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The emerging SARS-CoV-2 variants of concern

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***Abstract*:** Since emerging from Wuhan, China, in December of 2019, the coronavirus (SARS-CoV-2) has been causing devastating severe respiratory infections in humans worldwide. With the disease spreading faster than the medical community could contain it, death tolls increased at an alarming rate worldwide, causing the World Health Organization to officially sanction the SARS-CoV-2 outbreak as a pandemic, leading to a state of worldwide lockdown for the majority of the year 2020. There have been reports of new strains of the virus emerging in various parts of the world, with some strains displaying even greater infectivity and transmissibility. Areas of the emerging variant of concern arise from countries like the United Kingdom, South Africa, Brazil, and India. These mutations carry a lineage from N501Y, D614G, N439K, Y453F, and others, which are globally dominated by clades 20A, 20B, and 20C. This literature review intends to identify and report SARS-CoV-2 variants that are currently evolving and their disease implications.

Keywords: 501Y.V1, 501Y.V2, 501.V3, ACE2, B.1.1.7, COVID-19, D614G, E484K, genetic variations, N439K, N501Y, SARS-CoV-2, spike mutations, variants of concern, Y453F

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Introduction

The novel coronavirus of 2019 (COVID-19) pandemic is primarily due to the respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has affected millions of individuals worldwide.[1,2] As of 11 May 2021, according to the World Health Organization (WHO), cumulative confirmed cases and deaths due to COVID-19 were 158 million and 3.2 million, respectively.[3] The single-stranded SARS-CoV-2 is a ribonucleic acid (RNA) virus with a genetic configuration similar to that of the SARS outbreak from 2002 to 2004, SARS-CoV-1.[1,2,4] The structural proteins involved in SARS-CoV-2 are the RNA-containing nucleocapsid (N) protein and the three viral envelope proteins, which are S (spike), E (envelope), and M (membrane).[1,2,4] The mechanism of action of SARS-CoV-2 is cell entry *via* attachment of the spike protein to angiotensin-converting enzyme 2 (ACE2) receptors located on human cells.[1] The virus can be transmitted *via* respiratory droplets and aerosols.[1] A unique property of SARS-CoV-2 that has made it highly pathogenic and increased its susceptibility for transmission is the polybasic cleavage site.[5] This cleavage site on SARS-CoV-2 allows the activation of multiple spike proteins simultaneously, which effectively increases the pathogenicity, virulence, and species-to-species transmission.[5]

Since the pandemic began in China in December 2019, thousands of variants of SARS-CoV-2 have emerged.[4,6,7] The WHO defined the SARS-CoV-2 variant of concern (VOC) as a variant with increased transmissibility, virulence, and decreased response to available diagnostics, vaccines, and therapeutics.[8] The first major variant was observed in September in the United Kingdom (UK).[6,9] The variant, termed Variant of Concern 202012/01 (VOC 202012/01), causes point mutations of asparagine to tyrosine in the receptor-binding domain (RBD) of the spike protein.[6,9–11] This N501Y mutation became a

growing concern due to the virus being able to adhere to the ACE2 receptor more strongly.[9,10] Currently, the N501Y variant has been detected in over 40 countries outside of the UK.[9,10] The second major variant, that emerged in the last quarter of 2020, was the 501Y.V2 variant in South Africa.[9,10] This strain had a similar mechanism of action to the N501Y in the UK.[9,10] The 501Y.V2 variant has been detected in many countries outside of South Africa and is characterized by mutations in the S protein, including residues in the RBD—K417N, E484K, and N501Y.[9,12] Also, another variant with multiple mutations emerged in Denmark termed the "Cluster 5."[13] These point mutations occurred among four different amino acids in the spike protein.[13] Additionally, this Cluster 5 variant is immune to neutralizing antibodies.[13] The emergence of variants has highlighted the importance of early identification due to the potential for higher infectivity, transmissibility, and risks of mortality.[14,15] This paper aims to report on SARS-CoV-2 genetic variants of concern and their implication on the continuously evolving COVID-19 disease process.

