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Review Article

Evolution of the SARS-CoV-2 pandemic in India

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a bat-derived beta-coronavirus, that emerged around December 2019. In spite of the lesser genomic diversity of CoVs in general, a steady accumulation of mutations spread over its genome have been noted, resulting in the emergence of several clades and lineages. Majority of these mutations are random and non-functional changes; however a few variants of concern (VOC) and variants of interest (VOI) designated by the WHO since late 2020 have implications to diagnostics, pathogenicity and immune escape. This review discusses the various nomenclatures depicting the SARS-CoV-2 evolution, the designated VOCs and VOIs and the mutations characterizing these variants. The evolution of SARS-CoV-2 in India and the implications to vaccine efficacy and breakthrough infections is also addressed.

Introduction

Around December 2019, a novel coronavirus (CoV) began to circulate among humans in Wuhan, China. The virus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), by the International Committee on Taxonomy of Viruses. The disease COVID-19, caused by the virus was declared a pandemic by the World Health Organization (WHO) in March 2020. As of May 18, 2022, more than 520 million confirmed cases have been reported worldwide with over 6.2 million fatalities [https://covid19.who.int/]. The impact of SARSCoV-2 across the globe has established it among the most notorious pandemic that has ever been recorded in human history.

Like the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) of 2003 and the Middle East respiratory syndrome (MERS) CoV of 2012, SARS-CoV-2 is also a bat-derived beta CoV. Genomic comparisons suggest that it shares maximum genetic identity (96.3%) with a horseshoe Bat CoV and 82% with the human SARS-CoV-1.[1] Unlike the majority of the RNA viruses, CoVs in general have lesser genomic diversity due to a restrained mutation rate. This is a result of the proofreading activity of the exoribonuclease. Most random, non-functional changes in the genome seldom become fixed and are majorly useful for tracing transmission chains. Despite this, the accumulation of mutations in the relatively large genome (~29.8 kb) of the SARS-CoV-2 has been noted to have implications for diagnostics, pathogenicity and immune escape. Several variants of concern (VOC) and variants of interest (VOI) have been designated for SARS-

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CoV-2 by the WHO since late 2020. Viral genome sequencing and genetic characterization have thus emerged as an essential tool for the epidemiological investigation of the SARS-CoV-2 evolution and in formulating strategies for control such as vaccines, antivirals and antibody therapies.

Genome structure of the SARS-CoV-2

The genome of SARS-CoV-2 comprises a single-stranded, positive-sense RNA. It is composed of 13–15 open reading frames encoding about 7096 residues long polyprotein which consists of many structural and non-structural proteins (NSP). Polyproteins pp1a and pp1ab are encoded by open reading frames 1a and 1b, which are followed by structural proteins (Fig. 1). pp1ab is encoded by the ribosomal frameshift mechanism of the gene 1b. These polyproteins are further processed by virally encoded proteinases and produce 16 NSPs that play important roles as enzymes in replication and survival in host cells. The major enzymes are the NSP3, main protease (Mpro), NSP5, papain-like protease (PLpro) and NSP12, RNA-dependent RNA polymerase (RdRP).

There are four major structural proteins namely spike (S), envelope (E), membrane (M), nucleocapsid (N), and 8 accessory proteins that are encoded at the 3' terminal region of the genome. The NSPs are found to be well conserved in CoVs belonging to the same family while the structural proteins share high sequence similarity to the sequence of the corresponding protein of SARS-CoV-1, and MERS-CoV.[2] The S protein plays a key role in the life cycle of the virus and host defense response. It is also responsible for binding to the host cell surface receptor, angiotensin-converting enzyme 2 (ACE2), through the receptor-binding domain (RBD) in the S1 subunit, followed by the fusion of the S2 subunit to the cell membrane.

Ongoing evolution of SARS-CoV-2 - from clades and lineages to variants of concern and variants of interest

Since the first full genome of the Wuhan strain was submitted to the global database, the repository, Global Initiative on Sharing All Influenza Data (GISAID) (https://www.gisaid.org/), has seen unprecedented growth in the number of sequences deposited. As of March 18, 2022, 9,353,626 whole-genome sequences (WGS) of SARS-CoV-2 from across the world have been shared on the publicly available platform.

