# Genetic Variants of SARS CoV-2; Mutations and Mechanism of Survival

**Laiju Kuzhuppillymyal Prabhakarankutty[1], Manojan Kannan Kandiyil[2], Sreekanth Kavitha Sivaraman[3]***

[1]Department of Microbiology and Immunology
Faculty of Biological Sciences
Laboratory of Immunology and Virology
Autonomous University of Nuevo Leon, Ave. Pedro de Alba s/n
San Nicolas de Los Garza, Nuevo Leon 66455, Mexico.

[2]Department of General Medicine
Sree Gokulam Medical College and Research Foundation
Venjaramoodu.P.O, Trivandrum – 695607, Kerala, India

[3]Department of Biochemistry and Molecular Biology
Sree Gokulam Medical College and Research Foundation
Venjaramoodu.P.O, Trivandrum – 695607, Kerala, India
***Corresponding Author** (e-mail: sree9in@rediffmail.com)

*Abstract— Irrespective of the control measures, Covid-19 pandemic is continuing as an unending saga with progressive reports coming out from various parts of the world with modified versions of SARS Cov-2. These modifications are genome specific and are considered as viral adaptive mechanism to survive in a host cell and transmit the infection. These mutations can alter the viral genome sequence either by random replication errors or through RNA-editing mechanism of the host cell and generate new variants which are more virulent and with modified survival mechanisms. These new variants are categorized as Variants of Concern (VOC), Variants of Interest and Variants of High Consequence. The first two are reported from different countries and no viral variants that rise to the level of the third one have been reported so far. There are many proposed mechanisms by which how a mutation occurs to modify the existing viral genome to create new variants and how they can survive inside a host cell. This review highlights different variants of the virus, their unique features and mechanism by which they integrate with the host cell. An understanding of the genome of these variants with possible mutations and mechanism of survival will help to design and implement better treatment strategies and protective measures in the future.*

***Keywords— Covid-19; SARS Cov-2; Mutation; RNA-editing; Variants of Concern; Variants of Interest; Variants of High Consequence.***

## INTRODUCTION

Irrespective of the vaccination along with medications, episode of Covid-19 infection affecting the population is continuing in a same phase alarmingly. However, the symptoms are mild to moderate with high recovery rate without hospitalization but with proper medication and social distancing. Increase in the transmissibility of Covid-19/ SARS CoV-2 and associated complications have made scientists to review critically the mechanism of the viral infection in host cell. Interestingly, there are drastic modifications occurred in the genetic makeup of this virus from time to time as per the host environment leading to a kind of adaptive mechanism inside the cell causing further transmission of the infection from host to host and survival of the virus. One possibility which is already proposed was the constant morphological changes of the virus to adapt different conditions worldwide [1]. However, the mechanism associated with this is much drastic with modifications in viral genome. Hence it is particularly important to understand the different variants and how significant are the mutations in the survival of this virus and making the pandemic perpetual. This review is highlighting on the genetic variants of SARS Cov-2 and the major differences between each variant. Understanding the viral morphology and genetic variation is possibly an added advantage for the scientific fraternity to manage the pandemic with much effective vaccines and medications.

## Covid-19 virus

There is much understanding about the viral morphology and their mode of transmission. Morphologically, Covid 19 virus is a spherical one covered with an envelope. Since it is a retrovirus, it contains single stranded RNA attached to nucleoproteins as its genetic material. There are spikes of proteins projecting from the surfaces of this spherical virus and they help in attaching with the host cells when transmission occurs. With the matrix proteins, RNA-nucleoprotein complex is embedded in a capsid [2] and this single stranded positive sense RNA (Mr6X106) can integrate and could cause sufficient changes with the host cell genome [3]. Antigenic epitopes are carried by the glycoproteins present on the virus and with help of them the recognition and neutralization of antibodies occur [4]. These glycoproteins can attach to the host cell with these antigenic epitopes. Regarding fast transmission of the infection from human to human, it is mainly through the droplets of an infected person when encounters each other [5]. However, now there is evidence of the presence of several viral variants around causing the pandemic an endless episode.

## Genetic variants of SARS-CoV-2

SARS-CoV-2 is a single stranded RNA virus genome of ~ 30 Kb that codes 27 proteins from 14 open reading frames (ORF). Two thirds of the viral genome (ORF1ab) includes nonstructural proteins NSP1-NSP16, and one-third consists of the major structural proteins such as Spike glycoprotein (S), membrane glycoprotein (M), Envelope protein (E), and nucleocapsid protein (N) (Fig 1). Spike protein has two subunits, S1 to recognize and bind to the host cell with angiotensin-converting enzyme 2 (ACE2) and S2 for host cell membrane fusion [6,7]. Contagious and pathogenic nature of a virus is related to the S protein, thus any mutation at this site or near to them are crucial [8]. To establish an infection in a host cell, the genetic material of the virus must enter the host cell and starts to use host cell's machinery to duplicate itself. Chances are there for errors to occur during this process and as a result a virus that is similar but not exactly the copies of the parent virus may be born. These errors in the viral genetic material called mutation results in the generation of new virus and is known as a variant or more precisely a 'mutant variant' of the virus.