Methodology

An electronic literature search was performed predominantly using databases such as PubMed, Google Scholar, EBSCOhost, Mendeley, and MedLine Plus. The search was limited to applicable journals and articles published from the initial emergence of the virus, 1 January 2020, until 11 May 2021. A manuscript was selected if it was relevant to the topic of genetic mutations or variants of SARS-CoV-2. Listed keywords were sought to narrow and navigate the search process. They include but were not limited to COVID-19, SARS-CoV-2, Variants of Concern, genetic variations, spike mutations, N501Y, D614G, N439K, Y453F, E484K, B.1.1.7, 501Y.V1, 501Y.V2, 501.V3, and ACE2.

Variants of SARS-CoV-2

SARS-CoV-2 infection utilizes the ACE2 receptor and the transmembrane serine protease (TMPRSS2) to spread disease by infecting human respiratory cells.[16] The entry of SARS-CoV-2 into the human body depends on the attachment of the viral spike (S) proteins to cellular receptors, like ACE2.[17–19] Also, S protein priming by human cell proteases, such as TMPRSS2, plays a role in the pathogenic entry of coronaviruses.[17] Differences in the interactions between proteins encoded by ACE2 human alleles and SARS-CoV-2 S proteins are being evaluated to better understand the prognosis of COVID-19 disease.[20] In other words, ACE2 and TMPRSS2 are important determinants for the pathophysiology of SARS-CoV-2 mutation(s), especially given the current manifestations in various variants, expressions, and epigenetic aspects observed in COVID-19 patients.[21,22]

Variants of SARS-CoV-2 are further being assessed, to determine whether a specific variant's transmissibility, clinical presentation, severity, or impact on countermeasures (i.e., diagnostics, therapeutics, and vaccines) hinders the disease process.[9,14,15,23] Therefore, priority has been placed on tracking the following mutations circulating worldwide: D614G (B.1 lineage), N501Y (several lineages), E484K (several lineages), K417 (several lineages), L452R (several lineages), Q677 (several lineages), and others.[9] D614G, a mutation of SARS-CoV-2 which emerged in early 2020, has a substitution in the gene encoding the S protein.[9] The D614G was the dominant form for several months worldwide, with increased infectivity and transmission.[7,9,24] This mutation replaced the initial SARS-CoV-2 strain originally identified in China (NC_045512)[24] and has not been shown to produce severe illness or alter the efficacy of the present laboratory diagnostics, therapeutics, vaccines, or public health preventative measures.[9,14,15] N439K was found to be less infectious than variant D614G; however, N439K still showed infectivity of COVID-19, making it a variant of interest and concern.[25] Receptor-binding motif (RBM) mutation is widespread among the second most commonly identified mutation in the RBD as of late 2020, N439K, which arose from lineage B.1 from the D614G mutated background.[9,26] N439K RBM mutation has independently emerged in multiple lineages, showing increased affinity in the spike protein for ACE2, resisting several monoclonal antibodies (a therapeutic approach), and escaping some polyclonal responses.[26] "Cluster 5" or Y453F variant, which emerged in August of 2020, may potentially evade the immunity of convalescent individuals, further suggesting that this variant may challenge the vaccine strategy should it spread.[27]

Therefore, emphasis is placed on characterizing the transmission capacity and the effect of this new variant.[27]

Originating from N501Y, the last VOC, the year 2020, month 12, variant 01, referred to as SARS-CoV-2 VOC 202012/01 or B.1.1.7, emerged in the UK, containing 23 nucleotide substitutions from the initial SARS-CoV-2.[9,15,28–30] This variant has shown increased transmissibility within the population.[15,31] Furthermore, VOC 202012/01 has a deletion at the position 69/70del that affects the performance of diagnostic polymerase chain reaction (PCR) assays with an S gene target which is not expected to pose a significant concern, as most facilities globally use PCR assays with multiple targets.[9,28] Since December 2020, this variant (B.1.1.7) has been detected in 110 countries/territories/areas.[9] Variant 501Y.V2, yet another subtype of N501Y mutation, is different from the UK 202012/01 variant.[9] The South African originating 501Y.V2 has caused the rapid displacement of other lineages circulating in Eastern Cape, Western Cape, and KwaZulu-Natal provinces, which may suggest increased transmissibility.[13,32]

