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An overview on SARS-CoV-2 variants

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ABSTRACT

The prevalence of SARS-CoV-2 variants in different provinces poses a major health concern around the world. These emerged variants are highly infectious and overriding most of the population in a short duration of time. The variant of concern (VOC) is altered mutational changes that persistently occur in the receptor-binding site (RBD) of spike protein and substantially increases the binding affinity of the virus particle. Characteristic mutational changes and functionality of surface decorated spike proteins of emerged diverse variants have direct implications on the rate of transmissibility through higher affinity with RBD. Enhanced virulence, frequent re-infection, and obdurate resistance against medicaments advocated dominancy of them. This review paper shed a light on different contagious variants (Alpha, Beta, Gama, and delta) and their underlined mechanisms involved in binding with host cells (Angiotensin-converting enzyme- 2).

Keywords: SARS-CoV-2 variants, Angiotensin-converting enzyme- 2, Variant of concern, Spike protein, Receptor-binding site

INTRODUCTION

The SARS-CoV-2 virus is constantly changing its structural specifications including spike proteins and become more diverse. We can understand it as a proliferation of growing branched trees. As each branch of the tree is different from others, variants of the SARS-CoV-2 virus are also unlike. As the pandemic continues variant has become the latest concern with notable examples detected in South Africa, Brazil, UK, and India. These variants are complicated as each one is made up of a collection of mutations and all of which have the potential to change the SARS- CoV- 2 virus in unexpected ways. Viruses can't replicate by themselves without living organisms hence surface decorated spike proteins facilitate effective attachment with host cells. Viruses can multiply by copying their genomes over and over. But like an old photocopier machine, these multiplied copies are not always perfect and an imperfect copy is declared as a variant. The variant of concern (VOC) is a term that is used for severe acute respiratory syndrome (SARS-Cov-2) virus. It is an expression of mutation that persistently occurs in the receptor-binding site (RBD) of spike protein and substantially increases the binding affinity of the virus particle. The recent emergence of new variants of the SARS-Cov-2 virus may be associated with several potential mechanisms like increased frequency of transmission, the severity of disease, host shifts, and infection to immune-compromised patients. The fate of the mutant virus depends upon its natural selection, once selected it becomes a dominant variant that possesses the increased potential of transmission, replication, and also the ability to escape from the immune system of the host. In the current situation exhaustive monitoring is being conducted for SARS-Cov-2 variants: Alpha (B.1.1.7), BETA (B.1351), GAMMA (P.1), and DELTA (B.1.617.2)

ALPHA variant (VOC 202012/01 or 20B/501Y.V1)

ALPHA variant (VOC 202012/01 or 20B/501Y.V1) also referred to as the U.K variant is one of the dominant variants of the SARS-Cov-2 virus that was detected in late 2020 in the United Kingdom [Shi et al.2021]. It is believed to be an issue of concern since it exhibits 40-80% more transmission chances than the wild-type virus [Greaney et al.2021]. The variant is characterized by a high speed of transmission that has contributed to increased incidence of spread of disease, hospitalization, and impact on the health care system. Retrospective observational studies indicate that not only it has a high transmission rate rather it also has an increased rate of mortality, which is estimated to be nearly 36% more than the ancestral virus i.e. SARS-CoV-2 [Davies et al.2020].

Mutations in Alpha variants are observed in the gene coding for the production of spike proteins that are present on the surface of the virus and allow the viral particle to penetrate in the host cell by binding with ACE-2 receptors that are expressed on the host cell. The major mutation responsible for enhanced virulence is N501Y that is an example of substitution mutation which occurs at the 501st position of amino acids, asparagine (N) has been replaced with tyrosine (Y) as depicted in figure 1 [Davies et al. 2021]. *In silico* studies have demonstrated the fact that N501Y mutation has resulted in

the formation of shorter H-bond (bond length of 2.94 A◦) as compared to its counterpart (wild type, SARS-CoV-2) that results in stable interaction between RBD and ACE-2 receptors further the mutation results in negative binding free energy (BFE) -7.18Kcal/mol as compared to wild type with -2.92 Kcal/mol, as a result of both these combining factors the binding affinity of the variant has increased which is the main contributing factor for high transmission rate[Cao et al.2021]. The other form of mutation associated with the variant is H69/V70 deletion in which one of the recurrent mutations observed at the amino-terminal domain (NTD) of S protein and emerged independently in at least six lineages of the SARS-CoV-2 virus prevalent in Europe. Protein structure modeling shows that H69/V70 deletion could result in modification of the immunodominant epitopes situated at variable loops within NTD, conferring opposition to neutralization by sera from both convalescent patients and vaccinated individuals [Liu et al.2019]. The third form of mutation the exact effect of which on the virulence property of virus is not yet clearly known is P681H that is present adjacent to the amino acids 682–685, the furin cleavage site (FCS) identified at the S1/S2 in the spike protein, the mutation promotes the entry of viral particles into the respiratory epithelial cells [McCarthy et al.2021], moreover, the insertion of FCS enhances the activities of a transmembrane serine protease (TMPRRS) and thus increases the infectivity [Hoffmann et al.2020].