The rapid diversification of SARS-CoV-2 strains enabled delineation into clades and sub-clades. Differing nomenclatures such as GISAID,[3] NextStrain,[4] PangoLIN,[5] based on varied approaches were proposed. The GISAID nomenclature system for clades is based on shared marker mutations. For instance, clade 'G' that rose sharply in February 2020 and spread worldwide was characterized by the S:D614G marker. Clade names and extensions were triggered when a clade could be further subdivided based on the same criteria of marker mutations. Currently, GISAID has 10 phylogenetic groups, starting from two groups, S and L; L is split into V and G, and then G further evolving into GH, GR, and GV. Further, GR evolved into GRY and GK, which is the presently predominant clade. Two linked SNPs at sites 8782 (T → C) and 28,144 (C → T), resulting in a mutation L84S in the ORF8 protein, adequately defined the L and S lineages of SARS-CoV-2. With S remaining at moderate levels, L is split into the subsequent GISAID clades that continued to circulate. Compared to the GISAID clades, more detailed lineages were assigned by the Phylogenetic Assignment of Named Global Outbreak LINeages (Pango lineage) tool. The Pango lineages are a dynamic, hierarchical nomenclature that describes a lineage as a set of sequences noted in a geographically distinct region showing evidence of ongoing transmission in the region. For instance, the GRY clade in GISAID corresponds to Pango lineage B.1.1.7 while the newer clade GK corresponded to Pango lineage B.1.617.2. The advantage of the PangoLIN nomenclature system was that it could help facilitate tracking viral imports across the globe.

The NextStrain, which is a Year-Letter nomenclature provides large-scale diversity patterns, and clades that continue for several months and show considerable geographic spread are labeled. Every clade name, in this system, is designated by the year when the clade emerged and a capital letter starting with A for the respective year. Overall, the clades were labeled as 19A, 19B, 20A, 20B, 20C, and so on and currently at 20M.

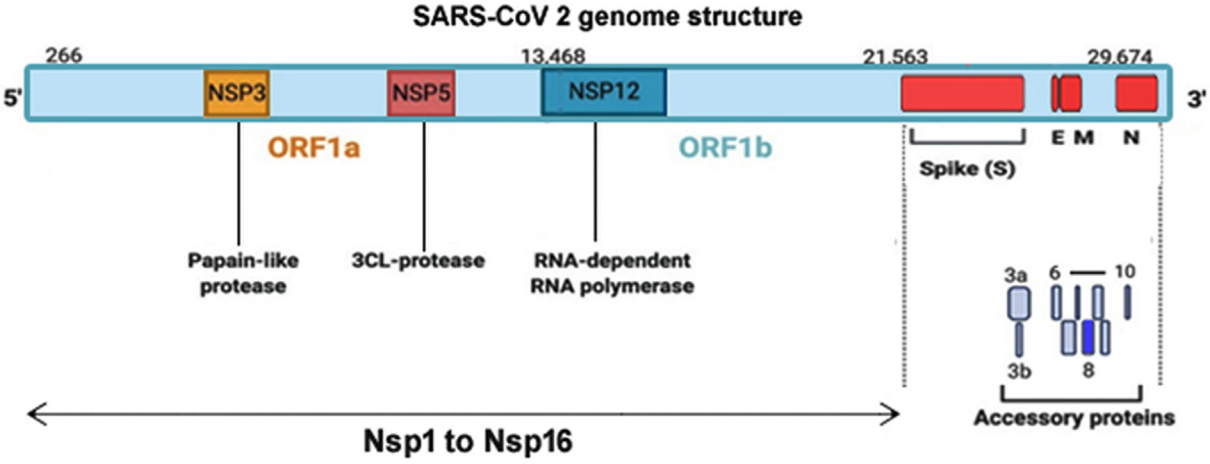

Fig. 1 – Genomic organization of SARS-CoV-2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

A table depicting the correspondence between the clades/lineages in these different nomenclature systems and the list of marker mutations is shown in Table 1.

