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The SARS-CoV-2 Genome, its Variants and their Various Way of Immunization

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Abstract:- COVID-19, severe acute respiratory syndrome (SARS-CoV-2) being causative agent of the major outbreak of respiratory infection with a very low mortality rate. In this review article, we discuss here the basic virus of SARS- CoV-2, including the genome and its proximal origin, the specific mutations, the global variants, its adverse epidemiology, various therapies and immunization against the SARS-CoV-2

Keywords:- *SARS-CoV-2, GLOBAL VARIANTS OF CORONAVIRUS, EPIDEMIOLOGY, IMMUNIZATION, MUTATIONS, VARIANTS, VACCINE, MONOCLONAL ANTIBODIES, SARS, MERS.*

I. INTRODUCTION

SARS-CoV-2 genome and its proximal origin:

By the end of December 2019, a member of highly infectious group of viruses known as the corona virus, it was designated as SARS-CoV-2 making corona viruses an emerging health concern twenty first century[1]. The outbreak took place as an unusual viral pneumonia in the city of Wuhan, China. Later on slowly it becomes global threat[3].

Coronavirus is a notorious group of viruses having extreme definition of virulence by the mechanism it causes and infects the range of pathogenicity, the ability to go undetected by the immune response. They usually find to infect different animals and can induce very mild to fatal infections (usually related to the respiratory and pulmonary systems)[1]. These enveloped viruses are accompanied by a positive single stranded RNA genome of about approximately 30,000 bases with 5' cap structure and 3' poly a tail belonging to coronaviridae family[2].

They are genetically categorised into four important genera: Alpha coronavirus, Beta coronavirus, gamma coronaviruses, and Delta coronavirus. The Alpha and Beta coronaviruses infect humans and mammals, gamma coronavirus usually infects the aves and Delta coronavirus predominantly infects reptiles[2].

The SARS-Cov-2 causative agent of the present coronavirus disease (COVID-19) belongs to genus Beta-CoV which makes if the third major coronavirus outbreak in the last 20 years after SARS(severe acute respiratory syndrome) and MERS (middle east respiratory syndrome) in 2002 and 2012 respectively[1].

SARS-CoV-2 genome tends to show similarity in the proximal genome origin to SARS and MERS. The genome of coronaviruses usually includes diverse number of open reading frame (ORF). Initial 5' ORF(ORF 1a/b) usually makes up about 2/3 of genome and gets translated in the host cell via the rough endoplasmic reticulum. It translates the rough endoplasmic reticulum into pp1a and pp1ab protein which get cleaved by proteases and yield 16 non-structural proteins (nsp 1-16)[3].

The 3' ORF has equivalence to the remaining third of genome comprising of accessory and structural proteins. The 6 accessory proteins are encoded by ORF 3a, ORF 6, ORF 7a,ORF8aand ORF10 genes. Their functions are unknown[2]. The 4 major structural proteins are: the surface spikes(s) protein that identifies receptors of host cells [angiotensin converting enzyme 2(ACE2)] binds to it and guides the penetration of virus into host cell and envelope(E) protein, the matrix protein(M) and nuecleocapsid(N) protein binds RNA and is significant for assembly[3].

Proteins encoded by ORF1a and ORF1ab are crucial for replication of the virus. Except for in the S gene, 90% of the amino acid entity of SARS-CoV-2 is similar to SARS-CoV.By studyingthe five conserved replicative domains at pp1 ab (3CL pro, ZBD, HEL1, NiRAN, RdRp), the coronairidae study group of international committee of taxonomy of viruses had estimated patristic distances between that of SARS-CoV-2 and known viruses and SARS-CoV-2 got assigned as being distinct from all bat and tangolins[3]

