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Mini review

SARS-CoV-2 Mutations and their Viral Variants

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ABSTRACT

Mutations in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occur spontaneously during replication. Thousands of mutations have accumulated and continue to since the emergence of the virus. As novel mutations continue appearing at the scene, naturally, new variants are increasingly observed.

Since the first occurrence of the SARS-CoV-2 infection, a wide variety of drug compounds affecting the binding sites of the virus have begun to be studied. As the drug and vaccine trials are continuing, it is of utmost importance to take into consideration the SARS-CoV-2 mutations and their respective frequencies since these data could lead the way to multi-drug combinations. The lack of effective therapeutic and preventive strategies against human coronaviruses (hCoVs) necessitates research that is of interest to the clinical applications.

The reason why the mutations in glycoprotein S lead to vaccine escape is related to the location of the mutation and the affinity of the protein. At the same time, it can be said that variations should occur in areas such as the receptor-binding domain (RBD), and vaccines and antiviral drugs should be formulated by targeting more than one viral protein.

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In this review, a literature survey in the scope of the increasing SARS-CoV-2 mutations and the viral variations is conducted. In the light of current knowledge, the various disguises of the mutant SARS-CoV-2 forms and their apparent differences from the original strain are examined as they could possibly aid in finding the most appropriate therapeutic approaches.

1. Background information

Mutations in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occur spontaneously during replication. Thousands of cumulative mutations have occurred since the emergence of the virus [1]. As novel mutations continue to emerge, naturally, new mutants are increasingly observed. Most of the mutations that occur in the SARS-CoV-2 genome have no notable effect on the spread and the virulence of the virus, and hence on the course of the disease [2]. The greatest concern about such emerging mutations is a risky change that could lead to an increase in the severity of the infection or a failure on the effects of vaccines currently being developed. This is mainly because the viral signals may escape the immune protection which originate from a preceding infection or vaccination [3]. The first occurrence of any mutation is difficult to correlate with the continuity of the alterations. Understanding the significance of the alterations may be possible through experimental studies, by showing a link between the mutation in question and a subtle change in viral biology. However, testing the effect of thousands of mutants takes considerable time and effort.

As the case with other CoVs, the SARS-CoV-2 genome contains at least 23 open reading frames (ORFs) [4]. The SARS-CoV-2 genome contains ORFs that are responsible for the production of non-structural proteins (Nsps) [5]. ORFs encode at least 4 main structural proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins [6]. Among these, the most notable mutations are those in the gene encoding the S protein, which is associated with viral entry into the cells. There are currently around 4000 mutations in the S protein gene. There are a few mutations in the region called the receptor-binding motifs (RBMs) of the S protein, the region responsible for viral entry through its interaction with the human angiotensin-converting enzyme 2 (hACE2) receptor on the host cells [7].

In our review, we conducted a literature survey under the scope of the exponentially increasing SARS-CoV-2 mutations and the numerous viral variations as the outcome. In the light of current knowledge, we aim to elaborate SARS-CoV-2′s ever changing disguises into novel mutant forms in various locations around the world, to analyze what features of such upcoming mutants differ from its original manifestation, and to emphasize the apparent discrepancies, which may be able to, in return, possibly aid in finding solutions for developing novel therapeutic approaches.

2. An overview of SARS-CoV-2

CoVs are a group of infectious pathogens that cause a wide range of clinical conditions such as respiratory, enteric, hepatic and neurological diseases. Highly pathogenic human CoVs belong to the *Coronaviridae* family. CoVs are divided into four genera: alpha-CoV, beta-CoV, gamma-CoV and delta-CoV. As well-known today, SARS-CoV-2 is an RNA coronavirus responsible for the coronavirus disease 2019 (COVID-19) outbreak. Proven to be the novel pathogen of COVID-19, SARS-CoV-2 belongs to the beta-CoV genus, a linear, single-stranded RNA genome of approximately 30 kb, and the Sarbecovirus sub-gene, as seen in Table 1 [14].

CoVs are enveloped viruses with positive sense RNA genomes with a single cistern of approximately 26−32 kb, which have the largest known genome size for an RNA virus. Seven CoVs – i.e., GC-V-229E, Human CoV-NL63 (hCoV-NL63), human CoV-OC43 (hCoV-OC43), human CoV-HKU1 (hCoV-HKU1), SARS-CoV, Middle East respiratory syndrome CoV (MERS-CoV), SARS-CoV-2 – have infected humans to date [15] (Table 1). The estimated mutation rates of CoVs are moderate or high compared to other single-stranded positive-sense RNA (+ssRNA) viruses. The antigenic surface of SARS-CoV-2 is quite different compared to other CoVs. Both the SARS-CoV-2 and the SARS infections have many common features. Both cause respiratory diseases. They are transmitted from animals to humans as an intermediate host. Both airborne and can be transmitted via respiratory fluids, which are fine droplets released during respiration from an infected person [16]. People with the SARS-CoV-2 infection tend to transmit more rapidly than those with the SARS infection (Table 2).

SARS-CoV had emerged as a major cause of severe lower respiratory tract infection in humans in 2002. In some studies conducted at that time, new strains and the possibility of future outbreaks were mentioned [22,23]. The severe and sudden symptoms resulting in atypical pneumonia with dry cough and persistent high fever in severe cases of the acute respiratory virus have revealed the importance of CoVs as potentially lethal human pathogens, and the identification of several zoonotic reservoirs has reappeared.

SARS-CoV-2 is the seventh CoV known to infect humans [24]. The world experienced its first international health emergency in the 21st century with the disease called SARS, in 2003. SARS had first started in China and soon spread to Asia, North America and Europe, causing 800 deaths in approximately 30 countries. Similarly, cases of pneumonia of unknown etiology were reported on December 31, 2019 in Wuhan, Hubei Province, China. It was identified on January 7, 2020, that the disease agent was an unprecedented CoV (2019-nCoV) in humans.

Table 1
Comparison of SARS-CoV, MERS-CoV and other human coronaviruses (hCoVs) by species, genome, genome length and percentage (%) similarity to the SARS-CoV-2 genome.

No	Viral Strain	Variety	Genome	Genome Length (bp)	Similarity Ratio to the SARS-CoV-2 Genome (%)	References
1	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	Beta (β)	SARS-CoV	29,751	82.45	[8]
2	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	β	MERS-CoV	30,119	69.58	[9]
3	Human Coronavirus-NL63 (hCoV-NL63)	Alpha (α)	hCoV NL63	27,553	65.11	[10]
4	Human Coronavirus-229E (hCoV-229E)	α	hCoV 229E	27,317	65.04	[11]
5	Human Coronavirus-HKU1 (hCoV-HKU1)	β	hCoV HKU1	29,926	67.59	[12]
6	Human Coronavirus-OC43 (hCoV-OC43)	β	hCoV OC43	30,741	68.93	[13]

2.1. SARS-CoV-2 structural properties and the replication cycle

SARS-CoV-2 has typical features among the CoV family, belongs to the beta-CoV 2b group and is an enveloped +ssRNA virus [25]. SARS-CoV-2 encodes the basic structural proteins of S, M, E and N, as seen in Fig. 1. Also as observed in Table 1, the SARS-CoV, MERS-CoV, hCoV-HKU1 and hCoV-OC43 proteins have sequencing similarities with SARS-CoV-2 proteins [26].

