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# Genomics and molecular immunopathogenesis of SARS-CoV-2 variants of interest in Nigeria

**Oyejide Afolabi Olaniyan[1], Dolapo Damilare Olugbile[2], Adeola Victor Kolawole[2], Adepeju K. Olowookere[2], Tomiwa Williams Adeniji[2], Adebola M. Olaniyan[2], Ibraheem A. Ajetunmobi[3], Omolola O. Onayemi[3], Taiwo Omololu Omotoso[4], Paul Olusegun Adepoju[5], Adeolu Sunday Oluremi[5], Olalekan Ademola Kemiki[6], Oluwatosin Opeyemi Ogunwola[7], Samuel D. Adepoju[1], David B. Olugbodi[8], Afolabi A. Salawu[1,9,] Samuel S. Taiwo[2,10], Ayodele Ademola Adelakun[511]* and Oyejide Afolabi Olaniyan[2]**

[1]Department of Chemical Pathology, LAUTECH Teaching Hospital, Ogbomoso, Nigeria.
[2]Department of Medical Microbiology and Parasitology, LAUTECH Teaching Hospital, Ogbomoso, Nigeria
[3]Department of Haematology and Blood Transfusion Science, LAUTECH Teaching Hospital, Ogbomoso, Nigeria
[4]Department of Clinical Pharmacology, University College Hospital, Ibadan, Nigeria.
[5]Department of Medical Laboratory Science, Babcock University, Ilishan-Remo, Nigeria.
[6]Molecular Biology and Tissue Culture Laboratory, Babcock University Teaching Hospital, Ilishan-Remo, Nigeria.
[7]Philip's Project Centre, Bola Tinubu Diagnostic Centre, Lagos State University Teaching Hospital, Ikeja, Nigeria.
[8]Department of Histopathology and Morbid Anatomy, LAUTECH Teaching Hospital, Ogbomoso, Nigeria.
[9]Deparment of Chemical Pathology, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.
[10]Department of Medical Microbiology and Parasitology, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.
[11]Department of Medical Laboratory Science, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

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**The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has spurred global interest. Since the first recognition of SARS-CoV-2, thousands of genomic mutations have been developed and more are still to come for the ability of SARS-CoV-2 to rapidly evolve and adapt is due to its high mutability, which allows new lineages and variants to emerge. These mutations result in changes to the virus properties, such as severity and transmissibility, making it even more difficult to contain. Hence, the increased release of data that are sequencing-related; more mutations as well as genetic SARS-CoV-2 diversity were declared to understand the viral variants, therefore, is useful in countries with little or no facilities for surveillance. In this review, our research team summarized several literatures including: Clinical reports, cohort studies, reviews, case series, and editorials to present a descriptive impression of the variation in the basic molecular structure of SARS-CoV-2. Thus, providing an overview of the nomenclature of all circulating variants, characteristics of mutant variants and possible consequences of mutation of variants of interest in Nigeria.**

**Key words:** Coronaviruses, COVID-19 pandemic, genetic diversity, mutation.

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the aetiologic agent of the novel coronavirus disease 2019 (COVID-19) had continued to mount global public health concerns, with attendant to pathological events and unprecedented consequences. First reported in Wuhan, China in December 2019 (Wang et al., 2020;

WHO, 2020), COVID-19 had nonetheless spread to most countries in the world. According to WHO as at September 2021, there have been 226,844,344 confirmed cases of COVID-19, including 4,666,334 deaths, while 5,634,533,040 vaccine doses had been administered. Beyond spread, (SARS-CoV-2) had not ceased to evolve around the world, generating new variants of interest and concern.

Therefore, generating unfamiliar approach that enhanced viral capacity for spread as well as evasion from vaccines and drug interventions (Chen et al., 2021; Xie et al., 2021; Plante et al., 2021; Liu et al., 2021a, b). As the global community battles this novel virus through rigorous screening of individuals for the existence of infection, there is also an improved need for a genomic analysis of the virus which is expected to reveal more about the spread and infection characterization. A sequences pool from numerous countries of the world would help in evaluating the mutational propensities of the virus as it crosses different geographical locations, conditions as well as diverse cultures people, deviations of genetic as well as immune status (Bajaj and Purohit, 2020). Complete genome viruses sequencing is not only an important tool for the diagnostics and vaccines development, but also vital in studying virus pathogenicity virulence, tracking evolutionary paths as well as the genetic suggestion being studied among viruses and their hosts (Maurier et al., 2019).