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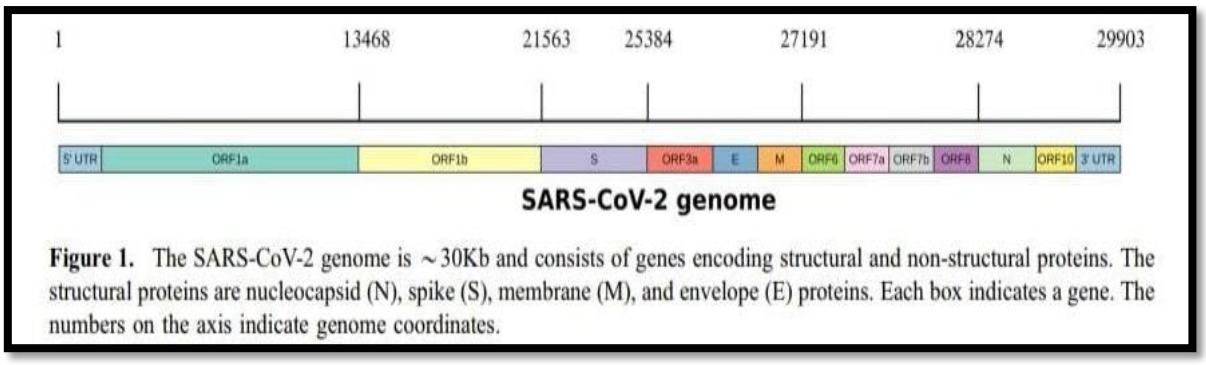

Figure 1. The SARS-CoV-2 genome is ~30Kb and consists of genes encoding structural and non-structural proteins. The structural proteins are nucleocapsid (N), spike (S), membrane (M), and envelope (E) proteins. Each box indicates a gene. The numbers on the axis indicate genome coordinates.

II. MUTATION

A higher virulence was observed with SARS-CoV-2 variants with G614 gene in the S protein replaced by original variants since March2020. There is no clinical support between the D614G alternation and its increased pathogenicity[2]. Viruses with S protein along with G614 showed much infectious tires than viruses with S protein along with D614[1].

Another important significant SARS-CoV-2 mutation for evaluation becomes the polymorphism of the nucleotide at position 28,144A of the nucleotide resulting in substitution of Amino acid for ORF8 protein at Ser for Lys at residue. These made a sub clade named 'clade S'[1].

Many studies have revealed the mutation in the spikes protein of SARS-CoV-2 which elaborates the mutation of D614 G point of the spikes protein. There are a numerious point mutations including one in the polymerase gene[1]. A delection in the ORF7a gene and a detection in the nsp2 gene has been an extensive report. Recently an analysis of the data set of more than 17,000 sequences from GISAD showed detection of 9 nucletide in nsp1 gene (nucleotides 686 to 694 corrsponding to amino acid 241-243) frequencies of genome deletion was 0.44% [2].

More than 28,000 spikes gene sequenced in May 2020 showed a D614 G mutation. C and T mutation in the 5' unstable region at position 241, a non-synonymous C to T mutation at position 1440 and in RNA polymerase gene and a synonymous C to T mutation at position 3037[2].

The D614G mutation with higher nasopharyngeal RNA in patients infected with SARS-CoV-2 supported for an advantage of mutation in transmission[1].

Table 1:- A representation of Various Variants of SARS-COV-2 in different countries around the globe and it's attributes.

Name (Pango lineageexternal icon)a	Spike Protein Substitutions	Name (Nextstrainexternal iconexternal icon)b	WHO Labeld	First Detected	BEIexternal icon Reference Isolatec	Attributes
B.1.525	**Spike**: A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L	20A/S:484K	Eta	United Kingdom/Nigeria – December 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Potential reduction in neutralization by convalescent and post-vaccination sera 22

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B.1.526	**Spike:** (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)	20C/S:484K	Iota	United States (New York) – November 2020	NR-55359external icon	Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment; however, the clinical implications of this are not known.7 Alternative monoclonal antibody treatments are available.14 Reduced neutralization by convalescent and post-vaccination sera 22, 24
B.1.526.1	**Spike:** D80G, 144del, F157S, L452R, D614G, (T791I*), (T859N*), D950H	20C		United States (New York) – October 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Potential reduction in neutralization by convalescent and post-vaccination sera22
B.1.617	**Spike:** L452R, E484Q, D614G	20A		India – February 2021		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Reduced neutralization by post-vaccination sera 25, 26
B.1.617.1	**Spike:** (T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	20A/S:154K	Kappa	India – December 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Potential reduction in neutralization by post-vaccination sera 26

ISSN No:-2456-2165

B.1.617.2	**Spike:** T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N	20A/S:478K	Delta	India – December 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Potential reduction in neutralization by post-vaccination sera 21
B.1.617.3	**Spike:** T19R, G142D, L452R, E484Q, D614G, P681R, D950N	20A		India – October 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Potential reduction in neutralization by post-vaccination sera 26
P.2	**Spike**: E484K, (F565L*), D614G, V1176F	20J	Zeta	Brazil – April 2020		Potential reduction in neutralization by some EUA monoclonal antibody treatments 7, 14 Reduced neutralization by post-vaccination sera 22, 23

III. VARIOUS VARIENTS OF COVID 19

IOTA VARIANT:

The WHO received various reports of anegative impact on the health of people due to the SARS-CoV-2 pandemic.