BETA variant (20H/501Y.V2)

BETA variant (20H/501Y.V2) also referred to as the South African variant was first spotted in the metropolitan area of the Eastern Cape province of South Africa in October 2020 [Shahhosseini et al.2021]. It became the dominating virus causing the spread of disease by the end of 2020 suggesting its high rate of transmission; however, there are no supporting pieces of evidence related to the virulence nature of the mutant virus. Several researchers reported that the main target population for this variant includes healthy young individuals with no underlying health complications [Tegally et al.2020, Misra et al. 2021].

The B.1351 strain has 12 non-synonymous and one deletion mutation as compared to the wild strain that was initially found in the Wuhan region. Major mutations are observed in the genes coding for the spike proteins while the minor mutations are observed in genes coding for the envelope and viral proteins. N501Y, K417N, and E848K are the mutations of concern [Lesley et al. 2020]. The molecular dynamics studies suggest that N501Y and E848K mutations are responsible for switching of charges on the flexible loops of S- RBD and thus promote the formation of favorable bonds with ACE-2 receptors. K417N and E848K confer the alterations in the receptor-binding motif (RBM) of RBD [Baker T. 2021]. All these changes in the mutant variant have contributed toward an increased affinity for host cell and thereby high penetration and enhanced incidence of transmission are common attributes associated with the Beta variant. The B.135 lineage also possesses the ability to escape from the neutralization mechanism [Nelson et al.2021].

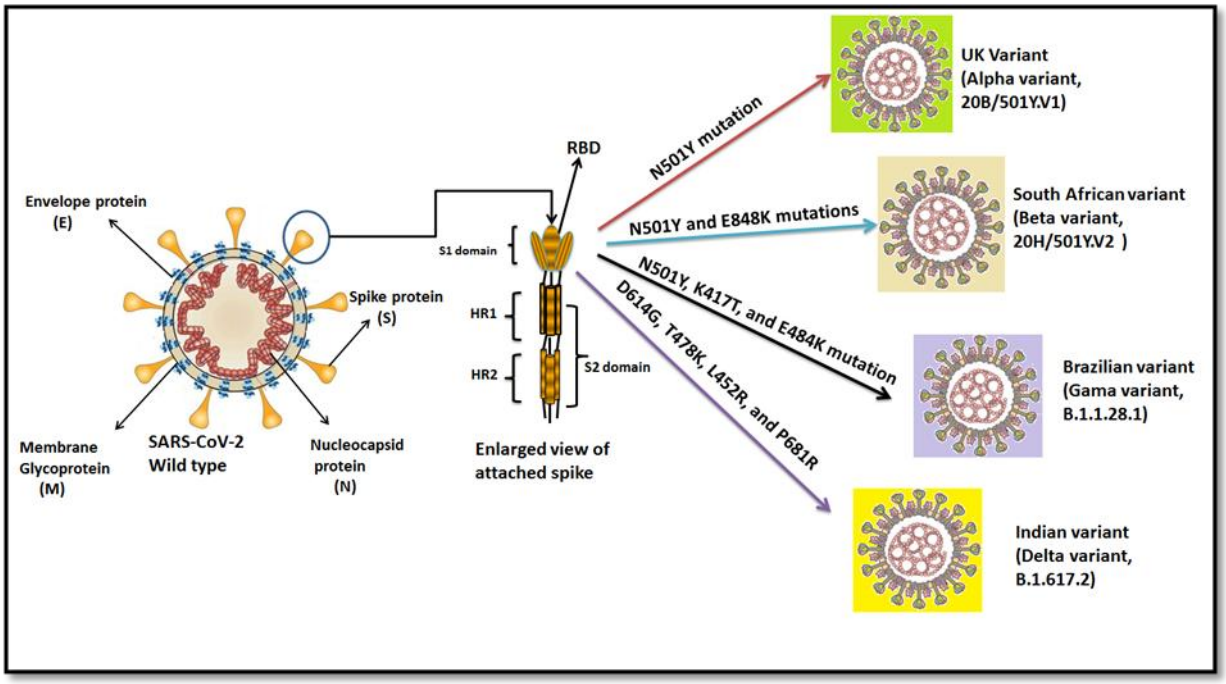

Figure 1: Different variant of concern (VOC) of SARS-CoV-2

GAMMA (B.1.1.28.1) Variant

The Gamma variant also designated as P.1 Variant was first detected by Japan's National Institute of Infectious disease [Tegally et al.2021]. In January 2021 it was the major circulating virus in Brazil so it is commonly known as the Brazilian variant [Avanzato et al. 2020]. The mutant form is associated with high instances of transmission and also shows the enhanced incidence of re-infections. Initial reports suggested the presence of two separate P.1 and P.2 descendants of Brazilian lineage B.1.1.248 [Sabino et al. 2021].