Severe acute respiratory syndrome coronavirus 2 is an enclosed virion measuring about 120 nm in diameter, belonging to the subfamily Orthocoronavirinae, family Coronaviridae, order Nidovirales, and realm Riboviria. The viron particle comprises positive-sense-single ribonucleic acid (RNA) strand with a genome 29.99 kb size encoding for multiple nonstructural and physical proteins (Lu et al., 2020; Chan et al., 2020). The virus enters into type II pneumocytes of the lungs through angiotensin converting enzyme-2 (ACE2) receptor (Ou et al., 2020), and subsequently replicates, then migrates down the airways to enter alveolar epithelial cells. In summary, SARS-CoV-2 replication in the lungs might induce a robust immune response, with pathogenesis mimicking that of mild viral pneumonia to severe acute respiratory distress syndrome (Ni et al., 2020; Baj et al., 2020).

No doubt, the elimination of the present pandemic appears difficult due to continuous emergence of mutant strains from the original viral strain. Currently, there is little comprehensive research on the different variants and mutations of the coronavirus and their impending impact on the global community. Thousands of mutant strains have been indentified since the emergence of the virus (Li et al., 2020). Most of the mutations recorded in SARS-CoV-2 genome have not been documented to have notable effects on the spread, the virulence, nor course of the disease (Chen et al., 2020). This is most likely because the viral signals might escape the immune guard originating from a previous infection or vaccination (Collier et al., 2021).

This review presents the molecular characterization of SARS-CoV-2 variants. The current understanding was highlighted by providing an overview of the nomenclature of all publicly available circulating variants in Nigeria, as well as, identifying genetic viral variants characteristics in mutational changes view and possible consequences of mutation of variants of interest in Nigeria.

## MATERIALS AND METHODS

The literature materials for this review were obtained through a web search. Online databases including Website of science (WoS), Public Biomedical (PubMed), PubMed Central, Google Scholar, Scopus and Medline were searched for useful publications using keywords: Coronavirus pandemic, Pathophysiology of COVID-19, SARS-CoV-2 Genome, COVID-19 immunopathogenesis, genomics of SARS-CoV-2, clinical features of COVID 19, COVID-19 in Nigeria, Biochemistry of SARS-CoV-2, Variants of SARS-CoV-2, Variants of interest in SARS-CoV-2 and Genetic Mutations of SARS-CoV-2. The relevant articles were 145 released between January 2020 and September 2021 and significant number of them was indexed by WoS. The articles included clinical reports, cohort studies, reviews, case series, and editorials. Articles that met the aim of this review were further screened and examined while those that were not written in English language were excluded; and out of 145 articles obtained a total of 43 eligible articles were then summarized into our final draft.

## DISCUSSION

### Molecular basis of SARS-COV-2 virology

There are seven known human coronaviruses (hCoV) identified so far, out of which two are alpha-coronaviruses (hCoV-229E and hCoV-NL63) and five are beta-coronaviruses (hCoV-HKU1, hCoV-OC43, SARSCoV, MERS-CoV, and SARS-CoV-2). Patients who are infected with hCoV-229E, hCoV-NL63, hCoV-OC43, and hCoV-HKU1 manifest only common cold (Paules et al., 2020). Nonetheless, SARS-CoV, MERS-CoV and SARS-CoV-2 cause severe acute respiratory syndrome (SARS). Like other human corona viruses, SARS-CoV-2 genome consists of single-stranded positive-sense RNA, genome of 29–30 kb in size with 5′-cap and 3′-poly-A tail structure (Zhu et al., 2020; Wu et al., 2020), and a low G + C content of 38% as attributed to other Corona viruses (Lu et al., 2020). As a result, SARS-CoV-2 genome is

*Corresponding author. E-mail: adelakuna@babcock.edu.ng.

unbalanced at raised temperature comparable to the hCoV-OC43 genome (63% A+U and 37% G+C), and the hCoV-NL63 genome (66% A+U and 34% G+C) (Brant et al., 2021).

