



The viral phoenix: enhanced infectivity and immunity evasion of SARS-CoV-2 variants

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Abstract

SARS-CoV-2 pandemic continues with emergence of new variants of concerns. These variants are fueling the third and fourth waves of pandemic across many nations. Here we describe the new emerging variants of SARS-CoV-2 and why they have enhanced infectivity and possess the ability to evade immunity.

The coronavirus disease that started in 2019, named COVID-19, has induced more than 210 million cases and 4 million deaths in September 2021, following the infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, Sharma et al. 2020, 2021). Actually, many scientific issues remain unanswered such as the virus origin, transmission and adaptation, and the role of environmental factors such as pollution (Chen et al. 2021a, b; Choi et al. 2021a, b; Dai et al. 2021; Khan et al. 2021; Roviello and Roviello 2020; Paital and Agrawal 2021; Sun and Han 2021; Ufnalska and Lichtfouse 2021). Despite the design and massive administration of several vaccines, the pandemic continues with emergence of new variants of concerns, similarly to the Greek mythological phoenix, an immortal bird that cyclically regenerates by obtaining new life by arising from the ashes of its predecessor. These variants are fueling the third and fourth waves of the pandemic across many nations. Here, we describe the new emerging variants of

SARS-CoV-2 and why they have enhanced infectivity and possess the ability to evade immunity.

Variants of concern

SARS-CoV-2 has slower mutation rate than other RNA viruses due to the presence of the proofreading 3'-5' exonuclease nsp14 (Robson et al. 2020). However, many viral genome replications that occur during the pandemic are increasing the genetic diversity of SARS-CoV-2. Most mutations are detrimental to virus fitness, yet mutations beneficial to virus survival and transmission are selected and accumulated over time to give rise to variants with enhanced transmissibility, hence leading to a rapid rise of worldwide infections. Variant of concerns are variants for which there is significant evidence to have increased transmissibility, disease severity, and immune evasion potency. Currently, four variants of SARS-CoV-2, alpha—lineage B.1.1.7, beta—lineage B.1.351, gamma—lineage P.1, and delta—lineage B.1.617.2 are recognized as variants of concern by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) (Table 1). The two main features that control the natural selection of SARS-CoV-2 are the extreme variability of disease severity and the temporal patterns of viral shedding. Patients with SARS-CoV-2 infection undergo a range of clinical symptoms, from no symptoms to critical illness and death (Garcia 2020). About one fourth of infections are asymptomatic cases (Alene et al. 2021). Theoretically, direct selection pressure against virulence of SARS-CoV-2 is likely very weak because of the wide symptomatic spectrum and the fact that the peak viral load and transmissibility occur days before symptom onset.

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Table 1 Variants of concern according to the Centers for Disease Control and Prevention, on December 8, 2021

Nextstrain Clade ^(b)	WHO Classification	Pango Lineage ^(a)	Sequence change	Spike Protein Substitutions	First Identified
20I/501Y.V1	Alpha	B.1.1.7	Δ(21,767~21,773) Δ(21,991~21,993) G23012A T23042C A23063T C23271A A23403G C23604A C23709T T24506G G24914C G25135C	(E484K*) (S494P*) N501Y A570D D614G P681H T716I S982A D1118H (K1191N*)	United Kingdom
20H/501.V2	Beta	B.1.351 B.1.351.2 B.1.351.3	A21801C A22206G Δ(22,283~22,291) G22813C G23012A A23063T A23403G C23664T	D80A D215G 241~3 del K417N E484K N501Y D614G A701V	South Africa
20J/501Y.V3	Gamma	P.1 P.1.1 P.1.2	C21614T C21621A C21638T G21974T G22132C A22812C G23012A A23063T A23403G C23525T C24642T	L18F T20N P26S D138Y R190S K417T E484K N501Y D614G H655Y T1027I	Japan Brazil
21A/S:478 K	Delta	B.1.617.2 AY.1 AY.2 AY.3	C21618G G21770T C21846T G21987A Δ(22,028~22,033) A22034G C22227T G22335T G22813C T22917G C22995A A23403G C23604G G24410A	T19R (V70F*) T95I G142D E156- F157- R158G (A222V*) (W258L*) (K417N*) L452R T478K D614G P681R D950N	India

