

## Review Article



# SARS-CoV-2 Delta (B.1.617.2) Variant: A Unique T478K Mutation in Receptor Binding Motif (RBM) of Spike Gene

Hyunjung Jhun <sup>1,†</sup>, Ho-Young Park <sup>2,†</sup>, Yasmin Hisham <sup>3</sup>, Chang-Seon Song <sup>4</sup>, Soohyun Kim <sup>3,4,\*</sup>

<sup>1</sup>Technical Assistance Center, Korea Food Research Institute, Wanju 55365, Korea

<sup>2</sup>Research group of Functional Food Materials, Korea Food Research Institute, Wanju 55365, Korea

<sup>3</sup>Laboratory of Cytokine Immunology, Department of Biomedical Science and Technology, Konkuk University, Seoul 05029, Korea

<sup>4</sup>College of Veterinary Medicine, Konkuk University, Seoul 05029, Korea

## OPEN ACCESS

Received: Aug 24, 2021

Revised: Sep 28, 2021

Accepted: Sep 29, 2021

### \*Correspondence to

#### Soohyun Kim

Laboratory of Cytokine Immunology,  
Department of Biomedical Science  
and Technology, Konkuk University, 120  
Neungdong-ro, Gwangjin-gu, Seoul 05029,  
Korea.

E-mail: soohyun@konkuk.ac.kr

<sup>†</sup>These authors contributed equally to this work.

Copyright © 2021. The Korean Association of Immunologists

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Hyunjung Jhun

<https://orcid.org/0000-0002-3694-9715>

Ho-Young Park

<https://orcid.org/0000-0002-9966-9059>

Yasmin Hisham

<https://orcid.org/0000-0003-1708-7205>

Chang-Seon Song

<https://orcid.org/0000-0002-4158-6402>

Soohyun Kim

<https://orcid.org/0000-0002-0322-7935>

## ABSTRACT

Over two hundred twenty-eight million cases of coronavirus disease 2019 (COVID-19) in the world have been reported until the 21<sup>st</sup> of September 2021 after the first rise in December 2019. The virus caused the disease called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Over 4 million deaths blame COVID-19 during the last one year and 8 months in the world. Currently, four SARS-CoV-2 variants of concern are mainly focused by pandemic studies with limited experiments to translate the infectivity and pathogenicity of each variant. The SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  variant of concern was originated from United Kingdom, South Africa, Brazil/Japan, and India, respectively. The classification of SARS-CoV-2 variant is based on the mutation in *spike* (*S*) gene on the envelop of SARS-CoV-2. This review describes four SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  variants of concern including SARS-CoV-2  $\epsilon$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants of interest and alert. Recently, SARS-CoV-2  $\delta$  variant prevails over different countries that have 3 unique mutation sites: E156del/R158G in the N-terminal domain and T478K in a crucial receptor binding domain. A particular mutation in the functional domain of the *S* gene is probably associated with the infectivity and pathogenesis of the SARS-CoV-2 variant.

**Keywords:** COVID-19 delta; SARS-CoV-2; T478K; Receptor binding motif (RBM); *Spike* gene

## INTRODUCTION

Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)  $\delta$  (B.1.617.2) is the most notorious variant among numerous SARS-CoV-2 variants. Delta variant of SARS-CoV-2 shows a high transmissible capability, and its spread is in a much faster manner than other variants. Furthermore, it is more infectious and contagious comparing to previous variants (1-7). Therefore, instantaneously the SARS-CoV-2  $\delta$  variant was classified as one of the variants of concern by the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (US-CDC). This variant contributed to severe illness and death, especially with unvaccinated people (8,9).

Angiotensin-converting enzyme 2 (ACE2) was characterized as a SARS-CoV receptor about 18 years ago (10). ACE2 is considered the foremost binding receptor of SARS-CoV-2 without

**Conflict of Interest**

The authors declare no potential conflicts of interest.

**Abbreviations**

ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; RBD, receptor-binding domain; RBM, receptor binding motif; *S*, spike; *S*, subunit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US-CDC, United States Centers for Disease Control and Prevention; WHO, World Health Organization; WT, wild type.

**Author Contributions**

Conceptualization: Jhun H, Park HY, Kim S; Data curation: Kim S; Formal analysis: Kim S; Funding acquisition: Jhun H, Kim S; Investigation: Kim S; Supervision: Kim S; Validation: Park HY, Kim S; Visualization: Kim S; Writing - original draft: Kim S; Writing - review & editing: Jhun H, Park HY, Hisham Y, Song CS, Kim S.

solid biochemical data (11-18). This consideration found a wide agreement due to the sudden outbreak of coronavirus disease 2019 (COVID-19) between December 2019 and May 2020 that demanded an urgent finding to overcome this pandemic. SARS-CoV-2 caused the lockdown of all over the world except certain countries considering COVID-19 as a regular respiratory viral infectious disease.

COVID-19 vaccines were distributed all over the world since January 2021, with some differences between countries. Mainly, there are 4 types of current COVID-19 vaccines; whole SARS-CoV-2 virus, mRNA, adenovirus, and subunit recombinant protein, which are almost based on the genetic information of *spike (S)* gene on the envelop of SARS-CoV-2 except SARS-CoV-2 viral vaccine (19-22). The *S* gene codes 1,273 amino acid residues with a signal peptide at N-terminus and a single  $\alpha$ -helix transmembrane domain following a short cytosolic domain. These three structural domains support that the *S* gene is a typical membrane molecule in a mammalian cell similar to the structural domains found in the IL-1 $\alpha$  receptor (23-25). The *S* gene is divided into 16 subdomains by more structural information than functional property except for the receptor binding domain (RBD). The suggested RBD amino acid residue of SARS-CoV-2 is varied according to studies (12,13,16,21,26,27). Besides the COVID-19 vaccine, neutralizing Abs were developed to treat COVID-19 patients. These therapeutic neutralizing Abs are against the RBD of spike protein since this domain is known for interacting with ACE2 in host cells (28,29).

So far, 4 different types of COVID-19 vaccines have been introduced to immunize individuals as following: 1) SARS-CoV-2 viral (inactivated) vaccine uses the whole virus to immunize individual after a certain process to kill virus preventing infection (30); 2) SARS-CoV-2 mRNA vaccine is to deliver the whole codon of *S* gene mRNA into a cell to express spike protein. The vaccinated individuals generate Abs against foreign spike Ag that eventually protect the individual from SARS-CoV-2 viral infection (31); 3) SARS-CoV-2 adenovirus vector vaccine is to use adenovirus to deliver the whole codon of *S* gene into a cell to express spike protein and the mechanism is similar to mRNA vaccine (32-34); 4) SARS-CoV-2 protein vaccine is to use recombinant spike protein prepared using expression systems in various cells, recently insect cells were used to ensure the native conformation expression to immunize individual, which generates Abs against spike protein to protect individual (35-37). The ultimate goal of the COVID-19 vaccine is to generate neutralizing Abs to protect an individual from SARS-CoV-2 viral infection as well as to prevent the spread of SARS-CoV-2 through some differences in method to generate Abs.

