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REVIEW

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Present variants of concern and variants of interest of severe acute respiratory syndrome coronavirus 2: Their significant mutations in S-glycoprotein, infectivity, re-infectivity, immune escape and vaccines activity

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Summary

Newly arising variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are now a threat to global public health and are creating COVID-19 surges in different countries. At the same time, there is limited knowledge about these emerging variants. Even if research data are available, it is varyingly scattered. In this review, we have discussed the appearance of significant alarming SARS-CoV-2 variants in the entire world. The study also discusses the properties of the substantial variant of concern (VOC) variants such as B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.427 (Epsilon) and B.1.429 (Epsilon). At the same time, the characteristic properties of some significant variant of interest (VOI) variants like B.1.525 (Eta), B.1.526 (Iota) (sublineage B.1.526.1), B.1.617 (sub-lineages B.1.617.1 (Kappa), B.1.617.2 (Delta) and B.1.617.3), P.2 (Zeta), P.3 (Theta), B.1.616 and B.1.427 have also been discussed. Here, we have explained some essential mutations for the VOC and VOI variants such as K417T/N, L452R, E484K, N501Y, D614G and P681R. Consecutively, we also highlighted the crucial clinical characteristics of the variants, such as transmissibility, infectivity, re-infectivity, immune escape, vaccine activity and vaccine escape. Our comprehensive review will provide updated information on the newly appearing variants of SARS-CoV-2 and help the researchers to formulate strategies to curtail the COVID-19 pandemic.

KEYWORDS

immune escape, major SARS-CoV-2 variants, mutations, vaccine activity, VOC, VOI

Abbreviations: CDC, Centers for Disease Control and Prevention; CFR, case fatality ratio; COVID-19, Coronavirus disease 2019; GISAID, global initiative on sharing all influenza data; hACE, human angiotensin I-converting enzyme 2; ORF, open reading frame; R0, reproduction number; RBD, receptor-binding domain; RT-PCR, reverse transcription polymerase chain reaction; S-glycoprotein, spike-glycoprotein; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America; VOC, variant of concern; VOI, variant of interest; WHO, World Health Organization.

All the authors contributed equally.

1 | INTRODUCTION

The devastating effects of the COVID-19 pandemic have brought noteworthy health crises throughout the globe. The pandemic has generated significant social problems and even has shut down communities in different countries throughout the world.[1–4] In addition, the world is facing an economic crisis, creating a vulnerable condition in developing world countries. As of 11 June 2021, COVID-19 has infected 174,502,686 peoples as per World Health Organization (WHO) data. Meanwhile, 3,770,361 peoples have died from this disease so far. The scientists are putting their best efforts into searching the different therapeutic and development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5–8]

The rise of infections and death cases has been observed in several world regions after the spread of novel SARS-CoV-2 variants. Due to a new variant, COVID-19 cases gradually increased in the UK in November 2020. The country has to go through a lockdown to contain the spread of variants.[9] Similarly, due to the spread of a novel SARS-CoV-2 variant, a steady rise of COVID-19 cases was noted in India. The spread of the variant has created a second wave of infection of COVID-19 cases in the country. The country has currently imposed lockdown partially in several regions of the country.[10] Newly emerging variants are now a threat to global public health gain. The genome sequence data of SARS-CoV-2 were first provided by the Chinese researcher, Professor Zhang, and his colleagues at Fudan University in the first week of January 2020. The team deposited the sequence into the GenBank for the use of further studies.[11,12] After the SARS-CoV-2 detection in China, it was observed that several SARS-CoV-2 new variants came into existence with time and different geographic locations as a consequence of genetic evolution (Figure 1). SARS-CoV-2 new variants genome sequences are submitted quickly to the global initiative on sharing all influenza data (GISAID) and GenBank databases. Around the world, most scientists are submitting their genome sequences of the variants into the GISAID database, and it is a well-known database for the genome sequences for this virus. As of 12 June 2021, 1,938,109 sequences have been submitted to the GISAID database. Utilising this database, scientists are trying to delineate several vital factors of the new variants, such as mutations, pathogenicity, virulence, transmissibility and antigenicity.

It has been observed that mutations in the genome sequence have generated a definite change, giving rise to the new variants of the SARS-CoV-2.[13,14] Mutations are prevalent in the viral genomes. Mutations occur due to the consequences of viral replication.[15] In general, higher mutation rates are recorded in RNA viruses compared to DNA viruses.[16] However, fewer mutations are noted in the coronaviruses than in RNA viruses because the virus can produce an enzyme with proof correction machinery. This enzyme corrects several errors that occur during replication.[16] Nevertheless, it has been observed that this virus has made several single mutations throughout the genome compared to the wild type (genome

