme 2 (ACE2) receptor of the spike protein of COVID-19 and most probably leading to an

https://doi.org/10.1016/j.nmni.2021.100929

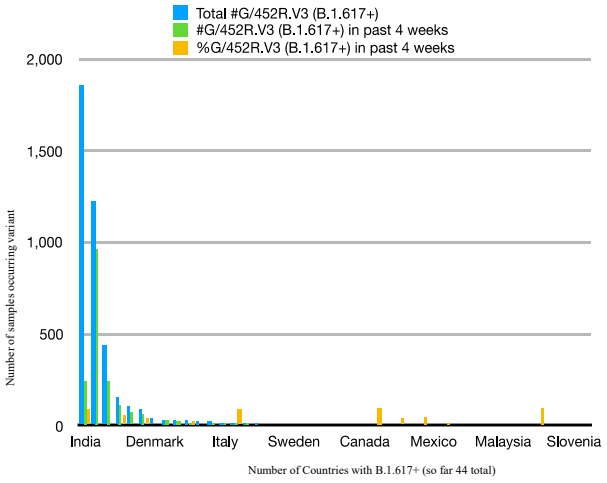

FIG. 1. Distribution of samples carrying recently emerged B.1.617+ variant.

increased rate of infection [14]. Moreover, other mutations such as E484K/E484Q increase the binding affinity by altering electrostatic interactions, while at the same time to create newer hydrogen bondings [15]. In addition, the N501Y increases stronger hydrophobic interactions of RBD–ACE2 and produces more hydrogen-bonding networks [16]. The K417N implicates this interaction of RBD binding to ACE2 alone or with N501Y and E484K together and improves the overall binding affinity of this complex [15,16]. Last but not least, the D614G mutation stabilizes the spike protein for efficient entry within the host cell [17].

The lineage B.1.617+ was first identified in Maharashtra (western part of India) when an analysis was performed on samples collected from this region. It has shown that an increase of ~60–70% of samples with E484Q and L452R mutations increases the transmission capacity of this variant resulting into more infection [6,18]. Recently, these two mutations, along with third mutation, P618R, have been comprehended in other parts of India (first seen in West Bengal), and this is now called B.1.618 lineage. Moreover, when the Indian National Centre for Disease Control was looking for samples for hitherto unknown variants such as higher transmissibility, fast infectivity etc., this lineage B.1.617+ came into the picture. The B lineage, along with other sublineages of B.1.617, is shown in Table 1. Furthermore, B.1.617.2, which contains these two mutations, also leads to an increase in virulence by reducing the antibody binding affinity, as well as immune evasion [18]. Now, B.1.617.2 becomes an important variant in the Indian context as it appears with an increasing prevalence from just 1% to 70% within March to May 2021 [19]. Instead, the B.1.1.7 had already dominated in Britain and >114 countries, including India [9]. Nonetheless, the latest data on GISAID shows B.1.617.2 (Delta variant) is spreading almost four times faster than B.1.1.7 (Alpha variant) (https://www.gisaid.org/hcov19-variants/). The latest studies on Delta versus Alpha variant in the United Kingdom, including Northern Ireland, indicate a higher rate of severe disease transmission, hospitalization and increased risk for emergence attention in individuals carrying the Delta variant [5]. Interestingly, a secondary analysis, which was performed in the United Kingdom (29 March–11 May 2021), uncovered a higher attack rate among cases with the Delta variant [5]. The B.1.617.2 is likely to have a selective advantage over other lineages for such a short period of increased transmissibility, infectivity or possibly escape from natural immunity [20–22]. Currently, many lineages are circulating at this time in India and worldwide, and the rapid expansion of B.1.617.2 (Delta variant) over other lineages could possibly be due to natural selection and genetic displacement of the SARS-CoV-2 genome [19,23].