In this review, we dissect the mutation sites at the RBD spike found in the delta variant, the most infections and faster spread variant, along with the remaining variant of concern, SARS-CoV-2  $\alpha$ ,  $\beta$ , and  $\gamma$ . As well as we include SARS-CoV-2  $\epsilon$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants of interest and alert from US-CDC (<https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>) to identify critical mutation sites of  $\delta$  variant to analyze the current crisis of COVID-19 pandemic.

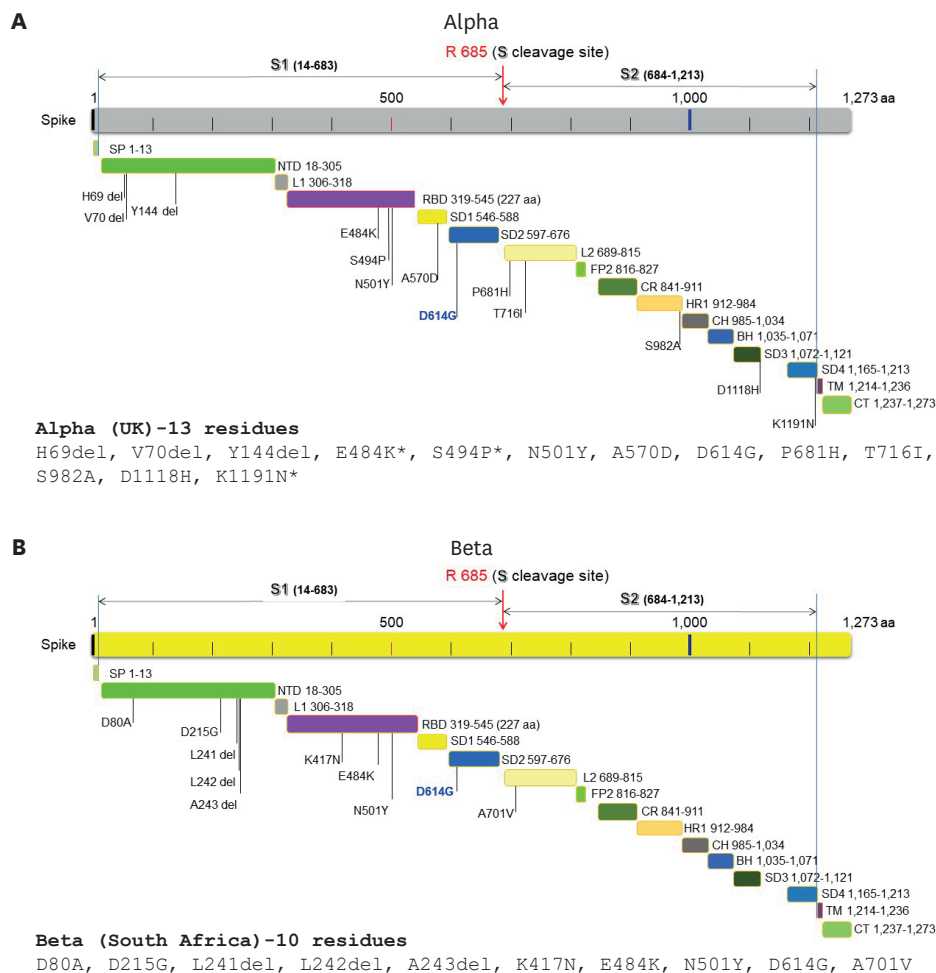
**SARS-CoV-2  $\alpha$  (B.1.1.7) VARIANT**

SARS-CoV-2  $\alpha$  (B.1.1.7) variant was originally reported in United Kingdom (UK) (38) and studies suggested this variant increased 50% infectivity as well as severity based on hospitalizations and the case of fatality (39). SARS-CoV-2  $\alpha$  variant has 13 mutation sites

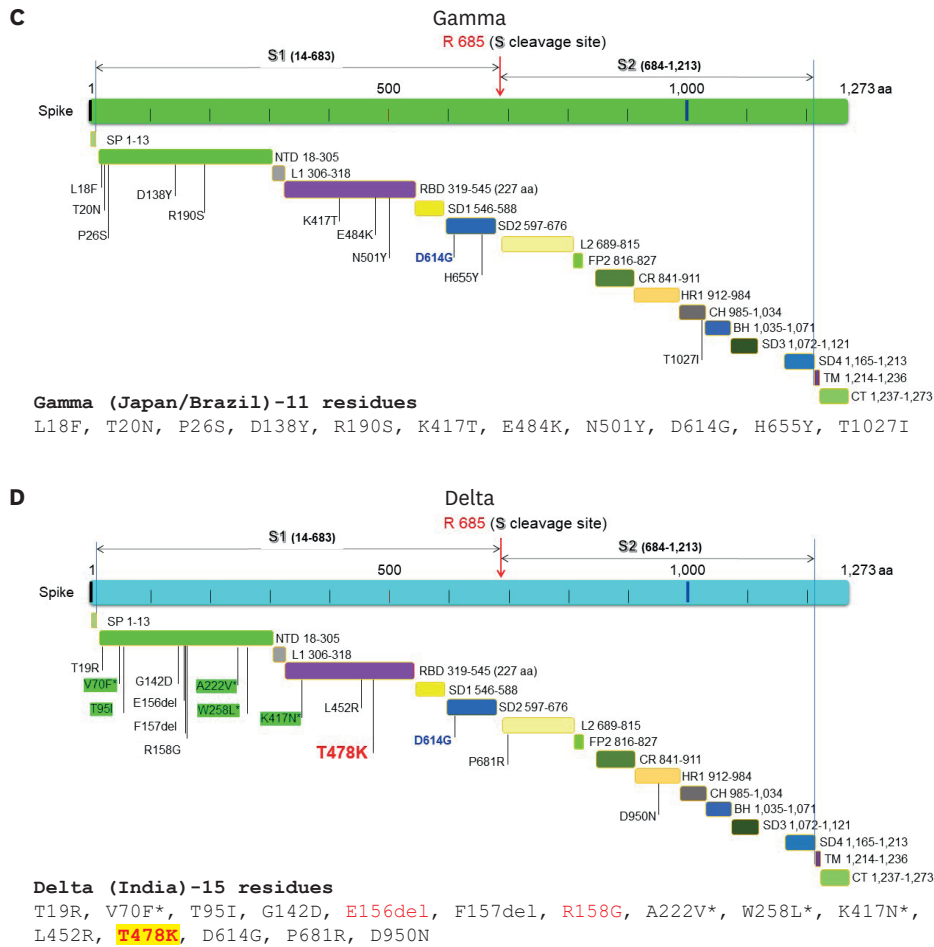
in *S* gene (Fig. 1A), which is the third largest number among four SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  variants of concern and six SARS-CoV-2  $\epsilon$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants of interest or alert (Table 1). The  $\alpha$  variant has 3 mutations, E484K, S494P, and N501Y in RBD, which is well characterized by protein structure utilizing diverse methods (12,16,17,27) and the rest of mutation sites in *S* gene presents in functionally uncharacterized domain (Fig. 1A).

