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Review Article

Microbiology

A Spotlight on Novel Coronavirus (COVID – 19) with Various Types of Strains

Souvik Biswas[1*], Dipan Roy[2], Biplab Debnath[1], Arijit Das[1], Rajarshi Nath[1], Mrinmoy Nag[3], Poushali Boral[1], Poulomi Biswas[4], Debajit Dewan[5], Nabanita Pramanick[3], Utkalika Sarkar[6], Souvik Chattopadhyay[7], and Soumya Datta[1]

[1]*Bharat Technology, Jadurberia, Uluberia, Howrah – 711316, West Bengal, India*

[2]*Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi – 835215, Jharkhand, India*

[3]*Bengal College of Pharmaceutical Sciences and Research, Durgapur – 713212 West Bengal, India*

[4]*Eminent College of Pharmaceutical Technology, Moshpukur, Barbaria, Barasat – 700126, West Bengal*

[5]*Haldia Institute of Pharmacy, Hatiberia, Haldia, Purba Medinipore – 721657, West Bengal, India*

[6]*Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata – Group of Institution, 124, B.L Saha Road, Kolkata – 700053, West Bengal, India*

[7]*Pandaveswar School of Pharmacy, Pandaveswar, Paschim Bardhaman – 713346, West Bengal*

Abstract: Deadly COVID-19 viruses have raised a pandemic situation in the year 2019, causing serious and contagious respiratory infections in humans. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is the main causative agent for this disease outbreak. The pandemic created a critical impact on the global economy. The emergence of SARS-CoV-2 in late 2019 was followed by a period of relative evolutionary stasis that lasted about 11 months. Since, late 2020, SARS-CoV-2 evolution has been characterized by the emergence of sets of mutations. This resulted so far, in over 2.7 million deaths and near about 122 million infection cases. Most mutations in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) genome are either deleterious and swiftly purged or relatively neutral. As far as the concern is the variants it impacts the virus characteristics, including antigenicity and transmissibility in response to the modification of the human immune profile. In recent days, COVID-19 affected cases are rapidly increasing and it became difficult to inhibit this virus as they are continuously mutated in the host cell forming various new strains like B.1.1.7, B.1.351, P.1, P.2, B.1.1.529, etc. These monitoring, surveillance of variation, and sequencing efforts within the SARS-CoV-2 genome enabled the rapid identification of the first some of Variants of Concern (VOCs) in late 2020, where genome changes became the most observable impact on virus biology and disease transmission. In this review article, we tried to focus and spot the light on the genetic diversification of various strains, their nature, similarities and dissimilarities, mechanism of action, and the prophylactic interventions which could prevent this life-threatening disease in the long run.

Keywords: COVID-19, SARS-CoV-2, B.1.1.7, B.1.351, B.1.1.529, Contagious, Genetic Diversification, Prophylactic Interventions, Life-Threatening Disease, VOC

***Corresponding Author**

Souvik Biswas , Bharat Technology, Jadurberia, Uluberia, Howrah – 711316, West Bengal, India

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1. INTRODUCTION

Before the new year, in December 2019, an epidemiological breakdown of the third novel coronavirus took place which causes acute respiratory disease in the patients of Wuhan, China. Before this, in 2003, SARs-CoV, the first novel, made an appearance in Guangdong, China, and took away the lives of 774 people. After nine years, in Saudi Arabia, another strain of CoV developed with the identity of "Middle East Respiratory Syndrome Coronavirus (MERS-CoV)" which causes approximately 861 deaths with a terrified case-fatality rate of 34.4%. With the use of the next-generation sequencing technique, a new human-infecting coronavirus was identified, which was officially named the 2019 "novel coronavirus (2019-nCoV)". After that on 11th February 2020, "2019-nCoV" or "novel coronavirus" was officially renamed COVID-19 and the causative agent was termed "Severe Acute Respiratory-Syndrome Coronavirus 2 (SARs-CoV-2)". Based on the research of scientists, due to the tendency of mutation and recombination of the coronavirus, a swap in the genomic sequence of SARs-CoV-2 took place, which in turn has enhanced the virulence.[1] The virus contains two circulating strains - the deadly strain "L" and the less virulent one "S". According to the recent health authority protocol, particular antiviral treatments for COVID-19 are not available to date. In critical situations, with oxygen insufficiency and life-threatening conditions, immunoglobulin G transfusion and passive immunisation through convalescent plasma can be used as a rescue treatment. A huge number of pharmaceutical and biotech companies, across the globe, are making randomised sets of clinical trials to find out the effective vaccines and drugs. Besides these, many companies are working on anti-viral RNA for combating this virus. Now-a-days, new drug combinations, introduced in prescriptions, have shown promising results. For example: - Antiviral drug, Remdesivir + Antimalarial drug, Chloroquine, and Chloroquine + Azithromycin has proved highly effective in COVID-19 treatment[2,3]. Most recent research about different variants of coronaviruses has shown that SARS-CoV and SARS-CoV-2 have similarities in their pathogenesis as well as in biochemical interaction. Both can act upon Angiotensin-converting Enzyme -2 (ACE-2) receptors. Not only in human ACE-2 receptors, but this SARS-CoV-2 can also interact with ACE-2 receptors of rabbit, rhesus monkey, pig, dog, and cat.[3] Due to the presence of a vast host range, all animals show different susceptibilities and alter efficiency to SARS-CoV-2 infections. The main target cells for SARS-CoV-2 are the alveolar ciliated epithelial cells present in the bronchus and also the type 2 pneumocytes present in the lungs producing an inflammatory response in the lower respiratory tract. It binds to the surface receptor called angiotensin-converting enzyme 2 (ACE2) receptors via S glycoprotein (spike protein) and forms a complex. After binding to the ACE2 receptors, the cell surface-associated transmembrane protease enzyme serine 2 (TMPRSS2), cathepsin L, and furin proteolytically processed the entire complex as well as cleaved off the trimeric structure of S glycoprotein or spike protein.[4] S glycoprotein consists of two subunits named S1 and S2. The S1 subunit also includes two functional domains like N terminal domains and C terminal domains. If we analyse the structure of the spike protein, it was found that the C terminal domain consists of 211 amino acid regions (amino acid sequence 319-529).[5] It plays a major role in neutralizing antibodies. The S2 subunit mainly helps to stick the virus on the cellular membrane by endocytosis. Depending on the binding affinity with ACE2 receptors, SARS-CoV-2 differs from SARS-CoV in five residues like Y455L, L486F, N493Q, D494S, and T501N. The interaction between the receptors and SARS-CoV-2 depends on the changes in those five residues. SARS-CoV-2 contains four residue motif which helps in the formation of a more compact framework of receptor binding. Hence it strengthened the ACE2 receptor binding affinity on the N terminal helix in the case of SARS-CoV-2 rather than in SARS-CoV.[6] Moreover, it has been noticed that TMPRSS2 is highly present on the lungs' epithelial tissues and smoothed the entryway of the virus by accumulating with cathepsin L. There are mainly two conformation states for SARS-CoV S protein, one is lying down conformation state which helps in immune invasion and another one is standing up conformation state which helps in receptor binding phenomenon. Recent research on the efficacy of the coronavirus showed that SARS-CoV-2 is 10-20 times more infectious than SARS-CoV. After invading into the host cell, antigen-presenting cell (APC) stimulates the inflammatory cascade which triggers the host immune response.[7] Antigen-presenting cells (APC) manifest two functions:

- At first, it introduces foreign antigen to the CD4+ T helper cells.
- Then it releases interleukin - 12 cytokines for further stimulation of T helper cells. CD8+ T killer cells are also stimulated by these T helper cells and target the foreign antigen. Hence these CD8+ T killer cells indirectly stimulate the B cells for the production of antigen-specific antibodies.[7-8]

2. CORONAVIRUS

The term "Coronavirus" has been obtained from a Latin word, "corona" which means "crown", due to having crown-like spikes on its surface. These crown-like spikes are nothing but positive-sense RNA viruses that come under the coronaviridae subfamily of the Nidovirales order. Based on their genomic structure, they are sub-categorized into- alpha, beta, gamma, and delta coronaviruses, amongst which alpha- and beta coronaviruses mostly caused respiratory complications in humans and gastroenteritis in other animals.[3] Through electron microscope, it is observed that virions of CoVs contain large peplomers, which appear like crowns visually (Fig 1), hence the name corona, meaning "crown or "halo." The circulating strains were causing mild symptoms like sore throat, cough, fever, headache, and runny nose in immunosuppressed people.[2]

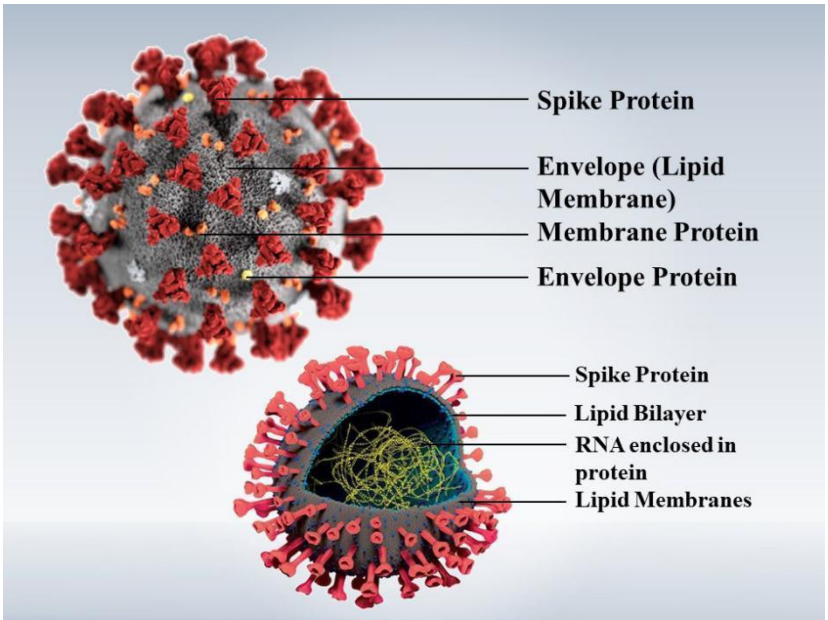

Fig 1: Structure of COVID 19[1]

Fig 1 *depicted the structure of COVID-19. This figure shows the location of the spike protein, lipid bilayer, membrane protein, and envelope protein.*

3. ORIGIN OF SARS-COV-2

The animal origins of coronaviruses are – either bats or mice cause disease in humans. Previous exposure to beta coronaviruses in humans has the involvement of direct exposure in animals without bats. MERS-CoV and SARS-CoV are referred to directly in people from dromedary camels and civet cats respectively. Spike proteins cover the surface of the SARS-related coronaviruses, and contain mutation receptor-binding domain (RBD). This RBD binds with the angiotensin-converting enzyme-2 (ACE-2) receptor situated in the gastrointestinal tract, kidneys, heart, and lungs which results in the viral entry into the target cells.[4] In terms of the genomic sequence, RBD for SARS-CoV-2 appears to be a customised form of its most firmly related virus, RaTG13, taken from samples (Rhinolophus affinis). Therefore, it is predicted that SARS-CoV-2 which originated from bats, after mutation, infected other animals as well. The altered form of the virus enhanced the RBD exposure to ACE-2 in humans as well as in other animals also, like Malayan ferrets and pangolins (Manis javanica; a long-stout, ant-eating animal), on the other hand, it reduced RBD and ACE-2 exposure to mice and civets. Pangolin is believed to be a central component of SARS-CoV-2. There was a preliminary prediction that SARS-CoV-2 came out as a man-made fraud of an existing coronavirus, though no strong justifications regarding this statement are still not found. Certain changes observed in the RBD of SARS-CoV-2 are different and could not be predicted depending upon the genetic predisposition used previously.[4-5] It is depicted in Table 1 and Table 2.

Table 1: Comparison of the biological features of SARS-CoV-2, SARS-CoV, and MERS-CoV

Biological Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Possible natural storage area	Bat	Bat	Bat
Possible medium keeper	Malayan Pangolins and turtles	Palm civets	Camel
Genealogy of Beta coronavirus	B	B	C
Predominant cellular receptor	ACE2	ACE2	Dipeptidyl peptidase 4 (DPP4, also known as CD26)
Symptoms	Severe acute respiratory syndrome, 4.2% mortality rate	Severe acute respiratory syndrome, 11% mortality rate	Severe acute respiratory syndrome, 34% mortality rate

Table 1 depicted the difference between SARS-CoV-2, SARS-CoV, and MERS-CoV according to some biological features. From this table, it is noted that MERS-CoV has the highest mortality rate of all.

Table 2: Epidemiological comparison model of SARS-CoV-2, SARS-CoV, and MERS-CoV

Epidemiological Factors	SARS-CoV-2	SARS-CoV	MERS-CoV
Outbreak date	December 2019	November 2002	September 2012
Confirmed cases	4,731,458 (19 May 2020)	8,096 (31st July 2003)	2,519 (31st January 2020)
Total death	316,169 (19 May 2020)	774 (31st July 2003)	866 (31st January 2020)
CRF	6.6%	9.6%	34.4%
Incubation period (Range)	3.0 (0-24.0)	6.4 (2-10)	7 (2-17)
Major roots of transmission	Respiratory aspirate, droplets, contacts, and feces	Respiratory aspirate, droplets, contacts (World Health, 2003)	Unprotected contact with infected dromedary camels or infected people
Age in years (range)	56 (22-92), in Wuhan, China 63 (56-70), in Lombardy region, Italy 63 (0-107), in the New York City	39.9 (1-91)	50.21 (2-109)
The proportion of health workers	3.8%	23.1%	19.1%
Male: Female ratio	1.06:1	1:1.25	1:2.52
Risk areas	Europe, America	China	Saudi Arabia
Rate of transmission (R_0)	2-2.5	1.7-1.9	0.7

Table 2 depicted that according to the epidemiological factors there is some difference between SARS-CoV-2, SARS-CoV, and MERS-CoV. From this table, it is noted that MERS-CoV has the highest severity rate of all.