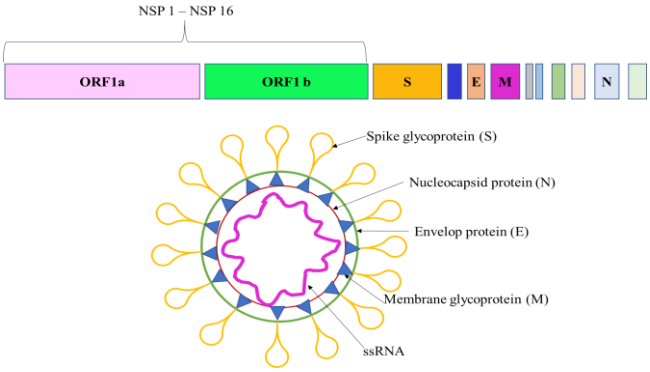


Fig 1: SARS-CoV-2 genome

Mutations can alter viral genome sequence either by random replication errors or through RNA editing mechanism of the host cell. A mutation is synonymous when there is no change in the encoded amino acids, whereas a non-synonymous mutation occurs when a protein acquires a change [6]. In a phylogenetic analysis, nucleotide substitution frequency of different SARS-CoV2 genome by Mishra et.al revealed that a greater number of viral genomes from Asian and American continents demonstrated more than one amino acid substitution, whereas, in European viral genomes the number of nucleotide substitutions found more than once or only once, suggesting that the SARS-CoV-2 genome follows a scheduled rise on attacking human hosts [9]. Out of the 2325 genomes they analyzed, 107 nucleotide substitutions were found from American genomes, 162 were from Europe and 65 were from Asia. These nonsynonymous mutations at 58, 94 and 37 positions where mostly present in the Nsp2, Nsp3 Spike and ORF9 regions reveals that many effective mutations are happening across the continents and ORF9 could be a potential candidate for studying about the mutation after Spike protein. Such a virus when possess one or more novel mutations are mentioned as the original virus variant and are classified as variants of concern, variants of interest and variants of high consequence [10].

## Variants of concern (VOC)

A variant is considered as a variant of concern when there is evidence of an increase in transmissibility, more serious diseases with increased number of hospitalization or death rates, significant reduction in neutralization by antibodies generated through previous infection or vaccination, decreased vaccination efficiency of diagnostic detection failures when reported [10]. VOC might require one or more appropriate public health actions like notification to World Health Organization (WHO), reporting to Center for Disease Control and Prevention (CDC), local and regional efforts to control spreading, increase the number of testing or research to determine the vaccine efficiency and treatments (Data collected from CDC.https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Concern). Important variants of concern are given in Table 1.

| WHO Label | Pango Lineage | Origin | Key Spike mutations | Other mutations | Characteristics |
|---|---|---|---|---|---|
| Alpha | B.1.1.7 | United Kingdom | 69del, 70del, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N | T1001I, A1708D, I2230T, Q27stop, R52I, Y23C, D3L, S235F | 1. ~50% increased transmissibility<br>2. Increased hospitalization and death rate due to severity.<br>3. No impact on EUA monoclonal antibody treatments<br>4. Little impact on neutralization by convalescent and vaccination sera. |
| Beta | B.1.351 | South Africa | D80A, D215G, 241DEL 242DEL, 243DEL, K417N, E484K, N501Y, D614G, A701V, L18F, R246I | T265I, K1655N, H2799Y, S2900L, K3353R, D4527Y, T5912I | 1.~50% increased transmissibility<br>2. Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment.<br>3. Decreased neutralization by convalescent post vaccination sera.<br>4. Increased risk of reinfection. |
| Epsilon | B.1.427 | California, USA | L452R, D614G | | 1. ~20% increased transmissibility<br>2. Accessible to monoclonal antibodies but have moderate decrease in the susceptibility to the combination of bamlanivimab and estesevimab.<br>3. Decreased neutralization by convalescent and post vaccination sera. |
| Epsilon | B.1.429 | California, USA | S13I, W152C, L452R, D614G | | 1. ~20% increased transmissibility<br>2. Accessible to monoclonal antibodies but have moderate decrease in the susceptibility to the combination of bamlanivimab and estesevimab.<br>3. Decreased neutralization by convalescent and post vaccination sera. |
| Gamma | P.1 | Japan/Brazil | L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y,D614G, H655Y, T1027I | | 1. Significantly decreased susceptibility to the combination of bamlanivimab and estesevimab but feasible to EUA monoclonal antibody treatment.<br>2. Decreased neutralization by convalescent and post vaccination sera.<br>3. Increased ~2.4% transmissibility<br>4. No significant evidence on its severity and or mortality.<br>5. Possible high risk of reinfection |