In SARS-CoV-2, replicase genes constitute the first two-third of the genome. These replicase genes encode for large structural polyproteins – pp1a and pp1ab which are later converted through proteolytic cleavage into 16 nonstructural proteins using multiple proteases. The remaining one-third of the genome is composed of Open Reading Frames (ORFs) for structural proteins like spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Liu et al., 2014; Chan et al., 2020). In addition to both structural and non-structural encoding sequence, genome also contains leader and transcription-regulatory sequence (TRS) such as TRS-L and TRS-B, which are charged with intermittent synthesis of intermediate negative strands of subgenomic RNAs (sgRNA). The SARS-CoV-2, trimeric glycoprotein, is made up of 1273 amino acids. It comprises two subunits, S1 and S2 (Ou et al., 2020). S1 is responsible for the viral entry by attaching to host cell ACE2 receptor through the S1 receptor-binding domain (RBD), whereas the S2 subunit allows virus-cell viral fusion with cellular membranes (Chan et al., 2020; Ou et al., 2020).

## The central DOGMA

The start of SARS-CoV-2 infection was with the virion addition to the cells targeted mostly via connections of the S proteins with host-cell's angiotensin-converting enzyme 2 (ACE2) receptor (Zhou et al., 2020; Wrapp et al., 2020; Walls et al., 2020; Yan et al., 2020). Proteolytic S protein cleavage primed by transmembrane protease serine2 (TMPRSS2) results in protein structural changes that initiate virus-host membrane fusion and the viral gRNA release into the host cell cytoplasm.

Both ACE2 as well as TMPRSS2 are expressed on many cell types, with highest expression in lungs, intestinal epithelial and endothelial cells, allowing SARS-CoV-2 to target various organs that are vital (Hoffmann et al., 2020; Hamming et al., 2004; Lukassen et al., 2020; Davidson et al., 2020). Asian SARS-CoV-2 reproduces completely in the infected cells cytoplasm. The positive sense viral RNA genome (+gRNA) serves directly as a messenger RNA (mRNA) for translation of the ORF1a and ORF1b as well as a template for RNA transcription. Subsequent interactions of the nonstructural proteins (nsps); including viral RNA-dependent RNA polymerase (RdRP), lead to formation of a replication transcription complex (RTC) on the template of +gRNA for RNA record, as well as, viral subgenomic RNA (sgRNA) synthesis inside double membrane vesicles (DMVs) (Wolff et al., 2020; Klein et al., 2020). The newly synthesized sgRNAs on the loose DMV encode viral structural as well as accessory proteins. Eventually, the newly structured gRNA is encapsidated with N proteins, surrounded by a viral cover as well as released from the infected cells (Hartenian et al., 2020).

## Genetic mutation exhibited by SARS-COV-2

The natural by-product that results from the genomic order of SARS-CoV-2 throughout the replication process is mutation (Wang et al., 2020; Sanjuan and Domingo-Calap, 2016). The fate of these newly arising mutations is mostly decided by natural selection processes. Mutations within the viral genome which favours its survival are maintained, frequency as new variants, while those deleterious are excluded from the viral population. This process facilitates viral replication, transmissibility and/or immune escape (Rodpothong and Auewarakul, 2012; Livnat, 2013).

## Naming of SARS-CoV-2 variants

The established systems for naming and tracking SARS-CoV-2 genetic lineages have been grouped into three, namely: GISAID, Nextstrain, and PANGO. These systems classified the virus into monophyletic groups of distinct pathogenic and genetic features called 'clades' (Karki et al., 2015; Zhao et al., 2020).

### *Phylogenetic assignment of named global outbreak (PANGO) lineages*

A total 81 SARS-CoV-2 virus lineages were identified. The lineages of key concern were A, B and B.1. Additional six lineages, A.1 to A.6 were known from lineage A, while descendant of two sublineages, A.1.1 and A.1.3 were known from A.1. Sixteen lineages openly created from lineage B. The B.1 lineage is the main known lineage sub-classified into more than 70 sub-lineages (Rambaut et al., 2020a).

### *Nextstrain*

A total 11 main clades were recognized. These clades were named by the discovery year. 19A and 19B: were recognized during the early outbreak at Wuhan while 20A was acknowledged in Europe during March 2020 outbreak. 20C and 20D were inherently diverse sub-clades of 20A. 20D to 20I appeared in early summer in 2020 (Guan et al., 2020).

### *Global initiative on sharing all influenza data (GISAID)*

The acknowledged nine major clades were: GH, GRY, G,

S, O, GV, L and V (Guan et al., 2020).

