Review Article

Emerging Variants of SARS Cov-2 "A New Challenge of 2021 for the World"

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Abstract

The emergence of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOC) possess a significant threat to international public health because of the rapid variations in the SARS-CoV-2 genome, that may alter viral phenotype such as virulence, transmissibility, and ability to evade the host immune responses, making diagnostic & clinical management more difficult. The most prevalent variants of concern (VOCs) share mutations in the spike protein encoding gene secondly, on its S1 unit. United Kingdom, South Africa, Brazil, and India are among the highlighted regions for the reported cases of the emergent variants of concern. This literature study aims to discover and describe existing SARS-CoV-2 mutations that are responsible for the origin of novel variants with the special focus on the newly emerged deadly Indian Variant "Delta Variant (B.1.617.2). Secondly, the effectiveness of the vaccines against the emerging variants has also been discussed.

Keywords: SARS-CoV-2, Variants, Delta Variant, B.1.617.2, Mutations, variants of concern (VOCs), Vaccines, Spike protein

1. Introductıon

By the end of December, 2019, the world got trapped by a life threatening lethal virus, known as the "*Coronavirus*" that was declared as a cause of the pandemic, by World Health Organization (WHO) in March, 2020 [1]. The COVID-19 was first reported in "Wuhan", the capital of "Hubei Province" in China [2]. Covid-19 pandemic has been reported as the 5th flu pandemic after 1918's pandemic [3, 4]. Unfortunately, the causative agent, novel coronavirus, proved to be deadly. Scientifically, the classification of coronavirus is followed as order *Nidovirales*, family *Coronaviridae*, and genus *β-Coronavirus* [5, 6]. Different studies have showed that this novel coronavirus is evolved from SARS Coronavirus, so it is named as "SARS Coronavirus 2 (SARS-CoV-2)" [6, 7]. By the passage of time the COVID-19 is becoming devastating due to the variation in its causative agent [3]. According to CDC ten different variants of SARS-CoV-2 have been reported within eighteen months of this pandemic [8]. The reason for this huge and quick variation is its positive sense single-stranded RNA based genome [9, 10, 11]. The mutation rate of RNA genome is always high due to low rate of proofreading activity of "RNA-dependent RNA Polymerase (RdRP)" and in case of SARS-CoV-2 this high mutation rate is leading to the continuous evolution of this virus [12]. Another reason for the rapid change in the Coronavirus genome is its ability of genetic recombination [11, 13]. The four variants alpha, beta, delta, and gamma have got special attention and are termed as Variants of Concern [8]. The phylogeny of these emerging variants with the passing time is depicted in the (Figure 1). Eleven protein coding genes are present in SARS-CoV-2. Mutations in both structural and non-structural proteins have been reported [14]. But the mutations in spike (structural) protein is the main area of interest (Figure 2).

