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Review Article

Adaptation of new variants: A game changer in the evolution of SARS-CoV-2

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ABSTRACT

The World Health Organization classified Omicron and Delta variants as "variants of concern" because these variants stand as a warning that the epidemic is far from ended. Because of the pandemic's vast population size, long incubation period, and the diversity of environment, novel variants have been introduced into SARS-CoV-2 genome all over the world. The ability of virus to develop under selection pressure is aided by protective immune system of the host body. The environment of host body shapes its genetic fitness, dispersion, and evolution. Emerging viruses have used recombination and reassortment to create novel antigenic combinations that may enhance the process of cross-species dispersion. The tracking of SARS-CoV-2 genetic variants over time may aid in our knowledge of viral evolution, behavior, and infection trajectory.

Keywords: Coronavirus, Delta Variant, Mutation, Natural selection, Omicron, SARS-CoV-2

INTRODUCTION

Coronaviruses are Ribonucleic acid (RNA) RNA viruses with a positive strand that can acquire lot of genetic variation during replication in a short period of time. This is because of their high rate of nucleotide mutations.[1] Coronaviruses are grouped into four separate genera based on genetic and serological characterization: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*,[2-5] which come under the family *Coronaviridae*. *Alphacoronavirus* and *Betacoronavirus* generally infect mammals, *Gammacoronavirus* infects birds and mammal like white beluga whale and bottlenose dolphins whereas *Deltacoronavirus* infects birds and mammals other than human.[5-7]

A coronavirus strain discovered in a bat sample from Yunnan Province, China, in 2013, is the closest known relative of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). "RaTG13" is the name given to this strain, indicating that it was found in horseshoe bat *Rhinolophus affinis*, in 2013. It is widely known that "RATG13" and its genomic sequence are 96% identical to that of SARS-CoV-2.[8]

The World Health Organization (WHO) has proactively monitored variations in SARS-CoV-2 and reported 27 variants so far [Table 1].[9]

The SARS-CoV-2 variations are further classified in three groups depending on their virulence characteristics

Table 1: List of variants.

S. No.	Pango lineage	WHO label	Earliest documented samples	Classified by WHO as
1.	B.1.1.7	Alpha	United Kingdom September 2020	VOCs
2.	B.1.351	Beta	South Africa May 2020	VOCs
3.	P.1	Gamma	Brazil November 2020	VOCs
4.	B.1.617.2	Delta	India October 2020	VOCs
5.	B.1.1.529	Omicron	Multiple countries November 2021	VOCs
6.	C.37	Lambda	Peru December 2020	VOI
7.	B.1.621	Mu	Colombia January 2021	VOI
8.	B.1.1.318	-	Multiple countries January 2021	VUMs
9.	C.1.2	-	South Africa May 2021	VUMs
10.	B.1.640	-	Multiple countries September 2021	VUMs
11.	B.1.427 B.1.429	Epsilon	United States of America March 2020	Formerly monitored variants
12.	P.2	Zeta	Brazil April 2020	Formerly monitored variants
13.	P.3	Theta	Philippines January 2021	Formerly monitored variants
14.	B.1.526	Iota	United States of America November 2020	Formerly monitored variants
15.	B.1.525	Eta	Multiple countries December 2020	Formerly monitored variants
16.	B.1.617.1	Kappa	India October 2020	Formerly monitored variants
17.	AV.1	-	United Kingdom March 2021	Formerly monitored variants
18.	AT.1	-	Russia Federation January 2021	Formerly monitored variants
19.	R.1	-	Multiple countries January 2021	Formerly monitored variants
20.	B.1.466.2	-	Indonesia November 2020	Formerly monitored variants
21.	B.1.1.519	-	Multiple countries November 2020	Formerly monitored variants
22.	B.1.523	-	Multiple countries May 2020	Formerly monitored variants
23.	B.1.619	-	Multiple countries May 2020	Formerly monitored variants
24.	B.1.620	-	Multiple countries November 2020	Formerly monitored variants
25.	B.1.214.2	-	Multiple countries November 2020	Formerly monitored variants
26.	B.1.630	-	Dominican Republic March 2021	Formerly monitored variants
27.	C.36.3	-	Multiple countries January 2021	Formerly monitored variants

VOCs: Variants of concern, VOI: Variants of interest, VUMs: Variants under monitoring

Variants of interest (VOI)

VOI is a SARS-CoV-2 mutant with a genetic capacity that influences viral features such as illness severity, immunological escape, transmissibility, and diagnostic escape, according to the WHO. The WHO has found that a VOI results in a significant amount of community transmission.