+ssRNA viruses, a large group that includes human pathogens such as SARS-CoV, replicate in the cytoplasm of the infected host cells. Replication complexes are generally associated with modified host cell membranes [27]. The SARS-CoV replication is driven by the membrane-bound viral enzyme complex. This complex is often linked to modified intracellular membranes. CoVs and other members of the Nidovirus family have a polycistronic genome, and use a variety of transcriptional and (post-) translational mechanisms to regulate their expression [28,29]. Post-translational modifications are covalent modifications of proteins after they are translated by ribosomes. It identifies new functional groups such as phosphate and carbohydrates, expands the chemical repertoire of 20 standard amino acids through post-translational modifications, and plays important roles in regulating the folding, stability, enzymatic activity, subcellular localization and interaction of a protein with other proteins [30]. Viruses that maintain compulsory cell life receive support from the protein synthesis mechanisms of the host cells after respiration. For this reason, after the polypeptides are synthesized, they modify protein functions by creating covalent modifications [31]. The gene encoding the replicase/transcriptase (this gene is commonly referred to as "replicase"), contains nearly two-thirds of the CoV genome, the largest known RNA genome to date. The replicase gene consists of ORFs 1a and 1b. ORF1b is expressed by a ribosomal frameshift near the 3′-terminal of the ORF1a. Thus, the SARS-CoV genome translation yields two polyproteins (pp1a and pp1ab) that are auto-proteolytically cleaved into 16 Nsps by proteases found in Nsp3 and Nsp5 [32,33].

2.2. Entry into the cell

The default gateway, the cellular receptor, or SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) [34,35]. Both SARS-CoV-2 and SARS-CoV use hACE2 as the input receptor and human proteases as input activators. The S protein, the leading viral surface protein, mediates the entry of SARS-CoV-2 into the cell. To fulfill the function of SARS-CoV-2, the receptor binds to hACE2 via the receptor-binding domain (RBD) and is proteolytically activated by human proteases. It is thought-provoking that the recombinant hACE2 (rhACE2) significantly reduces viral utilization in human cell-derived organoids [36], possibly serving as a decoy for virus binding.

Normally, ACE2 acts in regulating blood pressure. However when the CoV binds to ACE2, a series of chemical changes occur, that effectively inter-connect the membranes around the cell and the virus, allowing the RNA of the virus to enter the cell. To enter the host cells, CoVs first bind to a cell surface receptor for viral attachment, then penetrate into the endosomes, and eventually join the viral and lysosomal membranes [37,38].

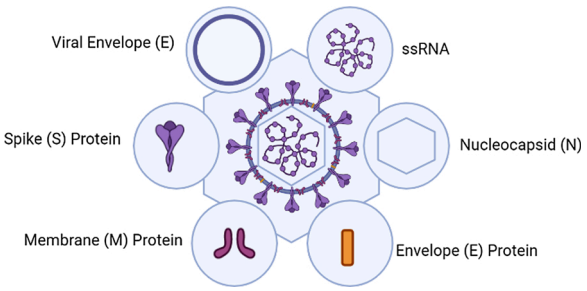

Fig. 1. The to-date defined surface protein structure of of SARS-CoV-2 (+ssRNA: single-stranded positive-sense RNA).

Protease activators have also been studied for SARS-CoV-2 entry at the receptor level. Both the transmembrane protease serine 2 (TMPRSS2) and lysosomal proteases are important for SARS-CoV-2 entry [39,40]. A successful viral entry requires proteolytic processing of the viral coat glycoprotein S, which is able to be carried out by TMPRSS2. Both camostat and the camostat-related agent nafamostat [41] block SARS-CoV-2 replication in human cells which express TMPRSS2. CoVs use the endo-lysosomal pathway to enter the cell before reproducing.

The CoV life cycle includes several potentially targetable steps: i) endocytic entry into host cells (via ACE2 and TMPRSS2), ii) RNA replication and transcription (helicase-containing transcription), and RNA-dependent RNA polymerase (RdRp) activation, translation and proteolytic processing of viral proteins, and iii) viron assembly and release of new viruses through exocytic systems [42] (Fig. 2).

3. Mutations in the spike (S) protein

The entry of SARS-CoV-2 into the cell takes place through the S protein [43], which has an important role in viral infection and pathogenesis [44]. The S protein consists of two subdomains: i) S1, and ii) S2. The S1 protein consists of an N-terminal domain (NTD) and a C-terminal domain (CTD) (Fig. 3). These two domains act as RBD and can bind various sugars and proteins [45]. S1 recognizes and binds to hACE2 receptors. S2 facilitates fusion through conformational changes [46,47]. While the S1 domain varies even among a single CoV species, the S2 domain is the most reserved region of the S protein.

The S protein found in the SARS-CoV-2 genome is of great importance ACE2 receptor binding and membrane fusion of the virus, and running scientific studies on therapeutic approaches and on the formation of immune response. Therefore, mutations that occur in the S protein, especially the RBD in the S gene, should be thoroughly examined.

There are currently around 4000 mutations in the S protein gene. The well-known mutations are listed in Table 3.

3.1. Mutations in the receptor-binding domain (RBD) of SARS-CoV-2

The S protein RBD is defined as the critical determinant of viral tropism and infectivity. Therefore, more attention should be paid to whether mutations in the RBD of circulating SARS-CoV-2 strains alter

Table 2
Percentage (%) of sequential similarity of SARS-CoV, MERS-CoV, HCoV-HKU1 and HCoV-OC43 proteins with SARS-CoV-2 proteins.

Protein	Severe Acute Respiratory Syndrome Coronavirs (SARS-CoV) (%)	Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (%)	Human Coronavirus-HKU1 (HCoV-HKU1) (%)	Human Coronavirus-OC43 (HCoV-OC43) (%)	References
S (Spike)	97.71	32.79	30.50	31.26	[17]
E (Envelope)	96.00	36.00	28.00	20.00	[18]
M (Membrane)	89.59	39.27	35.29	38.74	[19]
N (Nucleocapsid)	85.41	48.47	34.28	35.20	[20]
Receptor-Binding Domain (RBD)	74.41	18.75	24.44	22.83	[21]