4. MUTATION

Because of science fiction, the word "mutant" has been associated with popular culture that is rare and dangerous. In reality, viruses like SARS-CoV-2 cause COVID-19, change all the time, and often this process does not increase the risk of infecting people. New strains of the virus are expected to occur over time. Sometimes a new variation appears and disappears. Sometimes, new alternatives emerge and continue. Modification is simply a genetic mutation: a set of all-encompassing genetic instruction details that need to work with the virus. These genetic mutations are found in the so-called Genome sequence.[6-7] When a virus replicates, this set of commands needs to be copied, but errors can get in the way of this process. It's like copying handwriting. The virus acts randomly so errors while copying may occur. Depending on where the genetic defects are found, they may have a negative or positive impact on the ability of the virus to replicate itself. In most cases, these errors are harmless and do not affect the path of the virus affecting individuals. In fact, in many cases, genetic mutations can weaken a virus. But in some cases, mutations can give the virus a chance – which may look like the one's happening in the UK and South Africa. The genome is the genetic material of the body, and contains all the necessary instructions for reconstruction, to develop that body.[8-10] Genomic sequencing is the process of finding the perfect DNA sequence (in SARS-CoV-2 is an RNA sequence) of an organism's genome at a single time. It analyses the virus sample taken from a patient and then it is compared with other cases, to determine if the virus is contagious or not.[11-13]

Recent technological advances have enabled the genes of SARS-CoV-2 – the causative virus of COVID-19, to be followed within a few days of the case being identified. This is very important because it means that we can use these genomes to inform public health policy in the event of an ongoing outbreak. For the first time, genomic sequencing can guide public health response to an imminent epidemic in real-time.[14,15]

4.1 Information About Various Types of Strains

4.1.1 B.1.1.7 Variants (US: Kent)

B.1.1.7, was first recognized on 20th September 2020 in the United Kingdom. Other names used for this version are VOC 202012/01 and - 20I/501Y.V1. The key mutations in this pedigree are- the deletion of H69 / V70, Y144 deletion, N501Y, A570D, and P681H (Fig 2). There's a common key mutation in spike protein, it is S106/G107/F108 deletion of non-structural protein 6 (NSP6). Data of transmission rate has increased from 36% to 75%, higher secondary attack rate up to 10-13%. Rather, GISAID's hoard for the novel coronavirus was "G", which has now evolved into a mutant called 'GR'.[16,17] It is noted that the level of severity of the disease is caused by an increased risk of hospitalisation, the severity of the disease, and mortality. Neutralising ability shows a slight decrease, but neutralising titles remain above levels that are expected to provide some form of protection. The potential effects of the vaccine should not have a significant impact on the post-vaccine neutralisation by Oxford-AstraZeneca, Pfizer BioNTech, Novavax, Moderna, and Pfizer, as well as the Bharat vaccine. Any significant changes in the treatment of the disease with Pfizer, Oxford-AstraZeneca, and Novavax. Evidence to prevent infection is limited. About the reduction of the effect, apparently for "AstraZeneca".[18,19] Potential impact on the diagnosis of the" S" Gene Target Failure (SGTF). No effect on the Ag-RDTs is observed. Till now 125 Countries have been affected. Origin B.1.1.7 is the special case of SARS-CoV-2, the causative virus of COVID-19. It is assumed that one of the different models has a special meaning, and this is estimated as 40% -80% (and most of them, starting from the middle and upper-end range) of the coverage area, are more contractable than the SARS-CoV-2 which are the wild type that started in November 2020. The attempt to detect this virus was made in September, the time of the COVID-19 pandemic in the United Kingdom, which started to grow rapidly in the middle of December, and is correlated with a remarkable increment in the number of SARS-CoV-2 infections all over the country.

This growth is predicted to be at least partially the result of one or more than one mutations in the spike protein of the virus.[20] From January 2021, more than half of the entire SARS-CoV-2 genome sequence is produced in the United Kingdom. This has raised questions regarding the number of other unidentified major models around the world. On 2nd February 2021, Public Health England stated about their recognition regarding a few numbers of B.1.1.7, VOC-202012/01 genomes with E484K mutations, the mimic Variant of Concern 202102/02 (VOC-202102/02). Lineage B.1.351 also contains this mutation.[21]

4.1.1.1 VOC - 202102/02 (Bristol) & VUI - 202102/01 (Liverpool)

Two latest local variants of the SARS-CoV-2 virus were first recognized in the United Kingdom. A new feature of the VOC-202102/02, for the first time, has been detected in Bristol and has been designated as a "make" option. This is the fourth version of the problem that was identified by the advisory group named, "New and Emerging Respiratory Virus Threats Advisory Group" (NERVTAG). As a variation, VUI 202102/01, first found in Liverpool, England, was placed in a research study.[22,23]

- B.1.1.7 with E484K is the official name of the Bristol strain or it can be written as VOC-202102/02 (a variant of concern). The mutation of the Kent variant was observed once again earlier this year, after trying to replicate the South African version. The mutation of this variant is E484K, already the native of South African and Brazilian variants. Studies in the research lab reflect that the antibodies which are also known as spike proteins are not easily able to get in touch with the virus and are unable to stop it from unlocking the human cells as well as access entry to it. After the recognition of a new strain for the first time, as per the concern of the researchers, the signs are matched with the versions that are already in circulation. Instances of this function for the first time were found in February in Bristol, hence its nickname, "The Bristol Model". There were twenty-one cases in the South West of the city and Bristol, as well as 13 elsewhere in the UK, suggesting that the surge tests have helped to stop the spread.[24,25]
- A.23.1 with E484K is the official name of the Liverpool strain and VUI-202102/01 is the variant that is still under investigation. The origin of this strain is Wuhan, and along with E484K, (Fig 2 and Fig 4) the mutation was identified in South Africa, and Brazil as variations. It is known as the "Liverpool variant" as its first identification place is Liverpool Women's Hospital, in January. It results in fifty-nine Covid cases, confirmed in the UK. But blitz testing is used to find the novel coronavirus and health personnel are requested to get a free NHS test, even in case of a runny nose also.[26,27]

4.1.1.2 *Spike Protein Mutation*

In Bristol, the variant is the mutation of VOC-202012/01, first detected in Kent. The 21 cases of the "Bristol" variety were observed in the analysis of the "Public Health England (PHE)", also known as VOC's 202102/02. It consists of a spike protein mutation named E484K. A group of researchers believes it can act as a support system for the body's immune system, the drift of the virus, and reduce the effectiveness of the vaccine. The VUI 202102/01, also known as the "Liverpool" variant involves E484K spike protein mutation along with some changes that were seen only in the United Kingdom. The latest research shows that up to the present day 51,500 genomically established and suspected cases of a variant of the B.1.1.7, have been recorded.[28,29]

4.1.2 B.1.525 Variants (Nigeria and United Kingdom)

It is also known as VUI-202102/03 (variant under investigation). Here the next strain clade is 20C. GISAID clade for this strain is G/484K.V3. The key spike mutations include Q52R; Y144 deletion; H69-V70 deletion; E484K; F888L; D614G; and Q677H. On the 16th of February, PHE confirmed that the new version, known as the B.1.525, was found in the United Kingdom. In the first instance, 33 cases of the disease have been identified by sequencing the genetic basis of more than 70,000 positive test results. Since then, significant growth of more than 300 was observed. Some countries like Denmark, the USA, France, Italy, Spain, and Australia where the B.1.525 is also identified. The particular geographical origin is still unknown, but the origin of this variety goes back to the end of December, in Nigeria, and the United Kingdom.[30,31] The scientists of the University of Edinburgh first identified this species, and has some similar characteristics to the Kent strain, but has some additional changes. E484K **(**Fig 2 and Fig 4) mutation is one of them, which was also detected in South Africa and Brazil. Scientists believe that it can help to ensure that the vaccine is less effective.[32,33]

