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Review

Newly Detected VOC 202012/01: Review

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Abstract

COVID-19 was primarily detected in Wuhan of China, in December 2019. So far, SARS-CoV-2 with RNA as a genetic material has undergone mutations giving rise to multiple variants. Mutation of a virus is considered to be a process of adaptation to the environment as a survival strategy. This phenomenon needs to be analyzed scientifically to make the world alert from its probable side effects. Therefore, this review paper focuses on the continuing evolution of SARS-CoV-2 leading to its new form VOC 202012/01.

1. Introduction:

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection has affected the entire globe and caused the health problems since December 2019. The higher number of sudden genetic alterations in the genetic make of SARS-CoV-2 has now generated multiple heirs from the strain of Wuhan fooling the immunity of hosts [1]. Proteins that are responsible structure of SARS-CoV-2 are membrane (M), nucleocapsid (N), spike (S), and envelope (E) proteins. Glycoprotein of surface S has a function regarding interaction in the company of the angiotensin-converting enzyme 2 (ACE2) receptor of the host along with fast spread across humans [2].

Nsps, synthesized as a result of breakup of the open reading frame 1ab (ORF1ab) polyproteins of virus, accumulate together to accelerate transcription and replication of it.

RNA-dependent RNA polymerases (RdRps) (nsp12) are proteins that are having many domains that catalyze template of RNA dependant phosphodiester bond synthesis linking ribonucleotides in the availability of ions of divalent metal [3,4]. It is the crucial constituent, which regulates synthesis of RNA of virus with the help of Nsp7 and Nsp8. Additionally, 5 proteins that are accessory are encoded via ORF6, ORF3a, ORF7a ORF8, and ORF10 genes [4,5].The mutation rate of RNA viruses is significantly high,

and it corresponds to virulence modulation and ability of evolution, traits that are considered valuable for viral adaptation to the environment [6]. Intervention by immune system of human induces viral mutations.

Not only fast worldwide spread but also transmission of SARS-CoV-2 offers the viral particle valuable chances for the nature selected rare-acted but crucial mutations [6]. Generally, many mutations by viruses are not harmful; mutations, for example, D614G found on the spike (S) protein survival capacity of viruses [3]. It is crucial to know the infectivity of SARS-CoV-2 that altered following the ongoing mutations and thereby predicting tendency of infection that may occur in future [7]. The lineage 501Y circulated earlier with the 501N lineage in Wales during the late autumn 2020. Later, another variant of the 501Y lineage was named as B.1.1.17 by CoG-UK [8].

It started spreading in September and became dominant in December 2020. Previously recorded results indicated that SARS-CoV-2 genomes that are having novel hotspots of mutation are coming into role continuously [8]. Studies also suggest that D614G gene mutation aided in the alteration of spike-trimer hydrogen bond interaction, due to which the RBD is re-oriented into an 'up' conformation resulting in the increase of ACE-2 receptor binding and infectivity [9]. This review paper focuses on the continuing evolution of SARS-CoV-2 leading to its new form VOC 202012/01.

2. Mutation:

The SARS-CoV-2 entry is a significant problem all over the globe. The emergence and re-emergence of the virus can be considered as an adaptation strategy for the virus to the environment [10]. The RNA and DNA viruses that consist of RNA as a replicative intermediate have been observed to display higher mutation rates that have been evaluated in 10^{-3} and 10^{-5} mis-incorporations per incorporated nucleotide [11]. The knowledge of mutation rates has helped in understanding and management of resistance for drug, programs of vaccination, immune escape, pathogenicity, and the emergence of the new mutated strains [11].

Mutation rates among viruses are due to errors in the action of a polymerase enzyme and capacity of the virus to repair mismatches in DNA through the process of proofreading as well as repair process that occurs after replication [11,12]. Other factors those are responsible for the cause of mutation includes enzymes of host, spontaneous injury to nucleic acid, and also genetic entities that are special and present in genomes of some viruses.