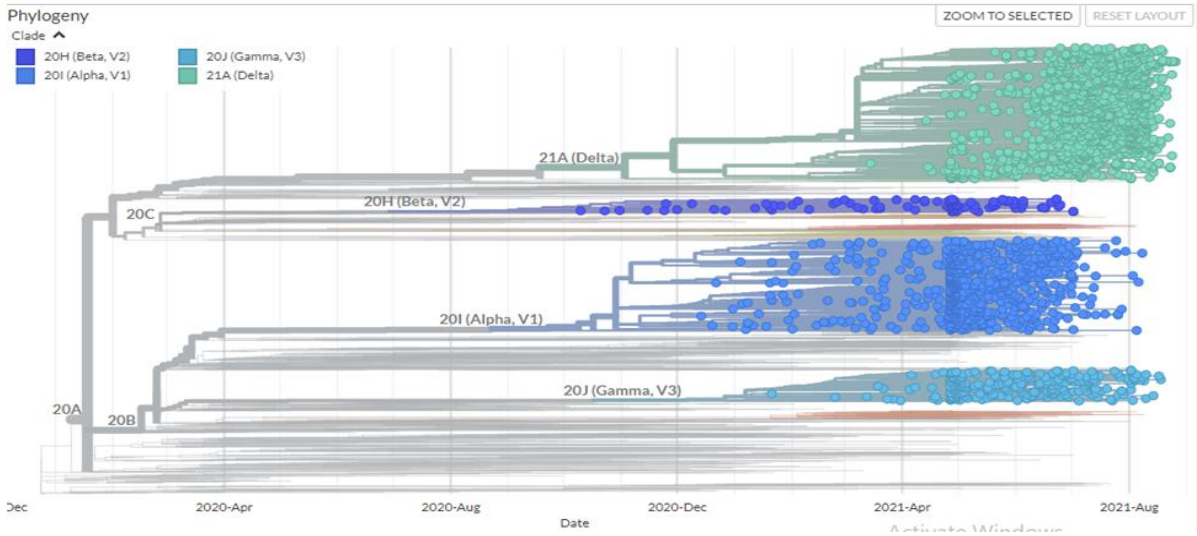

Figure 1: Phylogeny of the emerging clades of Coronavirus

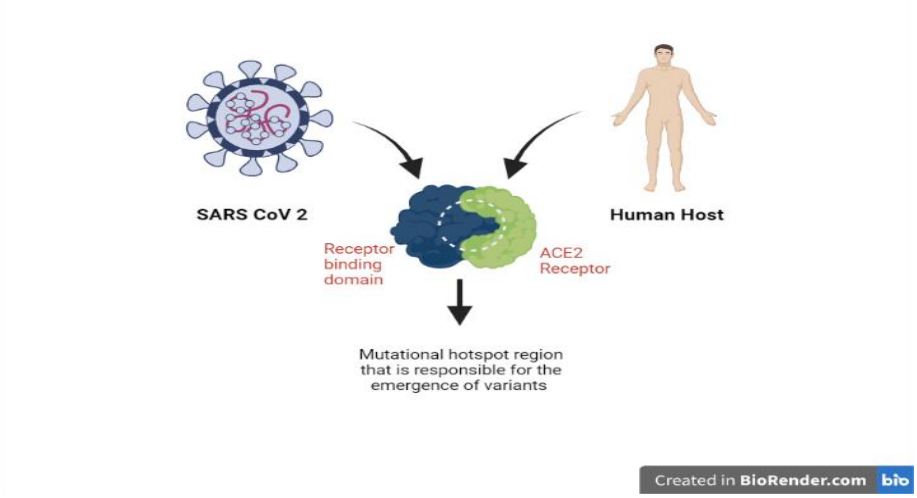

Figure 2: Mutational hotspots for the generation of SARS- CoV-2 variants

Spike (S) proteins are present on the outer surface of coronavirus [8, 15, 16]. The virus uses the receptor binding domain (RBD) of spike protein as a key to enter into host's cell [17]. The RBD of spike protein interact with "Angiotensin-Converting Enzyme 2 (ACE2) receptor" present on the plasma membrane of host's cell [17, 18]. The expression of ACE2 receptor is observed mainly in lungs which makes lungs more susceptible to coronavirus infection [19]. Beside lungs ACE2 receptors are also expressed in heart, kidney, and endothelial cells of intestine [20]. The mutations in the spike (S) protein are making SARS-CoV-2 more contagious and transmissible. Mutated S protein is a result of missense mutation in one of the codon of ORF2 gene, the 2nd largest gene of the virus [14]. This mutation is primary cause for the evolution of "Variants of Concern (VOC)" of SARS-CoV-2. The mutation has led to multiple spike protein substitutions among the variants of concern but the D614G substitution in S protein is common to all variants and step up the interaction of S protein and ACE2 receptors of human cells [21]. A summary of SARS-CoV-2 VOC is provided in following table with special reference to spike protein substitutions (Table 1).

Table 1: Summary of SARS-Cov-2 Variants of Concern (VOC) [8]

WHO Label	First Identified Location	Pango Lineage(s)	Name (Nextstrain)	Spike Protein Substitutions
Alpha	United Kingdom	B.1.1.7	(20I/501Y.VI)	69del, 70del, 144del, A570D, D1118H, D614G, E484K, K119N, N501Y, P681H, S494P, S982A, T716I
Beta	South Africa	B.1.351 B.1.351.2 B.1.351.3	(20H/501.V2)	241del, 242del, 243del, A701V, D80A, D215G, D614G, E484K, K417N, N501Y
Delta	India	B.1.617.2 AY.1 AY.2 AY.3	(21A/S:478K)	A222V, D614G, D950N, E484K, G142D, K417N, L452R, P681R, R158G, T19R, T95I, T478K, V70F, W258L
Gamma	Brazil/Japan	P.1 P.1.1 P.1.2	(20J/501Y.V3)	D138Y, D614G, E484K, H655Y, K417T, L18F, N501Y, P26S, R190S, T20N, T1027I