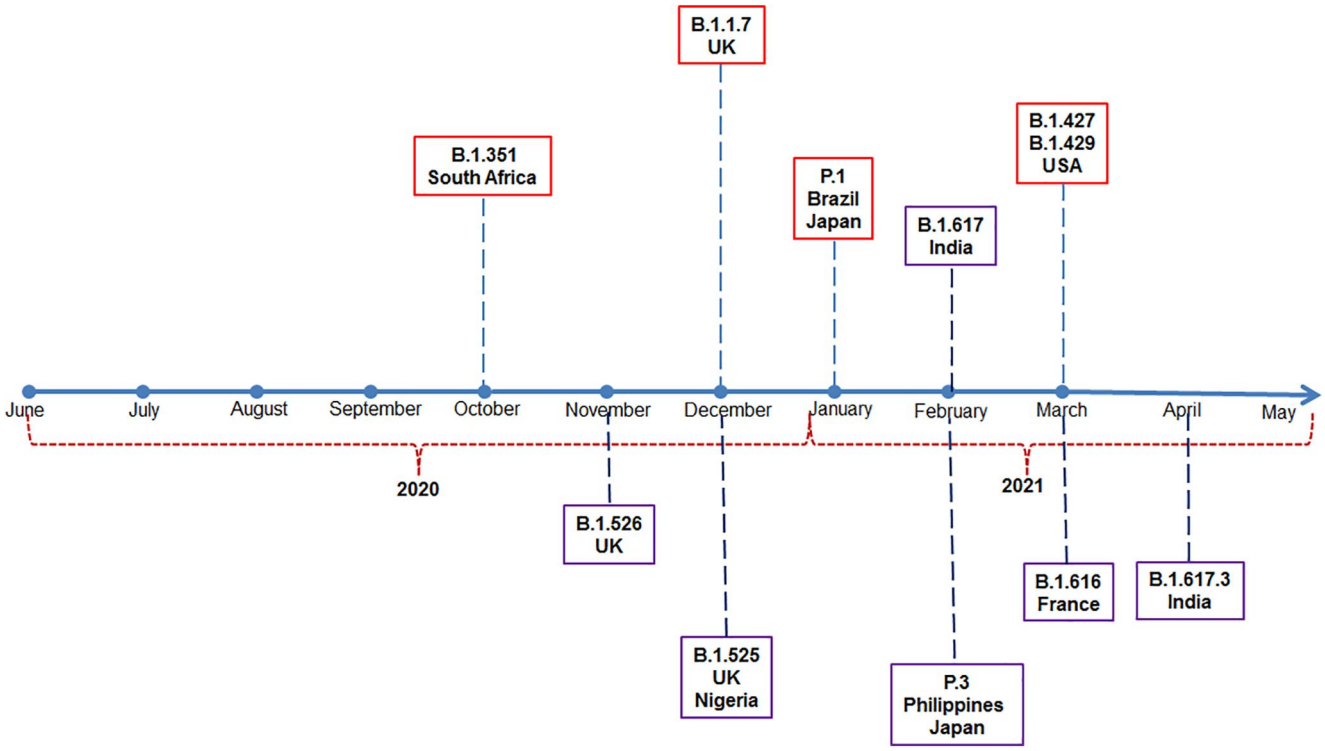

FIGURE 1 A timeline depicting the origin time of some significant variants of SARS-CoV-2. The variants of concern are marked into the red box and variants of interest marked into the violet box. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

from the Wuhan strain in China, which was sequenced in the first week of January 2020).[17,18] Several factors are associated with the generation of viral mutations. One of the significant causes is the intervention of the human immune system. The machinery involved in the immune system can cause interference in the genome to introduce viral mutations. Another important cause of mutation in the genome of this virus is the rapid transmission and quick spread rate. Moreover, RNA viruses are prone to rapid mutations as compared to DNA viruses. These factors provide considerable opportunities for SARS-CoV-2 with natural selection, which generates favourable and rare-acted mutations (Figure 2).[19,20] Significant studied SARS-CoV-2 mutations in the S-glycoprotein are K417T/N, L452R, E484K, N501Y and D614G, responsible for generating different kinds of significant variants.

During the last one and half years, several variants of this virus came into existence. Some of the significant variants are B.1.351 (South Africa), B.1.1.7 (UK), P.1 (Brazil/Japan), B.1.427 (USA), B.1.617 (India) and B.1.429 (USA).[10,21–23] Among these variants, WHO, Centers for Disease Control and Prevention (CDC) (USA) and European Centre for Disease Prevention (ECDC) (Europe) has entitled some variants as significant variants and termed them as variants of concern (VOCs) and variants of interest (VOIs). VOC has appeared as a worry for various countries as they emerged as a greater threat to public health with superior infectivity and transmissibility. At the same time, these variants harm the COVID-19 epidemiology blueprint and have an increased virulence pattern. Thus, VOC can alter the COVID-19 clinical manifestation. Even, it may reduce the efficacy of available vaccines and therapeutics and may obstruct the present ability of reverse transcription polymerase chain reaction (RT-PCR) assays to detect variants.[24,25] Similarly, VOI appeared due to amino acid alterations associated with increased community transmission, and these variants have been detected in various countries.[24,25]

In this manuscript, we have discussed the alarming appearance of these variants throughout the world. The article also discusses the properties of the significant VOCs and VOIs, important mutations for the VOCs, and VOIs such as K417T/N, L452R, E484K, N501Y, D614G and P681R. Consecutively, we have illustrated the transmissibility, infectivity, re-infectivity immune escape, vaccine activity and vaccine escape of new variants.

2 | APPEARANCE OF VARIANTS OF SARS-CoV-2 IS ALARMING THROUGHOUT THE WORLD

Several SARS-CoV-2 variants have appeared as a global threat throughout the world (Figure 3). It has raised various major questions among scientists about the nature of the variants and their consequences. One of the significant variants is the B.1.1.7, which originated in the UK.[26] Frampton et al. found that the disease was augmented due to the transmissibility of the variant. Using a cohort study in the UK hospital, the researchers concluded that the variant was not associated with the severity of the disease in the hospitalised cohort.[27] Another lineage that was found spreading throughout South Africa was B.1.351 variant.[28] Zhou et al. found that this variant has immune escaping abilities and can escape from the neutralisation of monoclonal antibodies due to the E484K mutation.[29] At the same time, P.1 variant of SARS-CoV-2 was identified from the genome sample collected from the Manaus city in Brazil. This variant was genome sequenced from the collected sample and was found associated with re-infection in Manaus.[30,31] At the same time, the other two variants (B.1.429 and B.1.427) were detected from Colorado, USA. Both of these variants spread throughout the USA and are now a public health concern in USA.[32] Jacobson et al. found these two variants re-infected the healthcare personnel even after vaccination. The phenomenon was observed in the medical centre in Northern California, USA. Among the infected samples, N501Y mutation and E484K mutation were observed.[33] Some other significant variants are B.1.525 (UK/Nigeria), B.1.617 (India), P.2 (Brazil), P.3 (Philippines/Japan) and B.1.616 (France), which are affecting public health and hindering the efforts to contain this pandemic.

Acquisitions of several mutations give rise to several significant variants, and natural selection determines the fate of a newly generated mutation. Therefore, natural selection is the determinantal factor about the existence and the consequence of the variants.

3 | PROPERTIES OF THE SIGNIFICANT VOCs

Five SARS-CoV-2 variants are regarded as VOCs by the WHO and the CDC (USA) as of 27 May 2021 (Table 1). The most significant variants are as follows.

