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Review Article

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

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ABSTRACT

Over two hundred twenty-eight million cases of coronavirus disease 2019 (COVID-19) in the world have been reported until the 21st 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 α, β, γ, and δ 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 α, β, γ, and δ variants of concern including SARS-CoV-2 ε, ζ, η, ι, κ, and B.1.617.3 variants of interest and alert. Recently, SARS-CoV-2 δ 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) δ (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 δ 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).

Angiostatin-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, angiostatin-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.

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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 a-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-1α 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 α, β, and γ. As well as we include SARS-CoV-2 ε, ζ, η, ι, κ, 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 δ variant to analyze the current crisis of COVID-19 pandemic.

SARS-CoV-2 α (B.1.1.7) VARIANT

SARS-CoV-2 α (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 α variant has 13 mutation sites

in *S* gene (**Fig. 1A**), which is the third largest number among four SARS-CoV-2 α, β, γ, and δ variants of concern and six SARS-CoV-2 ε, ζ, η, ι, κ, and B.1.617.3 variants of interest or alert (**Table 1**). The α 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 β (B.1.351) VARIANT

SARS-CoV-2 β (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 α variant, whereas K417N does not present in SARS-CoV-2 α variant. Unlike SARS-CoV-2 α variant, 9 mutation sites of SARS-CoV-2 β variant are detected