Variants of concerns (VOCs)

VOCs share the same characteristics as VOI but they are more likely to cause an increase in hospitalizations or fatalities, as well as a substantial decline in antibody response from a previous infection and impaired therapy and vaccination efficacy. In addition, these strains are more transmissible than VOI. When evidence of a strain satisfies at least one of these criteria, it is upgraded from VOI to a VOC.

Variants under monitoring (VUMs)

VUMs are SARS-CoV-2 variants having genetic alterations that are anticipated to modify viral properties with fewer indication that it might pose future risk; however, information of phenotypic or epidemiological impact is still uncertain, requiring further surveillance.

Scientists are trying to figure out what role coronavirus variations, such as B.1.617.2 (Delta variant), are playing in India's COVID-19 outbreaks, which is the world's fastest growing variant. The Delta variant has been found in more than 130 countries around the world, according to the WHO, causing widespread alarm. It was labeled a "VOI" by the WHO, implying that it may include changes that make the virus more transmissible, produce more severe illness, or escape vaccination immunity. Indian SARS-CoV-2 Genomic Consortium reported on March 24, 2021, that it has discovered "a novel double mutant form" after sequencing fewer than 1% of coronavirus samples gathered by its member laboratories throughout the nation. Scientists were concerned because the variation had characteristics with two concerning lineages: Those originally found in California (B.1.427 and B.1.429) and those detected in South Africa (B.1.351) and Brazil (P.1) according to the Phylogenetic Assignment of Named Global Outbreak Lineages (PangoLin) software which is developed by members of the laboratory of Andrew Rambaut in 2020.

This novel variety has spread quickly, accounting for more than 60% of all coronavirus infections in Maharashtra, India's state with the highest number of COVID-19 cases. In fact, due to replicating errors generated as viruses reproduce in their host cells SARS-CoV-2, human immunodeficiency virus, and influenza viruses, which all encode their genetic instructions using molecular RNA, mutate more often than other types of viruses. Now, a new variant B.1.1.529 that has almost 32 mutations in the spike protein is spreading like a wild fire which was first reported in South Africa and on November 26, 2021, the WHO named it as "Omicron" and classified it as a "VOC." It is more transmissible than Delta variant and resistant to vaccination.[10]

The new variants quickly adapt themselves to the local human populations causing widespread concerns to the health experts. Following paragraphs describe factors contributing toward fast spread and adaptation of new variants.

HOST BODY ENVIRONMENT

SARS-CoV-2 is a highly virulent genetic variation due to its fast evolution in response to various host body environments and exceptional environmental stability. The pathogen is supported by a variety of host body environments, putting tremendous selection pressure on the pathogen genome. The pathogen evolves new characteristics through genetic evolution, which is then spontaneously picked by a vulnerable human host where it multiplies and ultimately causes disease and death. Furthermore, high environmental stability aids viral survival and propagation outside of the host body.[11]

The host body is a crucial element in the formation of the COVID-19 host pathogenic relationship,[12] as here is where molecular evolution takes place. The virus goes through many genetic alterations during replication to obtain its altered characteristics to fight for survival and infection establishment inside the host body. The SARS-CoV-2 virus then produces a unique spike protein receptor-binding domain (RBD) with a high degree of receptor binding property to human cells and adapts to match the character inside the host body. Natural selection eventually leads to its establishment in the host and it can cause infection.