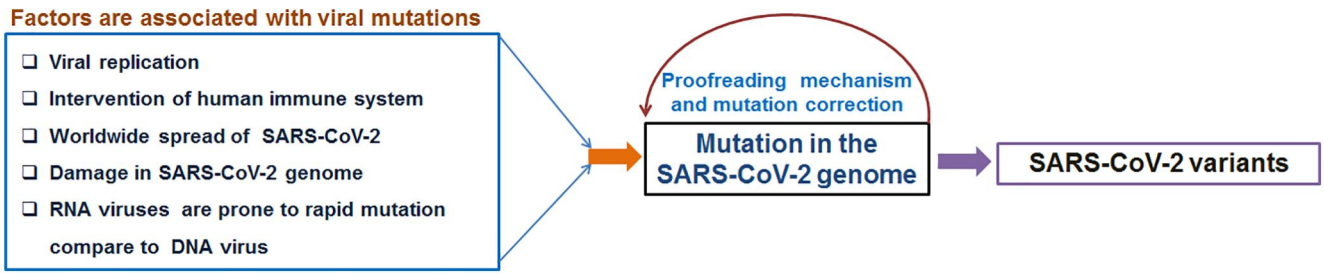

FIGURE 2 Fundamental factors and the processes associated with the SARS-CoV-2 mutation. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

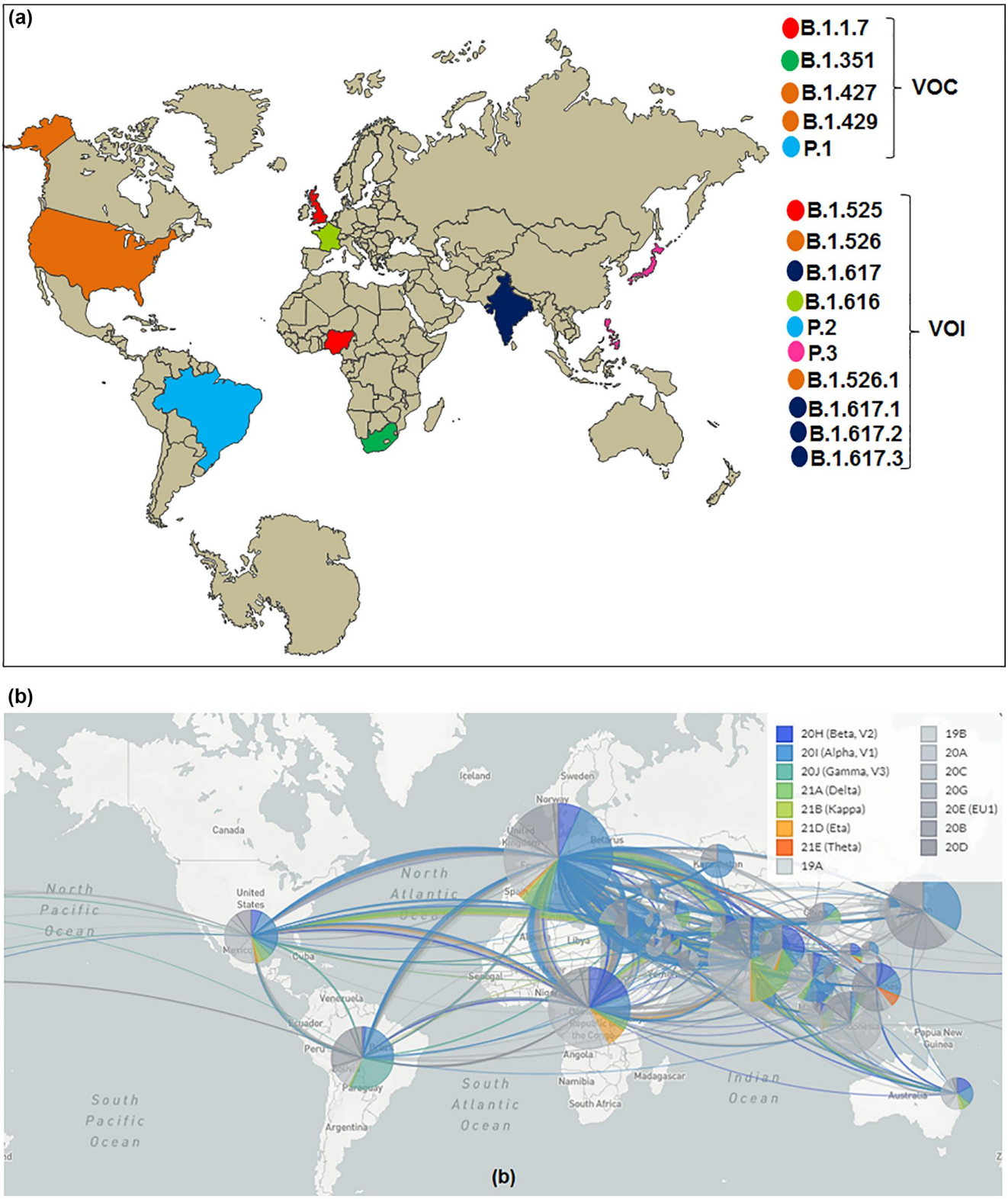

FIGURE 3 The origin, distribution and transmission of newly emerging SARS-CoV-2 variants. (a) Origin of variants of concern and variants of interest. (b) Distribution and transmission of newly emerging variants of SARS-CoV-2. The figure focused on Asia – subsampling which was developed using the Nextstrain server on 10 June 2021. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

TABLE 1 SARS-CoV-2 variant of concern and their mutations in RBD and S-protein (other than RBD region)

Sl no.	Variant name (Pango lineage)	Country of origin	Clade (as described by Nextstrain)	Variants name provided by WHO	Mutations	
					S-protein (Other than RBD region)	RBD
1.	B.1.1.7	UK	20I/501Y.V1	Alpha	69del, 70del, 144del, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N	E484K, S494P, N501Y
2.	B.1.351	South Africa	20H/501Y.V2	Beta	D80A, D215G, 241del, 242del, 243del, D614G, A701V	K417N, E484K, N501Y
3.	B.1.427	USA	20C/S:452R	Epsilon	D614G	L452R
4.	B.1.429	USA	20C/S:452R	Epsilon	S13I, W152C, D614G	L452R
5.	P.1	Japan/Brazil	20J/501Y.V3	Gamma	L18F, T20N, P26S, D138Y, R190S, D614G, H655Y, T1027I	K417T, E484K, N501Y

Abbreviations: RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

3.1 | B.1.1.7 (Alpha) variant

The B.1.1.7 variant is also defined as 20I/501Y.V1, as described by the Nextstrain database, and GR/501Y.V1, as described by the GISAID database. Hence, 20I/501Y.V1 and GR/501Y.V1 are known as Nextstrain clade and GISAID clade, respectively. However, both are similar identity of the B.1.1.7 variant. B.1.1.7 variant was identified in a clinical sample collected in the UK during September 2020. This variant was responsible for the augmented infection in different parts of England, especially the eastern and south-eastern parts of England. The variant was even found responsible for the infection in other regions of the London municipality. Due to the rapid spread of this variant, the daily mortality rate was increased in the country. The highest mortality was noted during January 2021.[26] Afterwards, B.1.1.7 variant spread to other 30 countries and was detected in the USA between 29 December 2020 and 12 January 2021. Galloway et al. have predicted that the transmission of the B.1.1.7 variant might threaten the USA healthcare prospects.[34] High transmissibility of this variant in comparison with non-VOC was reported by Volz et al. They have concluded that B.1.1.7 variant may have considerable transmission gain compared to non-VOC. However, more infection cases were observed among the patients below the 20-years age group than non-VOC lineages.[35] Several significant mutations accumulated in this variant throughout the genome. Various vital mutations in the receptor-binding domain (RBD) region of this strain are E484K, S494P and N501Y (Figure 4a). Other than the mutations in the RBD region, other major mutations in S-glycoprotein are 69del, 70del, D614G, 144del, A570D, S982A, P681H, D1118H, T716I and K1191N.[36] Graham et al. observed that this variant is resistant to neutralisation through the neutralising antibodies (nAbs).[37]