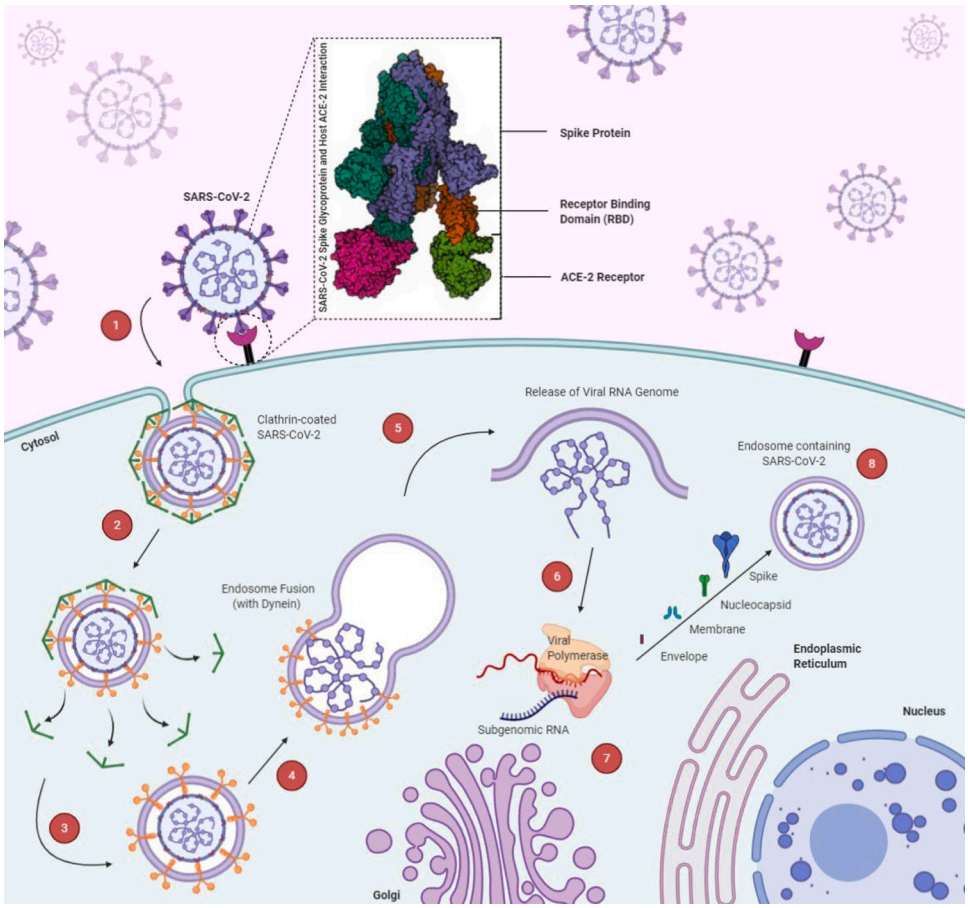

Fig. 2. Cell entry of SARS-CoV-2, replication cycle and synthesis of viral components. 1: SARS-CoV-2 binds via the S glycoprotein to the ACE-2 receptor expressed in the host cell. 2. SARS-CoV-2 enters the cell with clathrin-coated pits. 3. The clathrin structures are separated from the main structure. 4. Endosome fusion (with dynein) takes place to release the viral RNA genome. 5. The dynein units are separated from the structure and the endosome begins to open. 6. The opening of the endosome and release of the viral RNA genome. The viral RNA genome is synthesized using host ribosomes, viral polymerase. 7. Genomic and subgenomic RNA synthesis takes place in the synthesis of viral proteins. Then, with the help of ribosomes, viral RNAs are transmitted and viral proteins are synthesized. 8. Viral components come together to form the endosomal structure, then to make up for SARS-CoV-2.

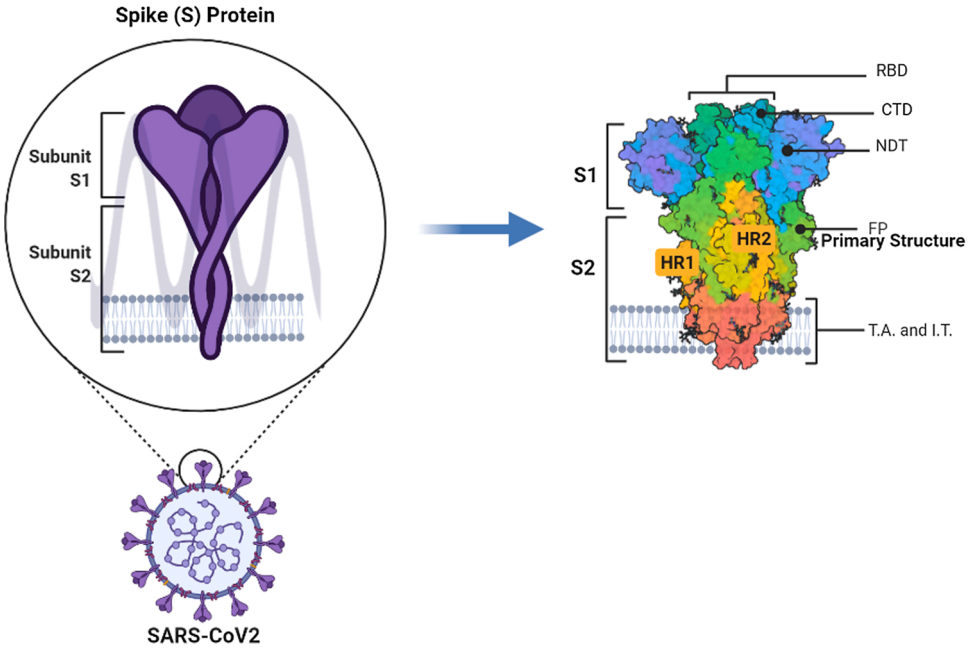

Fig. 3. The structure of the SARS-CoV-2 spike (S) protein. (RBD: receptor binding domain; NDT: N-terminal domain; FP: fusion protein; T.A.: transmembrane anchor and I.T.: intracelluar tail).

the receptor-binding affinity and cause these strains to be more contagious. RBD mutation analysis provides information about the changes in SARS-CoV-2. The RBD CoV genome in the S protein is the most variable part [48]. Six RBD amino acids are critical for binding to ACE2 receptors and determining the seven major sequences of the SARS-CoV-like virus. While analyses suggest that SARS-CoV-2 can bind human ACE2 with

Table 3
The molecular location and geographical distribution of mutations in the S gene region.

S Gene Mutation	Molecular Location and the Related Probable Impact	References
D614G	Severe acute respiratory syndrome Coronavirus (SARS-CoV) epitope-interprotomer stabilization, Asp614-to-Gly	[51,52, 53]
L8V/W	Single peptide	[53]
H49Y	Spike 1 (S1) protein N-terminal domain (NTD), Cytosine/Timine (C/T) change at the 21.707 positions	[53,54]
Q239K	S1 NTD	[53]
V367F	Up/Down conformation	[53]
G476S	Receptor-binding domain (RBD)	[53]
V615I/F	SARS-CoV antibody-dependent enhancement (ADE) epitope	[53]
A831V	Potential fusion protein in the S2 protein subunit	[53]
D839Y/N/E	S2 subunit	[53]
S943P	Heptad repeat 1 (HR1) fusion core	[53]
P1263L	Cytoplasmic tail	[53]
L5F	Single peptide	[53]
Y145 H/del	S1 NTD	[53]
N439K	RBD	[2]
L452R	RBD	[2]
T478I	RBD	[2]
E484D	RBD	[2]

high-affinity, computational analyses reveal that the interaction is not so ideal and that the RBD sequence differs from those shown to be optimal for receptor binding in SARS-CoV [49]. Thus, the high-affinity binding of the SARS-CoV-2 S protein to human ACE2 is most likely the result of natural selection on an hACE2 or human-like ACE2, which allows for another emerging optimal solution for binding [50]. This is strong evidence that SARS-CoV-2 is not a product of targeted manipulation. There are 725 present non-degenerate mutations in the SARS-CoV-2 S protein. Among such, 89 mutations involved in the binding of the SARS-CoV-2 S protein and ACE2 which occurrs in the RBD. Moreover, 52 of the 89 mutations are on the CRBM, the RBD region that is in direct contact with ACE2. Many mutations on RBD such as N439 K, L452R, T478I and E484D are noted to have significant free energy changes. Mutations in the RBM take up 58 % (52 of 89) of all mutations on the RBD, potentially increasing the complexity of antiviral drug and vaccine development. This overall analysis suggests that mutations in the RBD enhance the binding of the S protein and ACE2, leading to the more infectious SARS-CoV-2 [2]. Based on the up-to-date literature survey performed in this study, we retrieved 28 different S protein variants. Out of these variants, 12 belong to the RBD region, only.