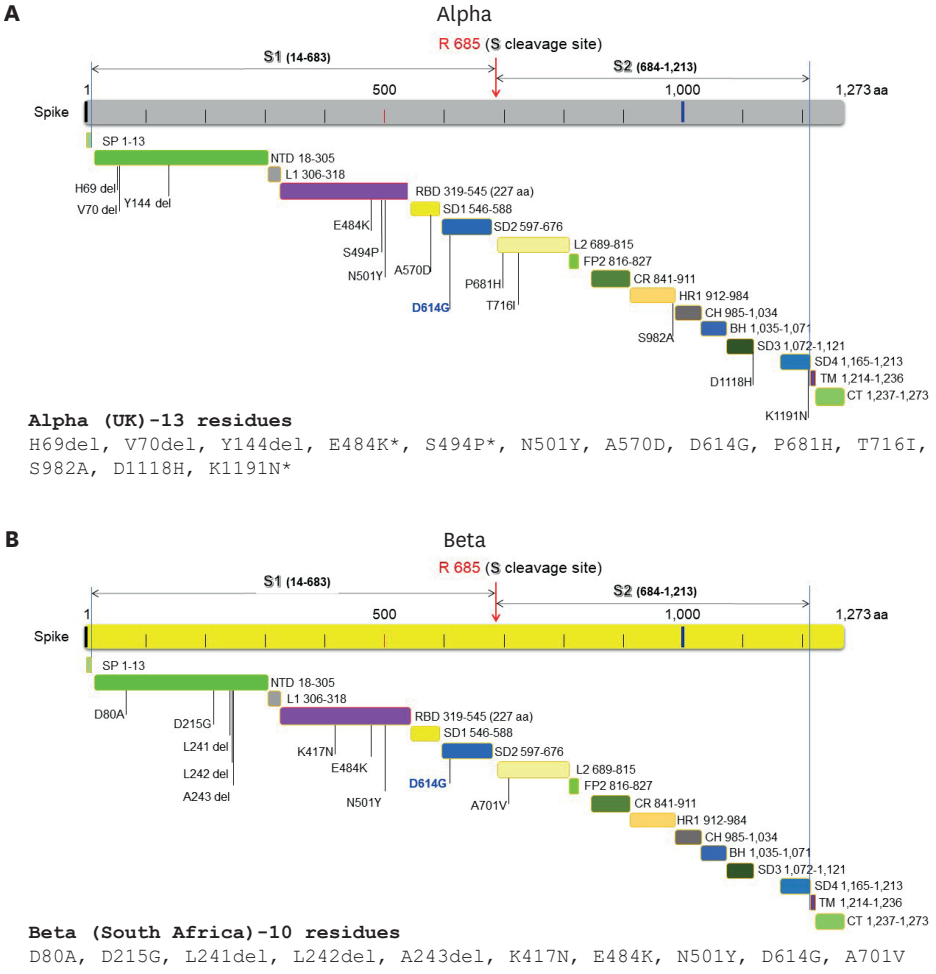

Figure 1. Schematic drawing of 16 subdomains in spike glycoprotein of SARS-CoV-2. The spike glycoprotein is composed of 16 subdomains. The S1 region (R685) cleavage site is indicated at the top. SARS-CoV-2 α, β, γ, and δ variant mutation sites were indicated by specific amino acid substitution. The common D614G in all ten variant (**Table 1**) was indicated by bold blue letter. (A) SARS-CoV-2 α variant has 13 mutation sites were listed at the bottom. (B) SARS-CoV-2 β variant has 10 mutation sites were listed at the bottom. (C) SARS-CoV-2 γ variant has 11 mutation sites were listed at the bottom. (D) SARS-CoV-2 δ variant has 15 mutation sites were listed at the bottom. A unique residue of SARS-CoV-2 δ 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, β-hairpin; TM, transmembrane domain; CT, cytosolic domain. (continued to the next page)

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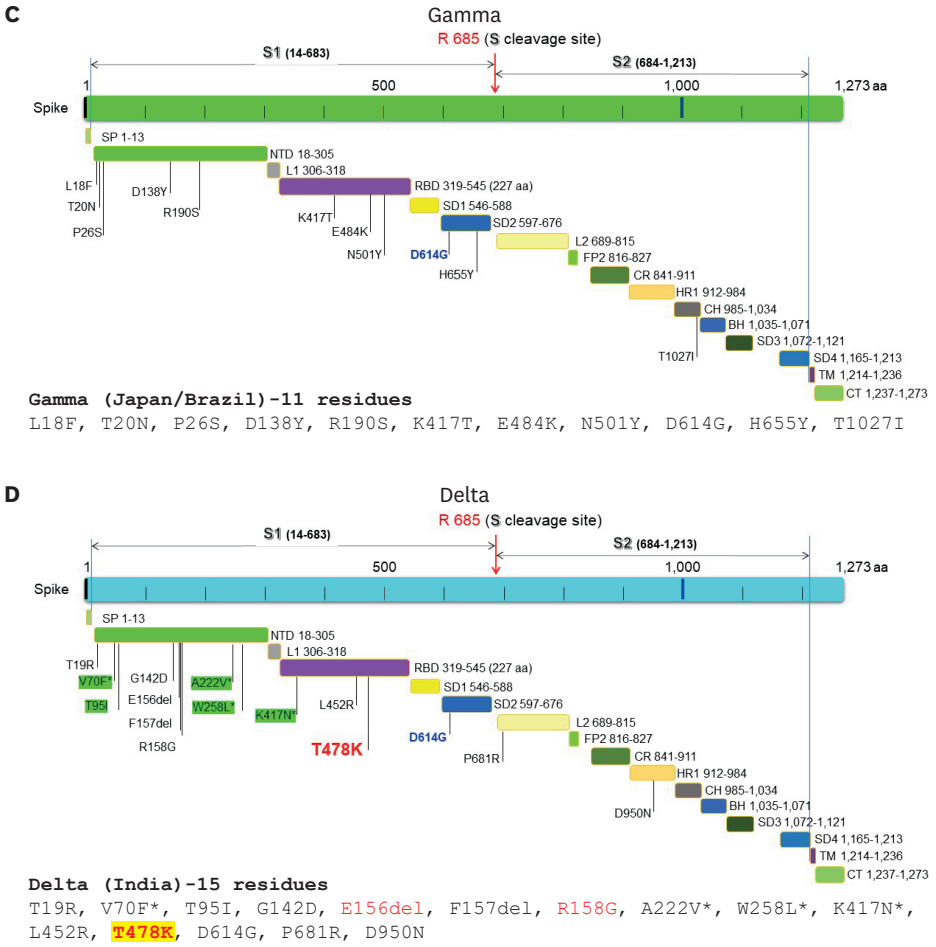

Figure 1. (Continued) Schematic drawing of 16 subdomains in spike glycoprotein of SARS-CoV-2. The spike glycoprotein is composed of 16 subdomains. The S1 region (R685) cleavage site is indicated at the top. SARS-CoV-2 α, β, γ, and δ variant mutation sites were indicated by specific amino acid substitution. The common D614G in all ten variant (**Table 1**) was indicated by bold blue letter. (A) SARS-CoV-2 α variant has 13 mutation sites were listed at the bottom. (B) SARS-CoV-2 β variant has 10 mutation sites were listed at the bottom. (C) SARS-CoV-2 γ variant has 11 mutation sites were listed at the bottom. (D) SARS-CoV-2 δ variant has 15 mutation sites were listed at the bottom. A unique residue of SARS-CoV-2 δ 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, β-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 α variant.