Variants SARS-CoV-2 with a D614G substitution in the gene encoding the spike protein emerges in late Germany or early February 2020. Earlier report of the D14G mutation variants of SARS-CoV-2 from the United Kingdom of grate Briton, north on island, kingdom of Denmark republic of South Africa,Brazil, California of great concern [6].

Various studies conducted across the world in different animal model demonstrate that DG14G mutation has increase the pathogenicity and virulence of strain [1].

United Kingdom of Great Britain:

The variant got identical in genomic surveillance by covid-19 genomic UK/COG-UK. It is aconsolium which goes analysing genome sequence and data all around UK-COG-UK is the largest contributors to the global covid-19 database GISAID [5].

The variants specifically results in multiple mutation of the gene encoding for the spike protection of the SARS-CoV-2 along with genome region of the RNA nucleotide. Deeper subjective analysis suggests that it is much more of virulent strain with increase transmissibility and pathogenicity than the previous variant circulation [6].

COG-UK recognises one of these mutations as N501Y at a point in the spike protein that usually binds to the ACE 2receptor. Locus of mutation in the receptor binding domain of spike glycoprotein increases the probability that the variant is antigenically distinct from the variants priorly [5].

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European centre for disease prevention and control claimed that the phylogenetic analysis announce that the cluster differ by 29 nucleotide substitution from the original Wuhan strain [6].

Variant D614Gbeing the previous dominant strain due to increase chance of infection and transmissibility showed around 4000 mutation in the spike protein [6].

Epidemiological dynamics of the SARS-CoV-2 in the South Africa:

The outbreak of the second wave of Covid-19 epidemic began around on October 2020. Along with DG14G five more and non-synonymous mutations resulted in spike protein D215G, E484K, N501Y, A701V, D80A. Additionally three more mutation leads to substitution in the spike protein emerged at end November (R2461,K4171,L18F) a fue samples also showed deletion of three amino acids from position 242 to 244 across NGS-SA [7].

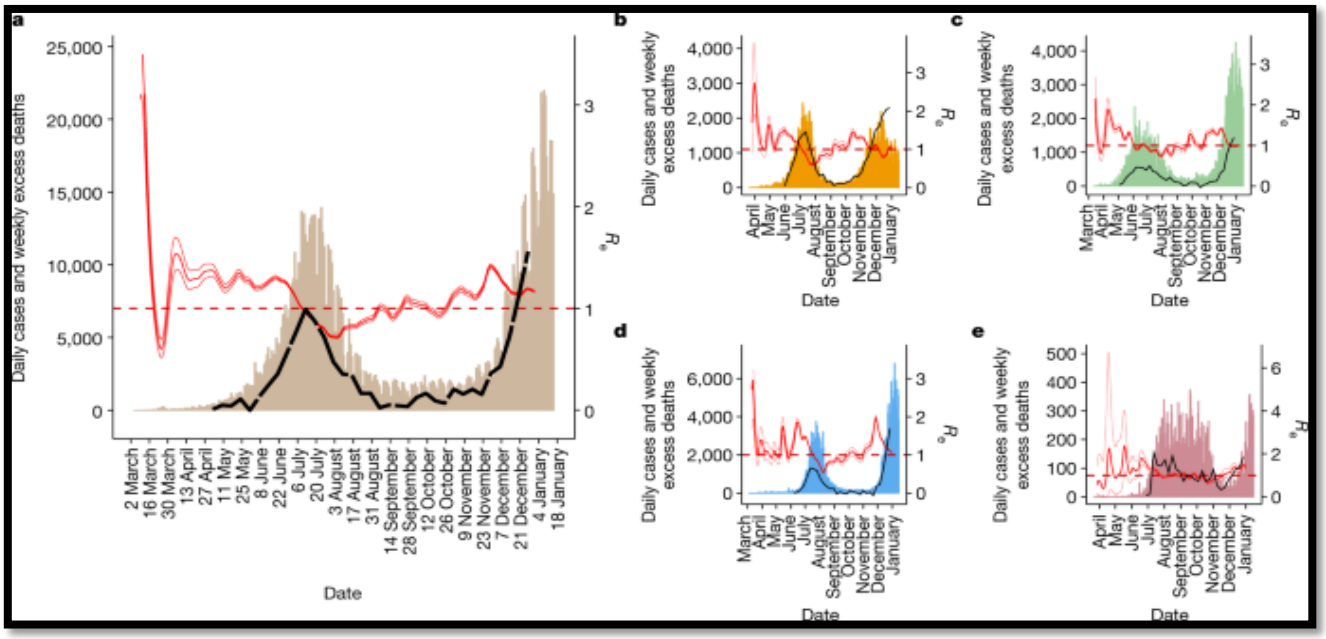
Main lineage identified in South Africa during first wave (B.1.1.54, B.1.1.56 and C.1) in the spike protein mutation (D614G) [6].