3.2. *Important mutations in the RBD and other domains of the S protein*

3.2.1. *D614G*

The D614G (Asp614-to-Gly)) mutation was first detected in Germany and China in late January 2020 [55]. It has become a worldwide mutant thereafter [56]. D614G was determined as the most prominent sequence variation with a rate of 56 % in experiments performed on experimental animals with the SARS-CoV-2 virus isolated in Anatolia [57]. It was formed by replacing the natural form of Asp614 with Gly in the S protein [58]. The D614G strain was accompanied by two different mutations. The first was a silent cytosine thymine (CT) mutation in the Nsp3 gene at position 3.037 and the second is a CT mutation of amino acid change at position 14.409 (RdRp P323 L), resulting in an RdRp [51]. The D614G mutation increased transduction in many cell types, including lung, liver, and colon cells. It is also more resistant to proteolytic cleavage. Accordingly, it is 4–9 times more contagious [52], however not an escape mutation [59].

3.2.2. *S943P*

The S943P mutation was the first to occur in the S protein in Belgium. In Belgium, 23 S943P mutations were found in 284 SARS-CoV-2 S sequences, but not among the remainder of the 6,063 S sequences sampled worldwide from outside of Belgium. As a result, the AGT (S) → CCT (P) mutation emerged [60]. The S943P mutation is a result of recombination of different viruses in an infected host and has evolved significantly [61,62].

3.2.3. *V483a*

The V483a mutation was first seen in North America [63]. V483a occurred in the S1 domain RBM of the S protein found in the virus genome [64]. This mutation occurs when the hydrophobic alanine replaces the hydrophobic valine, an important amino acid residue in the RBM region of glycoprotein S at position 483, and is caused by the transition from thymine (uracil) to cytosine at the genome position 23010 [65]. Since the V483a mutation site is not in direct contact with the ACE2 receptor [66], no significant change was observed without binding to the ACE2 receptor [62]. The RNA replication rate in the resulting mutant strain causes the virus to mutate in the host, resulting in the mutant strain to have strong drug resistance.

3.2.4. *E484K*

The E484K mutation, which was first observed in South Africa, is a rapid spread mutation found in the variants of South Africa (B.1.351) [67] and Brazil (B.1.1.28) [68]. This mutation in the S protein suggests that the virus is further developing and may become resistant to vaccines [69].

3.2.5. *COH.20G/501Y*

The COH.20G/501Y variant has a 20G backbone and was identified in Columbus independent of the 20G variant available in Ohio [70]. The S N501Y mutation, located within the RBD, is of particular concern for two reasons: i) its increased affinity to ACE2 [71,72], and ii) that it may impact association of receptor binding neutralizing antibodies including those in the Regeneron cocktail [71,73].

3.2.6. *L452R*

The L452R mutant was first detected in Denmark in March 2020. In California, the mutant prominently spread in Los Angeles. This mutation was found in 45 % of the existing samples in California [74]. This mutation weakened antibody neutralization and increased the virus's ability to infect [75].

3.2.7. *Q677*

The Q677 mutation was first noticed in New Mexico and Louisiana. In some strains, its 677th amino acid glutamine (Q) has been converted to proline (P). This variant is known as Q677P. In other strains, the same amino acid has transformed into histidine (H). This variant is also named Q677H [75]. This mutation has enabled SARS-CoV-2 to enter the human cells more easily due to its Q location [76].

3.2.8. *P681H*

The P681H mutation has been observed worldwide as of December 31, 2020 [77]. P681H results from a loss of proline and a gain of histidine containing imidazole. It also has mutations that result in cysteine residues. This potentially causes breakdown of the disulfide bridges in and around the RBD [77]. It is not thought to be associated with increased infection or spread, yet studies are ongoing [78].

3.2.9. *E484Q*

The E484Q mutation is caused by the change between glutamic acid (El) and glutamine (Q) at position 484. It causes an increase in ACE2 affinity in the B.1.617 double mutation strain seen in India [79,80].

3.2.10. *K417*

The K417 spike protein has been observed in several strains, mainly P.1 and B.1.351. This mutation is manifested as K417 N in the B.1.351

strain and as K417 T in the P.1 strain [80,81].

3.2.11. S477G/N

The S477 residue has the highest number of mutations in the RBD. It occurs as a result of amino acid changes at position 477. An increased binding affinity for hACE2 is observed with S477G and S477N, the two most frequently demonstrated mutations of S477 [82].

4. Some SARS-COV-2 variants recently associated with rapid spread

RNA viruses, one of which is SARS-CoV-2, are defined by a high mutation rate, one million times higher than their host. Viral mutagenic ability depends on several factors, including the quality of viral enzymes that replicate nucleic acids like RdRp. The mutation rate drives viral evolution and genome variability, thus allowing viruses to escape host immunity and hence develop drug resistance [83].

A number of SARS-CoV-2 variants have emerged worldwide since the COVID-19 outbreak. The fastest-spreading variants recently detected in UK, South Africa and Brazil have been the focus of attention (Fig. 4). Scientists suspect that variants have the potential to affect certain mutation patterns, their infectivity, virulence and/or their ability to escape from parts of the immune system. Second, it could render vaccine-induced or naturally immune humans vulnerable to re-infection with the new variants to SARS-CoV-2, and such possible effects are still under investigation.

4.1. B.1.1.7, 20I/501Y.V1, VOC202012/01

The B.1.1.7 variant was first seen in UK and began to spread rapidly. After a short time, it was seen in particularly India, the Netherlands, Switzerland, France, Brazil, Finland, Belgium, Mexico, Bangladesh, Turkey, China (Bejing and Wuhan), South Korea, 62 European countries, Asia and UK [84]. The B.1.1.7 strain N5014, P681H, H69-V70 and Y144/145 have significant mutations in the deletion processes. The reason for this rapid spread is due to the N501Y mutation increasing the receptor binding affinity. The variant also has a deletion at positions 69 and 70 of the S protein [85]. Furthermore, the B.1.1.7 variant appears to have a 30 % higher mortality rate along with other variants of SARS-CoV-2 [86].

4.2. B.1.351, 20C/501Y.V2

The B.1.351 variant originated in South Africa. B.1.351 contains 9 S mutations in addition to those of D614G, including a cluster of mutations (e.g., 242-244del & R246I) in NTD, three mutations (K417N, E484K, & N501Y) in RBD, and one mutation (A701V) near the furin cleavage site [87]. There is a growing concern that these new variants could impair the efficacy of current monoclonal antibody (mAb) therapies or vaccines. This is mainly because many of the mutations reside in the antigenic supersite in NTD16,17 or in the ACE2-binding site (also known as the RBM) which is a major target of potent virus-neutralizing antibodies [88].

