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New biothreat of JN.1 variant SARS CoV-2: viral genome, mutations and comparison with Delta and Omicron variants – a brief commentary

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ABSTRACT:

SARS-CoV-2, the etiologic agent of COVID-19, is susceptible to mutations and emerged into many variants. This study aims to investigate a new variant called JN.1 with a remarkable number of mutations reported from many countries. All viral members of *Coronaviridae* are single-stranded RNA viruses. It is noteworthy that all variants possessed RNA that can behave directly as mRNA (positive polarity). Due to this property, these variants can have rapid transmissibility, leading to a pandemic disease in a short span of time. When a variant replicates in a susceptible cell during the biosynthesis stage, it frequently leads to RNA replication errors. Due to these replication errors, there is expression of new genes that will lead to the formation of new viral proteins. Due to repeated RNA replication errors, variants like Alpha, Beta, Gamma, and others have evolved in SARS-CoV-2. JN.1 subvariant of Omicron possesses more than 35 amino acid mutations in the spike protein. Due to these mutations, JN.1 has acquired easy transmissibility, increased virulence, and resistance to available COVID-19 vaccines. World Health Organization (WHO) recently classified JN.1 as a 'variant of interest' (VOI).

Keywords: COVID-19, SARS-CoV-2, JN.1, Variant, Delta variant, Omicron variant, Mutation.

SARS-CoV-2 is the causative agent of COVID-19 that has caused disease in pandemic proportions. COVID-19 emerged from Wuhan, China, and then spread to many parts of the globe. Similar to SARS-CoV-2, another virus called SARS-CoV was reported in 2002 in the Guangdong Province of China[1]. In 2012, a virus called MERS-CoV was identified in Saudi Arabia. These coronaviruses belong to RNA viruses that are classified under the *Coronaviridae* family. The genome of SARS-CoV-2 is single-stranded and positive sense in nature. This virus belongs to the *Coronaviridae* family and is related to other coronaviruses that cause diseases in animals and humans[2]. Three important coronaviruses have been identified so far: SARS-CoV, MERS-CoV, and SARS-CoV-2. SARS-CoV and MERS-CoV were also responsible for huge mortality and morbidity[3].

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Coronaviruses are genetically unstable and prone to high mutations, due to viral replication errors, which may result in minor or major antigenic changes. Major changes may lead to the formation of new variants[4], while minor antigenic changes may result in new subvariants. Important variants of SARS-CoV-2 are Alpha, Beta, Gamma, Delta, and Omicron[5]. Due to these properties, since the start of the COVID-19 pandemic, many new variants and subvariants have evolved. Surprisingly, these variants were found to be heterogeneous and expressed variable severity and transmissibility of the disease[6], showing different degrees of virulence and pathogenicity. They have also shown geographical predilection, with some variants constantly isolated from some specific countries[7]. Among these variants, Alpha, Beta, Delta, and Omicron have caused severe mortality around the world.

As previously mentioned, SARS-CoV-2, the virus that caused COVID-19, is genetically very unstable and tends to undergo frequent mutations. Since the World Health Organization (WHO) declared COVID-19 a pandemic, new variants of SARS-CoV-2 have developed. These include Alpha, Beta, Gamma, Delta, Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda, Mu, and Omicron variants[8]. During the COVID-19 pandemic, five waves have been reported[9] from different parts of the world. High morbidity and mortality were reported[10] due to the emergence of new virus variants. According to the severity and spread of these variants, they have been grouped into variants of interest (VOI), variants of concern (VOI), and variants under monitoring (VUM). Among these reported variants, extremely high fatality rates were reported mainly from Alpha, Beta, Delta, and Omicron variants[11].

A new subtype of the Omicron variant, JN.1, was identified in December 2023 from USA[12]. JN.1 has been reported from Denmark, Spain, the United Kingdom, Portugal, South Africa, France, Finland, Australia, Italy, and India[13]. In addition to clinical cases, this variant was observed in wastewater samples from Denmark, Spain, Israel, and Portugal. By the end of January 2024, an additional thirty-two countries have reported[14] cases of JN.1. The earlier variants, such as Delta and Omicron, were homogenously present throughout the world.