SARS-CoV-2 γ (P.1) VARIANT

SARS-CoV-2 γ (P.1) variant first reported in two countries Brazil and Japan, and it has completely different Pango linage, P.1 (**Table 1**) (45). The SARS-CoV-2 γ variant has 11 mutation sites in *S* gene (**Fig. 1C**). Like SARS-CoV-2 β 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 β variant except K417 is substituted by T instead of N. The significant difference of SARS-CoV-2 γ variant from SARS-CoV-2 α and β 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, α	H69del, V70del, Y144del, E484K*, S494P*, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N*	VOC (38,39)
B.1.351	S. Africa	Beta, β	D80A, D215G, L241del, L242del, A243del, K417N, E484K, N501Y, D614G, A701V	VOC (40)
P.1	Brazil/Japan	Gamma, γ	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	VOC (45)
B.1.617.2	India	Delta, δ	T19R, V70F*, T95I, G142D, E156del, F157del, R158G, A222V*, W258L*, K417N*, L452R, **T478K**, D614G, P681R, D950N	VOC (48-50)
B.1.427/B.1.429	US-California	Epsilon, ε	S13I, W152C, L452R, D614G	VOC (19-Mar-2021) VOI (29-Jun-2021) (52,53,61)
P.2	Brazil	Zeta, ζ	E484K, F565L*, D614G, V1176F	VOI (55)
B.1.525	UK/Nigeria	Eta, η	A67V, H69del, V70del, Y144del, E484K, D614G, Q677H, F888L	VOI (54)
B.1.526	US-NY	Iota, ι	L5F, D80G*, T95I, Y144del*, F157S*, D253G, L452R*, S477N*, E484K, D614G, A701V, T859N*, D950H*, Q957R*	VOI (55)
B.1.617.1	India	Kappa, κ	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 α, β, γ, and δ VOCs and six SARS-CoV-2 ε, ζ, η, ι, κ, 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 δ variant was indicated as bolded and underline. The rest of two unique δ 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 γ variant has few reports compared to other SARS-CoV-2 variant of concern (46,47).

SARS-CoV-2 δ (B.1.617.2) VARIANT

SARS-CoV-2 δ (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 δ 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 κ (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 δ variant in terms of the mutation sites. SARS-CoV-2 δ variant shares three common mutation sites, L452R, D614G, and P681R with SARS-CoV-2 κ 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 α and δ variants of concern but SARS-CoV-2 δ variant P681 is substituted by H instead of R. The L452R mutation site presents in three SARS-CoV-2 ε and ι variants from US. SARS-CoV-2 ε (B.1.427/B.1.429) variant was detected in California US whereas ι (B.1.526) variant was reported in New York US (**Table 1**). The comparison of SARS-CoV-2 δ 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 ε, ζ, η, ι, κ, AND B.1.617.3 VARIANT OF INTEREST AND ALERT

Six SARS-CoV-2 ε, ζ, η, ι, κ, 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 ε

(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 ε and ζ has 4 mutation sites, which is the least number of mutation sites among ten SARS-CoV-2 variants (**Table 1**). SARS-CoV-2 ζ variant is similar to γ (P.1) variant according to Pango lineage, but the mutation sites show different pattern between these two variants (**Table 1**). SARS-CoV-2 ζ variant has the common mutation sites E484K and D614G. The L452R mutation site is found in SARS-CoV-2 δ variant of concern along with SARS-CoV-2 ε, ι, κ, 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 α, β, γ, ζ, η, ι, κ, and B.1.617.3 variants, however, SARS-CoV-2 κ 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 δ and ε variants (**Table 1**).