EXTERNAL ENVIRONMENT

The external environment plays a role in the transmission of SARS-CoV-2 from one host to another by providing a favorable environment for the virus's stability and survival outside its host body, resulting in more variability and transmissibility than other coronaviruses.[13] It has been seen that in extremely hot weather, people tend to live scattered, whereas in cold weather, they tend to live in groups, thus giving more chance for transmission of the coronavirus. During the winter season, there is less availability of sunlight, so Vitamin-D levels are also low in people. Because of that, Vitamin-D deficient persons have reduced immunity to combat with coronavirus infection. Vitamin-D is important for the activation of immune system and it possesses anti-inflammatory and immunoregulatory characteristics.[14] Low temperature and low humidity have been found to be

supportive of coronavirus stability, with progressive increases in both parameters inactivating the virus more quickly.

MIGRATION

Migrations, changes in dietary preferences, and lifestyle patterns have all exposed the human population to new environmental niches as it has developed.[15-17] When people travel so often, especially in different countries, there is more chance for the accumulation of variants and mix up of their genetic constituents that may give rise to different strains. They have also interacted with a wide spectrum of novel microbes. Both of them are now in a race to evolve and establish themselves in this host pathogenic interaction by exerting enormous selection pressure on each other. This is when nature or the environment, as a major player, comes into action. Beyond the game of nucleotides, nature eventually picks the preponderance of genetic make-up and determines the winner from the beginning of life.

SPIKE PROTEIN AND EXPRESSION OF ANGIOTENSIN-CONVERTING ENZYME-2 (ACE2) RECEPTOR

SARS-CoV-2 contains a 30 kb genome,[8,18] similar to other coronaviruses, and encodes four structural proteins: Spike protein (S), envelop protein (E), membrane protein (M), and nucleocapsid protein (N).[19,20] The SARS-CoV-2 spike protein, which allows the virus to enter host cells, shows purifying selection and ancestral recombination signatures, resulting in an efficient S protein capable of infecting humans and other animals.[4,5] Korber *et al*. (2020) showed that there are now more SARS-CoV-2 viruses circulating in the human population worldwide that carry the G614 version of the spike protein rather than the D614 form that was first discovered in the first human cases in Wuhan, China.[4,21]

SARS-CoV-2's S protein, unlike those of other bat coronaviruses, is particularly effective in binding human ACE2[22] and so promotes the virus's fast spread throughout worldwide populations.[23-25] The expression pattern of the ACE2 receptor is a significant deciding factor for pathogen susceptibility, according to a recent genetic study on the SARS-CoV-2 ACE2 human receptor variance in different populations.[26] The genomic diversity and expression of the ACE2 receptor coding sequence in different SARS-CoV-2-infected populations throughout the world can impact SARS-CoV-2 binding and susceptibility. The circulating SARS-CoV-2 genome was subjected to severe selection pressure as a result of this ACE2 receptor, and the virus evolved to establish infection with its many genetic variants in a pandemic form around the world.[11,26]

POLYBASIC CLEAVAGE SITE

Through the addition of 12 nucleotides at the S1-S2 border, the SARS-CoV-2 spike glycoprotein has a functional polybasic (furin) cleavage site.[27,28] Follis *et al*., 2008 (Quoted by Rehman *et al*., 2020) found that insertion of a furin cleavage site at the S1-S2 junction enhances cell-cell fusion in an experimental study with SARS-CoV. For polybasic cleavage sites, insertion or recombination enhances the acquisition of converting low pathogenicity into highly pathogenic forms in CoVs. Polybasic cleavage sites have not been found in pangolin betacoronaviruses or bat betacoronaviruses.[8,29] Because the virus needs both mutation and the polybasic cleavage site for proper human ACE2 receptor binding, CoVs may have used a natural evolutionary process to mutate and acquire the polybasic cleavage site. For natural selection to achieve an ACE2 expressing gene that is similar to the human ortholog, a significant population density is necessary.