Millions of deaths have been reported due to Delta and Omicron variants in the previous years. Nevertheless, as of today, no deaths have been reported due to JN.1[15], but hospitalization has been noticed in a significant proportion (95%) of patients. JN.1 is a new lineage from the Omicron SARS-CoV-2 variant, and it is totally different from the circulating ancestral BA.2.86 and XBB.1.5 variants. The striking feature of the JN.1 variant is its possession of a significant number of mutations[16]. The salient feature of the JN.1 variant is that it possesses a remarkable number of mutations at significant sites in the viral spike protein (S) (Figure 1). Due to the enormous number of mutations in the virion, it can enhance its transmissibility and acquire more severity, and it may not be neutralized by existing COVID-19 vaccines[12]. Genetic studies[17] on JN.1 have exhibited more than 35 amino acid changes in the viral spike protein. A high number of amino acid mutations in spike protein can result in the emergence of a new variant different from the Omicron variant (Figure 2), but the JN.1. viral RNA has conserved 89% of genetic homology with the Omicron variant.

Among the 35 mutations, notable spike mutations in JN.1 are I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, and F486P. D339H mutation is considered to be very important because it is associated with increased transmissibility and virulence of JN.1 variant[16].

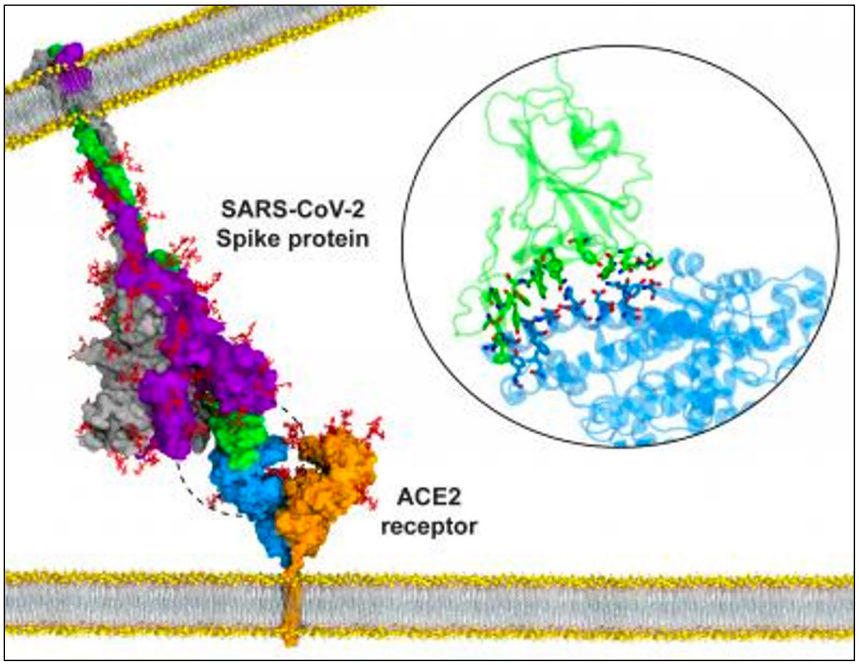

Figure 1. Binding of SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 (ACE-2) receptor on the host cell membrane. Image credit: Ahmet Yildiz, University of California, Berkeley; Mert Gur, Istanbul Technical University.