However, because of the increasing evolution of the virus, and the continuous improvement in the comprehension of the impacts of variants, these working definitions can be adjusted. In cases where variants do not meet all the criteria listed above, they are designated as Variants of Interest (VOI) or Variants of Concern (VOC), and those which have potential of posing a diminishing risk relative to other circulating variants may be further classified, in consultation with the WHO Virus Evolution Working Group (WHO, 2022).

**Variants of concern (VOC):** These are variants with increased transmissibility or detrimental change in COVID-19 epidemiology, increase in virulence or change in clinical disease presentation, decrease in effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics (WHO, 2021).

**Variants of interest (VOI):** These are variants with hereditary changes that are expected or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape. They are known to cause important community transmission or numerous COVID-19 clusters, in many countries with growing relative occurrence alongside growing case number over time, or other specious epidemiological effects to suggest a risk to global public health (WHO, 2021).

## Circulating variants of SARS-CoV-2 in Nigeria

According to the report of The Nigerian Centre for Disease Control, about 55 different SARS-CoV-2 lineages were known to be circulating in Nigeria and they are changing rapidly (NCDC, 2021). This diversity indicated multiple introductions of the virus into Nigeria from different parts of the world, and community transmission. All SARS-CoV-2 strains naturally undergo genetic mutation over time. Mutation considered an adaptive mechanism that enhances survival and reproduction compared to progenitors. Mutant viruses, therefore, were more frequently encountered due to natural selection, more efficient transmission, severity of disease, evasion of immunological memory, as well as, existing diagnostic techniques (NCDC, 2021).

## Variants of concern (VOC)

### *Lineage B.1.1.7*

Lineage B.1.1.7 (also called 501Y.V1) is a phylogenetic cluster, first discovered in England, and is associated with increased transmissibility which might suggest natural selection of the virus at level of population. It is the dominant SARS-CoV-2 variant circulating in the UK and has also been documented in several other countries with resources for genomic surveillance (Rambaut et al., 2020b).

Between November 2020 and January 2021, Nigeria recorded a total of 29 cases with the B.1.1.7 variant strain and have since then been further detected in Nigeria. These strains were detected from cases in Lagos, Edo, Federal Capital Territory (FCT), Kwara, Osun and Oyo states (NCDC, 2021).

Seventeen lineage-defining mutations had been identified prior to its detection in early September 2020. By December 2020, it accounted for about 28% of cases of SARS-CoV-2 infection in the UK, and population genetic models suggest this variant is spreading 56% more quickly than other lineages (Davies et al., 2021). The variant has no record of an important effect on administered vaccine efficacy or diagnostic and/or therapies. Significant mutations have been noted to be exhibited by this variant. Maybe, mutations in the receptor-binding domain region of this strain includes: E484K, S494P and N501Y, whereas 69del, 70del, D614G, 144del, A570D, S982A, P681H, D1118H, T716I and K1191N mutations are establish on the S-glycoprotein (Akkiz, 2021). Graham and his colleagues (Graham et al., 2021) perceived that this variant is resistant to neutralization by neutralizing antibodies.

### *B.1.617 variant (Sublineages B.1.617.2 (Delta))*

This variant was first recorded in October 2020 at Maharashtra state in India. It was accountable for the notable surge in infections which resulted in a second wave of the pandemic in India during April 2021 (Chakraborty et al., 2021; Vaidyanathan, 2021). The first confirmed case of the SARS-CoV-2 Delta variant; also known as lineage B.1.617.2, was declared on July 2021. The variant which was detected in a traveler to Nigeria possessed unique genetic modifications at E484Q, D111D, G142D, L452R, D614G, and P681R (NCDC, 2021). The E484Q, L452R, as well as P681R mutations were the main circulatory variants (WHO, 2021). Currently, three sub lineages have been documented for this variant which are: B.1.617.1, B.1.617.2, and B.1.617.3 [ECDC web]. In B.1.617.2, the notable mutations at the receptor binding domain which included L452R and T478K, while the main mutations in the S-glycoprotein were T19R, G142D, D614G, P681R, 157del, R158G, 156del, and D950N (Kumar, 2021). Following analytical results of Yadav et al. (2022), they deduced that the influence of this lineage was found to be deactivated by the presently available COVID-19 vaccine, and that the variant has no recorded effect on immune evasion and therapies.