Variants of concern and variants of interest

The Virus Evolution Working Group of WHO has been continuously monitoring the evolution of SARS-CoV-2 since the beginning of the pandemic. The emergence of variants, posing an increased risk to public health, toward the end of 2020 necessitated the announcement of VOIs and VOCs. This was done in order to prioritize global monitoring and implement disease control measures for the ongoing pandemic. By definition, a VOC is one which has been demonstrated to be associated with one or more of the following changes at a global public health level (a) an increase in transmissibility or detrimental change in COVID-19 epidemiology; OR (b) increase in virulence or change in clinical disease presentation; OR (c) decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics (www.who.int). The possible attributes of a VOC could hence be a detrimental effect on diagnostic test targets, decreased susceptibility to therapeutics, or decreased neutralization by antibodies from previous infection or vaccination.

A VOI, on the other hand, is a variant with (a) genetic changes that could affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic, or therapeutic escape; AND (b) identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside an ,increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health (www.who.int).

The designated VOCs and VOIs are listed in Table 2.

Evolution of SARS-CoV-2 in India

The first three cases of SARS-CoV-2 in India were reported on January 30, 2020 as imported cases in Kerala from Wuhan. The first two full genomes were obtained using next-generation sequencing from clinical specimens of two of these cases, India, as imported cases from Wuhan, China. Further, genome sequencing, as well as virus isolation, was undertaken from positive clinical specimens from the imported cases of SARS-CoV-2 via Italian tourists, Indians evacuated from Iran and Italy and the suspected contacts in India. Thereafter, SARS-CoV-2 cases increased exponentially and India experienced

Table 1 – Correspondence of different clade nomenclature systems and the marker mutations.

WHO name	GISAID clade	Nextstrain clade	Pangolin lineage	Major Marker
	L	19A	B	WIV04- Ref Seq
	S	19B	A	NS8:L84S
	V	19A	B.2	NSP6:L37F + ORF3a:G251V
	G	20A	B.1	S:D614G
Beta	GH	20C	B.1	S:D614G + ORF3a:Q57H
Gamma	GR	20B	B.1.1.1	S:D614G + N:G204R
	GV	20A.EU1	B.1.177	S:D614G + S:A222V
Alpha	GRY	20I/501Y.V1	B.1.1.7	S:D614G + N:G204R + S:N501Y
Delta	GK	21A	B.1.617.2	S:D614G + S:T478K
Omicron	GRA	21K	B.1.1.529	S:D614G + N:G204R + S:E484A

Table 2 – The variants of concern and variants of interest.

WHO label	Pango lineage	GISAID clade	Nextstrain clade	Additional amino acid changes monitored	Earliest documented samples
Variants of concern (VoCs)					
Alpha	B.1.1.7	GRY	20I	+S:484K +S:452R	United Kingdom, Sep-2020
Beta	B.1.351	GH/501Y.V2	20H	+S:L18F	South Africa, May-2020
Gamma	P.1	GR/501Y.V3	20J	+S:681H	Brazil, Nov-2020
Delta	B.1.617.2	G/478K.V1	21A, 21I, 21J	+S:417N +S:484K	India, Oct-2020
Omicron	B.1.1.529	GRA	21K, 21L 21M	+S:R346K	Multiple countries, Nov-2021
Variants of interest (VOIs)					
Eta	B.1.525	G	21D	+S:484K	Multiple countries, Dec-2020
Iota	B.1.526	GH	21F	+S:253G	United States of America, Nov-2020
Kappa	B.1.617.1	G	21B	+S:452R	India, Oct-2020
Lambda	C.37	GR	21G	+S:452Q	Peru, Dec-2020
Mu	B.1.621	GH	21H		Colombia, Oct-2020
Theta	P.2	GR	20B		Brazil, Apr-2020
Zeta	P.3	GR	21E		Philippines, Jan-2021

three major COVID-19 waves. The total number of cases as of March 18, 2022 was 43,004,005 with 516,281 deaths [https://covid19.who.int/region/searo/country/in].

The genomic surveillance was undertaken continuously and sequences of SARS-CoV-2 were analyzed phylogenetically by comparing with other available sequences at GISAID to reveal the diversification and the genetic variants.[6] The first two entries were identified as the S and L clades, while the Italy cases were of clade G and the Iran entries were identified as clade 'O' (B.4 lineage). As a part of nation-wide genomic surveillance, the geographic distribution of SARS-CoV-2 clades and variants circulating in different parts of India between January and August 2020 was also studied by ICMR-NIV.[7] Representative positive cases from different states and union territories (UT) in India were collected every month through the VRDLs in the country and analyzed using next-generation sequencing. Altogether, 1603 samples were received from twenty-five states and UTs. The analysis of 689 sequences revealed that the northern part of India largely reported the 'GH' clade, whereas the southern part reported the 'GR', with a few exceptions.