### SARS-CoV-2 $\beta$ (B.1.351) VARIANT

SARS-CoV-2  $\beta$  (B.1.351) variant was first reported from South Africa and it has 10 mutation sites in *S* gene (Fig. 1B) (40). Five mutation sites present in NTD with 3 serial deletions at L241del, L242del, and A243del. Two mutation sites, E484K and N501Y in critical RBD are identical to that of SARS-CoV-2  $\alpha$  variant, whereas K417N does not present in SARS-CoV-2  $\alpha$  variant. Unlike SARS-CoV-2  $\alpha$  variant, 9 mutation sites of SARS-CoV-2  $\beta$  variant are detected



**Figure 1.** Schematic drawing of 16 subdomains in spike glycoprotein of SARS-CoV-2. The spike glycoprotein is composed of 16 subdomains. The S1 region (R685) cleavage site is indicated at the top. SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  variant mutation sites were indicated by specific amino acid substitution. The common D614G in all ten variant (Table 1) was indicated by bold blue letter. (A) SARS-CoV-2  $\alpha$  variant has 13 mutation sites were listed at the bottom. (B) SARS-CoV-2  $\beta$  variant has 10 mutation sites were listed at the bottom. (C) SARS-CoV-2  $\gamma$  variant has 11 mutation sites were listed at the bottom. (D) SARS-CoV-2  $\delta$  variant has 15 mutation sites were listed at the bottom. A unique residue of SARS-CoV-2  $\delta$  variant was indicated with a large bolded red letter. The 16 subdomains of spike protein were illustrated by different colors with specific residues on the right. SP, signal peptide; NTD, N-terminal domain; L, loop; SD, subdomain; FP, fusion peptide; CR, connected region; HR, heptad repeat; CH, central helix; BH,  $\beta$ -hairpin; TM, transmembrane domain; CT, cytosolic domain. (continued to the next page)



**Figure 1.** (Continued) Schematic drawing of 16 subdomains in spike glycoprotein of SARS-CoV-2. The spike glycoprotein is composed of 16 subdomains. The S1 region (R685) cleavage site is indicated at the top. SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  variant mutation sites were indicated by specific amino acid substitution. The common D614G in all ten variant (Table 1) was indicated by bold blue letter. (A) SARS-CoV-2  $\alpha$  variant has 13 mutation sites were listed at the bottom. (B) SARS-CoV-2  $\beta$  variant has 10 mutation sites were listed at the bottom. (C) SARS-CoV-2  $\gamma$  variant has 11 mutation sites were listed at the bottom. (D) SARS-CoV-2  $\delta$  variant has 15 mutation sites were listed at the bottom. A unique residue of SARS-CoV-2  $\delta$  variant was indicated with a large bolded red letter. The 16 subdomains of spike protein were illustrated by different colors with specific residues on the right. SP, signal peptide; NTD, N-terminal domain; L, loop; SD, subdomain; FP, fusion peptide; CR, connected region; HR, heptad repeat; CH, central helix; BH,  $\beta$ -hairpin; TM, transmembrane domain; CT, cytosolic domain.

in subunit (S) 1 region, where the enzyme cleaves between N-terminal S1 (14–685 amino acid residues) region and C-terminal S2 (686–1,213 amino acid residues) region of spike extracellular protein (Fig. 1B) prior to SARS-CoV-2 entering a host cell (41-44). A single point mutation A701V presents in the S2 region that is distinct from SARS-CoV-2  $\alpha$  variant.

## SARS-CoV-2 $\gamma$ (P.1) VARIANT

SARS-CoV-2  $\gamma$  (P.1) variant first reported in two countries Brazil and Japan, and it has completely different Pango lineage, P.1 (Table 1) (45). The SARS-CoV-2  $\gamma$  variant has 11 mutation sites in *S* gene (Fig. 1C). Like SARS-CoV-2  $\beta$  variant, most mutation sites locate in S1 region of *S* gene except a single mutation site T1027I in Central helix domain of S2 region. Surprisingly, three K417T, E484K, and N501Y mutation sites in the critical RBD of *S* gene are identical to SARS-CoV-2  $\beta$  variant except K417 is substituted by T instead of N. The significant difference of SARS-CoV-2  $\gamma$  variant from SARS-CoV-2  $\alpha$  and  $\beta$  variants is that

**Table 1.** Ten SARS-CoV-2 variants and their spike mutation sites

Pango Linage	Origin	Variant name (Greek Alphabet)	Spike Protein Mutations	Classification (WHO/CDC)
B.1.1.7	UK	Alpha, $\alpha$	H69del, V70del, Y144del, E484K*, S494P*, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N*	VOC (38,39)
B.1.351	S. Africa	Beta, $\beta$	D80A, D215G, L241del, L242del, A243del, K417N, E484K, N501Y, D614G, A701V	VOC (40)
P.1	Brazil/Japan	Gamma, $\gamma$	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	VOC (45)
B.1.617.2	India	Delta, $\delta$	T19R, V70F*, T95I, G142D, <b>E156del</b> , F157del, <b>R158G</b> , A222V*, W258L*, K417N*, L452R, <b>T478K</b> , D614G, P681R, D950N	VOC (48-50)
B.1.427/B.1.429	US-California	Epsilon, $\epsilon$	S13I, W152C, L452R, D614G	VOC (19-Mar-2021) VOI (29-Jun-2021) (52,53,61)
P.2	Brazil	Zeta, $\zeta$	E484K, F565L*, D614G, V1176F	VOI (55)
B.1.525	UK/Nigeria	Eta, $\eta$	A67V, H69del, V70del, Y144del, E484K, D614G, Q677H, F888L	VOI (54)
B.1.526	US-NY	Iota, $\iota$	L5F, D80G*, T95I, Y144del*, F157S*, D253G, L452R*, S477N*, E484K, D614G, A701V, T859N*, D950H*, Q957R*	VOI (55)
B.1.617.1	India	Kappa, $\kappa$	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	VOI (50)
B.1.617.3	India	None	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	Alert (51)

Four SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  VOCs and six SARS-CoV-2  $\epsilon$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 VOIs and alert. All variants are listed with Pango lineage, origin, variant symbol, and mutation residue with amino acid change. The unique T478K mutation site of  $\delta$  variant was indicated as bolded and underline. The rest of two unique  $\delta$  variant mutation sites were indicated by red letter. VOC, variant of concern; VOI, variant of interest. \*Detected in some sequences but not all.

there are no deletion sites in NTD domain though no specific function of NTD domain in S1 region (**Fig. 1C**). Unfortunately, SARS-CoV-2  $\gamma$  variant has few reports compared to other SARS-CoV-2 variant of concern (46,47).

## SARS-CoV-2 $\delta$ (B.1.617.2) VARIANT

SARS-CoV-2  $\delta$  (B.1.617.2) variant was first detected in India in October 2020 (48-50) and has become the most prevalence variant in the European countries in the middle of April 2021 according to European Centre for Disease Prevention and Control. SARS-CoV-2  $\delta$  variant has 15 mutation sites in S gene, which is the greatest number of mutation sites among ten SARS-CoV-2 variants (**Table 1** and **Fig. 1D**). The SARS-CoV-2  $\kappa$  (B.1.617.1) (51) and B.1.617.3 (50) variants were reported in India at the same time between October and December 2020. These two SARS-CoV-2 variants are the closest variants to the SARS-CoV-2  $\delta$  variant in terms of the mutation sites. SARS-CoV-2  $\delta$  variant shares three common mutation sites, L452R, D614G, and P681R with SARS-CoV-2  $\kappa$  and B.1.617.3 variant (**Table 1**). The D614G mutation site exists all four SARS-CoV-2 variants of concern as well as all six SARS-CoV-2 variants of interest and alert.