As time evolves, so do the various mutations of SARS-CoV-2. Mutation E484K, connected with several lineages, has been shown to avoid select antibodies; whereas K417 mutation, also seen among several lineages which include B.1.351 and the P.1 of Brazil (an offshoot of B.1.1.28, but a close relative of the B.1.351), may bind more tightly to cells.[8] E484K has given rise to the B.1.525/B.1.526 lineage seen spreading among New York residents, perhaps because this version is more capable of evading antibodies, as well as binding more tightly to human cells due to the co-S477N mutation.[8,33,34]

Surging in late 2020, mutation L452R also referred to as the CAL.20C, a variant with lineages B.1.427 and B.1.429, has not yet been shown to be more infectious, though the numbers of confirmed cases are increasing throughout the state of California.[9,35,36] Furthermore, one unique lineage of interest with increased infectivity and immune escape is B.1.617, the "double mutant" that carries two prominent mutations: E484Q and L452R. This E484Q has a similar translocated location as E484K, which allows the virus to evade select types of antibodies. However, B.1.617, the predominant variant in India identified in October 2020, is responsible for the spread of deadly cases in the western state of Maharashtra and is vastly spreading in the UK, USA, and other locations. Another variant found to be spreading in Bengal, B.1.618, also known as "triple mutant," is suspected to have evolved from B.1.617 and has the V382L mutation in addition to E484Q and L452R.[9,37–39]

The emergence of variants, particularly from the lineage of B.1.1.7, has raised global scientific concern.[9,40] These clade and lineage nomenclatures in Table 1 aid in the genomic epidemiology of SARS-CoV-2 and tracking of the variants as shown in Figure 1. Therefore, multiple sources and the Global Initiative on Sharing Avian Influenza Data (GISAID), an open-access genomics consortium, were used to extract information to further identify genome sequences of SARS-CoV-2.[41] The marker mutations of six phylogenetic groupings comprise the nomenclature system for major clades: S, L, V, G, GH, and GR.[41] Initially, the human coronaviruses (hCoVs) split early from L (originating in Wuhan, China) to S; L into V and G; and later G into GH and GR.[41] The clades identified in Table 1 are further detailed by the tool referred to as the Phylogenetic Assignment of Name Global Outbreak LINeages (PANGOLIN), providing a comprehensive understanding of the COVID-19 pandemic.[41] Furthermore, clades are defined by the year they emerged and are assigned a new alphabetical letter based on discovery: 19A (first appearing in 2019), 19B (appearing after 19A), 20A (new emergence at the beginning of 2020), 20B, and 20C.[41–43]

Discussion

SARS-CoV-2, like many coronaviruses, is surrounded by a membrane.[1,2] To gain access to the host, the virus uses glycoproteins to fuse its membrane to that of the cell where replication takes place. The spike protein is a glycoprotein composed of a chain of 1273 amino acids.[19] Three spike molecules combine to form a functional unit known as a trimer.[19] In the case of SARS-CoV-2, there are approximately 26 trimers on a virus, one of which binds to the ACE2 protein initiating the release of the viral genome through fusion.[17–19]

Table 1. Clade and lineage nomenclature to understand genomic epidemiology of active coronaviruses.

