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SARS-Cov-2: Interaction Between Mutations and Variants and Their Influence on Treatment and Preventive Strategies

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1. Abstract

Since the emergence of the SARS-CoV-2 induced COVID-19 pandemic, millions of patients have been diagnosed for the disease and many of them have died worldwide. SARS-CoV-2 has been undergoing genetic changes leading the disclosure of new variants. Since the unfolding of SARS-CoV-2, several recurrent mutations, particularly in the spike protein, emerge during human-to-human transmission or spillover events between humans and animals, generating distinct daunting variants. Here, we intend to provide a comprehensive awareness into mutational profiles characterizing each SARS-CoV-2 variant, focusing on spike mutations known to modulate viral infectivity and/or antigenicity. The variants and their specific relevant mutations that were associated with any clinical/diagnostic impact reported in the literature have been focused. Furthermore, 1,223,338 full-length high-quality SARS-CoV-2 genome sequences were retrieved and used to accurately define the specific mutational patterns in each variant. Characterizing these variants and their related mutations is important in tracking SAR-CoV-2 evolution and understanding the efficacy of vaccines and therapeutics based on monoclonal antibodies, convalescent-phase sera, and direct antivirals. An electronic search was conducted in Lit Covid, PubMed, Google Scholar, WHO and Centers for Disease Control and Prevention databases. Search terms included COVID-19, SARS-CoV-2, mutations, variants, interactions, treatment and prevention. Our study provides a comprehensive survey of the mutational profiles characterizing the important SARS-CoV-2 variants and the interactions between them and their influence on treatment and prevention strategies.

2. SARS-Cov-2 Mutations and Their Viral Variants

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 develop drug resistance [1]. A number of SARS-CoV-2 variants have emerged worldwide since the COVID-19 outbreak. The fastest-spreading variants recently detected in United Kingdom, South Africa and Brazil have been the focus of attention. Most famous scientists suspects that variants have the potential to affect certain mutation patterns, their infectivity, virulence and/or their ability to escape from the immune system. Secondly, they could render vaccine-induced or naturally immune humans vulnerable to re-infection with the new variants to SARS-CoV-2, and such effects are still under investigation.

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

The B.1.1.7 variant was first seen in United Kingdom and began to spread rapidly. After a short time, it was seen in India, Netherlands, Switzerland, France, Brazil, Finland, Belgium, Mexico, Bangladesh, Turkey, China (Beijing and Wuhan), South Korea, 62 European countries, Asia and United Kingdom [2]. 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 [3]. Furthermore, the B.1.1.7 variant appears to have a 30 % higher mortality

rate along with other variants of SARS-CoV-2 [4].

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

The B.1.351 variant originated in South Africa, contains 9 S mutations in addition to those of D614G, including a cluster of mutations (e.g., 242-244del and R246I) in the National Transit Database (NTD), three mutations (K417N, E484K, & N501Y) in Receptor-Binding Domain (RBD), and one mutation (A701V) near the furin cleavage site [5]. 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 NTD or in the ACE2-binding site (also known as the RBM) which is a major target of potent virus-neutralizing antibodies [6].

4.1. P.1

The P.1 variant is one of Brazil's detected variants of SARS-CoV-2, a descendant of B.1.1.28 variant, which is a highly diverse variable, including the E484K, K417T and N501Y mutations, this was identified in 42 % of the positive individuals [7]. Viruses that show co-mutations with the P.1 variant cause concern that they may carry a more infectious risk [8]. 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.

4.2. P.2

The P.2 variant was first forged in the US in November 2020. It contains the mutations T95I, D253 G, L5F, S477N, E484K, D614G, A701V [9]. It spreads rapidly, and neutralization has been observed to be reduced in patients harboring these mutations [10].

4.3. B.1.525

The B.1.525 variant was first determined in December 2020 and identified in many countries, especially Denmark. It 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 United Kingdom, in that it includes the mutations S:69-70 and S:144 of B.1.1.7 (501Y.V1) [11].

4.4. B.1.526

B.1.526 was first identified in New York [12]. This variant contains the mutations L5F, T95I, D253G, E484K, D614G and A701V [13]. This variant is thought to spread in countries with high seroprevalence. It poses a threat on therapeutic approaches because it harbors previously unseen S protein mutations. Besides, inoculated plasma is shown to negatively affect the neutralization titer [14].