REASSORTMENT AND RECOMBINATION

When numerous viral genome segments infect the same animal or tissue at the same time, new viral progeny with multiple parent genome sets emerge. This process is known as "gene reassortment" and it is employed by viruses to evolve.[30]

According to recent research by Zhou *et al*., SARS-CoV-2 ancestors may have leapt into humans, acquired genetic characteristics through adaptation, and remained undetected throughout human-to-human transmission. Once it adapted to these changes, it became pandemic and produced enough instances to trigger the immune systems that detected it.[8,29,31]

The global expansion and exponential increase of the SARS-CoV-2 population (inside human hosts) have added to the genome's mutational diversity, allowing for more recombination chances. RNA polymerase in viruses must employ distinct RNA prototypes when creating negative or positive strands, resulting in homologous or non-homologous RNA recombination. This recombination model is called "copy and choice model."

If animals with various coronaviruses come into close contact and exchange viruses, recombination between the strains can occur, resulting in diversity. Unfortunately, it appears that such occurrences in SARS COV-2's evolutionary history have resulted in the development of a powerful strain capable of infecting human cells readily.[4]

MUTATION

Mutation in viral genomes is regarded as a fundamental component of their environment and it continues to be a significant aspect in their evolution. Huge population size of RNA viruses and fast mutation rates allow for rapid genotype

adjustment, allowing for speedy adaptations in a quickly changing environment. Positive selection drives to fix the positive fitness benefits of advantageous alleles, whereas negative selection eliminates lethal and deleterious alleles from a population. Mutations have a particular effect on viral reproductive success.[32]

Non-synonymous mutations can change the function of the proteins produced. As a result, natural selection is likely to affect them. On the other hand, synonymous mutations are less visible to natural selection since they have no visible effect on the resultant proteins. In fact, the reported ratio of non-synonymous to synonymous mutations is substantially lower than estimates from other coronaviruses, implying that the SARS-CoV-2 genome is subjected to intense purifying selection.[4]

The mutations L452R and E484Q appear to impair the spike RBD's interfacial interaction with certain neutralizing antibodies.[33-36] The monoclonal antibody (mAb) casirivimab (REGN10933) which is used to combat with coronavirus infection interacts with the RBD by forming two hydrogen bonds between the RBD's E484 and the antibody's Y53 and S56. The mAb P2B-2F6 (that has neutralizing activity against SARS-CoV-2) has direct interaction with residues L452 and E484.[34,35] In comparison to the wild-type strain, structural analysis revealed that the two RBD mutations L452R and E484Q may reduce the binding capacity of REGN10933 and P2B-2F6 antibodies to the variant strains.[34,35,37] Another recent study found that the L452R mutation can bypass the human leukocyte antigen-24 restriction on cellular immunity while simultaneously increasing viral infectivity (Motozono *et al*., 2021).[38]

SUMMARY

A microbial species natural inclination is to discover a convenient means to convey information and adapt to new environments to evolve.[39] In the case of viruses, particularly RNA viruses, the likelihood of ongoing viral genome circulation across various host species is substantial. During this time, the pathogen is under a lot of selection pressure from the host environment. The virus's decision to live or die is influenced by the environment in which it is housed. When a virus becomes effective, it is naturally chosen and modified to establish its character by exerting pathogenic effects on the host's genetic structure. When this process is repeated by exposure to different environments, it can progress to the point where it can produce a pandemic; otherwise, pathogen evolution is at an end.[11]

CONCLUSION

The modern human population is extremely dynamic and is subjected to a wide range of severe environmental circumstances. The widespread cohabitation and lifestyle pattern increase the risk of virus cross-transmission and create a vulnerable setting for the emergence of novel viral illnesses. The development of variations as a result of the accumulation of convergent mutations during the COVID-19 second and third waves should be explored further for their public health implications across the country. The formation and evolution of the SARS-CoV-2 are crucial for surveillance, the development of effective treatments for managing the epidemic, and SARS-CoV-2 prevention. In clinical practice, other than the development and testing of new SARS-CoV-2 vaccines, genomic surveillance will be useful to anticipate outbreaks, enabling the Infection Control Committee to initiate the required steps to combat cluster epidemics.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

The second author Prof. R. G. Saini is a member of Editorial Board of AUJMSR.

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