Interestingly, the latest study has investigated the variant B.1.617+ with mutations (L452R, E484Q and P681R) in different other combinations and showed that this was barely affecting the efficiency of cellular entry and to elude immunity when elicited with neutralizing antibodies and BNT162b2 mRNA vaccine. Further, they described that the mutation P681R contributes to increased pathogenesis through syncytium formation as observed in hamsters and also in humans, for a higher infected growth rate in India [24]. Conversely, a recent study from India has shown a likely equal neutralizing capacity for B.1.617 among the vaccinated individuals and the recovered COVID-19 patients [25].

Increased transmission of the virus at this stage is incredible, given the fact that what we have understood about the other spike mutations present in B.1.1.7, B.1.351, B.1.1.28 etc. and what we are still trying to learn about newer emerging variants in other locations. Yet, India has limited SARS-CoV-2 epidemiological, clinical and seroprevalence data, which is not sufficient to understand the true extent of the epidemic.

The effectiveness of using antiviral and anti-inflammatory drugs has not been proven yet in India and throughout the world for COVID-19. However, their usage is parallelly important and effective for emergency practices. The advent of subsequent novel VOI(s) or VOC(s) one after the others highlight the prominence and attentiveness for early identification, detection and extensive genomic surveillance globally. Genomic surveillance and genetic epidemiology are used to invigilate new VOCs in the virus over time. The continuous emergence of novel variants in SARS-CoV-2 reiterates the importance of genomic surveillance worldwide for the welfare of humanity. It includes appropriate sample collections, viral genomic sequencing, data processing, storage and curation with the help of other clinical and epidemiological datasets. This can help us at least to answer further robust questions and provide

TABLE 1. Summary details on SARS-CoV-2 lineages, including pre-existing variants of concerns and recently identified variant B.1.617 from India

Origin	First reported	Lineage/sub-lineage/ Designation	Total mutation	Total amino acid change	Main mutations with amino acid changes in spike	Countries found	References
United Kingdom (Kent)	December, 2020	B.1.1.7 (VOC-20DEC-01)	23	17	Δ69/70, Δ144, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N	~114	Rambaut *et al.*, 2020 Davies *et al.*,., 2021
South Africa (Eastern Cape)	October, 2020	B.1.351 (VOC-20DEC-02)	23	17	D80A, D215G, Δ241/242/243 K417N, E484K N501Y, D614G A701V	45	Tegally *et al.*,., 2020
Japan/Brazil (Rio de Janeiro)	January, 2021	B.1.1.28 (VOC-21JAN-02)	35	17	L18F, T20N P26S, D138Y R190S, K417T E484K, N501Y D614G, H655Y T1027I, K417N	21	Voloch *et al.*,., 2020
United States (California)	May, 2021	B.1.427/B.1.429 (CAL.20C)	11	5	L452R, S13I, W152C	30	Zhang *et al.*,., 2021
India (Maharashtra)	February 2021	**B.1.617** B.1.617.1 *VUI-21APR-01*	>15	6	D614G, L452R[a], E484Q[a], P618R[a], Q1071H, E154K del681	~34 Until May 8	(outbreak.info, cdc.gov)
		B.1.617.2 VOC-21APR-02	>15	6	D614G, L452R[a], T478K[a], P681R[a], D950N, T19R del157/158	~31 Until May 8	(outbreak.info, cdc.gov)
		B.1.617.3 *VUI-21APR-03*	>15	5	D614G, L452R[a], E484Q[a], P618R[a], T19R	~4 Until May 8	(outbreak.info, cdc.gov)

[a]Shows functional important mutations probably involved in pathogenesis in India.

accurate information in the framework settings (e.g., policy recommendations, managing current and future VOC and overall staying ahead of the next pandemic). Furthermore, the dynamic virulency of SARS-CoV-2 challenges the development of next-generation vaccines, better genomic services and surveillances, which can help us save humanity against future coronaviruses.

Contributions

All the survey analysis, review writing and editing were conducted by LK. LK approved the final manuscript.

Transparency declaration

The author declares there is no competing interests.

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