With the emergence of the new VOCs, the Indian SARS-CoV-2 Genomics Consortium was established for sentinel surveillance in December 2020, with the help of ten Regional Genome Sequencing Laboratories. The early detection of genomic variants with public health implication was undertaken through the screening of international travelers/contacts and 5% of community samples. So far, under Indian SARS-CoV-2 Genomics Consortium ICMR-NIV has sequenced more than 8000 SARS-CoV-2 genomes from COVID-19 positive international travelers as well as from the community. In early 2021, of 212 positive samples, 27 were identified as the VOC Alpha.[8] The analysis of the genome sequences of the SARS-CoV-2 from Maharashtra (November 2020 to May 2021) helped detect the VOC, Delta and VOI, Kappa.[9]

As of March 18, 2022, 166,574 WGS from India are deposited in GISAID. The state wise distribution of SARS-CoV-2 and the trend of the clade distribution in India are depicted in Fig. 2 a and b, respectively. Among the 28 states and 8UTs, Maharashtra followed by Kerala, Delhi, Andhra Pradesh, and West Bengal have generated the maximum number of WGS (Fig. 2a). The trend of clades over the period from the start of the pandemic to date shows that since February 2021, the GK clade (Delta variant) was predominant and thereafter since December 2021, the GRA (Omicron) variant replace GK to become the dominant strain (Fig. 2b).

Mutations characterizing the variants of concern and variants of interests

Mutations in viruses are an important mechanism for their evolution, fitness, and survival. Though at the beginning of the COVID-19 pandemic, the viral diversity was low, positive selection conferring benefits such as increased transmissibility and better fitness has now resulted in higher mutational rates. The functional characterization of these mutations, however, remains under-investigated.

Among the VOCs, the Alpha variant (B.1.1.7) was characterized by 17 amino acid mutations or deletions, the Beta (B.1.351) variant 9, Gamma (P.1) 16, and Delta (B.1.617.2) variant 20 and Omicron 46 (Table 3) (https://outbreak.info/situation-reports#voc). All the VOCs possessed the D614G mutation in the S protein. Within the S protein, a few RBD mutations such as those at positions 417, 478, 484, and 501 are shared between the Alpha, Beta, Gamma, Delta, and Omicron variants (Table 3). Mutations E484K and N501Y are located within the receptor-binding motif (aa position 437–508) of the RBD (331–528) that interacts with ACE2. Spike RBD residue E484 interacts with residue K31 on ACE2, K417 with D30 and N501 with Y41 (Fig. 3), suggesting that mutations at these positions may affect the binding affinity of SARS-CoV-2 with ACE2. In addition, E484 and K417 are important binding sites for neutralizing antibodies and hence result in immune escape (Fig. 4). *In vitro* evidence also suggests that mutations K417N and E484K reduce recognition by human antibodies.[10–13]

VOC Delta contains mutations, L452R, T478K, and P681R within the S protein. Residue L452 interacts with ACE2 residues E35, E37, and D38 and mutation L452R can result in increased electrostatic interactions, leading to an increase in