(*)=detected in some sequences but not all

^aPhylogenetic Assignment of Named Global Outbreak (PANGO) Lineages is a software tool developed by members of the Rambaut Lab. The associated web application was developed by the Centre for Genomic Pathogen Surveillance in South Cambridgeshire and is intended to implement the dynamic nomenclature of SARS-CoV-2 lineages, known as the PANGO nomenclature

^bNextstrain, a collaboration between researchers in Seattle, USA and Basel, Switzerland, provides an open-source tool for visualizing the genetics of outbreaks. The goal is to support public health surveillance by facilitating understanding of the spread and evolution of pathogens

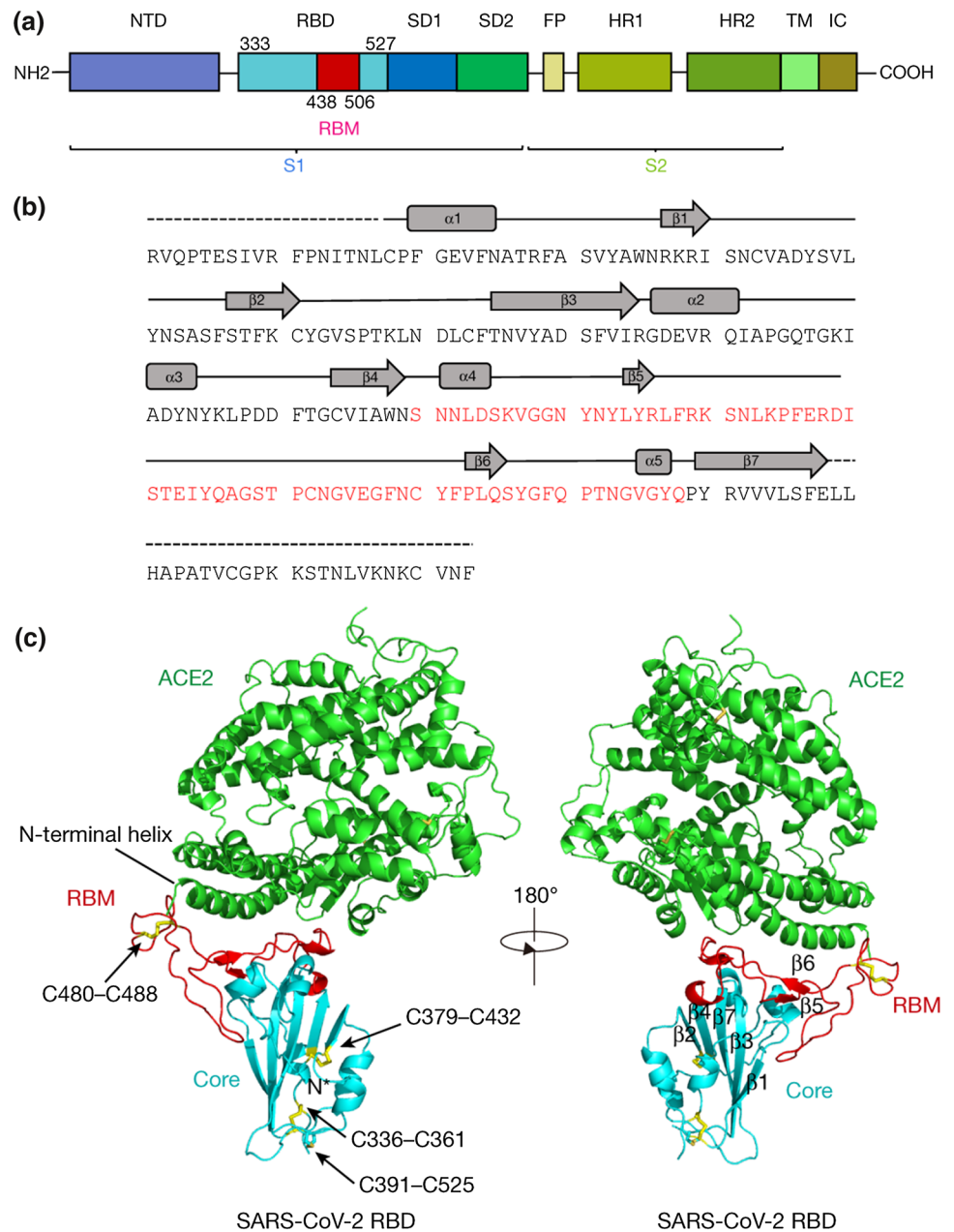
However, there is evidence that all four variants of concern have increased disease severity (<https://www.ecdc.europa.eu/en/covid-19/variants-concern>).