4.1.3 B.1.351 Variants (South Africa)

This variant belongs to the 20H/501Y.V2 strain clade and in the year 2020, it was first recognized in South Africa's "Nelson Mandela Bay". It has another name VOC 202012/02. B.1.351 has several spike proteins like K417N, E484K, and N501Y, (Fig 2), and those spike proteins are mutated in different steps. The transmission of B.1.351 is many times higher than B.1.1.7. It is rapidly mutated into the host cells hence it's difficult to cure. Mutations occur in B.1.351 by deleting the L242/A243/L244 or S106/G107/F108 from non-structural protein 6. The infection can be severe if the person is hospitalised, due to the high transmission ability of this strain. It also increases the risk of reinfection by decreasing the neutralising capacity. One of the most important characteristics of B.1.351 is that it can rapidly replace other strains and shows its effect on the host cell. The vaccine induces a reduction in the neutralisation of antibodies against the 501Y.V2 strain. AstraZeneca and Novavax are efficient for this particular strain. Moderna vaccines also produced high levels of antibodies to neutralise the virus.[34,35]

4.1.4 B.1.1.28.1 or P.1 Variants (Brazil)

Lineage P.1 is a Brazilian strain. "National Institute of Infectious Diseases" first identified it in the year 2021 in Japan. It belongs to the 20J/501Y.V3 strain clade and it's also known as B.1.1.28.1 or VOC-202101/02. It contains three spike proteins namely N501Y, E484K, and K417T (Fig 2 and Fig 4). P.1 lineage is more lethal like 10-80% lethal in younger individuals due to its higher transmissibility than other viral strains. This P.1 variant has two different types of subvariant such as 28-AM-1 and 28-AM-2 which were continuously mutated in the host cells.[36-38] It was reported that P.1 causes less severity but there is a chance of reinfection in those patients who have already been affected by SARS-CoV-2. It has also been seen that Oxford-AstraZeneca, Moderna, and Pfizer vaccines are potentially able to neutralise this strain whereas Sinovac.[38]

4.1.5 B.1.1.28.2 or P.2 Variants (Brazil)

P.2 strain was detected in Brazil and belongs to the 20J strain clade. It has another name B.1.1.28.2. P.2 contains some specific spike proteins namely L18F, F157L, P26S, D614G, E484K, T20N, V1176F, and S929I.[39-41]

4.1.6 B.1.429 Variants (California)

Cedars - Sinai Medical Centre, California first detected B.1.429 variants in the year 2020. It has another name CAL.20C/L452R and belongs to the 20C/S:452R strain clade. Multiple types of mutations occur in several spike proteins of B.1.429 lineage and those specific spike proteins are D1183Y and I4205V in the ORF1ab-gene, and L452R, W152C, and S13I among the spike proteins of S-gene. The transmission rate is relatively higher than other strains. It also has some similarities with B.1.427.[39,40]

4.1.7 B.1.526 Variants (New York)

At the end of November 2020, a variant called B.1.526 was first found in New York City (UK), and in a little over a month, 35-40% of people are infected. Based on an alarming rise, B.1.526 was identified as VOC and labelled as the Iota variant by WHO. Two identified mutations in spike protein E484K and S477N are responsible for the transmission of it.[41] Phylogenetic investigation reveals that B.1.526 variant has a characteristic of both the spike as well as non-spike protein mutations. The five significant spike protein mutations of B.1.526-S477N and B.1.526-E484K are L5F, D253G, T95I, D614G, and A701V with either E484K or S477N have been identified. The non-spike mutations of B.1.526 variants are P323L in ORF1b-nsp12; T85I in ORF1a-nsp2; Q88H in ORF1b-nsp13; L438P in ORF1a-nsp4, a 9bp deletion Δ 106-108 in ORF1a-nsp6; Q57H in ORF3a; and P199L and M234I in the N-terminal domain of spike protein (Fig 2 and Fig 4). The mutation E484K along with D253G in spike protein makes this variant more infectious and increases its ability to transmit than the B.1.1.7 variant in the United Kingdom. More recently another sub-lineage of B.1.526 has been identified with substitution L452R in spike protein, not reported as VOC or VOI.[42,43]

4.1.8 B.1.617 Variants (India)

India is now suffering from the second wave of SARS-CoV-2. About 4-5 million people are infected and around 40-50 thousand people have died from a new strain of coronavirus B.1.617. As per WHO (World health organization), B.1.617 is a new Indian variant coronavirus, noticed in late 2020. At first, B.1.617 variant swapped all over India and spread to 70 countries throughout the world. B.1.617 variant has split into three lineages, among them, the first one is B.1.617.1, the second one is B.1.617.2, and the last one is B.1.617.3. Among these, the B.1.617.2 are termed as Delta variant, which is identified as a variant of concern (VOC) and highly transmissible, as per WHO. As per, the Indian SARS-CoV-2 consortium on Genomics (INSACOG), the delta variant (B.1.617.2) is the main reason for the second wave in India. Another variant B.1.617.1 is labelled as the Kappa variant, has been identified as a Variants of Interest (VOI), and the last one B.1.617.3 still does not represent any VOC or VOI, as per WHO. Various phylogenetic analyses reported, that in the spike protein like E484Q, D614G, D111D, L452R, T478K, G142D, and P681R respectively, B.1.617 possessed significant mutations, including within the receptor-binding domain (RBD). The mutation (D614G) in the S gene (spike protein), replaced D (aspartic acid) with G (glycine) in the RBD. Aspartic acid is a bulkier amino acid than glycine, which allows the virus to bind better with the human cell receptor (ACE2 receptor) and take enter more easily. In another mutation, L452R, E484Q, and P681R decreased the neutralization potential of selected monoclonal antibodies (mAbs) in the furin cleavage site.[44,45] This increases its ability to transmit better and more infectious. The various mutations in gene S of the sub-variants of B.1.617 are

- B.1.617.1: E154K, L452R, G142D, Q1071H, E484Q, P681R, T95I, D614G
- B.1.617.2: D950N, L452R, (G142D),157del, D614G, R158G,156del, P681R, T19R, T478K
- B.1.617.2.1/AY.1: Under B.1.617.2, another variant is reported in India which is known as the Delta Plus variant. The lineage is B.1.617.2.1/AY.1). B.1.617.2 is related to Delta so; this Delta Plus is the variant of Delta. Delta Plus variants have the K417N mutation. Like Delta, it has a mutation in the spike protein region of the RNA virus. For this reason, it is more transmissible. The Delta Plus variant was first reported by Public Health England on 11th June. It is also treated as a variant of concern.
- B.1.617.3**:** L452R, G142D, P681R, D614G, D950N, T19R, E484Q

These are the spike mutation of these sub-variants.[46-49]

