REVIEW

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SARS-CoV-2 Variants of Concern and Their Properties

SARS-CoV-2 Endişe Verici Varyantları ve Özellikleri

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ABSTRACT

Since its first detection in December 2019, SARS-CoV-2 has resulted in the morbibidity of 174 million and mortality of 3.74 million people. As a typical Ribonucleic acid virus, SARS-CoV-2 undergoes genomic changes during its replication to maintain its evolutionary adaptation. Continous mutation has led into the emergence of numerous variants. Currently, the variants distinguished as the 'Variants of Concern' are the B.1.1.7 lineage (The United Kingdom variant) , B.1.351 (The South African variant), B.1.1.248/B1.1.28/P1(Brazilian Variant) , B.1.427/B.1.429 lineage (The Californian variant) and B.1.617.2 lineage (Indian variant). These variants impose a huge concern due to their properties of higher transmission and evasion of the immune system. The continuous emergence of such variants can be contained by vaccinating the population to reduce the circulation of the virus and by maintaining the major protective measures against the disease.

ÖZET

Aralık 2019'da tespit edilmesinden bu yana, SARS-CoV-2, 174 milyon insanın morbiditesine ve 3.74 milyon insanın mortalitesine neden olmuştur. Tipik bir Ribonükleik asit virüsü olarak, SARS-CoV-2, evrimsel adaptasyonunu korumak için replikasyonu sırasında genomik değişikliklere uğrar. Zaman içindeki sürekli mutasyonlar, çok sayıda varyantın ortaya çıkmasına neden olmuştur. Şu anda, 'Endişe Verici Varyantları' olarak ayırt edilen varyantlar B. 1.1.7 soyu (Birleşik Krallık varyantı), B. 1.351 (Güney Afrika varyantı), B. 1.1.248/B1.1.28/P1 (Brezilya varyantı), B. 1.427/B.1.429 soyu (Kaliforniya varyantı) ve B. 1.617.2 soyu (Hint varyantı) içermektedir. Bu Varyantlar, yüksek bulaşma özellikleri ve bağışıklık sisteminden kaçma yetenekleri nedeniyle büyük bir endişe yaratmaktadır. Bu tür varyantların sürekli ortaya çıkışı, virüsün dolaşımını azaltmak için popülasyonun aşılanması ve hastalığa karşı ana koruyucu önlemlerin sürdürülmesi ile kontrol edilebilir.

Keywords:
SARS-CoV-2
Variants of concern
Mutation
Immune system.

Anahtar Kelimeler:
SARS-CoV-2
Endişe verici varyantlar
Mutasyon
Bağışıklık sistem.

1. INTRODUCTION:

In December of the year, 2019 cases of viral pneumonia with the unknown etiologic agent were seen in the Chinese city of Wuhan. Patients were presented to the hospitals with symptoms like fever, malaise, dry cough, and dyspnea (1). On March 11 2020 the WHO declared that COVID-19 can be characterized as a pandemic due to the fast level of spread and mortality (2). Since the detection of the first case, the virus has been spreading at a very fast speed. By June 7, 2021, 174 million people worldwide had been infected with the virus. The death rate due to the virus also reached 7.34 million (3).

COVID-19 is a 70-90 nm in diameter, spherical enveloped virus-containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid composed of matrix protein (4). The coronaviruses RNA genome which codes for 4 major structural proteins: the nucleocapsid (N) protein, the transmembrane (M) protein, the envelope (E) protein, and the spike (S) protein (5).

As a typical RNA virus, SARS-CoV-2 maintain the average the evolutionary rate of roughly 10^{-4} nucleotide substitutions per site per year with mutations arising during every replication cycle. Thus, this mutation rate has led to the birth of SARS-CoV-2 strains containing key mutations that affect the severity of the disease, immune evasion, and treatment tolerance by the virus.