### *Variants of interest (VOI)*

**B.1.525 (Eta) variant:** In February 2021, a new variant

was discovered in Nigeria and also reported in the UK, called B.1.525 variant, which is also known as 20A/S.484K and G/484K.V3, defined by the Nextstrain and the GISAID respectively. Only 159 sequences from this lineage was deposited on GISAID by February 2021, out of which Nigeria was the one of the most frequent country of origin, accounting for approximately 25% of the sequences (O'Toole and Hill, 2021). The first detected case of B.1.525 variant in Nigeria was in a sample collected in November, 2020 from a patient in Lagos State (NCDC, 2021). Since its discovery, the novel variant has got diffused to different parts of the world; it has also been recently defined as a lineage of international significance [O'Toole and Hill, 2021]. For example, the identification of the variant has continued to create a test for public healthcare personnels in Brazil (Pereira et al., 2021). Since its discovery, significant mutations have been reported on the S-glycoprotein chain which was: A67V, 144del, D614G, 69del, ss70del, Q677H and F888L. In addition, E484K mutation is a significant mutation that has been reported on the receptor binding domain (RBD) of spike protein (Chakraborty et al., 2021).

### *Significant mutation of the variant of interest (VOI) and immunopathogenesis in Nigeria*

**K417T/N mutations:** Two important mutations that are found in the receptor binding domain region (RBD) - K417T and K417N were associated with a conformational S protein change. These mutations have been found to be accountable for the antibody escape characteristic of the virus (Boehm et al., 2021; Greaney et al., 2021). Also, these mutations were associated with the human angiotensin converting enzyme 2 (hACE2) binding affinity of the virus. Therefore, SARS-CoV-2 variants that manifest these mutations usually had increased infectivity due to increased affinity of binding to hACE2 (Khan et al., 2021).

**E484K mutation:** This mutation is connected with the conformational change in the flexible loop S protein RBD region. In addition, it is connected to the hACE2 virus binding, the increased infectivity of these alternatives, and the immune evasion phenomenon (Khan et al., 2021; Lohr et al., 2021). Jangra and colleagues (Jangra et al., 2021) stated its influence on nAbs binding, consequently, the decreased antibody neutralization triggering the re-infection, as recorded in the SARS-CoV-2 re-infected patients in Brazil (Nonaka et al., 2021).

**N501Y mutation:** The N501Y variant (replacement of Asparagine to Tyrosine at 501 amino acid position) is connected with the alteration in the Spike glycoprotein RBD region. Zhao et al. (2021) estimated the variant-specific case fatality ratio (CFR) using an instrument called time-varying representation statistical framework, as well as, they calculated changes in CFR. They deduced that N501Y substitution is associated with a possibility of case fatality for COVID-19 patients. Ali et al. (2021) discovered that this mutation results in a strain that binds with ACE2 in a manner similar to that of Monte Carlo sample as well as molecular dynamic simulations, and that the molecular association all through binding might contribute more than 40% of total binding energy. By using whole genome sequencing as well as Swiss-wide diagnostic screening, researchers recognized that this mutation is connected with increased transmission as well as rapid spread of the new variants in Switzerland (Mansbach et al., 2021).

**L452R mutation:** It was previously documented that other variants of SARS-CoV-2 such as VOC B.1.429, B.1.427, B.1.617 (and its sublineages) and VOI B.1.427 exhibited this mutation (Thakur et al., 2021). It has been connected with the alteration in the RBD region. Marked inactivity of therapeutic antibodies and increased spread of the virus has been strongly linked with the genetic changes arising from this mutation. Researchers found that it is related with more than 18–24% higher transmissibility. At the same time, a 20-fold decrease was observed in neutralizing titers from vaccine recipient individuals as well as improving patients (Deng et al., 2021).

**D614G mutation:** A substitution of aspartic acid (D) to glycine (G) at 614 amino acid position was found in the S-glycoprotein outside the RBD region, among the domains of S1 and S2. The mutation was noted in all the reported VOC variants such as P.1, B.1.427, B.1.1.7, B.1.429, as well as, B.1.351. This mutation is also found in the S-glycoprotein outside the RBD region of all the stated VOIs including B.1.525. Therefore, it is a highly important mutation in the newly appearing SARS-CoV-2 variants. Through in vitro experiments, it has been observed that variants with G-form carries an amino acid replacement D614G, highly infectious, and is associated with higher viral loads in the upper part of the airway in the respiratory tract (Mansbach et al., 2021). Also, this S-glycoprotein mutation is connected with enlarged transmissibility of the new variant (Plante et al., 2021; Zou et al., 2021).