3.2 | B.1.351 (Beta) variant

The B.1.351 variant is also defined as 20H/501Y.V2, as described by the Nextstrain database, and GH/501Y.V2, as described by the GISAID database. Therefore, 20H/501Y.V2 and GH/501Y.V2 are known as Nextstrain clade and GISAID clade, respectively. The variant was detected from South Africa in December 2020 and was traced in the Eastern Cape region. After that, it was detected from the KwaZulu and Western Cape regions.[38] The variant was even detected from Zambia, located in the southern part of Africa,[39] indicating circulation of this variant throughout the country. Simultaneously, the variant also got transferred to various countries. Yadav et al. reported that the variant was detected in India, imported through a traveller.[40] In March 2021, the variant was identified in Germany through a rapid antigen test.[41] During January–February 2021, the clinical laboratory identified the variant from Maryland, USA.[42] It was observed that this variant has more hACE2 binding affinity. The researchers showed that the variant has 4.62 times more RBD-hACE2 binding affinity than the RBD of SARS-CoV-2.[43] The variant is also associated with public health hazards such as re-infections. Staub et al. found that B.1.351 accounted for four re-infection cases in Luxembourg, Europe.[44]

Several mutations have accumulated in the genome of this variant. Among them, one deletion mutation and 12 non-synonymous mutations are significant in comparison with the Wuhan strain. The mutations in the RBD region are K417N, E484K and N501Y (Figure 4a). Other than the RBD, S-glycoprotein mutations are D80A, D215G, 241del, 242del, 243del, D614G and A701V. Some variants demonstrate escape from neutralising monoclonal antibodies due to mutations like K417N, E484K and N501Y. It was observed that this variant could escape from vaccine-induced sera and natural sera.[29] One clinical trial was conducted in South Africa to understand the protection or efficiency of the AstraZeneca COVID-19 vaccine (AZD1222) against the B.1.351 variant in infected individuals. The trial evaluated the vaccine protection due to the infection of this variant in COVID-19 patients with mild to moderate symptoms. During the evaluation process of the clinical trial, two-dose regimen of this vaccine was selected. No protection was observed in the patients (mild-to-moderate patients) due to the infectivity of this variant.[45]

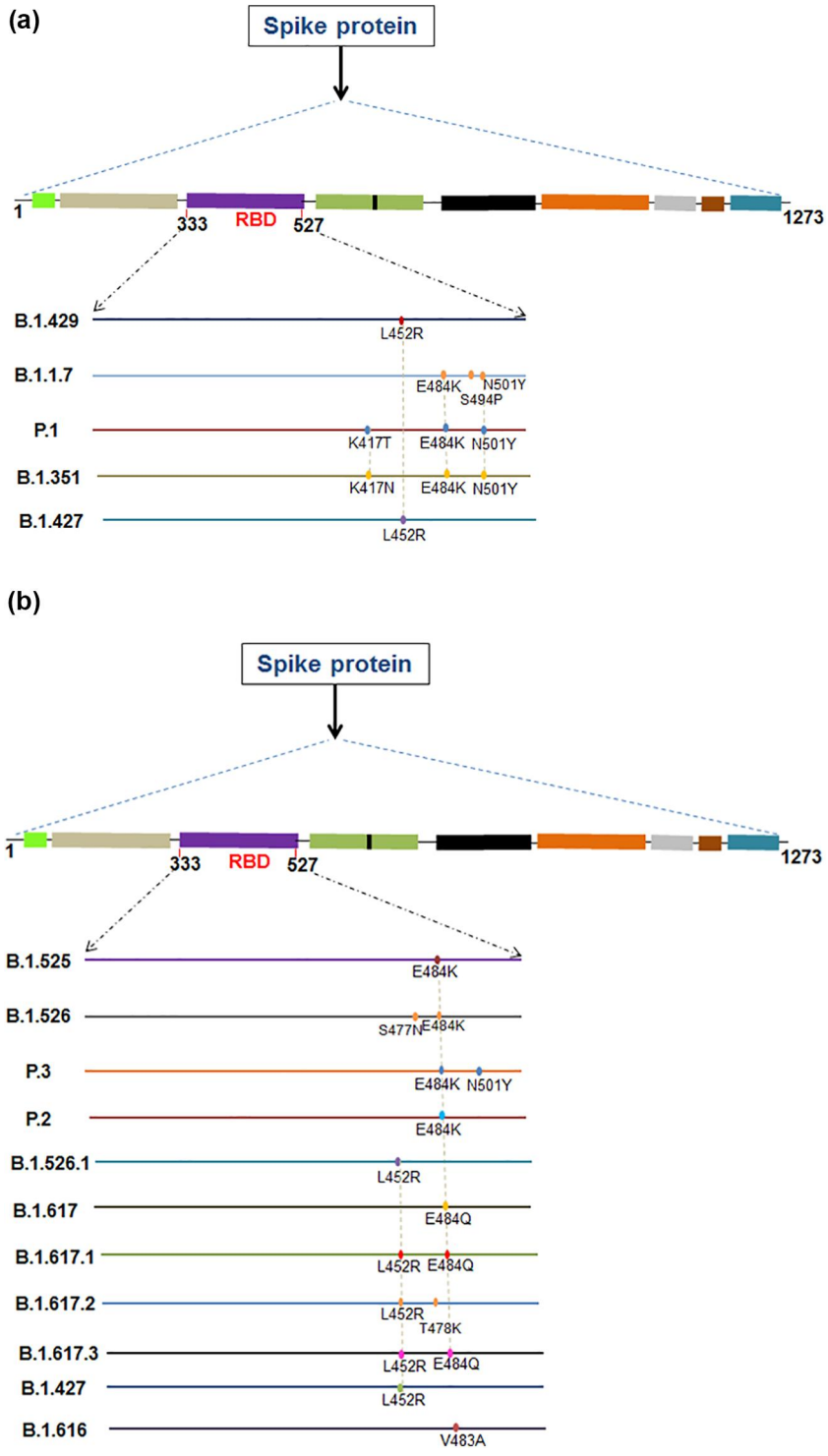

FIGURE 4 The schematic diagram showing the position of the significant mutations in the receptor-binding domain (RBD) region in variant of concern (VOC) and variant of interest (VOI). The diagram depicts the position of significant mutations in the RBD in VOC. (b) The diagram depicts the position of significant mutations in the RBD in VOI