2. MAJOR SARS-COV-2 STRAINS

In the earlier stages of the pandemic, the virus was divided into two types; the L and S strains of SARS-CoV-2. These two major types were identified based on the presence of two single nucleotide polymorphisms (SNPs) at the 28,144 nucleotide in the genome. These are the "L" haplotype (Where C is substituted by T and Leucine is coded) and "S" haplotype (Where C is present and Serine is coded) (6). With the increase of variations in the genome of the virus, it has become essential to develop a nomenclature system which can include all the clades. So far Rambaut et al., Nextrain and Global Initiative on Sharing All Influenza Data (GISAID) have developed several nomenclatures for SARS-CoV-2 and all these nomenclature techniques can be used for the categorization of the virus subtypes and identification of the most globally circulating strains (7). One of the main classification criteria of SARS-CoV-2 by this method is the presence of a specific group of

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mutations.

In addition to this, certain organizations like the Centers For Disease Control and Prevention (CDC) have lately been using the terms 'Variants of Interest' and 'Variants of Concern' to address the newly discovered strains of the virus (8). Variants of interest refer to variants with mutations that are predicted to affect receptor binding, interaction with antibodies and the efficacy of treatments. The European Center for Disease prevention and control (ECDC) has categorized the variants B.1.525, P.3, B.1.616, B.1.617.1, B.1.617.3, B.1.620, B.1.621 as Variants of Interest (9). The Variant of Concern strains includes new variants with a characteristic of higher transmission ability. These variants may have developed the strength to neutralize antibodies generated from previous infections. Evidence of failures in treatments and diagnostic tests are also some of the defining characteristics of them. The main objective of this review is to describe the Variants of Concern. Moreover, it aims to discuss the characteristic mutations of the variants and their effects on the transmissibility of the disease and immune responses.

3. VARIANTS OF CONCERN

Up to this date, several variants of SARS-CoV-2 which have been considered as variants of concern due to their impact on public health have been identified. These are:

A. The B.1.1.7 lineage or Variant of Concern 2020/12 (The UK variant).
B. B.1.351 lineage or 501Y.V2 (The South African variant)
C. B.1.1.248/B1.1.28/P1 or 501Y.V3 (The Brazilian Variant)
D. B.1.427/B.1.429 lineage (The Californian variant)
E. B.1.617.2 Lineage (Indian variant) (10).

One of the depicting features of all of these variants is the presence of a common mutation D614G (11). The D614G mutation in was first identified in Germany in a sample collected in January and by March the mutation has spread throughout Europe. By April this mutation was dominantly seen in samples collected from Europe and North America (12). In the Global Initiative on Sharing All Influenza Data (GISAID) system of SARS-CoV-2 variant classification, strains containing the D614G the mutation is categorized in the G clade (13). Some studies found that the mutation 614G in the S protein along with variant 4715L in the ORF1ab are significantly correlated with fatality rates in 28 countries and 17 states in the United States of America (14).

A. The B.1.1.7 lineage or The UK Variant

The B.1.1.7 variant is one of the newest strains of the the virus which emerged in the UK in the mid of September 2020. This strain has been named SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, the year 2020, month 12, variant 01) (15). Initial analysis indicates that the variant may spread more readily between people and several investigations are still ongoing to determine if this variant is associated with any changes in the severity of symptoms, antibody response or vaccine efficacy. This variant is characterized by the presence of a range of 14 mutations resulting in amino acid changes and three deletions. From these mutations, five amino acid replacements (D614G, A222V, N439K, Y453F and N501Y), one deletion is thought to be significant as they are located in the spike protein, especially the Receptor Binding Domain (RBD) (16). The N501 is located in the RBD peripheral region where the initial contact between the human Angiotensin Converting Enzyme-2 (ACE-2) and the RBD occurs. Studies performed in mouse indicated that mutation in the N501 i.e N501Y can increase the binding affinity between RBD and ACE2 (17). Another significant mutation in this variant is the P681H which is found directly near the furin cleavage site. This mutation is predicted to increase infection by promoting increased membrane fusion and is associated with higher viral load in Reverse Transcriptase- quantitative PCR (RT-qPCR) tests (18). The 69-70 and 144 deletions found in the solvent accessible β-hairpin loops in the N-terminal Domain (NTD) was first detected during the SARS-CoV-2 transmission in the mink population in Denmark. In normal, conditions monoclonal antibodies from convalescent COVID-19 patients interact with NTD of S protein. Thus it is predicted that the presence of these deletions can confer the virus an antibody resistance (19). Similarly, the presence of N439K and Y453F results in the increased affinity of the virus with the ACE2 thus leading to an increased viral transmission.