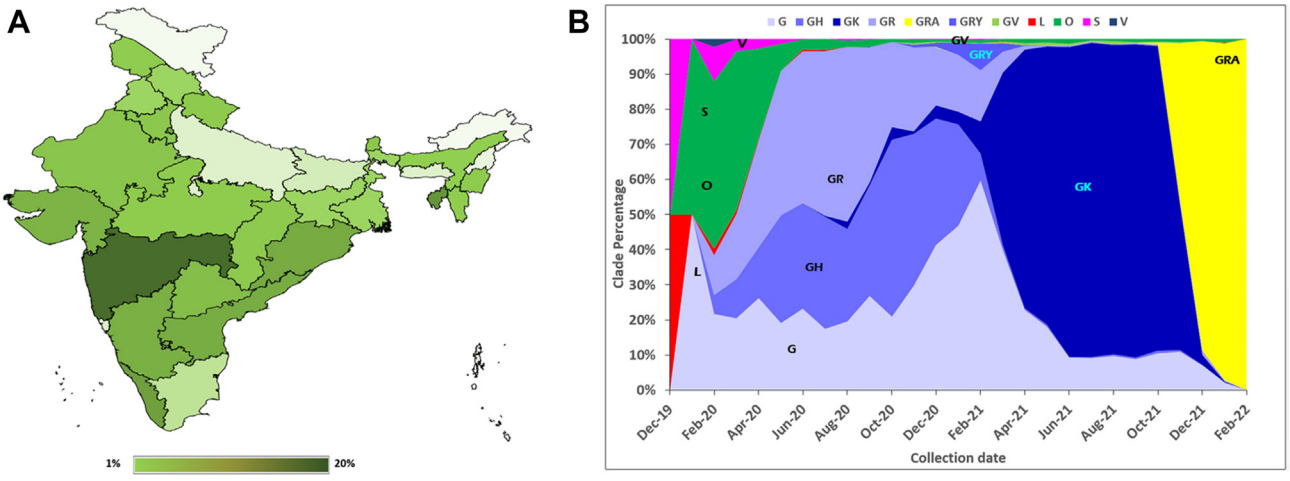

Fig. 2 – The state wise distribution of SARS-CoV-2 (a) and the trend of the clade distribution in India (b).

Table 3 – SARS-CoV-2 VoCs and their marker mutations in the genome.

Lineage	Total changes in genome	Non synonymous mutations with reference to Wuhan ref. strain	Spike mutations [RBD]
B.1.1.7/GRY/ALPHA	17	ORF1ab: T1001I, A1708D, I2230T, Deletion 3675-3677SGF ORF8: Q27stop, R52I, Y73C N: D3L, S235F	Deletion 69-70HV, 144Y, [**N501Y**], A570D, P681H, T716I, S982A, A1118H
B.1.351/GH/BETA	9	E: P71L N: T205I ORF1a: K1655N	D80A, D215G, [**K417N, E484K, N501Y**], A701V
P.1/GR/GAMMA	16	ORF1ab: S1188L, K1795Q Del 11288:9 ORF3a:G174C ORF8:E92K N:P80R	L18F, T20N, P26S, D138Y, R190S, [**K417T, E484K, N501Y**,] H655Y, T1027I
B.1.617.2/GK/DELTA	20	ORF1b: P314L, G662S, P1000L ORF3a: S26L M: I82T ORF7a: V82A, T120I ORF8: D119I, del 120/121 N: D63G, R203M, D377Y	T19R, G142D, E156G, del 157/158, **[L452R, T478K],** P681R, D950N
B.1.529/GRA/OMICRON	46	ORF1a: K856R, S2083I, del2084/2084, A2710T, T3255I, P3395H, del3674/3676, I3758V ORF1b: P314L, I1566V E: T9I M: D3G, Q19E, A63T ORF8: S84L N: P13L, del31/33, R203K, G204R	A67V, del69/70, T95I, G142D, del143/145, del212/212, [**G339D, S373P, S375F, S477N, T478K, E484A, Q493R,Q498R, N501Y, Y505H**], T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K L981F

stability of the S-ACE2 complex and thus viral infectivity. Furthermore, abolition of the hydrophobic surface patch through the L452R mutation can lead to a reduction in antibody-mediated neutralization.[9,10,14] The mutation T478K in the S protein can also increase electrostatic interactions with ACE2 and may result in increased binding affinity, similar to the S477N mutation.[15,16] T478K is also located within a neutralizing epitope and in combination with L452R