The P.1 variant that belongs to B.1.1.248 lineage has the highest number of mutations. The variant is supposed to have 17 non-synonymous and 4 synonymous mutations that are responsible for increased transmission rate, elevation in re-infection, and evasion of antibody-mediated defense mechanism [Buss et al. 2021]. The prime mutation reported includes N501Y, K417T, and E484K. The mutation E848K is one of the mutations that have worried the researchers, which is shared by the P.1 and the B.1.351 variants. The effect of the mutation has been evaluated for its neutralization ability of sera from convalescent or vaccinated patients considering their SARS-CoV-2 spike immunoglobulin G (IgG) antibody titer [Jangra et al.2021]. Studiesperformed using authentic clinical viral isolates to determine inherent viral fitness and the potential impact of additional mutations outside of the spike on sensitivity to neutralizing antibodies also demonstrated that low global antibody levels or declining antibody responses are linked with a loss of cross-reactivity against emerging variants [Planas et al. 2021].

DELTA (B.1.617.2) variant

DELTA variant is named as B.1.617.2 according to the Plango lineage. The variant was first found in India in December 2020 [Ledford et al.2021]. It is one of the most devastating mutant viruses found to be circulating across the continents since the time. The variant is associated with the rapid rate of transmission that has resulted in outbreaks in countries. The attack rate of the mutant form is 50-60% more as compared to the Alpha variant as reported by PHE (Public health England) [Lau et al.2021]. Initially under the category of variants under investigation (VUI) found a place in the category of variants of concern (VOC) in May 2021[Kirby T. 2021].

There are a total of 13 mutations that have altered the nature of the virus. The mutations are primarily responsible for altering the sequence of amino acids that consecutively results in altered Spike proteins. The prime mutations present in the variant are D614G, T478K, L452R, and P681R. The substitution at position 614, an aspartic acid-to-glycine substitution, is shared with other highly transmissible variants like Alpha, Beta, and Gamma [Singh et al.2021]. Table1 compiled characteristics features of different variants of concern (VOCs).

L452R involves substitution at position 452, a leucine-to-arginine that is responsible for strong binding between the viral particle and ACE-2 receptor [Li et al.2020]. P681R is responsible for substitution at position 681, a proline-to-arginine that boosts cell-level infectivity of the variant by promoting the cleavage of the S precursor protein to the active S1/S2 configuration [Koshy et al. 2021].

Table1: Significant characteristics features of VOCs and their neutralization effects

Variants (WHO label)	Name (Lineage)	Site of initial detection	Types of mutations	Characteristic features	Effect on neutralization efficacy
ALPHA	B.1.1.7	United Kingdom	N501Y H69/V70P681H	High transmission High severity of disease	Moderate reduction in neutralization efficacy of sera
BETA	B.1351	South Africa	N501Y K417N E848K	High transmission High incidence of reinfection	Significant reduction in neutralization efficacy of sera
GAMMA	P.1	Japan/ Brazil	N501Y K417N E848K	High transmission High incidence of reinfection	Significant reduction in neutralization efficacy of sera
DELTA	B.1.617.2	India	D614G T478K L452R P681R	High transmission High severity of disease	Significant reduction in neutralization efficacy of sera

The Delta variant that was the prominent reason for the second wave of COVID pandemics in India is believed to have undergone mutation that has resulted in the origin of the Delta plus variant. The Delta plus variant is still categorized as a variant of interest and not a variant of concerns the adverse consequences of its spread in the community are still not understood. Scientists have explained that the mutation in the Delta variant of SARS-CoV-2 was resisting the monoclonal antibody treatment for COVID-19 [Haseltine et al.2021].

CONCLUSION

The occurrence of mutations in the SAR-CoV-2 virus is not a new virological event. It is a phenomenon that is based on the principle of natural selection. Multiple mutations have occurred in the genetic code of the Corona virus i.e. long RNA nucleotides (30000). Those mutations that are of particular importance to viruses and provide an edge over wild type in terms of increased replication, high transmission rate, and elevated severity of disease, and even chances of re-infection are found to be dominating and prevailing in society. The chances of mutations will increase in time due to the high rate of transmission and upcoming situations can be more challenging. The current time extremely entails strengthening health sectors through providing sufficient medico-facility and taking preventive measures for subsiding virulence of emerged variants.

Conflict of interest: None

Author's contribution: Mrs. Anupriya Kapoor proposed the current title and conceptualized the article. Dr. Shashi Kiran Misra critically reviewed the whole content. Dr. Ajay Kumar Yadav and Dr. Arpit Katiyar supervised the collected details and data. Ms. Aditi Awasthi envisaged literatures.

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