Intriguingly, the P681 mutation site exists in SARS-CoV-2  $\alpha$  and  $\delta$  variants of concern but SARS-CoV-2  $\delta$  variant P681 is substituted by H instead of R. The L452R mutation site presents in three SARS-CoV-2  $\epsilon$  and  $\iota$  variants from US. SARS-CoV-2  $\epsilon$  (B.1.427/B.1.429) variant was detected in California US whereas  $\iota$  (B.1.526) variant was reported in New York US (**Table 1**). The comparison of SARS-CoV-2  $\delta$  variant with other variants revealed 3 unique mutation sites, E156del, R158G, and T478K, which were indicated by red letter (**Table 1** and **Fig. 1D**). In addition, T478K mutation site in critical RBD was highlighted by yellow with bolded red letter (**Table 1**).

## SARS-CoV-2 $\epsilon$ , $\zeta$ , $\eta$ , $\iota$ , $\kappa$ , AND B.1.617.3 VARIANT OF INTEREST AND ALERT

Six SARS-CoV-2  $\epsilon$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants of interest and alert were reported beside the four SARS-CoV-2 variants of concern according to US-CDC (**Table 1**). SARS-CoV-2  $\epsilon$

(B.1.427/B.1.429) variant emerged around May 2020 and increased from 0% to >50% of sequenced cases from September 2020 to January 2021 in California US and exhibited an 18.6~24% increase in transmissibility comparing to wild type (WT) (52,53). The reason why CDC and WHO classified it as a variant of concern in early of March 2021, however, currently this variant became classified as a variant of interest for further monitoring according to WHO and US-CDC (Table 1).

SARS-CoV-2  $\epsilon$  and  $\zeta$  has 4 mutation sites, which is the least number of mutation sites among ten SARS-CoV-2 variants (Table 1). SARS-CoV-2  $\zeta$  variant is similar to  $\gamma$  (P.1) variant according to Pango lineage, but the mutation sites show different pattern between these two variants (Table 1). SARS-CoV-2  $\zeta$  variant has the common mutation sites E484K and D614G. The L452R mutation site is found in SARS-CoV-2  $\delta$  variant of concern along with SARS-CoV-2  $\epsilon$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants (50) of interest and alert. The D614G mutation site presents in all ten SARS-CoV-2 variants (Table 1). E484 mutation site presents in eight SARS-CoV-2  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\zeta$ ,  $\eta$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants, however, SARS-CoV-2  $\kappa$  and B.1.617.3 variants have Q substitution instead of K. Interestingly, E484 mutation site is not present in only two SARS-CoV-2  $\delta$  and  $\epsilon$  variants (Table 1).

SARS-CoV-2  $\eta$  (B.1.525) variant of UK and Nigeria has 8 mutations sites containing 3 deletion sites, H69del, V70del, and Y144del in NTD of S1 region. Moreover, it has three unique sites, A67V, Q677H, and F888L beside two common mutation sites, E484K and D614G (Table 1) (54). SARS-CoV-2  $\iota$  (B.1.526) variant of New York US has 14 mutations sites, which are the largest number of mutation sites among the ten SARS-CoV-2 variants except SARS-CoV-2  $\delta$  variant of concern (Table 1) (55). This variant is similar to  $\eta$  (B.1.525) variant according to Pango lineage, but the mutation sites at the RBD show different pattern between these two variants (Table 1). SARS-CoV-2  $\iota$  variant of New York US contains mixed mutation that found among several variants, as following on 9 mutation sites: D80G presents in  $\beta$  variant with A substitution; T95I presents in  $\kappa$  variant with R substitution; Y144 deletion presents in  $\alpha$  variant; F157S presents in  $\delta$  variant by deletion; L452R presents in  $\delta$ ,  $\epsilon$  (B.1.427/B.1.429),  $\kappa$ , and B.1.617.3 variant; E484K presents in  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\zeta$ , and  $\eta$  as well as in  $\kappa$ , and B.1.617.3 variant but with Q substitution in  $\kappa$  and B.1.617.3 variant; D614G presents in all variant; A701V presents in  $\beta$  variant; D950H presents in  $\delta$  and B.1.617.3 variant but with N substitution. The rest of 5 mutation sites are, L5F, D253G, S477N, T859N, and Q957R and are unique for SARS-CoV-2  $\iota$  variant (Table 1).

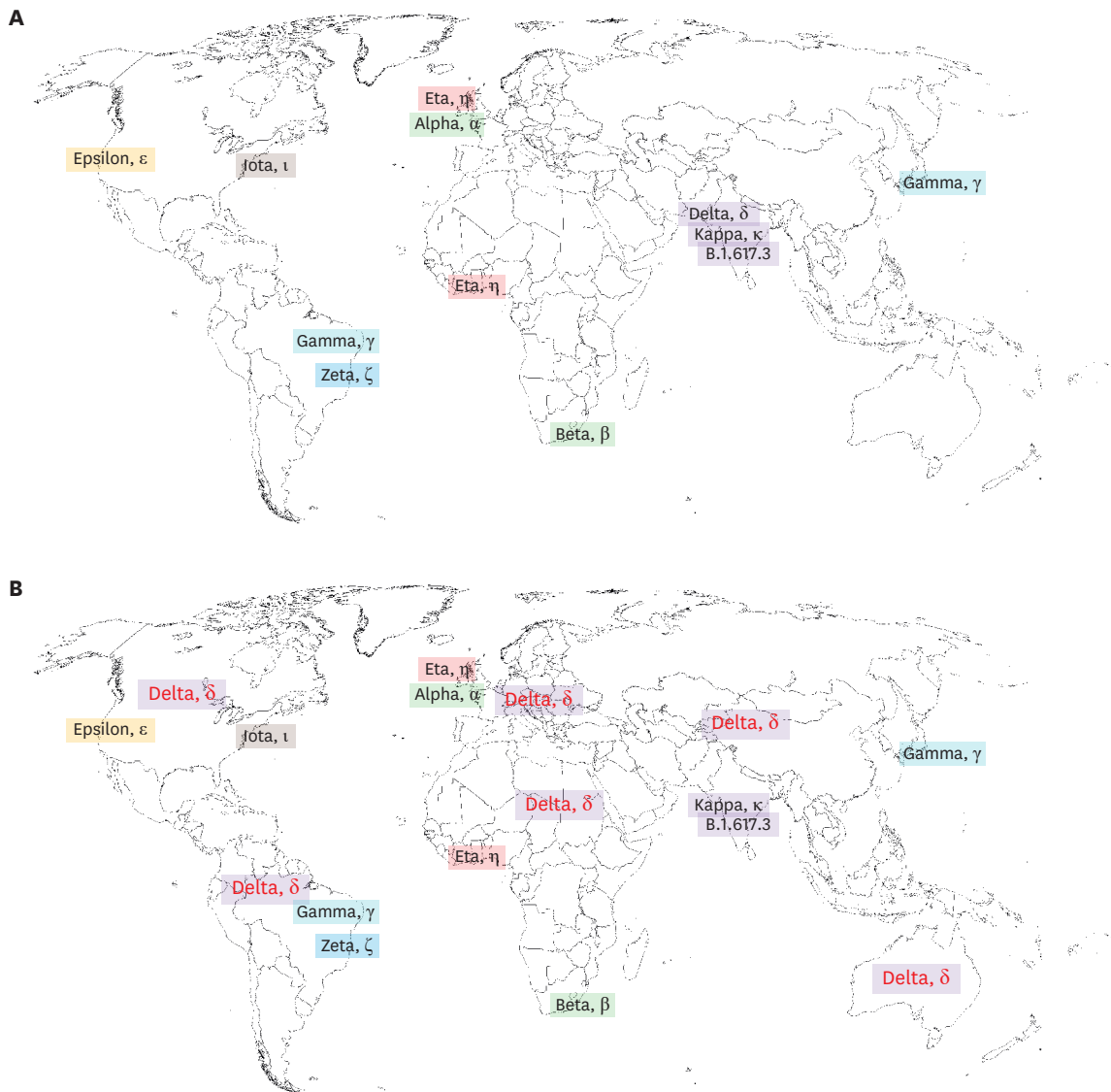
The last two SARS-CoV-2  $\kappa$  (B.1.617.1), and B.1.617.3 variants were originated from India (50,51) and are highly similar to the SARS-CoV-2  $\delta$ , which is currently considered as the most problematic variant. These three Indian originated variants share 5 mutation sites, T19R, G142D, L452R, D614G, and P681R. One mutation is common between  $\delta$  and B.1.617.3 variants, D950N, and one mutation site is unique to  $\kappa$  variant, Q1071H. Moreover, SARS-CoV-2  $\kappa$ , and B.1.617.3 variants harbor the mutation site of E484Q, which found in the other variants with a substitution of K instead of Q.