4.3. P.1

One of Brazil's detected variants of SARS-CoV-2 is the P.1 variant, a descendant of B.1.1.28. This a highly diverse variable, which includes the E484K, K417T and N501Y mutations, was identified in 42 % of the positive individuals [68]. Viruses that show co-mutations with the P.1 variant cause concern that they may carry a more infectious risk [89]. As a matter of fact, the inclusion of a common mutation allows it to be contaminated similar to the South African variant as well as to create more re-emerging risks.

4.4. P.2

This variant was first coined in the US in November 2020. It contains the mutations T95I, D253 G, L5F, S477N, E484K, D614G, A701V [90], spreads rapidly, and neutralization has been observed to be reduced in patients harboring this mutation [91].

4.5. B.1.525

The B.1.525 variant, which was first determined in December 2020 and identified in many countries, especially Denmark, is similar to the E484K, Q677H, F888L variants. In addition, B.1.525 is similar to the highly transferable variant B.1.1.7, which also occurs in UK, in that it includes the mutations S:69-70 and S:144 of B.1.1.7 (501Y.V1) [92]. However, further research is necessary to assess whether B.1.525 causes more contagiousness and more severe outcomes.

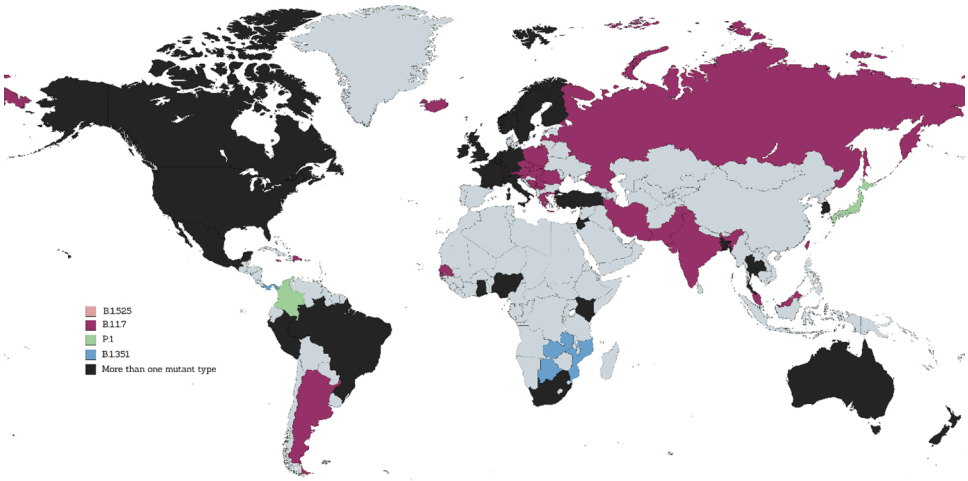

Fig. 4. Countries with the fastest-spreading variants. B.1.1.7: Denmark, United States of America, France, Spain, Belgium, Netherlands, Italy, Switzerland, Ireland, Turkey, Israel, Portugal, Austria, Sweden, Australia, Finland, Germany, Norway, Nigeria, Slovakia, Ghana, India, Singapore, New Zealand, Jordan, Canada, Romania, Luxembourg, South Korea, Brazil, United Arab Emirates, Iceland, Poland, Czech Republic, Sri Lanka, Northern Macedonia, Saint Lucia, Aruba, Hong Kong, Thailand, Montenegro, Mexico, Ecuador, Bosnia and Herzegovina, Hungary, Latvia, Slovenia, Greece, Guadeloupe, Jamaica, Barbados, Kosovo, Bangladesh, Gambia, Cayman Islands, Republic of Serbia, Malaysia, Democratic Republic of the Congo, Taiwan, Pakistan, Peru, Iran, Argentina, Mayotte, Curaçao, Oman, Senegal, Kuwait, Dominican Republic, Trinidad and Tobago, South Africa, B.1.351: Mayotte, United Kingdom, Belgium, France, Netherlands, Switzerland, Mozambique, Botswana, Zambia, New Zealand, Australia, Austria, Denmark, United States of America, Turkey, Germany, Ireland, Israel, Kenya, Finland, Sweden, United Arab Emirates, Ghana, South Korea, Thailand, Spain, Canada, Portugal, Luxembourg, Singapore, Democratic Republic of the Congo, Italy, Norway, Panama, Bangladesh, P.1: Brazil, Switzerland, Colombia, Italy, Belgium, Japan, France, United States of America, Netherlands, French Guiana, Spain, South Korea, Mexico, Faroe Islands, Peru, B.1.525: Denmark, United Kingdom, Nigeria, United States of America, France, Canada, Ghana, Australia, Netherlands, Jordan, Singapore, Finland, Mayotte, Belgium, Spain. More than one mutant type is seen at once in the blackened countries or regions.

4.6. B.1.526

B.1.526 was first identified in New York [93]. This variant contains the mutations L5F, T95I, D253G, E484K, D614G and A701V [94]. This variant is thought to spread especially in countries with high seroprevalence. It poses a threat on therapeutic approaches because it harbors previously unseen S protein mutations. Moreover, inoculated plasma is shown to negatively affect the neutralization titer [95].

4.7. B.1.427/B.1.429

The variant B.1.427/B.1.429 first appeared in California. It spread rapidly in 25 countries in the US and onward [96]. The emergence of this mutation was triggered by the acquisition of the L452R mutation, which is markedly resistant to mAbs [97,98]. More research is needed to determine whether this variant, known as CAL20C, is more contagious than other forms of the virus.

4.8. B.1.617

Currently available in eight countries, the B.1.617 mutation was first seen in India in October 2020 [99]. It is the first strain where the E484Q and L425R mutations were first seen together. The effect of these mutations individually on SARS-CoV-2 is well known; however, the combined effect of these mutations still remains unknown [100].

4.9. B.1.1.298

First defined in June 2020 in a mink farm in Denmark [96], although it shows similar variations with the B.1.1.7 mutation, B.1.1.298 also contains the Y453F, I692V and M1229I mutations. Although it is reported as an escape mutation, it is seen in fewer people compared to other variants in the current situation, however it is a variant with a high mutation potential [101]. This variant has also been recently reported to cause a 4-fold increase in hACE2 affinity [102].

4.10. P.3

The P.3 variant occurs in South Africa, Brazil and the United Kingdom. It has also been reported recently in the Philippines [103]. Includes E484K, N501Y and P681H S mutations found in rapidly spreading variants such as B.1.351, P.1 and B.1.1.7 variants [104,105]. It is thought that it may have important effects with ACE2 receptor affinity and neutralizing antibodies in studies [106].

4.11. Lambda (C.37)

The lambda (C.37) variant, first seen in Peru in August 2020, was identified by the World Health Organization in June 2021 [107,108]. Later, it was seen in 26 countries, especially in America, Europe and Oceania [109]. C.37 variant B.1.1.7, B.1.351. and P.1 variants as a result of a deletion in the ORF1A gene [110]. It also harbors mutations Δ246-252, G75V, T76I, L452Q, F490S, D614G and T859N in the S protein. It spreads rapidly with a high prevalence [108]. This variant shows increased infectivity and immune evasion from antibodies [109] (Table 4).