Table 1: Important variant of concern, their mutations, and characteristics

All these variants share a common predominant mutation D614G. E484K and N501Y are present in all except B.1.427 and B.1.429. D614G is a nonsynonymous mutation affecting SARS-CoV2 infectivity by replacing an aspartate with glycine at the position 614 of the spike glycoprotein [10]. Raghav and colleagues reported that this mutation increases spike protein interaction with the Transmembrane serine protease 2 (TMMPRSS2) which is responsible for shedding of the subunit S1 from S2 [11]. Korber and colleagues reported that this mutation is responsible for the increased infectivity due to a higher RNA viral load in the respiratory tract of patients [12]. It is also reported that D614G mutation increase the infectivity by enhancing S protein incorporation into the virion [13]. Mutations N501Y and E484K are in the receptor-binding motif (RBM) of the spike glycoprotein where the virus contacts with the hACE2 receptor [10]. Mutation N501Y take place at the position 501 to change the amino acid asparagine to tyrosine, as this is in one of the six important RBM sites, causes alterations in antigenicity whereas in the mutation E484K amino acid glutamic acid changes to lysine at the position 484 [7]. Reports say that co-occurrence of N501Y mutation and E484K mutation can make large conformational changes in the spike glycoprotein structure also.

## Variant of interest

When a SARS-CoV-2 variant in comparison with the reference isolate acquires changes in virulence, antigenicity, epidemiology, changes that have a negative effect on the available diagnostic protocols, vaccines, and therapeutics, is known as a variant of interest. They possess mutations that trigger amino acid changes and are considered as a causative agent of community transfer [10]. Appropriate public health actions are needed for a variant of interest like upgrading existing laboratory protocols and epidemiological investigations to find out the intensity of infection spreading, severity of the disease, effectiveness of the treatment and to check efficacy of the current vaccines to control them. Important variants of interest are given in Table 2 (Data collected from CDC (https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Concern).

| WHO name | Pango lineage | Origin | Key spike mutations | Characteristics |
|---|---|---|---|---|
| Eta | B.1.525 | United Kingdom/Nigeria | A67V, 69del, 70del, 144del, E484K, D614G, Q6771I, F888L | Potential reduction in neutralization by convalescent, post vaccination sera, and EUA monoclonal antibody treatments |
| Iota | B.1.526 | New York, USA | L5F, T95I, D253G, S477N, E484K, D614G, A701V | Reduced neutralization by convalescent, post vaccination sera, and bamlanivimab-etesevimab combination treatment. |
| Kappa | B.1.617.1 | India | T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H | Potential reduction in neutralization by post vaccination sera, and EUA monoclonal antibody treatments |
| Delta | B.1.617.2 | India | T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N | Potential reduction in neutralization by post vaccination sera, and EUA monoclonal antibody treatments |
| Zeta | P.2 | Brazil | E484K, F565L, D614G, V1176F | More resistant and potential reduction in neutralization by post vaccination sera and EUA monoclonal antibody treatments. |
| Theta | P.3 | Philippines | E1092K, H1101Y, D614G | Have some of the same mutations as the other VOCs. |
| Epsilon | B.1.427/B.1.429 | California, USA | L452R, W152C, S13I, D614G | ~20% increased transmissibility decreased neutralization using convalescent and post vaccination sera. |

Table 2: Important variants of interest, their mutations and characteristics

## How the mutation helps the virus to survive with the proposed mechanisms

Entry of SARS-CoV-2virus is facilitated with the interaction of S protein with a wide range of receptors including ACE2, Dipeptidyl Peptidase 4 (DPP4), Aminopeptidase-N (ADN) and sialic acid [14]. However, studies have reported about the viral susceptibility with extra and intra pulmonary immune and non-immune cells in the absence or deficiency of ACE2 [15, 16]. Some studies propose that S-protein utilize other receptor cells for the entry and establishing an infection in host cells [17, 18]. These reports also reveal the interaction of S-protein with various immune receptors like Neurolipin-1 (NRP1), C-lectin type Receptors (CLR), Mannose Receptor (MR), Dendritic Cell-Specific Intracellular adhesion molecule-3-Grabbing Nonintegrin related (L-SIGN) and Macrophage Galactose-type Lectin (MGL), Toll-Like Receptors (TLR) 1, 4 and 6; and the non-immune receptors like Glucose Regulated Protein 78 (GRP78). These immune and non-immune receptors and the protein may introduce an alternative mechanism for