## SUSCEPTIBILITY OF SARS-CoV-2 VARIANTS TO MONOCLONAL Ab TREATMENT

Food and Drug Administration (FDA) has asserted an Emergency Use Authorization (EUA) FDA for the emergency uses of the unapproved anti-SARS-CoV-2 monoclonal Ab. Currently,

there are three monoclonal Abs for COVID-19 treatment, bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab according to US-CDC. These virus-neutralizing Abs intend to disallow the entry of the virus into human cells through blocking its attachment and are mainly directed against the spike protein (29).

Early 2020 SARS-CoV-2  $\alpha$  and  $\beta$  variant of concern from UK and S. African variant of COVID-19 were targeted to check the efficacy of first vaccine and the treatment of neutralizing Ab. The conclusion was that there is some escape of these variants, but the vaccine has a protective effect with adenovirus vector and mRNA vaccine. Most studies of SARS-CoV-2  $\alpha$  and  $\beta$  variant of concern performed in EU and US whereas limited studies were conducted with SARS-CoV-2 viral vaccine, which was used widely in China, Southeast Asia, and South America (Fig. 2A) (40,46,56-58). Several reports attempted to study the impact of SARS-CoV-2 variants on the susceptibility of monoclonal Abs. SARS-CoV-2  $\alpha$  variant exhibited a



**Figure 2.** The occurrence of ten SARS-CoV-2 variants located in the world map. (A) The world map showed the origin of the ten SARS-CoV-2 variants although SARS-CoV-2 originated from Wuhan China. (B) The spread of SARS-CoV-2  $\delta$  variant in 6 continents including other nine SARS-CoV-2 variants.

little or no susceptibility impact on EUA monoclonal Ab treatments (57). However, SARS-CoV-2  $\beta$ ,  $\gamma$ , and  $\iota$  variants showed a significant reduction in susceptibility to the combination of bamlanivimab and etesevimab, although the other EUA monoclonal Ab treatments are still accessible (59). Whereas three variants that are originated from India ( $\delta$ ,  $\kappa$ , and B.1.617.3) as well as  $\eta$  variant, have revealed a potential reduction in neutralization by EUA monoclonal Abs (59,60). Moreover, it has been reported that convalescent and mRNA vaccinated individuals both exhibited neutralizing titers were reduced 2- to 3.5-fold against  $\epsilon$  (B.1.427/B.1.429) variants of interest relative to WT pseudoviruses (61).

Therefore, the office of the Assistant Secretary for Preparedness and Response has paused the distribution of bamlanivimab and etesevimab (EUA 094) to all states as of June 25<sup>th</sup> of 2021. Moreover, the prevalence of the SARS-CoV-2  $\beta$  and  $\gamma$  variant circulating with increasing frequency. The US FDA recommends using the alternative authorized monoclonal Ab therapies because no impact or susceptibility to EUA monoclonal Ab treatments providing a minimal impact on neutralization by convalescent and post-vaccination sera (40,46,50,55-58,61,62).

However, current data revealed that most delta variant lineages are sensitive to the combination of bamlanivimab and etesevimab. Bamlanivimab and etesevimab were authorized in all U.S. states as of September 15<sup>th</sup> of 2021 based on the updated and current data. Yet, according to the CDC, there is some combination of spike mutation sites listed as substitutions which may have a high impact on reducing the susceptibility to the combination of bamlanivimab and etesevimab according to US-CDC. Among them E484Q and L452R, that are present in both SARS-CoV-2  $\kappa$ , and B.1.617.3 variants of interest and alert. Therefore, mutations found on the *S* gene in different combinations may highly influence the behavior of the virus, and thus affect the classification of the current and forthcoming variants.

## DELTA VARIANT SURGES WORLDWIDE

SARS-CoV-2 variants are currently disseminated in different locations within the world as shown in **Fig. 2A**. It is true that isolating individuals and preventing contact between individuals may be the best way to stop respiratory infectious diseases like COVID-19. However, social activity is very important to develop human culture since the history of humankind has begun. The unusual epidemic of COVID-19 for the last one year and 8 months led an expert and individual to rush finding a solution immediately to overcome the COVID-19 pandemic. As the aim is to terminate this pandemic as soon as possible, most of the treatment options including medicines and vaccines were approved without proper effectiveness assessment. To this end, this determination could affect the process of finding the right solution.

It is necessary to understand the characteristic of each SARS-CoV-2 variant to stop the spread of the COVID-19 pandemic. The *S* gene of SARS-CoV-2 was focused by researchers and pharmaceuticals since it is known that SARS-CoV-2 penetrates via spike protein interacting with ACE2 receptor on the surface of the host cell (12,16,20,21,27). All effort of vaccine and neutralizing Ab to prevent SARS-CoV-2 infection depends on spike protein alongside some treatment to block viral replication in the host cell. Thus, SARS-CoV-2 variants were classified by their mutation sites in the *S* gene (**Table 1**).

As of September 2021, SARS-CoV-2  $\delta$  variant of concern had been detected in 162 countries across 6 continents according to the global initiative on sharing avian flu data (GISAID:



<https://www.gisaid.org/hcov19-variants/>) (61). The spread of SARS-CoV-2  $\delta$  variant in 6 continents was indicated with the red letter in **Fig. 2B**. The three unique mutation sites, E156del, R158G, and T478K in the SARS-CoV-2  $\delta$  variant must be investigated if a recent outbreak of COVID-19 depends on the mutation sites in the *S* gene of SARS-CoV-2  $\delta$  variant.