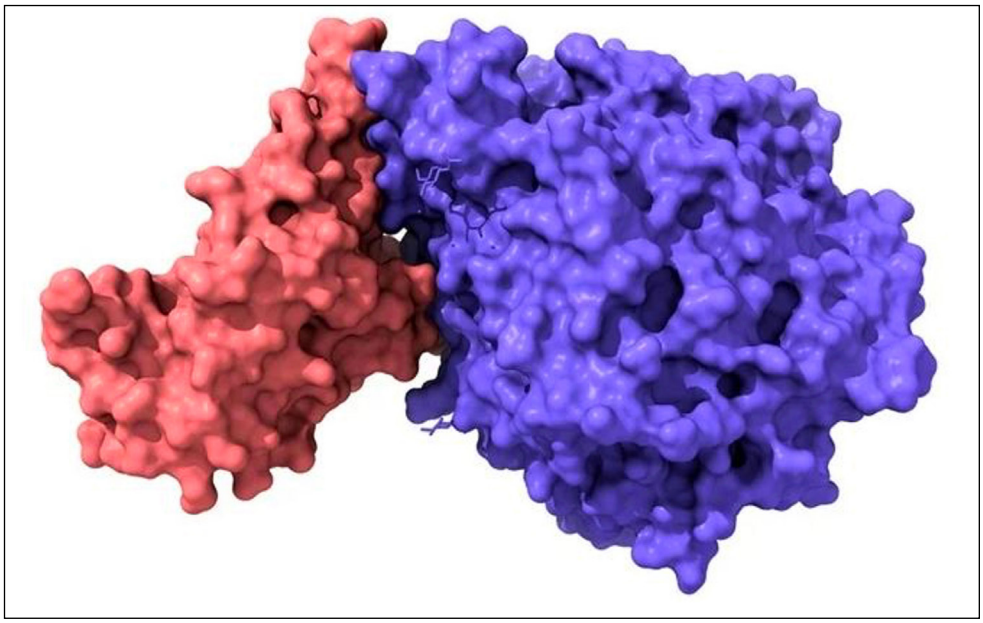

Figure 2. SARS-CoV-2 spike receptor-binding domain (pink) complexed with its receptor ACE2 (blue). Image credit: Volodymyr Dvornyk/ Shutterstock.com.

Due to the enormous amino acid sequence changes, JN.1 has the potential to show increased transmissibility. Due to this reason, within a short span of time, this variant has been isolated in many parts of the world. Moreover, people who have developed SARS-CoV-2 antibodies due to previous infections may not be protected against the JN.1 variant. This is due to the significant changes in amino acid sequences that have occurred in the JN.1 spike protein[18].

Even though there were variations in spike protein, the severity of the disease caused by JN.1 did not alter so far. This may be attributed to the fact that the conservation of genes responsible for the virulence of the JN.1 variant is maintained. Under these circumstances, the currently available vaccines may not be effective for JN.1 variant[19]. It may pose a danger that already COVID-19-vaccinated individuals might get infected with JN.1, and this may lead to a surge in hospitalization of COVID-19 patients around the world. However, this may be overcome with the development of a new vaccine that can neutralize the mutated JN.1 virus, since the existing vaccines have shown very good efficacy against Delta, Alpha, Omicron, and other variants[15].

However, there is a universal pattern observed in all infectious diseases. In any emergence of infectious disease, during the initial outbreak, many people are involved, causing a rapid surge with very high morbidity and mortality. It may occur in many waves; then, it slowly settles like a seasonal flu with mild symptoms.

Research has shown that there has been no significant difference in JN.1 variant efficacy of monoclonal antibodies and antiviral treatment with already circulating variants[20]. SARS-CoV-2, the agent of COVID-19, also follows the same typical wavy pattern of infectiousness, epidemiology, and severity. Now, the whole world is experiencing COVID-19 in a settling phase, during which the eruption of new viral variants with varying severity is a common phenomenon. We propose that it may take another year for the COVID-19 disease to convert into a 'seasonal viral flu'.

SARS-CoV-2, the virus that causes COVID-19, is susceptible to undergo spontaneous mutations. During viral replication, the virus often exhibits 'errors'. Due to these replication errors, the new virions produce viral proteins with different amino acid composition. Usually, in SARS-CoV-2, the spike protein is highly sensitive to high mutations. These changes may be minor or major based on the conserved amino acid sequences. If these changes are few or minor, then they will not have any impact on human health. But if there are major changes, the existing vaccines may not work for the new/modified virions.

The JN.1 variant of SARS-CoV-2 has expressed many mutations, leading to several changes in the amino acid composition of the viral spike protein. Due to this reason, this variant showed rapid transmissibility, but the mortality rate for this new variant is negligible. This may be attributed to its immunological cross-reactivity and protection with already circulating variants. Another reason for the lower mortality may be the vaccinations. New variants similar to JN.1. may evolve in the future, but already existing subtypes and herd immunity will offer protection. Even if some new variants exhibit increased virulence, it is expected to show up like 'common cold/flu' like syndromes.

Further detailed research on molecular biology, pathogenicity, and immune aspects of the JN.1 variant is required.

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None.

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The research data associated with the paper is available.

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