Table 4
Comparison of the fastest-spreading variants.

Muation Type	First Detected Country	Potential effects on contagion, virulence and escape from immunity	References
B.1.1.7	United Kingdom	• Thought to have greater than 30 percent increased transmissibility.	[84–86]
B.1.351	South Africa	• *In vitro* studies suggest a potential for immune escape following natural infections and a small effect on the potency of vaccine-induced antibodies.	[87]
P.1	Brazil	• Effect on transmissibility and/or virulence and potential for immune evasion is unknown.	[68,89]
P.2	United States	• Spreads rapidly, and neutralization has been observed to be reduced in patients harboring this mutation	[91]
B.1.525	Multiple	• Mutation that could allow it to evade immunity-conferring neutralizing antibodies.	[92]
B.1.526	New York	• Contains mutansons that have never been seen before, and decreased neutralization was observed in the sera of patients harboring this mutation.	[93,95]
B.1.427/ B.1.429	California	• This mutation is significantly resistant to monoclonal antibodies, but there are no clear data on its effect on spread.	[97,98]
B.1.617	India	• The E484Q and L425R mutations are coexisting, and the compound effect of this mutation is still unknown.	[99,100]
B.1.1.298	Denmark	• Has caused a 4-fold increase in hAce2 affinity and was identified as an escape mutation in *in vitro* experiments.	[94]
P.3	South Africa, Brazil and the United Kingdom	• It is a variant associated with ACE2 receptor affinity and neutralizing antibodies.	[103–106]
Lambda (C.37)	Peru	• It is spreading rapidly and shows increased infectivity and immune evasion from antibodies	[107,108, 110]

5. Emergence and observation of CoV viral variants by country

Characterization of the genetic variants of SARS-CoV-2 is crucial for tracking and evaluating its spread across countries. Table 5 shows the variants of SARS-CoV-2 by country, and the changes and effects on the virus. The genomic variability of SARS-CoV-2 samples scattered around the world may be under geographically specific etiological influences. Continuous monitoring of mutations will also be crucial in tracking the movement of the virus between individuals and across geographic areas.

After February 2020, it was observed that the viral genomes presented distinct point mutations were clearly discernible in different geographic regions. Three distinct repetitive mutations were detected in Europe and North America. The number and occurrence and the median value of virus point mutations recorded in Asia have increased over time [83]. It has been determined that the RdRp mutation at position 14408 in European viral genomes is associated with a larger number of point mutations compared to viral genomes from Asia.

Two clinical isolates from India were sequenced. Sequence analysis was performed on S protein of Indian isolates according to Chinese Wuhan isolates. Point mutations were identified in Indian isolates. One of the two isolates was found to harbor a mutation in the RBM at position 407. It has been determined that arginine (a positively charged amino acid) is replaced by isoleucine (hydrophobic amino acid) in this region. With this, a secondary change in the structure of the protein in the region has been demonstrated, and this could potentially alter the receptor binding of the virus [109].

However, given the small sample size, it is difficult to determine whether D614G is the dominant species in these countries. A recent report supports the high prevalence of D614G in Europe [121].

Three variants (H49Y, T573I and D614G) found in the Mexican population show multiple sequence alignments of SARS-CoV-2 S proteins. These variants are away from the RBD of the S protein. G614 is neutralized by a polyclonal antibody similar to D614. To date, this variant has become the dominant form, replacing the wild type (WT)

Table 5
Coronavirus (CoV) mutations and effects by country. (BCSIR: Bangladesh Council of Scientific and Industrial Research, NILMRC: National Institute of Laboratory Medicine and Referral Center).

Mutation Name / Position	Change/Impact	Countries	References
407	Receptor-Binding Domain (RBD), Arginine → Isoleucine, it can alter receptor binding.	Global	[109]
D614G	Spike (S) protein, Adenine(A) →Guanine (G) exchange	India, Netherlands, Switzerland, France, Brazil, Finland, Belgium, Mexico, Bangladesh (BCS on-NILMRC-006, BCS-007-NILMRC, BCS-NILMRC-008), Turkey	[54,111, 112]
A23403G	Nucleotide mutation, increased viral effect in patients.	India	[57,113]
H49Y	Cytosine/Thymine (C/T) exchange in position 21707	Mexican	[54]
T573I	T/I change, nonpolarization and more hydrophobicity	Mexican	[54]
T4402C	Open Reading Frame 1ab (ORF1ab)	China (Bejing), South Korea	[114]
G5062T		China, South Korea	[114]
C8782T	NSP4	China	[57,114, 115]
C17373T		China (Wuhan), Singapore, US	[116]
C20692T		China (Wuhan)	[116]
T28144C	ORF8 missense point mutation	China	[100]
G29868C	3′terminal loop	China	[114,116]
C29095T	Nucleocapside (N) gene	China, United States of America	[114,116]
R203K	N gene, increase in transmission speed.	Russia, United States of America, Europe, Bangladesh (BCSIR-NILMRC-006, BCSIR-NILMRC-007, BCSIR-NILMRC-008)	[117,111]
G204R	N gene, increase in transmission speed.	Russia, United States of America, Europe	[117]
C26750T	Membrane (M) gene	Russia, Europe	[117]
M1499I	ORF1b	Russia, Europe	[117]
G17964T	ORF1b	Europe	[117]
V480I	Non-structural protein 2 (Nsp2)	Bangladesh (BCSIR-NILMRC-006)	[111]
G339S	Nsp2	Bangladesh (BCSIR-NILMRC-006)	[111]
G204R	N	Bangladesh (BCSIR NILMRC-006, BCSIR-NILMRC-007, BCSIR-NILMRC-008)	[111]
Q172R	Nsp3	Bangladesh (BCSIR-NILMRC-006)	[111]
I120F	Nsp2	Bangladesh (BCSIR-NILMRC-006, BCSIR-NILMRC-007, BCSIR-NILMRC-008)	[111]
P323L	Nsp12	Bangladesh (BCSIR-NILMRC-006, BCSIR-NILMRC-007, BCSIR-NILMRC-008)	[111]
K59N	Nsp12	Bangladesh (BCSIR-NILMRC-007)	[111]
P822S	Nsp3	Bangladesh (BCSIR-NILMRC-008)	[111]
23403	A→G	Turkey	[112]
3037 (F106 F)	C→T, ORF1ab	Turkey	[112]
14408 (P4715 L)	C→T, ORF1ab	Turkey	[112]
11083	G→T, ORF1ab	Turkey	[112]
1397	G→A, ORF1ab	Turkey	[112]
18877	C→T, ORF1ab	Turkey	[112]
1059	T→A, ORF1ab	Turkey	[112]
8782	C→T, ORF1ab	Turkey	[112]
R60C	Main protease (M^{pro})	Vietnam	[118]
A406V	RNA-dependent RNA polymerase (RdRp)	India	[118]
VUI-202012/01	S protein	United Kingdom, Ireland, Bulgaria, Slovakia, Israel, Luxembourg, Portugal, Denmark, Netherlands, Norway, Italy, Belgium, France, Austria, Switzerland, Liechtenstein, Germany, Sweden, Spain, Malta, Poland	[84,119]
K417N	RBD	South Africa	[120]
E484 K	RBD	South Africa	[120]
N501Y	RBD	South Africa, United Kingdom	[120]

according to the mutation levels in the world presented in the Nextstrain database.The H49Y variant is produced with the C/T change at the 21.707 positions. The properties of H/Y residues vary from positive to neutral charge, causing a reduction in total free energy, while D614G-substituted mutants exhibit stabilizing structure, suggesting a prevalent role in S protein evolution. Although these are minute changes due to the chemical nature of the substitution, they are expected to take place at the structural level [54].