4.1.9 B.1.1.318 Variants (United Kingdom)

The New UK Covid-19 strain was first identified in England on February 15 through a routine genomic horizon scan by Public Health England (PHE). and was designated as " Variant Under Investigation" or VUI on February 24th, 2021. The New UK variant is known as B.1.1.318 or can be termed as VUI-202102/04. The variant contains a protein spike mutation called "E484K" which is present in two other VUIs of the UK. However, it does not feature the N501Y mutation which has been spotted in all VOCs (Variants of Concern). It is observed that E484K has a role in the reduction of the effectiveness of vaccines in preventing Covid-19 virus attacks, but more work is needed to understand this. As of March 2021, there were 16 genomically confirmed cases in England, and no deaths have been reported as of March 2021. The World Health Organisation (WHO) said these mutational changes are "natural and expected". It is an RNA virus so it is more prone to mutation than DNA viruses. Sometimes these mutational changes could be so small that there's no difference in the virus properties or behaviour. But sometimes virus mutations can change the surface proteins of the virus and it can spread the infection rapidly.[50-53]

4.1.10 P.3 Variants (Philippines)

Philippines Covid-19 Variant or P.3 is another type of variant of SARS-CoV-2. It was first recognized on February 18th, 2021 in the Philippines. The World Health Organization simplified the name of this variant and P.3 was contemplated as a variant of interest (VOI) and labelled as theta variant on June 1st, 2021. In Central Visayas, two mutations of COVID-19 are confirmed by the Department of Health of the Philippines through genome sequencing of the samples. P.3 carries various types of protein spike mutations, including E484K and N501Y. In the E484K mutation, the virus changes the shape of its surface

spike proteins. P.3 could be more resistant to the current generation of Covid-19 vaccines. More analysis is needed to establish the effectiveness of the vaccines on the P.3 variant. P.3 also has the same N501Y mutation seen in the UK variant. This N501Y mutation makes it easier for the virus to attach to human cells. These variants are not officially named and the identification of the full sequence is still pending.[54,55] Japan detected the variant on a traveller from the Philippines on March 12th, 2021. The Department of Health confirmed on March 13th, 2021 that the mutated strain was a new variant, and the lineage P.3 designation was given to this recognized strain.[56]

4.1.11 B.1.1.298 Variants (Danish or Denmark)

The Danish variant B.1.1.298 was first discovered among some workers on a mink farm in June 2020. This strain contains two N-terminal deletions such as deltaH69 and deltaV70 similar to B.1.1.7. There are three mutations of spike proteins e.g., Y453F, I692V, M1229I, and D614G (Fig 2 and Fig 4). Among those spike proteins, Y453 electrostatically interacts with H34 in hAce2. However, the mutations of Y453F increase the affinity with hAce2 by four-fold. This strain was rapidly transmitted into a few hundred people and continuously mutated into the host cells as it owes high mutation capability in animals. It is not as significant as others SARS-CoV-2 strains.[57-58]

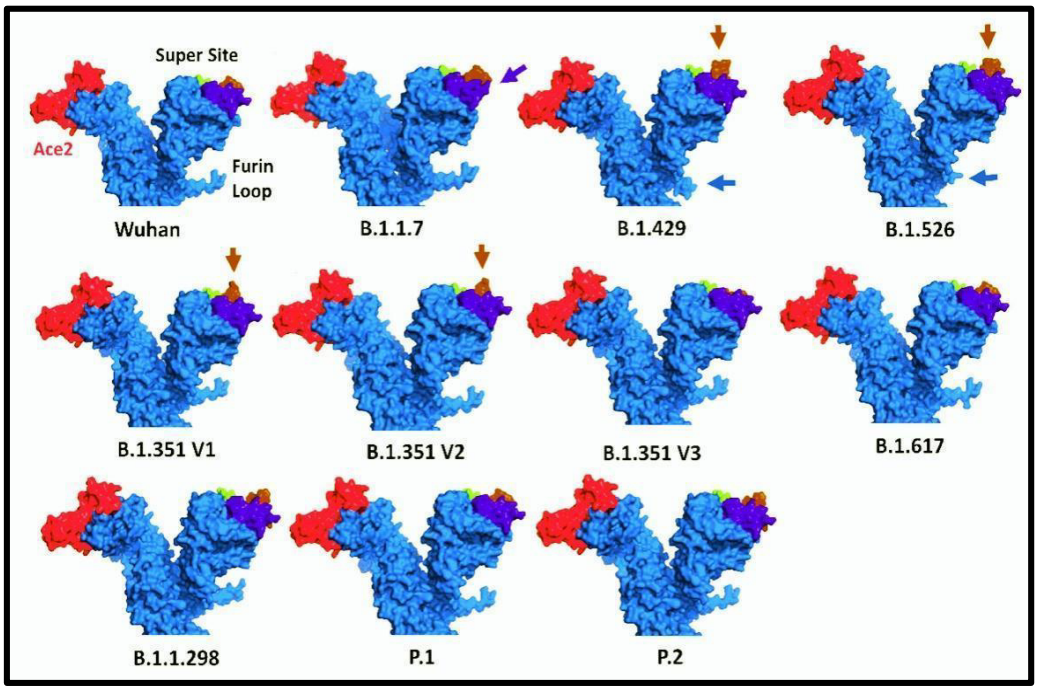

Fig 2: Models of the various strains with their spike proteins and geographical distribution[59]

Fig 2 depicted the model of the various strains. The location of the spike proteins is also visible in this diagram. This diagram also shows the geographical distribution according to the position of the spike protein.

4.1.12 B.1.616 Variants (France)

The PANGO lineage of B.1.616, first emerged in France on Jan.2021. There were some substitutions in the spike protein mainly: H66D, Del144/145, Q949R, G669S, H655Y, V483A, N1187D, and D215G. The previous name for this following strain was: HCoV-19/France/BRE-IPP04392/2021. The GISAID code is GH. The genotype of this variant is clade 20C, with a variant name: 20C/655Y (B.1.616). The coronavirus variant, which is the cause of the deadly upsurge in France is a part of standard tests that can only be found deep in the lungs, according to a new study.[60,61] B.1.616 strain is characterised through the changes in 9 amino acids along with the deletion of S protein, with different mutations in the structural and non-structural proteins, in comparison with the parent strain from Wuhan. It is also worth noting that the amino acid exchange of V483A in the receptor-binding domain is close to the change in the E484K, which is associated with a reduced neutralisation. Scientists in the west of France said that only 15% of the patients in the study who had a variant of B.1.616 tested positive for a standard nasopharyngeal swab, compared to 97% for all other varieties in circulation in France.[62,63]

4.1.13 B.1.1.7 + B.1.429 Variants (US UK)

The key mutation of this strain is N501Y. For this reason, it speeds up the transmission. This strain is also under VUI (Variants Under Investigation).[64,65] L452R is also present in this variant as a result it can also increase the transmissibility and antibodies can be escaped from vaccines for this reason.[66,67]

4.1.14 B.1.621 Variants (South America)

The Mu variant is a COVID-19 viral variant. The Mu variant is the colloquial name for the B.1.621 variant, which is the technical nomenclature. The letter Mu is pronounced myoo or moo and is a Greek letter.[68,69] A new strain of a virus has evolved as a result of a mutation (or mutations) in the genomic structure of the virus. The Mu variety was discovered in South America for the first time. Due to media reports of incidents in the United States and the World Health Organisation's classification of the Mu variant, awareness of the variant increased in the United States in early September 2021.[70-71] WHO designated the Mu variation as a "Variant of Interest" in September 2021, indicating that genetic modifications could

make it more severe and transmissible. The Mu variant was categorised with the Lambda variant at the time.[72-74]