Variant got detected through intensified genomic surveillance that evicted in response to arapid resurgence 501Y,V2 uses detected in sample from 196 health centres. The rapid expansion of 501Y.V2 and almost complete displacement of others lineage in multiple regions strongly suggest a selective advantage for this variants [1].

501Y.V2 lineage has three substitution affect key sites in RBD (K41 7N, E484K and N501Y). N501Y substitution has identified in lineage in UK designation-B.1.1.7) [7].

N501Y Substitution previously had shown through deep mutation seining to increase binding capacity to ACE receptor and immune escape from neutralization antibodies in convalcent plasma [6].

Figure 2:- Dynamics of Epidemiology of SARS-COV-2 mutant variants in South Africa.



ZETA variant/ Covid 19 reorts from Brazil:

In Brazil until April 14th 2020 mortality rate was (5.68%). It is P.1 strain which is support to be more fatal but shows less transmit ability by the original Covid 19 strain [6].

It has 17 amino acid changes 10 from spike protein and 3 designated to be N501Y, E484K and K417T. it was first identified by (NIID) national institute of infection Diseases, Japan.

It has been labelled gamma variant by the WHO. It has two distant sub variants 28-AM-1 and 28-AM-2 and both carry E48K, K417T, N501Y mutations. It was first detected in October 2020 in Rio de Janerio, Brazil

THETA- variant

P-3 variant got identified in Philippines on 18th Feb 2021, it has lineage from P.1 variant and both these variants have a lineage B.1.1.28 [6].

DELTA variant- lineage- B.1.617:

It was discovered in India in October 2020. It spread over at least 20 countries and was selected in about 53 countries. Public health England (PHE) designated B.1.617 as variants under investigation, VUI-21 April 2021. It was a synonymous mutation [8].

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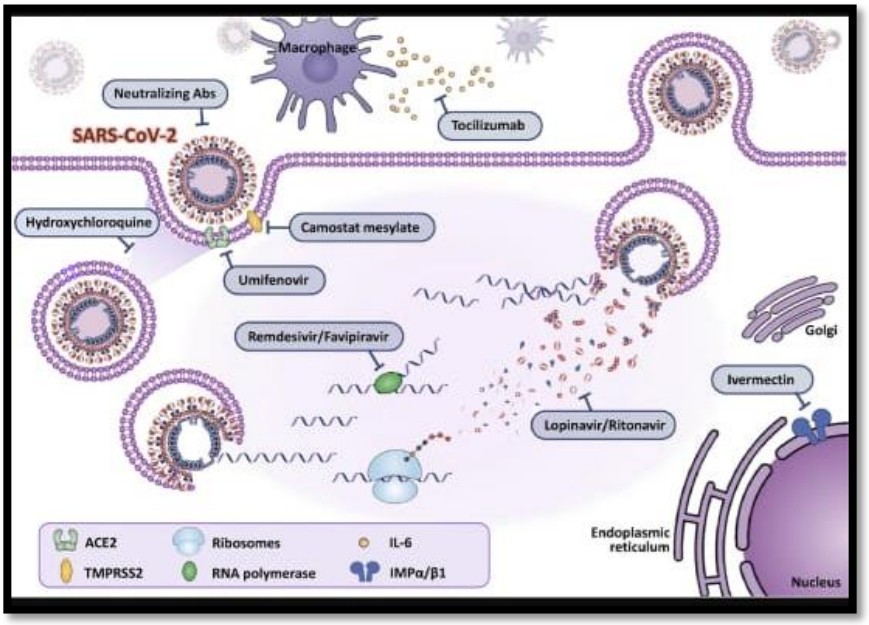
IV. IMMUNIZATION

All aged people amonst specific populationare susceptible to SARS-CoV-2 and it can suffer from its virulating pathogenicity. Clinical treatment does differ with age and for age[1]. Generally, older people with an age of more than a 60 years are more likely to develop a severe infection. Severe pulmonary diseases are likely to developed and its health care includes hospitalization and in many unfortunate cases the patient tents to die [2].