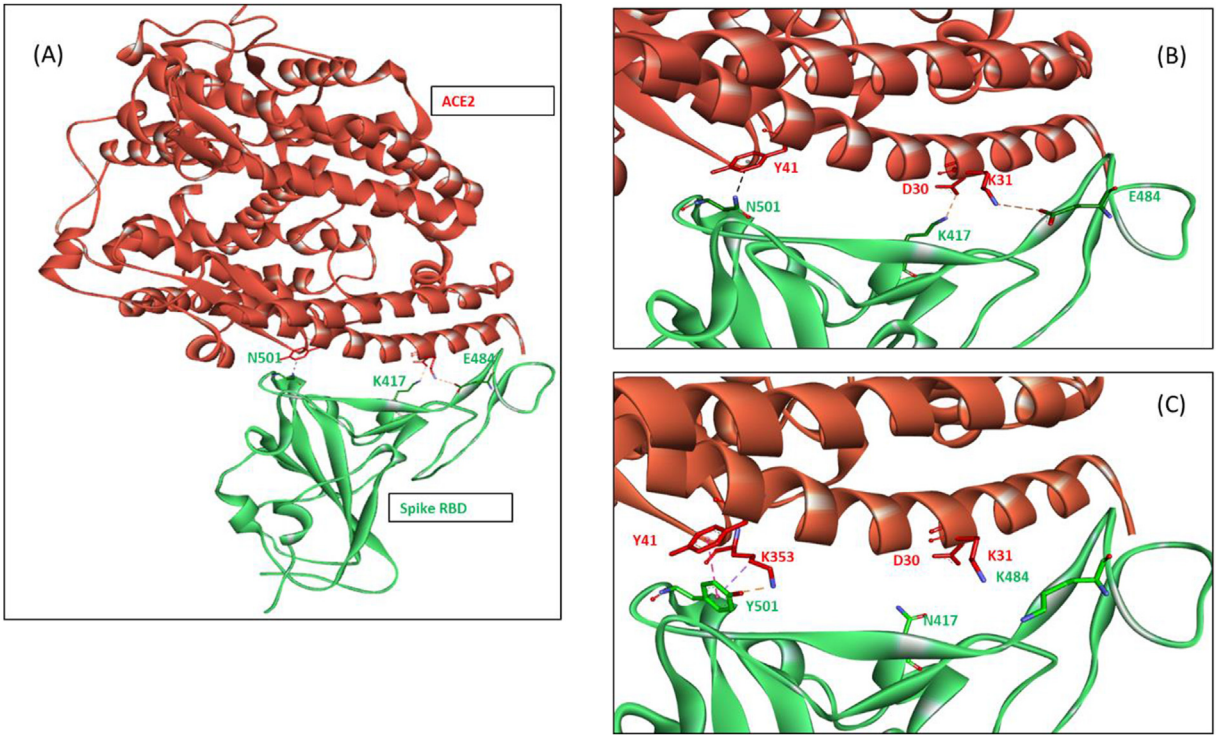

Fig. 3 – Effect of key mutations N501Y, K417N, and E484K on ACE-2 binding. (a) Complex of spike RBD with ACE2. Interacting residues in wild type and mutant strains are shown in (b) and (c), respectively. ACE-2, angiotensin-converting enzyme 2; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