4.1.15 B.1.1.529 Variants (South Africa)

The COVID-19 viral variant Omicron is a COVID-19 viral variant. It was discovered in South Africa for the first time. On November 26, 2021, the WHO's Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) classified this strain as OMICRON under the Variants of Concern (VOC) category. The first instance of OMICRON in South Africa was reported on November 9, 2021, when a patient with COVID-19 was found. According to the researchers, OMICRON and other SARS-CoV-2 variant sequences evolved in tandem, with OMICRON diverging quite early, possibly around mid-2020. OMICRON clades were discovered using Receptor Binding Domain (RBD) research. There are 60 mutations in the Omicron variety (50 nonsynonymous mutations, 8 synonymous mutations, and 2 non-coding mutations). There are 32 mutations in the spike protein.[75,76] The variant comprises 30 amino acid changes, three small deletions, and one tiny insertion in the spike protein, 15 of which are in the receptor-binding domain (residues 319–541). In other genomic locations, it has multiple deletions and insertions. This variation also has three mutations at the furin cleavage site. The furin cleavage site boosts SARS-CoV-2 infectivity (Fig 3).[77] It has 2 sub pango lineage. These are BA.1 and BA.2. Both are under in VUM.

- Spike Protein**:** A67V, Δ 69-70, T95I, G142D, Δ 143-145, Δ 211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F (Fig 3)
- ORF1ab

➢ nsp3: K38R, V1069I, Δ 1265, L1266I, A1892T
➢ nsp4: T492I
➢ nsp5: P132H
➢ nsp6: Δ 105-107, A189V
➢ nsp12: P323L
➢ nsp14: I42V

- Envelope Protein: T9I
- Membrane Protein: D3G, Q19E, A63T
- Nucleocapsid Protein: P13L, Δ 31-33, R203K, G204R

Changes in the spike protein indicate that the Omicron variety is likely to have more transmission than the original SARS-CoV-2 virus. It has a high rate of replication. It replicates 70 times quicker in the bronchus, the major route entering the lungs. It was discovered that Omicron travelled more slowly from the throat to the lungs. The new virus replicates in the lungs at a pace that is less than a tenth of that of the original virus. It has been noted that the Omicron variant has three sub-strains. According to WHO, these are BA.1, BA.2, and BA.3.[78]

- N501Y increases the binding of ACE2 receptors, potentially enhancing transmission. The combination of N501Y and Q498R may increase binding affinity even further.
- Because H655Y is close to the furin cleavage point, it may speed up spike cleavage, aiding transmission.
- The furin cleavage site is polybasic close to N679K, which could speed up spike cleavage and promote transmission.
- P681H has been shown to increase spike cleavage, which could help with the transmission.

Omicron does not influence cell syncytia, according to the mechanism of action of that variation. Cell fusion is not induced by the Omicron version. As a result, the cell is revealing less infection. In the lungs, Omicron had a low viral burden. This indicates that the magnitude is smaller than the Delta and Wuhan strains. The replication rate is higher in this variation, but the replicate has a low viral load.[79]

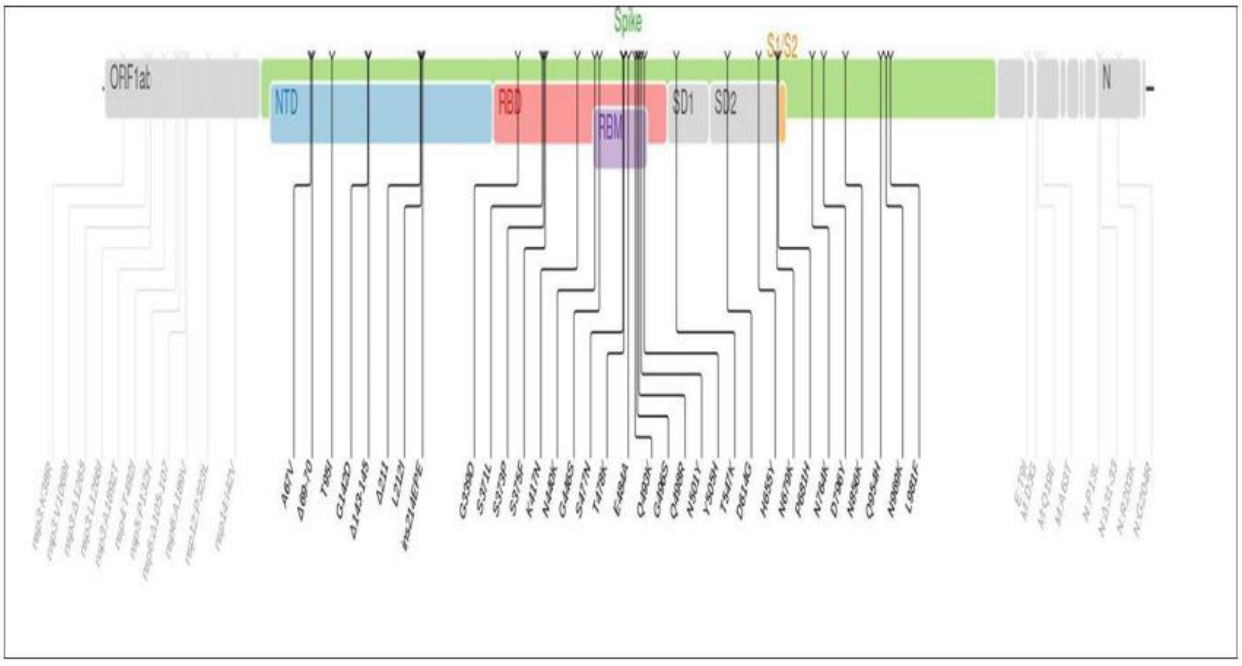

Fig 3: Spike protein of Omicron variant[77]

Fig 3 depicted the spike protein of the Omicron variant. N501Y spike protein increases the binding with ACE2 receptors. H655Y, N679K, and P681H are responsible for the speedy transmission.

4.1.16 B.1.640.2 Variants (Cyprus)

On January 7, 2022, it was discovered for the first time in Cyprus. It is a hybrid of Delta and Omicron types. Because 'Omicron'-like genetic structures were discovered within Delta Genomes, the discovery was given the moniker 'Deltacron.' It shares the same genetic basis as the Delta variation, but with 10 Omicron mutations. Until today, WHO had not acknowledged this variation.[80] Deltacron is a product of lab contamination, according to some researchers, and this version is not a real combination of the two types. On a phylogenetic tree, they do not form a cluster. It's unlikely to be a biological recombinant of the Delta and Omicron lineages. Due to the presence of the same genetic structure as Omicron, it may have similar transmissibility.[81,82]

4.2 Rate of Transmission for Mutation

The virus's spikes can more easily bind to receptors on human cells according to the modified variety known as B.1.1.7, which was first discovered in the United Kingdom. Despite not being a particularly deadly virus, B.1.1.7 causes more deaths than the original strain would have due to its high infectivity. In areas where SARS-CoV-2 is maintained under control, B.1.1.7 has the potential to proliferate. The two most notable mutant strains to date, B.1.1.7 and 501.V2, both from South Africa, do not appear to be resistant to immunizations or acquired immunity. Pfizer stated that preliminary research indicates that the vaccine is effective against the B.1.1.7 mutations (Table 7).[83]