3.3 | P.1 (Gamma) variant

P.1 variant, defined as B.1.1.28.1, belongs to B.1.1.28 lineage. It is a significant variant worldwide, first identified in Brazil (late 2020 to January 2021) from the clinical genome sequence.[21,46] This variant is responsible for generating the second wave in Brazil with high infection rate.[31] The P.1 variant is also known as 20J/501Y.V3, as described by the Nextstrain database, and GR/501Y.V3, as described by the GISAID database. Therefore, 20J/501Y.V3 and GR/501Y.V3 are known as Nextstrain clade and GISAID clade, respectively. Thus, both are the similar identity of the P.1 variant. The variant is responsible for re-infections in the Amazonian area of Brazil.[47] The variant is also accountable for the re-infection of the São Paulo State.[48] The variant got transmitted outside Brazil and circulated in different countries throughout the world. Di Giallonardo et al. observed that the P.1 variant was transmitted to several parts of Italy.[49] At the same time, the

variant was also detected in Uruguay and Japan.[50,51] The researchers found three significant mutations from the genome sequence of this variant, which are E484K, K417T and N501Y.[51]

Several mutations have accumulated in the genome of the P.1 variant. Some significant mutations are found in the S-glycoprotein, ORF1ab, ORF8 and N protein. The S-glycoprotein of this variant gathered the highest number of mutations compared to the Wuhan strain. About 12 mutations in the S-glycoprotein of this variant have been reported. The mutations in the RBD region are K417T, E484K and N501Y (Figure 4a). Other than RBD, the S-glycoprotein mutations are T20N, R190S, D614G, P26S, D138Y, H655Y, L18F and T1027I. Due to these mutations, the P.1 variant shows augmented resistance to nAbs.[51,52]

3.4 | B.1.429 (Epsilon) and B.1.427 (Epsilon) variants

The B.1.427 variant was detected from California, USA. The variant was described as VOC by CDC, USA, but it is entitled as VOI by the WHO. The B.1.427 variant is also known as 20C/S:452R as defined by the Nextstrain database. Some significant mutations were found in the S-glycoprotein. One mutation in the RBD region is L452R (Figure 4a). Another primary mutation in the S-glycoprotein other than the RBD is D614G.

The B.1.429 variant was also identified from California, USA. The variant was described as VOC by CDC, USA, but it is entitled as VOI by the WHO. The B.1.429 variant is also known as 20C/S:452R as defined by the Nextstrain database. Some significant mutations were noted in the S-glycoprotein. The one considerable mutation is located in the RBD (L452R) (Figure 4a). S-glycoprotein mutations, other than the RBD, are S13I, W152C and D614G.

After continuous surveillance during January–March 2021, these two variants were identified from Colorado, USA, and were found highly contagious. These variants are accountable for more severe illness.[32] Another study found post-vaccination infections among healthcare workers by these variants in the northern part of California.[53] Conversely, McCallum et al. reported the immune escape properties of these two variants.[54]

4 | PROPERTIES OF THE SIGNIFICANT VOIs

There are 11 VOIs according to the WHO and the CDC (USA) as of 27 May 2021 (Table 2). The significant variants are as follows.

4.1 | B.1.525 (Eta) variant

B.1.525 variant was found in the UK and also in Nigeria. The B.1.525 variant is also known as 20A/S.484K, as defined by the Nextstrain database. Similarly, the name G/484K.V3 is given by the GISAID database. Therefore, 20A/S.484K and G/484K.V3 are known as Nextstrain clade and GISAID clade, respectively. This novel variant has got transmitted to different parts of the globe. Pereira et al. reported that the identification of the variant had created a challenge for public healthcare personals in Brazil.[55] Similarly, the B.1.525 was also reported from Nigeria.[56]

Significant mutations are reported in the S-glycoprotein (A67V, 69del, 70del, 144del, D614G, Q677H and F888L). Other than S-glycoprotein, one considerable mutation is noted in the RBD (E484K) (Figure 4b).

4.2 | B.1.617 variant and its sublineages (B.1.617.1 (Kappa), B.1.617.2 (Delta) and B.1.617.3)

This variant was first detected from the Maharashtra state in India. The B.1.617 variant is also known as G/452R.V3, as defined by the GISAID database, hence G/452R.V3 is known as GISAID clade. Presently, this variant is circulating throughout India. It is accountable for the sudden surge in infections and resulted in a second wave of infections in India during April 2021.[10,57] WHO described this variant as VOI.[53] At the same time, ECDC defined this variant as VOC during May 2021.[58] Some significant mutations are found in the S-glycoprotein of this strain. The one considerable mutation is located in the RBD (L452R). However, mutation (E484K) was observed in the RBD of some samples, while it was found absent in others.[53] Other than the RBD, important mutations in the S-glycoprotein are D614G and P681R. Using clinical isolates of this variant, Yadav et al. investigated the neutralisation of B.1.617 using covaxin (BBV152) vaccine sera. The analysis is underway, and the results are yet to be published.[59]

Presently, three sublineages have been observed for this variant which are B.1.617.1, B.1.617.2 and B.1.617.3. These all sublineages are described as VOC by ECDC during May 2021.[58] In B.1.617.1, RBD mutations are E484Q and L452R. Other than the RBD, important mutations in the S-glycoprotein are T95I, D614G, E154K, P681R, G142D and Q1071H. In B.1.617.2, RBD mutations are L452R and T478K (Figure 4b). Similarly, other than the RBD, major mutations in the S-glycoprotein are T19R, G142D, D614G, P681R, 157del, R158G, 156del and D950N. Conversely, in B.1.617.3, RBD mutations are L452R and E484Q. Similarly, other than the RBD, major mutations in the S-glycoprotein are T19R, G142D, D614G, P681R and D950N. Yadav et al. determined the neutralisation antibody titer from the sera of the covishield (AstraZeneca and Serum Institute of India) vaccinated individuals. They found that the persons were protected from the B.1.617.1 variant regarding severity and mortality after 4 weeks of second dose vaccination.[60]