The mutation rates of viruses can be determined by numerous processes such as action of 3-exonuclease, natural injury to nucleic acid, polymerase infidelity, and replication mode [11,12] Few of these processes underline comprehensive diversity patterns in viruses viz. dissimilarities between viruses that posses both RNA as well as DNA as genetic materials, large and small genomic viruses, and between double-stranded along with single-stranded viruses, but the basis of these differences between the viruses are still unknown [10].

After the onset of the pandemic, it was studied that the genomes of SARS-CoV-2 exhibited different point mutations within various areas in relation with their geographies. Initially, three repeated mutations at positions 1408, 3036, 23403 were identified in Europe as well as another three at positions 17746, 17857, and 18060 in North America [13]. According to Pachetti et al. [5], the mutation of RdRp at position 14408 available in the genome of viruses belonging to Europe since 20 February, 2020 is related with more point mutations in comparison to genomes of viruses that belong to Asia.

Since RdRp is not simple with proofreading tasks combined with co-factors of viruses, for example, ExoN, nsp7, and nsp8, it is speculated that the mutation has impaired its activity of proofreading [5]. The probable answer may be alteration in the RdRp structure, which does not affect its catalytic activity but alters its binding capability with co-factors (ExoN, nsp7and nsp8) altering its mutation rate [5].

3. New Variants:

3.1 VOC 202012/01:

A distinct phylogenetic cluster was identified in the observation data of COG-UK. This variant was designated

as variant under Investigation 202012/01 (VUI 202012/12) on the detection, and after assessment, it was re-designated as Variant of Concern 202012/01 (VOC 202012/01) or B.1.1.7 lineage, first emerged in three regions of England: London, the South East and the East England (table 1) [14]. On 14 December 2020, the authorities of North Ireland and the United Kingdom of Great Britain announced to World Health Organization that a novel variant of SARS-CoV-2 was detected by genome sequencing of virus [13]. Initial reports indicated that the variant might readily infect people. This cluster has been growing rapidly over December 2020 and had been detected in another places in the UK, representing continued spread [14,15].

Total 1108 cases infected with SARS-CoV-2 VOC 202012/01 had been detected in the UK till 13 December 2020. The variant was discovered during an epidemiological and virological investigation that began in December 2020 owing to an unexpected rise of COVID-19 patients in South East England. From week 41 to week 50, more than 50 percent of isolates were reported as the viral variant strain in South East of England. Majority of the COVID-19 victims from whom this new strain has been isolated belonged to the age group under 60 years [16]. This new variant is characterized by 17 mutations (three deletions and 14 non-synonymous mutations) and multiple spike protein mutations (deletion 144, deletion 69-70, N501Y, P681H, D614G, T716I, S982A, A570D,D1118H) in addition to mutations from other areas of genome [17].

Three of the mutations have a prospective importance in relation with biology. According to the Global Initiative on Sharing Avian Influenza Data (GIASID), N501Y mutation has been noted in countries including Australia and South Africa [18,19]. The sequence analysis revealed that the N501Y mutation of the virus recorded in not only South Africa but also the United Kingdom originated separately (table 1). The importance of the mutation P681H is still unspecified.

Still, it is placed near the site of cleavage of furin in the spike protein (which is a crucial region for the process of infection with spread) [20]. The amino acid removal at positions 69 and 70 in the S protein results in various lineages of SARS-CoV-2 (that circulate) (related to get away from immunity in the patients, who are immunocompromised and helps infectivity of virus in vitro). Further, the deletion results into the failure of diagnostic assays that are commercially implemented to identify the gene that encodes the spike glycoprotein (S-gene drop out) and these S-gene target failures are frequent because of the novel variant [21]. There is a possibility that N501Y mutation may modify spike protein's binding affinity to receptor and this mutation either single-handedly or in combination with deletion of the amino acid at positions 69 and 70 in the N-terminal domain (NTD) results into the increased viral transmission [22].