**P681R mutation:** The mutation can be detected adjoining to the furin cleavage site. It might have a significant impact on the S1/S2 region cleavage, thereby influencing the virus cell entry. Although sufficient research evidence is not available yet, this mutation might also have a significant effect on the infectivity (Conti et al., 2020).

### *Synopsis of the possible consequences of variants of interest in Nigeria*

A lot of countries have established extensive genetic

surveillance as well as reporting systems, yet numerous regions across the globe still have a long way to go (Lemey et al., 2020). Many African countries have far lesser records of sequences compared to their cumulative case counts (Lu et al., 2021; Inzaule et al., 2021). Significantly, Nigeria, which is the most occupied country in Africa, has only small number of reported SARS-CoV-2 orders, relative to the recorded cases number.

To place in perspective, the majority of the SARS-CoV-2 genome sequences publicly available from Nigeria had been made through the help of the African Centre of Excellence for Genomics of Infectious Disease (ACEGID), which concurrently helps other African countries (www.acegid.org). Nevertheless, the Nigeria status being the epicenter of commerce as well as travel in Africa increases the risk of infection spread. Hence, unnoticed increase of a highly infectious, virulent, viral variant with potential mutations that might facilitate immune escape. Consequently, Nigeria could have major repercussions for the whole continent. Therefore, increased sample collection and sequencing would go a long way in strengthening the national and continental public health value of COVID-19 surveillance efforts (Ozer et al., 2021). The possible consequences of Variants of Interest in Nigeria include:

**Increased transmissibility:** D614G mutation is associated with higher viral loads in the upper part of the airway in the respiratory tract (Lu et al., 2021) and increased transmissibility of the new variant [Inzaule et al., 2021]. For example, variants with similar mutation such as D614G ([Conti et al., 2020), B.1.1.7 (Rahimi and Abadi, 2021) and B.1.617 (Cherian et al., 2021) of SARS-CoV-2 has been connected with faster transmissibility. D614G mutation in Spike glycoprotein was established to increase viral entry into airway epithelial cells as well as confers improved transmissibility among infected patient in Nigeria (Ozer et al., 2021)

**Possible impact on vaccine effectiveness:** Spike glycoprotein of the virus assigns to ACE2 receptor in respiratory tract for viral entry, vital target for neutralizing antibody, as well as, a target for vaccine action (Koyama et al., 2020). Though, mutation (s) that is added in the spike glycoprotein such as E484K and L452R could lead to immune escape from deactivating antibody as well as replacing other circulating variants by increasing transmissibility at a large level of populace. According to a study among individuals who previously had COVID-19 infections in Oyo State Nigeria by Ozer et al. (2021), it was found out that in addition to improved viral entry efficiency, reduced antibody neutralization and viruses carrying B.1.525 Spike proteins were also detected in convalescent serum. Thus, Genomic virus sequencing should be done from fully vaccinated individuals admitted to hospital with possible case of re-infection with SARS-CoV-2 infection to recognize the new variants (Koyama et al., 2020). Global spread of this new variant can be reduced by efficient genomic surveillance that monitors viral immune responses and vaccine effectiveness.

**Severity of infection:** Majorly Lineage B.1.1.7 variant with similar pattern of mutations as B.1.525, has been connected with improved infection severity, hence continuous study should be in place to understand the possible severity of infection associated with this variant (Rahimi and Abadi, 2021).

**Possible effect on diagnosis:** Mutations in the S-glycoprotein variant of SARS-CoV-2 touches the spike protein discovery by RT-PCR. Nonetheless, most of the commercially available PCR protocols are using multiple targets as well as this discusses no important influence on diagnosis (Korber et al., 2020).

## CONCLUSION

Substantial policies and guidelines are in place to prevent COVID-19 spread through pharmaceutical and non-pharmaceutical measures. However, emergence of SARS-CoV-2 variants resulting from mutations made infection and re-infection more threatening and containment efforts unfruitful. Genetic viral mutations increase viral spread, nasopharyngeal viral load, immune escape, improved resistance to monoclonal/polyclonal antibodies from convalescence sera/vaccine, as well as an improved virulence. Therefore, it is apt to study emerging mutations as well as genetic SARS-CoV-2 modifications as it is cogent for understanding the viral variants.

This study therefore recommends continuous molecular surveillance of SARS-CoV-2. This process would promote and enhance prompt recognition of new mutants and positively influence current international preventive measures and COVID-19 control measures.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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