4.5. 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 [15,16]. The emergence of this mutation was triggered by the acquisition of the L452R mutation, which is markedly resistant to mAbs (17,18). More research is needed to determine whether this variant (CAL20C, is more contagious than other forms of the virus.

4.6. B.1.617

Currently available in eight countries, the B.1.617 variant was first seen in India in October 2020 [17]. 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 [18].

4.7. B.1.1.298

This variant was first defined in June 2020 in a mink farm in Denmark [15], although it shows similar variations with the B.1.1.7 mutation, the variant (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 present scenario, however it is a variant with a high mutation potential [19]. This variant has also been recently reported to cause a 4-fold increase in hACE2 affinity [20].

4.8. P.3

The P.3 variant occurs in South Africa, Brazil and the United Kingdom. It has also been reported recently in the Philippines [21]. 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 [22]. It is thought that it may have important effects with ACE2 receptor affinity and neutralizing antibodies [23].

4.9. 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 [24]. Later, it was seen in 26 countries, especially in America, Europe and Oceania [25]. C.37, B.1.1.7, B.1.351. and P.1 variants occur as a result of a deletion in the ORF1A gene [26]. These also harbors mutations Δ246-252, G75V, T76I, L452Q, F490S, D614G and T859N in the S protein and spreads rapidly with a high prevalence. These variants show increased infectivity and immune evasion from antibodies [25].

4.10. Emergence and Observation of CoV Viral Variants in Different Countries

Characterization of the genetic variants of SARS-CoV-2 is important for evaluating their spread across countries. The genomic variability of SARS-CoV-2 samples scattered around the world may be under geographically specific etiological influences. Continuous observance of mutations will also be important in tracking the movement of the virus between individuals and across geographic areas. After February 2020, it was observed that the viral genomes presenting distinct point mutations were clearly visible 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 [3]. It has been determined that the RdRp mutation at position 14408 in European viral genomes is linked 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 [25]. 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 [26, 27]. 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 according to the mutation levels in the world presented in the Next strain 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 [28]. 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 [28], C8782T was the dominant mutation reported worldwide in the SARS-CoV-2 gene mutation [29,30]. This mutation is always associated with the ORF8 gene segment T28144C [30,31, 32], coexisting with a missense point mutation. The C17373T silent mutation, which was noticed in Singapore and the US, was also observed in Wuhan. C20692T was restricted to Wuhan and is present with the G29868C gene mutation of the 3'-terminal loops. The C29095T mutation of the gene coding the N protein has also been reported in the US [29,30]. 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 [33]. 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 [32]. 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 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 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 flexibility and ability to increase the transmission rate rather than change the virulence [32]. 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 [18]. 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 (3037 C > T and 14.408C > T) in the ORF1ab region. 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 constantly 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 [33]. The three-dimensional crystalline 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 pattern 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 [34]. 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 revealed that both strains showed 2 mutations to reduce the stability of the protein. Molecular Dynamics 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 [35]. In UK, the first variant to be investigated in December 2020 was named VUI-202012/01. According to a recent study, this variant has been 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 (36).

South Africa was the most severely affected region in Africa, with more than 56,000 extreme natural deaths (almost 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 Receptor-Binding Domain. Two, E484 K and N501Y, are within the RBM, which is the main functional design 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 [37].

5. Prospects (View)

Since the emergence of SARS-CoV-2 virus, a wide variety of drug compounds affecting the binding sites of the virus are 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. 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 highly possible. 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 leads 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 occurring 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.

6. Argumentation

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 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. SARS-CoV-2 virus gets into the body when one touches the mouth, nose and eyes with virus-contaminated hands. The presence of the SARS-CoV-2 strains can be attributed to the diversity of the COVID-19 cases in different regions. Analysis of the 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.

7. Conclusions

The spike glycoprotein undergoes a persistent process of genetic changes such as a large variety of point mutations and deletions underlying the presently identified SARS-CoV-2 variants. Although experiments based on infection models are limited, there is clear evidence that spike mutations, particularly in the receptor binding domain, play an important role in changing SARS-CoV-2's infectivity and antigenicity. Comprehensively, this strengthened the need for continuing molecular observation programs to guide the development and usage of vaccines and of therapeutics based on an antibody produced by a single clone of cells and convalescent-phase sera. Simultaneously, the increasing circulation of variants with immune evasion mutations supports the need to update periodically the formulation of the current vaccines and to test the efficacy of monoclonal antibodies in clinical use against newly arising variants in order to avoid potential loss of clinical efficacy.

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