Young people and children might catch only mild symptoms of the infection or go asymptomatic.Risk of infection is not much higher in pregnant women either[1].In December 2019, in Wuhan,China early transmission of SARS-CoV-2 was linked withsea foodmarket. It is known that transmission of Corona Virus is much higher than previous SARS-CoV and MERS. It wasassumedthat the RO of 2.5 has been proposed for SARS-CoV-2 compared to 3.0 for SARS-CoV[1].



[4]

Figure 3:- Immunization against SARS-CoV-2

V. DIAGNOSIS

Molecular detection of SARS-CoV-2 nucleic acid is detected using kits targeting ORF1b (RdRp), N,S,E genes. Corona Virus got detected from a range of different respiratory and pulmonary sources. The viral load being higher in lower tract of the respiratory system[4]. Rarely, viral RNA samples were also detected in the intestinal tract through respiratory samples were found to be negative[3].

Chest CT could quickly identify a patient when molecular detection went busy. CT scanning along with swab test would be performed among patients testing negative at nucleic acid screening. Exent of accuracy in various serology test are nuclear and differ in sensitivity to results[4].

Chloroquine and hydroxychloroquine have been controversial drugs that create hindrance in entry portal and transmission of SARS-CoV-2. These drug tends to usually prevent glycosylation of receptors and increase the PH while interfering with membrane fusion[1].

Blocking the strategy of S protein binding to the ACE via soluble recombinant hACE 2, specific monoclonal antibodies and fusion inhibitors have proven as a potential therapy[3].

Nucleotide replication inhibitors comprise flavilavir(T-105), ribaviridin, remdesivir(GS-5734), lopinavir and ritonavir[2].

Immunomodulatory agent inhibit the inflammatory response, dexamethasone is used. Tocilizumab and sarizumab, 2 types of interflukin specific antibodies attenuate the cytokine[2]. Bevacizumab is an anti-vasual medication (VEGF) reduces pulmonary edema. Eeulizumab being a monoclonal antibody inhibits proinflammatory complement protein C5[1].

Convalescent plasma therapy and the most effective method being vaccination are used for COVID 19 control [4].

VI. CONFLICT OF INTEREST

The COVID-19 pandemic has put enormous strain on our health-care systems, highlighting the critical role of molecular evolution, as outlined in this article. Significant progress was made in the fight against anomalous pneumonia just a few days after the first cases were reported: the virus was isolated, sequenced, recognised, and genetically defined within a few days. Because of its evolutionary connection to SARS-CoV corona viruses, it was given the designation SARS-CoV-2. Molecular and serological assays have been examined and are now used in regular diagnostics based on its genetic characteristics. This

article depicts the latest review on the molecular evolution,immunological treatment and epidemological distribution of the SARS-CoV-2 virus following the pandemic outbreak.The virus's fine details have been improved thanks to phylogenetic research and homology modelling. A crucial step would be to look for viral mutations that have low or no pathogenic potential.

VII. CONCLUSION

Keeping an eye on new mutant strains and regional disease outbreaks is critical during the second wave of the Corona Virus. SARS-CoV-2 mutations can make it more infectious by allowing it to escape immune systems through adaptive alterations that increase affinity for host cell receptors. The virus will be subjected to novel selection pressures and evolution modes as several vaccinations are pushed out in the coming year. India has only deposited roughly 6,400 genomes of the more than 10.4 million SARS-CoV-2 samples it has collected so far (0.06 percent).Taking use of developments in genomic epidemiology by monitoring and increasing sequencing efforts in response to local spikes will go a long way toward keeping track of variants of concern while their biology and impact are investigated more thoroughly. Examining the virus through the lens of genomics has proven to be crucial in addressing critical pandemic management concerns. The extent to which genomic monitoring can answer these questions and prevent outbreaks is only limited by the amount of data available, and it will be critical in the future to control the pandemic.

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