Phylogenetic analysis of the variant discloses that there are extremely low figure of intermediary forms between the novel variant and the earlier circulating lineages communicated to GISAID. The difference between the cluster and the original Wuhan strain is 29 nucleotides, which is higher according to the current molecular clock that is equivalent to about two substitutions for each genome for each month. The fraction of non-synonymous mutations in the spike protein for VOC 202012/01 is to a great extent higher than that is usually anticipated from mutations that occur randomly [17].

Shockingly, from samples collected in November 2020, 3 sequences from Denmark with one from Australia cluster with the UK variant, which indicate that the viral variant has transmitted globally, even if the extent is unknown [17]. It is reported that the VOC 202012/01 in the East, East of England, and London regions is more transmissible (40-70%) than previous circulating viruses and showed to have an accelerated estimated reproduction number Rt (range of 1.5-1.7) [15].

3.2. Increased Transmissibility:

There might be a possibility that the N501Y mutation alters the receptor binding affinity. This mutation alone or the removal of amino acids at positions 69 and 70 might

significantly enhance the viral transmission. This is dependent on the position of the 501 residues in the spike RDB and data indicates that N501Y increases the interactions of spike protein with human ACE2. N501Y is one of the artificially produced RBD variants that showed to exhibit this behavior. It is recommended to consider that this spike mutation is the only variant reported till date in mouse-adapted SARS-CoV-2 as well as in infection of ferrets [23].

3.3 Antigenicity b:

A number of antibodies that are monoclonal have been studied, amd only one (LYCoV016) indicated reduced capacity to neutralize SARS-CoV-2 variants with mutations at position 501. However, there is no neutralization data on N501Y from polyclonal sera from infection, which is natural [23].

3.4 Possible cause of variation:

The high number of S protein mutations, the high sequencing coverage, and other genomic characteristics of the variant in the United Kingdom indicate that this variant has not evolved through slow accumulation of mutations [17]. There might be a possibility that the variants have evolved during pressure of selection from the continuous vaccination programs as the noticeable hike doesn't match the time frame of such activities [17]. One description for the arrival of the variant is extended SARS-CoV-2 infection in a singleton person who is having diminished immunocompetence.

This lengthened infection might result into the gathering of mutations that escape from immunity at an increased rate. Additionally, there is a possibility that a virus transmitted to humans from the infection of different susceptible animal species have adaptation processes [15]. This induced a variant's emergence with several S protein mutations (RBD mutation Y453F and deletion at positions 69-70) in Denmark during infection among mink [15]. Mink associated multiple S protein mutations were recorded in the Netherlands. There might also be a possibility that the variant has appeared all the way through spread in nations with almost nil or very less coverage of sequencing [15].

This hypothesis is not creditable enough because random mutations acquired during transmission of the virus cannot exhibit a high proportion of spike protein mutations and unexplored transmission for a longer span for the accumulation of a higher number of mutations (10 months) [15]. According to the GISAID EpiCoV database along with a press release from South Africa, there was a similar fast raise of a variant with the spike protein mutation N501Y, two RDB mutations, and numerous spike protein mutations [15,24].

4. Continuing Evolution:

RNA viruses are most likely to evolve to adapt to the environment, and since the genetic material of SARS-CoV-2 is RNA, it is continuously evolving. SARS-CoV and SARS-CoV-2 belong to the *Coronaviridae* family and have 30%dissimilarities due to mutations caused by the processes of genetic recombination, post replicative mechanism, and gene deletion [25]. Similarities between SARS-CoV-2 and SARS-CoV has helped predict upcoming patterns of the pandemic, and most likely, there are forthcoming variants of SARS-CoV-2 similar to the previous pandemic situation caused by SARS-CoV [25].

The uncanny similarities of the clinical features of SARS-CoV-2 with SARS and MERS suggest that it has emerged due to mutation most likely from its ancestor SARS-CoV. The rate of evolution of coronavirus might lead to the discovery of novel coronavirus and zoonotic incidences [25].