Several common gene mutations have been observed in between the SARS-CoV-2 sequences in China. These mutations are common across countries and follow standard roles. Highlights are T4402C, G5062T, C8782T, C17373T, C20692T, T28144C, C29095T and G29868C. The T4402C mutation causing a silent mutation was recorded in the ORF1a/b gene segment. This mutation is frequently associated with the C8782T, G5062T and T28144C mutations. Similar T4402C and G5062T point mutations were observed in both, isolated in the South Korean strain [114], C8782T was the dominant mutation reported worldwide in the SARS-CoV-2 gene mutation [114,115]. This mutation is always associated with the ORF8 gene segment T28144C [117], coexisting with a missense point mutation. The C17373T silent mutation, which was noticed in Singapore and the US, was also observed in Wuhan [1]. C20692T was restricted to Wuhan and is present with the G29868C gene mutation of the 3′-terminal loop. The C29095T mutation of the gene coding the N protein has also been reported in the US [114,116].

In terms of mutation variants in the genes coding the structural proteins, typical to the European isolates, several additional mutations have been identified, including a synonym mutation in the gene M (C26750T), characteristic to the Russian isolates [122]. The double mutation, R203K and G204R, in the gene coding the N protein that had previously appeared in Europe began to spread, and quickly became dominant in Russia. The results show that the viral genome of most of the Russian isolates has evolved with the accumulation of new mutations associated with increased viral transmission. Generation of 20A seems to be one of the most common, showing the European origin of Russian isolates. This is based on mutational and phylogenetic analyses of the SARS-CoV-2 genomes isolated in Russia in March-April 2020. However, in Russia, unlike in Western Europe, the triple mutation - G28881A, G28882A and G28883C - which results in double substitution of R203K and G204R in the N protein, has spread and become the

dominant form. Thus, by the end of April 2020, the double mutated R203K and G204R genome abundance was over 69.5 % and 32.6 % in Russia and in Europe, respectively [117].

In the US, the number of genomes belonging to the same subclass identified by the R203K and G204R mutations was even lower, accounting for 13.3 %. The observed variant was likely to to have emerged in Russia in early March 2020. Further spread of the variant was accompanied by the formation of new subtypes with accumulation of the characteristic mutations in the gene M (C26750T) or ORF1b (M1499I or G17964T), following subsequent divergence due to new single (mostly synonymous) mutations in the ORF1ab gene. The rapid spread of the variant with double mutations R203K and G204R in gene N may be indicative of its adaptability and ability to increase the transmission rate rather than modulate the virulence [117].

The sequencing of three SARS-CoV-2 genomes were reported in Bangladesh. Evidence reveals the first signs in Bangladesh in May-June 2020, followed by constant human-to-human transmission, thus leading to sampled infections. Compared to hCoV-19/Wuhan/WIV04/2019 for the BCSIR-NILMRC-006 strain, eight mutations were found, including Nsp2_G339S, N_R203K, N_G204R, Nsp3_Q172R, S_D614G, Nsp2_I120F, Nsp12_P323L. Six mutations were found in BCSIR-NILMRC-007, S_D614G, N_R203K, N_G204R, Nsp12_K59N, Nsp2_I120F and Nsp12_P323L. Genomic mutations S_D614G, N_R203K, N_G204R, NSP2_I120F, Nsp12_P323L, and Nsp3_P822S were observed in BCSIR-NILMRC-008. A unique mutation, Nsp2_V480I, was observed in the BCSIR-NILMRC-006 genome sequence compared to the genome sequences found in GISAID CoVsurver (GISAID Initiative_CoVsurver_files) [98].

According to mutation analysis, 59 of the 80 isolates from Turkey in the S protein 23.403A > G (D614G) signed contained the mutation, and this clearly manifested itself to be a frequent mutation (73 %). Most samples with the D614G mutation were strongly associated with two other mutations in the ORF1ab region (3037 C > T and 14.408C > T). These co-occurring mutations have recently been identified as being characteristic to one of the major SARS-CoV-2 variants occurring in Europe. It is assumed that the 14,408C > T (P4715 L) and 3037 C > T (F106 F) variants in ORF1ab occur at high frequency and are associated, resulting in mutations in RdRP/Nsp12 and Nsp3 gene. RdRP/Nsp12 is a key component of the replication/transcription mechanism, and therefore the leucine mutation at position 4715 of RdRP/Nsp12 could potentially affect its function. Moreover, the proline to leucine mutation has been consistently observed as a common mutation in Europe (51.6 %) and North America (58.1 %). C3037T, A23403G and C14408T are the most common mutations found in the isolates from Turkey (73 %) [112].

The three-dimensional crystaline structure of the s2m RNA element of the SARS-CoV-2 indicates that the mutated guanosine 19 in Australian isolates is critical in tertiary contacts to form an RNA base quartet containing two adjacent G-C pairs (G19, C20, G28 and C31). Since s2m plays an important role in viral RNA to replace host protein synthesis, it is assumed that the degradation of s2m can significantly alter viral viability or infectivity. The s2m sequence of CoVs is highly conserved, and spontaneous changes in this motif are likely due to recombination as mutation is not expected. Due to the high frequency of recombination events occurring in CoVs, RNA recombination can either improve the adaptation process to its new host, such as to humans, or cause unpredictable changes in virulence during infection [123].

The single amino acid mutation was observed in the virus's main proteinase (M^{pro}) of the SARS-CoV-2 Vietnam isolate, R60C, and in the RdRp of the SARS-CoV-2 Indian isolate, A408 V. *In silico* findings have revelaed that both strains showed 2 mutations to reduce the stability of the protein. Molecular Dynamics (MD) simulation studies on M^{pro} also confirmed that point mutation affects the stability of proteins and binding of the inhibitor. *In silico* studies found that the M^{pro} catalytic active amino was found to be surrounded by a strand (142-145, 175-200), short helix (40-43, 46-50) and beta leaf regions (25-27, 164-167). The R60C mutant is found in the helix adjacent to the short helix (H2) forming the catalytic channel. A loss of conserved ionic interaction between arginine amide nitrogen and the carboxylic oxygen atom of aspartic acid at position 48 of the catalytic channel was observed [118].

In UK, the first variant to be investigated in December 2020 was named VUI-202012/01. According to a recent study, this variant is progressing faster than the other existing variants. Cases have been detected in approximately 60 different local government districts. Due to the S protein, changes in the binding properties to host ACE2 receptors can cause the SARS-CoV-2 virus to become more rapid in its spread among humans. The R-value for this variant is thought to be increased by 0.4, or 70 %. According to the data obtained so far, there is no evidence that this variant has a higher probability of causing serious illness or a higher mortality rate [119].