Evolving viral keys unlock cell entrance

Amid rapid spread of COVID-19, transmissibility is a major selective force for SARS-CoV-2. Indeed, higher viral loads are increasing the transmission rate and, in turn, more transmission can be accompanied by more severe illness. The transmission rate is mainly controlled by the recognition and binding of the virus to host cells.

The spike (S) protein of SARS-CoV-2 plays a key role in the receptor recognition and cell membrane fusion process (Hoffmann et al. 2020; Luchini et al. 2021). In the host cell membrane, the angiotensin-converting enzyme 2 (ACE2) has been identified as the viral receptor (Fig. 1). The S glycoprotein mediates the entry of the virus into host cells through its receptor-binding domain (RBD) and ACE2 interaction (Wan et al. 2020; Yan et al. 2020). The crystal structure of the S glycoprotein bound to ACE2 has been determined (Lan et al. 2020). SARS-CoV-2 has an almost identical binding complex as SARS-CoV-1, the coronavirus strain that caused the death of 9% of patients in 2003, but SARS-CoV-2 displays a tenfold higher binding affinity

Fig. 1 **a** Overall topology of the spike monomer of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). **b** Sequence and secondary structures of SARS-CoV-2 receptor-binding domain (RBD). The RBM sequence is shown in red. **c** Overall structure of the SARS-CoV-2 RBD bound to ACE2. ACE2 is shown in green. The SARS-CoV-2 RBD core is shown in cyan and receptor-binding motif (RBM) in red. Disulfide bonds in the SARS-CoV-2 RBD are shown as sticks and indicated by arrows. The N-terminal helix of ACE2 responsible for binding is labeled. ACE2: angiotensin-converting enzyme 2; FP: fusion peptide; HR1: heptad repeat 1; HR2: heptad repeat 2; IC: intracellular domain; NTD: N-terminal domain; SD1: subdomain 1; SD2: subdomain 2; TM: transmembrane region. Adapted from Lan et al. (2020) with permission from *Nature*



(Li et al. 2005). Indeed, in the SARS-CoV-2 receptor-binding domain, hydrogen bonds are formed between amino acid residues of host ACE2 and the following sites of the virus spike protein: K417, G446, Y449, N487, Y489, Q493, T500, N501, G502, and Y505. A salt-bridge connection has also been identified between the virus K417 site and the D30 site of host ACE2 (Lan et al. 2020). Here, mutations in the receptor-binding domain of the spike protein can result in higher affinity to ACE2 and can thus lead to an increase in infectivity and transmissibility of the virus. For instance, N501 is mutated in alpha, beta, and gamma variants. Mutations in K417 are found in beta, gamma, and delta plus variant-lineage AY.1.

Zoonosis

Human-to-animal and animal-to-human transmission, favored by pollution, are very likely routes for the pandemic origin and propagation, and for vaccine failure (He et al. 2021a,b). Research on interspecies transmission reveals that amino acid residues play major roles in the virus transmissibility. For instance, the Danish Cluster 5 variant has spread from human to minks as a reverse-zoonotic transmission in Denmark then followed by minks to human transmission (Oreshkova et al. 2020; Oude Munnink et al. 2021). This variant contains the Y453F mutation in its receptor-binding domain of the S glycoprotein which is associated with a fourfold higher affinity to ACE2 (Welkers et al. 2021). A mouse adapted SARS-CoV-2 strain carry Q493K, Q498Y and P499T mutations (Leist et al. 2020). Tiger and lion were infected with SARS-CoV-2, which contain F456Y or Y505H mutations in the receptor-binding domain, respectively (McAloose et al. 2020).