4.3 | P.2 (Zeta) variant

P.2 variant was first identified in Brazil in April 2020. It is also known as B.1.1.28.2, belonging to B.1.1.28 lineage. It is now circulating in several countries throughout the world. Recently, the variant was detected in Uruguay.[50]

TABLE 2 SARS-CoV-2 variant of interest and their mutations in RBD and S-protein (other than RBD region)

Sl no.	Variant name (Pango lineage)	Country of origin	Clade (as described by Nextstrain)	Variants name provided by WHO	Mutations	
					S-protein (other than RBD region)	RBD
1.	B.1.525	UK/Nigeria	20A/S.484K	Eta	A67V, 69del, 70del, 144del, D614G, Q677H, F888L	E484K
2.	B.1.526	USA	20C	Iota	L5F, T95I, D253G, D614G, A701V	S477N, E484K,
3.	B.1.526.1	USA	20C	-	D80G, 144del, F157S, D614G, T791I, T859N, D950H	L452R
4.	B.1.617	India	20A	-	D614G, P681R	L452R, ±E484Q
5.	B.1.617.1	India	20A/S:154K	Kappa	T95I, G142D, E154K, D614G, P681R, Q1071H	L452R, E484Q
6.	B.1.617.2	India	20A/S:478K	Delta	T19R, G142D, 156del, 157del, R158G, D614G, P681R, D950N	L452R, T478K
7.	B.1.617.3	India	20A	-	T19R, G142D, D614G, P681R, D950N	L452R, E484Q
8.	P.2	Brazil	20J	Zeta	F565L, D614G, V1176F	E484K
9.	P.3	Philippines/Japan	-	Theta	141/143del, D614G P681H, E1092K, H1101Y, V1176F	E484K, N501Y,
10.	B.1.616	France	20C	-	H66D, G142V, 144del, D215G, D614G, H655Y, G669S, Q949R, N1187D	V483A
11.	B.1.427	USA	20C/S.452R	Epsilon	S13I, W152C, D614G	L452R

Abbreviations: RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

The P.2 variant is also known as 20B/S.484K, as defined by the Nextstrain database. Therefore, 20B/S.484K is also known as Nextstrain clade. Significant mutations are found in the S-glycoprotein of this strain (F565L, D614G and V1176F). Other than S-glycoprotein, one considerable mutation has been observed in the RBD (E484K) (Figure 4b).

4.4 | P.3 (Theta) variant

P.3 variant was identified in Japan and the Philippines during February 2021. It is also known as B.1.1.28.3, corresponding to B.1.1.28 lineage. Several significant mutations are found in the S-glycoprotein (141/143del, D614G P681H, E1092K, H1101Y and V1176F). Other than S-glycoprotein, two significant mutations are located in the RBD, which are E484K and N501 (Figure 4b). At the same time, the immune evasion characteristic of this variant was reported by Ferraz et al. The study analysed the immune evasion through the model generation of the electrostatic surface potential of RBD.[61]

4.5 | B.1.616 variant

B.1.616 variant was identified in France during January 2021. Fourati et al. described the variant as Clade 19B.[62] However, the Nextstrain server describes it as the 20C clade. Transmission of this variant is low because the variant does possess a mutation that is not associated with the transmission.

Several important mutations are reported in the S-glycoprotein (141/143del, D614G P681H, E1092K, H1101Y and V1176F). The two significant mutations are located in the RBD (E484K and N501Y) (Figure 4b).

5 | SIGNIFICANT MUTATIONS FOR THE VOCs AND VOIs

Several significant mutations are observed in the VOCs and VOIs (Figure 5a and 5b). We also noted the country-wise significant mutations for the VOCs and VOIs in Table 3. Some important mutations are described below.