South Africa was the most severely affected region in Africa, with more than 56,000 extreme natural deaths (about 950 per million population) by December 2020. Three mutations of this new strain (K417 N, E484 K and N501Y) are in the key regions of the RBD. Two, E484 K and N501Y, are within the RBM, which is the main functional motif that interfaces with the hACE2 receptor. The N501Y mutation was recently identified in a new strain (B.1.1.7) in UK and there is some preliminary evidence that this may be more contagious. The E484K mutation is so rare that it is present in <0.02 % of sequences from outside of South Africa. E484 resides in the RBM and interacts with the K31 interaction hotspot residue of hACE2. This is the most striking difference in the RBD-hACE2 complex between SARS-CoV-2 and SARS-CoV, and benefits SARS-CoV-2′s improved binding affinity to hACE2. While all the effects of this new lineage in South Africa have yet to be determined, these findings highlight the importance of coordinated molecular surveillance systems around the world [120].

6. What the future holds

Since the SARS-CoV-2 virus first emerged, a wide variety of drug compounds affecting the binding sites of the virus have been being studied. Drug trials and vaccine studies are continuing. However, considering the frequency of mutation of the SARS-CoV-2 virus in all drug and vaccine studies, it is necessary to try multiple therapeutic combinations in different mutation types and to compare such studies, preventing possible pathways before the virus mutates. The lack of effective therapeutic and preventive strategies against hCoVs necessitates drug and treatment research. It has previously been shown that designing a broad-spectrum inhibitor in a conservative target is a viable method for developing anti-CoV therapeutics, given the high rates of mutation and recombination observed in viral replication.

The SARS-CoV-2/B.1.1.7 variant has been detected in the US and more than 30 countries, predominantly in England. The B.1.1.7 variant, which exhibits rapid growth and transmission, has the potential to affect healthcare, pandemic management and prevention. However, B.1.1.7, which is transmitted more efficiently than other SARS-CoV-2 variants, has been suggested to be a no neutralization escape variant for existing vaccines and infection. In addition, mAbs specific to the RBD showed full activity against the variant. However, all this shows that the development of SARS-CoV-2 and the emergence of new variants which serve for the immune system escape mechanism are becoming more likely. All this information indicates that our fight against SARS-CoV-2 may still continue in the next 10 years. Large-scale studies on different mutant types in various geographic regions around the world are not yet in the desired intensity. Conducting related studies in increased numbers will pave the way for the efficacy of therapeutic approaches to be developed for the virus in question. Different therapeutic approaches against SARS-CoV-2 have been shown according to different types of CoVs (SARS-CoV, MERS-CoV, etc.), which are similar to SARS-CoV-2, in terms of the location and effectiveness of variation.

If different types of viruses have different serological characteristics,

a different vaccine for each subtype will be more effective in preventing COVID-19. Epidemiological studies should be conducted in different countries to understand the pathogenicity course of these subtypes.

The reason why the mutations in glycoprotein S lead to vaccine escape is related to the location of the mutation and the affinity of the protein. However, more evidence is necessary to better understand whether the variants will respond to the vaccines. It probably suggests a situation where we would have to give more than one vaccine, of which the options will possibly vary over time. At the same time, it can be said that variations should be mostly occuring in areas such as the RBD, and vaccines and antiviral drugs should be formulated by targeting more than one viral protein. With the current vaccine developments, antibodies are produced against many regions in the S protein. A single change is unlikely to make the vaccine less effective. However, this can happen as more mutations emerge over time.

Laboratory experiments will be necessary to understand if and how the genomic changes in SARS-CoV-2 may or may not be linked to increases in cases. Nevertheless, many studies have suggested that the new strain does not cause a more severe illness. We must practice active surveillance to detect changes in SARS-CoV-2 as they occur.

7. Discussion

It has been reported that 7 CoVs, including SARS-CoV-2, infect humans in the CoV family with a +ssRNA genome of approximately 30 kb. The rest are SARS-CoV, MERS-CoV, hCoV-NL63, hCoV-229E, hCoV-HKU1 and hCoV-OC43. When the percentage (%) similarity in the sequencing of SARS-CoV, MERS-CoV, hCoV-HKU1 and hCoV-OC43 proteins with SARS-CoV-2 proteins is examined, it is understood that the strain with the highest similarity to SARS-CoV-2 is SARS-CoV.

The S glycoprotein RBD is a critical determinant for viral tropism and infectivity. Mutations in this region will change the affinity of the RBD and show the different infective consequences of the strains. The fact that the most variable region of the CoV family is the RBD causes different strains to emerge and such strains already show different infective profiles. The binding of the SARS-CoV-2 S protein with a high affinity to the ACE-2 receptor is a result of natural selection.

The excess of SARS-CoV-2 S mutations poses a great difficulty in the SARS-CoV-2 targeted therapy and vaccination processes. Mutations, which are one of the largest obstacles in the development of antiviral drug and vaccine formulations, have a crucial role in the preparation, administration and follow-up of vaccines and antiviral drugs.

RNA viruses that exhibit a higher mutation rate than what the host allows them, may escape host immunity and develop drug resistance. This mutation rate drives viral evolution and genome change. Clearly distinguishable mutations of viral genomes have emerged in different geographies. The presence of such mutations is supported by clinical findings. The D614G, S943P and V483a mutations, viral protein mutants, and the emergence of viral strains due to block mutation, play an important role in CoV evolution. Recombination contributes significantly to the viral evolution in the current pandemic. Since viruses mutate during replication, the effect of the antibody concentration produced prior to infection can also be lost. A single amino acid change associated with the mutation rate is effective in the emergence of a new variant with the same epitope. Also, the increase or decrease of hydrogen bonds in receptor interactions is associated with changes in affinity.

The presence of the SARS-CoV-2 strains can be attributed to the heterogeneity of the COVID-19 cases in different regions. Analysis with genomic sequencing has shown that SARS-CoV-2 has transformed into a less contagious strain that affects a number of COVID-19 cases in different regions. The time when different SARS-CoV-2 strains become dominant in a country or a region may indicate the time it will need to overcome the peak of COVID-19 cases. Prospective epidemiological studies of the strains should be conducted to confirm these assumptions. To modulate virus pathogenicity, potential drugs targeting that site can be designed depending on the localization of a given mutation.

Contributors' statement

All authors contributed to the study conception and design, while Pelin KILIC additionally conducted the overall supervision of the review. Material preparation, data collection and analysis were performed by Begum COSAR, Zeynep Yagmur KARAGULLEOGLU, Sinan UNAL, Ahmet Turan INCE, Dilruba Beyza UNCUOGLU, Gizem TUNCER, Bugrahan Regaip KILINC, Yunus Emre OZKAN, Hikmet Ceyda OZKOC, Ibrahim Naki DEMIR, Ali EKER, Feyzanur KARAGOZ, Said Yasin SIMSEK, Bunyamin YASAR, Mehmetcan PALA, Aysegul DEMIR, Irem Naz ATAK, Aysegul Hanife MENDI, Vahdi Umut BENGI, Guldane CENGIZ SEVAL, Evrim GUNES ALTUNTAS, Devrim DEMIR-DORA and Pelin KILIC, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare there are no competing interests.

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