the viral entry and infection on host cells and the receptor binding motif of the S-protein interacts with ACE2 for its endocytosis into human host cells [19]. IL-1beta, Il-6 and TNF-alpha will be released in patients with serious COVID-19 resulting to immunopathological complications like vasoconstriction and pulmonary injury. There are explanations that mannosylated N-glycan and O-glycan elements of the S-protein can recognize GRP78, CLRs and TLRs and combine with them to facilitates their entry and accelerate infection on host cells [19]. Apart from that, Blood Dendritic Cell Antigen-2 (BDCA-2), Dendritic cell immunoreceptor (DCIR), C-type Lectin-like Receptor2 (CLEC2), Dendritic cell-associated C-type lectin-1 and 2 (Dectin-1 and 2), Lectin-like Oxidize low-density lipoprotein receptor-1 (LOX-1), Dendritic cell natural killer lectin group receptor-1 (DNGR1), liver and lymph node sinusoidal endothelial cell C-type lectin (LSEC) and TLR-3, 5 , 7 and 8 may not collaborate directly with the S-protein, but may have other functions in COVID-19 infection [19].

Reports are giving evidence that CD209L/L-SIGN and the related protein CD209/DC-SIGN can act as receptors for SARS-CoV-2 entry. Removing N-glycosylation sequence at the site N92 of CD209L improved binding capacity of S-RBD with CD209L and there is heterodimerization of CD209L and ACE2 that enhances the viral entry and cell infection when bind with receptors indicating that CD209L and CD209 can play as alternative receptors for the viral entry, even in vascular system [17]. ScRNA-seq analysis done by Gao et al., confirmed the expression of CLRs in bronchoalveolar and other innate immune cells and lymphoid organs indicating that DC-SIGN, MR and MGL may serve as alternative receptors for SARS-CoV-2 entry to a host cell in the absence of ACE2 [18]. Choudhury and Mukherjee studied the interaction of TLRs with the SARS-CoV-2 spike protein and found that TLR4 have a strong binding capability to spike protein and is the most potent innate immune receptor that activates proinflammatory reactions [20]. In D614G mutation, occurs a substitution of aspartic acid by a glycine at the site 614 of the S-protein potentially alter receptor binding capacity of the virus. This mutation increases viral fitness, transmission, infectivity, viral replication and thus an increased viral load in infected patients. Apart from this, D614G spike has more of 1-RBD “up” conformation which increases exposure to antibodies proposes that this mutation is unlikely reduce the vaccine ability to control COVID-19 [21].

Lineage B.1.1.7 has 17 mutations; eight of them are in the S-protein with six substitutions, and two deletions. Four mutations are on ORF1ab, three on ORF8 and two on N-protein. Three mutations N501Y, ΔH69/ΔV70 and P681H at the S- protein is critical as they are interacting with ACE2 receptor thus enhance viral transmission and infectivity. Y144 deletion contributes immune escape to many monoclonal antibodies making the existing control measures less effective [10]. Lineage B.1.351 has various mutations. Out of them K417N, E484K and N501Y are in the RBD, L18F, D80A and D215G are in the N-terminal domain (NTD) of S-protein and A710V is in the loop. N501Y mutation increase viral affinity to hACE2 receptor which in turn increases the transmission and infectivity. Mutation K417N is associated with neutralizing antibody escape which reduces protection against re-infection and the existing vaccines are less effective [21]. Lineage P.1 possess mutations like the variant B.1.351, however, P.1 is more resistance to neutralization monoclonal antibodies due to the E484K mutation at the RBD [10]. Deng and colleagues reported that B.1427/B.1429 carries S13I, W152C and L452R mutations in the spike protein and causes an increase in transmissibility and resistance to neutralization by antibodies obtained from the previous infection or vaccination [22]. L452R mutation stabilized the interaction of spike protein and ACE2 receptor by making structural changes in the region that promotes the interaction among them. Mutations W152C and S13I increases the infectivity. They propose that the mutation of L452 residue in a hydrophobic pocket induces conformational changes in RBD because of the neutralization of antibody binding.

## Conclusions

There are several studies highlighting the mutations occurred to Covid-19 virus resulting in the generation of new mutant variants. These variants have high virulence and have immense capacity to survive in the host cell and further progress transmission of the infection in an integrated way. Survival of the virus in a host cell as per the genetic alterations needs to be considered as an adaptive mechanism by the virus for its survival. Irrespective of the variants, mechanisms adopted to survive in host cell is unique and that modifies the receptors and other cells according to the viral fitness and survival. It should be considered that the viral mutation is a drastic one to generate new variants for survival as per the host environment and other conditions. In accordance with that when treatment strategies are planned, should be equipped with measures to overcome these genetic alterations, and should be targeted to the specific variants for better prognosis. Much more genetic studies are needed in this aspect to eradicate the pandemic at the earliest.

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