Clades/ Nomenclature/ Phylogenetic Groupings*/**	Initial clade identified**	PANGOLIN lineage**	Variant mutation adaptation***	Notes*
L	19A	B		Wuhan, China December 2019 Disappearing worldwide
S	19B	A		1st mutation of L strain (beginning of 2020) Seen in Spain and restricted areas in the USA
V	19A	B		Appearance mid-January 2020 Disappearing worldwide
G	20A	B.1.525 B.1.160 B.1.617.1 B.1.617.2 B.1.258 B.1.221	N439K	Appearance mid-January 2020 Most widespread to date Increasing in prevalence
GR	20B 20B 20B 20D 20F 20I/501Y.V1	B.1.1 B.1.1.277 B.1.1.302 B.1.1.1 D.2 B.1.1.7	N501Y D614G	G mutated to GR at the end of February 2020. Most prevalent in Europe, Italy, and South America Increasing in prevalence
GH	20C 20C 20C 20C 20G 20H/501Y.V2 20J/501Y.V3	B.1.427 B.1.429 B.1.526 B.1.367 B.1.2 B.1.351 P.1	N501Y D614G	G mutated to GH at the end of February 2020. Most prevalent in North America, France, and Germany Increasing in prevalence D6146 mutation spread first around the world***** N501Y evolved into several lineages - P.1 (Brazil), B.1.351 (South Africa), and B.1.1.7 (UK)*****
GV	20E (EU1)	B.1.177		
Others****/*****			Y453F	Mink**** Cluster 5****
			E484K	Evolved into many lineages that can avoid several antibodies*****
			K417	The virus binds more tightly to cells and includes several lineages like P.1 and B.1.351*****
			L452R	The variant of concern particularly in California*****
			Q677	Found in USA lineages, but has not yet proven to be more infectious*****

Summarized list recreated from Science Daily,[42] Nextstrain,[43,**] GISAID,[41,***] Bayarri-Olmos *et al.*,[27,****] and the New York Times.[9,*****]

Viruses are constantly mutating, and this results in the upsurge of new variants. With the ongoing spread comes the expansion of SARS-CoV-2 as it adapts and acquires selective advantages. Currently, multiple variants are circulating globally. From the lineage nomenclature described in Table 1, a newfound lineage B.1.1.7 has resulted in numerous genetic mutations.[9] This strain was