SARS-CoV and SARS-CoV-2 share Receptor Binding Domain (RBD) and S protein domain along with novel viral host cell entry and replication proteins with respect to their structure. More than 95% of sequences show the similarity between SARS-CoV 3CLpro and RdRp protease with that of SARS-CoV-2 and both have a genetic similarity of 79% in their sequences. Both the viruses have a common component (human ACE2 receptor), which suggests that the genetic modifications in newly arrived pathogen do not alter the recognition of the human cell receptor. Since, the binding of SARS-CoV-2 with human ACE2 is weak with the assistance of its spike protein, explaining the mechanism behind the less potential infection than the previous pandemic [25].

Table 1: The emerging variants as of January, 2021. [26,27]

Name	Mutation	Geographical Origin
B.1.1.7 lineage (20I/501Y.V1 Variant of Concern (VOC) 202012/01)	Mutation in the RBD of S protein at the position in which asparagine has been replaced by tyrosine. P618H: It is observed near the S1/S2 furin cleavage site. Deletion at positions 69 and 70.	United Kingdom [26][27]
B.1.351 lineage (20H/501Y.V2)	It has many mutations in the spike protein,that include E484K, K417T, and N501Y. It does not have the deletion at position 69/70. [26][27]	**South Africa [26] [27]**
P.1 lineage (20J/501Y.V3)	It is a branch of the B.1.1.28 lineage. It contains three mutations in the RBD of S protein, including K417T, E484K and N501Y. [26][27]	United States [26][27]
Lineage B.1.1.248	This variant has ten mutations in its spike protein, which includes N501Y and E484K.[26][27]	Brazil [26][27]

5. Other Variants:

5.1. 501Y.V2 (a.k.a. B.1.351):

This variant was found in Nelson Mandela Bay, South Africa, in October 2020 with manifold mutations in the spike protein N501Y (table 1). It does not contain the removal of amino acids at positions 69 and 70 as in the UK variant (VOC 202012/01) [14]. However, there is no availability of a proof to indicate that this variant causes highly severe disease or any alteration to the efficacy of the vaccine [14].

5.2. B.1.207:

Two SARS-CoV-2 sequences have been identified that have one non-synonymous mutation in the S protein (P681H) in common to the VOC 202012/01 (B.1.1.7). The P681H residue is near the S1/S2 furin cleavage site [14]. The undistinguishable features of the mentioned viruses suggest that the SARS-CoV-2 possibly mutate and generate more variants in the upcoming future.

6. Efficacy of the vaccine:

Vaccines generally produce antibodies against many areas in the spike protein, and as a result, a single change would most likely not render the vaccine ineffective [28]. There is currently no evidence on whether the vaccines would produce antibodies against the VOC 202012/01 and other variants that are yet to come in the future. Therefore, vaccine developers may need to reconsider testing with new variants as a precautionary measure and study the differences in the vaccine's effectiveness between the existing and new variants [15].

7. Future Perspective:

With the continuing evolution of SARS-CoV-2, it seems that the containment and treatment of the disease will be a long process. To tame the uncontrollable pandemic over the next few years, research regarding the mutations and possible evolution is a matter of concern. Since the virus can mutate into several forms, it is a threat to human life. An increasing number of variants might also pose a risk to the vaccine's efficacy across the globe.

Research should be carried out to find a solution to curb the proliferation of the virus. The SARS-CoV-2 studies should also focus on creating animal models that recapitulate the multiple aspects of human diseases and the safety and effectiveness of the vaccine. Considering the infection pattern and reappearance of SARS-CoV, MERS-CoV and the present SARS-CoV-2, research should be continued to interpret the possibility of reappearance of coronaviridae members.

8. Conclusion:

Since the first appearance of SARS-CoV-2, quite a high number of variants have evolved. It is most likely that upcoming variants can be expected in a few years. If the number of variants keeps on increasing, it is possible that the vaccines across the globe would be less effective.

Further studies would be required to conclude the details of the new variants and the vaccine's efficacy against the existing and upcoming variants.

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