Currently, the B.1.1.7 variant is the most commonly observed variant of SARS-CoV-2 globally and a total of 824,608 whole-genome sequences of this variant have been uploaded to the GISAID (20). Since its first detection in the UK, a total of 249,637 cases has been reported in the country (21). Similarly, this variant has been the most prevalent one among the Türkish population. According to reports from the Ministry of Health, 85% of the Covid-19 cases in April 2021 were the B.1.1.7 variant (22).

B. B.1.351 lineage or the South African Variant

Another lately discovered variant is the B.1.351 or the N501Y.V2. This variant was first detected in South Africa on 2 January 2021. Its defining amino acid mutations are K1655N in the ORF1a, N501Y, E484K, D215G, D80A, K417N in the S protein, P71L in the E protein and T205I in the N protein (23). Some studies have reported that this variant have reported that this variant shows more resistance towards neutralization by convalescent plasma and vaccinee sera athan other variants (24). The E484K interacts with the K31 residue in the human ACE to moderately increase the affinity of the RBD protein with the ACE. Three of these mutations are in the RBD (K417N, E484K and N501Y) and are associated with high numbers of infections and increased transmissibility. E484K in combination with K417N, and N501Y induces conformational changes in spike protein and this can result in the evasion of antibodies against the virus (18). Since the main targets of type 1 and type 2 anti SARS-C0V-2 antibodies lie in the RBD sites which are specific for binding with the ACE, the presence of K417N, E484K and N501Y have shown to increase the resistance towards these antibodies (25). For instance A study by Houriiyah Tegally et.al. have indicated that the mutations N501Y and K417N may play a role in the resistance against type

1 antibody, while E484K may provide immune evasion against antibody type -2 (23). It has also been reported that IgG antibody from convalescent sera and vaccinated individuals exhibited decreased reactivity against this variant while no reduction was seen with the UK variant. These findings were further confirmed using the Viral Neutralization test and ACE inhibition test (26). So far a total of 21,018 whole-genome isolates which belonged to the South African variant have been uploaded into the GISAID database out of which 544 were originated from Turkey (20).

C. B.1.1.28 variant or the 501Y.V3 or P.1 (Brazilian Variant)

The third variant of concern, the B.1.1.28 variant or the 501Y.V3 or P.1 lineage, was identified in samples collected after November 2020 in Manaus, Brazil. This variant is characterized by the presence of 12 mutations (i.e. L18F, T20N, D614G, P26S, D138Y, R190S, H655Y, T1027I, V1176, K417T, E484K, and N501Y) in the spike protein out of which three mutations are located in the RBD (L18F, K417N, E484K) (27). One of the mutations in the S protein namely, N501Y is shared with the UK and the South African variants while L18F, K417T and E484K are also found in the South African isolates respectively. The presence of these mutations in this variant contributes to the transmissibility and evasion of antibody-mediated immunity. Specifically speaking, the presence of L18F, K417N, E484K in the RBD may enhance the interaction of hACE2 with the virus resulting in increased transmission. In agreement with this speculation, a study from the city of Manaus has recorded an increased transmission rate of 1.4 up to 2.2. then the other variants which were previously present in the city (28). Up to date, there is no available data about the efficacy of vaccines towards this variant but since it shares many mutations with the South African variant similar patterns antibody neutralization with the South African variant may be observed (10). So far a total of 26,053 whole-genome isolates which belonged to the South African variant have been uploaded into the GISAID database out of which 21 were originated from Turkey (20).