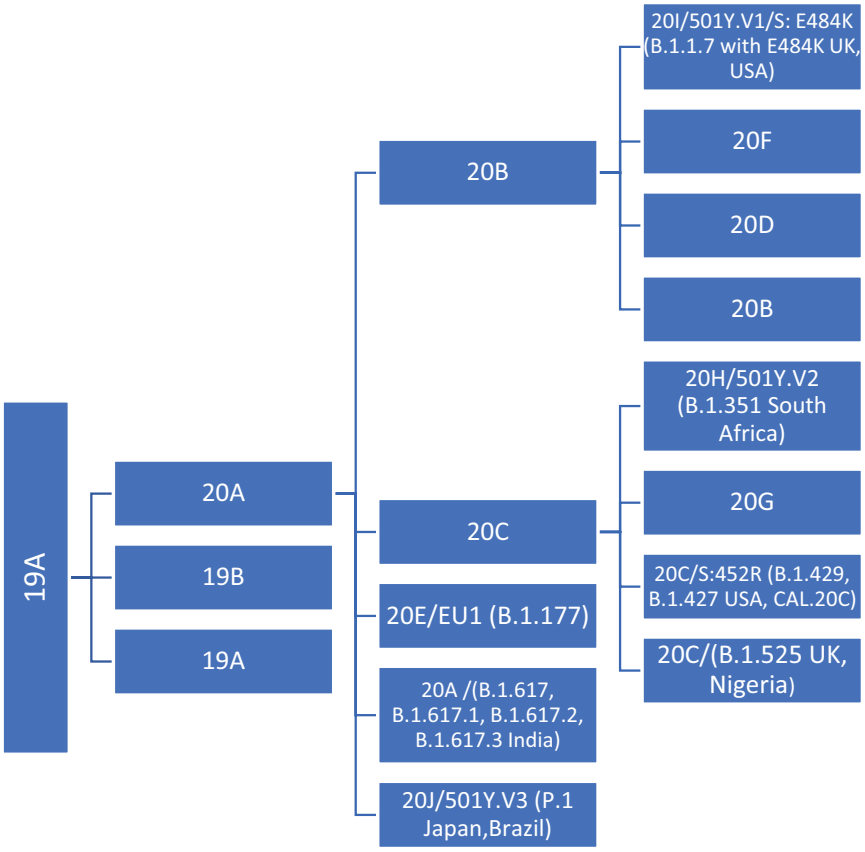

Figure 1. Chart showing the track of SARS-CoV-2 variants. Data recreated from Nextstrain.[43]
Note. 19A and 19B emerged in Wuhan and led the outbreak early in the course of disease transmissibility. 20A originated from 19A and influenced the European outbreak, which has since spread globally. 20B, 20C, 20D, and 20E are all derived from 20A. 20B and 20C are globally distributed, whereas 20D has been seen mainly in South Africa, South America, and southern Europe. Furthermore, 20E is localized in Europe. 20F comes from 20B and is located primarily in Australia. 20G arises from 20C and is detected primarily in the USA. 20H and 20I include two variants of concern (VOCs) emerging from N501Y; 501Y.V2 in South Africa and 501Y.V1 in the UK while 20J has the VOC 501Y.V3 or P1 which emerged from Brazil and Japan. The Indian VOC B.1.617 originated from 20A.

first reported in the UK, accounting for the majority of cases in England, and in comparison to the other lineages spreads quickly.[7,9,44,45] In addition to this lineage, several other variants have been noted and their implications could have potential consequences for efficacious spread, disease severity, evasion of detection by specific diagnostic tests, changes in therapeutic agents, and vaccine-induced immunity.[9,14,46] It is essential that the scientific community closely track the following mutations:

N501Y rapidly spreads as part of the B.1.1.7 and 501.V2 clades with an affinity for ACE2 receptors in humans.[9,47] This has been studied and shown to be indicative of natural selection, resulting in high transmissibility within a population.[48,49] Furthermore, a newer variant referred to as B.1.1.248 lineage has several mutations in the S protein, including N501Y and E484K.[50] This isolate has similarities with the isolate from the UK and South Africa. The variant isolate of E484K belonging to B.1.1.248, reported in the first week of 2021 in Brazil, also known as 501.V3 or P.1, is not identical to the new isolate identified in Japan, even though it is believed to have been carried *via* passengers aboard a flight from Brazil to Tokyo, Japan.[51] As a result, safety protocols should be enforced.

D614G, like N501Y, is also suggestive of natural selection and has been seen to infect many geographic regions.[48,51,52] It is proposed that this mutation resulted from viruses harboring 614G

leading to an outbreak of the D614G mutation,[53] where the (D) stands for aspartic acid at residue 614 of the spike viral protein that converts to glycine (G).[54] When a phylodynamic analysis was conducted of 25,000 sequences in the UK, it was found that those with 614G spread faster and contributed to more phylogenetic clusters than those with 614D.[54] The increased transmission rate of 614G viruses was confirmed in mouse models. Moreover, spike D614G (G614 virus) from hamsters infected with SARS-CoV-2 revealed higher infectious titers in the upper *versus* lower respiratory tract, supporting the evidence of increased transmission within humans.[55] In design, the current vaccines available within the USA are based on the original D614 sequence.[55] Sera from hamsters with D614G showed higher neutralization titers, which indicates that the efficacy of vaccines in clinical trials to protect against COVID-19 will not be compromised.[55]