2. SARS-CoV-2 Delta Variant (B.1.617.2)

At the present time, the "SARS-CoV-2 Delta Variant (B.1.617.2)" commonly known as "Indian Variant" has got a serious attention of the world. The delta variant was first appeared in "India" at the end of 2020 and has now spread in 80-90 countries of world [22, 23]. This Delta lineage is categorized into the 3 sub-groups "B.1.617.1", "B.1.617.2", and "B.1.617.3". Out of these three subgroups B.1.617.2 has been declared as the Variant of Concern {VOC} and increased infectivity rate is the major reason behind it [24].

3. Prevalent mutations in Subgroup "B.1.617.2" Delta variant

According to the **"**Whole-Genome Sequence Analysis of DELTA Variant at Ayass Bioscience, LLC", (B.1.617.2) has been originated due to the 09 most prevalent mutations in spike gene, out of which 5 mutating regions resides in "N Terminal domain", one mutation in the "Furin Cleavage site", one mutation in "Spike S2 subunit and two mutation in the "Receptor Binding Domain (RBD) [24]. All the mutations that contribute in the emergence of the delta variant are enlisted in the (Table 2). The prevalent mutation in the emerging variant has been shown in the (Figure 3).

Figure 3: Mutations with > 75% prevalence in lineage B.1.617.2 [24]

Table 2: Characteristic Mutations of "B.1.617.2" Delta Variant [24]

Gene	Amino Acids
ORF1b	**P314L**
ORF1b	**G662S**
ORF1b	**P1000L**
S	**T19R**
S	**G142D**
S	**E156G**
S	**del157/158**
S	**L452R**
S	**T478K**
S	**D614G**
S	**P681R**
S	**D950N**

ORF3a	**S26L**
M	**I82T**
ORF7a	**V82A**
ORF7a	**T120I**
ORF8	**D119I**
ORF8	**del120/121**
N	**D63G**
N	**R203M**
N	**D377Y**

4. Transmissibility of Delta variant

It has been showed that delta variant is more transmissible and contagious than other variants of concern [25, 26, 27]. On 22nd May 2021, Public Health England said that it is likely that delta variant is more transmissible than alpha variant and the magnitude of the change in transmissibility remains uncertain [28]. Public Health Sectors across the world are facing difficulties to cope with the delta variant because of its resistant to basic preventable measures for COVID-19 disease.

The delta variant is responsible for almost 90% of COVID-19 cases in India and United Kingdom (UK). The rate of delta variant transmission is so high that it accounted for 20.6% cases of COVID-19 from early May 2021 to early July 2021 in US [23]. According to an estimation delta variant is approximately 60% more transmissible [29]. A study conducted in "Guangdong Province" of China also showed that delta variant possesses short generation time and incubation period with high reproductive number which are the key factors for high transmission rate and 97% increased transmission rate was observed [30]. It has been showed that delta variant is not only responsible for rise in COVID-19 cases, but it is also displacing the "SARS-CoV-2 Alpha Variant". The rapid growth rate of delta variant is the main cause for this displacement and cases of alpha variant has dropped by 28% within two months of April and May 2021 in US and obviously the spike protein substitutions are main cause of this rapid transfer of virus. Beside D614G spike protein substitution, the E484K, P614R, T478K, and L452R are also the key substitution in spike protein and responsible for increased transmission rate of delta variant [23, 31].

Different substitutions contribute in its own to increase the transmissibility of virus. The L452R substitution weakens the process neutralization of delta variant by antibodies [32]. The T478K and E484K substitutions help escape of delta variant from antibodies [33].

5. Characteristics of Delta Patients

Age group and gender characteristics based data has been mentioned in the (Figure 4, 5).