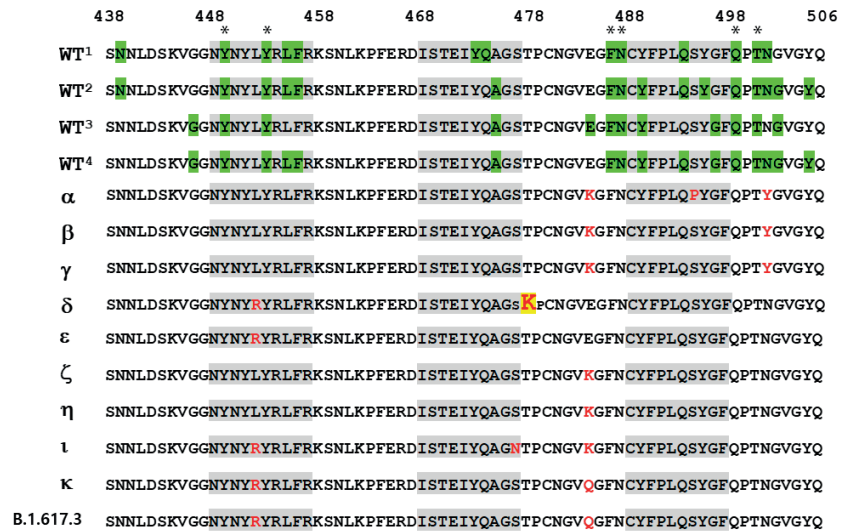
The greatest way to turn over the COVID-19 pandemic is through herd immunity by effective vaccination or natural infection. In early 2021, EU and US began SARS-CoV-2 vaccination along with a very tight lockdown of international borders. Many countries reported that the infection rate was reduced in the case of COVID-19 (<https://ourworldindata.org/coronavirus>) after April–June 2020. This is probably associated with a successful vaccination program in different countries. However, recently a new wave of SARS-CoV-2  $\delta$  variant starts from India and spread worldwide in July 2021. The studies suggested that this variant probably escaped from an already developed vaccine or neutralizing Ab (48). The most recent study showed that the evidence of Ab escape and individuals infected previously with the SARS-CoV-2  $\beta$  and  $\gamma$  variants were likely more susceptible to reinfection by the SARS-CoV-2  $\delta$  variant, whereas vaccine based on SARS-CoV-2  $\alpha$  (B.1.1.7) was likely to provide the broadest protection against current variants (63). Still, this could not be explained by the mutation sites in the *S* gene because there is no association between SARS-CoV-2  $\alpha$  and  $\delta$  variants.

## A UNIQUE MUTATION SITE FOR DELTA VARIANT: T478K

Surprisingly, the two closest variants to the delta variant, SARS-CoV-2  $\kappa$  and B.1.617.3, did not spread out from India, which have been reported at the same time in India. Direct comparison of *S* gene mutation sites in SARS-CoV-2  $\delta$  variant with SARS-CoV-2  $\kappa$  and B.1.617.3 variants revealed a single mutation site. The T478K was found within the critical receptor binding motif (RBM) of *S* gene suggested by Lan et al. (12), which is indicated with a large font with a red-letter (**Fig. 1D** and **Fig. 3**). Besides this mutation, there are two additional unique mutation sites of SARS-CoV-2  $\delta$  variant, E156del and R158G with red letters in the NTD of S1 region with no known functionality (**Table 1**).

Therefore, we aligned the amino acid sequences of the critical RBM for the ten SARS-CoV-2 variants, which were reported for directly interacting with ACE2 in 4 different studies (12,16,17,27). The crucial binding residues in each study were highlighted by green in RBM and there are some differences in the upper 4 lines from these 4 different studies of WT<sup>1</sup>–WT<sup>4</sup>. The analysis of ACE2 binding sites revealed that only 6 residues, which are indicated with an asterisk on the top, are common interaction sites among twenty-one suggested interacting residues. These 6 residues account for only 28.5% of twenty-one suggested interacting residues from 4 different studies. It is an unanticipated result since the protein complex structure was obtained from the same SARS-CoV-2 spike and ACE2 protein (12,16,17,27).

In addition to this, ACE2 binding residues in *S* gene were directly compared with the mutation sites of the ten SARS-CoV-2 variants. It is not surprising that there is a minor correlation between the ACE2 interacting 21 residues (green highlight) and the ten SARS-CoV-2 variants mutation sites (red letter) in **Fig. 3**. Only two mutation sites, E484K/Q (27) and N501Y (12,16,17), are present in ACE2 interaction sites among 6 mutation sites in the RBM of the ten SARS-CoV-2 variants. Astonishingly, critical protein structure studies were not able to identify the unique T478K mutation site of  $\delta$  variant and the common L452R mutation site of  $\delta$ ,  $\epsilon$ ,  $\iota$ ,  $\kappa$ , and B.1.617.3 variants (**Fig. 3**). So far, this could be due to the *in vitro* condition comparing



**Figure 3.** Mutation sites in the RBM of ten SARS-CoV-2 variants. The alignment of spike RBM in the ten SARS-CoV-2 variant was directly compared to the receptor binding residues that were reported by WT<sup>1</sup> (16), WT<sup>2</sup> (17), WT<sup>3</sup> (27), and WT<sup>4</sup> (12). The twenty-one receptor interaction residues in WT<sup>1</sup>-WT<sup>4</sup> were highlighted by green color in upper 4 lines. The six common ACE2 interaction sites were indicated with asterisk (\*) on the top (12,16,17,27). The mutation sites of four SARS-CoV-2 α, β, γ, and δ variants of concern and six SARS-CoV-2 ε, ζ, η, θ, κ, and B.1.617.3 variants of interest and alert were indicated by red letter. The unique T478K mutation site of δ variant was indicated by a large red font with yellow highlight.

to the complex system of viral infection in host. In addition, mutations could influence the interaction motif and thus provide a stronger interaction with the amino acid residue substitutions. However, more investigations are needed to figure out these possibilities.

## CONCLUSION

It is necessary to investigate whether these mutation sites in SARS-CoV-2 δ variant contribute to the unusual outbreak of COVID-19 caused by SARS-CoV-2 δ variant all over the world. The analysis of mutation sites in the critical RBM of spike protein on the SARS-CoV-2 variants ascertained a distinct T478K mutation in the SARS-CoV-2 δ variant. It is great period to prepare a vaccine or a neutralizing antibody against SARS-CoV-2 δ variant to prevent another wave of SARS-CoV-2 pandemic although there is no experimental evidence to confirm the significance of the T478K mutation in the SARS-CoV-2 δ variant.

## ACKNOWLEDGEMENTS

This paper was written as part of Konkuk University's research support program for its faculty on sabbatical leave in 2022. This work was supported by National Research Foundation of Korea (NRF-2021R1F1A1057397). This research was supported by Main Research Program (E0210503-01) of the Korea Food Research Institute (KRFI) funded by the Ministry of Science and ICT.