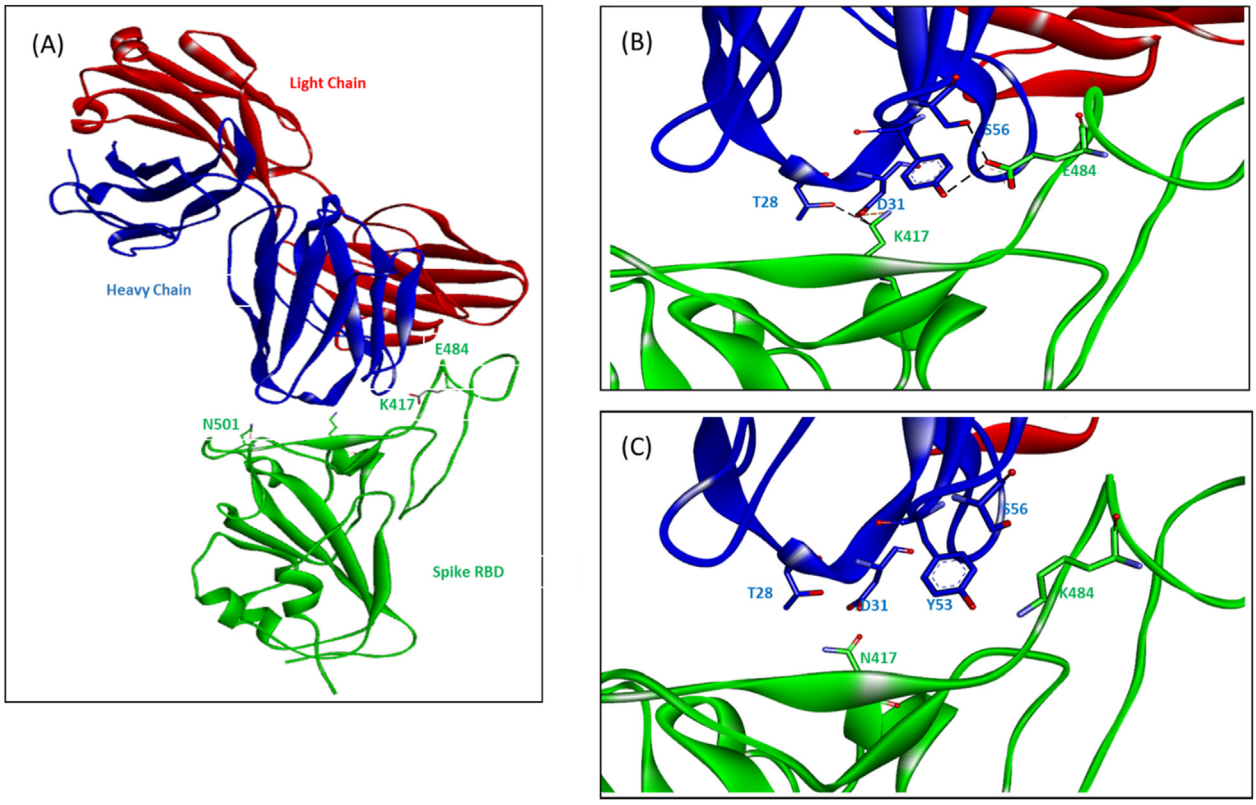

Fig. 4 – Neutralization escape of antibodies directed to the ACE2-binding epitopes by substitutions at residue positions 417 & 484. (a) Complex of spike RBD with monoclonal antibody REGN10933. Interacting residues in wild type and mutant strains are shown in (b) and (c), respectively. ACE-2, angiotensin-converting enzyme 2; RBD, receptor-binding domain.

may result in reduced neutralization by monoclonal antibodies, convalescent and vaccinated sera.[17] Mutation P681R (Table 3) in the spike residue, adjacent to the SARS-CoV-2 S1/S2 furin cleavage site (aa 681–684), may increase the rate of S1/S2 cleavage and membrane fusion resulting in enhanced infectivity.[18] This can explain the increased replication efficiency in human airway systems of the Delta variant in comparison to the Alpha variant. P681 is also located within an antigenic epitope and results in host immune response variations.[19] Sub-lineages, AY.1/AY.2 of the Delta variant and Omicron also contain the K417N mutation and several other mutations in the RBD and these must be monitored for altered antibody neutralization and transmissibility.

In addition to amino acid substitutions, spike deletions such as at 69/70 and 143/145 are known to be functionally significant. Spike 69-70del were noted in both Alpha and Omicron variants (except the BA.2 sublineage) and resulted in S-gene target failure in diagnostic assays.[8] These strains also demonstrated higher transmissions with an increased reduction in neutralization by antibodies.[20] The 143/145del that resulted in the loss of a negative surface charge further conferred antibody resistance.[21]

As seen in Table 3, apart from the mutations in the S protein, changes in the other regions of the genome also need to be critically evaluated for functional significance.

Vaccine efficacy studies and conclusion

Spike mutations in emerging variants and their sub-lineages pose challenges for vaccine-mediated immunity and thus breakthrough infections. Virus neutralization studies undertaken at ICMR-NIV for the different VOCs showed that the neutralizing antibody titers of sera collected from Covaxin vaccine recipients against SARS-CoV-2 with the VOC Alpha were comparable to the reference strain B.1. On the other hand, 3.0 and 2.7 fold reduction in titers were noted in the case of the Beta and Delta variants, respectively.[22,23] Recent studies have indicated substantial immune response in Omicron infected breakthrough and unvaccinated individuals against SARS-CoV-2 VOCs.[24] Emergence of novel SARS-CoV-2 variants is especially vital as vaccine-mediated immunity provides strong selection pressure for SARS-CoV-2 evolution. Though complete vaccine failure is unlikely, immune escape variants may necessitate updating of the SARS-CoV-2 vaccines in future.

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Disclosure of competing interest

The author has none to declare.

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