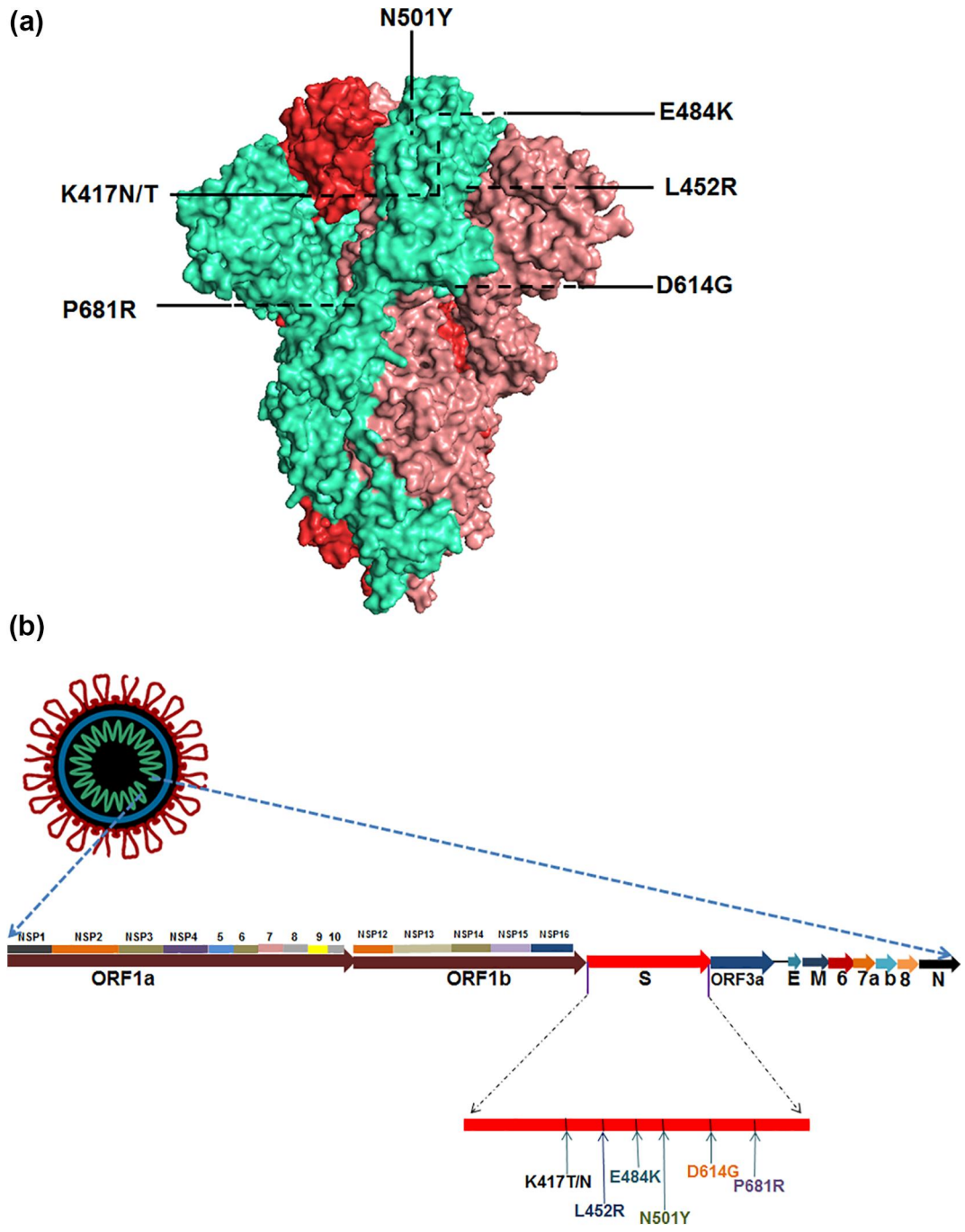

FIGURE 5 Position of some significant mutations in the S-glycoprotein. (a) Position of some crucial mutations in the 3D structure of S-glycoprotein. (b) Position of some essential mutations in a schematic diagram of S-glycoprotein

5.1 | K417T/N mutations

The two mutations, K417T and K417N, are significant mutations that are found in the RBD region. K417T is noted in the P.1 variant and the K417N in the B.1.351 variant. K417T mutation is associated with a conformational change of S protein. At the same time, K417N is also related to a conformational change of S protein. Both of these two mutations are responsible for the antibody escape characteristic of the virus.[63,64] Specifically, these two mutations are associated with the hACE2 biding of the virus. The affinity of binding to hACE2 increases the infectivity of new SARS-CoV-2 variants.[65]

5.2 | L452R mutation

This mutation is associated with the change in the RBD region of VOC B.1.429 and B.1.427 variants from the USA. Similarly, the mutation is also noted in the RBD region of the B.1.617 variant and its

TABLE 3 Country-wise, different significant RBD mutations on spike protein of SARS-CoV-2

Sl no.	Country name	Significant mutation
1.	India	E484K, S477N, A520S, N440K, S494P, L452R, E484Q, N501Y, P384L
2.	Singapore	N439K, F490L, N501Y, E484K, L452R, S477N, K417N, N440K
3.	Brazil	E484K, N501Y, K417T
4.	UK	S477N, N439K, N501Y, S494P
5.	Mexico	L452R, T478K
6.	Italy	N440K, N439K, L452R, S477N, N501Y, E484K, K417T, Q414K
7.	USA	E484K, A520S, N501Y, N501T, S477N, L452R, S494P
8.	Australia	L452R, N501T, N439K, S477N, N501Y, L455F
9.	UAE	K417N, E484K, N501Y, N439K, N440K, S477N
10.	South Africa	D215G, N501Y, E484K, K417N, A701V, L18F, D80A

Abbreviations: RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

sublineages (B.1.617.1, B.1.617.2 and B.1.617.3). It is also found in the VOI B.1.427 variant which is originated from USA. This mutation is associated with increased infectivity, higher transmission and a reduction in neutralisation by specific therapeutic antibodies. Researchers found that it is associated with more than 18%–24% higher transmissibility. At the same time, a 20-fold reduction was observed in neutralising titers from vaccine recipient individuals and convalescent patients.[66]

5.3 | E484K mutation

This mutation is associated with the change in the RBD region of VOC B.1.1.7, B.1.351 and P.1 variants. Likewise, the mutation is also noted in the RBD region of VOI P.2, P.3, B.1.525, B.1.526 and sublineages B.1.617.1 and B.1.617.3 of B.1.617 variant. This mutation is related to the hACE2 biding of the virus and is reported for the augmented infectivity of new variants.[65] Lohr et al. reported that the immune escape phenomenon during Bamlanivimab therapy in patients infected with a new variant (B.1.1.7) was because of E484K mutation.[67] Jangra et al. reported that this mutation influences the binding of nAbs and thus reduces antibody neutralisation.[68] The mutation is also associated with the re-infection, as noted in the SARS-CoV-2 re-infected patients in Brazil.[69]

5.4 | N501Y mutation

This significant mutation is associated with the change in the RBD region of VOC B.1.1.7, B.1.351 and P.1 variants. At the same time, the mutation is also noted in the RBD region of the VOI P.3 variant.

Zhao et al. evaluated the variant-specific case fatality ratio (CFR) using a statistical framework of time-varying representation and calculated changes in CFR. They concluded that N501Y substitution is associated with a possibility of case fatality for COVID-19 patients.[70] Using Monte Carlo sampling and molecular dynamic simulations, Ali et al. found that this mutation confirms a sturdy binding resemblance to ACE2. This mutation is accountable for the superior electrostatic interactions in the interaction site and is responsible for a powerful hydrogen bond formation between residue T500 of S-glycoprotein and residue D355 of ACE2 near the mutation site. Finally, they concluded that the molecular association during binding might contribute above 40% of the binding energy of total binding energy.[71] By utilising whole genome sequencing and Swiss-wide diagnostic screening, researchers established that this mutation is associated with the transmission and rapid spread of the new variants in Switzerland.[72]

5.5 | D614G mutation

This significant mutation is found in the S-glycoprotein protein outside the RBD region. The mutation is noted from all the reported VOC variants (P.1, B.1.427, B.1.1.7, B.1.429 and B.1.351). At the same time, the mutation is also noted in the S-glycoprotein outside the RBD region of all the reported VOI (B.1.525, B.1.526 (sublineage B.1.526.1), B.1.617 (all sublineages like B.1.617.1, B.1.617.2 and B.1.617.3), P.2, P.3, B.1.616 and B.1.427). Therefore, it is a very significant mutation in the newly appearing SARS-CoV-2 variants.

Mansbach et al. described that this rapid transition of a variant with G-form carried an amino acid substitution D614G. This mutation with G-form provides a favourable environment for an open conformational state of S-glycoprotein. Through the in vitro experiments, researchers observed that G-form is highly infectious and is related to higher viral loads in the upper part of the airway in the respiratory tract.[72] Similarly, this S-glycoprotein mutation is associated with the transmissibility of the new variant.[73] Furthermore, scientists found that this mutation causes a 1.7 to 2.4-fold reduction in SARS-CoV-2 nAb, elicited through the BNT162b2 vaccination.[74]

5.6 | P681R mutation

This significant mutation is also found in the S-glycoprotein protein outside the RBD region. It is located in the VOI B.1.617, and it is all sublineages such as B.1.617.1, B.1.617.2 and B.1.617.3.