SARS-CoV-2 η (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 ι (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 δ variant of concern (**Table 1**) (55). This variant is similar to η (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 ι variant of New York US contains mixed mutation that found among several variants, as following on 9 mutation sites: D80G presents in β variant with A substitution; T95I presents in κ variant with R substitution; Y144 deletion presents in α variant; F157S presents in δ variant by deletion; L452R presents in δ, ε (B.1.427/B.1.429), κ, and B.1.617.3 variant; E484K presents in α, β, γ, ζ, and η as well as in κ, and B.1.617.3 variant but with Q substitution in κ and B.1.617.3 variant; D614G presents in all variant; A701V presents in β variant; D950H presents in δ 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 ι variant (**Table 1**).

The last two SARS-CoV-2 κ (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 δ, which is currently considered as the most problematic variant. These three Indian originated variants share 5 mutation sits, T19R, G142D, L452R, D614G, and P681R. One mutation is common between δ and B.1.617.3 variants, D950N, and one mutation site is unique to κ variant, Q1071H. Moreover, SARS-CoV-2 κ, 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 α and β 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 α and β 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 α variant exhibited a

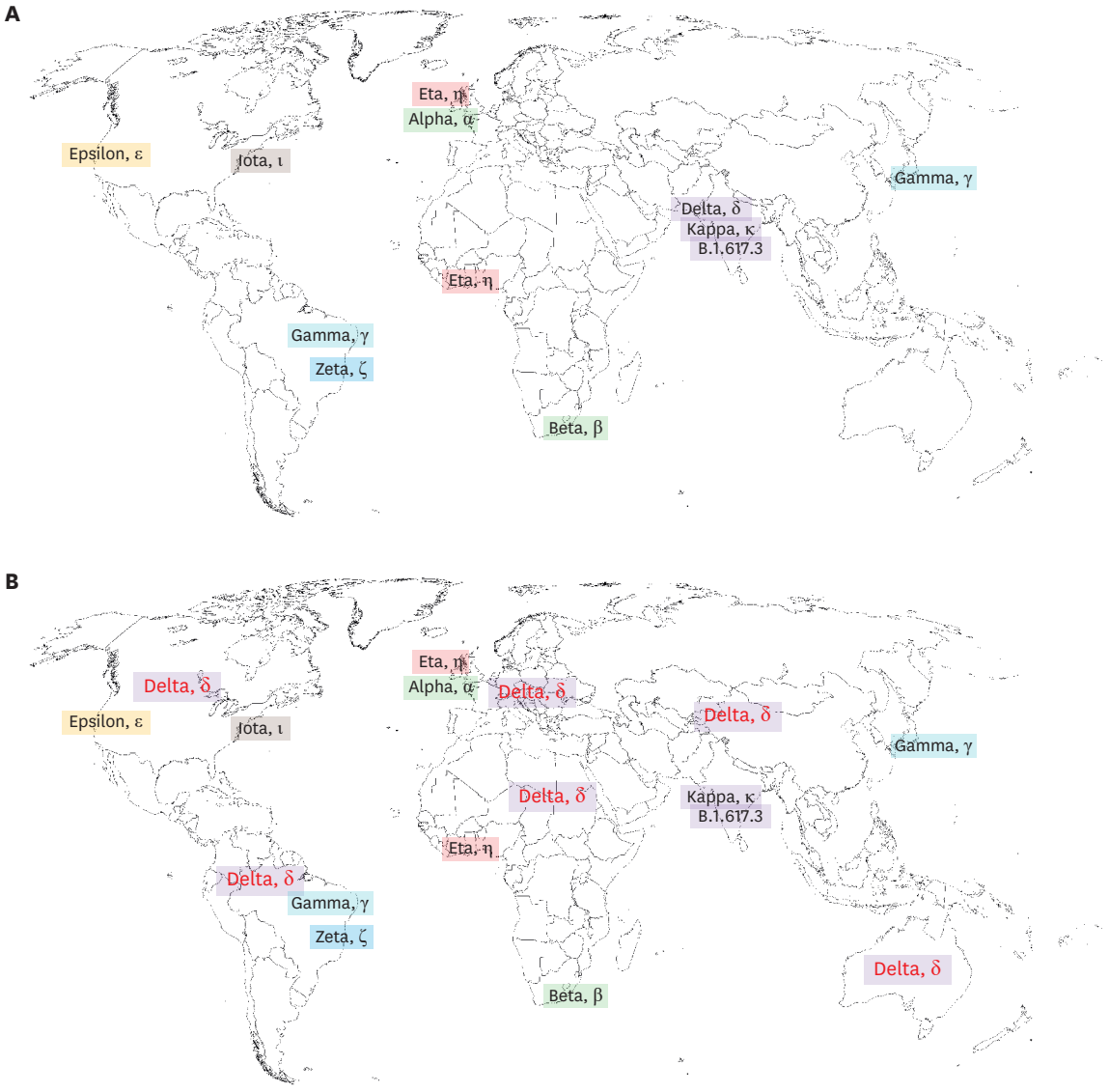

Figure 2. The occurrence of ten SARS-CoV-2 variants located in the world map. (A) The world map showed the origin of the ten SARS-CoV-2 variants although SARS-CoV-2 originated from Wuhan China. (B) The spread of SARS-CoV-2 δ variant in 6 continents including other nine SARS-CoV-2 variants.