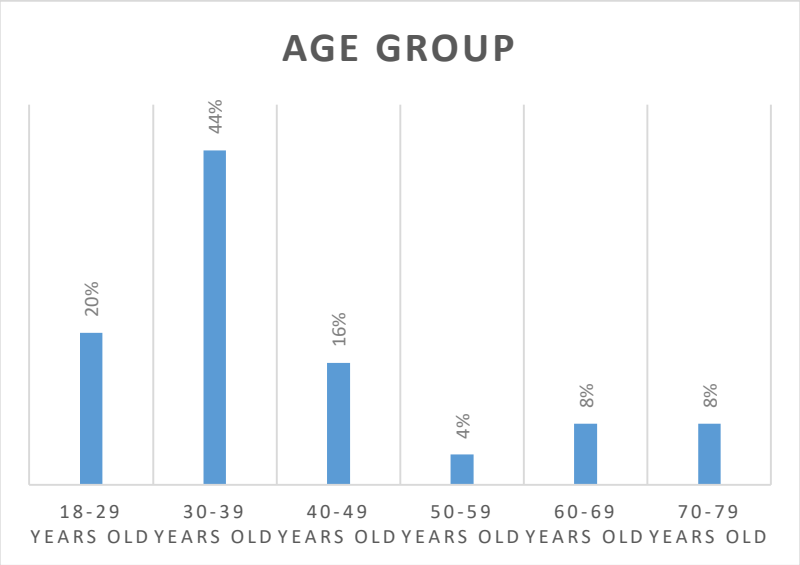

Figure 4: Prevalance of Delta variant in different age groups

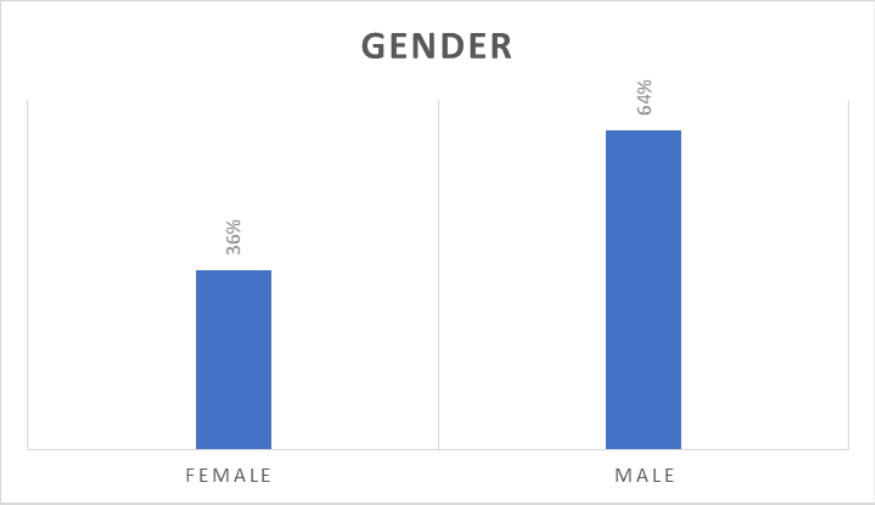

Figure 5: Prevalance of Delta variant according to gender

6. Signs, Symptoms and Antigenicity of Delta variant

The sign and symptoms caused by delta variant are mostly common with other variants of concern, but the rate of hospitalization of patients infected with delta variant has found to be high at least 2 times compared with alpha variant [34, 35]. Emerging variants are basically associated with the changes in the RBD, and it has been observed that the novel variants exhibit the decreased neutralization by the previously generated antibodies via Natural infection or by the Vaccination. A study has showed that some monoclonal antibodies were not able to bind with the S protein of delta variant and failed to neutralize it. The delta variant possesses a little response to sera collected from naturally immunized persons. But the vaccination of people infected previously from COVID-19 has showed a protective role of vaccines against VOC including the delta variant. In contrast, in non-vaccinated people the delta variant is more likely to neutralize the antibodies and finds its way easier to enter inside the host cell [30]. A reporting has also showed that delta variant is spreading even faster in countries having low vaccination rate.

7. Effectiveness of Vaccines against the variants

Scientists and different vaccine manufacturing companies are now in continuous effort to find whether the vaccines against alpha variant are also effective against delta variant or not. Surprisingly, some analysis has showed that vaccines against alpha variant are also effective against delta variant [36, 37]. PHE said, " The data of rising COVID-19 cases shows that there is a high risk of hospital admission for patients with delta variant compared with alpha variant, but the analysis revealed that two doses of vaccine will provide a high degree of protection against hospital admission, estimated to be more than 90% [27]. RNA based "Pfizer-BioNTech" has found to be 88% effective against COVID-19 caused by delta variant. The non-replicating viral vector based "AstraZeneca" has found to be 60% effective against COVID-19 caused by delta variant [23]. The "inactivated SARS-CoV-2 vaccines" have proved to be 59% effective against the delta variant [38]. The 1st wave of COVID-19 pandemic has already caused a havoc in the world. The lockdown strategy has affected mainly the economy and education system across the world [39, 40]. The global community is still facing the impacts of first wave caused by alpha variant and at the meantime second wave of delta variant is also rising. The vaccination process has proved to be effective against this pandemic, but the rate of vaccination is still low in many countries and also the emerging strains of COVID-19 virus showed some resistance to the vaccines. Thus, a long-term planning is still required against the COVID-19 pandemic [41].