The mutation was observed adjoining to the furin cleavage site. It might have a consequence on the cleavage of the S1/S2 region and thereby in virus cell entry. The mutation might also have an effect on the infectivity of this variant.[75]

6 | NEW VARIANTS AND THEIR IMPACT ON TRANSMISSIBILITY, INFECTIVITY AND RE-INFECTIVITY

Several models have been developed to assume improved transmissibility of new variants. Scientist calculates the basic reproduction number (R0), evaluates the peak viral load and the viral shedding time to understand the transmissibility. Graham et al. tried to find the cause of the increased number of infections with the B.1.1.7 variant. They observed the augment in the effective reproduction number (Rt) of the UK variant (B.1.1.7). Due to national and regional lockdowns, the Rt value can be decreased. Even the increase in the rate of re-infection can be lowered.[76] However, re-infection can be prompted by the new variants. Romano et al. noted the re-infection cases by the P.1 variants in São Paulo city of Brazil.[48] At the same time, four re-infection cases by the B.1.351 were recorded in Luxembourg.[44] Researchers reported that a higher transmission rate was noted in B.1.1.7 with 43%–82%.[77] Similarly, a 2.6 times higher transmission rate was found in the case of P.1.[78]

The significant mutation D614G is associated with the increased transmissibility of the new variants.[79] This mutation is found in the S-glycoproteins of all VOC and VOI with amplified transmissibility. In addition, Hou et al. have validated that the D614G mutation is responsible for enhanced transmission in an animal model.[80]

7 | NEW VARIANTS AND THEIR IMPACT ON DIAGNOSTICS

New variants may possess an amplified risk of likely probe/primer mismatch. This probe or primer mismatch could obstruct the capability of present RT-PCR assays to detect the new variants.[81] For that reason, Jain et al. has recorded 132 probe or primer sequences from different public literature using about 5862 distinctive variants. In addition, they observed about 286 genomic regions with low variability. These genomic areas are the continuous stretch of ≥20bps.[82] However, more research will be required to search for the new probe/primer to identify the new variants by RT-PCR assays. At the same time, other rapid diagnostic assays should be developed to detect the newly evolving variants.

8 | NEW VARIANTS AND THEIR IMPACT ON IMMUNE ESCAPE, VACCINES ACTIVITY, AND VACCINE ESCAPE

Immune escape is a concern for the new variants. Several exponents have been noted for the immune escape characteristic. To understand the affinity between antibody and variants (especially VOCs), Ferraz et al. developed a model of electronic surface in RBD. The study observed the cross-reactivity between the VOCs and elicited nAbs. Due to lower cross-reactivity between the VOC and the elicited nAb, the VOC can escape from the immune system, a phenomenon possessed by the new variants with their significant mutations.[61] Conversely, Garcia-Beltran et al. illustrated that the numerous variants of SARS-CoV-2 could escape different vaccines such as mRNA 1276 and BNT162b2 due to several mutations in RBD (K417T/N, E484K and N501Y).[83] It has been noted that B.1.1.7 gained a significant and critical mutation (E484K). Due to the mutation, the immune sera from a human subject with Pfizer/BioNTech vaccination (mRNA-based vaccine) modestly reduced in neutralising titers against the UK variant (B.1.1.7) compared to wild-type pseudoviruses.[84] At the same time, only 10% protection was observed by the ChAdOx1 vaccine from AstraZeneca against COVID-19, infected with another variant (B.1.351), as observed in South Africa. Researchers found that a two-dose vaccine regime cannot protect individuals re-infected with COVID-19 with mild-to-moderate symptoms due to the B.1.351 variant.[85] The same vaccine showed 75% protection against the UK variant (B.1.1.7).[86] Likewise, an analysis from Israel noted that mRNA-based vaccine BNT162b2 (Pfizer/BioNTech) was less effective against B.1.351 than other emerging variants.[87] From the significant mutations analysis, Wang et al. developed a model where they hypothesise that mutations in RBD might disrupt antibody recognition abilities, which may be a threat to the current COVID-19 vaccines. Thus, these mutations may be entitled as vaccine escape mutations.[88] We also recorded the vaccine escape mutations of the new variants in Table 4.

However, the development of a next-generation vaccine for COVID-19 may be one solution for vaccine escape. This next-generation vaccine should posse alternative epitopes from the different emerging variants. Bhattacharya et al. developed a vaccine using alternative epitopes from the significant variants of SARS CoV-2 and Wuhan strain through immunoinformatics approach.[95] However, more research data are needed in this direction.

9 | CONCLUSION

The development of emerging variants, especially VOCs and VOIs, is now a global challenge. Due to new variants, different countries are facing massive COVID-19 surges and a drastic rise in mortality. New variants are capable of more rapid transmission and immune escape. Some mutations, such as D614G, E484K and N501Y, are advantageous to viral survival. On the other hand, every county has started a COVID-19 vaccination program to end the pandemic. Therefore,

TABLE 4 Vaccine efficacy by significant variants of SARS-CoV-2

Sl no.	Variant	Vaccine name and efficacy				Reference
		AstraZeneca AZD1222	Pfizer/BioNTech – BNT162b2	Novavax NVX-CoV2373	Janssen (J&J) – Ad26.COV2.S	
1.	B.1.1.7	Previously the vaccine efficacy was noted 81%, now 70% against B.1.1.7	Efficacy was 90%–95%, in prevalence of B.1.1.7 the vaccine efficacy observed 81.5%	The vaccine efficacy was reduced from 95.6% to 85.6% in occurrence of B.1.1.7	-	89–91
2.	B.1.351	Showing only 10% efficacy	100% effective	Efficacy showing 51% against B.1.351	52% efficacy against the moderate disease, and 72% against severe disease (South Africa). 72% efficacy (USA)	85,91–93
3.	P.1	-	Efficacy lowered 6.7%	-	-	93,94

Abbreviations: RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

first, every country should understand the efficacy of the available vaccines against these new variants. There is a knowledge gap about the VOI in the area of transmissibility, infectivity, re-infectivity, immune escape and vaccine activity. Thus, intense research strategies are required in these directions. Moreover, healthcare and hospital preparedness are compulsion for every nation to fight against the emerging variants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, data curation, writing, supervision: Chiranjib Chakraborty. Validation, formal analysis: Manojit Bhattacharya. Formal analysis, review and editing: Ashish Ranjan Sharma. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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