## REFERENCES

1. Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, Sabo RT, Hall N, Foreman A, Schubert PL, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings - Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1059-1062.  
[PUBMED](#) | [CROSSREF](#)
2. Dagpunar J. Interim estimates of increased transmissibility, growth rate, and reproduction number of the COVID-19 B.1.617.2 variant of concern in the United Kingdom. *medRxiv* 2021. doi: 10.1101/2021.06.03.21258293.  
[CROSSREF](#)
3. Liu Y, Rocklöv J. The reproductive number of the delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med* 2021:taab124.  
[PUBMED](#) | [CROSSREF](#)
4. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, Liu Z, Guo Q, Zou L, Zhang H, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 delta variant. *medRxiv* 2021. doi: 10.1101/2021.07.07.21260122.  
[CROSSREF](#)
5. Ong SWX, Chiew CJ, Ang LW, Mak TM, Cui L, Toh MPHS, Lim YD, Lee PH, Lee TH, Chia PY, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (alpha), B.1.315 (beta), and B.1.617.2 (delta). *Clin Infect Dis* 2021:ciab721.  
[PUBMED](#) | [CROSSREF](#)
6. Riemersma KK, Grogan BE, Kita-Yarbro A, Halfmann PJ, Segaloff HE, Kocharian A, Florek KR, Westergaard R, Bateman A, Jeppson GE, et al. Shedding of infectious SARS-CoV-2 despite vaccination. *medRxiv* 2021. doi: 10.1101/2021.07.31.21261387.  
[CROSSREF](#)
7. Shi Q, Dong XP. Rapid global spread of the SARS-CoV-2 delta (B.1.617.2) variant: spatiotemporal variation and public health impact. *Zoonoses* 2021;1:1-6.  
[CROSSREF](#)
8. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021;385:585-594.  
[PUBMED](#) | [CROSSREF](#)
9. Sheikh A, McMenemy J, Taylor B, Robertson C; Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021;397:2461-2462.  
[PUBMED](#) | [CROSSREF](#)
10. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450-454.  
[PUBMED](#) | [CROSSREF](#)
11. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun* 2020;525:135-140.  
[PUBMED](#) | [CROSSREF](#)
12. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 2020;581:215-220.  
[PUBMED](#) | [CROSSREF](#)
13. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. *Nature* 2020;581:221-224.  
[PUBMED](#) | [CROSSREF](#)
14. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathog* 2018;14:e1007236.  
[PUBMED](#) | [CROSSREF](#)
15. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260-1263.  
[PUBMED](#) | [CROSSREF](#)
16. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020;367:1444-1448.  
[PUBMED](#) | [CROSSREF](#)

17. Yuan M, Wu NC, Zhu X, Lee CD, So RT, Lv H, Mok CK, Wilson IA. A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. *Science* 2020;368:630-633.  
[PUBMED](#) | [CROSSREF](#)
18. Yuan Y, Cao D, Zhang Y, Ma J, Qi J, Wang Q, Lu G, Wu Y, Yan J, Shi Y, et al. Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. *Nat Commun* 2017;8:15092.  
[PUBMED](#) | [CROSSREF](#)
19. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. *JAMA* 2021;325:1318-1320.  
[PUBMED](#) | [CROSSREF](#)
20. Hong J, Jhun H, Choi YO, Taitt AS, Bae S, Lee Y, Song CS, Yeom SC, Kim S. Structure of SARS-CoV-2 spike glycoprotein for therapeutic and preventive target. *Immune Netw* 2021;21:e8.  
[PUBMED](#) | [CROSSREF](#)
21. Kim S, Lee JH, Lee S, Shim S, Nguyen TT, Hwang J, Kim H, Choi YO, Hong J, Bae S, et al. The progression of SARS coronavirus 2 (SARS-CoV2): mutation in the receptor binding domain of spike gene. *Immune Netw* 2020;20:e41.  
[PUBMED](#) | [CROSSREF](#)
22. Martinez-Flores D, Zepeda-Cervantes J, Cruz-Reséndiz A, Aguirre-Sampieri S, Sampieri A, Vaca L. SARS-CoV-2 vaccines based on the spike glycoprotein and implications of new viral variants. *Front Immunol* 2021;12:701501.  
[PUBMED](#) | [CROSSREF](#)
23. Kim B, Lee Y, Kim E, Kwak A, Ryoo S, Bae SH, Azam T, Kim S, Dinarello CA. The interleukin-1 $\alpha$  precursor is biologically active and is likely a key alarmin in the IL-1 family of cytokines. *Front Immunol* 2013;4:391.  
[PUBMED](#) | [CROSSREF](#)
24. Kwak A, Lee Y, Kim H, Kim S. Intracellular interleukin (IL)-1 family cytokine processing enzyme. *Arch Pharm Res* 2016;39:1556-1564.  
[PUBMED](#) | [CROSSREF](#)
25. Lee S, Kim E, Jhun H, Hong J, Kwak A, Jo S, Bae S, Lee J, Kim B, Lee J, et al. Proinsulin shares a motif with interleukin-1 $\alpha$  (IL-1 $\alpha$ ) and induces inflammatory cytokine via interleukin-1 receptor 1. *J Biol Chem* 2016;291:14620-14627.  
[PUBMED](#) | [CROSSREF](#)
26. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005;309:1864-1868.  
[PUBMED](#) | [CROSSREF](#)
27. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell* 2020;181:894-904.e9.  
[PUBMED](#) | [CROSSREF](#)
28. Chen RE, Winkler ES, Case JB, Aziati ID, Bricker TL, Joshi A, Darling TL, Ying B, Errico JM, Shrihari S, et al. *In vivo* monoclonal antibody efficacy against SARS-CoV-2 variant strains. *Nature* 2021;596:103-108.  
[PUBMED](#) | [CROSSREF](#)
29. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol* 2021;21:382-393.  
[PUBMED](#) | [CROSSREF](#)
30. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science* 2020;369:77-81.  
[PUBMED](#) | [CROSSREF](#)
31. Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, Himansu S, Schäfer A, Ziwawo CT, DiPiazza AT, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature* 2020;586:567-571.  
[PUBMED](#) | [CROSSREF](#)
32. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, Bellamy D, Bibi S, Bittaye M, Clutterbuck EA, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;396:467-478.  
[PUBMED](#) | [CROSSREF](#)
33. Frater J, Ewer KJ, Ogbe A, Pace M, Adele S, Adland E, Alagaratnam J, Aley PK, Ali M, Ansari MA, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial. *Lancet HIV* 2021;8:e474-e485.  
[PUBMED](#) | [CROSSREF](#)
34. Hassan AO, Kafai NM, Dmitriev IP, Fox JM, Smith BK, Harvey IB, Chen RE, Winkler ES, Wessel AW, Case JB, et al. A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2. *Cell* 2020;183:169-184.e13.  
[PUBMED](#) | [CROSSREF](#)

35. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, Plested JS, Zhu M, Cloney-Clark S, Zhou H, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med* 2020;383:2320-2332.  
[PUBMED](#) | [CROSSREF](#)
36. Wang J. New strategy for COVID-19 vaccination: targeting the receptor-binding domain of the SARS-CoV-2 spike protein. *Cell Mol Immunol* 2021;18:243-244.  
[PUBMED](#) | [CROSSREF](#)
37. Yang J, Wang W, Chen Z, Lu S, Yang F, Bi Z, Bao L, Mo F, Li X, Huang Y, et al. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. *Nature* 2020;586:572-577.  
[PUBMED](#) | [CROSSREF](#)
38. Arif TB. The 501.V2 and B.1.1.7 variants of coronavirus disease 2019 (COVID-19): a new time-bomb in the making? *Infect Control Hosp Epidemiol* 2021;1-2.  
[PUBMED](#) | [CROSSREF](#)
39. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CA, Russell TW, Tully DC, Washburne AD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science* 2021;372:eabg3055.  
[PUBMED](#) | [CROSSREF](#)
40. Wu K, Werner AP, Moliva JL, Koch M, Choi A, Stewart-Jones GBE, Bennett H, Boyoglu-Barnum S, Shi W, Graham BS, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. *bioRxiv* 2021. doi: 10.1101/2021.01.25.427948.  
[CROSSREF](#)
41. Barrett CT, Neal HE, Edmonds K, Moncman CL, Thompson R, Branttie JM, Boggs KB, Wu CY, Leung DW, Dutch RE. Effect of clinical isolate or cleavage site mutations in the SARS-CoV-2 spike protein on protein stability, cleavage, and cell-cell fusion. *J Biol Chem* 2021;297:100902.  
[PUBMED](#) | [CROSSREF](#)
42. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proc Natl Acad Sci U S A* 2009;106:5871-5876.  
[PUBMED](#) | [CROSSREF](#)
43. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proc Natl Acad Sci U S A* 2005;102:11876-11881.  
[PUBMED](#) | [CROSSREF](#)
44. Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. *Antiviral Res* 2013;100:605-614.  
[PUBMED](#) | [CROSSREF](#)
45. Claro IM, da Silva Sales FC, Ramundo MS, Candido DS, Silva CA, de Jesus JG, Manuli ER, de Oliveira CM, Scarpelli L, Campana G, et al. Local transmission of SARS-CoV-2 lineage B.1.1.7, Brazil, December 2020. *Emerg Infect Dis* 2021;27:970-972.  
[PUBMED](#) | [CROSSREF](#)
46. Gidari A, Sabbatini S, Bastianelli S, Pierucci S, Busti C, Monari C, Luciani Pasqua B, Dragoni F, Schiaroli E, Zazzi M, et al. Cross-neutralization of SARS-CoV-2 B.1.1.7 and P.1 variants in vaccinated, convalescent and P.1 infected. *J Infect* 2021;83:467-472.  
[PUBMED](#) | [CROSSREF](#)
47. Wang P, Casner RG, Nair MS, Wang M, Yu J, Cerutti G, Liu L, Kwong PD, Huang Y, Shapiro L, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *bioRxiv* 2021. doi: 10.1101/2021.03.01.433466.  
[CROSSREF](#)
48. Yadav PD, Nyayanit DA, Sahay RR, Sarkale P, Pethani J, Patil S, Baradkar S, Potdar V, Patil DY. Isolation and characterization of the new SARS-CoV-2 variant in travellers from the United Kingdom to India: VUI-202012/01 of the B.1.1.7 lineage. *J Travel Med* 2021;28:taab009.  
[PUBMED](#) | [CROSSREF](#)
49. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *Euro Surveill* 2021;26:  
[PUBMED](#) | [CROSSREF](#)
50. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, Planchais C, Porrot F, Robillard N, Puech J, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. *Nature* 2021;596:276-280.  
[PUBMED](#) | [CROSSREF](#)
51. Chen LL, Lu L, Choi CY, Cai JP, Tsoi HW, Chu AW, Ip JD, Chan WM, Zhang RR, Zhang X, et al. Impact of SARS-CoV-2 variant-associated RBD mutations on the susceptibility to serum antibodies elicited by COVID-19 infection or vaccination. *Clin Infect Dis* 2021;ciab656.  
[PUBMED](#) | [CROSSREF](#)

52. Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, Sotomayor-González A, Glasner DR, Reyes KR, Gliwa AS, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. *medRxiv* 2021. doi: 10.1101/2021.03.07.21252647.  
[CROSSREF](#)
53. Martin Webb L, Matzinger S, Grano C, Kawasaki B, Stringer G, Bankers L, Herlihy R. Identification of and surveillance for the SARS-CoV-2 variants B.1.427 and B.1.429 - Colorado, January-March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:717-718.  
[PUBMED](#) | [CROSSREF](#)
54. Ozer EA, Simons LM, Adewumi OM, Fowotade AA, Omoruyi EC, Adeniji JA, Dean TJ, Zayas J, Bhimalli PP, Ash MK, et al. Coincident rapid expansion of two SARS-CoV-2 lineages with enhanced infectivity in Nigeria. *medRxiv* 2021. doi: 10.1101/2021.04.09.21255206.  
[CROSSREF](#)
55. Annavajhala MK, Mohri H, Wang P, Nair M, Zucker JE, Sheng Z, Gomez-Simmonds A, Kelley AL, Tagliavia M, Huang Y, et al. Emergence and expansion of the SARS-CoV-2 variant B.1.526 identified in New York. *medRxiv* 2021. doi: 10.1101/2021.02.23.21252259.  
[CROSSREF](#)
56. Collier DA, De Marco A, Ferreira IATM, Meng B, Datir RP, Walls AC, Kemp SA, Bassi J, Pinto D, Silacci-Fregni C, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. *Nature* 2021;593:136-141.  
[PUBMED](#) | [CROSSREF](#)
57. Emary KR, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, Blane B, Bonsall D, Cicconi P, Charlton S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021;397:1351-1362.  
[PUBMED](#) | [CROSSREF](#)
58. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, Wang M, Yu J, Zhang B, Kwong PD, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 2021;593:130-135.  
[PUBMED](#) | [CROSSREF](#)
59. Jangra S, Ye C, Rathnasinghe R, Stadlbauer D; Personalized Virology Initiative study group. Krammer F, Simon V, Martinez-Sobrido L, Garcia-Sastre A, Schotsaert M, et al. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. *Lancet Microbe* 2021;2:e283-e284.  
[PUBMED](#) | [CROSSREF](#)
60. Greaney AJ, Loes AN, Crawford KHD, Starr TN, Malone KD, Chu HY, Bloom JD. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. *Cell Host Microbe* 2021;29:463-476.e6.  
[PUBMED](#) | [CROSSREF](#)
61. McCallum M, Bassi J, De Marco A, Chen A, Walls AC, Di Iulio J, Tortorici MA, Navarro MJ, Silacci-Fregni C, Saliba C, et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. *Science* 2021;373:648-654.  
[PUBMED](#) | [CROSSREF](#)
62. Elbe S, Buckland-Merrett G. Data, disease and diplomacy: GISAID's innovative contribution to global health. *Glob Chall* 2017;1:33-46.  
[PUBMED](#) | [CROSSREF](#)
63. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, Nutalai R, Zhou D, Mentzer AJ, Zhao Y, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell* 2021;184:4220-4236.e13.  
[PUBMED](#) | [CROSSREF](#)