D. B.1.427/B.1.429 lineage (Californian Variant)

B.1.427 and B.1.429 lineage or the Californian variants of concern was first detected in May 2020. These variants contain amino acid mutations S13I, W152C in the NTD and the L452R in the RBD regions of the S protein (29). This variant was reported in about 50% of the total Covid cases in California with an increased transmission rate increase (18.6-24%) than the wild-type strain (30). The main culprit for this could be the L452R mutation which increases the interaction between the RBD and the ACE receptor by promoting structural changes to the protein (31). These variants have been detected in the 42 states of the US and 29 countries. These variants have shown moderate resistance to neutralization by different types of antibodies excerpted from vaccinated and previously infected patients (30). For instance, A study by McCallum et.al confirmed that the mutation L452R was able to reduce or even eliminate the neutralizing ability of 14 monoclonal antibodies specific to the RBD (31). In the GISAID, 44,398 isolates confirmed to be B.1.427 / B.1.429 lineage have been uploaded since its first detection, and only 2 of these isolates were originated from Turkey (20).

E. B.1.617.2 (The Indian variant)

B.1.617.2 or the Indian variant characterized by the presence of mutations T19R, Δ157-158, L452R, T478K, D614G, D950N and P681R was first reported in India in December 2020. This variant become the most dominant strain in India by mid of April 2020 and started spreading to 44 other countries (32). This strain is categorized as a variant of concern by the CDC and European Center for Disease Control and Prevention (ECDC) because of its high transmission rate (8-9). The variant was initially named as 'The double mutant' variant because of the presence of two important mutations that were previously the hallmarks of the South African variant and the Californian variant (L452R and E484Q). Even though there is no recorded invitro neutralization test data so far, the L452R is thought to contribute to the immune evasion by reducing neutralization of antibodies and increased transmission of the variant. Similarly the P681R may play a role in increasing replication which can result in leading to high viral loads thus higher pathogenic potential (33). Even though further detailed study about the effect of this variant toward vaccines is required, the earlier study indicated that the antibodies produced after taking the Pfizer vaccine was approximately 80% less effective against some of the mutations in the variant (34). In the GISAID, 31,353 isolates confirmed to be of the Indian lineage have been uploaded since its first detection, and only 3 of these isolates were originated from Turkey (20).

Conclusion and Future Perspective

The rise of new variants of SARS-CoV-2 have created a huge concern in the fight against the pandemic mainly due to fear of increased transmission, severity as well as immune escape. The variants classified as the 'Variants of Concern' have already exhibited some of these properties to an alarming extent. However to have a solid stand on the transmissibility, severity and the immune escape capabilities of the variants, collection of good quality genomic sequencing along with detailed clinical outcomes and long-term follow-ups are required. Another challenge faced due to the existence of these variants is the partial ineffective of the currently used diagnostic tests for the virus. Due to the presence of mutations and long deletions in the locations of the genome normally detected by the currently used RTqPCR protocols, false-negative results can be reported. Therefore, diagnostic tests for the virus should be designed to be inclusive of the most significant changes observed in the new variants.

As an RNA virus, SARS-CoV-2 undergoes continuous changes in its geneom as a result of adaptive evolution. This continuous change will obviously result in the birth of other variants that may have a more severe effect. Vaccination is considered to be the most effective way to combat newly appearing variants. Even though the efficacy of some of the authorized vaccines may decrease due to the presence of certain mutations, it is still recommended that vaccination should continue. Vaccination can provide immunity towards the majority of the variants and the

more people get vaccinated the less virus circulation will appear, this in turn can result in the decreased emergence of newer strains. In conclusion, consistent genomic sequencing of samples collected should always be adhered to for close surveillance of new variants with potential threatening effects.

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