N439K has a single amino acid change and has decreased sensitivity to neutralizing antibodies.[56] According to various studies, B.1.617 is the prevalent variant devastating India, which carries L452R spike mutation, and another, referred to as a "double mutant"[8] **Y453F** has an RBD which has seen an increased ACE2 binding.[57] This permits an immune escape from monoclonal antibodies, leading to an escape from the REGN10933.[58] Another strain has emerged in South Africa with B.1.351[9,59] lineage (Figure 1), also known as 20H / 501Y.V2, but has not been shown to have as many mutations nor contain the deletion 69/70 as seen with B.1.1.7.[9,49] Emerging data suggest that the UK VOC B.1.1.7 may be associated with an increased risk of death.[9,31] A diverse set of lineages with two main clusters from the 20G and the 20C lineage was identified in California.[9,35] The larger cluster consisted of a novel variant defined by five mutations descended from cluster 20C and is designated as CAL.20C (20C/S:452R; /B.1.429) (Figure 1).[35] As of 22 January 2021, CAL.20C has been reported in 26 states in the USA and other countries.[9,35] Furthermore, a new variant strain known as B.1.526 is reported to be spreading at an alarming rate in New York City since November 2020.[9] Spike mutation E484K is present in about half of this lineage, with a smaller fraction having S477N instead of E484K.[9,32,60,61]

Pathogenicity study showed that the cell surface Toll-like receptors (TLRs), especially TLR4, are probably involved in the recognition of molecular patterns from SARS-CoV-2 to induce inflammatory responses. Also, the S1 subunit of SARS-CoV-2 was shown to possess greater mutability potential when compared with the equivalent peptides found in MERS-CoV and SARS-CoV, which may explain its transmissibility in humans and across species with ease.[46,62] Thus, the S protein is a major structural protein of SARS-CoV-2[21,22,62] and the variants are a result of its modifications. This protein sequence is the target of the current vaccines produced by Pfizer/BioNTech and Moderna/National Institute of Allergy and Infectious Diseases (NIAID).[63–65] The scientific and medical communities are confident that the vaccine will be effective against the new variants.[64,65] However, it is uncertain whether the strength of the vaccine could potentially be reduced given that many mutations would be needed to completely escape the antibodies.[64,65] Currently, many trials and studies are being conducted to test whether the efficacy of the vaccines is uncompromised due to the variants, and should they be compromised, the vaccines would have to be redesigned.[45,66,67] The efficacy of ChAdOx1 nCoV-19 (AstraZeneca vaccine) against the B.1.1.7 variant of SARS-CoV-2 has been reported to be equivalent to the efficacy of the vaccine against other lineages.[68] Similarly, the mRNA-based SARS-CoV-2 vaccines from Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) elicit antibody responses against the RBD, which is the major target of neutralizing antibodies, in a manner that resembled natural infection.[65] However, the study further showed that variants that carry K417N/T, E484K, and N501Y mutations, such as the UK (B1.1.7/501Y.V1), South African (501Y.V2), and Brazil (B1.1.28/501.V3) variants, can reduce the neutralization potency of vaccine plasma.[65]

Therefore, close surveillance of the S protein must take place as the virus mutates to make certain the effectiveness of the authorized vaccines.[64,65] Also, vaccines against COVID-19 need to be updated regularly and the immunity monitored to compensate for viral evolution that may arise from the mutations.[65] In any instance, preventative measures such as social distancing, face mask use, and regular handwashing with soaps and water, or the use of hand sanitizers must be

upheld to slow the spread and help countries reduce hospitalizations and deaths. Therefore, additional research and investigations are required to fully comprehend the impact of each specific SARS-CoV-2 variant. Because of its complexity, this requires time, concerted effort, and collaboration by all concerned to effectively tackle and eliminate the disease caused by the virus.[9,14]

Conclusion

The infectious SARS-CoV-2 (COVID-19) virus is responsible for millions of casualties worldwide. It is the cause of a global pandemic, and its mutations form genetic variants that are yet to be fully understood. Furthermore, it is crucial to understand the new variants, to assess their impact on the rate of transmission, resilience, and mortality. The recent upward trend of COVID-19 cases can be attributed to these variants and their ability to transmit adeptly. Their pathological makeup makes them more resilient than the original strain and able to bind to receptor proteins more efficiently. However, further research is required to fully understand these variants and increase the accuracy of treatments to save lives. The public should consider vaccination along with the prescribed preventative measures, such as wearing a face mask, washing hands frequently, and practicing social distancing for the best chance of avoiding contracting the virus.

Author contributions

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Ethical statement

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