SARS-CoV-2 Variants of Concern, Variants of Interest, and Variants Under Monitoring (According to WHO Label) [84-86]

1. Variants of Concern

A SARS-CoV-2 variant that satisfies the VOI criteria. It has some significance (Table 6). These are increased transmissibility, a negative shift in COVID-19 epidemiology, an increase in virulence or a change in clinical illness presentation, and a decrease in the efficacy of public health and social measures, as well as current diagnostics, vaccines, and therapies. It is depicted in Table 3.[86]

Table 3: Model for VOC (According to WHO Label)[86-88]

WHO Label	Pango Lineage	GISAID Clade/Lineage	Nextstrain Clade	Earliest Documented Samples	Date of Designation	Transmission Rate
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I (V1)	United Kingdom, Sep-2020	18-Dec-2020	Very high, linked to 60% total cases
Beta	B.1.351	GH/501Y.V2	20H (V2)	South Africa, May-2020	18-Dec-2020	Increased transmissibility
Gamma	P.1	GR/501Y.V3	20J (V3)	Brazil, Nov-2020	11-Jan-2021	Very high with high transmission rate
Delta	B.1.617.2	G/478K.V1	21A	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021	40-60% more transmissible than Alpha
Omicron	B.1.1.529	GRA	21K, 21L, 21M	Multiple Countries, Nov-2021	VUM: 24-Nov-2021 VOC: 26-Nov-2021	Highest transmission rate of all

Table 3 depicted that the above strains are under the VOC Model which is known as Variants of Concern. This table was prepared according to the WHO Label. Delta and Omicron variants have a greater transmissibility rate.

2. Variants of Interest

A genetic mutation associated with changes in receptor binding, lower neutralisation by antibodies developed against previous infection or vaccination, reduced treatment efficacy, potential diagnostic impact, or projected increase in transmissibility or disease severity (Table 6).[86] There are some characteristics. These are:

- Specific genetic markers are expected to have an impact on transmission, diagnostics, treatments, or immune evasion.

There's evidence that it's the source of an unusually high number of cases or outbreak clusters.[87] It is depicted in Table 4.

Table 4: Model for VOI (According to WHO Label)[86-88]

WHO Label	Pango Lineage	GISAID Clade/Lineage	Nextstrain Clade	Earliest Documented Samples	Date of Designation	Transmission Rate
Epsilon	B.1.427/B.1.429	GH/452R.V1	21C	United States of America, Mar-2020	5-Mar-2021	The variant accounted for 53% of cases sampled
Zeta	P.2	GR/484K.V2	20B/S.484K	Brazil, Apr-2020	17-Mar-2021	Not clearly understood
Eta	B.1.525	G/484K.V3	21D	Multiple countries, Dec-2020	17-Mar-2021	Almost same as alpha variant

Theta	P.3	GR/1092K.V1	21E	Philippines, Jan-2021	24-Mar-2021	Moderate transmission rate
Iota	B.1.526	GH/253G.V1	21F	United States of America, Nov-2020	24-Mar-2021	Has not been reported in any other country
Kappa	B.1.617.1	G/452R.V3	21B	India, Oct-2020	4-Apr-2021	It shows community transmission
Lambda	C.37	GR/452Q.V1	20D	Peru, Dec-2020	14-Jun-2021	It increases mutation so it has greater transmission rate
Mu	B.1.621	GH	21H	Colombia, Jan-2021	30-Aug-2021	Higher than others

Table 4 depicted that the above strains are under the VOI Model which is known as Variants of Interest. This table was prepared according to the WHO Label. All of the strains of this table are under investigation.

3. Variants Under Monitoring

A SARS-CoV-2 variant with genetic changes that are suspected to affect virus characteristics, with some indication that it may pose a future risk, but evidence of phenotypic or epidemiological impact is currently unclear, necessitating increased monitoring and repeat assessment until new evidence becomes available.[86] It is depicted in Table 5.

Table 5: Model for VUM or FMV (According to WHO Label)[86]

Pango Lineage	GISAID Clade	Nextstrain Clade	Earliest Documented Samples	Date of Designation	Transmission Rate
B.1.1.318	GR	-	Multiple countries, Jan-2021	02-Jun-2021	Not clearly understood as those strains are under VUM as well as FMV. They have no impact on the overall epidemiological situation and do not carry any characteristics
C.1.2	GR	-	South Africa, May 2021	01-Sep-2021	
B.1.640	GH/490R	-	Multiple countries, Sep-2021	22-Nov-2021	
B.1.630	GH	-	Dominican Republic, Mar-2021	12-Oct-2021	
B.1.620	G	-	Multiple countries, Nov-2020	14-July-2021	
B.1.619	G	20A/S.126A	Multiple countries, May 2020	14-July-2021	
B.1.1.523	GH	-	Multiple countries, May 2020	14-July-2021	
B.1.1.519	GR	20B/S.732A	Multiple countries, Nov-2020	02-Jun-2021	

Table 5 depicted that the above strains are under the VUM and FMV Model which is known as Variants Under Monitoring. All of the strains in this table are suspected new strains of SARS-CoV-2 as they have some virus characteristics. Epidemiological factors are unclear so they are under Variants Under Monitoring. Some of the strains are under Formerly Monitored Variants as they have no impact on the overall epidemiological situation.

4.3 Overview of SARS-Cov-2 Variants

Table 6: SARS-CoV-2 Overview Chart[89]

Signs and Symptoms	Original Variants	VOI	VOC	VOHC
Cough	28%		35%	
Fatigue	29%		32%	
Headache	30%		32%	
Muscle Aches	21%		25%	
Sore Throat	19%		22%	
Fever	20%		22%	
Loss of Taste	19%		16%	
Loss of Smell	19%		15%	
Disease Transmissibility	Yes	No	Yes	Yes
Disease Severity	Less	Less	More	More
Diagnostic Testing Failures	No	No	No	Yes

Table 6 depicted that the overview of SARS-CoV-2 variants where it is showed that symptoms, disease transmissibility, disease severity and diagnostic testing failure.

4.4 SARS-Cov-2 Overall Mutation with Mechanism

Table 7: Mutation of SARS-CoV-2[89]

Variant	Role of the Mutation	Mutation Location	Mutation
UK (20I/501Y.V1) South Africa (20H/501Y.V2) Brazil (20J/501Y.V3)	May increase ACE2 binding	RBD	S:N501
Brazil (20B/S.484K)	May increase ACE2 binding	RBD	S:E484
UK (20I/501Y.V1)/B.1.1.7	May alter recognition by antibodies	Spike N-terminal domain	S:H69-
South Africa (20H/501Y.V2) Brazil (20J/501Y.V3)	Reduction in binding for monoclonal antibody	Spike N-terminal domain	S:L18F
South Africa (B.1.1.529)	May increase ACE2 binding	Spike N-terminal domain	S:N501Y
Danish or Denmark (B.1.1.298)	May increase hAce2 binding	Spike N-terminal domain	S:Y453F
Philippines (P.3)	Attach to human cells	Spike N-terminal domain	S:E484K and S:N501Y
United Kingdom (B.1.1.318)	-	Spike N-terminal domain	S:E484K
India (B.1.617)	May increase ACE2 binding	RBD	S:D614G
New York (B.1.526)	May increase ACE2 binding	Spike N-terminal domain	S:P199L and S:M234I
California (B.1.429)	-	Spike N-terminal domain	S:452R
France (B.1.616)	-	RBD	S:V483A

Table 7 depicted that the overall mutation status of SARS-CoV-2 strains. In this chart it is shown that the mutation location, role of mutation and specific spike protein of mutation.