Immune evasion

As worldwide vaccination progresses, the immune evasion potency becomes a stronger selective force in viral evolution. Indeed, the antigenic ability of the virus can change as mutations alter the protein structure. Some mutations can lead to reduced effectiveness of the existing vaccines which were developed against the original strain of the virus. For example, the receptor-binding motif (RBM) is a small patch of about 70 amino acids located in the receptor-binding domain of the host ACE2. In this domain, amino acid residues not only form bonds with the virus spike protein, but also serve as antibody binding epitopes for many neutralizing antibodies. Here, the weakening of some neutralizing antibody binding is attributed to mutations of residues K417 and E484 (Chen et al. 2021a, b; Wise 2021). K417N mutations have been found in beta and delta plus variants. Gamma variant

contains a K417T mutation. E484K mutation is found in beta and gamma variants. The N-terminal domain (NTD) is another major target for neutralizing antibodies. Two deletion mutations, 69–70 Δ HV and 144 Δ Y, in the N-terminal domain of the spike protein confer the resistance against the NTD-directed antibodies to alpha variants. The resistance against NTD-targeting antibodies of beta variant largely comes from the R246I mutation. The P26S, L18F, T20N, D138Y, and R190S mutations play similar roles in immune evasion of the gamma variant.

There are heightened concerns about the existing COVID-19 vaccine effectiveness against current and emerging variants of SARS-CoV-2. Potency of vaccine-induced neutralizing antibodies against SARS-CoV-2 variants showed several fold reductions against gamma and delta variants, and about 20–40 fold decreases against beta variant (Noori et al. 2021). However, the impact of this neutralization titer reduction on vaccine effectiveness is hard to predict. Although neutralizing antibody levels are predictive of immune protection, the threshold of neutralization for vaccine protection is not known yet (Khoury et al. 2021). Furthermore, the impact of the other potential protective factors besides neutralizing antibody levels, such as T-cell mediated immunity and memory B-cell, has not been fully understood yet.

Delta variant

SARS-CoV-2 is expected to continuously change. Some variants will emerge and replace existing variants. The Delta variant is currently the subject of the main concern. Delta variant contains L452R and T478K in the receptor-binding motif and P681R in the S1/S2 cleavage site in its spike protein. Delta variants are rapidly spread globally and reached actually more than 90% of new cases in US (<https://covid.cdc.gov/covid-data-tracker/#variant-proportions>). The delta variant is highly contagious. The transmission rate is 2 to 3 times higher than original virus, and the viral load in respiratory tract is about 1,000 times higher than original virus (Li et al. 2021). Delta variants show reduced sensitivity to sera from vaccinated individuals (Planas et al., 2021). However, current vaccines are still highly effective against the delta variant (Nasreen et al. 2021; Sheikh et al. 2021). For instance, only modest difference of the vaccine effectiveness between delta and alpha variants was reported when two doses of the BNT162b2 Pfizer–BioNTech or the Oxford–AstraZeneca ChAdOx1 nCoV-19 vaccines were received (Lopez Bernal et al. 2021). However, some vaccinated can not only be infected with Delta variants but also may spread virus to others (Brown et al. 2021).

As SARS-CoV-2 spread rapidly, there is a higher chance that new variants can escape immune surveillance, thus rendering current vaccines ineffective. Thorough investigations

of variant infection cases and close monitoring of the emergence of new variant are urgently needed. Expediting vaccine deployment and implementing other mitigation measures including mask wearing and social distancing are critical in preventing the emergence and transmission of vaccine escape variants of SARS-CoV-2. Moreover, in the long run, research on alternative cures and prevention measures is definitively needed to outsmart the virus adaptation (Dai et al. 2021).

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