8. Strategy used by mRNA based vaccines (PfizerBionTech and Moderna-1273) against variants

As the pfizer and Moderna are the mRNA based vaccines and have depicted the highest efficacy against the SARS-CoV-2 [42], so manufacturers of both the vaccines are trying their level best to made it effective against the emerging variants as well. These vaccines have the mRNA of spike protein gene and it has been reported that many of the mutational regions in the emerging variants also belong to the S gene. So, the manufacturers are changing the Spike protein gene in accordance with the acquired mutation so that the vaccine could be effective against these variants [43]. It has been depicted in the (Figure 6).

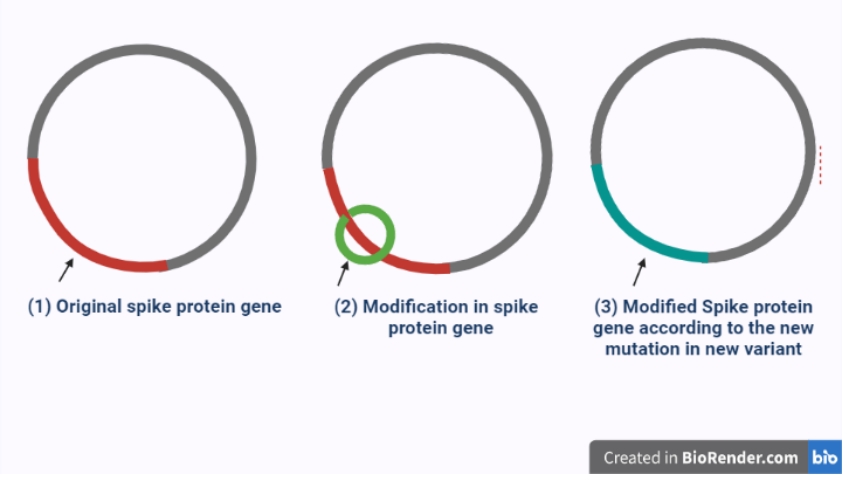

Figure 6: Modification of the spike protein gene in order to make the effective Pfizer/Moderna vaccine against newly emerged SARS CoV-2 variants

9. Therapeutic Efficacy against the Delta variant

It has been reported that the "B.1.617" Delta variants, S protein-mediated entry can be effectively prohibited by the "Etesevimab (LY-CoV016)" secondly by the "Imdevimab (REGN10987)" and can also be inhibited by the combination of Casirivimab (REGN10933) and Imdevimab [44]. On the other hand, B.1.617 was resistant against Bamlanivimab (LY-CoV555) [45].

10. Diagnostic Efficacy for the Delta variant

In accordance with the current situation, the already present dignostic molecular tests are able to detect the patient infected with the variant of SARS CoV-2 but in order to find out about the type of the variant, one must undergo the sequencing analysis of the genomic sample. Now a days the reported variants have the frequent mutations in the S protein region of the gene, so the target site of currently designed molecular test also contains some conserved regions in addition to the S gene regions, such as the multiplex RT PCR has the main 3 target regions: N genes, ORF1ab, E genes [44].

11. Conclusion

Millions of people have died as a result of the highly contagious SARS-CoV-2 (COVID-19) virus. It is the source of a worldwide pandemic, and its mutations result in genetic variations that are yet unknown. Emerging VOCs have the potential to affect clinical and global health outcomes, emphasizing the need for genomically tailored therapeutic approaches in the future. Also, it's critical to provide fair access to COVID-19 vaccinations while simultaneously focusing on the repositioning or finding of an effective SARS-CoV-2 medication. Until then, current vaccinations are the sole effective weapon in the fight against SARS-CoV-2 and its variations. Newly developed mRNA based vaccines have exhibited the potential to directly target both existing and emerging SARS-CoV-2 variants. On the other hand it is challenge for the scientists to make the other vaccines effective against these emerging contagious variants.

Conflict of Interest

All the authors don't have any conflict of interest regarding this manuscript.

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