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little or no susceptibility impact on EUA monoclonal Ab treatments (57). However, SARS-CoV-2 β, γ, and ι 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 (δ, κ, and B.1.617.3) as well as η 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 ε (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 25th of 2021. Moreover, the prevalence of the SARS-CoV-2 β and γ 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 15th 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 κ, 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 δ 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 δ 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 δ variant must be investigated if a recent outbreak of COVID-19 depends on the mutation sites in the *S* gene of SARS-CoV-2 δ 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 δ 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 β and γ variants were likely more susceptible to reinfection by the SARS-CoV-2 δ variant, whereas vaccine based on SARS-CoV-2 α (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 α and δ variants.

A UNIQUE MUTATION SITE FOR DELTA VARIANT: T478K

Surprisingly, the two closest variants to the delta variant, SARS-CoV-2 κ 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 δ variant with SARS-CoV-2 κ 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 δ 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^{1}–WT^{4}. 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 δ variant and the common L452R mutation site of δ, ε, ι, κ, and B.1.617.3 variants (**Fig. 3**). So far, this could be due to the *in vitro* condition comparing

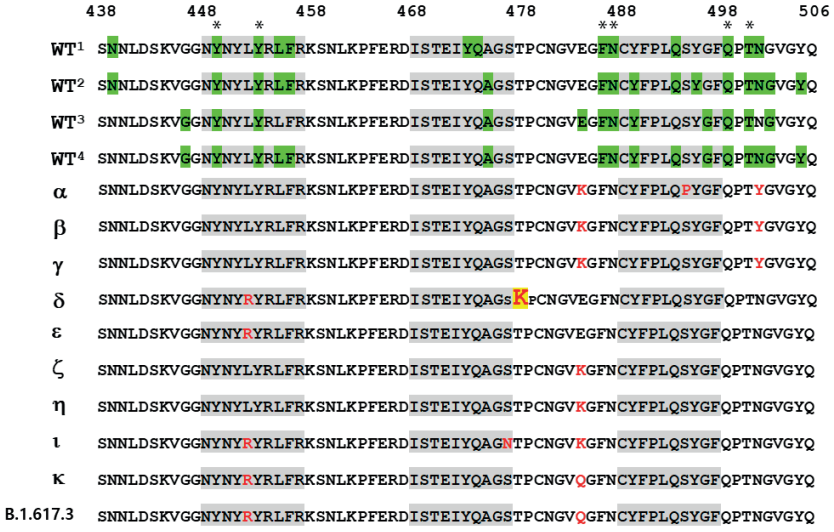

Figure 3. Mutation sites in the RBM of ten SARS-CoV-2 variants. The alignment of spike RBM in the ten SARS-CoV-2 variant was directly compared to the receptor binding residues that were reported by WT[1] (16), WT[2] (17), WT[3] (27), and WT[4] (12). The twenty-one receptor interaction residues in WT[1]–WT[4] 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, ι, 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.

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