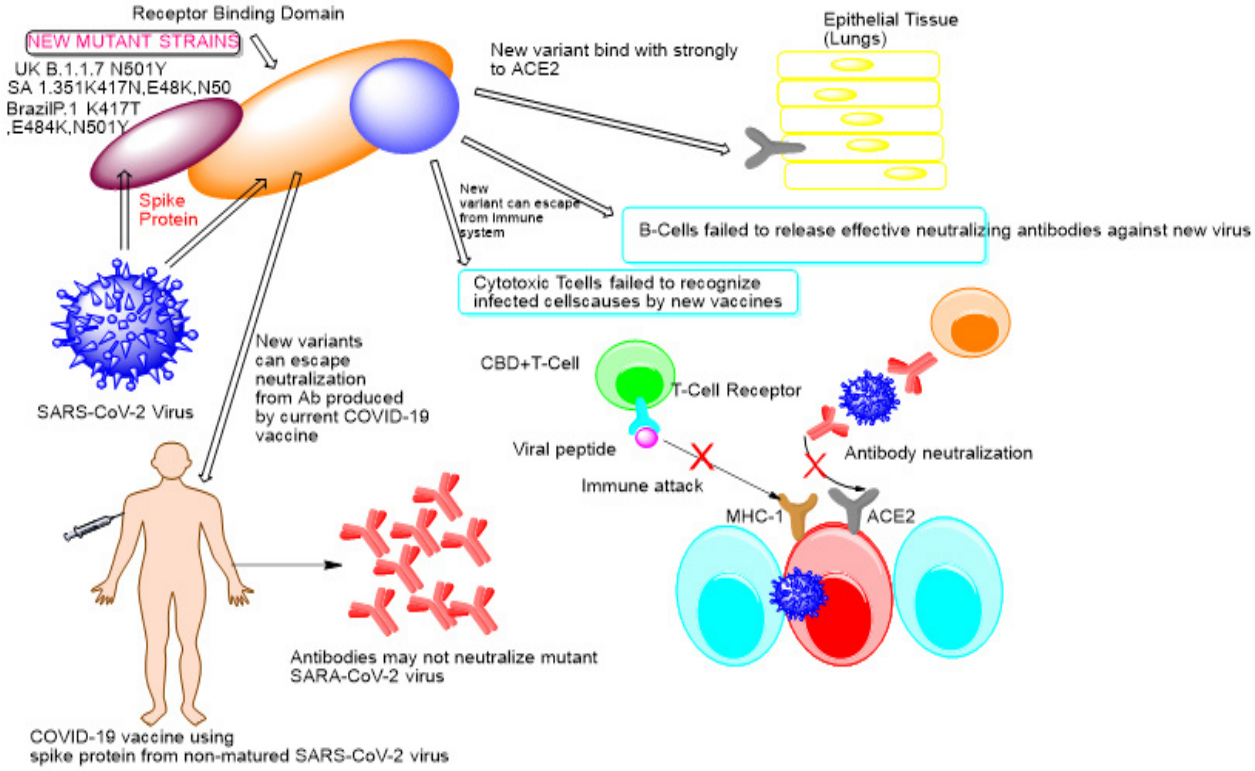

Fig 4: Mechanism of Action of SARS-CoV-2 Mutation[88]

Fig 4 depicted that the mechanism of action of SARS-CoV-2 mutation. In this diagram it has been clearly shown that how new mutated strain binds with the receptor.

5. CONCLUSION

It can be concluded that the adaptability of the viral genome and the continuous appearance of escape mutations or the dynamic evolution of B.1.351, B.1.1.7, B.1.617, and P.1, suggest that SARS-CoV-2 can become a seasonal virus like influenza with the need of re-adjusting the vaccines. Several spike proteins like N501Y, E484K, and K417N (for B.1.1.7 and

B.1.351), E484K, N501Yand K417T (for P.1), and D614G (for B.1.617) are responsible for the mutation of the strains. D614G is also present in the Delta Plus variant. It also has a K417N spike protein mutation. These are the spike proteins that are responsible for the mutation and transmissibility. In the Omicron variant, N679K is responsible for the speedy transmission where furin cleavage is also attached with it.

6. LIST OF ABBREVIATION

SARs-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
2019-nCoV: Novel Coronavirus 2019
COVID-19: Coronavirus Disease 2019
RNA: Ribonucleic Acid
MERS-CoV: Middle East Respiratory Syndrome Coronavirus
SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus
RBD: Receptor Binding Domain
RaTG13: Rhinolophus Affinis
ACE-2: Angiotensin-Converting Enzyme 2
DPP4: Dipeptidyl Peptidase-4
TMPRSS2: Transmembrane Protease Enzyme Serine 2
CD4+ T: Cluster of Differentiation 4 T Helper Cell
CD8+ T: Cluster of Differentiation 8 T Helper Cell
VOC: Variant of Concern
VOI: Variant of Interest
VUM: Variants Under Monitoring
VOHC: Variant of High Consequence
FMV: Formerly Monitored Variants
INSACOG: Indian SARS-CoV-2 consortium on Genomics
GISAID: Global Initiative on Sharing All Influenza Data
Ag-RDTs: Antigen-Detecting Rapid Diagnostic Tests
NERVTAG: New and Emerging Respiratory Virus Threats Advisory Group
hAce2: Human Angiotensin-Converting Enzyme 2
ORF: Overlapping open Reading Frames

7. AUTHORS CONTRIBUTION STATEMENT

Mr. Souvik Biswas selected the topic, did the overall planning, and edited all the pictures of this manuscript. Mr. Dipan Roy checked the similarity index after the completion of writing. Dr. Biplab Debnath checked the manuscript and guided the co-authors. Mr. Arijit Das and Mr. Rajarshi Nath searched the literature and collected all the data. Dr. Mrinmoy Nag helped co-authors during the writing of the manuscript. Ms. Poushali Boral, Ms. Poulomi Biswas, Mr. Debajit Dewan, Ms. Nabanita Pramanick, and Ms. Utkalika Sarkar drafted about all covid strains accordingly. Mr. Souvik Chattopadhyay and Mr. Soumya Datta checked the language and grammatical errors of the manuscript.

8. ACKNOWLEDGMENT

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9. HIGHLIGHTS OF THE MANUSCRIPT

- ✓ SARS-CoV-2 can become a seasonal virus like influenza.
- ✓ Omicron variant which is found in India recently.
- ✓ Spike proteins are responsible for mutation and transmissibility.
- ✓ N501Y, E484K, and K417N (for B.1.1.7 and B.1.351), E484K, N501Y and K417T (for P.1), and D614G (for B.1.617) are responsible for the mutation.
- ✓ Furin ring is responsible for infectivity.
- ✓ In the Omicron variant, N679K is responsible for the speedy transmission.

10. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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